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Chapter

Multi-Institutional Data Collection and Analysis via the Pediatric Proton/Photon Consortium Registry

Nicholas J. DeNunzio, Miranda P. Lawell and Torunn I. Yock

Abstract

Care of patients with proton therapy has increased in the past decade. It is important to report on outcomes and disease specific utilization of particle therapy. In this chapter, we review our experience in developing a registry for pediatric patients treated with radiation to assess outcomes and provide a platform for shared research interests.

Keywords: Pediatric cancer, radiation therapy, particle therapy, proton registry

1. Introduction

Pediatric cancers comprise a simultaneously rare but highly varied cadre of diseases. They account for less than 1% of all new cancer diagnoses made in the United States each year with nearly 17,000 projected in 2020 for patients under 20 years of age [1]. These can be classified as liquid tumors (leukemias and lymphomas) and solid tumors originating in central nervous system (CNS) and non-CNS sites. While many patients undergo radiotherapy (RT) as part of standard disease management, a significant portion of treatment paradigms does not include RT outright or requires RT to the entire body (e.g. total body irradiation in conditioning for stem cell transplants in patients with leukemia), thereby obviating the need for highly technical delivery methods such as proton radiotherapy (PRT). The number of patients available for study, therefore, is substantially less such that studying treatment outcomes is challenging and limits the ability of any one radiation center to amass clinical data and generate timely empirical results.

Survival and toxicity outcomes associated with PRT, as with photon radiotherapy (XRT), can be obtained through inquiries ranging in quality from single-institution retrospective studies to prospective randomized phase three clinical trials. However, in the pediatric population, randomized trials are not feasible given lack of equipoise among parents of patients and caregivers between proton- and photon-based radiation. In addition, low disease prevalence, varied disease management options, and varied anatomic sites can result in limited data availability. Consequently, collaboration among institutions is needed to obtain a critical mass of data that enables meaningful outcomes research. Children's Oncology Group (COG) and the International Society of Pediatric Oncology (SIOP) are cooperative

groups that work together to try to answer critical treatment-related questions on the more common pediatric malignancies. However, access to cooperative group data for ad hoc studies is limited, even among cooperative group members. Furthermore, these groups are focused on primary disease-specific endpoints and typically do not prioritize the collection of data on health outcomes and morbidity that can affect health-related quality of life. Importantly, COG has a registry called Project:EveryChild that attempts to capture limited information and biological specimens on all patients with a pediatric malignancy or benign tumor. However, the only information collected on RT is whether a patient was treated with it but no information on dose, site, timing of radiotherapy, or other factors that can play a role in disease control and other health outcomes [2].

To address these challenges, the Pediatric Proton/Photon Consortium Registry (PPCR) was initiated in 2010 [3–5], first focusing exclusively on studying clinical outcomes after PRT. Herein we describe the PPCR's administrative structure and processes, collected data (including patient demographics), and our vision for how the PPCR may further evolve.

2. PPCR overview

The PPCR is a consented registry established by and centrally coordinated through a team at Massachusetts General Hospital (MGH). Nineteen institutions are currently contributing data while 11 are in the process of joining [6]. Pediatric patients treated with radiation prior to 22 years of age are offered enrollment and all treatment exposures and baseline patient health and tumor characteristics are collected. The registry also tracks survival and treatment-related toxicity for all and patient-reported quality-of-life (PedsQL) data on a voluntary basis at 14 institutions. The PPCR enrolled its first participant in October, 2012 and was initially designed to collect data on the pediatric proton cohort. Then in 2018, after input from the National Cancer Institute (NCI) and various stakeholders, patients treated with any radiation modality became eligible to enroll. The PPCR was jointly funded by the NCI/MGH Federal Share of Proton Income research fund until 2019 and is now funded predominantly through MGH research funds and philanthropic donations.

2.1 Site acquisition

All radiation centers that treat pediatric patients are welcome to join, although current laws hinder some centers from joining among those based outside the United States, Canada, and Australia. Once clinicians at an institution express interest in participating, they are provided the current protocol, informed consent form, financial disclosure form, signature and delegation of responsibilities logs, and investigator agreement. The interested investigator(s) will then begin the regulatory proceedings needed to open the study at their institution. Unlike involvement in other registries and cooperative groups, there is no central cost to join though institutions are responsible for supporting the staff needed to complete study-related tasks.

