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Racial Differences in the Risk of Second Primary Bladder Cancer Following Radiation Therapy among Localized Prostate Cancer Patients

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Abstract

Objectives: To investigate the race-specific second primary bladder cancer (SPBC) risk following prostatic irradiation.

Methods: Louisiana residents who were diagnosed with localized prostate cancer (PCa) in 1996–2013 and received surgery or radiation were included. Patients were followed until SPBC diagnosis, death, or Dec. 2018. The exposure variable was type of treatment (radiation only

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AUTHOR CONTRIBUTION STATEMENT

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vs. surgery only). The outcome was time from PCa diagnosis to SPBC diagnosis, stratified by race. Fine and Gray's competing risk model was applied with death as a competing event and adjustment of sociodemographic and tumor characteristics. We used 5 years and 10 years as lag time in the analyses.

Results: A total of 26,277 PCa patients with a median follow-up of 10.7 years were analyzed, including 18,598 white and 7,679 black patients. About 42.9% of whites and 45.7% of blacks received radiation. SPBC counted for 1.84% in the radiation group and 0.90% in the surgery group among white patients and for 0.91% and 0.58%, respectively, among black patients. The adjusted subdistribution hazard ratio of SPBC was 1.80 (95% CI: 1.30–2.48) for radiation recipients compared to surgery recipients among white patients; 1.93 (95% CI: 1.36–2.74) if restricted to external beam radiation therapy (EBRT). The SPBC risk was not significantly different between irradiated and surgically treated among blacks.

Conclusions: The SPBC risk is almost two-fold among white irradiated PCa patients compared to their counterparts treated surgically. Our findings highlight the need for enhanced surveillance for white PCa survivors receiving radiotherapy, especially those received EBRT.

Keywords

prostate cancer; radiation therapy; second primary bladder cancer; racial difference

INTRODUCTION

Prostate cancer is the most commonly diagnosed noncutaneous malignancy among males in the United States (U.S.) [1]. Every man in the U.S. has an average lifetime risk of developing prostate cancer of 11% (about 1 in every 9 men) [1]. Due to the improvement in screening and clinical therapies, the survival of prostate cancer has improved greatly since 1993 [1, 2]. Between 2009 and 2015, about 78% of prostate cancer patients were diagnosed with localized disease, in which the 5-year survival rate is greater than 99% [1]. There are more than 3 million prostate cancer survivors in the U.S. [2, 3].

Current guidelines recommend radical prostatectomy or radiation therapy to treat localized prostate cancer [4]. Many prostate cancer patients choose radiation therapy instead of surgery due to the higher risk of adverse side effects associated with surgery, such as erectile dysfunction and urinary incontinence [5, 6], which can have a significant influence on the patient's quality of life [7]. Radiation therapy is associated with lower risk of these side effects [7]. However, second primary cancer is a potential long-term consequence of radiation therapy [8–13], which becomes particularly relevant given the increased life expectancy of prostate cancer survivors. There is a growing body of research examining the association between radiation therapy and second primary cancer [11, 13–16]. Second primary bladder cancer (SPBC), which occurs within radiation field, has been associated with increased incidence among irradiated prostate cancer patients [13, 17–21].

Despite the evidence of increased SPBC risk associated with radiation therapy, very few studies characterized patient subpopulations who are more sensitive to the radiation-induced SPBC risk. Such characterization has the promise to support precision medicine, specifically

on treatment decisions and post-treatment surveillance. It has been well documented that non-Hispanic white males [22, 23], especially at an older age, have a much higher bladder cancer incidence rate than other racial groups. Previous research discovered 12 genetic loci linked to primary bladder cancer in the white population, but less evidence was presented for the black population [24–31]. Genetic predisposition could interact with radiation exposure to increase the SPBC risk among prostate cancer survivors. It is unknown whether radiation-induced SPBC risk varies across different racial groups of prostate cancer patients. This study aimed to investigate race-specific SPBC risk following prostate irradiation.

