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Clinical Investigation: Late Effect

Incidence of Second Malignancies Among Patients Treated With Proton Versus Photon Radiation

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Summary

This study represents the first comparative analysis of second cancer incidence rates for cohorts treated with proton or photon radiation. We compared the incidence of second cancers in 558 patients treated with proton radiation with a matched Surveillance, Epidemiology, and End Results cohort of 558 photon-treated patients. After we adjusted for sex, age at treatment, primary site, and year of diagnosis, proton therapy was not associated with an increased risk of second malignancy (adjusted hazard ratio, 0.52; $P = .009$).

Purpose: Proton radiation, when compared with photon radiation, allows delivery of increased radiation dose to the tumor while decreasing dose to adjacent critical structures. Given the recent expansion of proton facilities in the United States, the long-term sequelae of proton therapy should be carefully assessed. The objective of this study was to compare the incidence of second cancers in patients treated with proton radiation with a population-based cohort of matched patients treated with photon radiation.
Methods and Materials: We performed a retrospective cohort study of 558 patients treated with proton radiation from 1973 to 2001 at the Harvard Cyclotron in Cambridge, MA and 558 matched patients treated with photon therapy in the Surveillance, Epidemiology, and End Results (SEER) Program cancer registry. Patients were matched by age at radiation treatment, sex, year of treatment, cancer histology, and site. The main outcome measure was the incidence of second malignancies after radiation.
Results: We matched 558 proton patients with 558 photon patients from the Surveillance, Epidemiology, and End Results registry. The median duration of follow-up was 6.7 years (interquartile range, 7.4) and 6.0 years (interquartile range, 9.3) in the proton and photon cohorts, respectively. The median age at treatment was 59 years in each cohort. Second malignancies occurred in 29 proton patients (5.2%) and 42 photon patients (7.5%). After we adjusted for sex, age at treatment, primary site, and year of diagnosis, proton therapy was not associated with an increased risk of second malignancy (adjusted hazard ratio, 0.52 [95% confidence interval, 0.32-0.85]; $P = .009$).
Conclusions: The use of proton radiation therapy was not associated with a significantly increased risk of secondary malignancies compared with photon therapy. Longer follow-up of these patients is needed to determine if there is a significant decrease in second malignancies. Given the limitations of the study, these results should be viewed as hypothesis generating.

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Introduction

Advances in therapy have improved the prognosis of cancer patients over the past 30 years (1), but long-term follow-up has shown a risk of late morbidity from treatment. A major concern is an increased risk of second cancers associated with radiation (2). A large, population-based analysis noted an 8% risk of second malignancies among cancer survivors treated with radiation between 1973 and 2002 (3). Several studies have shown an increased risk of second cancers after radiation for prostate cancer (4), Hodgkin lymphoma (5), and pediatric malignancies (6).

The standard method for delivering external beam radiation therapy at all cancer centers uses photon radiation. An alternative, proton radiation, is available only in a few centers worldwide. Proton radiation reduces dose to adjacent normal tissues and should decrease the risk of late effects from radiation, including second malignancies. Protons typically allow for more precise dose delivery because of their unique physical properties. Protons deposit energy in a sharp peak, known as a Bragg peak, and this rapid dose falloff allows for decreased radiation to adjoining normal tissue by a factor of 2 to 3 (7).

Proton radiation was initially used to increase radiation dose to radioresistant tumors in critical locations, such as the eye or base of the skull (8, 9). Proton radiation was also used in children because of concerns about radiation-induced late effects, including the risk of secondary cancers when using photon beams (9, 10). However, it has been postulated that neutrons produced as a side product during passively scattered proton treatments might increase the incidence of second cancers (11, 12). During the delivery process, proton interactions produce some neutrons. These neutrons have a greater relative biological efficacy than photons and may have a higher potential for causing second malignancies (13, 14).

Given the recent expansion of proton facilities in the United States, the long-term sequelae of proton therapy should be carefully assessed. We studied the incidence of second cancers among patients treated with passively scattered protons at the Harvard Cyclotron, the largest cohort in the world with long-term follow-up, and compared rates of second cancers with a population-based cohort of matched patients treated with photon radiation.

