Chapter

Clinical Trials Evaluating Proton Therapy

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Abstract

Although proton therapy was developed almost 80 years ago, widespread clinical implementation has been limited until the past decade. With the growing use of proton therapy, there is a desire to prove the equivalence or superiority of proton therapy across a number of cancer disease sites. Dozens of clinical trials have been developed to accomplish this within individual institutions, among a few centers, and across national and international networks such as the National Cancer Institute's National Clinical Trial Network. The protocols include proton therapy imbedded in trials with photon therapy as well as randomized photon vs. proton trials. This chapter provides an overview of the design of such trials as well as some of the challenges facing protocols with proton therapy.

Keywords: proton therapy, clinical trials, protocols, randomized, phase II, phase III, National Cancer Institute, National Clinical Trial Network

1. Introduction

1.1 Clinical trial importance

Clinical trials are an important step to ensuring the safety and efficacy of medical treatment. For radiation therapy, clinical trials have allowed us to look at important questions like dose escalation, fractionation, and new radiotherapy technologies. Much like the use of instensity-modulated radiation therapy (IMRT) was critically reviewed in the early 2000s, proton therapy has come under careful scrutiny over the past decade. Many radiation therapy departments commissioned proton therapy centers and began to integrate protons into their clinical practice.

1.1.1 Safety and efficacy

Most people who work in radiation therapy have seen the striking treatment plan comparisons between proton therapy and traditional photon therapy for a pediatric craniospinal case, noting the marked reduction in dose to organs at risk and normal tissue outside of the target region [1]. These in-silico studies are even more exciting given the potential reduction in secondary cancer for pediatric patients. The potential benefits in these studies come with corresponding risk; if the beam modeling or treatment delivery positioning is not accurate, there is a risk of high overdose to normal tissue or severe underdose of the target. For this reason, the National Cancer Institute (NCI), the American Society for Radiation Oncology (ASTRO), and other

groups have encouraged methodical, careful study of the clinical benefits of proton therapy through clinical trials [2].

The potential benefits of proton therapy are also complicated by the higher biological effectiveness of protons as compared with photons. The current clinical practice in the US is to use a relative biological effectiveness (RBE) of 1.1 for protons, but studies have shown that the true biological response is more complicated and variable [3]. While the higher RBE of protons is a potential benefit for killing tumor cells, there is potential increased biological risk to critical organs proximate to the target. Clinical trials with proton therapy can allow us to look at both sides of the coin by analyzing the correlation between RBE and clinical outcomes.

1.1.2 Evidence for insurance

Insurance companies have played a role in driving the development of randomized proton vs. photon clinical trials as well. Due to the higher up-front cost of proton therapy for many disease sites, insurance companies have asked for data showing marked improvement in survival outcomes for patients treated with proton therapy in order to cover treatment costs. As discussed later in the chapter, this presents a bit of a catch-22 in clinical trial accrual, as insurers are waiting for trial data to approve coverage, but trial data is nearly impossible to collect without insurance coverage for patients enrolled on-study.

1.2 Clinical trial landscape in the US

1.2.1 Clinical trial groups

The largest clinical trial system that supports proton therapy protocols in the US is the National Clinical Trial Network (NCTN), funded by the NCI. The NCTN is made up of four adult and one pediatric clinical trial groups, as well as a partnership with the Canadian Cancer Trials Group. Most of the proton therapy studies run through the NCTN are large-scale, multi-institutional Phase II and Phase III trials. These trials either randomize patients to proton or photon therapy to compare treatment outcomes or imbed proton therapy as a possible treatment modality in a study designed to answer a different clinical question. The NCI has also funded proton clinical trials outside of the NCTN [4–7]. These are often run by a single proton center "sponsor" in partnership with other proton facilities and funded through NCI grants.

Outside of the NCI, there are several other groups that help sponsor clinical trials for proton therapy. The National Association for Proton Therapy (NAPT) is a nonprofit group that helps facilitate proton therapy research collaborations. Most of the operational proton therapy centers in the US are members of NAPT. The Patient-Centered Outcomes Research Institute (PCORI) provides funding for clinical trials comparing proton vs. photon therapy for prostate and breast treatment. The NCI also has a Childhood Cancer Data Initiative (CCDI) that collects standard patient data, including proton therapy data, in a central repository for data sharing and analysis within the research community.