MATERIALS AND METHODS

Study Population

Eligibility criteria of the study population included 1) Louisiana residents diagnosed with microscopically confirmed localized prostate cancer between 1996 and 2013; 2) race as white or black; 3) prostate cancer as the first primary cancer; 4) having surgery only or radiation only therapy as a first-course treatment; and 5) having at least 5 years follow-up. Prostate cancer was defined with International Classification of Diseases for Oncology, Third Edition (ICD-O-3) site code C619 and morphology codes 8000–8576, 8940–8950, or 8980–8981. The localized stage was defined based on Surveillance, Epidemiology, and End Results (SEER) summary stage [32]. Patients treated with both surgery and radiation in their first course treatment were excluded. All patients were followed until the end of 2018. Data were collected by the Louisiana Tumor Registry, one of the SEER registries.

Since there is no clearly defined latency period of secondary bladder cancer, we followed previous studies using 5 years as lag time in the main analysis, and 10 years in the sensitivity analyses (patients whose interval between prostate cancer diagnosis and SPBC diagnosis or death was shorter than 5 years and 10 years were excluded, respectively) [11, 33, 34] (Supplemental Figure 1).

Variables

The exposure variable is the type of treatment (surgery only vs. radiation therapy only). Surgery included prostatectomy, transurethral resection of the prostate, and local tumor destruction. Any form of radiation therapy and specific type of radiation therapy (external beam radiation therapy [EBRT] vs. non-EBRT) were analyzed. The outcome variable was time from prostate cancer diagnosis to SPBC diagnosis. Death during follow-up was considered a competing event. Patients were censored on December 31, 2018, if they did not develop SPBC or die during follow-up. All the analyses were stratified by race (white vs. black).

Covariates included age at diagnosis (<50, 50–59, 60–69, 70–79, 80+), marital status (married or living with a partner, single or separated or widowed or divorced, unknown), insurance type (uninsured, insured [by private insurance or Medicare], any Medicaid, insured but unknown specifics, unknown) [35], census tract population under the federal poverty level (<20%, ≥20%), tumor size (T1, T2), and grade (well differentiated, moderately

differentiated, poorly or undifferentiated, unknown). Tumor size T1 and T2 were defined based on the American Joint Committee on Cancer (AJCC) staging.

Statistical Analysis

Categorical variables were compared with Chi-square test. In the survival analysis, the event was the diagnosis of SPBC. Patients who did not have SPBC diagnosis could die during the follow-up or remain alive at the end of the follow-up. Cox proportional hazard model treats the patients who did not have event occurrence as censoring, with an assumption that every censored subject has the equal chance of developing event at the time censored (assumption of independence). However, patients who died during the follow-up had no chance to develop SPBC, which was a competing event of SPBC. The assumption of independence may not be satisfied for these patients. In our study, as the study population was the prostate cancer patients with average age greater than 60, the percentage of death (competing event) during the follow-up was high (30.26%). Cox proportional hazard model could result in inaccurate estimates of the survival rates. Thus, we applied Fine and Gray's competing risk model [36] to compare the SPBC risk between surgically treated patients and irradiated patients with death as a competing event. With the presence of a competing event, Fine and Gray's model keeps participants who developed the competing event within the risk set and assigns a lower weight to these participants. This method can effectively avoid overestimating the risk of SPBC. To control potential confounding from patient's sociodemographic status, multivariable models adjusted for patient's age at diagnosis, marital status, insurance, and census tract poverty level. Final models also adjusted for prostate cancer characteristics at diagnosis (tumor size and grade). Proportional hazard assumptions were tested by the Schoenfeld residuals, where the P-value of the correlation coefficient of the Schoenfeld residual and survival time greater than 0.05 indicates the proportional hazard assumption met.

In addition to the multivariable analyses, we conducted propensity score analysis as a secondary analysis. In each racial group, we calculated propensity score as the probability of receiving radiation therapy for each participant based on the same covariates used in multivariable analyses (age at diagnosis, marital status, insurance, census tract poverty level, tumor size and grade), using logistic regression with logit function [37]. With 0.25 times standard deviation as caliper for one-to-one matching, we selected surgery treated patients and radiation treated patients with equal propensity score [37]. We conducted competing risk analysis in the matched sample.

Furthermore, subdistribution cumulative incidence function (CIF) was plotted, which showed and compared the cumulative incidence of SPBC among study groups while controlling the competing effect from death.