Methods and Materials

We identified 5398 patients treated with proton radiation therapy from January 1973 to December 2001 at the Harvard Cyclotron in Cambridge, MA. We excluded patients receiving therapy to the eye; patients treated for metastatic disease, acromegaly, or arteriovenous malformations; and patients with a history of malignancies. We also excluded 571 patients not residing in the United States at the time of treatment. This resulted in a cohort of 1407 patients with nonmetastatic cancer treated with proton therapy. Of these patients, 373 had no follow-up appointments at the Massachusetts General Hospital, could not be reached by mail or phone, and were excluded. The remaining 1034 proton patients had follow-up times extending from the time of treatment until 2007.

We sought to match each of the 1034 proton patients with a similar patient treated with photon radiation therapy from 1973 through 2007 using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program cancer registry. SEER includes 14 population-based cancer registries and 3 supplemental registries covering 28% of the US population (1). We identified 221,817 patients with nonmetastatic

Table 1 Characteristics of matched proton, matched photon, and unmatched proton patients

	Matched photon vs matched proton			Unmatched proton vs matched proton	
	Matched proton	Matched photon	*P* value*	Unmatched proton	*P* value*
No. of patients	558	558	-	476	-
Sex [n (%)]			-		<.001
Male	393 (70%)	393 (70%)	-	250 (53%)	
Female	165 (30%)	165 (30%)	-	226 (47%)	
Median age at treatment (IQR) (y)	59 (28)	59 (29)	.98	43 (29)	<.001
Median y of treatment (IQR)	1993 (12)	1993 (11)	.35	1993 (9)	<.001
Follow-up time (IQR) (y)	6.7 (7.4)	6.0 (9.3)	.14	5.5 (6.3)	.02
Primary tumor site [n (%)]					
Central nervous system	178 (32%)	178	-	71 (15%)	
Head and neck	133 (24%)	133	-	390 (82%)	
Genitourinary	186 (33%)	186	-	0 (0%)	
Musculoskeletal	43 (7.7%)	43	-	6 (1.3%)	
Gastrointestinal	15 (2.7%)	15	-	1 (0.2%)	
Lung	2 (0.4%)	2	-	0 (0%)	
Lymphoma	1 (0.2%)	1	-	4 (0.8%)	
Other	0	0	-	4 (0.8%)	
Incidence rate of s cancer (per 1000 person-y)	6.9	10.3	.085†	5.6	.50

Abbreviation: IQR = interquartile range.

* *P* value based on χ^2 test for categorical variables and Wilcoxon rank sum test for continuous variables in comparison to matched proton patients.

† Based on log–rank test.

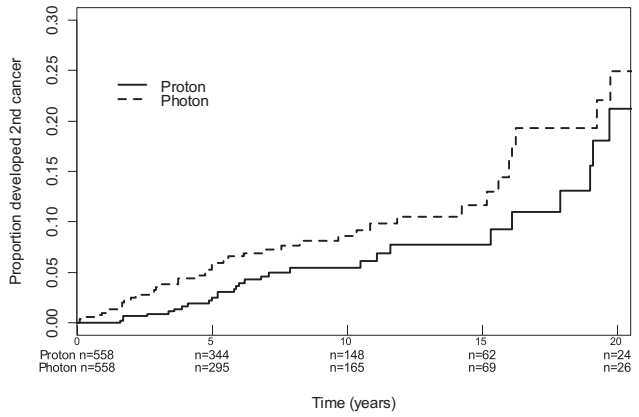

Fig. 1. Cumulative incidence curves for second cancer after radiation therapy for proton patients (solid line) and photon patients (dotted line) (log−rank $P = .085$).

cancer treated with external beam photon radiation. We excluded patients from Los Angeles County, who potentially may have been treated with proton therapy at the Loma Linda Proton Treatment Center. The study protocol was approved by the institutional internal review board.

Data for the proton patients, including tumor characteristics, radiation data, and date and pathology of second malignancies, were abstracted from pathology reports, radiology reports, operative notes, and clinic visit notes in accordance with a standardized protocol. Patients were also contacted by mail and scripted telephone calls to obtain data. The second cancer incidence was verified by review of pathology reports. All malignancies were included as second cancers, with the exceptions of basal cell and squamous cell carcinoma of the skin (which are not reported by the SEER registries). The current analysis is based on proton data collected through February 28, 2007. Proton patients were censored at the date on which they were last in contact with researchers. During the period under study, nearly all patients treated at the Harvard Cyclotron received some photon radiation (typically 20% of their treatment) in addition to the proton radiation.

