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ORIGINAL ARTICLE

Impact of prostate cancer radiotherapy on the biological behavior and specific mortality of subsequent bladder cancer

Xiaoxiao Guo[1,3] · Min Liu[1] · Huimin Hou[1] · Shenjie Liu[1] · Xianbo Zhang[2] · Yaqun Zhang[1] · Pengjie Wu[1] · Cheng Pang[1] · Jianye Wang[1]

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Abstract

Background The impact of different radiotherapy modalities on the development and characteristics of second primary bladder cancers (BCa) and BCa-specific mortality (BCa-SM) remains unclear. Thus, we evaluated the incidence and biological behavior of subsequent BCa and related survival in patients who underwent radiation therapy for prostate cancer (PCa).

Methods A total of 530,581 patients in the surveillance, epidemiology, and end results database with localized PCa between 1988 and 2013 were identified. PCa treatments included radical prostatectomy (RP), external beam radiotherapy (EBRT), radioactive implants (RI), and combined EBRT and RI (EBRI). A multivariable competing risk analysis based on a proportional sub distribution hazards model was used to determine the impact of different radiotherapy modalities on BCa incidence and specific mortality.

Results Incidence of BCa was significantly high in patients treated with EBRT, RI, and EBRI vs. RP [sub distribution hazard ratio (SHR) 1.41, $P<0.001$; SHR 1.58, $P<0.001$; SHR 1.56, $P<0.001$, respectively]. BCa following EBRT, RI, and EBRI were more commonly non-urothelial (3.3%, 2.9%, 3.3%, respectively, versus 1.2%) and T4 (3.5%, 6.1%, 5.0%, respectively, versus 1.6%) compared with RP. RI associated with a higher rate of BCa metastasis than RP (2.6% vs. 1.1%). Prior EBRT, RI, and EBRI increased BCa-SM (SHR 1.44, $P=0.001$; SHR 1.21, $P=0.047$; and SHR 1.42, $P=0.032$, respectively).

Conclusions Patients receiving radiotherapy for PCa have a higher risk of BCa. BCa after EBRT, RI, and EBRI is more likely to be non-urothelial, stage T4, and with increased BCa-SM. Prior RI associated with a higher rate of BCa metastasis.

Keywords Prostate cancer · Bladder cancer · Radiotherapy · Cancer-specific survival

Introduction

Bladder cancer (BCa) is the seventh most common cancer in men and is the most common malignancy arising from the urinary tract [1]. Risk factors for BCa include inherited genetic predispositions and external exposures. Inherited genetic factors, such as variants of the slow acetylator *N*-acetyltransferase 2 and glutathione *S*-transferase mu 1 null genotype, have been confirmed as risk factors for BCa. Smoking is recognized as the most important external risk factor for BCa [2]. Ionizing radiation is also a possible external risk factor [3, 4].

The phenomenon of radiation-induced carcinogenesis has been known since the 1800s, and this has been widely reported in the literature for decades. Preston et al. reported that survivors of the Hiroshima and Nagasaki atomic bombing are predisposed to developing radiosensitive solid tumors, such as those of the breast, colon, thyroid, lung, and urinary bladder [5]. The association between malignancy and radiation exposure has also been identified in Chernobyl nuclear accident survivors [6]. The underlying biological mechanisms of radiation-induced BCa are complex. Radiation can lead to aberrant mutations in p53 or $p27^{kip1}$ [4, 7], leading to up-regulated ubiquitination and sumoylation [7], which could contribute to urothelial carcinogenesis. The micro environmental changes induced by chronic long-term, low-dose radiation also appear to promote angiogenesis and

✉ Jianye Wang
wangjy@bjhmoh.cn

1 Department of Urology, National Center of Gerontology, Beijing Hospital, No. 1 DaHua Road, Dong Dan, Beijing 100730, People's Republic of China

2 Department of Endocrinology, National Center of Gerontology, Beijing Hospital, Beijing, China

3 Peking Union Medical College, Beijing, China

remodeling of the extracellular matrix that could facilitate invasion as well as progression of pre-existing initiated cells to malignancy [8].

According to current guidelines, radiotherapy (RT) is the standard treatment for localized PCa [9, 10], particularly in patients with clinically localized prostate cancer (PCa). As long-term survival after these treatments has increased, concerns over late sequelae have intensified. One area of particular interest is the risk of second primary malignancies. The effect of radiotherapy on the development of second primary BCa has been partially investigated [11, 12], and the impact of prior RT on stage, histology, and location of subsequent BCa is still uncertain. Further, data on the association between previously administered RT modalities and BCa-specific survival are scarce.