Outside of the US, several groups in Europe and Asia have proton therapy protocols open or in development. The Japan Clinical Oncology Group (JCOG) is funded by Japan's National Cancer Center Research and Development Fund and conducts studies with proton therapy [8]. The European Organization for Research and Treatment of Cancer (EORTC) operates clinical trials within Europe and currently has two protocols with proton therapy embedded [9]. The European Society for Radiotherapy (ESTRO) recently established the European Particle

Therapy Network (EPTN), which conducts a number of prospective studies looking at proton (and carbon) therapy, and works in concert with the EORTC [10, 11]. Global collaborations on clinical trials have been limited so far. The US has the largest catalog of proton therapy clinical trials and has sought participation of international proton centers, but the many steps to opening the protocols (NCTN membership, state department clearance, baseline approval quality assurance) have slowed down collaboration. The clinical trial groups are working on streamlining these processes to allow for expanded international partnerships in the future.

2. Randomized proton vs. photon trials

In order to move past in-silico studies that promise superior dosimetry with proton therapy, clinical evidence is needed. One of the best ways to get these data are through randomized clinical trials. For proton therapy trials, randomization is generally structured with two arms: proton vs. photon. In order to get enough patients for statistical significance, these trials require a lot of patients (usually hundreds) and are typically run as multi-institutional studies. These large randomized studies may be designed to show superiority of proton therapy or to demonstrate non-inferiority [12]. Most NCTN randomized proton vs. photon trials have a primary endpoint of assessing overall survival. Secondary endpoints include progression-free survival, local control, toxicities, cognitive outcomes, symptoms burden, quality of life, cost effectiveness, and cost–benefit economics. While proton therapy generally has a higher up-front cost, it is hypothesized that proton therapy may be more cost-effective for some disease sites due to reduction in acute and long-term toxicities and associated medical costs.

Typically NCTN clinical trial data is only assessed for objectives explicitly listed in the protocol and analysis outside the original scope is only permitted after the trial has been closed several years. For this reason, somewhat indefinite exploratory objectives are written into the protocol to allow for analyses that may not be understood at the time of protocol development. For randomized proton vs. photon trials within the NCTN, exploratory objectives include biospecimen and imaging data collection for the assessment of biomarkers.

Most randomized proton vs. photon studies randomize 1:1, though some protocols have randomize 2:1 in favor of proton therapy. The two arms typically have the same radiobiological dose prescription, though some studies like NRG Oncology/RTOG 1308 have low dose and high dose arms.

2.1 Challenges of randomized proton vs. photon trials

Clinical trials can be challenging for a number of reasons - increased personnel effort to coordinate patient enrollment and data submission, increased operational costs, low patient interest, and low physician engagement – but randomized proton vs. photon trials face a number of unique challenges.

2.1.1 Treatment planning

One unique aspect of proton vs. photon trials is that it is common to create treatment plans for patients using both modalities to ensure that both can meet the planning dose constraints required by the protocol [13]. This may require increased time on the part of the participating institutions, though many proton centers may already be creating double plans for insurance purposes.

Treatment planning itself is different between proton therapy and photon therapy. The planning target volume (PTV) that is commonly used for photon plans is generally not used in the same way for proton therapy. Instead of uniform expansion from clinical target volume (CTV) to the PTV, proton treatment plans may have one pre-defined lateral margin, and a different margin in the direction of the beam range that depends on the maximum beam energy [14, 15]. In this way, the proton "PTV" is beam-specific. This presents a challenge for clinical trial data analysis, as most protocols are written with historical photon PTV constraints. Future protocols should be designed with this in mind.

Furthermore, proton therapy treatment planning has started to shift away from the standard lateral and range margins in favor of robust optimization of the CTV [16, 17]. There are many different ways to report dose when using robust optimization (e.g. voxel-wise worst-case approach, scenario-wise worst-case approach, delivered dose variance) [18]. Clinical trials should soon consider how robustly optimized treatment planning data will be collected to ensure appropriate data comparison between the proton and photon arm. This highlights the crucial role that physicists and data (i.e. Digital Imaging and Communications in Medicine (DICOM)) experts play in the development of clinical trials.

