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Scientific Article

The Pediatric Proton and Photon Therapy Comparison Cohort: Study Design for a Multicenter Retrospective Cohort to Investigate Subsequent Cancers After Pediatric Radiation Therapy

Amy Berrington de González, DPhil,[a,*] Todd M. Gibson, PhD,[a] Choonsik Lee, PhD,[a] Paul S. Albert, PhD,[a] Keith T. Griffin, MS,[a] Cari Meinhold Kitahara, PhD,[a] Danping Liu, PhD,[a] Matthew M. Mille, PhD,[a] Jungwook Shin, PhD,[a] Benjamin V.M. Bajaj, MPH,[b] Tristin E. Flood, MS,[b] Sara L. Gallotto, MS,[b] Harald Paganetti, PhD,[b] Safia K. Ahmed, MD,[c] Bree R. Eaton, MD,[d] Daniel J. Indelicato, MD,[e] Sarah A. Milgrom, MD,[f] Joshua D. Palmer, MD,[g] Sujith Baliga, MD,[g] Matthew M. Poppe, MD,[h] Derek S. Tsang, MD,[i] Kenneth Wong, MD,[j,k] and Torunn I. Yock, MD[b]

[a]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland; [b]Department of Radiation Oncology, Massachusetts General Hospital/Harvard Medical School, Boston, Massachusetts; [c]Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota; [d]Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, Georgia; [e]Department of Radiation Oncology, University of Florida College of Medicine, Jacksonville, Florida; [f]Department of Radiation Oncology, University of Colorado School of Medicine, Aurora, Colorado; [g]Department of Radiation Oncology, James Cancer Hospital at the Ohio State University Wexner Medical Center and Nationwide Children's Hospital, Columbus, Ohio; [h]Department of Radiation Oncology, University of Utah—Huntsman Cancer Institute, Salt Lake City, Utah; [i]Radiation Medicine Program, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada; [j]Radiation Oncology Program, Children's Hospital Los Angeles, Los Angeles, California; and [k]Keck School of Medicine, University of Southern California, Los Angeles, California

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Purpose: The physical properties of protons lower doses to surrounding normal tissues compared with photons, potentially reducing acute and long-term adverse effects, including subsequent cancers. The magnitude of benefit is uncertain, however, and currently based largely on modeling studies. Despite the paucity of directly comparative data, the number of proton centers and patients are expanding

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Research data are not available at this time. Data will be stored in an institutional repository according to FAIR principles and made available upon request at the completion of data collection.

*Corresponding author: Amy Berrington de González, DPhil; E-mail: amy.berrington@icr.ac.uk

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exponentially. Direct studies of the potential risks and benefits are needed in children, who have the highest risk of radiation-related subsequent cancers. The Pediatric Proton and Photon Therapy Comparison Cohort aims to meet this need.

Methods and Materials: We are developing a record-linkage cohort of 10,000 proton and 10,000 photon therapy patients treated from 2007 to 2022 in the United States and Canada for pediatric central nervous system tumors, sarcomas, Hodgkin lymphoma, or neuroblastoma, the pediatric tumors most frequently treated with protons. Exposure assessment will be based on state-of-the-art dosimetry facilitated by collection of electronic radiation records for all eligible patients. Subsequent cancers and mortality will be ascertained by linkage to state and provincial cancer registries in the United States and Canada, respectively. The primary analysis will examine subsequent cancer risk after proton therapy compared with photon therapy, adjusting for potential confounders and accounting for competing risks.

Results: For the primary aim comparing overall subsequent cancer rates between proton and photon therapy, we estimated that with 10,000 patients in each treatment group there would be 80% power to detect a relative risk of 0.8 assuming a cumulative incidence of subsequent cancers of 2.5% by 15 years after diagnosis. To date, 9 institutions have joined the cohort and initiated data collection; additional centers will be added in the coming year(s).

Conclusions: Our findings will affect clinical practice for pediatric patients with cancer by providing the first large-scale systematic comparison of the risk of subsequent cancers from proton compared with photon therapy.