2.2 Team composition

The coordinating team at MGH consists of five individuals: principal investigator (PI), project manager, biostatistician, and two clinical research coordinators (CRC). The coordinating team is responsible for central registry oversight and

reporting, patient registration, database management, monitoring, and quality assurance. Individual site team composition is dependent on available resources and ranges from a single physician up to a staff of eight. Notably, limited institutional resources is the most commonly reported barrier to participation.

2.3 Regulatory structure

Each site uses its own Institutional Review Board (IRB) and abides by its own institutional regulations. The site's protocol and consent forms are approved by the coordinating team at MGH. Eight centers use the Western Institutional Review Board, Inc., in lieu of a local IRB. To streamline ongoing review and protocol changes, the coordinating team compiles study changes into a single annual amendment submission that is implemented study-wide.

2.4 Consent and enrollment

All children and young adults (<22 years of age) who receive radiation at one of our participating institutions are eligible and invited to enroll. For this minimal-risk study, informed consent may be obtained by any member of the study team (e.g. CRC, research nurse, advanced practice provider, physician/PI) and must be obtained prior to completing any study-related procedures. Most patients are enrolled at some point during their primary treatment, although prior radiation treatment does not exclude them from being eligible. PedsQL study consent is sought in the first week of treatment to facilitate timely completion of the baseline survey. All patients are centrally registered at the coordinating center and assigned a study identification number (SIDN). The registry's goal is to capture all pediatric patients treated with RT. However, some patients decline to enroll, which can introduce bias in the collected data. To mitigate this effect, basic, non-identifying demographic information is gathered on patients who decline to participate, including their reason for doing so. This facilitates identifying barriers to registry enrollment and meaningful disparities between participants and patients who do not consent. Participants remain on study until death, withdrawal of consent, or study termination.

2.5 Data infrastructure and collection

Clinical data and patient-reported outcomes are collected and managed using the REDCap platform available through the National Institutes of Health [7–9]. This is a no-cost, web-based software platform for collecting and managing data and administering online surveys. Each study site is assigned its own data access group and can only see records entered by users within this group.

Participants are entered into the database using their assigned SIDN. Data are collected at the following time points, each with its own specifications: baseline (pre-RT), during treatment, and follow-up. A total of 1,604 data variables provide information on demographics, diagnosis and associated genetic factors, imaging dates and results, all cancer-related treatments, survival outcomes, and all treatment-related toxicities. Question formats allow for quantitative and qualitative responses and include drop-down boxes, radio buttons, check-boxes (multiple selections), text with validation (dates, numbers), and text without validation. Branching logic streamlines data input by displaying relevant data variables based on prior selections. Radiation plans (inclusive of planning scan, contours, and dose files) and pertinent diagnostic imaging (e.g. magnetic resonance imaging) are collected and managed using MIM Software Inc.'s MIMcloud (Cleveland, OH; [10]), which is a

secure internet-based file transfer service. Files that are uploaded to MIMcloud are anonymized by SIDN and then stored on a centrally housed server that is maintained by the coordinating center.

PedsQL Core Module surveys, added in September, 2015 as a voluntary component of the PPCR, collect data on physical, emotional, social, and cognitive functioning [11, 12]. Surveys are administered to patients at the beginning and end of treatment, and annually thereafter. For patients under five years of age, surveys are completed by the parent only. For patients aged 5–18 years, both the parent and child complete the surveys. For patients over the age of 18, no parental survey is given. REDCap's survey functionality allows participants to complete the survey electronically as well as receive a secure link by email or text to access follow-up surveys. This REDCap function directly deposits the patient's responses into the database, thereby obviating the need for manual data entry.

Each site has permission through the consent process to contact their site's participants, families, and home physicians to request outside medical records and update the database. This is critical as proton therapy centers are quaternary referral centers and the majority of patients return to their home institution for continued oncologic care, which makes longitudinal follow up more difficult [13].

2.6 Data safety and monitoring

All data entered into REDCap are monitored for timeliness of submission, completeness, and adherence to protocol requirements. Ongoing monitoring procedures include: (1) review of all participant consents and study eligibility at registration; (2) database review for discrepancies and potential errors; (3) remote or on-site monitoring; (4) monthly reports that identify missing data that are vital to the integrity and completeness of the dataset and are subject to a higher standard of data monitoring.

