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Original Article

Increased distance from a treating proton center is associated with diminished ability to follow patients enrolled on a multicenter radiation oncology registry

Miranda P. Lawell [a,1], Benjamin V.M. Bajaj [a,1], Sara L. Gallotto [a], Clayton B. Hess [a], Brooke E. Patteson [a,b], Jessica A. Nartowicz [a], Megan J. Giblin [a], Ruth A. Kleinerman [c], Amy Berrington de Gonzalez [c], David H. Ebb [b], Nancy J. Tarbell [a], Shannon M. MacDonald [a], Elizabeth A. Weyman [a], Torunn I. Yock [a,*]

[a] Departments of Radiation Oncology, Massachusetts General Hospital; [b] Pediatric Hematology/Oncology, Massachusetts General Hospital, Boston; and [c] Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, USA

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ABSTRACT

Purpose: Consistent follow-up and data collection are necessary to identify long-term benefits/detriments of proton radiotherapy. Obtaining comprehensive clinical follow-up can be difficult and time-intensive for proton centers. Here we evaluate what factors affect maximum follow-up time among MGH Pediatric Proton Consortium Registry (PPCR) participants. *Patients and methods:* Enrollment in the PPCR was offered to any patient <22 years receiving protons. Patients were excluded from analysis if they were taken off study due to death or withdrawal. Distance from MGH was calculated by the great-circle formula. We utilized both univariate and multivariate analyses to determine risk factors associated with follow-up time. *Results:* 333 PPCR patients enrolled between 10/2012 and 03/2017 were included. Median follow-up was 2.4 years (<1–5.5), and median distance away from the proton center was 256.4 km (<1.6–16,949.6). Distance from MGH significantly predicted follow-up time: patients living outside the Boston Metropolitan Statistical Area, >121 km from the proton center, had average follow-up that was 0.53 years less compared to those living within 121 km ($p = 0.0002$). Loss in average follow-up was also associated with Medicaid insurance, treatment delay due to insurance, and non-White race. Those co-enrolled on a proton trial or seen at a facility had significantly increased follow-up by almost one year ($p < 0.0001$). *Conclusion:* Patients living further from treating proton center have shorter follow-up durations. Increased distance from treating centers may adversely affect clinical outcomes research. Enhanced sharing of medical information among care providers and improved collection methods are needed to effectively evaluate the benefits of proton therapy.

Compared to the best available photon techniques, proton radiotherapy is a promising radiation modality that better localizes radiation dose to the targeted tumor bed while simultaneously better sparing dose to surrounding normal tissues [1]. Proton radiotherapy has particular promise in improving the late effect profile in pediatric cancer patients requiring radiotherapy because children are especially susceptible to the adverse effects of radiotherapy. While there is ample dosimetric evidence that this is true [2–5], clinical outcome evidence remains limited [6]. Therefore, the Pediatric Proton Consortium Registry (PPCR) was established to expedite proton outcomes research and determine if proton radiotherapy leads to improved treatment outcomes in our pediatric patient population over traditional photon radiotherapy modalities [7–9]. To effectively evaluate the long-term benefits of proton radiotherapy, this multi-institutional registry collects comprehensive data during baseline, treatment, and follow-up time points, including: diagnostic information, adjuvant treatments (surgery, chemotherapy, radiation), adverse events/side effects, DICOM radiation treatment plans, imaging, disease and survival status, and related evaluations (neurocognitive, audiology, laboratory, etc.) Additionally, the PPCR collects the PedsQL Core and Fatigue health related quality of life inventory [10]. The collection of clinical follow-up data on patients is challenging and resource-intensive. Over 85% of pediatric patients treated with proton radiotherapy at Massachusetts General Hospital (MGH) is referred by and travel from an external institution. Although annual follow-up

* Corresponding author at: Massachusetts General Hospital, Department of Radiation Oncology, Harvard Medical School, Francis H. Burr Proton Therapy Center, 55 Fruit Street, Room 110, Boston, MA 02114, USA.
E-mail address: tyock@mgh.harvard.edu (T.I. Yock).
[1] Co-first authorship.