Therefore, the primary objective of this study was to investigate the impact of PCa treatments on the risk of developing second primary BCa; secondary objectives included identification of characteristics and cancer-specific survival from subsequent BCa. These parameters were then compared with that of those developing BCa after RP alone. These results may help identify those who are at increased risk of subsequent BCa, and may predict risks of BCa among patients receiving RT for prostate cancer.

Patients and methods

Study population

The study relied on the surveillance, epidemiology, and end results (SEER) program database. SEER is a population-based cancer registry that encompasses approximately 26% of the population of the United States, and has 98% completeness in ascertaining cases. Patients diagnosed with histologically confirmed localized PCa [International Classification of Diseases for Oncology (ICD-O) site code 61.9, histological code 8140] between 1988 and 2013, and aged between 40 and 85 years, were identified. Following PCa treatment, patients were followed up until 2015 to assess incidence of second primary tumors. Only patients with non-regional and non-metastatic (N0, M0) PCa at diagnosis were considered. Patients of unknown race, incomplete clinicopathologic and/or therapeutic method data, and with other malignancies were excluded.

Variable definition

The individuals in this cohort received PCa treatment with external beam radiotherapy alone (EBRT), radioactive implant alone (RI), combined external beam radiotherapy and radioactive implant (EBRI), and radical prostatectomy alone (RP). The time to development of secondary BCa (latent period) was calculated by subtracting the total BCa follow-up duration from the PCa follow-up duration. Previous studies had an exclusion period (2 months–5 years) from diagnosis to secondary cancer to minimize the effect of diagnostic bias. We used an exclusion latent period of 3 years for the BCa-SM analyses. For analyses of BCa incidence and BCa-SM, ages were considered to be the ages at diagnosis of PCa and BCa, respectively. Patients were divided into three groups according to age (< 65 years, 65–74 years, and ≥ 75 years) and were designated as lymph node-positive or -negative according to lymph node status. The metastasis status was considered a dichotomous variable (metastasis-positive or -negative).

Statistical analyses

Demographic and clinical characteristics were summarized using descriptive statistics. The associations between PCa treatment and the risk of BCa incidence or BCa-SM were evaluated using a competing risk regression model with the Fine and Gray's test [13]. For BCa incidence analysis, the data of patients without subsequent BCa were treated as censored data; BCa and death without BCa were considered as two competing events. Multiple linear regression analysis was used to investigate the duration of the latent period from the PCa treatments. In the BCa-SM analysis, the data of surviving patients were treated as censored data. BCa-SM and other mortality (OM) were considered as two competing events. Multivariate competing risk analysis was based on proportional sub distribution hazard models. All analyses were performed using R version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org) with the R package "cmprsk." Variables were considered significant predictors if P values were < 0.05.

Results

Among the 530,581 individuals included in the PCa cohort, 297113 (56.0%), 143,679 (27.1%), 56,138 (10.6%), and 33,651 (6.3%) received RP, EBRT, RI, and EBRI, respectively. Patients who received EBRT, RI, and EBRI were older than those who underwent RP alone (70, 66, and 67 years, respectively vs. 63 years; $P < 0.001$). Patients treated with RP were mostly of clinical stages T3 and T4 (18.5% and 1.7%, respectively). The median follow-up period for patients who received RP, EBRT, RI, and EBRI were 86 [interquartile range (IQR) 44–139], 73 (IQR 38–116), 88 (IQR 54–123), and 89 (IQR 53–132) months, respectively. Finally, 3580 (1.2%), 2712 (1.9%), 1068 (1.9%), and 673 (2%) individuals in the RP, EBRT, RI, and EBRI groups, respectively, developed BCa. Table 1 summarizes the characteristics of the PCa cohort.