2.7 Data usage

All institutions have unfettered access to their own data and can use their data for operational planning, quality purposes, or research purposes. Data can be extracted manually or via REDCap's built-in reporting features. For use of multi-center data, investigators may submit a "Request for Data" (RFD) through a REDCap questionnaire. RFDs are then reviewed by the PPCR coordinating center and each site PI. Each PI can decide whether to include their site's data in the requested project. Data are available for investigator-initiated research and for investigators wishing to partner with the PPCR to answer questions in pediatric oncology.

3. Data and patient characteristics

This collaborative effort aims to expedite investigations into and understanding of pediatric patient survival, treatment toxicity, and impacts on quality of life after RT by pooling data from multiple institutions and making them available for study to participating investigators. Data are qualitative and quantitative in nature, inclusive of patient demographics, dosimetric statistics of the radiation target and healthy tissues, and neoadjuvant and/or adjuvant treatments that are administered as part of standard comprehensive cancer care. In addition, dose distribution data are curated, which are critical in providing a higher level of granularity in dosimetric studies.

To date, the PPCR has enrolled more than 3,200 patients, with a steady annual accrual of about 450 patients in recent years. Notably, the COVID pandemic has

slowed accrual in 2020 due to the various institutional responses that put non-COVID research on hold to focus attention on the health crisis. Patients have a median age of ten years and are mostly residents of the United States (76%), male (57%), White/Caucasian (71%), and non-Hispanic/Latino (71%) (**Table 1**, **Figure 1**, **Figure 2**). RT has been delivered using protons in 99% of participants, reflecting that the bulk of institutions that joined were proton centers prior to 2018 when enrollment criteria

	Total (n = 3260)
Characteristics	
Age at RT (years)	9.74 (<1–27.7)
Sex	
Male	1860 (57.1%)
Female	1400 (42.9%)
Race [α]	
Black or African American	242 (7.4%)
Arabic/Middle Eastern	35 (1.1%)
Asian	171 (5.2%)
White/Caucasian	2329 (71.4%)
Native American/Alaska Native	16 (0.5%)
Native Hawaiian or Other Pacific Islander	11 (0.3%)
Unknown/Not Specified	425 (13.0%)
Other	29 (0.9%)
Missing	42 (1.3%)
Ethnicity	
Hispanic or Latino	353 (10.8%)
Not Hispanic or Latino	2305 (70.7%)
Unknown or Not Reported	602 (18.5%)
United States Residency[β]	
United States	2461 (75.5%)
Non-United States	542 (16.6%)
Not Reported	257 (7.9%)
Tumor Site	
CNS	1929 (59.2%)
Non-CNS	1299 (39.8%)
Missing	32 (1.0%)
Radiation Modality[α]	
Protons	3238 (99.3%)
Photons	188 (5.8%)
Electrons	7 (0.2%)

[α]*Totals sum >100% due to multiple selections per patient.*
[β]*Due to IRB restrictions, patient residency is not reported for some patients.*

Table 1.
Characteristics of PPCR participants.