In addition to the nuances of physical dose, randomized proton vs. photon trials need to consider the implications of radiobiology. The NCTN currently uses an RBE of 1.1, but many proton centers are starting to consider variable RBE in their treatment planning practices [19, 20]. If variable RBE treatment planning becomes standard, clinical trials will need to incorporate it into treatment planning constraints, and determine what patient data needs to be collected to appropriately compare different treatment plans.

2.1.2 Patient preference

One challenge with randomized clinical trials comparing proton therapy with photon therapy is patient preference. This manifests when a patient is randomized to one arm but has a strong desire to be treated on the other arm, and thus goes off protocol. Patients randomized to the photon arm may decide they want proton therapy instead due to an impression gathered through independent online research or a preference for the "latest and greatest" technology. Conversely, some patients randomized to the proton arm may go off protocol to receive photon therapy due to mistrust of a new, "unproven" technology.

2.1.3 Insurance denial

Another challenge of proton trial accrual is insurance denial for proton therapy [21]. This is particularly challenging in the case of randomized proton vs. photon trials because it can make it harder to reach accrual goals on the proton arm of the protocol. Insurance denials of proton therapy can also skew the patient demographics of the proton arm. For example, Medicare is significantly more likely to cover proton therapy than private insurers, which can skew the age of the proton cohort toward older participants [22]. This older patient cohort might have comorbidities or other characteristics that make it challenging to compare outcomes data between the two arms. Lastly, the process of appealing insurance denials can lead to delays in the start of radiation treatment [23]. Clinical trial patients may already wait slightly longer for treatment to start due to clinical trial requirements such as pre-treatment reviews of the treatment plan. These delays might result in a patient going off trial to pursue treatment sooner.

One way to counteract the deleterious effect of proton insurance denial on randomization is to use a 2:1 randomization in favor of proton therapy. This gives the trial more opportunities to accrue proton patients, even if insurance challenges persist. But most proton centers choose to challenge insurance denials, and the best way to combat insurance denial is through support networks and sharing of resources. The NAPT offers a guide for patients on steps to deal with insurance denial, many of which are applicable to clinical teams as well [24]. Many proton centers have dedicated personnel to manage insurance appeals. For the NCTN, proton insurance denials are a frequent topic at operations management and proton working group meetings. These forums allow physicians to share successful techniques to overcome insurance barriers. Physicians have banded together to publish pleas for insurance companies to change the insurance approval process for proton therapy [25]. Some proton therapy centers have negotiated with insurance companies to reimburse proton therapy at the cost of IMRT, picking up the rest of the costs themselves [25]. The NCI has also advocated on behalf of proton therapy centers in the context of clinical trial insurance reimbursement for randomized NCTN protocols [26].

2.1.4 Logistics of partnerships with proton centers in other cities, countries

Due to the limited number of proton therapy centers, many randomized proton vs. photon trials encourage partnerships between one proton center and any number of photon clinics. There are many considerations when establishing a partnership between two institutions, such as who gets "credit" for the clinical trial accrual, how clinical trial reimbursement is allocated between the institutions, which personnel have rights to upload patient data to the appropriate portals, etc. There is a possibility that a photon clinic might partner with a proton center in another country. In this case, the logistics of travel reimbursement (if provided) should be addressed, as well as clinical trial membership and state approval if the trial is run through the NCTN. This type of partnership may become increasingly common as clinical trials for carbon therapy are being developed, with most carbon centers located in Europe and Eastern Asia. A few concepts have been proposed that randomize IMRT treatment to centers in the US, and carbon therapy to centers abroad [27].

3. Imbedded proton trials

In addition to randomized proton vs. photon clinical trials, there are a number of trials that imbed proton therapy as one of several allowed treatment modalities. This practice was most common this past decade in pediatric trials, such as those conducted by the Children's Oncology Group (COG), but has been applied to adult trials as well. While the superiority of proton therapy outcomes might not be the primary endpoint of these studies, the hope is that with enough data, secondary analyses can be performed to look at proton patient cohorts compared to others.

