Original Article

Second Cancer Risk After Primary Cancer Treatment With Three-Dimensional Conformal, Intensity-Modulated, or Proton Beam Radiation Therapy

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BACKGROUND: The comparative risks of a second cancer diagnosis are uncertain after primary cancer treatment with 3-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), or proton beam radiotherapy (PBRT). **METHODS:** Pediatric and adult patients with a first cancer diagnosis between 2004 and 2015 who received 3DCRT, IMRT, or PBRT were identified in the National Cancer Database from 9 tumor types: head and neck, gastrointestinal, gynecologic, lymphoma, lung, prostate, breast, bone/soft tissue, and brain/central nervous system. The diagnosis of second cancer was modeled using multivariable logistic regression adjusting for age, follow-up duration, radiotherapy (RT) dose, chemotherapy, sociodemographic variables, and other factors. Propensity score matching also was used to balance baseline characteristics. **RESULTS:** In total, 450,373 patients were identified (33.5% received 3DCRT, 65.2% received IMRT, and 1.3% received PBRT) with median follow-up of 5.1 years after RT completion and a cumulative follow-up period of 2.54 million person-years. Overall, the incidence of second cancer diagnosis was 1.55 per 100 patient-years. In a comparison between IMRT versus 3DCRT, there was no overall difference in the risk of second cancer (adjusted odds ratio [OR], 1.00; 95% CI, 0.97-1.02; $P = .75$). By comparison, PBRT had an overall lower risk of second cancer versus IMRT (adjusted OR, 0.31; 95% CI, 0.26-0.36; $P < .0001$). Results within each tumor type generally were consistent in the pooled analyses and also were maintained in propensity score-matched analyses. **CONCLUSIONS:** The risk of a second cancer diagnosis was similar after IMRT versus 3DCRT, whereas PBRT was associated with a lower risk of second cancer risk. Future work is warranted to determine the cost-effectiveness of PBRT and to identify the population best suited for this treatment. ***Cancer* 2020;0:1-9**.
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KEYWORDS: neoplasms, proton therapy, radiotherapy, conformal, radiotherapy, intensity-modulated, radiotherapy, second primary.

INTRODUCTION

One-half of patients with cancer receive radiation therapy (RT).[1] RT increases the risk of second cancer by 1.2-fold to 3-fold in adults and by 6-fold to 10-fold in pediatric patients.[2-4] Modern RT modalities consist of 3-dimensional conformal radiation (3DCRT) and intensity-modulated radiation (IMRT), which use photons, and proton beam radiation (PBRT), a form of particle-based RT. These techniques differ substantially in their dose distributions, giving rise to long-standing speculation that they may pose different second cancer risks based on theoretical considerations and modeling studies.[5-8]

However, real-world clinical data comparing second cancer rates between radiation modalities are lacking. Empirical studies would require large numbers of patients and/or long follow-up to draw meaningful conclusions. Moreover, PBRT requires specialized technology and is not widely available. For these reasons, epidemiological studies have been extremely challenging, and sufficiently powered randomized comparisons for the endpoint of second cancer are likely not feasible.

Here, we investigated this question in a retrospective cohort study using the National Cancer Database (NCDB). The NCDB includes a large sample size and relatively detailed information regarding RT and other potential confounders, such as chemotherapy and sociodemographic factors,[9] enabling a comparison of risks of second cancer after primary treatment with 3DCRT, IMRT, or PBRT.

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See related Editorial on pages 1-3, this issue.