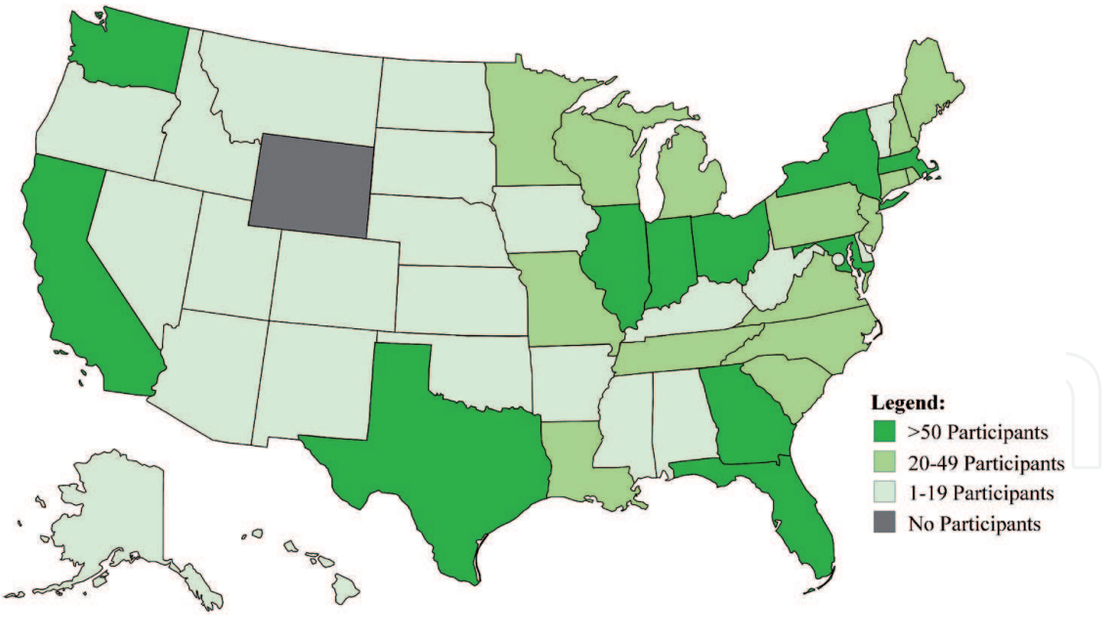

Figure 1.
Participant residency by state in the United States.

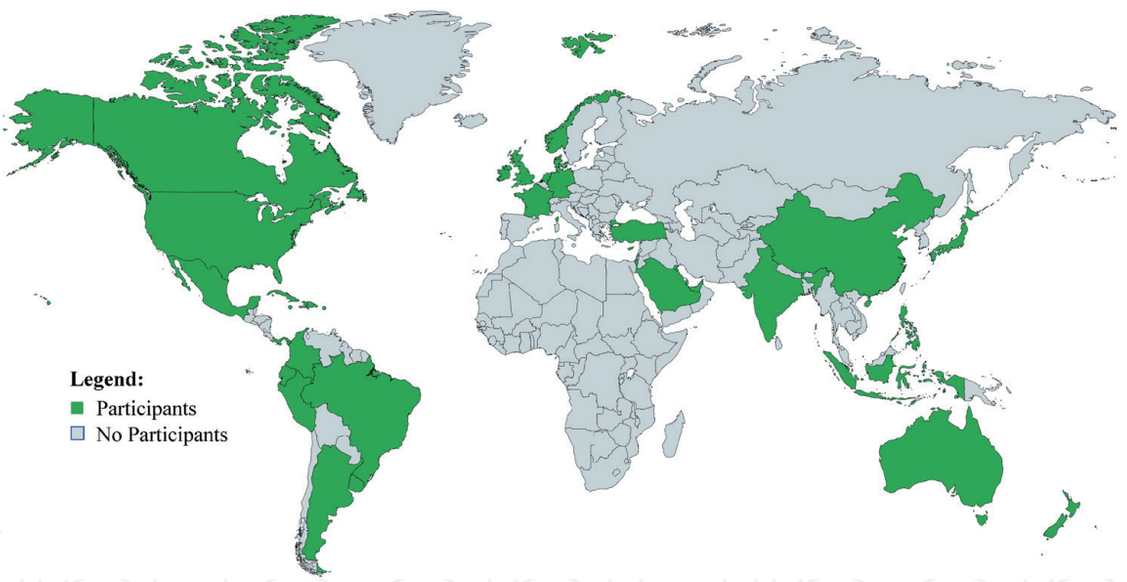

Figure 2.
Participant residency by country.

became agnostic of radiation modality. Nearly 60% of the tumors treated in this cohort originated in the CNS (**Table 1**, **Figure 3**), which is the most common site of solid tumors in the pediatric population.

Since its inception, the PPCR's structure and scope have developed and expanded to adapt to the ongoing treatment landscape to address this unmet need within pediatric radiation medicine. For instance, in 2018 patients treated with XRT were made eligible for enrollment [14]. Incorporation of these data will facilitate photon/proton comparison studies that are critical for better understanding the strengths and weaknesses of PRT. This is especially true for developing dose constraints for organs at risk as these may not be identical across RT modalities. Such is the case for the brainstem, whose PRT dose limit was reduced on the most recent COG ependymoma protocol (ACNS0831). While the topic is controversial, there is some concern that there may be an increased risk of brainstem injury with PRT compared to XRT using a typical relative biological effectiveness dose conversion of 1.1 for PRT [15–18].

