International Journal of Particle Therapy 13 (2024) 100627

Contents lists available at ScienceDirect

International Journal of Particle Therapy

journal homepage: www.sciencedirect.com/journal/ijpt

Secondary Cancer in Prostate Cancer Patients Treated With Advanced External Beam Radiation Therapy

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ARTICLE INFO

Keywords:
Localized prostate cancer
Secondary tumor
Radiation therapy
Proton beam therapy
Stereotactic body radiation therapy

ABSTRACT

Purpose: Previous studies have shown that external beam radiation therapy is associated with an increased risk of second primary cancer (SPC) among prostate cancer (PCa) patients, but the relative risks associated with newer and advanced radiation modalities such as proton beam therapy (PBT) and stereotactic body radiation therapy (SBRT) are unclear. This study aimed to assess the relative probability of SPC among patients treated with these newer modalities compared to intensity-modulated radiation therapy (IMRT).

Patients and Methods: Using the National Cancer Database (NCDB), N0M0 PCa cases diagnosed between 2004 and 2018 were identified. Second primary cancer probabilities were compared among those treated with curative-intent PBT, SBRT, and IMRT. Multivariable logistic regression and inverse probability of treatment weighting were used to generate adjusted odds ratios (aORs) and 95% confidence intervals (CIs).

Results: In total, 133 898 patients were included, with a median age of 69 years and median follow-up of 6.4 years. As their first course of treatment, 3420 (2.6%) received PBT, 121 211 (90.5%) received IMRT, and 9267 (6.9%) received SBRT. Compared with IMRT, PBT and SBRT were associated with lower SPC risk (aORs and 95% CIs, PBT: 0.49 [0.40-0.60], SBRT: 0.57 (0.51-0.63), $P < .001$). Inverse probability of treatment weighting analyses corroborated these results.

Conclusion: In this large national cohort, PBT and SBRT performed similarly and were associated with reduced SPC risk compared to IMRT when used as the first course of treatment.

Introduction

Radiation therapy (RT) has been associated with an increased risk of developing a second primary cancer (SPC) due to the exposure of normal tissue to radiation.[1-3] The absolute rates of SPC are relatively low in prostate cancer (PCa) survivors,[4,5] but the long survival rates and frequent use of RT make SPC incidence an important topic in PCa research.[6,7]

Among PCa survivors, SPCs commonly occur in the immediate surrounding organs (eg, the bladder and rectum) and often correspond with integral radiation exposure.[8,9] To spare normal tissues from exposure, advanced radiation technologies, such as proton beam therapy (PBT) and stereotactic body radiation therapy (SBRT), with high in-field targeting accuracy, steep dose gradients, and reduced out-of-field exposure, are increasingly being utilized.[10-13] The targeted delivery methods of these technologies may improve toxicity and quality of life and are expected to reduce the risk of SPC, but strong evidence is still lacking.[11-15]

Here, we perform a retrospective cohort analysis of US men with localized PCa undergoing definitive therapy between 2004 and 2018 to provide a comprehensive comparison of SPC occurrence among patients treated with PBT, SBRT, or intensity-modulated radiation therapy (IMRT) as the initial course of treatment. Previous studies have utilized the National Cancer Database (NCDB) and Surveillance, Epidemiology, and End Results database to assess SPC incidence among PCa survivors treated with radiation,[16,17] but none have performed an extensive comparison of PBT and other radiation modalities with careful handling of the data heterogeneity rooted in the real world setting, as we do here using inverse probability of treatment weighting (IPTW) and subgroup analyses. Accounting for this heterogeneity is important because

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https://doi.org/10.1016/j.ijpt.2024.100627
Received 9 February 2024; Received in revised form 11 August 2024; Accepted 15 August 2024

patients often have limited access to advanced techniques, necessitating longer travel distances for treatment and potentially leading to shorter and inconsistent follow-up times. Therefore, stratification by travel distance and follow-up time subgroups allows for more fair comparisons of SPC incidence due to possible differences in data reporting. We hypothesize that, due to the steep dose gradients and lower overall integral dose achieved with PBT or SBRT, the incidence of SPC would be lower with PBT and SBRT compared with IMRT.

Patients and methods

Data source

A retrospective cohort analysis was performed using the NCDB 2019 Participant User File (PUF) for PCa, which contains data for patients diagnosed with or treated for PCa at Commission on Cancer-accredited facilities between 2004 and 2019.[18] The NCDB is a hospital-based registry system that includes more than 70% of all diagnosed cancers in the United States.[19]

Inclusion and exclusion criteria

Men diagnosed with localized PCa between 2004 and 2018 were identified. Patients with clinical stage N0M0 prostate adenocarcinoma, whose PCa diagnosis was their only primary cancer or the first in the sequence, were included. Patients undergoing PBT, SBRT, or IMRT as their initial course of treatment were eligible. Those treated with more than 1 modality were excluded. Radiation volume was limited to the prostate.