RESULTS

A total of 26,277 prostate cancer patients with a median follow-up of 10.7 years were analyzed in this study, including 18,598 white and 7,679 black patients (Table 1). With 541 patients who remained alive and whose date of last contact was prior to the end of the study, the completeness of follow-up was 97.04%. About 56% of patients received

surgery. Surgically treated patients were younger, more likely to be married or living with a partner, have private insurance or Medicare coverage, live in census tracts with <20% of the population under federal poverty level, and have a T2 tumor or well to moderately differentiated tumor than radiation treated patients ($P < 0.0001$ for each). The average age at prostate cancer diagnosis for surgery recipients and radiation recipients was 62.16 years and 69.07 years among white patients ($P < 0.0001$), and 60.62 years and 65.55 years among black patients ($P < 0.0001$). Black patients were more likely to be uninsured or covered by any Medicaid than white patients. More than 70% of white patients and less than 40% of black patients lived in census tracts with <20% of the population under federal poverty level. The frequency of using EBRT among all irradiated patients was 74% in white patients and 80% in black patients. The proportion of SPBC was higher in radiation recipients than surgery recipients among white patients (1.84% vs. 0.90%, $P < 0.0001$) and black patients (0.91% vs. 0.58%, $P = 0.09$). The proportion of all-cause death was also higher among patients receiving radiation than those receiving surgery (45.07% vs. 25.68% among white patients, $P < 0.0001$; and 38.01% and 26.01% among black patients, $P < 0.0001$).

From the crude model, the subdistribution hazard ratio (sHR) of developing SPBC associated with radiation compared to surgery was highly significant in white patients but marginally significant in black patients (white: sHR: 2.07, 95% confidence interval [CI]: 1.60–2.67, $P < 0.0001$; black: sHR: 1.65, 95% CI: 0.97–2.79, $P = 0.06$) (Table 2). After controlling sociodemographic factors (age at diagnosis, marital status, insurance, and census tract poverty level), the sHR remained significant in white patients (sHR: 1.72, $P = 0.0003$), but not significant in black patients (sHR: 1.48, $P = 0.16$). With additional adjustment for tumor characteristics (tumor size and grade), the sHR increased to 1.80 and remained significant (95% CI: 1.30–2.48, $P = 0.0004$) for white patients and became insignificant for black patients (sHR: 1.15, 95% CI: 0.61–2.17, $P = 0.68$). The proportional hazard assumptions were met in every model. From the secondary analysis with propensity score matching, the sHR remained similar for black patients but decreased slightly for white patients. The significance of the associations remained same in the primary and secondary analyses. The CIF confirmed the higher risk of SPBC associated with radiation in both white and black patients (Figure 1).

The results remained similar when using 10 years lag time (Table 3). Among white patients, the adjusted sHR of developing SPBC was 1.91 (95% CI: 1.12–3.23, $P = 0.02$) with 10 years lag time. Both the crude and adjusted sHRs were not significant for black patients with 10 years lag time.

Table 4 shows the risk of SPBC by specific radiation type. Compared to surgically treated white patients, EBRT white patients had 1.93 times (95% CI: 1.36–2.74, $P = 0.0002$) and non-EBRT white patients had 1.33 times (95% CI: 0.84–2.12, $P = 0.23$) the hazard of SPBC, after adjusting for all the confounders. Among black patients, the adjusted sHR was 1.18 (95% CI: 0.60–2.31, $P = 0.23$) for EBRT patients and 1.21 (95% CI: 0.35–4.22, $P = 0.77$) for non-EBRT patients. CIF curves showed that EBRT patients had the highest SPBC risk and surgically treated patients had the lowest risk for white patients (Figure 2).

DISCUSSION

In this population-based retrospective cohort study, about 1% of localized prostate cancer survivors developed SPBC during a median follow-up of 10.7 years. The SPBC risk was higher among radiation recipients, especially EBRT treated patients than surgically treated patients. However, after stratifying by race, radiation-induced SPBC risk was significant only among white patients. Using 5 years and 10 years lag time yielded similar results.