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appointments at the treating proton center are encouraged, logistical travel and financial barriers exist for patients. Therefore, follow-up collection largely depends on effective communication between the treating proton center, the external home institution, and the family. Here we examined the associated patient factors that can affect the duration of follow-up we have on the patient. In particular, we focus on the distance between the patient's home and the treating proton facility and discuss strategies to improve follow-up collection.

The PPCR is a multi-institutional registry of childhood cancer patients treated with proton radiotherapy [7,8]. Any patient <22 years receiving radiation is eligible to participate in the registry, with 88% of patients ultimately enrolling. As of December 1, 2018, there were 2,430 participants enrolled across the 14 participating institutions. The PPCR follows participants for life and collects information on long-term health outcomes. The registry study relies on referring physicians and participants to share follow-up notes and health information. Annual letters are sent detailing information about the study and ways to schedule an appointment or contact the study team. Means of collecting follow-up include: fax, mail, e-mail, phone, and updates to the electronic medical record (EMR) and rely heavily on contact with the participant's home institution. A portion of these PPCR participants are also co-enrolled on one of seven prospective phase II proton trials, which in contrast to the registry, require definitive follow-up assessments at specified time points to accurately describe the incidence and severity of toxicity in patients [11–14]. Each proton trial has a designated clinical research coordinator assigned to track and obtain information on patients followed at external institutions. Due to resource limitations, these more rigorous data collection efforts do not occur for patients enrolled solely on the PPCR.

Patients and methods

We analyzed data on 425 PPCR participants consented at MGH between 10/2012 and 03/2017 with a minimum of 1 year since their last radiation treatment. Patients were excluded from analysis if they withdrew consent or died and if they did not identify by any race. Maximum follow-up time was calculated by subtracting the radiation start date from the date of latest recorded follow-up and reported in years. Distance from MGH was calculated with the great-circle formula by converting patient and institution postal code into geographical coordinates and reported in both kilometers and miles. The great-circle formula measures the shortest distance between two points on the surface of a sphere, as commonly referred to "as the crow flies". Massachusetts General Hospital is located in Boston, Massachusetts, therefore we hypothesized that participants living within the Boston Metropolitan Statistical Area encompassing MGH would have greater average follow-up time, as it would be easier to return for follow-up to either MGH or one of its close partners' hospitals [15]. To differentiate between those located within the Boston Metropolitan Statistical Area, distances were dichotomized into two groups consisting of those living within and outside a 121 kilometer (km) (75 mile) radius of MGH, which encompasses the cities included within the Boston Metropolitan Statistical Area. Median income was calculated using adjusted gross income data based on 2015 individual income tax statistics by postal code [16]. Methods of obtaining follow-up included: (1) "on-site", patient visits at MGH; (2) "external facility" in which patient clinical records were sent from the referring hospital or participant, or (3) "other", which include updates from participants obtained through phone, e-mail, or mail correspondence that were not a clinical document. Patient parameters collected included: age at radiation start, miles from MGH, gender, race, consent language, primary tumor site, domestic versus international residency, disease progression, insurance type, treatment delay due to insurance, referral pattern, chemotherapy use, treatment on or per a COG trial, median income by zip code, participation in a concurrent prospective proton trial, and method of obtaining last follow-up (on-site, external facility, or other).

Statistical methods

We performed an analysis of variance (One-Way ANOVA) test with Tukey's multiple pairwise comparisons to determine if mean follow-up duration differed significantly across the three methods of follow-up, and univariate and multivariate linear regression to determine the association between patient characteristics and follow-up duration. To account for missing median income data on our international patients, multiple imputation with predictive mean matching was used. Parameters were selected and included in the multivariate model based on a combination of factors including clinical relevance, results from univariate analyses, significance in the multivariate model, model fit through adjusted R-squared, and association with both the exposure (distance from MGH) and outcome of interest (follow-up time). The statistical analysis was performed using R version 3.4.3.

Results

Out of a total of 425 participants, 92 were excluded from the analysis for missing race information and being removed from the study due to death or withdrawal of consent, including not-reconsenting at 18 years of age [17]. The final sample size was 333 participants (Table 1).