In the SEER cohort, registrars collect the month and year of diagnosis for each cancer, cancer site, histology, tumor characteristics, and treatments (including radiation). SEER also reports additional cancers diagnosed for patients who remained living in areas covered by SEER registries.

For both cohorts, histology and disease sites were classified according to the *International Classification of Diseases for Oncology* codes.

Proton patients were matched with SEER registry patients by cancer site, histology, age at treatment (±10 years), year of treatment (±5 years), and sex. If a given proton patient had multiple potential photon matches, the closest match in age was selected. The patient characteristics of the proton and photon cohorts were compared by use of χ^2 tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Age at treatment was analyzed as a continuous variable. Histology was categorized as adenocarcinoma, meningioma, sarcoma, glioma, squamous cell carcinoma, lymphoma, and other. The site of primary cancer was categorized as central nervous system, head and neck, genitourinary, musculoskeletal, and other (lung, gastrointestinal, lymph nodes).

Person-years of follow-up was calculated from the date of radiation initiation until death or the last day of follow-up for patients in whom a second malignancy did not develop and until the date of second cancer diagnosis for those in whom a second malignancy developed. For patients in the photon cohort, the date of radiation therapy was estimated as the month of diagnosis. We calculated an observed incidence rate for second cancers after proton or photon radiation for all patients. The incidence of second cancers for proton therapy- and photon therapy-treated patients was assessed by use of cumulative incidence curves. A log-rank test was used to compare the distributions of times to second cancers for the 2 groups of patients.

We used a Cox proportional hazards model to investigate the association between the type of radiation treatment (proton vs photon therapy) and the risk of a second cancer developing, after controlling for potential prognostic factors including age at treatment, sex, primary tumor site, and year of treatment. Adjusted hazard ratios for second malignancy development and the associated 95% confidence intervals were calculated for each covariate. Variables were considered to have a significant association with the development of a second cancer if the corresponding regression coefficient had an associated 2-sided $P < .05$.

Results

Of 1034 proton patients, 558 (53.9%) could be matched to 1 SEER photon-treated patient, for a total of 1116 patients in the final cohort. Of the 558 proton-treated patients and the 558 matched controls, 33% had prostate cancer, 32% had a primary tumor of the central nervous system, 24% had a primary cancer of the head or neck or the skull base, 7.8% had a musculoskeletal malignancy, 2.7% had a gastrointestinal malignancy, 0.4% had lung cancer, and 0.2% had a lymphoma. Overall, 44 proton patients and 44 photon patients were defined as pediatric patients because they received treatment when aged younger than 18 years.

We were unable to find matches for 476 proton-treated patients (46.0%). Unmatched proton patients were more likely to have rare cancers. Many of the unmatched proton patients had tumors of the head and neck (n = 393), including the base of the skull (n = 291) or the nasopharynx and sinuses (n = 93). General characteristics of the patients in the final matched proton cohort, photon cohort, and unmatched proton cohort are listed in Table 1.

The median duration of follow-up was 6.7 years (interquartile range, 7.4 years) for the proton patients and 6.0 years (interquartile range, 9.3 years) for the photon patients ($P = .14$). The median age of treatment was 59 years for each cohort.

Second malignancies developed in 29 patients (5.2%) in the matched proton cohort, whereas second malignancies developed in 42 patients (7.5%) treated exclusively with photon radiation. Second malignancies developed in 18 of 476 patients (3.8%) in the unmatched proton cohort.

The incidence rate of second malignancies was 6.9 cancers per 1000 person-years for the proton patients and 10.3 per 1000 person-years for the photon patients. The median time to development of the second malignancy was 6.0 years in the proton cohort and 4.75 years in the photon cohort ($P = .085$). Among proton patients, the second malignancies developed up to 23 years after initial treatment and 10 second malignancies (34%) occurred within 5 years of treatment. Among photon patients, the malignancies developed up to 20 years after initial photon treatment and 24 of the second malignancies (57%) occurred within the first 5 years after treatment. Second malignancies in the proton cohort included 26 solid tumors, 2 lymphomas, and 1 leukemia. Second

