Incidence and survival of secondary malignancies after external beam radiotherapy for prostate cancer in the Surveillance, Epidemiology, and End Results database

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ABSTRACT

Introduction: The study objective was to investigate the incidence of secondary bladder (BCa) and rectal cancers (RCa) after external beam radiotherapy (EBRT) for prostate cancer (PCa) compared to radical prostatectomy (RP) alone, and to compare cancer-specific survival of these secondary neoplasms to their primary counterparts.

Methods: This retrospective cohort study included men in the Surveillance, Epidemiology, and End Results cancer registry with a diagnosis of non-metastatic, clinically node-negative PCa treated with either RP or EBRT from 1995–2011 and allowed a minimum five-year lag period for the development of secondary BCa or RCa. Patients were divided into two eras, 1995–2002 and 2003–2011, to examine differences in incidence of secondary malignancies over time. Univariable and multivariable competing risk analyses with Fine-Gray subdistribution hazard and cause-specific hazard models were used to examine the risk of developing a secondary

BCa or RCa. Competing risks analyses were used to compare cancer-specific survival of primary vs. secondary BCa and RCa.

Results: A total of 198 184 men underwent RP and 190 536 underwent EBRT for PCa. The cumulative incidence of secondary BCa at 10 years was 1.71% for RP, and 3.7% for EBRT ($p<0.001$), while that of RCa was 0.52% for RP and 0.99% for EBRT ($p<0.001$). EBRT was associated with approximately twice the risk of developing a secondary BCa and RCa compared to RP. The hazard of secondary BCa following EBRT delivered during 2003–2011 was 20% less than from 1995–2002 ($p<0.09$, Fine-Gray model), while that of secondary RCa was 31% less ($p<0.001$) (hazard ratio 0.78, $p<0.001$) for Fine-Gray and cause-specific hazard models. In the Fine-Gray model, the risk of death from BCa was 27% lower for secondary BCa after RP compared to primary BCa, while the risk of death was 9% lower for secondary BCa after EBRT compared to primary BCa. There was no difference in RCa-specific survival between primary or secondary RCa after RP or EBRT.

Conclusions: The risk of BCa and RCa is approximately twice as high for men undergoing EBRT for localized PCa compared to RP, but that risk is declining, likely reflecting advancements in radiation delivery. The development of secondary RCa or BCa does not confer an elevated risk of death compared to their primary counterparts.

INTRODUCTION

One in eight men will be diagnosed with prostate cancer (PCa) in his lifetime.[1] The two main options for definitively treating clinically significant localized PCa are surgery and radiotherapy (RT). RT is thought to potentially increase the risk of developing a secondary malignancy and may negatively impact future local surgical procedures due to impaired tissue healing.[2] However, there remain inconsistencies in the literature regarding the strength of this association.[3,4,5] The risk of secondary malignancy has been reported to range from 0.1% to 6%,[6,7] with at least a 5 year lag from the time of radiation exposure to radiation-induced malignancy.[5]

There have been significant advances in radiation delivery over the last few decades. In the 1990s, three-dimensional conformal radiotherapy (3D-CRT), which uses images from computed tomography (CT) for planning, evolved from two-dimensional conformal radiotherapy (2D-CRT), which used X-rays; however, high doses of radiation were still delivered to the bladder and rectum with 3D-CRT[8]. Since then, technological advances have improved conformality of RT. Introduction of intensity-modulated radiotherapy (IMRT) became more widespread in the 2000s and has emerged as the standard of care, as it permits higher doses of radiation to be delivered to using multiple beams of radiation of varying intensities, while limiting toxicity to adjacent organs[8]. Image-guided radiotherapy (IGRT) and fiducial markers

have also improved radiation delivery by accounting for variations in position of the prostate gland and correcting these accordingly at the time of each treatment[9].

We investigate the incidence of secondary BCa and RCa in patients undergoing EBRT compared to patients undergoing RP alone. We aim to identify trends in the incidence of these secondary malignancies, given that technological advances have allowed more precise delivery of radiation to prevent unwanted effects on adjacent tissues. Moreover, we compare the cancer specific survival of these secondary neoplasms to patients who underwent RP alone and to patients with primary BCa and RCa.