Our results are in agreement with findings from previous research in two aspects. First, despite the fact that there was controversy regarding whether prostatic irradiation increases SPBC incidence [8–10, 13, 15, 19, 34, 38–48], the two most recent meta-analyses confirmed the radiation-induced SPBC risk [17, 18], which is consistent with our findings. In particular, similar to our results, both meta-analyses reported that EBRT is the radiotherapy type associated with significantly higher risk of SPBC [17, 18]. Second, in our study, the crude incidence rate of SPBC among prostate cancer survivors was low: 0.81% in the surgery group and 1.56% in the radiation group. This is in accordance with the range of 0.1% to 3.8% reported in previous research [9, 10, 34, 42], and is consistent with the rates from a study with a similar follow-up period [10]. However, as several studies demonstrated that the SPBC risk increases with an increased latency period [9, 38, 49], using different lag time in our study yielded similar estimates in the SPBC risk (adjusted sHR 1.80 and 1.91 when using 5 years and 10 years lag time, respectively).

To our knowledge, only one previous study reported the race-specific SPBC risk among prostate cancer survivors [11]. Davis et al. analyzed SEER data between 1992 and 2010 to compare the bladder cancer incidence among prostate cancer patients with it in the general population and reported the standardized incidence ratio (SIR) of SPBC was 1.04 (95% CI: 1.02–1.07) in white and 1.29 (95% CI: 1.17–1.41) in black [11]. They concluded that black prostate cancer survivors need to be more cautious about the SPBC than white patients, conflicting with our findings which showed that the impact of radiation on SPBC is stronger among white patients. The differences in the findings and conclusions between Davis' study and our study can be explained by the differences in comparator groups and statistical methods. Davis' study aimed to evaluate the second primary cancer burden among prostate cancer patients. Therefore, they compared the observed number of SPBC cases among all prostate cancer survivors (including patients receiving any type of treatment) with the expected number of bladder cancer cases in the general population. In contrast, we aimed to evaluate the effect of radiotherapy on SPBC and used competing risk analysis comparing the hazard of developing SPBC among irradiated patients and surgically treated patients. The potential limitation of using the general population as a comparison group is the diagnostic bias, where cancer survivors tend to receive more screening, potentially increasing the likelihood of detecting second primary cancers than among the general population [14, 17]. Our study used surgically treated patients as a comparison group, who should experience the same degree of post-treatment follow-up and cancer screening as irradiated patients, diminishing the diagnostic bias. Despite differences, both studies have clinical implications. As Davis' study emphasized the secondary cancer screening among all prostate cancer survivors, our study provided more evidence in individualized prostate cancer treatment.

A possible explanation of the higher SPBC risk among white prostate cancer survivors is the potential gene-environment interaction. White males have almost doubled the bladder cancer incidence rate in the general population compared to black males (40.58 vs. 20.78 per 100,000 person-years) in the U.S. [23]. Multiple chromosomal loci have been associated with increased risk for primary bladder cancer in the white population, but not in the black population [24–31]. Radiation is a well-established exogeneous carcinogen, which can increase the secondary cancer risk among cancer survivors [50]. Thus, the interaction between multiple susceptibility genes and exposure to radiation has the potential to increase the SPBC risk among white prostate cancer patients. A study by Chao and colleagues described the Caucasian race as a risk factor for second malignancy in adolescent and young adult cancer survivors [51]. Our patient cohort was not within this age demographic but suggested a potential genetic predisposition in whites. In addition, smoking could even further complicate the interaction. Smoking is a risk factor of bladder cancer. Previous research proposed the higher smoking rate as a possible contributing factor of higher bladder cancer incidence in white males than in black males [23]. As the smoking status was not available in our data, whether smoking plays different roles in bladder cancer occurrence among white and black radiation treated patients is unknown. Future studies need to collect data on smoking and control its confounding effect.

In the past two decades, intensive work has been done to explore the radiation-induced second cancer risk. For prostatic irradiation, bladder cancer is the most consistently reported subsequent malignancy type, followed by colorectal cancer [17]. However, as the majority of previous research examined the risk for the entire prostate cancer patient population, limited effort has been paid to identify the patient subgroups at higher SPBC risk, which can provide useful information to therapeutic decision making for individual patients. Our study can be the starting point in this field as the results indicate that white prostate cancer patients are at significantly higher risk of SPBC if treated with radiation than those treated surgically. Future studies should be designed to evaluate the patient subgroups defined by smoking, comorbidity, and genetic susceptibility. Smoking is the largest lifestyle risk factor for bladder cancer, which was estimated to account for 50% of bladder cancer cases [52]. Comorbidity is an important factor influencing patient's treatment decisions and second cancer risk. Urinary tract infections and viral infections have also been identified as risk factors for bladder cancer [53]. Genetic susceptibility is the unparalleled evidence for personalized treatment, where people with *N-acetyltransferase (NAT1* and *NAT2*) and *GSTM-1* null genotypes have been associated with increased susceptibility to bladder cancer [54]. Future research is needed to determine whether there is an interaction on SPBC risk between radiation therapy and smoking, medical condition, or genetic predisposition.