Table 2 Characteristics of matched pediatric proton patients

Age at treatment (y)	Duration of follow-up (y)	Primary cancer site	Primary cancer histology
16	9.0	Clavicle	Sarcoma
7	7.0	Arm	Lymphoma
17	8.0	Brain	Acoustic neuroma
11	10.0	Base of skull	Chordoma
13	15.7	Base of skull	Chordoma
16	2.9	Base of skull	Chondrosarcoma
1	11.0	Brain	Glioma
10	6.0	Brain	Meningioma
10	0.1	Spine	Sarcoma
2	1.0	Base of skull	Chordoma
15	8.1	Brain	Astrocytoma
6	2.0	Brain	Medulloblastoma
11	9.4	Brain	Glioma
6	5.2	Brain	Astrocytoma
6	6.8	Brain	Astrocytoma
6	1.9	Brain	Glioma
2	2.1	Brain	Medulloblastoma
8	0.3	Spine	Ependymoma
17	3.1	Brain	Pineoblastoma
16	7.2	Brain	Astrocytoma
11	3.0	Brain	Astrocytoma
4	8.3	Brain	Medulloblastoma
3	4.0	Brain	Ependymoma
2	1.0	Brain	Teratoid/rhabdoid
9	7.3	Brain	Medulloblastoma
15	3.5	Brain	Meningioma
10	7.0	Brain	Medulloblastoma
6	1.1	Brain	Astrocytoma
5	3.0	Brain	Medulloblastoma
13	1.4	Brain	Ganglioglioma
4	6.0	Brain	Medulloblastoma
3	5.2	Brain	Medulloblastoma
10	4.8	Brain	Astrocytoma
3	5.1	Brain	Ependymoma
5	5.3	Brain	Glioma
14	0.4	Spine	Ependymoma
8	1.3	Brain	Medulloblastoma
12	0.8	Brain	Astrocytoma
14	4.2	Brain	Astrocytoma
6	4.4	Brain	Medulloblastoma
7	1.2	Brain	Medulloblastoma
2	0.1	Head and neck	Rhabdomyosarcoma
7	2.1	Brain	Medulloblastoma
16	3.1	Brain	Medulloblastoma

malignancies in the photon cohort included 38 solid tumors and 4 lymphomas.

Cumulative incidence curves showing the incidence of second cancers for matched proton and photon patients are presented in Figure 1. The 10-year cumulative incidence rates for second malignancies were 5.4% for proton patients and 8.6% for photon patients.

A second cancer did not develop during this period in any of the matched proton or photon pediatric patients in the study. Of the initial cohort, 31 pediatric proton patients were not matched to a photon patient and were not included in the final analysis. None of the 31 unmatched pediatric proton patients had development of a second malignancy. Further details about the matched and unmatched pediatric proton patients are given in Tables 2 and 3. The median duration of follow-up for matched and unmatched pediatric proton patients was 4.1 years and 5.9 years, respectively. The median proton dose for matched and unmatched pediatric proton patients was 40 Gy and 45 Gy, respectively.

The results of the Cox proportional hazards model assessing time to second cancer are presented in Table 4. Potential confounding variables included in the final model are listed in the leftmost column. The adjusted hazard ratio of a secondary cancer developing for a patient treated with proton radiation in comparison with photon radiation was 0.52 (95% confidence interval,

Table 3 Characteristics of unmatched pediatric proton patients

Age at treatment (y)	Duration of follow-up (y)	Primary cancer site	Primary cancer histology
1	4.1	Base of skull/spine	Chordoma
4	7.6	Head and neck	Sarcoma
4	0.1	CNS	Sarcoma
5	5.1	Base of skull/spine	Sarcoma
7	1.9	Base of skull/spine	Chordoma
8	17.3	CNS	Giant cell tumor
8	15.6	Base of skull/spine	Chordoma
9	4.9	Base of skull/spine	Sarcoma
9	11.5	Base of skull/spine	Sarcoma
9	6.1	Base of skull/spine	Chordoma
10	10.8	CNS	Hemangioma
11	4.2	CNS	Sarcoma
11	1.1	CNS	Giant cell tumor
12	5.1	Base of skull/spine	Chordoma
13	18.3	CNS	Giant cell tumor
13	16.7	Base of skull/spine	Sarcoma
13	4	Base of skull/spine	Chordoma
13	1.5	Base of skull/spine	Chordoma
13	0.6	Head and neck	Sarcoma
15	6.8	Soft tissue	Carcinoma
16	24	Base of skull/spine	Sarcoma
16	10	CNS	Giant cell tumor
16	4.5	Base of skull/spine	Chordoma
17	24.8	CNS	Giant cell tumor
17	3.3	Base of skull/spine	Sarcoma
17	10.9	Base of skull/spine	Chordoma
17	16.4	Base of skull/spine	Chordoma
17	5.9	Base of skull/spine	Chordoma
17	2	Base of skull/spine	Chordoma
17	3	Head and neck	Sarcoma
17	6.3	CNS	Hemangioma

Abbreviation: CNS = central nervous system.