Table 1 Patient demographics and characteristics of prostate cancer

Variables	RP	EBRT	RI	EBRI	*P* value **EBRT/RI/EBRI vs. RP**
Total	297,113	143,679	56,138	33,651	
Race					< 0.001/< 0.001/< 0.001
Afro-American	248,237 (83.5%)	112,302 (77.9%)	47,041 (83.8%)	25,632 (76.2%)	
Caucasian	35,393 (11.9%)	22,955 (15.9%)	6832 (12.2%)	6484 (19.3%)	
Other	13,483 (4.5%)	8941 (6.2%)	2265 (4%)	1535 (4.6%)	
Age (years)					< 0.001/< 0.001/0.001
< 65	173,098 (58.3%)	37,063 (25.8%)	23,181 (41.3%)	13,229 (39.3%)	
65–74	102,780 (34.6%)	69,852 (48.6%)	25,156 (44.8%)	15,444 (45.9%)	
≥ 75	21,235 (7.1%)	36,764 (25.6%)	7801 (13.9%)	4978 (14.8%)	
Median (IQR)	63 (57–68)	70 (64–75)	66 (60–72)	67 (61–72)	
PCa clinical T stage					< 0.001/< 0.001/< 0.001
I	29,321 (9.9%)	73,644 (51.3%)	35,421 (61.3%)	16,876 (50.2%)	
II	165,404 (55.7%)	47,968 (33.4%)	15,617 (27%)	11,002 (32.7%)	
III	54,910 (18.5%)	5878 (4.1%)	355 (0.6%)	983 (2.9%)	
IV	5090 (1.7%)	650 (0.5%)	24 (0%)	49 (0.1%)	
NOS	42,388 (14.3%)	15,548 (10.8%)	6126 (10.9%)	4741 (14.1%)	
Year of PCa diagnosis					
1988–1992	21,594 (7.3%)	6879 (4.8%)	304 (0.5%)	326 (1%)	
1993–1997	31,927 (10.7%)	11,190 (7.8%)	1090 (1.9%)	1282 (3.8%)	
1998–2002	58,112 (19.6%)	28,417 (19.8%)	13,995 (24.9%)	10,671 (31.7%)	
2002–2006	83,158 (28%)	43,819 (30.5%)	23,846 (42.5%)	11,710 (34.8%)	
2007–2013	102,322 (34.4%)	53,374 (37.1%)	16,903 (30.1%)	9662 (28.7%)	
PCa follow-up (months)					
Median (IQR)	86 (44–139)	73 (38–116)	88 (54–123)	89 (53–132)	< 0.001/< 0.001/< 0.001
Total second primary BCa	3580 (1.2%)	2712 (1.9%)	1068 (1.9%)	673 (2%)	< 0.001/< 0.001/< 0.001

IQR interquartile range, *RP* radical prostatectomy, *EBRT* external beam radiotherapy, RI radioactive implant, *EBRI* external beam radiotherapy combined with radiotherapy implant, *PCa* prostate cancer, *BCa* bladder cancer, *NOS* localized prostate cancer without specific clinical T stage

Cumulative incidence of bladder cancer

Figure 1 shows the cumulative BCa incidence rate curves after stratification per primary PCa treatment. The 10-year BCa incidence rates were 1.28% (95% CI 1.25–1.31%), 2.25% (95% CI 2.19–2.30%), 2.31% (95% CI 2.22–2.39%), and 2.18% (95% CI 2.07–2.29%) for RP, EBRT, RI, and EBRI treatments, respectively. On the multivariable competing risk model (Table 2) adjustments were made for race, PCa stage, year of PCa treatment, and age at PCa treatment. Patients treated with EBRT, RI, and EBRI were more likely to develop subsequent BCa [sub distribution hazard ratio (SHR) 1.41, 95% CI (1.33–1.51] and $P < 0.001$, SHR 1.58, 95% CI (1.45–1.72) and $P < 0.001$, SHR 1.56, 95% CI (1.41–1.72) and $P < 0.001$, respectively). The multiple linear regression analysis (Table 3) suggested that EBRT was associated with a longer latent period than RP [$\beta = 4.85$, 95% CI (2.35–7.34), $P < 0.001$].

Characteristics of bladder cancers

As shown in Table 4, patients who underwent EBRT, RI, or EBRI were more likely to develop clinical stage T4 BCa compared to those who underwent RP (3.3%, 5.5%, 5.1%, respectively vs. 1.5%; $P = 0.002$, $P < 0.001$, $P < 0.001$, respectively). A significant increase in positive lymph nodes and metastasis was observed with RI compared to RP (4.3% vs. 1.5% and $P < 0.001$; 2.6% vs. 1.1% and $P = 0.006$, respectively). BCa developing after EBRT and EBRI were more likely to be non-urothelial (4.6%, 5.8%, respectively, vs. 2.7%, $P = 0.032$, $P = 0.010$, respectively). BCa in the dome and posterior wall was higher in the EBRT than the RP group (7.9 vs. 6.9%, 7.9 vs. 6.9%; $P = 0.377$), while BCa located at the neck was higher in the RI and EBRI groups compared with the RP group (7.8% and 7.5% vs. 5.7%, $P = 0.343$, $P = 0.752$, respectively).