To ensure adequate time for SPC development, patients were restricted to those with at least 2 years of known follow-up time from the start of treatment to death or last contact.[7,16] Based on prior literature,[20-22] analyses were further restricted to patients living within 250 miles of their treatment facility, so that access to treatment within the PBT cohort was similar to access to treatment within other cohorts, thus reducing the potential for bias. Cases with potentially incomplete data (indicated by a reference date flag value of 0 in the NCDB[23]) and patients who received palliative care were removed. In total, 133 898 patients were included in the study (Table 1).

Primary outcome

The primary outcome of interest was an SPC at any primary site, defined using the sequence number variable in the NCDB. The sequence number is updated when the facility learns of an unaccessioned tumor that affects the sequence.[23] A value of 00 indicated that the patient had no secondary malignancies, and 01 indicated that the patient had at least 1 secondary malignancy following the current PCa diagnosis. All patients with sequence number values of 02 or greater were excluded because SPC occurrence after PCa diagnosis could not be determined. Detailed information regarding the time to diagnosis and type of the SPC is unavailable in the NCDB, which only records data for the first course of treatment.

Treatment

Treatment modalities were categorized based on the phase I and phase II RT modalities reported in the NCDB. Reported phase I and II beam techniques were used to subcategorize IMRT and SBRT modalities. Only patients receiving RT for curative purposes (total dose $\geq$60 GyE for PBT and IMRT; 35-50 GyE for SBRT) were included in analyses. The target volume was limited to the prostate only. Patients treated with multiple modalities (eg, combined external beam RT and brachytherapy) were excluded.

Covariates

Facility/patient demographic and clinical factors included age, race/ethnicity, facility type, facility location by region, Charlson-Deyo comorbidity score (categorized as 0, 1, and 2+), T stage, prostate-specific antigen (PSA) value, Gleason score, androgen deprivation therapy (ADT), median income quartiles and educational attainment quartiles (measured as the percent without a high school degree) by zip code for 2008-2012 as surrogates for socioeconomic status, chemotherapy, insurance type, rurality of residence, travel distance to treatment facility (defined as crowfly distance from the treatment facility to the centroid of a patient's zip code of residence, categorized as short: < 12.5 miles, intermediate: 12.5-49.9 miles, and long: 50-250 miles), and follow-up time from the start of treatment to last contact or death (categorized as 2-4, 5-9, and 10+ years).

Statistical analysis

Descriptive statistics and univariate associations (eg, χ^2 test, analysis of variance (ANOVA)) were calculated to capture the distribution of covariates. A multivariable logistic regression model was fitted to the data with binarized SPC occurrence as the outcome of interest. All model covariates described previously were included in the model, with a backward selection criterion of 0.05. The fitted model was used to generate adjusted odds ratios (aORs) with 95% confidence intervals (CIs). To avoid multicollinearity in model fitting, the year of diagnosis was not considered in the multivariate analysis due to its high correlation with the length of follow-up.

To further minimize confounding, IPTW, a propensity score (PS)-based approach, was implemented.[24,25] The PS was defined as the conditional probability of being treated given the observed covariates.[26,27] In our case with a 3-level cohort, the PS was estimated using a multinomial logit model containing all previously listed covariates. Average treatment effect matching weights were then calculated using the PS.[28] Balance diagnostics were performed using absolute

Table 1
Selection diagram of the study population.

Selection and exclusion criteria	Sample size	Excluded
NCDB prostate PUF cancer cases	1 868 671	-
Invasive tumor behavior	1 868 331	340
AJCC N0 M0 and exclude any metastasis cases	1 485 931	382 400
The current cancer diagnosis was the only one or the first in the sequence	1 370 723	115 208
Study cohorts as PBT, IMRT, and SBRT	193 157	1 177 566
Radiation volume as prostate (whole or partial)	191 313	1844
Minimum 2 y of follow-up time	157 817	33 496
Travel distance to treatment facility < 250 miles	137 675	20 142
Remove cases that can no longer be updated and may not be current	133 984	3691
Remove patients receiving palliative care	133 898	86

Abbreviations: NCDB, National Cancer Database; AJCC, American Joint Committee on Cancer; PBT, proton beam therapy; IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy; PUF, Participant User File.

standardized difference, with absolute standardized difference < 0.1 indicating sufficient balance. A weighted multivariable logistic regression model for SPC was used to generate PS-weighted aORs and CIs.