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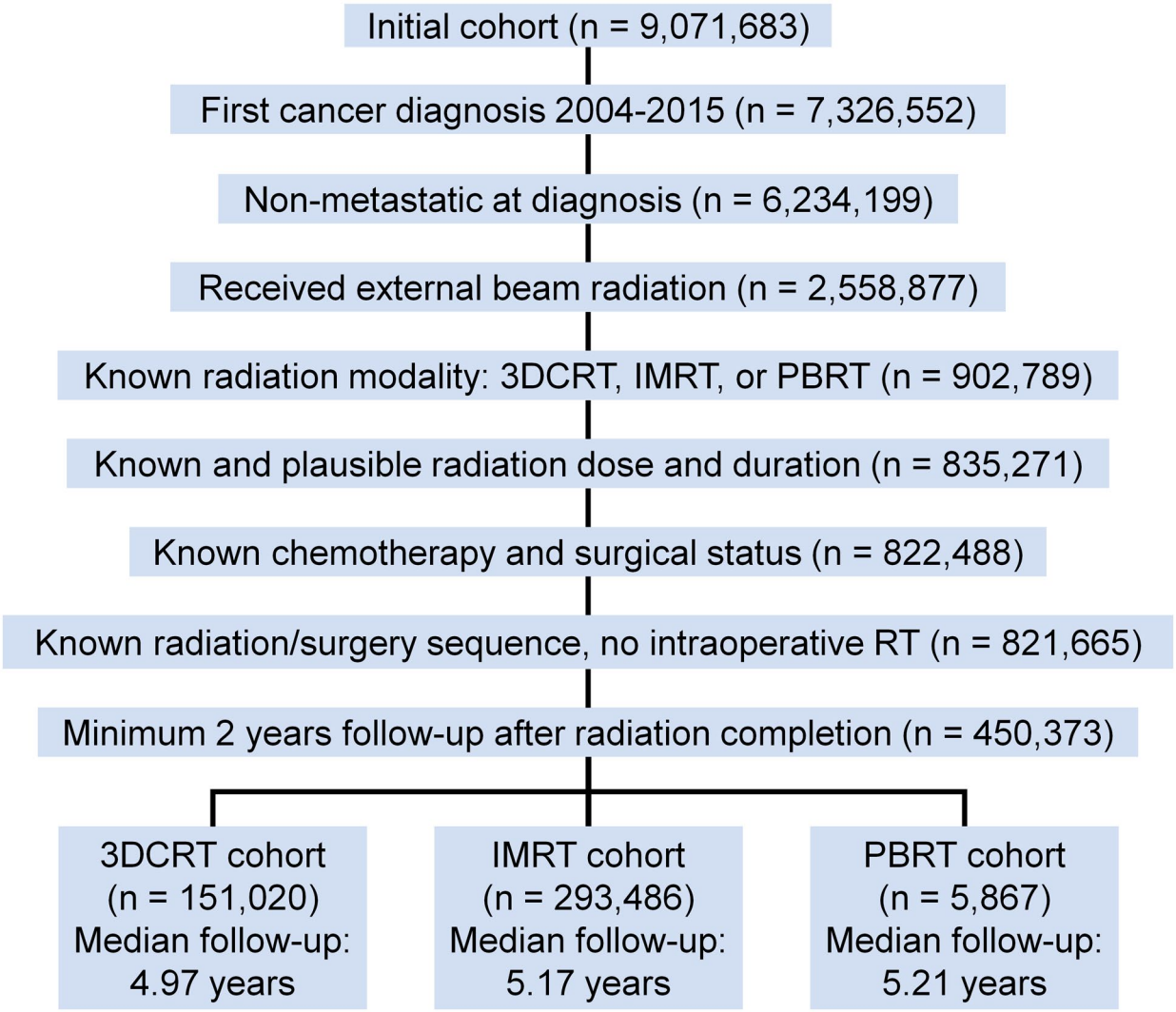

FIGURE 1. This is a Consolidated Standards for Reporting Trials (CONSORT)-style diagram for cohort identification. 3DCRT indicates 3-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; PBRT, proton beam radiation therapy.

MATERIALS AND METHODS

Data Source

The NCDB is a Commission on Cancer-accredited hospital registry capturing 70% of cancers in the United States.[9] Quality-control measures include greater than 600 automated consistency checks per patient record, regular facility audits, and at least 90% patient follow-up at reporting institutions over a 5-year period.[9] The current study was deemed exempt by the Institutional Review Board. Our results have not been verified by the NCDB, and the NCDB is not responsible for the statistical validity of our conclusions.

Inclusion and Exclusion Criteria

Pediatric and adult patients with a first cancer diagnosis between 2004 and 2015 who received RT using 3DCRT, IMRT, or PBRT techniques were identified. To ensure adequate follow-up for second cancers, patients were required to be nonmetastatic at diagnosis and to have at least 2 years of follow-up after radiation completion. This cutoff was selected because previous studies have demonstrated that the risk of second cancer is increased as early as 2 years after RT.[10,11] Exclusion criteria were unknown status of chemotherapy, surgery, or sequence of surgery and radiation; receipt of intraoperative RT; unknown radiation dose, fraction number, start date, or duration; and implausible RT treatment course (total dose >100 grays [Gy] or total fractions >60). Figure 1 illustrates the Consolidated Standards for Reporting Trials (CONSORT)-style diagram used for cohort identification.