Those who received follow-up care through methods categorized as "on-site", "external facility", or "other" had average follow-up durations of 3.12, 2.99, and 2.21 years, respectively. The ANOVA test indicated the association between method of follow-up and follow-up duration was significant ($p < 0.0001$). We used Tukey's method to conduct pairwise comparisons of the average duration of follow-up between the three methods of care and found that those with follow-up from "other" methods had 0.97 years less average follow-up duration compared to those seen "on-site" ($p < 0.0001$) and 0.78 less years than those seen at an external facility ($p = 0.0002$). However, there was no significant difference comparing those seen "on-site" to those seen at an "external facility" (difference = 0.18, $p = 0.74$). Therefore, method of follow-up was condensed into two categories ("other" and "on-site/external facility") for linear modeling. Univariate modeling (Table 2) indicated the following characteristics were associated with the length of time a participant had been followed for: co-enrollment on a trial ($p < 0.0001$), non-White race ($p = 0.002$), consent language ($p < 0.0005$), treatment delay due to insurance ($p = 0.0004$), international residency ($p = 0.011$), method of follow-up ($p < 0.0001$), and residency >121 km (75 miles) from MGH ($p = 0.002$). The following characteristics were not significantly associated with the duration of follow-up: sex ($p = 0.98$), age at radiation treatment ($p = 0.49$), reception of chemotherapy ($p = 0.33$), disease progression ($p = 0.96$), tumor type ($p = 0.14$), source of referral ($p = 0.10$), and median household income ($p = 0.61$). Enrollment in Medicaid was nearly significant ($p = 0.05$).

In the multivariate model (Table 2), distance from MGH, was significantly associated with the duration of follow-up when controlling for other predictors: patients living >121 km (75 miles) from the proton center which is outside the Boston Metropolitan Statistical Area, had average follow-up that was 0.53 years less compared to those living within this distance ($p = 0.0002$). We also found that patients co-enrolled on a proton trial had a significantly

Table 1
Patient characteristics ($N = 333$).

Median (range)	
Age at radiation start (years)	10.0 (<1–21.9)
Distance from MGH (km) (miles)	256.4 (1.5–16,949.6) 159.3 (<1–10,532)
Follow-up interval (years)	2.4 (<1–5.5)
Median Adjusted Gross Income	$82,690 (2,740–330,960)*
	N (%)
Gender	
Male	184 (55.3)
Female	149 (44.7)
Method of follow-up	
On-site/external facility	117 (35.1)
Other	216 (64.9)
Distance from MGH	
Within 121 km radius	131 (34.5)
Outside of a 121 km radius	249 (65.5)
Race	
White/Non-Hispanic	263 (79.0)
Non-White/Hispanic	70 (21.0)
Consent language	
English	312 (93.7)
Non-English	21 (6.3)
Primary tumor	
CNS	211 (63.4)
Non-CNS	122 (36.6)
International resident	
Yes	37 (11.1)
No	296 (88.9)
Disease progression or second tumor	
Yes	39 (11.7)
No	278 (83.5)
Missing	16 (4.8)
Insurance type	
Medicaid	81 (24.3)
Other	239 (71.8)
Unknown	13 (3.9)
Treatment delay due to insurance	
Yes	37 (11.1)
No	296 (88.9)
Referred by Pediatric/Medical Oncologist	
Yes	183 (54.9)
No	150 (45.1)
Chemotherapy received**	
Yes	204 (61.3)
No	129 (38.7)
Proton Clinical Trial co-enrollment	
Yes	149 (44.7)
No	184 (55.3)

CNS = central nervous system; MGH = Massachusetts General Hospital.
* Median Adjusted Gross Income missing for $n = 40$ participants.
** Accounts for chemotherapy received prior to, during, and after proton radiotherapy.

increased average follow-up by 0.96 years compared to those enrolled on the PPCR alone ($p < 0.0001$). Interestingly, patients that suffered a treatment delay to starting proton therapy due to insurance had an approximate half year loss in average follow-up ($B = -0.61$; $p = 0.004$). Although of borderline significance in the univariate analysis, Medicaid as the insurance provider was associated with 0.37 years less average follow-up compared to another insurance in the multivariate analysis ($p = 0.022$). Non-White/Hispanic race was also significant: Those who are non-White had 0.37 years less average follow-up in comparison to those who are White ($p = 0.025$).