A second multivariable logistic regression model with interactions was fitted to explore cohort heterogeneity, in which interaction terms for cohort, travel distance to the treating facility, follow-up time, and Charlson-Deyo comorbidity score were included as additional model effects. This model was used to generate stratified aORs and 95% CIs and to guide a subsequent subgroup analysis among patients with short travel distances and long follow-up times (refer to Table S1 for results). Restricting our analyses to this patient subgroup allowed for more fair comparisons of SPC incidence, as differences in follow-up time and travel distance to the treatment facility can affect data collection/reporting.

An additional subgroup analysis was performed to assess the relative risks of SPC by radiation cohort among patients with no comorbid conditions (refer to Table S1 for results). Patients without comorbidities are less likely to develop new primary malignancies, so SPC occurrence is anticipated to be more closely linked to RT within this subgroup.

All analyses were done in SAS V9.4 (Cary, NC) and SAS macros,[29] and the significance level was set at $P < .05$.

Results

Patient and treatment characteristics

As shown in Table 2, 3420 (2.6%) patients received PBT, 121 211 (90.5%) received IMRT, and 9267 (6.9%) received SBRT as their first course of treatment. The median (interquartile range) age by cohort was 67 (62-72) for PBT, 67 (62-73) for SBRT, 69 (63-74) for IMRT, and 69 (63-74) overall. Median follow-up times by cohort were 5.3, 5.2, and 6.6 years for PBT, SBRT, and IMRT, respectively, and 6.4 years overall. Patients who received PBT tended to travel farther for treatment even after restricting the travel distance to < 250 miles and were treated primarily at academic/research facilities located in large metropolitan areas, which differed from the geographic distributions of other cohorts. Patients treated with PBT or SBRT also tended to live in areas with higher median incomes compared to those treated with IMRT. The crude percentages of patients with SPC were lower among the PBT (3.0%) and SBRT (4.3%) cohorts compared to IMRT (8.6%) (Table 2).

Impact of radiation modality on second primary cancer

As illustrated in Table 3, the overall risk of SPC relative to IMRT, after adjusting for all available covariates, was lower among patients treated with PBT (aOR: 0.49, 95% CI: 0.40-0.60, $P < .001$) or SBRT (aOR: 0.57, 95% CI: 0.51-0.63, $P < .001$). The overall risk of SPC was also found to decrease with increasing travel distance (intermediate vs short: aOR: 0.84, 95% CI: 0.80-0.88; long vs short: aOR: 0.58, 95% CI: 0.51-0.65), increase with prolonged follow-up time (5-9 vs 2-4 years: aOR: 1.32, 95% CI: 1.26-1.39; 10+ vs 2-4 years: aOR: 1.38, 95% CI: 1.31-1.46), and increase with Charlson-Deyo comorbidity score (2+ vs 0: aOR: 1.20, 95% CI: 1.08-1.33; 1 vs 0: aOR: 1.15, 95% CI: 1.08-1.22) (all $P < .001$).

Comparison of radiation cohorts after inverse probability of treatment weighting

To further adjust for all observed confounding and achieve covariate balance among treatment cohorts, IPTW was performed with sufficient covariate balance (Figure S1). The unweighted and weighted models yielded similar aOR estimates, but the weighted models produced larger CIs due to the smaller effective sample sizes after PS-matched weighting (Tables 3 and 4). As shown in Table 4, after adjustment, the risk of SPC among patients receiving PBT and SBRT treatment was comparable (aOR: 1.16, 95% CI: 0.80-1.70, $P = .436$). Proton beam therapy was associated with lower SPC risk compared to IMRT (aOR: 0.59, 95% CI: 0.43-0.82, $P = .002$). Similarly, SBRT was associated with lower SPC risk compared to IMRT (aOR: 0.51, 95% CI: 0.36-0.72, $P < .001$).

Travel distance and follow-up time subgroup analysis

In Figure S2, we revealed patterns in the association of SPC risk relative to IMRT for each radiation modality across subgroups defined by travel distance to the treatment facility and length of follow-up time. The assessment of interaction terms in the multivariable logistic regression model allowed us to examine a heterogeneous association between RT cohort and SPC across those subgroups, likely reflecting differences in reporting practices that may bias results. For example, PBT and SBRT had reduced risk overall compared to IMRT, but the magnitude of risk reduction decreased among subpopulations residing closer to the treating facility (Figure S2a, interaction P-value < .001) and did not differ significantly by follow-up time (Figure S2b, interaction P-value = .670).