TABLE 1. Baseline Characteristics in the Three-Dimensional Conformal Radiation (3DCRT), Intensity-Modulated Radiation (IMRT), and Proton Beam Radiation (PBRT) Cohorts

Characteristic	No. of Patients (%)		
	3DCRT, n = 151,020	IMRT, n = 293,486	PBRT, n = 5867
Age, y			
Median [IQR]	60 [51-69]	64 [55-71]	63 [55-70]
Mean ± SD	60.0 ± 12.7	62.3 ± 12.4	59.4 ± 16.8
Total radiation dose, Gy, GyE			
Median [IQR]	60.0 [50.4-61.0]	66.0 [55.8-75.6]	79.2 [56.4-81.0]
Mean ± SD	56.3 ± 10.8	63.8 ± 13.4	68.9 ± 15.5
Dose per fraction; Gy, GyE			
≤2.5	135,427 (90)	280,830 (96)	5021 (86)
>2.5 and ≤5	14,404 (10)	9473 (3)	312 (5)
>5	1189 (1)	3183 (1)	534 (9)
Radiation boost: External beam			
No	53,823 (36)	175,491 (60)	4999 (85)
Yes	97,197 (64)	117,995 (40)	868 (15)
Chemotherapy regimen			
None	78,403 (52)	183,222 (62)	4885 (83)
Administered[a]	2306 (2)	4842 (2)	43 (1)
Administered, single agent	11,884 (8)	41,352 (14)	239 (4)
Administered, multiagent	58,427 (39)	64,070 (22)	700 (12)
Primary site surgery			
No surgery	28,843 (19)	161,523 (55)	4378 (75)
Surgery with preoperative RT	10,627 (7)	10,631 (4)	86 (1)
Surgery with postoperative RT	111,550 (74)	121,332 (41)	1403 (24)
Tumor category			
Head/neck	4906 (3)	55,330 (19)	672 (11)
Gastrointestinal	15,014 (10)	20,072 (7)	117 (2)
Gynecologic	5121 (3)	10,409 (4)	43 (1)
Lymphoma	6058 (4)	6372 (2)	133 (2)
Lung non–small-cell	10,181 (7)	8570 (3)	132 (2)
Prostate	10,113 (7)	118,800 (40)	3566 (61)
Breast	95,509 (63)	60,843 (21)	572 (10)
Bone/soft tissue	1823 (1)	3242 (1)	224 (4)
Brain/CNS	2295 (2)	9848 (3)	408 (7)
Length of follow-up, y			
Median [IQR]	5.0 [3.2-7.5]	5.2 [3.4-7.5]	5.2 [3.7-7.5]
Mean ± SD	5.6 ± 2.8	5.7 ± 2.6	5.8 ± 2.7
Analytic stage group			
Stage 0 or I	72,545 (48)	66,199 (23)	1432 (24)
Stage II	44,039 (29)	128,589 (44)	3353 (57)
Stage III	26,227 (17)	46,546 (16)	417 (7)
Stage IV	2317 (2)	33,397 (11)	134 (2)
Not applicable or unknown	5892 (4)	18,755 (6)	531 (9)
Race			
Non-Hispanic white	125,072 (83)	233,455 (80)	4824 (82)
Black	14,606 (10)	35,526 (12)	331 (6)
Hispanic	5725 (4)	12,901 (4)	368 (6)
Asian/Native American/Pacific Islander	4011 (3)	7509 (3)	226 (4)
Other or unknown	1606 (1)	4095 (1)	118 (2)
Sex			
Men	34,391 (23)	186,821 (64)	4471 (76)
Women	116,629 (77)	106,665 (36)	1396 (24)
Charlson comorbidity score			
0: No comorbidity	125,409 (83)	246,378 (84)	5130 (87)
1: Mild comorbidity	20,319 (13)	37,347 (13)	631 (11)
≥2: Increased comorbidity	5292 (4)	9761 (3)	106 (2)
Geographic region			
Central/Mountain/Pacific	69,454 (46)	115,677 (39)	4453 (76)
South	40,769 (27)	94,326 (32)	296 (5)
Northeast or unknown	40,797 (27)	83,483 (28)	1118 (19)
Insurance status			
Private	82,883 (55)	134,179 (46)	2998 (51)
Medicare	52,278 (35)	124,453 (42)	2422 (41)
Other government	10,669 (7)	23,441 (8)	279 (5)
None or unknown	5190 (3)	11,413 (4)	168 (3)