Introduction

Proton therapy has emerged as a preferred radiation therapy modality for some cancers because the physical properties of protons lower doses to surrounding normal tissues and therefore should reduce the acute and late-term adverse effects.[1,2] In 2010, there were 24 proton therapy centers operating around the world. By 2021 there were 99 centers in operation and another 60+ centers under construction or in the planning phase.[3] This is translating into rapid increases in patients treated with proton therapy, especially children, because they have the highest risks of late effects of radiation therapy, including radiation induced subsequent cancers.[4] A recent patterns-of-care survey of US centers found that 15% of pediatric patients undergoing radiation therapy were treated with proton therapy in 2016, a doubling since 2012. Half the patients were aged <10 years, and 25% were aged <5 years.[5] Central nervous system (CNS) tumors accounted for 50% and sarcomas for 25% of pediatric proton therapy patients, and proton therapy was the most common form of radiation therapy used for rhabdomyosarcoma, medulloblastoma, ependymoma, and Ewing sarcoma (>50%). Similarly steep increases were reported using data from the National Cancer Database for pediatric CNS malignancies, in which proton therapy use increased from <1% before 2004 to 15% by 2012 and 28% by 2017.[6,7]

Studies of children treated with conventional radiation therapy have established a wide range of late effects of radiation therapy, with the potential for high cumulative burden of subsequent malignancies.[8,9] These studies have led to efforts to reduce the amount of normal tissue exposure through treatment dose reduction, smaller target margins, and use of new more conformal techniques like intensity modulated radiation therapy (IMRT) and proton therapy.[10] With some, particularly older proton therapy treatment systems, however, this comes at the expense of increased scatter doses to the rest of the body from neutrons,[11,12] and neutrons are more carcinogenic than photons or x-rays.[13] In the absence of direct data, dose and risk modeling studies have suggested that proton therapy should lower second cancer risks in-field due to the overall lower integral dose.[14-16] For out-of-field risk caused by secondary and scattered radiation, radiation exposure depends on the delivery method, for example, passive scattering versus scanned delivery for protons. Modeling studies indicate that proton beam scanning results in the lowest out-of-field dose while data for photon treatments and passive scattering proton therapy can be comparable depending on the distance to the field.[17,18] The translation of out-of-field neutron doses into risk is hampered by large uncertainties on the carcinogenic effectiveness of neutrons (their relative biologic effectiveness [RBE] or weighting factor). These modeling studies are based on dose estimates from a small sample of patients ($n < 10$) and the models require many assumptions, including the RBE of protons and neutrons and the effect of fractionation on different second cancer sites.[19]

There are several randomized trials in progress for proton therapy in adults, but such trials are considered unethical for pediatric patients because it is thought that the dosimetric advantages of protons in children undermine the requirement for clinical equipoise.[20] Encouragingly, single-center evaluations and an analysis using the National Cancer Database have suggested that risk of subsequent malignancies after proton therapy in children could be lower than photon therapy.[21-23] However, these studies have various limitations for studying the late effects of proton therapy, including small sample size, lack of a formal comparison group, and short or likely incomplete follow-up.[24]

There is now widespread agreement that large-scale observational studies are urgently required to systematically compare acute toxicities, outcomes, and late effects of proton therapy and modern photon therapy in children.[25] The US Pediatric Proton/Photon Consortium Registry (PPCR) has successfully recruited 18 of the 23 eligible US pediatric proton centers to participate in building the registry, demonstrating the willingness of the pediatric proton therapy community to conduct research.[26,27] We have leveraged the success of this registry to begin development of a large multicenter Pediatric Proton and Photon Therapy Comparison Cohort. The aim is to develop a record-linkage cohort of 10,000 proton and 10,000 photon therapy patients treated from 2007 to 2022 to compare the risk of subsequent cancers after proton compared with photon therapy, including (1) the overall risk of any subsequent cancer, (2) quantification of dose-volume effects, and (3) the dose-response relationships for specific subsequent cancers. We describe the study design, sample size justifications, and exposure assessment methods.