3.1 Pediatric trials

To date, the standard method of including proton therapy in pediatric clinical trials has been to imbed protons in the protocols. The strategy recognizes the challenges of accrual to disease-specific radiation therapy protocols in pediatric patients and permits parallel treatment strategies for both photon and proton care to

successfully manage the study. Approximately 50% of pediatric malignancies are in the leukemia domain, therefore protocols requiring radiation therapy are directed to tumors of the central nervous system, sarcoma, renal, orbit including retinoblastoma, and lymphoma. Therapy volumes and target dose are uniform between proton and photon care with guidelines imbedded in the study to insure synergistic care for tumor control acknowledging subtle differences in planning target volumes and dose distribution to normal tissue. Both proton and photon patients need to meet the identical dose to tumor and normal tissue. Dose to normal tissue in most situations is more easily achieved with proton therapy. In pediatric studies, outcome analysis including imaging are part of the longitudinal aspect of protocol management, therefore colleagues in the COG and the Imaging and Radiation Oncology Core (IROC) can evaluate normal tissue endpoints with outcome imaging validation to review comparison plans in retrospect to acquire important outcome analysis for secondary study endpoints between proton and photon care.

One challenge pediatric trials have faced is the apparent racial disparities between who receives proton therapy, with non-Hispanic white pediatric patients significantly more likely to be treated with protons than black patients [28]. This presents a challenge to proportional racial representation in clinical trial data.

3.2 Adult trials

In the US, adult clinical trial groups have imbedded proton therapy in dozens of clinical trials. At times, proton therapy has been added through clinical trial amendments with the hope of boosting accrual to protocols struggling to accrue patients. For a number of reasons (small number of proton centers, insurance denials, competing proton-specific trials), this has not proven to be the silver bullet, however, and generally it's not recommended to add proton therapy as an allowable modality solely to improve trial accrual for adult protocols. Despite lower accrual numbers, proton therapy can be a good addition to a trial, adding the possibility of secondary analyses to look at proton therapy outcomes in relation to other treatment modalities.

4. Proton therapy registries

Outside of prospective clinical trials with proton therapy, there are a number of proton therapy registries. These are generally less structured than Phase II/Phase III trials and allow for more flexibility in which data are analyzed. The Proton Collaborative Group (PCG) is a registry of nearly six thousand proton patients in the US [29]. The PCG looks at survival outcomes and quality of life, and fosters peer review collaboration across centers for clinical trial development. The Pediatric Proton Consortium Registry (PPCR) is a multi-institutional collaborative registry of demographic and clinical data for pediatric patients treated with proton and photon therapy [30]. The goal of the PPCR is to compare benefits of the two radiotherapy techniques, such as disease outcomes and quality of life. Washington University School of Medicine and Radialogica, LLC have a Proton Therapy Registry for adult and pediatric patients that collects clinical and dosimetric data [31].

5. Conclusions

Proton therapy has great potential and in some cases, proven clinical benefit. The best way to gather evidence to secure proton therapy as a standard of care for

cancer treatment is through thoughtful, controlled clinical trials. Much work has already been done to this effect, and with so many clinical trials for proton therapy currently accruing, we will soon have data to answer the myriad questions related to proton therapy treatment outcomes.

Conflict of interest

The author declares no conflict of interest.

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References

[1] Howell RM, Giebeler A, Koontz-Raisig W, Mahajan A, Etzel CJ, D'Amelio AM Jr, Homann KL, Newhauser WD. Comparison of therapeutic dosimetric data from passively scattered proton and photon craniospinal irradiations for medulloblastoma. Radiation Oncology. 2012;7:116. DOI:10.1186/1748-717X-7-116. PMID: 22828073.

[2] Allen AM, Pawlicki T, Dong L, Fourkal E, Buyyounouski M, Cengel K, Plastaras J, Bucci MK, Yock TI, Bonilla L, Price R, Harris EE, Konski AA. An evidence based review of proton beam therapy: the report of ASTRO's emerging technology committee. Radiotherapy and Oncology. 2012;103(1):8-11. DOI:10.1016/j.radonc.2012.02.001.

[3] Paganetti H, Niemierko A, Ancukiewicz M, Gerweck LE, Goitein M, Loeffler JS, Suit HD. Relative biological effectiveness (RBE) values for proton beam therapy. International Journal of Radiation Oncology • Biology • Physics. 2002;53(2):407-421. DOI:10.1016/s0360-3016(02)02754-2.

[4] United States National Library of Medicine (NLM) - National Institutes of Health (NIH). Randomized Trial of Intensity-Modulated Proton Beam Therapy (IMPT) Versus Intensity-Modulated Photon Therapy (IMRT) for the Treatment of Oropharyngeal Cancer of the Head and Neck [Internet]. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT01893307. [Accessed: 2020-09-03].