TABLE 1. *Continued*

Characteristic	No. of Patients (%)		
	3DCRT, n = 151,020	IMRT, n = 293,486	PBRT, n = 5867
Year of diagnosis			
2004-2007	39,414 (26)	74,971 (26)	2058 (35)
2008-2011	55,075 (36)	122,928 (42)	1890 (32)
≥2012	56,531 (37)	95,587 (33)	1919 (33)
Median income quartile			
<$38,000 or unknown	22,257 (15)	49,546 (17)	523 (9)
$38,000-$47,999	34,641 (23)	68,678 (23)	1106 (19)
$48,000-$62,999	43,010 (28)	80,404 (27)	1547 (26)
≥$63,000	51,112 (34)	94,858 (32)	2691 (46)
Percentage without high school diploma			
>21.0% or unknown	19,345 (13)	43,805 (15)	920 (16)
13.0%-20.9%	35,641 (24)	73,713 (25)	1156 (20)
7.0%-12.9%	52,565 (35)	100,240 (34)	1818 (31)
>7.0%	43,469 (29)	75,728 (26)	1973 (34)
Urban/rural residence			
Metropolitan	123,911 (82)	241,220 (82)	5074 (86)
Urban	21,375 (14)	40,657 (14)	548 (9)
Rural or unknown	5734 (4)	11,609 (4)	245 (4)

Abbreviations: CNS, central nervous system; Gy, grays; GyE, gray equivalents; IQR, interquartile range; RT, radiation.
[a]It was unknown whether administration was single agent or multiagent.

To broadly analyze the effects of RT modality and extend the generalizability of this work, a diversity of primary cancers was considered for inclusion, spanning all solid nonskin tumors with ≥500 eligible patients. Excluded cancers were those rarely or not typically treated with RT (<5% of all cases; eg, ovary) or with limited follow-up because of a poor prognosis (median follow-up, <1 year; eg, pancreas). Cancers were grouped into 9 types based on anatomic site and organ system: head and neck, gastrointestinal, gynecologic, lymphoma, lung (non–small-cell), prostate, breast, bone/soft tissue, and brain/central nervous system. A full listing of primary cancers considered for inclusion is provided in Supporting Tables 1 and 2.

Determination of Second Cancer

The primary outcome was diagnosis of at least 1 second primary cancer, determined using a variable denoting the sequence of malignant neoplasms over a patient's lifetime.[9,12] For patients with a first cancer diagnosis, the variable is binary: 0 indicates a single lifetime primary cancer (no second cancer), and 1 indicates multiple primary cancers (ie, at least 1 second cancer); therefore, the timing, location, and histology of second cancers were not available. The variable is updated centrally by the NCDB if a new cancer arises later in the same patient.[9,12] To distinguish de novo cancers from recurrences of the original cancer, the NCDB considers tumor location, histology, and whether the medical record indicates a recurrence or metastasis, although these data are not available to end users.[2] Cutaneous squamous and basal cell carcinomas are not reported to the NCDB and do not count toward second cancers.

Statistical Analyses

The crude absolute incidence of second cancer was estimated using the Poisson distribution. To evaluate the comparative risk of second cancer between different RT modalities, multivariable logistic regression was used, adjusting for 18 covariates (Table 1) that may confound the association between radiation modality and the risk of second cancer (eg, length of follow-up after RT, radiation dose, age, chemotherapy) or the likelihood of its detection (eg, insurance status, income/education quartile). Primary analyses were performed for each of the 9 tumor types. Sensitivity analyses were performed in patients who had longer follow-up (≥5 years after RT) and in those who did not receive any systemic therapy to completely exclude potential confounding because of chemotherapy.