Our study has two strengths. Unlike most previous studies using data before 2010 [11, 19, 21], our data were from a more contemporary period, which can capture the effect of more recently popular types of radiotherapy. In addition, the use of advanced competing risk statistical model can take competing events such as death into account, which is particularly relevant for the investigation among prostate cancer patients who are usually at an older age. In spite of these strengths, it is worth noting that our study also has several limitations. First, the SEER registries collect only the first course cancer treatment, but not the second course or other following cancer treatment. In this study, patients receiving radiation therapy as the

second course prostate cancer treatment or as the treatment for other secondary cancers could be misclassified as surgery only patients. However, the number of misclassified patients should be small, as the majority of the localized prostate cancer patients have a good prognosis, and therefore do not need secondary treatment. It is important to note that only radiation recipients could be misclassified as surgery only patients, but no surgery only patients were misclassified as radiation recipients, and the direction of this misclassification could only dilute the true association. In other words, if radiation therapy is associated with increased SPBC risk, the true impact should be stronger than the association observed in this study. Secondly, we were not able to specifically evaluate the effect from the radiation dosage. The radiation dosage varies from 36.25 Gy at 7.25 Gy per fraction to 72 Gy to 80 Gy at 2 Gy per fraction for EBRT and from 115 Gy to 145 Gy for brachytherapy [4]. One previous study restricted EBRT treated patients to those receiving at least 60 Gy [13]. We did not apply this restriction due to the lack of data on radiation dosage. The more advanced techniques of EBRT, such as three-dimensional conformal radiotherapy, intensity modulated radiotherapy, and volumetric modulated radiotherapy, deliver the radiation with higher precision and reduce the radiation dosage to normal tissue, which could lower the SPBC risk. The few studies examining the effect of new radiation techniques are limited with small sample size and shorter follow-up duration [45, 55, 56]. Future studies are warranted to quantify the SPBC risk associated with the radiation dosage and the more advanced radiation therapy techniques. Thirdly, patient's smoking status, urinary tract infections, and viral infections are important risk factors for bladder cancer, but we lack the information on these variables. No previous data showed the degree to which smoking and infections influence patient's treatment selection, but further research is needed to examine the potential confounding effect of these risk factors. The fourth limitation was the relatively short follow-up time. As the SPBC is a long-term side effect of radiotherapy, longer follow-up time is needed to confirm the findings. Lastly, the study population was from a single state, which could limit the generalizability of the findings. Future studies using national patient population are needed to confirm the findings from this study.

CONCLUSIONS

This is the first study examining the race-specific radiation-induced SPBC risk among prostate cancer patients. With data from Louisiana, a southern state with high proportion of black population, we found the SPBC risk is almost two-fold among white prostate cancer patients treated with radiation therapy compared to their counterparts treated surgically. No significant association between radiation and SPBC was detected among black prostate cancer patients. As the secondary cancer screening remains important and necessary for all prostate cancer survivors, our findings highlight the additional cautions that white males need to take when they choose a prostate cancer treatment, and the need for enhanced urologist surveillance if they choose radiation therapy, especially EBRT. As this is the first study with data from a single state, more studies with nationally representative sample are needed to confirm the findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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LIST OF ABBREVIATION

US	United States
SPBC	second primary bladder cancer
ICD-O-3	International Classification of Diseases for Oncology, Third Edition
SEER	Surveillance, Epidemiology, and End Results
EBRT	external beam radiation therapy
AJCC	American Joint Committee on Cancer
CIF	Cumulative incidence function
sHR	subdistribution hazard ratio
SIR	standardized incidence ratio

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HIGHLIGHTS

- With a median follow-up of 10.7 years, second primary bladder cancer (SPBC) occurs in about 0.8% of surgically treated and 1.6% of radiation treated localized prostate cancer patients.
- The SPBC risk is almost two-fold among white prostate cancer patients treated with radiation therapy compared to their counterparts treated surgically.
- There is no significant association between radiation and SPBC among black prostate cancer patients.
- White males need to take additional cautions when they choose a prostate cancer treatment, and need enhanced urologist surveillance if they choose radiation therapy, especially external beam radiation therapy.