METHODS

Patient population

Data was extracted from the Surveillance, Epidemiology, and End Results (SEER) cancer registry. To determine the incidence of secondary BCa and RCa, we included men with a diagnosis of non-metastatic, clinically node-negative PCa who were treated with either RP or EBRT from 1995-2011. Patients who received adjuvant RT were included in the EBRT group. This time period was chosen to allow a 5-year lag period after completion of RT for development of a secondary malignancy. Patients who received brachytherapy, developed secondary malignancies less than 5 years after treatment, or with follow up time less than 5 years were excluded from the analysis. RT patients were grouped into 2 eras, 1995-2002 and 2003-2011, to determine if there was any difference in the incidence of secondary malignancies over time, considering advancements in technologies used to deliver radiation to the prostate.

To compare survival outcomes between secondary bladder and rectal malignancies with their primary counterparts, we included all cases of BCa and RCa between 2000 and 2016. We excluded females from the analysis given that all patients who developed secondary bladder and rectal malignancies after PCa in this study were male.

Statistical analysis

Descriptive statistics for baseline characteristics are reported as means and standard deviations for normally distributed continuous variables and were compared using Student's t-test. Medians and interquartile ranges (IQR) are reported for non-normally distributed continuous variables and were compared using the Wilcoxon sum rank test. Categorical variables are reported as counts and were compared using the chi square test.

Univariable and multivariable analyses using the Fine-Gray subdistribution hazard and cause-specific hazard models were performed to examine the risk of developing a secondary BCa or RCa in the EBRT group versus RP alone. To verify the proportional hazards assumption for the cause-specific hazard regression model, we examined Schoenfeld residuals and performed diagnostics on each covariate. Schoenfeld residual p-values were not interpreted, as the test was considered overpowered in this large sample size. The correlation coefficient was <0.2, indicating that the hazards are likely to be proportional. Furthermore, the log(-log(St))

survival function demonstrated that survival curves were parallel and equidistant from one another, therefore the assumption of proportional hazards holds in this instance.

To compare cancer-specific survival of primary vs. secondary BCa and RCa, competing risk analyses using the Fine-Gray subdistribution hazards and cause-specific hazards methods were also performed. The proportional hazard assumption was also verified for the covariates.

The primary comparisons for which statistical significance was assessed were: adjusted incidence of secondary RCa or BCa after EBRT vs RP, adjusted incidence of RCa or BCa before 2002 vs after 2003, and adjusted survival of secondary vs primary RCa or BCa stratified by PCa treatment. $P< 0.05$ was considered statistically significant for these analyses. No additional adjustment to control experiment-wise error was performed.

All statistical analyses were performed with SAS 9.4 (Cary, NC).

RESULTS

Incidence of secondary bladder and rectal malignancies after definitive treatment for prostate cancer

198,184 patients underwent RP, and 190,536 men underwent RT for PCa. Baseline patient characteristics are reported in Table 1. The mean age of RP patients was 60.7 years, and that of the RT patients was 68.3 years. When the RT patients are further divided into the pre- and post-IMRT time periods, the mean ages were 68.6 and 67.8 years respectively ($p<0.001$, data not shown). 1335 patients in the EBRT group and 713 patients in the RP group developed RCa, whereas 4841 patients in the EBRT group and 2270 patients in the RP group developed BCa. The 10-year cumulative incidence of secondary BCa was 1.71% for RP and 3.7% for EBRT ($p<0.001$) (Figure 1), while that of RCa was 0.52% for RP and 0.99% for EBRT ($p<0.001$) (Figure 2).

In the univariable analysis (Supplementary Table 1), development of a secondary BCa was associated with RT in both the Fine-Gray subdistribution and cause-specific hazard models. The development of a secondary RCa was associated with RT, older age, and earlier year of PCa diagnosis. In the multivariable analysis (Table 2), after controlling for age, race, year of diagnosis, and marital status, RT was associated with a HR of 2.12 of developing a secondary BCa (95% CI 1.98, 2.28) compared to RP in the Fine-Gray model and a HR of 2.53 (95% CI 2.36, 2.71) in the cause-specific hazard model.