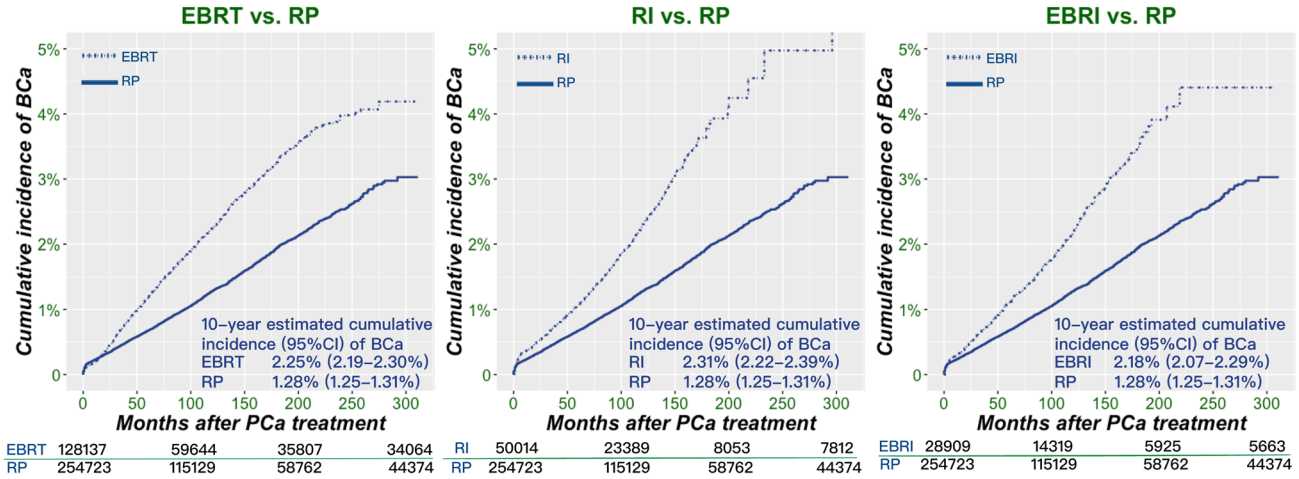

Fig. 1 Cumulative incidence curves to showing the probability of BCa incidence in the entire cohort, the 10-year cumulative incidences of BCa were presented. *BCa* bladder cancer, *CI* confidence interva, *RP* radical prostatectomy, *EBRT* external beam radiotherapy, *RI* radioactive implant, *EBRI* external beam radiotherapy combined with radiotherapy implant

Table 2 Multivariable competing risk regression analyses to predict the risk of developing bladder cancer

Variables	SHR	*P* value	95% CI	
			Lower	Upper
Race				
Caucasian	Ref.			
Afro-American	0.62	< 0.001	0.56	0.68
Other	0.57	< 0.001	0.50	0.66
Age				
< 65	Ref.			
65–74	1.84	< 0.001	1.73	1.95
≥ 75	2.13	< 0.001	1.97	2.30
PCa clinical T stage				
I	Ref.			
II	0.95	0.071	0.90	1.00
III	1.01	0.850	0.93	1.10
IV	1.12	0.280	0.92	1.37
Year of PCa treatment				
1988–1992	Ref.			
1993–1997	0.90	0.032	0.82	0.99
1998–2002	0.84	< 0.001	0.77	0.92
2002–2006	0.73	< 0.001	0.67	0.80
2007–2013	0.64	< 0.001	0.58	0.72
PCa treatment				
RP	Ref.			
EBRT	1.41	< 0.001	1.33	1.51
RI	1.58	< 0.001	1.45	1.72
EBRI	1.56	< 0.001	1.41	1.72

RP radical prostatectomy, *EBRT* external beam radiotherapy, *RI* radioactive implant, *EBRI* external beam radiotherapy combined with radiotherapy implant, *PCa* prostate cancer, *SHR* sub distribution hazard ratio, *CI* confidence interval

Table 3 Multiple linear regression analysis using latent period as the dependent variable