Based on these results and the need for long follow-up to adequately assess SPC incidence, we performed a subgroup analysis among patients traveling < 12.5 miles for treatment who were also followed for at least 10 years ($N = 18\,449$). Among this subgroup, 1807 (9.8%) had SPC. The estimated SPC risk associated with SBRT within this subgroup (aOR: 0.56, 95% CI: 0.38-0.83, $P = .004$) was similar to that observed in the whole population (Tables 3 and S1). The SPC risk associated with PBT was lower than IMRT among this patient subgroup (aOR: 0.80, 95% CI: 0.32-2.01, $P = .634$), but this difference was not significant due to the small sample sizes, especially within the proton cohort ($N = 78$) (Table S1).

No-comorbidity subgroup analysis

Because of the limited SPC data available in the NCDB, we ran an additional subgroup analysis among patients without comorbidities ($N = 113\,273$). Within this subgroup, 9036 (8.0%) had SPC. These patients were more likely to have SPC attributable to SPC because they were at lower risk of developing a new primary malignancy due to their lack of comorbid conditions. Within this subgroup, SBRT and PBT were associated with a similarly reduced risk of SPC compared to IMRT (Table S1). Second primary cancer risk estimates also did not differ significantly from those obtained using the entire population (Tables 3 and S1).

Discussion

Using a national cohort of patients with localized PCa, we show that the relative risk of SPC among patients treated with PBT or SBRT is significantly reduced compared to IMRT. The significance of these findings is that, for men with localized PCa undergoing definitive RT, PBT and SBRT treatment may mitigate the risk of SPC, and subsequent morbidity, compared with other commonly available RT options such as IMRT.

Although the retrospective nature of NCDB-related studies comes with the possibility of residual confounding, we are able to estimate the relative probabilities of SPC among RT cohorts with improved rigor by utilizing advanced statistical techniques that minimize selection bias through covariate balancing and by performing subgroup analyses. These analyses provide additional support for our primary analysis, as they indicate a consistent trend in SPC risk within travel distance, follow-up time, and patient comorbidity subgroups.

The highly targeted nature of PBT and SBRT is likely responsible for the observed reduction in SPC risk, since normal surrounding tissues are exposed to less radiation compared to conventional techniques. Specifically, PBT uses high-energy particles with unique physical properties that allow most of the dose to be deposited at a target depth

Table 2
Baseline characteristics by treatment cohorts.