Methods and Materials

Study population

Our goal is to develop a record linkage cohort of 10,000 proton and 10,000 photon therapy pediatric patients (defined as age <22 years) treated from 2007 to 2022 in the United States and Canada. The cohort will build on the success of the existing PPCR population, which includes actively consented patients from 24 participating proton and photon therapy centers.[26,27] We will expand this population by collecting data from medical records (passive enrollment) for all eligible proton and photon patients at these centers from the period before start of the PPCR (2007-2014) and those since 2015 who were not actively enrolled into the PPCR. Similarly, the photon comparison group will be obtained by collecting data from medical records for all eligible photon therapy patients at 5 to 10 major photon therapy centers (Table 1). Photon therapy patients will be included from the same set of diagnosis groups commonly treated with protons (CNS, sarcomas, neuroblastoma, and Hodgkin lymphoma). We anticipate that temporal changes in therapy beyond radiation modality will be modest for the eligibility period of 2007 to 2022, and data collection will include chemotherapy (including targeted and immunotherapies) and surgery. We estimate from Surveillance Epidemiology and End Results (SEER) registry data that about 2500 children with these cancer diagnoses are treated with initial radiation therapy annually in the United States and Canada,[28] which is an estimated population of 36,000 children treated with initial radiation therapy during the proposed study period from 2007 to 2022. Thus, assuming about half of these patients will have been treated with proton therapy, we expect it will be feasible to achieve our proposed sample size.

The successful PPCR collaboration established by Massachusetts General Hospital will form the foundation for the new cohort. Each center has a principal investigator and research staff who are now familiar with the processes for abstracting treatment data and uploading radiation therapy plans into a cloud based medical imaging storage system. The PPCR coordinating center uses the National Institutes of Health–supported Research Electronic Data Capture (REDCap) web-based system for the collection of patient and treatment information and the MIM cloud repository (MIM Software, Inc) for upload and storage of radiation treatment and imaging files. These systems are also being used for our expansion of data collection to include passively enrolled proton and photon patients at the PPCR proton therapy centers and newly recruited photon therapy sites. All US and Canadian radiation therapy centers who have treated more than 500 eligible pediatric patients since 2007 are eligible to join the study and can apply for funding to support data collection for the study via an open contracting process. We started in 2020 with a pilot phase with 3 photon therapy centers to develop data collection tools and study processes. We continued in 2021 with a further 6 centers joining the study (2 photon, 2 proton, and 2 photon/proton centers; Table 1) and are in the process of adding 4 new centers (University of Pennsylvania, MD Anderson Cancer Center, Texas Children's Cancer Center/Baylor College of Medicine, and California Protons Cancer Therapy Center); we plan to have subsequent contracting rounds, dependent on funding availability, until we reach our planned sample size.

Exposure assessment

We will collect anonymized electronic radiation therapy records in the form of Digital Imaging and Communications in Medicine (DICOM) radiation therapy files for all patients from the treatment centers. This will include computed tomography (CT) images of the treated area, the radiation therapy plans designed by radiation therapists, medical physicists, or dosimetrists at the centers, and the contours of the organs at risk segmented from the CT images. Data will be transferred from the treatment centers to a centralized data storage system and then to the supercomputing servers at the National Institue of Health. We will use state-of-the-art dose calculation methods known as the National Cancer Institute dosimetry system for radiation therapy (NCIRT), which has been previously established.[29-33] NCIRT addresses 3 challenges in dosimetry for retrospective epidemiologic studies of radiation therapy patients: individualized organ-level dose is required for

Table 1 Radiation therapy centers currently participating in the Pediatric Proton and Photon Therapy Comparison Cohort, including type of radiation therapy delivered and estimated numbers of eligible patients treated in 2007 to 2021

Site name	Modality	Operation date (protons)	Proton therapy type	Eligible proton patients	Eligible photon patients
Massachusetts General Hospital	Protons	2001	Passive scatter and pencil beam	1100	0
University of Florida	Protons	2006	Passive scatter, uniform scanning, and pencil beam	1500	0
Mayo Clinic: Rochester	Protons/photons	2015	Pencil beam	500	500
Emory University	Protons/photons	2018	Pencil beam	250-500	500
The Ohio State University/Nationwide Children's Hospital	Photons	-	-	0	500-1000
Children's Hospital Los Angeles	Photons	-	-	0	500-1000
University of Colorado Denver	Photons	-	-	0	500-1000
Princess Margaret Cancer Center, Toronto	Photons	-	-	0	1000
University of Utah	Photons	-	-	0	500-1000