Variables	β	*P* value	95% CI	
			Lower	Upper
EBRT vs. no-RT				
Age at PCa diagnosis	−0.08	0.327	−0.25	0.08
PCa follow-up period	0.63	< 0.001	0.61	0.66
Year of PCa diagnosis	−0.15	0.248	−0.40	0.10
EBRT	4.85	< 0.001	2.35	7.34
RI vs. no-RT				
Age at PCa diagnosis	−0.02	0.833	−0.23	0.18
PCa follow-up period	0.63	< 0.001	0.60	0.66
Year of PCa diagnosis	−0.23	0.163	−0.56	0.09
RI	0.83	0.376	−1.01	2.68
EBRI vs. no-RT				
Age at PCa diagnosis	−0.01	0.943	−0.23	0.21
PCa follow-up period	0.63	< 0.001	0.60	0.66
Year of PCa diagnosis	−0.20	0.245	−0.53	0.14
EBRI	0.96	0.195	−0.49	2.40

RP radical prostatectomy, *EBRT* external beam radiotherapy, *RI* radioactive implant, EBRI external beam radiotherapy combined with radiotherapy implant, *PCa* prostate cancer, *CI* confidence interval, β regression coefficient

Bladder cancer-specific mortality

4766 records were included in the analysis of BCa-SM. The respective cumulative incidence function (CIF) curves according to RT modalities are displayed in Fig. 2. The 10-year cumulative incidences of death for BCa developing after RP, EBRT, RI, and EBRI, were 11.2% (95% CI 10.3–12.2%), 15.7% (95% CI

Table 4 Patient demographics and characteristics of bladder cancer

Variables	RP	EBRT	RI	EBRI	*P* value RP vs. EBRT/RI/EBRI
Total	2085	1617	656	408	
Age (years)					< 0.001/< 0.001/< 0.001
< 65	206 (9.9%)	49 (3%)	31 (4.7%)	24 (5.9%)	
65–74	790 (37.9%)	367 (22.7%)	228 (34.8%)	111 (27.2%)	
≥ 75	1089 (52.2%)	1201 (74.3%)	397 (60.5%)	273 (66.9%)	
Median (IQR)	75 (69–80)	79 (74–83)	77 (72–81)	78 (72–82)	
BCa T stage					0.002/< 0.001/< 0.001
a	1165 (55.9%)	899 (55.6%)	358 (54.6%)	202 (49.5%)	
Is	170 (8.2%)	157 (9.7%)	36 (5.5%)	42 (10.3%)	
I	434 (20.8%)	310 (19.2%)	144 (22%)	81 (19.9%)	
II	211 (10.1%)	156 (9.6%)	74 (11.3%)	49 (12%)	
III	74 (3.5%)	42 (2.6%)	8 (1.2%)	13 (3.2%)	
IV	31 (1.5%)	53 (3.3%)	36 (5.5%)	21 (5.1%)	
Lymph node invasion					0.661/< 0.001/0.209
No	2053 (98.5%)	1595 (98.6%)	628 (95.7%)	405 (99.3%)	
Yes	32 (1.5%)	22 (1.4%)	28 (4.3%)	3 (0.7%)	
Metastasis					0.478/0.006/0.153
No	2062 (98.9%)	1595 (98.6%)	639 (97.4%)	400 (98%)	
Yes	23 (1.1%)	22 (1.4%)	17 (2.6%)	8 (2%)	
Histology					0.032/0.142/0.010
Urothelial	2028 (97.3%)	1543 (95.4%)	631 (96.2%)	385 (94.4%)	
Total non-urothelial	57 (2.7%)	74 (4.6%)	25 (3.8%)	24 (5.8%)	
Squamous	11 (0.5%)	17 (1.1%)	3 (0.5%)	(2%)	
Adenocarcinoma	9 (0.4%)	9 (0.6%)	3 (0.5%)	(0.5%)	
Small cell carcinoma	6 (0.3%)	12 (0.7%)	7 (1.1%)	3 (0.7%)	
Other non-urothelial	31 (1.5%)	36 (2.2%)	12 (1.8%)	10 (2.5%)	
Tumor location					0.377/0.343/0.752
Trigone of bladder	143 (12.4%)	129 (13.1%)	42 (11.3%)	26 (11.5%)	
Dome of bladder	79 (6.9%)	78 (7.9%)	28 (7.5%)	17 (7.5%)	
Lateral wall of bladder	367 (31.9%)	314 (31.8%)	123 (33%)	76 (33.6%)	
Anterior wall of bladder	40 (3.5%)	41 (4.2%)	12 (3.2%)	12 (5.3%)	
Posterior wall of bladder	204 (17.7%)	189 (19.2%)	46 (12.3%)	36 (15.9%)	
Bladder neck	66 (5.7%)	54 (5.5%)	29 (7.8%)	17 (7.5%)	
Ureteric orifice	73 (6.3%)	60 (6.1%)	27 (7.2%)	10 (4.4%)	
Overlapping lesion of bladder	179 (15.5%)	118 (12%)	66 (17.7%)	32 (14.2%)	
Follow-up (months)					
Median (IQR)	37 (16–70)	28 (11–56)	26 (12–50)	29 (9–53)	