0.32-0.85; $P = .009$). Patient age at treatment was also associated with the probability of a secondary cancer developing, with an adjusted hazard ratio of 1.05 (95% confidence interval, 1.03-1.08; $P < .001$) for each additional year of age. Primary tumor site and year of diagnosis were not significantly associated with the risk of second tumors.

We also performed an exploratory analysis of whether each second malignancy was likely to be in the primary field of radiation. With the proton cohort, we had sufficient medical record data to judge with certainty whether the second tumor occurred within the radiation field. With the SEER photon cohort, the treatment plans and detailed data regarding the location of the second cancer were not available. We examined the anatomic proximity of the primary and second malignancies based on typically treated radiation fields. In total, 3 of 29 proton patients (10%) were diagnosed with a second cancer that occurred in the prior field of radiation. In each case, at least part of the second tumor location received the full dose. In comparison, second cancers that occurred in areas likely to be in the prior field of radiation developed in 7 of 42 photon patients (16.7%) ($P = .20$). This included 2 prostate patients in whom a rectal carcinoma developed and 3 prostate patients in whom bladder cancer developed. Because of variations in clinical practice, secondary colon cancers that occurred among prostate patients were not considered to be second cancers at the primary site. Patients with second malignancies that occurred in the prior radiation treatment field are highlighted in Appendix E1.

Discussion

Improvements in cancer survivorship have increased awareness of the long-term sequelae of radiation therapy. Photon therapy has been associated with an increased risk of secondary cancers (2, 4, 15). Proton radiation allows for highly conformal therapy and likely reduces direct toxicities from treatment. However, the potential long-term benefits associated with this new technology when compared with conventional photon therapy are currently under investigation (11, 12). To our knowledge, this study presents the first comparative analysis of second cancer incidence rates for proton- and photon-treated patients.

We did not observe a significantly greater risk of a second cancer developing among patients treated with proton radiation compared with photon radiation, after adjusting for differences in patient characteristics. Overall, we observed 6.9 cancers per 1000 person-years for the proton patients and 10.3 cancers per 1000 person-years for the photon patients.

There are conflicting hypotheses about whether proton radiation has fewer late effects than photon therapy. Proton radiation is more targeted, and less tissue near the cancer site is exposed to

Table 4 Adjusted hazard ratio for development of secondary cancer

	Adjusted hazard ratio	Lower 95% CI	Upper 95% CI	*P* value*
Type of radiation therapy				
Photon	Reference	-	-	-
Proton	0.52	0.32	0.85	.009
Age at treatment in y	1.05	1.03	1.08	<.001
Sex	1.00	0.51	1.98	.99
Male	Reference			
Female	1.00	0.51	1.98	.99
Tumor site				
Primary CNS	Reference			
Primary head and neck	0.87	0.41	1.86	.72
Primary genitourinary	0.56	0.25	1.25	.16
Primary musculoskeletal	1.30	0.48	3.53	.60
Other (primary lung, gastrointestinal, lymphoma)	0.47	0.10	2.22	.34
Y of diagnosis	1.00	1.00	1.00	.48

Abbreviations: CI = confidence interval; CNS = central nervous system.

* We used a Cox proportional hazards model to assess the hazard for second cancers associated with proton versus photon radiation, adjusting for all variables in the table. Age and year of diagnosis were examined as continuous variables in the model; the hazard ratio reflects the hazard associated with each additional year.

radiation, which may lead to fewer second cancers. On the other hand, proton radiation creates neutron scatter dose, which has been associated with second cancers. For example, secondary sarcomas developed in 3 of 620 patients treated with fast neutron therapy at the Edinburgh Cancer Center from 1977 to 1984 (16). However, the carcinogenic potential of neutron doses produced by proton facilities is difficult to estimate because of a dearth of epidemiologic data (13, 17).

In our exploratory analysis, there was no significant difference in the proportion of second malignancies occurring within the primary field of radiation between the proton patients (10%) and photon patients (16.7%). This finding may suggest that the overall difference in second cancers was because of a reduction in the second cancers occurring outside of the primary proton field. Alternatively, there may exist a reduction of second tumor risk in the radiation field presumably because of less integral dose in the region of the tumor being treated, but this study was not powered to detect it.