Covariate	Level	Total	Treatment cohorts			*P*-value[a]
			Proton	IMRT	SBRT	
		N = 133 898 (100%)	*N* = 3420 (2.6%)	*N* = 121 211 (90.5%)	*N* = 9267 (6.9%)	
Secondary tumor	No	122 969 (91.8)	3316 (97)	110 782 (91.4)	8871 (95.7)	< **.001**
	Yes	10 929 (8.2)	104 (3)	10 429 (8.6)	396 (4.3)	
Age at diagnosis	Median (Q1-Q3)	69 (63-74)	67 (62-72)	69 (63-74)	67 (62-73)	< **.001**
Race-ethnic groups	Non-Hispanic White	102 098 (76.3)	2714 (79.4)	92 019 (75.9)	7365 (79.5)	< **.001**
	Non-Hispanic Black	21 361 (16)	353 (10.3)	19 650 (16.2)	1358 (14.7)	
	Asian-Indians-Pac	2964 (2.2)	122 (3.6)	2654 (2.2)	188 (2)	
	Hispanic	5813 (4.3)	177 (5.2)	5437 (4.5)	199 (2.1)	
	Other/Unknown	1662 (1.2)	54 (1.6)	1451 (1.2)	157 (1.7)	
Facility type	Nonacademic/Research program	93 520 (69.9)	401 (11.7)	88 457 (73)	4662 (50.3)	< **.001**
	Academic/Research program	40 363 (30.1)	3017 (88.3)	32 741 (27)	4605 (49.7)	
Facility location	Eastern	65 513 (48.9)	846 (24.8)	58 410 (48.2)	6257 (67.5)	< **.001**
	Central	49 332 (36.8)	536 (15.7)	46 468 (38.3)	2328 (25.1)	
	Mountain	4093 (3.1)	19 (0.6)	3719 (3.1)	355 (3.8)	
	Pacific	14 945 (11.2)	2017 (59)	12 601 (10.4)	327 (3.5)	
Charlson-Deyo score	0	113 273 (84.6)	2960 (86.5)	102 277 (84.4)	8036 (86.7)	< **.001**
	1	16 088 (12)	379 (11.1)	14 675 (12.1)	1034 (11.2)	
	2+	4537 (3.4)	81 (2.4)	4259 (3.5)	197 (2.1)	
T stage	T2	39 009 (29.1)	1126 (32.9)	36 139 (29.8)	1744 (18.8)	< **.001**
	Unknown	512 (0.4)	5 (0.1)	487 (0.4)	20 (0.2)	
	T1	87 614 (65.4)	2181 (63.8)	77 972 (64.3)	7461 (80.5)	
	T3	6306 (4.7)	106 (3.1)	6158 (5.1)	42 (0.5)	
	T4	457 (0.3)	2 (0.1)	455 (0.4)	0 (0)	
PSA	Unknown	2510 (1.9)	28 (0.8)	2353 (1.9)	129 (1.4)	< **.001**
	< 10	89 399 (66.8)	2657 (77.7)	79 311 (65.4)	7431 (80.2)	
	10-20	25 586 (19.1)	537 (15.7)	23 812 (19.6)	1237 (13.3)	
	> 20	16 403 (12.3)	198 (5.8)	15 735 (13)	470 (5.1)	
Gleason score	2-6	37 052 (27.7)	1260 (36.8)	31 957 (26.4)	3835 (41.4)	< **.001**
	7	60 655 (45.3)	1640 (48)	54 212 (44.7)	4803 (51.8)	
	8-10	34 016 (25.4)	513 (15)	32 983 (27.2)	520 (5.6)	
	Unknown	2175 (1.6)	7 (0.2)	2059 (1.7)	109 (1.2)	
ADT	No	69 162 (51.7)	2534 (74.1)	58 663 (48.4)	7965 (86)	< **.001**
	Yes	62 720 (46.8)	871 (25.5)	60 682 (50.1)	1167 (12.6)	
	Unknown	2016 (1.5)	15 (0.4)	1866 (1.5)	135 (1.5)	
Census median income quartiles 2008-2012	< $38 000	22 076 (16.5)	322 (9.4)	20 736 (17.1)	1018 (11)	< **.001**
	$38 000-$47 999	29 903 (22.4)	526 (15.4)	28 116 (23.2)	1261 (13.6)	
	$48 000-$62 999	35 883 (26.8)	919 (26.9)	33 004 (27.3)	1960 (21.2)	
	≥$63 000	45 843 (34.3)	1651 (48.3)	39 184 (32.4)	5008 (54.2)	
Percent no high school degree 2008-2012	≥21.0%	21 093 (15.8)	600 (17.6)	19 339 (16)	1154 (12.5)	< **.001**
	13.0%-20.9%	33 254 (24.9)	804 (23.5)	30 452 (25.1)	1998 (21.6)	
	7.0%-12.9%	44 791 (33.5)	986 (28.8)	40 899 (33.8)	2906 (31.4)	
	< 7.0%	34 663 (25.9)	1028 (30.1)	30 438 (25.1)	3197 (34.5)	
Chemotherapy	No	132 083 (98.6)	3396 (99.3)	119 498 (98.6)	9189 (99.2)	< **.001**
	Yes	493 (0.4)	18 (0.5)	473 (0.4)	2 (0)	
	Unknown	1322 (1)	6 (0.2)	1240 (1)	76 (0.8)	
Primary payor	Other government/Not Insured/Unknown	12 268 (9.2)	197 (5.8)	11 464 (9.5)	607 (6.6)	< **.001**
	Private	42 262 (31.6)	1277 (37.3)	37 572 (31)	3413 (36.8)	
	Medicare	79 368 (59.3)	1946 (56.9)	72 175 (59.5)	5247 (56.6)	
Urban/Rural 2013	Metro	110 892 (82.8)	3090 (90.4)	99 796 (82.3)	8006 (86.4)	< **.001**
	Urban	17 877 (13.4)	120 (3.5)	16 955 (14)	802 (8.7)	
	Rural	2307 (1.7)	13 (0.4)	2211 (1.8)	83 (0.9)	
	Unknown	2822 (2.1)	197 (5.8)	2249 (1.9)	376 (4.1)	
Great circle distance (miles)	Short	84 489 (63.1)	890 (26)	78 792 (65)	4807 (51.9)	< **.001**
	Intermediate	41 935 (31.3)	1383 (40.4)	37 096 (30.6)	3456 (37.3)	
	Long	7474 (5.6)	1147 (33.5)	5323 (4.4)	1004 (10.8)	
Year of diagnosis	2004-2008	38 195 (28.5)	681 (19.9)	36 453 (30.1)	1061 (11.4)	< **.001**
	2009-2013	50 606 (37.8)	1318 (38.5)	45 825 (37.8)	3463 (37.4)	
	2014-2018	45 097 (33.7)	1421 (41.5)	38 933 (32.1)	4743 (51.2)	
Years of follow-up time	2-4	48 291 (36.1)	1522 (44.5)	42 389 (35)	4380 (47.3)	< **.001**
	5-9	57 666 (43.1)	1514 (44.3)	52 201 (43.1)	3951 (42.6)	
	10+	27 941 (20.9)	384 (11.2)	26 621 (22)	936 (10.1)	
	Median (Q1-Q3)	6.4 (4-9.4)	5.3 (3.6-7.9)	6.6 (4.1-9.6)	5.2 (3.4-7.8)	
Phase I + phase II dose (Gy)	Mean (Std Dev)	74 (11.7)	79.3 (10)	76.7 (5.6)	36.4 (1.8)	< **.001**
	Median (Q1-Q3)	77.4 (74.8-79.2)	79.2 (78-81)	77.4 (75.6-79.2)	36.3 (35-36.3)	
	Min-Max	35-162.6	60-162	60-162.6	35-50	