Patients receiving RT for PCa had 1.94 times the risk of developing a secondary RCa compared to those receiving a RP in the multivariable Fine-Gray model (HR 1.94, 95% CI 1.69, 2.24). The cause-specific hazard multivariable model found that the HR of a secondary RCa was 2.24 (95% CI 1.96, 2.56) for RT compared to RP. Earlier year of diagnosis was also associated with increased risk of secondary RCa in both models, whereas older age was found to be a significant predictor in the cause-specific hazard model (HR 1.005, 95% CI 1.002, 1.008).

Incidence of secondary bladder and rectal malignancies after definitive treatment for prostate cancer over time

Table 3 summarizes the results of the multivariable competing risk analyses with the RT group divided into 2 eras (1995-2002 and 2003-2011). Patients who underwent RP were 57% (HR 0.43, 95% CI 0.40-0.46) and 62% (HR 0.38, 95% CI 0.36-0.41) less likely to develop a secondary BCa compared to those who received RT prior to 2003 in the Fine-Gray model and cause-specific hazard model respectively. Meanwhile, patients who underwent RT after 2003 had a 20% decrease in the risk of secondary BCa in the Fine-Gray model (HR 0.80, 95% CI 0.74-0.87). The decrease was not statistically significant in the cause-specific hazard model.

With regards to RCa, in the Fine-Gray model, men who had surgery had a hazard of 0.43 (95% CI 0.37-0.50) of developing a secondary cancer compared to men who received RT prior to 2003. In the cause-specific hazard model, this hazard was 0.40 (95% CI 0.34-0.45). Both models demonstrated a statistically significant decrease in risk of secondary RCa in patients who underwent RT after 2003 (HR 0.69, 95% CI 0.58-0.82 in the Fine-Gray model; HR 0.78, 95% CI 0.66, 0.94 in the cause-specific hazard model).

Comparison of cancer-specific survival between primary and secondary bladder cancer

Baseline demographic and clinical characteristics of patients with primary BCa are shown in Supplementary Table 2. The median follow-up times for patients with primary BCa, BCa after RP, and secondary BCa after RT for PCa were 45 months (range 0-203 months), 52 months (range 0-198 months) and 40 months (0-202 months) respectively. The cumulative incidence function for death from BCa is depicted in Figure 3.

In the univariable analysis, BCa developing after both surgery and RT for PCa had more favourable survival profiles compared to their primary counterparts (Supplementary Table 4). More advanced age, Black race, unmarried men, earlier year of diagnosis, and more advanced cancer stage were associated with decreased BCa-specific survival. In the multivariable cause-specific hazards model, there was a 31% reduction in risk in the hazard of death from BCa after RP compared to primary BCa (HR 0.69, 95% CI 0.60-0.81) (Table 4). Survival from secondary BCa after RT did not differ from primary BCa in this model (HR 0.97, 95% CI 0.89-1.06).

Using the Fine-Gray model for estimating subdistribution hazard ratios for BCa death in the competing risks analysis, there was a 27% reduction in risk in the cumulative incidence function for death (HR 0.73, 95% CI 0.63-0.85) for BCa after RP and a 9% reduction in risk for BCa after RT (HR 0.91, 95% CI 0.83-0.999; p=0.048) after adjusting for covariates.

Comparison of cancer-specific survival between primary and secondary rectal cancer

Baseline demographic and clinical characteristics of patients with RCa are shown in Supplementary Table 3. The median follow-up time for patients with primary RCa was 41 months (range 0-203), RCa after RP was 52 months (range 0-198), and secondary RCa after RT

for PCa was 40 months (range 0-202). The cumulative incidence function for death from RCa is depicted in Figure 4.

When comparing primary RCa to those that develop in patients who undergo surgery and RT for PCa, univariable analyses demonstrated better survival for RCa developing after RP (HR 0.66, 95% CI 0.52-0.84) in the Fine-Gray subdistribution hazard model and in the cause-specific hazard model (HR 0.62, 95% CI 0.49-0.79) (Supplementary Table 4). Those treated with RT had an increased risk of death (HR 1.22, 95% CI 1.06-1.41) in the cause-specific hazard model, but this was not statistically significant in the Fine-Gray subdistribution hazard model (HR 1.08, 95% CI 0.94-1.25). More advanced age, black race, unmarried men, earlier year of diagnosis, and more advanced cancer stage were associated with decreased RCa-specific survival.