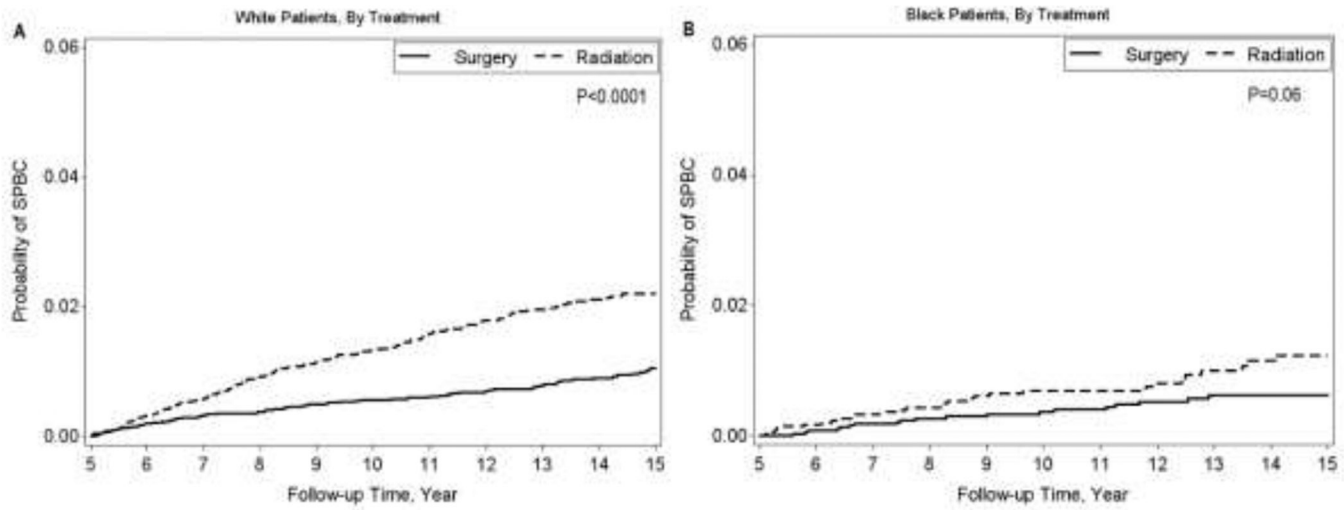

Figure 1.

Cumulative incidence function of second primary bladder cancer by treatment (radiation vs. surgery) among localized prostate cancer patients, stratified by race.