IQR interquartile range, *RP* radical prostatectomy, *EBRT* external beam radiotherapy, *RI* radioactive implant, *EBRI* external beam radiotherapy combined with radiotherapy implant, *BCa* bladder cancer

14.5–16.9%), 14.4% (95% CI 12.7–16.1%), and 17.0% (95% CI 14.5–19.5%), respectively. Multivariable analysis adjusted for age, BCa clinical stage, lymph node invasion, metastasis, and histology types showed that prior EBRT, RI, and EBRI were also independent predictors for BCa-SM [SHR 1.44 (95% CI 1.15–1.79), $P = 0.001$; SHR 1.21, (95% CI 1.01–1.64), $P = 0.047$; SHR 1.42 (95% CI 1.03–1.96), $P = 0.032$, respectively]. The results of multivariable competing risk regression analyses predicting BCa are shown in Table 5.

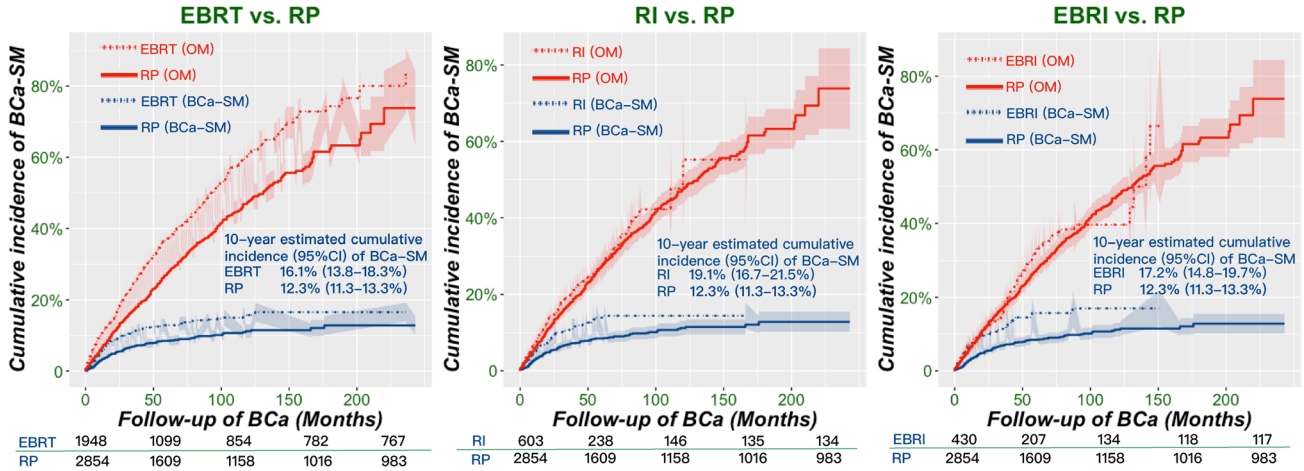

Fig. 2 Cumulative incidence curves of deaths to showing the probability of each competing event in the entire cohort, the 10-year cumulative incidences of BCa-SM were presented. The blue line represents cancer-specific mortality and red line represents competing mortality. *BCa* bladder cancer, *BCa-SM* bladder cancer-specific mortality, *OM* other mortality, *CI* confidence interva, *RP* radical prostatectomy, *EBRT* external beam radiotherapy, *RI* radioactive implant, *EBRI* external beam radiotherapy combined with radiotherapy implant

Table 5 Outcomes of the multivariate competing risk analysis for bladder cancer-specific mortality