dose-response analysis; dose calculation must cover the region close to tumor volume (in-field) as well as surrounding regions (out-of-field); and dose calculation must be rapid to deal with large numbers of patients. The photon and proton modules of NCIRT will be used for rapid in-field and out-of-field organ dose estimation for photon and proton (both passive scattering and pencil beam scanning beams) therapy patients, respectively.[29,31-33] Additional segmentation will be performed on the CT images for organs not contoured in the DICOM radiation therapy structure using automatic segmentation methods.[34] Limited coverage of CT images will be extended as needed using the precontoured anatomic phantom library.[30,35,36] Absorbed doses to major radiosensitive organs and tissues, including the brain, red bone marrow, thyroid, heart, and breast will be estimated. NCIRT can also provide volumetric dose distribution within a given organ volume. Critical organs such as the brain and heart will have detailed substructures.

Other cancer treatments will be collected from the electronic medical records, including all available information on chemotherapy. Potential confounders such as insurance status, cancer predisposing conditions (or results of genetic testing), and socioeconomic status (proxy measure based on median income of the residential ZIP code) will also be abstracted from the electronic medical records. The PPCR has established the feasibility of successfully collecting these variables from patient medical records.

Outcome ascertainment

Once collection of data for the cohort is complete, subsequent cancers and cause of death will be ascertained by linkage to the state and provincial cancer registries in the United States and Canada, respectively. This systematic follow-up mechanism is a critical component of the study design to minimize potential bias due to loss to follow-up. Treatment centers follow patients using active follow-up methods, and this is approach is very costly and potentially prone to loss to follow-up, especially many years after treatment. There is also the potential for differences in completeness of follow-up between proton centers and photon centers, especially when patients have been referred to a proton center from their primary treatment center. Due to the use of registry linkage for subsequent cancer ascertainment, our outcomes will include malignant neoplasms as well as the subset of benign tumors with systematic registry collection, such as meningiomas. Estimation of the organ-specific dose-response relationships for our third aim will require ascertainment of the location of subsequent tumors within the organ. Since these are not routinely available, we will work with the cancer registries to abstract the tumor locations from either medical records (preferred) or electronic pathology reports.

Table 2 Estimated sample size required to detect a given HR for all subsequent malignancies after proton therapy compared with photon therapy, with 80% power using 2-sided 5% significance tests according to cumulative incidence of second malignant neoplasm occurring 5+ years after diagnosis

Cumulative incidence (%) of subsequent malignancies by 15 y (photon therapy control group)	Number of pediatric cancer survivors per radiation therapy group	Expected number of subsequent malignancies based on cumulative incidence (photons)	HR with 80% power
1%	5000	50	0.5
	8000	80	0.6
	10,000	100	0.65
	15,000	150	0.7
1.5%	3000	45	0.5
	6000	90	0.6
	10,000	150	0.7
	15,000	225	0.75
2%	2500	50	0.5
	4000	80	0.6
	8000	160	0.7
	12,000	240	0.75
2.5%	2000	50	0.5
	3000	75	0.6
	6000	150	0.7
	10,000	250	0.77

Abbreviation: HR = hazard ratio.