Abbreviation: SPBC: second primary bladder cancer

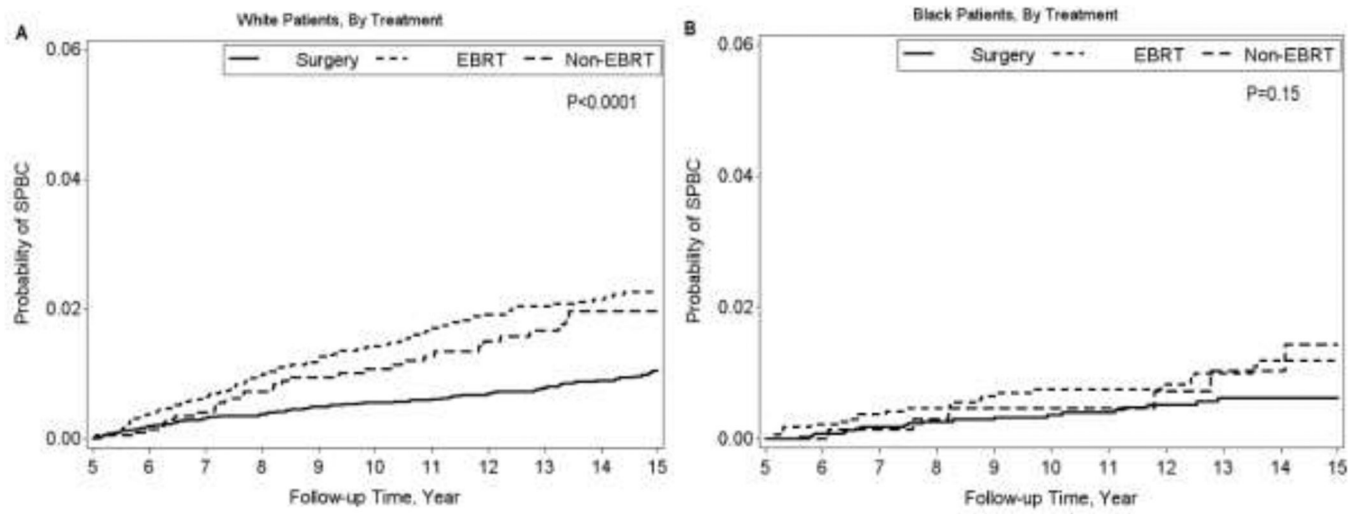

Figure 2.

Cumulative incidence function of second primary bladder cancer by treatment (external beam radiation therapy vs. other radiation therapy vs. surgery) among localized prostate cancer patients, stratified by race.

Abbreviation: SPBC: second primary bladder cancer; EBRT: external beam radiation therapy

Table 1.

Characteristics of localized prostate cancer patients diagnosed in Louisiana between 1996 and 2013.

Variables	All (N=26,277)			White (N=18,598)			Black (N=7,679)		
	Surgery n=14,791 (56.29%)	Radiation n=11,486 (43.71%)	P-value	Surgery n=10,624 (57.12%)	Radiation n=7,974 (42.88%)	P-value	Surgery n=4,167 (54.26%)	Radiation n=3,512 (45.74%)	P-value
Age group, years, %			<0.0001			<0.0001			<0.0001
<50	5.76	0.92		4.82	0.44		8.16	2.02	
50–59	33.52	12.42		31.80	9.47		37.92	19.13	
60–69	45.72	40.75		47.64	38.31		40.84	46.27	
70–79	13.18	41.91		13.86	46.89		11.45	30.61	
80+	1.82	4.00		1.89	4.89		1.63	1.96	
Age at diagnosis, mean (SD)	61.73 (7.95)	67.99 (7.39)	<0.0001	62.16 (7.81)	69.07 (7.02)	<0.0001	60.62 (8.18)	65.55 (7.63)	<0.0001
Marital status, %			<0.0001			<0.0001			<0.0001
Married or living with a partner	76.89	71.00		80.86	75.63		66.76	60.48	
Single, separated, widowed, or divorced	18.76	22.76		14.59	18.05		29.40	33.46	
Unknown	4.35	6.24		4.55	6.32		3.84	6.06	
Insurance type, %			<0.0001			0.0004			0.007
Uninsured	2.49	1.74		1.45	0.88		5.14	3.70	
Insured	53.13	52.01		54.11	53.16		50.61	49.40	
Any Medicaid	2.83	3.47		1.51	1.88		6.22	7.09	
Insured, No specifics	30.80	32.39		31.35	32.83		29.37	31.38	
Unknown	10.76	10.39		11.58	11.25		8.66	8.43	
Census tract population poverty <20%, %	65.86	61.76	<0.0001	76.20	74.09	0.001	39.50	33.77	<0.0001
Tumor size of T2, %	90.95	38.23	<0.0001	90.97	40.47	<0.0001	90.88	33.14	<0.0001
Grade, %			<0.0001			<0.0001			<0.0001
Well differentiated	4.09	2.72		4.17	2.87		3.89	2.36	
Moderate differentiated	55.06	54.10		56.83	55.51		50.54	50.91	
Poorly and undifferentiated	39.16	41.04		37.19	39.52		41.18	44.50	
Unknown	1.69	2.14		1.81	2.11		1.39	2.22	
Type of radiation, %									

Variables	All (N=26,277)			White (N=18,598)			Black (N=7,679)		
	Surgery n=14,791 (56.29%)	**Radiation n=11,486 (43.71%)**	**P-value**	**Surgery n=10,624 (57.12%)**	**Radiation n=7,974 (42.88%)**	**P-value**	**Surgery n=4,167 (54.26%)**	**Radiation n=3,512 (45.74%)**	**P-value**
EBRT	-	75.31	-	-	73.80	-	-	80.02	-
Non-EBRT	-	23.86	-	-	25.40	-	-	19.16	-
Unknown	-	0.84	-	-	0.80	-	-	0.83	-
SPBC, %	0.81	1.56	<0.0001	0.90	1.84	<0.0001	0.58	0.91	0.09
All-cause Death	25.77	42.91	<0.0001	25.68	45.07	<0.0001	26.01	38.01	<0.0001

Abbreviation: SD: standard deviation; EBRT: external beam radiation therapy; SPBC: second primary bladder cancer.