Variables	SHR	*P* value	95% CI	
			Lower	Upper
Age (years)				
< 65	Ref.			
65–75	1.45	0.100	0.93	2.28
> 75	1.82	0.007	1.18	2.79
PCa treatment				
RP	Ref.			
EBRT	1.44	0.001	1.15	1.79
RI	1.21	0.047	1.01	1.64
EBRI	1.42	0.032	1.03	1.96
BCa T stage				
a	Ref.			
Is	2.47	< 0.001	1.61	3.79
I	4.18	< 0.001	3.09	5.64
II	11.84	< 0.001	8.86	15.83
III	17.34	< 0.001	11.93	25.2
IV	24.02	< 0.001	16.51	34.93
Positive lymph nodes				
(Yes vs. no)	1.19	0.470	0.74	1.91
Metastatic				
(Yes vs. no)	2.41	< 0.001	1.47	3.94
Non-urothelial				
(Yes vs. no)	1.38	0.044	1.01	1.87

SHR sub distribution hazard ratio, *CI* Confidence interval, *Ref* reference group, *RP* radical prostatectomy alone, *EBRT* external beam radiotherapy alone, *RI* radioactive implant alone, *EBRI* external beam radiotherapy combined with radiotherapy implant

Discussion

This study analyzed a large cohort from a population-based database to investigate the impact of different RT modalities used for treating PCa on second primary BCa. We found that treatments for PCa variably affected subsequent BCa incidence, tumor stage, lymph node invasion, metastasis, and histological types. The results also demonstrated that EBRT, RI, and EBRI were predictors of higher BCa-SM.

Our study focused on patients with clinically localized PCa. This selection criterion was chosen because these patients have a longer survival and are, therefore, at an increased risk for second primary tumors compared with primary non-localized PCa. We found that EBRT increased the 10-year risk of second primary BCa by 76%. This finding was in accordance with previous results [11, 14, 15]. In contrast with previous studies, this study considered the impact of various radiotherapy modalities on the risk of subsequent BCa and revealed a significant higher risk of BCa in patients who received RI. The present results suggest that PCa patients treated in recent years had a lower risk of second primary BCa than those treated earlier. This may partially be explained by the implementation of advanced radiotherapy technologies, which have the potential to reduce risks of second primary tumors by limiting the volumes of tissue exposed to high doses of radiation. This is in contrast to older techniques, where a large volume of tissue was exposed to high doses of radiation, with consequent risks of morbidities and second primary cancers [16, 17].

The median latent period in the RP group was 67 months, which was similar to that in the previous study (5.8 years) [11]. Multiple linear regression analysis suggested that EBRT was associated with a longer latent period than RP,

while RI and EBRI were not. In absolute terms, these differences of latent period between the groups were small. This represents a challenge to our conceptual understanding that the latency of radiation-induced BCa is usually up to 5 or more years, which added to the baseline latency would result in a longer latent period in the RT groups. However, in older individuals, radiation risks after exposure are more influenced by promotion of pre-existing premalignant cells instead of initiation processes [18]. This possibly accelerated the process of radiation-induced carcinogenesis, resulting in shorter than expected latent periods among patients who had received RT.

Our results showed that EBRT, RI, and EBRI were associated with a higher rate of T4 BCa. This was consistent with prior reports [19, 20], which evaluated patients who underwent radical cystectomy after irradiation for PCa. A plausible explanation for the preponderance of advanced stage is the delayed diagnosis of BCa. It is conceivable that gross or microscopic hematuria after prior radiation may have been erroneously attributed to a urinary tract infection or hemorrhagic cystitis. Time may have elapsed, resulting in disease progression. Additionally, patients in our cohort with a history of prior radiation demonstrated a higher rate of metastatic BCa than those who received RP alone. On the basis of biology, if pre-existing BCa receives radiation, the tumor metastasis might be influenced by four mechanisms as described by von Essen [21], namely, radiation-induced release of tumor cells into the circulation, effects at distant normal tissue sites that might host metastases, radiation-induced changes in surviving tumor cells, and local control-mediated prolonging of metastatic cell release. Dose accumulation over longer periods probably resulted in further higher rates of metastases in the RI and EBRI groups as compared to the EBRT group. The full decay periods of Iodine-125 and Palladium-103, which were most commonly used for RI were 10 and 3 months, respectively. These periods were much longer than the radiation exposure time for hypofractionated or conventionally fractionated radiotherapy. The relatively higher incidence of node-positive cases in the RI group was probably due to limited pelvic lymph node dissection in patients with a history of EBRT or RP. EBRT or RP induces pelvic tissue reactions and adhesion formation, which makes dissection more difficult, especially in the plane between the rectum and the bladder or prostate, increasing the difficulty of radical cystectomy and limiting pelvic lymph node dissection. Regrettably, we did not find a previous study that investigated the association between the implantation methods and BCa metastasis. Of course, the mechanism of causes for the higher rates of metastases after RI need further investigation.