After adjusting for covariates in the multivariable analysis, those who developed RCa after RP had a 28% risk reduction in hazard of RCa death in the cause-specific hazards model (HR 0.72 95% CI 0.55, 0.93), but there was no difference in the RT group compared to primary RCa (Table 4). Furthermore, there was no statistically significant difference in survival between secondary and primary RCa using the multivariable Fine-Gray subdistribution hazard model.

DISCUSSION

RT and RP are considered acceptable options for the definitive treatment of localized PCa in men who have at least a 10-year life expectancy[10]. The risk of secondary malignancy after RT is generally quite low, ranging from 0.1% to 6% in the literature.[1,6,7] However, given the fact that the 10-year relative survival of men with localized PCa is 98-100%,[11,12] the long-term consequences of treatment should be considered, especially noting that RT may complicate future management of pelvic cancer through increased surgical complexity or inability to treat with further radiation. However, RP may also present challenges in terms of surgical management of subsequent pelvic malignancies.

We found that the risk of secondary BCa and RCa after undergoing EBRT for PCa is roughly twice the risk of those who undergo RP. However, those who do develop a secondary malignancy do not have a higher risk of death. Patients with secondary BCa had a lower risk of bladder-cancer specific death compared to those who have a primary BCa, while patients who develop a secondary RCa have a similar risk of death from RCa in comparison to those with primary RCa. This suggests that post-radiation secondary pelvic cancers may not necessarily be more aggressive than their primary counterparts, and prior RT does not substantially limit the efficacy of future cancer care. However, this hypothesis would need to be confirmed with pathologic information.

In this contemporary cohort of patients, the risk of secondary malignancy decreased with time. IMRT was introduced in the mid-1990's to early 2000's. A major advantage is its ability to distribute the dose of radiation to conform to the target organ while reducing the radiation dose delivered to adjacent organs, thereby reducing some of the morbidity associated with radiation exposure to these areas.[13] Originally, there were concerns that IMRT might be associated with a

higher risk of secondary malignancies due to its longer beam-on time and higher integral-dose.[6,14] A recent retrospective study, however, did not find any increased risk of secondary solid or hematologic cancers associated with IMRT compared to 3D-CRT, particularly for PCa diagnoses occurring in later calendar years.[15] We found that the risk of secondary BCa decreased by 20%, while that of secondary RCa decreased by 22-31% in patients who had RT for PCa after 2003, potentially reflecting a benefit of reduced radiation exposure to the rectum and bladder with IMRT. The use of IGRT, using fiducial markers or other techniques, may also account for improved outcomes. Zelefsky *et al*. compared outcomes in PCa patients receiving 86.4 Gy with or without IGRT.[16] At a median follow-up of 2.8 years, grade ≥2 urinary toxicity rates were 10.4% with IGRT compared to 20% without IGRT (p=0.02). However, no significant differences were seen in gastrointestinal toxicity between the two groups. They also reported improvement in PSA relapse-free survival outcomes in high-risk patients at 3 years (97% vs. 77.7%; p=0.05). Several other studies have attempted to quantify the risk of secondary malignancies after radiation for PCa. de Gonzalez *et al*. conducted a SEER study examining the incidence of secondary solid cancers after RT in 15 different cancer sites and found that relative risk of developing a secondary cancer after RT for PCa was 1.26 (95% CI 1.21, 1.30).[5] Another SEER study estimated the risk of developing a secondary malignancy associated with radiation for PCa was 1 in 290.[7] Brenner *et al*. found that this risk increases to 1 in 125 for patients surviving > 5 years and 1 in 70 for those who survive > 10 years. However, the mean year of treatment of the RT group was 1987, therefore the results may not be applicable to more contemporary methods of radiation delivery.

The differences in survival that may exist between secondary BCa and RCa and their primary counterparts have not been widely studied. With regards to secondary RCa specifically, Rombouts *et al*. reported a Fine-Gray subdistribution hazard of 1.89 (95% CI: 1.66–2.16) in a cohort of patients from the population-based Netherlands Cancer Registry who received radiation to the prostate from 1989 to 2007.[17] Yang *et al*. examined the prognosis of RCa that develop after pelvic radiation and found that the survival was worse than patients with primary RCa after propensity score matching patients by age at diagnosis, race, stage, chemotherapy, RT and surgery (HR for death 1.33, 95% CI 1.14, 1.55).[18] However, in our study, after adjusting for covariates in the multivariable model, no difference in survival was observed for secondary RCa after RT compared to primary RCa in either the Fine-Gray subdistribution hazard or cause-specific hazard models. When comparing primary RCa to those that develop in patients who undergo surgery or RT for PCa, patients who underwent surgery had the best disease-free survival. However, those in the surgery group are also more likely to be younger and healthier, therefore there is a selection bias that could account for them performing better than patients who develop primary RCa in the general population. Our results indicate that the cancer-specific survival of BCa after having undergone RP or EBRT is better than that of primary BCa. This may be due to ongoing monitoring for recurrence of their PCa. Hematuria would likely be