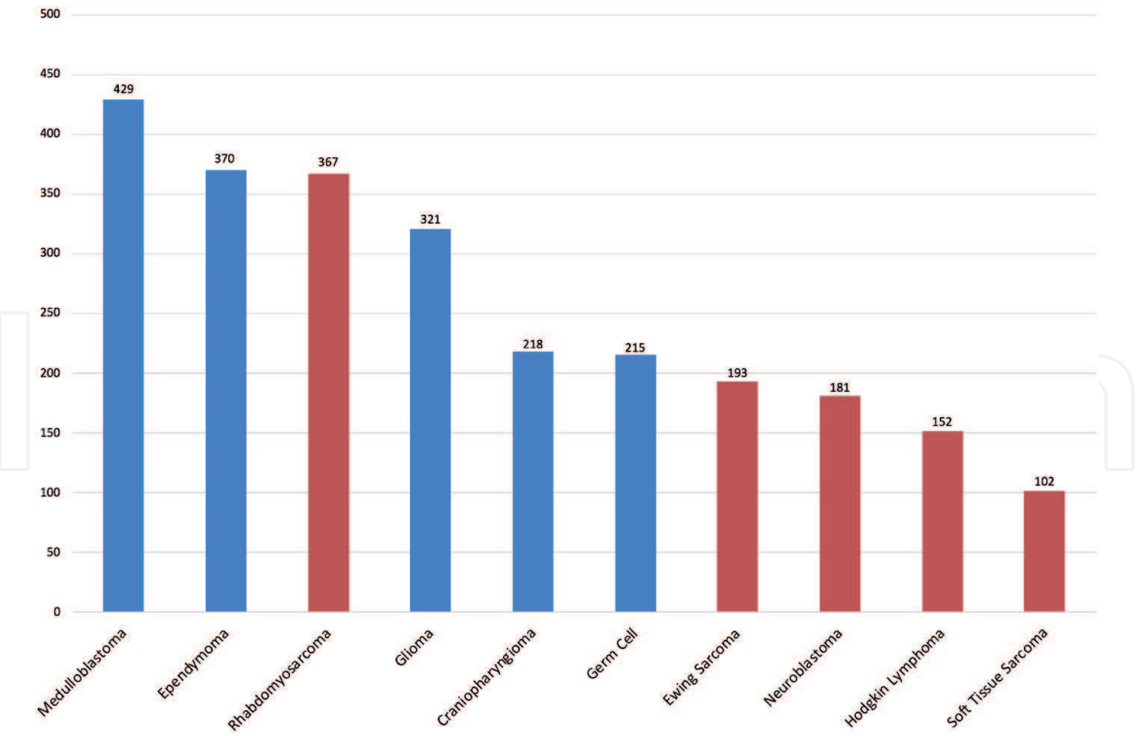

Figure 3.
Histogram showing the ten most-represented histologies in the PPCR. CNS tumors are shown in blue and non-CNS tumors are shown in red.

4. Future objectives

The PPCR has established a centralized, collaborative, and adaptive framework for data acquisition in pediatric patients receiving RT, with respect to treatment parameters and quality of life. This registry resource is now robustly able to better evaluate differences in practice patterns, dosimetric changes, and the clinical impacts of the treatments we deliver. The platform we have created is now being leveraged by the Epidemiology branch of the NCI to allow for large-scale cohort research. Furthermore, the PPCR study staff are also participating in the larger effort of the Childhood Cancer Data Initiative [19] recently started to accelerate the speed of research with the ultimate goal of improving cancer treatment and outcomes for pediatric patients.

Looking forward, we aim to continue to expand the network of participating institutions not only domestically, but also internationally - first into Canada and Australia and then into other countries that allow sharing of de-identified data. This will not only serve to continue to amass data for rare tumors for which single-institution studies are simply not feasible, but will also yield insights into variations in practice patterns and which treatment regimens are the most effective and safest. In addition, the dynamic nature of the registry facilitates incorporation of data from other treatment modalities (e.g. FLASH radiotherapy, other particle therapies, etc.), much like how photon-based treatment data have been incorporated recently. This will further expand our understanding of how to best manage pediatric malignancies by adapting data acquisition to ongoing technologic developments and changes in practice patterns. We encourage all to use this resource to improve cancer care and outcomes for pediatric cancer patients undergoing treatment as well as those who have completed therapy.

Author details

Nicholas J. DeNunzio, Miranda P. Lawell and Torunn I. Yock*
Harvard Medical School, Massachusetts General Hospital, Boston, USA

*Address all correspondence to: tyock@mgh.harvard.edu

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