[5] United States National Library of Medicine (NLM) - National Institutes of Health (NIH). Vertebral Body Sparing Craniospinal Irradiation for Pediatric Patients with Cancer of the Central Nervous System [Internet]. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04276194. [Accessed: 2020-09-03].

[6] United States National Library of Medicine (NLM) - National Institutes of Health (NIH). A Trial of Increased Dose Intensity Modulated Proton Therapy (IMPT) for High-Grade Meningiomas [Internet]. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT02693990. [Accessed: 2020-09-03].

[7] United States National Library of Medicine (NLM) - National Institutes of Health (NIH). Radiation Therapy (Hypofractionated Proton Beam Therapy or IMRT) for the Treatment of Recurrent, Oligometastatic Prostate Cancer Following Primary Localized Treatment [Internet]. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04190446. [Accessed: 2020-09-03].

[8] Nakamura K, Fukuda H, Shibata T, Kaba H, Takashima A, Tomii Y, Murooka A, Toshima H, Abe J, Katayama H, Kunieda F, Kimura A, Kanato K, Mizusawa J, Yamashita N. Current Status and Challenges in Jcog Data Center (DC) And Operations Office (OPS). Annals of Oncology. 2012;23(S11):X169. DOI:10.1093/annonc/mds570.

[9] European Organisation for Research and Treatment of Cancer (EORTC). Clinical Trials Database [Internet]. 2020. Available from: https://www.eortc.org/clinical-trials-database/#location=25. [Accessed: 2020-09-05].

[10] Weber DC, Langendijk JA, Grau C, Thariat J. Proton therapy and the European Particle Therapy Network: The past, present and future. Cancer radiothérapie: journal de la Société française de radiothérapie oncologique. 2020; (6-7):687-690. DOI:10.1016/j.canrad.2020.05.002.

[11] Weber DC, Grau C, Lim PS, Georg D, Lievens Y. Bringing Europe

together in building clinical evidence for proton therapy - the EPTN-ESTRO-EORTC endeavor. Acta Oncologica. 2019;58(10):1340-1342. DOI:10.1080/0284186X.2019.1624820.

[12] Frank SJ, Blanchard P, Lee JJ, Sturgis EM, Kies MS, Machtay M, Vikram B, Garden AS, Rosenthal DI, Gunn GB, Fuller CD, Hutcheson K, Lai S, Busse PM, Lee NY, Lin A, Foote RL. Comparing intensity-modulated proton therapy with intensity-modulated photon therapy for oropharyngeal cancer: The journey from clinical trial concept to activation. Seminars in Radiation Oncology. 2018;28(2):108-113. DOI:10.1016/j.semradonc.2017.12.002.

[13] Liao Z, Lee JJ, Komaki R, Gomez DR, O'Reilly MS, Fossella FV, Blumenschein GR Jr, Heymach JV, Vaporciyan AA, Swisher SG, Allen PK, Choi NC, DeLaney TF, Hahn SM, Cox JD, Lu CS, Mohan R. Bayesian adaptive randomization trial of passive scattering proton therapy and intensity-modulated photon radiotherapy for locally advanced non-small-cell lung cancer. Journal of Clinical Oncology. 2018;36(18):1813-1822. DOI:10.1200/JCO.2017.74.0720.

[14] Moyers MF, Miller DW, Bush DA, Slater JD. Methodologies and tools for proton beam design for lung tumors. International Journal of Radiation Oncology • Biology • Physics. 2001;49(5):1429-1438. DOI:10.1016/s0360-3016(00)01555-8.

[15] Moyers MF, Sardesai M, Sun S, Miller DW. Ion stopping powers and CT numbers. Medical Dosimetry. 2010;35(3):179-194. DOI:10.1016/j.meddos.2009.05.004.

[16] Liu W, Zhang X, Li Y, Mohan R. Robust optimization of intensity modulated proton therapy. Medical Physics. 2012;39(2):1079-1091. DOI:10.1118/1.3679340.

[17] Unkelbach J, Paganetti H. Robust proton treatment planning: Physical and biological optimization. Seminars in Radiation Oncology. 2018;28(2):88-96. DOI:10.1016/j.semradonc.2017.11.005.