Abbreviations: IMRT, intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy; PSA, prostate-specific antigen; ADT, androgen deprivation therapy. Bold values represent statistical significance with $p < 0.05$.

[a] The parametric *P*-value is calculated by ANOVA for numerical covariates and χ^2 test for categorical covariates.

Table 3
Multivariable logistic regression for secondary tumor.

			Secondary tumor = Yes		
Covariate**	Level	*N**	Odds ratio (95% CI)	OR *P*-value	Type 3 *P*-value
Treatment cohorts	Proton	3416	0.49 (0.40-0.60)	< .001	< **.001**
	SBRT	9247	0.57 (0.51-0.63)	< .001	
	IMRT	121 027	-	-	
Race-ethnic groups	NH-White	101 935	1.20 (1.13-1.28)	< .001	< **.001**
	Asian-Indians-Pac	2962	0.90 (0.77-1.06)	.211	
	Hispanic	5806	0.80 (0.70-0.90)	< .001	
	Other/Unknown	1658	0.48 (0.36-0.63)	< .001	
	NH-Black	21 329	-	-	
Facility type	Academic/Research program	40 311	0.87 (0.83-0.91)	< .001	< **.001**
	Nonacademic/Research program	93 379	-	-	
Facility location	Pacific	14 934	0.95 (0.89-1.03)	.199	**.005**
	Mountain	4072	0.87 (0.76-0.98)	.028	
	Central	49 281	1.04 (1.00-1.09)	.062	
	Eastern	65 403	-	-	
Charlson-Deyo score	2+	4532	1.20 (1.08-1.33)	< .001	< **.001**
	1	16 071	1.15 (1.08-1.22)	< .001	
	0	113 087	-	-	
T stage	T2	38 940	1.14 (1.09-1.19)	< .001	< **.001**
	Unknown	510	1.02 (0.73-1.43)	.893	
	T3	6299	1.00 (0.90-1.10)	.946	
	T4	457	1.14 (0.82-1.59)	.433	
	T1	87 484	-	-	
Gleason score	7	60 554	0.87 (0.83-0.92)	< .001	< **.001**
	8-10	33 967	0.82 (0.77-0.87)	< .001	
	Unknown	2175	1.19 (1.03-1.36)	.015	
	2-6	36 994	-	-	
ADT	Unknown	2015	1.05 (0.90-1.23)	.535	< **.001**
	Yes	62 618	1.11 (1.06-1.17)	< .001	
	No	69 057	-	-	
Census median income quartiles 2008-2012	≥$63 000	45 839	0.90 (0.84-0.96)	< .001	**.004**
	$48 000-$62 999	35 880	0.95 (0.89-1.02)	.147	
	$38 000-$47 999	29 898	0.97 (0.91-1.04)	.359	
	< $38 000	22 073	-	-	
Years of follow-up time	5-9	57 562	1.32 (1.26-1.39)	< .001	< **.001**
	10+	27 912	1.38 (1.31-1.46)	< .001	
	2-4	48 216	-	-	
Primary payor	Medicare	79 264	1.16 (1.07-1.26)	< .001	< **.001**
	Private	42 183	1.03 (0.94-1.11)	.559	
	Other government/Not Insured/Unknown	12 243	-	-	
Urban/Rural 2013	Unknown	2792	1.01 (0.87-1.18)	.854	< **.001**
	Rural	2296	1.35 (1.16-1.56)	< .001	
	Urban	17 844	1.06 (1.00-1.13)	.070	
	Metro	110 758	-	-	
Great circle distance (miles)	Intermediate	41 844	0.84 (0.80-0.88)	< .001	< **.001**
	Long	7447	0.58 (0.51-0.65)	< .001	
	Short	84 399	-	-	
Age at diagnosis		133 690	1.02 (1.02-1.02)	< .001	< **.001**