We assessed the effect of interaction between international residency and distance from MGH by differentiating between the following three categories: US residents who reside within 121 km (75 miles) of MGH, US resident that reside outside of the 121 km radius, and international residents (all of whom live >121 km from MGH). Controlling for race, consent language, co-enrollment, treatment delay, Medicaid insurance, and follow-up method we found that international residents experienced a 0.63 years decrement in follow-up time compared to US residents living close to MGH ($p = 0.02$), while US residents living >121 km had 0.52 less years of follow-up than that of US residents living close to MGH ($p = 0.0004$).

Discussion

The PPCR was established to expedite proton outcomes research and to better define the role of proton radiotherapy in the pediatric population requiring radiotherapy. Through this multi-institutional consented registry which collects detailed information including the DICOM radiation treatment plan, long-term follow-up is gathered. This registry has grown into a valuable resource capable of multiple and varied research projects [18–20]. The PPCR has most recently expanded to include enrollment of all pediatric radiotherapy patients irrespective of treatment modality, which has enhanced our ability to perform comparative effectiveness research on patients followed in a similar manner. Long-term follow-up efforts are necessary to fully evaluate the late effects benefits and possible detriments of proton radiotherapy relative to the best available photon treatments [21–23]. However, like other registries, the PPCR faces challenges in obtaining comprehensive clinical follow-up. With respect to our study, we have shown that follow-up is less likely to be complete the farther a patient lives away from the treatment center (i.e. greater than 121 km/75 miles), and that insurance factors (such as Medicaid), international residency, method of follow-up, and race, can impose further difficulties for obtaining the necessary follow-up.

The kind of medical insurance patients had influenced the amount of follow-up we were able to obtain and may be unique to the structure of the American Health Care system, where health care policy experts often refer to patients in one of 3 categories: the insured, the underinsured, and the uninsured—with the latter two categories of patients typically having more barriers to access needed health care. Patients who suffered a delay in starting treatment due to insurance issues in addition to those with Medicaid were found to have less follow-up time. We have found that patients with non-Massachusetts (out-of-state) Medicaid will often not have follow-up services covered, and are finding this increasingly with some low-cost private and international health insurers.

In our socio-economic status (SES) analysis, median adjusted gross income by zip code did not significantly impact the amount of follow-up one had in both the univariate and multivariate models. Although we didn't find this to be a major determinant in our study, we concede that the patient population that comes for treatment and follow-up enjoy a higher SES than the general US population. While we endeavor to mitigate the costs of travel and accommodation for both treatment and follow-up visits for our patients, it is likely that SES plays a role in a patients' ability both to seek initial proton radiotherapy.

Co-enrollment on a concurrent proton treatment trial and follow-up methods associated with visiting a medical care provider were the strongest predictors in our multivariate model of increased average follow-up. Patients co-enrolled on a treatment trial had nearly a year more follow-up time compared to those not co-enrolled ($p = <0.0001$). Those seen for follow-up either on-site or at an external facility also had on average a year more follow-up than those who provided information through other means ($p < 0.0001$). These data likely reflect the more rigorous follow-up methods employed by study staff which is costlier and time intensive, but clearly more effective in a patient population who is largely followed at other institutions. In contrast, the methods to obtain follow-up information on the PPCR participants are

Table 2
Univariate and multivariate results.