Power and sample size

For the primary aim of comparing the overall subsequent cancer rates between proton and photon therapy we estimated that with 10,000 patients in each treatment group there would be 80% power to detect a relative risk of 0.7 with a cumulative incidence of subsequent cancers of 1.5% by 15 years after diagnosis, or a relative risk of 0.8 with a cumulative incidence of 2.5% by 15 years (Table 2).[37] An analysis from the Childhood Cancer Survivor Study (CCSS) found that 5-year survivors who were treated with radiation therapy in the 1990s had a cumulative incidence of subsequent neoplasms by 15 years of approximately 2.5%.[38] For the secondary aim of estimating dose-response relationships for specific subsequent cancers, we used SEER 18 registry data to estimate potential case numbers. We restricted the SEER population to patients diagnosed before age 20 years with first cancers eligible for inclusion in our cohort (CNS, sarcomas, neuroblastoma, and Hodgkin lymphoma) who received a diagnosis between 2000 and 2012, treated with radiation therapy, and followed to 2017. This provided a SEER subset approximately equivalent to the expected study population for a cohort of patients treated 2007 to 2022 with follow-up for subsequent cancers up to 2027. We determined the rates of subsequent solid malignancies that occurred 5+ years after diagnosis in the SEER subset, corresponding to the typical latency period for radiation-related solid cancers.[39] Based on these rates, we estimated that in a population of 20,000 patients there would be approximately 150 subsequent brain tumors, 100 sarcomas and 70 thyroid cancers identified during the follow-up period. Treatment-related leukemias typically occur with a shorter latency after treatment, so using the same methodology we estimated about 100 subsequent leukemias would be identified starting 2+ years after diagnosis. These subsequent cancers with the highest expected case numbers will be prioritized for nested case-control analyses examining detailed dose-response relationships, and the expected case numbers are comparable to those in similar dose-response studies conducted in CCSS (eg, n = 106 brain tumors, n = 115 thyroid cancers, and n = 84 sarcomas).[39]

Analytical plan

The primary analysis will be time to diagnosis of any second cancer after proton therapy compared with photon therapy adjusting for potential confounders (attained

age, age at diagnosis, primary cancer diagnosis, primary cancer stage/risk category, other cancer treatments, insurance status, known cancer predispositions, and socioeconomic status) via propensity scores, and accounting for competing risks (ie, mortality). We will separately examine risk of any second malignancy according to primary cancer diagnoses for protons compared with photon therapy and test for effect modification by age at exposure, radiation therapy modality (passive scattering vs pencil beam or uniform scanning for proton therapy; IMRT vs 3-dimensional conformal radiation therapy for photon therapy) and chemotherapy. We will assess the risk of informative censoring, and conduct sensitivity analyses if necessary.

We will evaluate risk according to various dose-volume metrics by treatment modality (protons vs photons) for each primary tumor type, and according to age at diagnosis and calendar year of treatment. We will evaluate the goodness-of-fit for models with different (prespecified) dose-volume metrics to assess which metrics are most strongly related to the risk of specific subsequent malignancies. Statistical approaches for analyzing dose-volume effects are an area of active research and this data set will provide rich opportunities for further refining these approaches.[40,41]

Dose-response analyses including assessment of dose-volume effects will be conducted for the most common second cancers (brain tumors, sarcomas, thyroid cancer, and leukemia), which are among the most radiosensitive sites in children.[39] We will assess whether the dose-response is modified by therapy modality (passive scattering, pencil beam, or photons), age at exposure, sex, or time since exposure. Comparison of the dose-response by modality will provide insights into the RBE of protons and neutrons compared with photons; however, we recognize that there will be limited power to detect small differences.

Discussion

The goal of the NCI's Childhood Cancer Data Initiative (CCDI) is to accelerate data sharing to improve pediatric cancer treatment and survivorship. Our multicenter Pediatric Proton and Photon Therapy Comparison Cohort serves as an example of the research being facilitated by the CCDI, which has provided funding to support data collection. Our aim is to build a state-of-the-art radiation therapy cohort with individual electronic radiation therapy records and outcomes data from 20,000 pediatric patients with cancer treated in the modern era.

Nested case-control studies within childhood cancer survivorship studies in the United Kingdom, France, United States, and the Netherlands have quantified second cancer risks from high-dose photon therapy.[39,42-44] These cohorts include children treated from 1940 to 2000, which miss the introduction of proton therapy for children in the 21st century and, for photon therapy, the widespread transition to IMRT. The US cancer registries are another important source of information on second cancer risks after radiation therapy, but they do not currently collect data on radiation therapy modality. In contrast, the National Cancer Database does collect radiation therapy modality data but does not collect patient identifiers and relies on outcome information from the treatment centers, which as discussed earlier is unreliable for long-term follow-up and does not systematically capture the tumor site or date of diagnosis of subsequent cancers.[45] Several single center studies have provided estimates of the subsequent cancer risk or other side effects after proton therapy, such as brain stem necrosis,[46] but without a formal internal comparison population of photon therapy patients, the relative risks remain highly uncertain.[23,24]