In the current study, EBRT, RI, and EBRI were associated with a higher rate of non-urothelial carcinoma. Squamous cell carcinoma, adenocarcinoma, and small cell carcinoma make up a large proportion of non-urothelial carcinomas. In general, most published studies have shown a poor prognosis for non-urothelial carcinomas of the bladder [22–24]. Our results from multivariate analysis showed non-urothelial carcinoma to be an independent predictor of higher BCa-SM, and probably contributed to higher BCa-SM in the three RT groups.

EBRT offers potentially greater scatter radiation to the bladder, which is highly mobile structure, due to variations in organ filling which can shift its position relative to the prostate, thus probably resulting in the higher incidence of tumors located in the dome and posterior wall of the bladder. In contrast to the EBRT group, more tumors in the RI group were located in the bladder neck. This is most likely to be due to the smaller radiation radius of RI, producing lower impact in sites relatively distant from the prostate.

We demonstrated after competing risks analyses based on the proportional sub distribution hazards approach that BCa following EBRT, RI, or EBRI results in higher BCa-SM. This statistical method was chosen because the overall probabilities of BCa-SM are directly relevant to OM. If death due to other causes occurs before BCa-specific death, the incidence of the latter will be affected [25]. Yee and his colleagues reported there was statistical difference in cancer specific survival among non-irradiated and irradiated BCa patients. However, the small sample size provided insufficient statistical power to make accurate inferences [20]. Abern et al. used a competing risks model with PCa-SM as the competing event to compare the BCa-SM in patients following RP and any RT; they found that RT was associated with a higher BCa-SM [26]. In contrast with previous studies, these analyses were done based on RT treatment types to observe the precise effect of each of type on BCa outcomes. After we regarded OM as a competing event and adjusted for age and BCa characteristics, the association between EBRT, RI, and EBRI and higher BCa-SM, persisted. Potential mechanisms leading to higher BCa-SM after RT are as follows: (1) Increased incidence of stage IV tumors and/or non-urothelial carcinoma may result in poor BCa-SM in RT groups than in RP groups. (2) Response rates for intravesical BCG therapy may be impaired in those with prior RT. Patients with a history of RT who undergo radical cystectomy after failed BCG are more likely to be pathologically upstaged and have decreased recurrence-free survival [27, 28]. (3) The early complication rates in patients undergoing radical cystectomy after radiation therapy are higher than that of non-irradiated subjects [29, 30]. In our institution, we empirically found that the process of wound healing after transurethral resection of bladder tumors was slower in patients who received RT for PCa compared to those who did not receive RT; complications after radical cystectomy were more common in patients with history of RT.

This study has several advantages. Based on large-scale data from the SEER database and multivariate competing risk analysis, we clearly demonstrated that EBRT, RI, and EBRI for PCa do increase the risk of secondary primary BCa with higher BCa-SM. In addition, we analyzed the effect of prior RT on the latent period between PCa and BCa. This study is not devoid of limitations. Firstly, owing to the retrospective nature of the study, there might be a risk that the treatment administered was misclassified. Secondly, details on fractionation or prescribed dose of RT were lacking. Thirdly, information on confounders such as smoking and comorbidity status were unavailable in the SEER registry. To partially address this limitation, we excluded patients with other malignancies, and performed multivariable competing risk analyses. In conclusion, compared with patients treated with RP, patients treated with EBRT, RI, and EBRI have a significantly increased risk of developing second primary BCa within 10 years of RT for PCa. The discrepancy of latent period between the RP and RT groups was small. BCa following RT was more likely to be of stage IV. Furthermore, BCa following RI and EBRI are more likely to metastasized, and be located at the bladder neck, while BCa following EBRT is more likely to be located in the trigone and posterior wall. BCa after RT for PCa resulted in a worse BCa-specific survival. Proactive early detection and more aggressive management options are, therefore, necessary. However, results from observational studies should be viewed with caution. More intensive investigations are needed to determine the mechanisms by which RT affects the survival of second primary BCa.

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Compliance with ethical standards

Conflict of interest All authors have declared no conflict of interest.

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