In addition, pooled analyses were performed across all tumor types, with a variable included in the regression model specifying the tumor type. As further adjustment, propensity score matching was performed by itself or with multivariable regression (ie, doubly robust estimation).[13] Propensity scores were estimated by logistic regression on all covariates, and RT cohorts were matched to generate balanced subsets, which were assessed according to standardized differences (with a 0.10 cutoff to indicate balance).[14] The IMRT and 3DCRT cohorts were matched 1-to-1 with a caliper

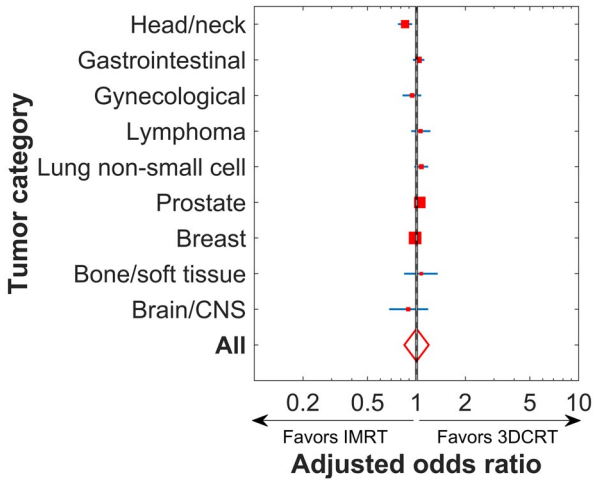

FIGURE 2. This is a forest plot of adjusted odds ratios (log axis) for the risk of second cancer for intensity-modulated radiation therapy (IMRT) relative to 3-dimensional conformal radiation therapy (3DCRT) by tumor type. Horizontal bars indicate 95% confidence intervals. Sizes of the markers are proportional to the relative number of cases. CNS indicates central nervous system.

width 0.40 times the standard deviation of the logits, as this minimized the standardized differences. Because the IMRT cohort was much larger than the PBRT cohort, they were matched 2-to-1 (without caliper) while ensuring all covariates were balanced.

Calculations were performed in MATLAB version R2018b (MathWorks, Inc). All tests were 2-sided, and $P < .05$ was used as the threshold for significance.

RESULTS

Cohort Description and Crude Absolute Incidence of Second Cancer

In total, 450,373 patients spanning 9 tumor types received 3DCRT (33.5%), IMRT (65.2%), or PBRT (1.3%) (Table 1). The median follow-up after completion of RT was 5.1 years (range, 2-13.8 years) overall and 7.4 years among patients who had >5 years of follow-up. The cumulative follow-up period was 2.54 million person-years. The crude absolute incidence of second cancer per 100 patient-years was 1.55 overall (95% CI, 1.53-1.57), 1.60 after 3DCRT (95% CI, 1.57-1.62), 1.55 after IMRT (95% CI, 1.53-1.57), and 0.44 after PBRT (95% CI, 0.37-0.52).

Comparison of IMRT Relative to 3DCRT

Most primary tumor types showed no difference in second cancer risk between IMRT and 3DCRT (Fig. 2).

TABLE 2. Overall Second Cancer Risk for Intensity-Modulated Radiation Relative to Three-Dimensional Conformal Radiation and Proton Beam Radiation Relative to Intensity-Modulated Radiation[a]

Cohort and Adjustment Method(s)	Adjusted OR (95% CI)	*P*
IMRT relative to 3DCRT		
Nonmatched, multivariable	1.00 (0.97-1.02)	.75
Matched, univariable	1.03 (1.00-1.06)	.04
Matched, multivariable	1.00 (0.98-1.03)	.75
PBRT relative to IMRT		
Nonmatched, multivariable	0.31 (0.26-0.36)	<.0001
Matched, univariable	0.30 (0.26-0.36)	<.0001
Matched, multivariable	0.29 (0.24-0.35)	<.0001

Abbreviations: 3DCRT, 3-dimensional conformal radiation, IMRT, intensity-modulated radiation; OR, odds ratio; PBRT, proton beam radiation; CI, confidence interval.
[a]Values were estimated using multivariable adjustment, matching, or both (with the same covariates used in Table 1).