[18] Yock AD, Mohan R, Flampouri S, Bosch W, Taylor PA, Gladstone D, Kim S, Sohn J, Wallace R, Xiao Y, Buchsbaum J. Robustness analysis for external beam radiation therapy treatment plans: Describing uncertainty scenarios and reporting their dosimetric consequences. Practical Radiation Oncology. 2019;9(4):200-207. DOI:10.1016/j.prro.2018.12.002.

[19] Willers H, Allen A, Grosshans D, McMahon SJ, von Neubeck C, Wiese C, Vikram B. Toward a variable RBE for proton beam therapy. Radiotherapy and Oncology. 2018;128(1):68-75. DOI:10.1016/j.radonc.2018.05.019.

[20] McNamara A L, Willers H, Paganetti H. Modelling variable proton relative biological effectiveness for treatment planning. British Journal of Radiology. 2020;93(1107):20190334. DOI:10.1259/bjr.20190334.

[21] Bekelman JE, Denicoff A, Buchsbaum J. Randomized trials of proton therapy: Why they are at risk, proposed solutions, and implications for evaluating advanced technologies to diagnose and treat cancer. Journal of Clinical Oncology. 2018;36(24):2461-2464. DOI:10.1200/JCO.2018.77.7078.

[22] Ning MS, Gomez DR, Shah AK, Kim CR, Palmer MB, Thaker NG, Grosshans DR, Liao Z, Chapman BV, Brooks ED, Tang C, Rosenthal DI, Garden AS, Frank SJ, Gunn GB. The insurance approval process for proton radiation therapy: A significant barrier to patient care. International Journal of Radiation Oncology • Biology • Physics. 2019;104(4):724-733. DOI:10.1016/j.ijrobp.2018.12.019.

[23] Yu NY, Sio TT, Mohindra P, Regine WF, Miller RC, Mahajan A,

Keole SR. The insurance approval process for proton beam therapy must change: Prior authorization is crippling access to appropriate health care. International Journal of Radiation Oncology • Biology • Physics. 2019;104(4):737-739. DOI:10.1016/j.ijrobp.2019.04.007.

[24] The National Association for Proton Therapy (NAPT). Patient Insurance Strategies. [Internet]. 2020. Available from: https://www.proton-therapy.org/patient-resources/insurance/. [Accessed 2020-09-02].

[25] Gupta A, Khan AJ, Goyal S, Millevoi R, Elsebai N, Jabbour SK, Yue NJ, Haffty BG, Parikh RR. Insurance approval for proton beam therapy and its impact on delays in treatment. International Journal of Radiation Oncology • Biology • Physics. 2019;104(4):714-723. DOI: 10.1016/j.ijrobp.2018.12.021.

[26] Vikram B, Denicoff A. NRG Insurer Letter D.o.H.H. Services. Editor. 2020: Available from: www.ctsu.org. [Accessed: 2020-08-26].

[27] United States National Library of Medicine (NLM) - National Institute of Health {NIH). Trial of Carbon Ion Versus Photon Radiotherapy for Locally Advanced, Unresectable Pancreatic Cancer (CIPHER) [Internet]. 2020. Available from: https://clinicaltrials.gov/ct2/show/NCT03536182. [Accessed 2020-09-02].

[28] Bitterman DS, Bona K, Laurie F, Kao PC, Terezakis SA, London WB, Haas-Kogan DA. Race disparities in proton radiotherapy use for cancer treatment in patients enrolled in Children's Oncology Group trials. JAMA Oncology. 2020;6(9):1465-1468. DOI:10.1001/jamaoncol.2020.2259.

[29] Proton Collaborative Group (PCG). Proton Collaborative Group [Internet]. 2020. Available from: https://pcgresearch.org/. [Accessed: 2020-09-27].

[30] Hess CB, Indelicato DJ, Paulino AC, Hartsell WF, Hill-Kayser CE, Perkins SM, Mahajan A, Laack NN, Ermoian RP, Chang AL, Wolden SL, Mangona VS, Kwok Y, Breneman JC, Perentesis JP, Gallotto SL, Weyman EA, Bajaj BVM, Lawell MP, Yeap BY, Yock TI. An update from the Pediatric Proton Consortium Registry. Frontiers in Oncology. 2018;8:165. DOI:10.3389/fonc.2018.00165.

[31] Multi-Site Proton Therapy Registry [Internet]. 2020. Available from: https://protonregistry.wustl.edu/. [Accessed: 2020-09-27].