Abbreviations: CI, confidence interval; OR, odds ratio; SBRT, stereotactic body radiation therapy; IMRT, intensity-modulated radiation therapy; NH, Non-Hispanic. Bold values represent statistical significance with $p < 0.05$.
*Number of observations in the original data set = 133 898. Number of observations used = 133 690.
**Backward selection with an alpha level of removal of 0.05 was used. The following variables were removed from the model: percent no high school degree 2008-2012, PSA, and chemotherapy.

without a large exit dose[12,13]; SBRT utilizes advanced immobilization and imaging techniques with steep dose fall-offs that allow high doses to deliver treatment to well-defined target regions in fewer fractions than conventional photon RT.[30,31] Clinical trials to assess the true nature of these benefits are still ongoing.[32]

Observational studies that utilize large-scale national cancer registry databases provide alternative approaches to assess these potential benefits, since they include many patients from diverse populations with long follow-up times. Compared to other cancer registries, the NCDB provides more robust reporting of radiation modality technique and dosage information and contains a well-defined sequence number variable that is updated annually to capture the development of new primary tumors among existing cases.[16] Together, these features make the NCDB a valuable data source for assessing the relationships between SPC and RT techniques, as is supported by its use in previous studies. For example, a similar study by Dee et al[17] found that the SPC probabilities associated with SBRT are comparable to those associated with surgery alone, but PBT was not included in their analysis, and they excluded all cases with < 5 years of follow-up. Another study by Xiang et al[16] reported much lower relative SPC risks among PBT versus IMRT recipients across 9 solid tumors, including PCa, but their analysis did not control for disease-specific confounding effects. Our previous experience also suggests that selection bias may be substantial for newly developed advanced technologies like PBT and SBRT, due to their limited accessibility, so they must be handled carefully.[33] By focusing solely on PCa survivors, expanding our analysis to include patients treated with PBT, and utilizing an analytic strategy that reduces confounding effects, we provide improved rigor in estimating the relative SPC probabilities by treatment modality within this population.

Fundamental differences were observed in the patient populations receiving PBT or SBRT compared to the other treatment cohorts. Proton

Table 4
Adjusted OR and 95% CI for pairwise comparisons of treatment cohorts after inverse probability of treatment weighting.

Cohort (treatment vs reference group)	Adjusted OR (95% CI)	*P*-value
PBT versus SBRT	1.16 (0.80-1.70)	.436
PBT versus IMRT	0.59 (0.43-0.82)	.002
SBRT versus IMRT	0.51 (0.36-0.72)	< .001

Abbreviations: OR, odds ratio; CI, confidence interval; PBT, proton beam therapy; SBRT, stereotactic body radiation therapy; IMRT, intensity-modulated radiation therapy.

beam therapy patients overwhelmingly received treatment at academic/research institutions, lived in more affluent areas, traveled longer distances to receive treatment, and had less follow-up time on average than other cohorts (Table 2). Similarly, SBRT patients generally lived in more affluent areas and had shorter follow-up times (Table 2). To adjust for the potential confounding effects of these and other clinical and demographic factors, we used multivariable regression and IPTW. Inverse probability of treatment weighting allowed us to create a pseudo-stratified randomized study population with balanced baseline covariates among the 3 treatment cohorts.

There are many factors unique to PBT, not directly measurable in the NCDB or controlled by multivariable modeling or PS adjustment, that may confound our findings. Specifically, access to PBT is much more limited than access to other treatments due to the small number of proton centers in the United States. There were only 3 operating centers in the country at the start of the study period (2004) and only 31 centers by the last year of treatment included in the study (2018).[34] This required patients who received PBT to travel farther for treatment and to bear the associated travel costs. As such, financial factors likely play a role. Proton beam therapy is more expensive on average than other types of treatment,[10,35] which may explain why a high proportion of the PBT cohort lived in regions with median incomes in the upper quartile (Table 2). Insurance coverage of PBT also differs by insurance type/plan; a recent study by McDonald et al[36] found that patients identifying as Black, Indigenous, or People of Color are significantly less likely to be on proton-favorable insurance plans, which widens the disparities in access to PBT. Patients treated with PBT may also be less likely to return to the treatment facility for follow-up visits due to the far travel distances, which could lead to an underdiagnosis of SPC within the PBT patient cohort, or may go outside of the NCDB system for follow-up visits and treatments, which could prevent cases from being updated appropriately. Travel distance to the treatment facility was included as a model covariate to try to adjust for this effect.