The sole exception was head and neck cancer, which had a modestly decreased second cancer risk with IMRT (adjusted [OR], 0.85; 95% CI, 0.77-0.94; $P = .001$). Similarly, the pooled analysis across all tumor types showed no difference between IMRT and 3DCRT (adjusted OR, 1.00; 95% CI, 0.97-1.02; $P = .75$) (Table 2; see Supporting Table 3). Similar results were seen in the matched cohorts and in sensitivity analyses that excluded patients who received chemotherapy and included those who had >5 years of follow-up (see Supporting Tables 4 and 5, Supporting Figs. 1 and 2).

Comparison of PBRT Relative to IMRT

Compared with IMRT, PBRT was associated with a significantly lower risk of second cancer for primary tumors of the head and neck (adjusted OR, 0.42; 95% CI, 0.22-0.81; $P = .009$) and prostate (adjusted OR, 0.18; 95% CI, 0.14-0.24; $P < .0001$). With the sole exception of non–small-cell lung cancer, the point estimates for all other tumor types also favored PBRT, although sample sizes were more limited, and they did not reach statistical significance (Fig. 3). Moreover, among patients who had >5 years of follow-up, second cancer risk after PBRT was significantly lower for those who had primary tumors of the breast (adjusted OR, 0.62; 95% CI, 0.41-0.95; $P = .029$) and of the head and neck and the prostate (see Supporting Fig. 3).

In the pooled analysis across all tumor types, PBRT was associated with a significantly lower risk of second cancer compared with IMRT (adjusted OR, 0.31; 95% CI, 0.26-0.36; $P < .0001$) (Table 2; see Supporting Table 6). Similar results were seen in the matched cohorts and in sensitivity analyses that excluded patients who received chemotherapy and included those who

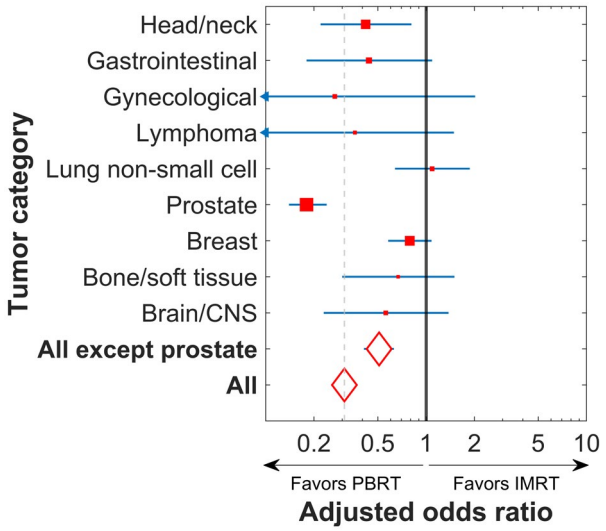

FIGURE 3. This is a forest plot of adjusted odds ratios (log axis) for the risk of second cancer for proton beam radiation therapy (PBRT) relative to intensity-modulated radiation therapy (IMRT) by tumor type. Horizontal bars indicate 95% confidence intervals. Sizes of the markers are proportional to the relative number of cases. CNS indicates central nervous system.

had >5 years of follow-up (see Supporting Tables 7 and 8, Supporting Figs. 3 and 4). Furthermore, the results did not vary significantly by age (P for interaction = .14); and, in subgroup analyses stratified by patient age, point estimates for second cancer risk favored PBRT across all age subgroups (see Supporting Figs. 5 and 6).

PBRT-treated patients without second cancer did not have shorter follow-up or increased deaths compared with IMRT-treated patients, suggesting that these factors did not spuriously limit the observation of second cancers (see Supporting Table 9).

DISCUSSION

In this national cohort study, the relative risk of a second primary cancer was similar after IMRT versus 3DCRT and was lower after PBRT versus IMRT. However, the absolute risk of second cancer was low at approximately 1.5 per 100 person-years, suggesting that the absolute benefit of PBRT may be limited in an unselected population. By comparison, the absolute risk of second cancer in the current study agrees with a prior study of women with breast cancer, not all of whom received radiation, in which the absolute crude rate for second (nonbreast) primary cancer was 1.0 per 100 person-years, and the mean follow-up duration was 8.3 years.[15]