Integral to understanding the potential benefits of proton therapy is the question of how the volume of irradiated tissue affects the risk of subsequent malignancy. To date, few studies have been able to assess this because they have not had information to reconstruct the dose-volume distributions efficiently or accurately; this is particularly challenging with paper-based records and traditional dosimetry approaches. Treatment fields have been used as proxy measures in a few studies. For example, a study in CCSS found that Wilms tumor and Ewing sarcoma patients who received less than 20 Gy of whole lung irradiation dose had a higher risk of second breast cancers than Hodgkin lymphoma patients treated with partial chest irradiation of 40 Gy.[47] Journy et al also led a novel analysis of esophageal cancer after radiation therapy for breast cancer and found that the volume of tissue exposed to 30 Gy or higher was the best predictor of risk.[41] Recent studies of radiation-related cardiac risk in CCSS have also demonstrated the value of incorporating dosimetry with dose-volume estimations.[48] We propose to collect electronic radiation therapy plans and radiation planning CT scans for the entire cohort and to use state-of-the-art methods to rapidly and efficiently develop complex dose maps. This will enable us to address this important gap in understanding of dose-volume effects and subsequent malignancy risk.

Most human data on the adverse effects of ionizing radiation are for photons.[11] The RBE for neutrons and protons, relative to photons, is primarily based on animal and cellular studies, and there are uncertainties about the potential variation in sensitivity of different tissues.[49] Several recent case series reported increased rates of brain necrosis in children treated with protons, highlighting the uncertainty about the behavior of protons in human tissues.[46,50-52] One explanation for this possible serious side effect is the variable and uncertain RBE for protons, which is understood based on cellular studies to range from 1.1 to 1.2, but varies in a complex manner with energy, distance, and possibly tissue.[53] The RBE for neutrons, which is energy-dependent and in the range of 5 to 20 or even higher, also comes primarily from cellular studies and varies in complex ways that are not fully understood, especially in humans.[12,54]

Our study design has several strengths, but also some limitations. Strengths of the retrospective passive record linkage approach include efficient and systematic long-term follow-up, which minimizes the risk of bias from differential outcome ascertainment between the proton and photon therapy centers. Electronic treatment plans with individualized phantoms also minimize measurement error compared with paper-based records and traditional dosimetry approaches. Although registry linkage for subsequent cancer ascertainment is an important strength of the study design there are also limitations including the risk of nondifferential outcome misclassification (such as recurrence misclassified as a subsequent tumor) and measurement error in the subsequent tumor location. Both of these issues could bias risk estimates toward the null. Finally, insufficient details for chemotherapy could result in some residual confounding. We will conduct quantitative bias analyses to evaluate all these potential limitations, systematically.[55]

Conclusion

Our study will have the potential to affect clinical practice for pediatric patients with cancer by providing the first large-scale systematic comparison of the subsequent cancer risk from proton compared with photon therapy. We will also gain new insights into radiation carcinogenesis from the assessment of dose-volume effects and quantification of the cancer risks from protons and neutrons, which have not been widely studied in humans.

Declaration of Competing Interest

Matthew M. Mille reports sponsored travel to scientific meetings. Daniel J. Indelicato received a grant from the National Cancer Institute within the past 36 months for participation on the National Cancer Institute Pediatric Clinical Institutional Review Board. Joshua D. Palmer received research grants from Varian Medical Systems, The Kroger Company, Genentech, and the National Institutes of Health, consultant fees from Huron Consulting, a speaker honorarium from Varian Medical Systems, and travel support from Novocure and Varian Medical Systems, and is a Novocure Advisory Board member. Sujith Baliga received a speaker honorarium from Varian Medical Center. Matthew M. Poppe received a speaker honorarium and travel support from Mevion and is an investor in PEEL Therapeutics. Derek S. Tsang is a consultant for Back Alley Film Productions, MD lawyers and received meeting registration support from Mevion Medical Systems. Torunn I. Yock received in-kind research support from MIM Software, Inc. No other disclosures were reported.

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