Proton beam therapy and SBRT are also relatively new technologies compared to IMRT, so they are associated with shorter follow-up times. Both PBT and SBRT require highly trained radiation oncologists, physicists, and therapists for treatment delivery, potentially limiting access to these treatments in the early years of the study. As a result, the referral and request rates of physicians and patients, respectively, for PBT or SBRT treatment were likely low toward the beginning of the study period, resulting in small sample sizes and potentially introducing sources of selection bias that contribute to the short follow-up times observed (median: 6.4 years). This is a major limitation of the NCDB and this analysis, contributing to the need for future studies with longer follow-up times to assess whether these trends hold.

For these reasons, the least-biased comparisons of SPC risk by treatment modality likely occur in the subgroup traveling short distances for treatment with long follow-up times, since the influence of related confounders such as the patient ability to travel, ease of access, and insufficient follow-up time is reduced. Therefore, we performed a subgroup analysis among patients with 10+ years of follow-up and travel distances < 12.5 miles. Although this subgroup analysis cannot fully account for the limitations discussed above, it helps to provide a more accurate picture of relative SPC incidence. It also supports the results of the full-population analysis, since SBRT and PBT were associated with a reduced chance of SPC compared to IMRT in this subgroup, and the estimated probabilities were similar in magnitude to those estimated using the whole population (Tables 3 and S1). The power of this analysis was limited by the small number of individuals treated with PBT and traveling short distances with long follow-up times, but the direction of SPC risk relative to IMRT was the same, which validates our primary analysis.

Another major limitation of the NCDB is that comprehensive details related to SPC, such as the date of secondary primary malignancies, type/location of SPC, and attribution to RT, are not recorded in the database. This meant that cases with SPC occurrence at sites distant from RT could not be excluded, reported SPCs could not be verified as true secondary malignancies associated with RT, and time-to-event analyses could not be performed. These drawbacks are highlighted in the editorial by Blanchard et al[37] in response to Dee et al,[17] and they apply to our analysis as well. However, for our primary analysis, we deemed it reasonable to assume that the incidence of SPC unrelated to RT is the same across cohorts based on previous literature.[5,7,9,38]

We performed another subgroup analysis among patients without comorbid conditions to try to account for these limitations. Patients without comorbidities are expected to be at lower risk of developing a new primary malignancy and, therefore, are more likely to have SPC attributable to RT treatment. Just as in the previous subgroup analysis, SBRT and PBT were associated with a reduced likelihood of SPC compared to IMRT and the relative risk estimates were similar to those obtained using the entire study population (Tables 3 and S1).

Despite the limitations associated with the retrospective design and NCDB, the large sample size, real-world setting, well-rounded analytic strategy, and consistent findings within our primary and subgroup analyses make this study worthy of further validation using other data sources (eg, Surveillance, Epidemiology, and End Results, Veterans Affairs database, clinical trials, or large provincial registries of single-payer health care systems).

Conclusion

In this large hospital-based data set of US men with PCa who received definitive RT, the probability of SPC occurrence was lower among patients receiving PBT and SBRT compared to IMRT. Further studies, including matured results of ongoing prospective clinical trials, will help to elucidate the true benefits of these advanced technologies and provide more definitive evidence about the relationship between radiation exposure and SPC development across treatment modalities.

Data Availability Statement

National Cancer Database 2019 Participant User File for prostate cancer is available and can be requested through the link here: https://www.facs.org/quality-programs/cancer-programs/national-cancer-database/puf/.

Author Contributions

Sarah Kulkarni: Conceptualization, Writing- Original draft, Formal analysis, Methodology, Software, Visualization. Sagar Patel: Conceptualization, Methodology, Writing- Original draft, Writing-Review and Editing. Yuxian Sun: Conceptualization, Formal analysis, Software. Ashesh Jani, Theresa Gillespie, Mark McDonald: Writing-Review and Editing. Yuan Liu: Conceptualization, Formal analysis, Funding acquisition, Methodology, Writing- original draft, Writing-Review and Editing, Software.

Declaration of Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding and Support

The research reported in this publication was supported in part by the Biostatistics Shared Resource of Winship Cancer Institute of Emory University and NIH/NCI under award number P30CA138292. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The data used in the study are derived from a deidentified National Cancer Database file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed or the conclusions drawn from these data by the investigator.

Supplementary material

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ijpt.2024.100627.

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