The equivalence for IMRT and 3DCRT is both provocative and reassuring. Previously, it was postulated that IMRT increased the risk of second cancers by 2-fold.[8,16] Although the high-dose region is more compact in IMRT, the lower dose region is expanded because of increased beam angles and higher monitor units, exposing more normal tissue to a low-dose bath.[16] Predictions of increased second cancers after IMRT were based on data extrapolated from atomic bomb survivors.[17] However, more recent data suggest that older models may overestimate the risk at low doses and underestimate the risk at high doses when the exposure is fractionated.[7,8,18,19] In fact, newer models have suggested that second cancer risk after IMRT is not increased and may even be reduced,[8,20-22] such as for head and neck cancer,[23] which we also observed. In one of the few studies to date, a Surveillance, Epidemiology, and End Results (SEER)-Medicare analysis found no difference in second cancers after prostate cancer treatment with IMRT versus 3DCRT.[10] Our results are consistent with these data and lend support to more modern radiobiologic models suggesting that second cancer risk is not increased with the use of IMRT.

Whereas radiation dose is redistributed between IMRT and 3DCRT, leading to a similar integral radiation dose,[24] PBRT reduces the total dose because protons deposit the majority of their energy at depth in a discrete burst (Bragg peak).[6,7,25] PBRT reduces the integral dose by 2-fold to 3-fold and may decrease the risk of second cancer by 2-fold to 15-fold compared with photon-based therapy, according to modeling studies.[6,7,25-29] However, clinical validation has been lacking because of limited follow-up and access to PBRT. A previous report comprised 558 patients who received proton treatment at a single institution matched to 558 (presumed photon) patients in the SEER database.[30] At a median follow-up of 6 to 7 years, the proton cohort had significantly fewer second cancers (adjusted hazard ratio, 0.52; P = .009). Recently, a Japan-based study reported a significantly lower risk of second cancer after prostate cancer treatment with carbon ion RT (another form of particle therapy, as is PBRT) versus photon-based RT (eg, IMRT) at median follow-up of 7.9 and 5.7 years, respectively. The results from both of these studies are consistent with our current findings.[31]

There were significant, fundamental differences in the baseline characteristics of patients who received proton versus photon-based RT (as depicted in Table 1). For example, it has been demonstrated that patients receiving PBRT are younger, healthier, and more commonly

reside in more affluent areas.[32,33] Accordingly, we used statistical techniques to adjust for age, comorbidity, and neighborhood income/education levels, among other sociodemographic variables. Similarly, we also addressed notable treatment imbalances, such as average delivery of higher RT doses to the PBRT cohort, using multivariable regression and propensity score matching. Importantly, we are not able to control for unmeasured confounders, which can only be fully addressed by a randomized trial. However, for the reasons given in the introduction, a randomized trial of photon versus proton-based radiation that is sufficiently powered for the primary endpoint of second cancer is likely not feasible.

Despite the significant relative decrease in second cancer risk in PBRT-treated patients, the absolute benefit was small because of the rarity of second cancers. In older patients, the clinical impact of this benefit is uncertain because of the low absolute risk of second cancer development and the presence of competing risks for mortality. Conversely, those more likely to benefit from PBRT are patients who face a higher absolute lifetime risk of second cancer. Pediatric and young adult patients are at increased risk because of their potential for long life expectancy and heightened susceptibility to treatment-induced malignancies.[16] In our study, the point estimates for second cancer risk favored PBRT across all age subgroups, including younger patients. Although the 95% CI crossed 1 among those aged <40 years, this may reflect a limitation in sample size, because only 4.3% of patients in the IMRT/PBRT cohorts were aged <40 years. Nonetheless, there was no significant interaction of PBRT with patient age.

Strengths of this study are its large sample size, with >2.5 million person-years of cumulative follow-up, the inclusion of diverse cancer types, and adjustment for multiple treatment-related and sociodemographic factors. In addition, the extent of radiation information in the NCDB is relatively detailed compared with other cancer registries, allowing dose and fractionation to be controlled for in the multivariable analyses. Another strength is the robust definition of second cancer, which follows a set of predefined tumor registry rules. It is unlikely that our findings are due to miscoding of recurrences of the original cancer as new primary cancers, because errors in coding are unlikely to be correlated systematically with the choice of radiation modality, and the multivariable analysis with patients who received IMRT and PBRT did not indicate an increased risk of second cancer with increasing stage of the primary cancer.