	Univariate analysis				Multivariate analysis				
	β	SE β	95% CI	*P*-value	β	SE β	B*	95% CI	*P*-value
Trial co-enrollment	0.95	0.15	0.67 to 1.2	<0.0001	0.96	0.13	0.34	0.70 to 1.22	<0.0001
Treatment delay	−0.86	0.24	−1.3 to −0.38	0.0004	−0.61	0.21	0.14	−1.03 to −0.20	0.004
>121 km (75 miles) from MGH	−0.50	0.16	−0.81 to −0.19	0.002	−0.53	0.14	0.18	−0.81 to −0.26	0.0002
Medicaid									
On Medicaid	−0.36	0.18	−0.71 to −0.01	0.05	−0.37	0.16	0.11	−0.69 to −0.05	0.022
Unknown	−0.88	0.40	−1.7 to −0.10	0.027	−0.38	0.34	0.05	−1.05 to 0.30	0.272
Race (Non-White/Hispanic)	−0.58	0.19	−0.95 to −0.22	0.002	−0.37	0.16	0.11	−0.69 to −0.05	0.025
Follow-up method: On-site and external facility	0.87	0.15	0.57 to 1.2	<0.0001	0.92	0.14	0.31	0.64 to 1.19	<0.0001
International residency	−0.62	0.24	−1.1 to −0.15	0.011	–	–	–	–	–
Sex	−0.004	0.15	−0.31 to 0.30	0.98	–	–	–	–	–
RT age	−0.009	0.013	−0.03 to 0.02	0.49					
Tumor type	0.24	0.16	−0.08 to 0.55	0.14	–	–	–	–	–
Source of referral	0.26	0.15	−0.04 to 0.57	0.10	–	–	–	–	–
Chemotherapy	0.15	0.16	−0.16 to 0.46	0.33	–	–	–	–	–
Disease progression	−0.01	0.22	−0.45 to 0.43	0.96	–	–	–	–	–
Median household income	$-6.0\ e^{-7}$	$1.2\ e^{-6}$	$-2.0\ e^{-6}$ to $1.7\ e^{-6}$	0.61	–	–	–	–	–
Non-English Speaker	−1.1	0.31	−1.7 to −0.47	0.0005					

less rigorous. Currently, the PPCR is not funded to allow for more resource-intensive practices in contacting the referring physicians/institutions to request medical records. As proton radiotherapy becomes a more widely accepted radiation modality, it remains imperative to study the benefits and possible detriments of this modality and how it can be improved in the pediatric population. To continue important outcomes-based research and to push the field forward, funding to collect this information for registry participants is a critical need, and other data collection methods will need to be explored. This registry effort can greatly augment the current PENTEC and QUANTEC efforts by improving our ability to quantify and correlate side effects to specific organ doses by using the radiation DICOM plans collected in the PPCR [24,25].

The prevalence within our sample of non-English speaking patients was relatively low, but we found a statistically significant correlation in the univariate analysis nonetheless. Non-English speakers comprised only 6.3% of our study population and although not significant in our multivariate model, had an average follow-up time of 1.1 years less than English speakers in the univariate analysis. Likewise, although our patient population is predominately of White/non-Hispanic race (79%), we found a significant loss of 0.37 years of follow-up among those who were non-White/Hispanic ($p = 0.025$).

The medical community urgently needs to develop more cost-efficient and effective means of data collection for patients treated with new technologies like proton radiotherapy. The PPCR is piloting an initiative at MGH to send a brief internet-based health assessment survey to participants to supplement the follow-up entered from clinical notes. If they indicate a health status change on the survey, we will target increased efforts to specifically gather their clinical medical information. Sharing of electronic medical records (EMRs) between institutions that use the same proprietary EMR remains promising in the collection of follow-up domestically. EPIC's Care Everywhere feature can enhance both real-time clinical care and research when patients that are shared across institutions with the same EMR provide authorization [26]. The PPCR continues to seek sustainable funding sources to invest in the resources that are needed to collect the necessary follow-up information required for robust research to improve patient outcomes.

We found that many factors contribute to our ability to obtain follow-up on pediatric cohort that is treated at a proton facility. Namely, increased distance from the treating center and health insurance restrictions contributed to the difficulty in obtaining follow-up. Identifying and understanding the factors that interfere with obtaining follow-up is pre-requisite to establishing both improved collection methods and access to care [27]. It is important to consider that other factors, in addition to data collection, influence the degree of follow-up data in the PPCR. Limited follow-up may also be a result of a patients' own barriers to receiving care, or reflective of an external institutions inability to track a patient as well. However new methods for following patients are needed to improve patient follow-up and will be a focus of the PPCR as it matures.

Summary

Consistent follow-up and data collection efforts are necessary to identify the long-term benefits of proton radiotherapy. Obtaining comprehensive clinical follow-up can be difficult and time-intensive for proton centers. Here we evaluate what factors affect maximum follow-up time among our consented Pediatric Proton Consortium Registry participants.

Conflicts of interest

Registry support received from the following companies: Ion Beam Applications (IBA, Neuve, Belgium), ProTom International, Inc (Flower Mound, Texas, USA), and Elekta (Stockholm, Sweden). The Radiation Planning and Image Software platform is provided by MIM Software Inc. Cleveland, Ohio, USA.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.01.007.

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