Table 2.

Subdistribution hazard ratio[a] of developing second primary bladder cancer for localized prostate cancer patients receiving radiation compared to those receiving surgery, stratified by race.

	White				Black			
	sHR	**95% CI**		**P-value**	**sHR**	**95% CI**		**P-value**
Crude model	2.07	1.60	2.67	<0.0001	1.65	0.97	2.79	0.06
Adjusted model 1[b]	1.72	1.28	2.30	0.0003	1.48	0.86	2.55	0.16
Adjusted model 2[c]	1.80	1.30	2.48	0.0004	1.15	0.61	2.17	0.68
Propensity score analysis[d]	1.48	1.03	2.12	0.03	1.19	0.49	2.87	0.70

Abbreviations: sHR: subdistribution hazard ratio; CI: confidence interval.

[a] Subdistribution hazard ratios were calculated from competing risk survival model with death during follow-up as a competing event.

[b] Adjusted for age at diagnosis, marital status, insurance, and census tract poverty level.

[c] Adjusted for all covariates in adjusted model 1, plus tumor size and grade.

[d] Propensity score was calculated as the probability of receiving radiation therapy for each participant based on age at diagnosis, marital status, insurance, census tract poverty level, tumor size and grade.

Table 3.

Subdistribution hazard ratio[a] of developing second primary bladder cancer for localized prostate cancer patients receiving radiation therapy compared to those receiving surgery, using 10 years lag time, stratified by race.

	White				Black			
	sHR	**95% CI**		**P-value**	**sHR**	**95% CI**		**P-value**
Crude model	1.62	1.08	2.43	0.02	1.21	0.52	2.80	0.65
Adjusted model 1[b]	1.65	1.03	2.64	0.03	1.51	0.70	3.28	0.30
Adjusted model 2[c]	1.91	1.12	3.23	0.02	1.41	0.62	3.22	0.41

Abbreviations: sHR: subdistribution hazard ratio; CI: confidence interval.

[a]Subdistribution hazard ratios were calculated from competing risk survival model with death during follow-up as a competing event.

[b]Adjusted for age at diagnosis, marital status, insurance, and census tract poverty level.

[c]Adjusted for all covariates in adjusted model 1, plus tumor size and grade.

Table 4.

Subdistribution hazard ratio[a] of developing second primary bladder cancer for localized prostate cancer patients receiving external beam radiation therapy and non-external beam radiation therapy, compared to those receiving surgery, stratified by race.

Model	Treatment type[b]	White				Black			
		sHR	95% CI		P-value	sHR	95% CI		P-value
Crude model	EBRT	2.12	1.62	2.79	<0.0001	1.70	0.98	2.97	0.06
	non-EBRT	1.88	1.28	2.78	0.002	1.48	0.61	3.62	0.39
Adjusted model 1[c]	EBRT	1.80	1.30	2.48	0.0004	1.53	0.85	2.74	0.16
	non-EBRT	1.42	0.94	2.15	0.10	1.51	0.59	3.84	0.39
Adjusted model 2[d]	EBRT	1.93	1.36	2.74	0.0002	1.18	0.60	2.31	0.63
	non-EBRT	1.33	0.84	2.12	0.23	1.21	0.35	4.22	0.77

Abbreviations: sHR: subdistribution hazard ratio; CI: confidence interval; EBRT: external beam radiation therapy.

[a] Subdistribution hazard ratios were calculated from competing risk survival model with death during follow-up as a competing event.

[b] Surgery was the comparison group.

[c] Adjusted for age at diagnosis, marital status, insurance, and census tract poverty level.

[d] Adjusted for all covariates in adjusted model 1, plus tumor size and grade.