Our current results should also be interpreted in the context of several limitations. First, it is not possible to link different cancers across time to the same patient in the NCDB,[9] which precludes knowing the anatomic location of second cancers. However, radiation tumorigenesis is not only in-field but also out-of-field as a result of internal scatter, machine leakage, secondary neutron production, and bystander effects.[5,6,11,16] For example, a SEER analysis of prostate cancer treated with RT or surgery found that irradiated patients had increased rates of second cancer arising not only in the bladder and rectum, but also in the lung.[34] In a study of pediatric patients treated with RT, 31% of second cancers occurred in regions receiving <2.5 Gy.[11] Also, dosimetric measurements have shown that distant tissues can receive doses that are clinically relevant to tumorigenesis.[26] In actual clinical practice, it can be challenging to determine whether a later cancer is radiation-induced even knowing its location, and RT can cause both solid tumors and leukemias (from bone marrow exposure).[10] In this respect, our study is a comprehensive, aggregate assessment of all second cancers after primary cancer treatment with a particular RT modality and parallels many previous analyses of second cancer risk after RT that were agnostic to tumor type and location.[2,30,31,35]

Second, our methodology did not allow us to determine the timing of second cancers, which precluded time-to-event analyses (eg, cumulative incidence). However, patients who received PBRT did not have shorter follow-up or increased death compared with those who received IMRT, suggesting that differences in follow-up, censoring, or death (as a competing risk) were unlikely to account for our findings. A related concern is that the follow-up duration in this study does not capture second cancers that develop beyond 10 to 12 years. However, prior studies have shown that RT-induced cancers can occur as early as 2 years after exposure,[10,11] and differential second cancer rates have been previously demonstrated within 5 to 7 years after RT for prostate cancer.[31,34,36] At shorter time points, any risk differences between RT modalities (and the statistical power to detect such differences) would be diminished. Despite this potential limitation, our study was able to identify significantly lower second cancer risk associated with PBRT. This was made possible by the large sample size and extensive cumulative follow-up period of 2.54 million person-years, which allowed for the detection of differences in an uncommon event. Moreover, we controlled for follow-up time in the multivariable model, and sensitivity analyses of patients who had >5 years of follow-up yielded similar findings. Conversely, we did not identify a difference between IMRT and 3DCRT. It is unclear whether they

are truly equivalent or whether our study simply did not have sufficient time in follow-up to detect a difference. It remains possible that the second cancer risks for IMRT versus 3DCRT could diverge with longer follow-up, as more second cancers occur.

Another limitation was the lack of detailed chemotherapy data (eg, specific agents and dosages), which was addressed with sensitivity analysis that excluded patients who received chemotherapy. Also, although precise radiation field borders are not available in the NCDB, our analysis controlled for radiation dose and fractionation as well as primary cancer subtype and stage, both of which are correlated with radiation field size and extent. Finally, data are unavailable for known cancer risk factors, such as smoking and obesity, which may be correlated with certain tumor types. However, analyses by tumor type were generally consistent with the pooled results. Also, lifestyle risk factors may be at least partially accounted for by variables that were included in the model, such as income, educational quartile, and comorbidity score. Interestingly, lung cancer was the only tumor type that did not have an adjusted odds ratio favoring PBRT, suggesting that perhaps the high prevalence of smoking in this population dominates second cancer development relative to the RT modality.

Pending randomized data, large-scale epidemiological studies can provide valuable insights. Our current results, although hypothesis-generating, are consistent with the conjectured reduction in second cancers with PBRT, although the absolute benefit may be small in an unselected population because of the rarity of second cancers. Furthermore, we did not find evidence that the use of IMRT gives rise to more second cancers compared with 3DCRT, although additional follow-up is required. Future work is warranted to determine the cost-effectiveness of PBRT and to identify the patients best suited for this treatment.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Michael Xiang: Conceptualization, data curation, formal analysis, investigation, methodology, writing–original draft, and writing–review and editing. **Daniel T. Chang:** Investigation, methodology, supervision, and writing–review and editing. **Erqi L. Pollom:** Conceptualization, investigation, methodology, project administration, supervision, and writing–review and editing.

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