The concern for second malignancies is particularly acute in children (18). Our study did not show any second malignancies among 88 proton- or photon-treated pediatric patients. However, this analysis was limited by the small number of pediatric patients and limited duration of follow-up.

Further follow-up of this cohort is warranted. Second malignancies can occur many years after initial therapy, and longer follow-up would be prudent. However, prior studies have shown an increased risk of second malignancies even with limited follow-up. For example, Swerdlow et al (19) showed a 2.4-fold relative risk of lung cancer in the first 4 years after treatment for lymphoma. This relative risk increased to 8.3-fold after 10 years. Similarly, with longer follow-up, we would expect that the incidence of second malignancies would increase in both the proton and photon cohorts.

There are several potential limitations of our study. First, this is an observational study, and patients were not randomly assigned to receive proton or photon treatments. Thus there is the possibility of selection bias and unobserved confounding factors. Nevertheless, the SEER database provides a large cohort of patients, allowing us to understand rates of second malignancies for patients with relatively rare tumors.

In addition, the method of data collection differed between the 2 cohorts. The data on the proton cohort were reliably obtained from patients and records following standardized protocols by trained staff. The SEER data for the photon cohort were collected by registry staff from medical records, and ascertainment of second cancers required diagnosis of the second cancer while patients were still living in SEER areas. If patients moved outside of SEER areas, the true number of second malignancies may be underestimated; thus it is possible that a greater number of photon patients had second cancers. Proton radiation may thus have even lower relative risks of second tumors than our results show.

The proton patients who were successfully matched to the SEER photon patients differed from unmatched proton patients, limiting the applicability of these findings to unmatched patients. Many of the unmatched proton patients had rare malignancies with relatively poor prognoses, such as base-of-skull chordomas. Patients with these rare diagnoses are preferentially referred to proton centers because sufficiently intense therapy with photons is difficult. Matched proton patients were also older than unmatched patients and had a longer duration of follow-up. In addition, 373 of 1408 proton patients were lost to follow-up. It is possible that these patients had second cancers at a rate different from patients in the final proton cohort.

The SEER database did not contain data about the radiation field size or dose. Among photon patients, an increased volume of irradiated tissue has been associated with an increased risk of second malignancies (18). Among proton patients, a smaller field size may lead to a greater number of scattered neutrons because of interactions between the protons and the devices shaping the field, leading to a larger proportion of second tumors outside the field (20). Alternately, a smaller proton field radiates less normal tissue, which could lead to fewer in-field second tumors. We were unable to match the patients on the field sizes. However, we matched according to the treatment site and histology in an attempt to control for this unmeasured factor.

Because we could not accurately determine which second malignancies were radiation induced, we included any second malignancies in the study. This methodology is in accordance with the SEER registries' practice in documenting subsequent malignancies after a primary cancer. In the *SEER Cancer Statistics Review, 1975 to 2000*, the cumulative incidence of a subsequent cancer developing among cancer survivors was 5.0% at 5 years and 8.4% at 10 years (1). Given our median follow-up of 6.7 years (proton) and 6.0 years (photon), the risk of second malignancy in our cohort is comparable to the cumulative incidence of second malignancy among cancer survivors in that publication.

In addition, we had no information about patients' chemotherapy regimens for either cohort. Various chemotherapeutic agents are known to be associated with second malignancies. We matched patients by histology and year of treatment to account for the changes in chemotherapy over time. We would not expect chemotherapy to differ by type of radiation.

Finally, most patients in the proton group received 20% of their total dose from photon radiation. The photon dose in the proton cohort may have contributed to the second cancer incidence in these patients; such a difference would bias the results to the null.

In conclusion, after we adjusted for known prognostic factors, there was a lower incidence of second cancers among cancer patients treated with proton radiation compared with patients treated with photon radiation. Because second cancers can appear many years after the initial radiation therapy, longer follow-up of these patients is needed. Given the limitations of the study, the reduced second tumor rate in the proton cohort that we observed should be viewed as hypothesis generating. Nevertheless, these findings are reassuring that the risk of second tumors was at least not increased when using protons compared with photons, but leave open the question as to whether proton radiation therapy decreases rates of second tumors in radiation-treated cohorts.

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