investigated sooner with cystoscopy if they already have an established relationship with a urologist, allowing for earlier identification of bladder tumors.

There are several limitations to our study. Firstly, this is a retrospective cohort study with unmeasured confounders and possible selection bias given that patients who undergo RP are more likely to be healthy and younger. Ideally, randomization would be able to account for these inherent differences in the study population. Moreover, information regarding the exact type and dosage of RT was not available. Ideally, we would have been able to stratify by 3D conformal RT and IMRT, as well as adjust for the radiation dosage and field size. Dividing the RT group into 2 "eras" from 1995-2002 and 2003-2011 was done to account for the lack of stratification by type of RT delivered. With lack of radiation field size data, we focused on secondary RCa and BCa, given the vicinity of these organs to the prostate. While at least a 5-year lag time is generally accepted as the time required to attribute a secondary malignancy to RT, the development of a secondary malignancy is more likely to be observed over a longer time period. Unfortunately, we are limited by the data available and the timing of the introduction of IMRT. Moreover, given that biochemical recurrence can occur years after RP, there is possible inclusion of some salvage RT cases in the surgery group, as SEER captures RT as a treatment only if it is carried out within 12 months of the diagnosis. Additionally, we do not have information regarding the use of proton therapy, androgen deprivation therapy, or use of neoadjuvant or adjuvant chemotherapy or radiation in patients who had primary bladder and RCa, therefore it is unclear if that may be contributing to survival differences. Lastly, information regarding germline testing results were not available to identify patients who may be at higher risk for other neoplasms. Despite these limitations, this is the first known analysis to evaluate differences in survival outcomes between primary and secondary bladder and RCa after definitive therapy for PCa.

CONCLUSIONS

The risk of BCa & RCa is approximately twice as high for men undergoing EBRT for localized PCa compared to RP. Men who develop a secondary BCa have a lower risk of cancer-specific death than primary BCa. Patients who received RT in 2003-2011 had a lower risk of developing a secondary malignancy compared to those who underwent RT prior to 2003, likely reflecting advancements in technology for radiation delivery.

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FIGURES AND TABLES

Figure 1. Cumulative incidence function of secondary bladder cancer. RP: radical prostatectomy; RT: radiation therapy.

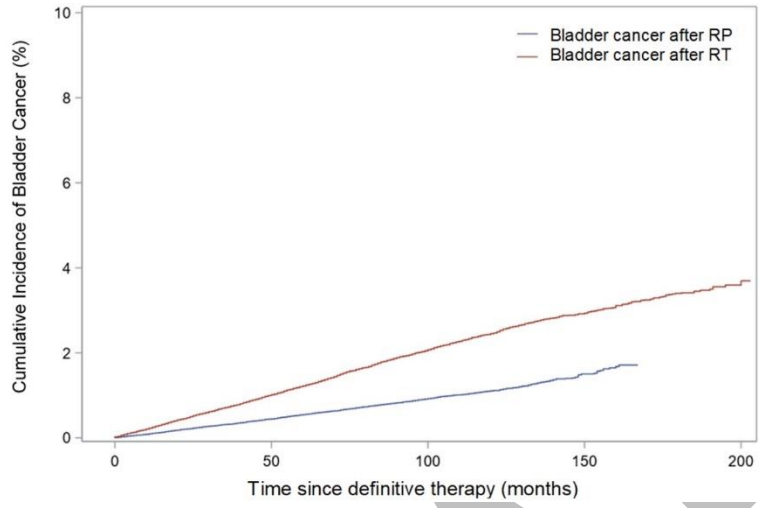

Figure 2. Cumulative incidence function of secondary rectal bladder. RP: radical prostatectomy; RT: radiation therapy.

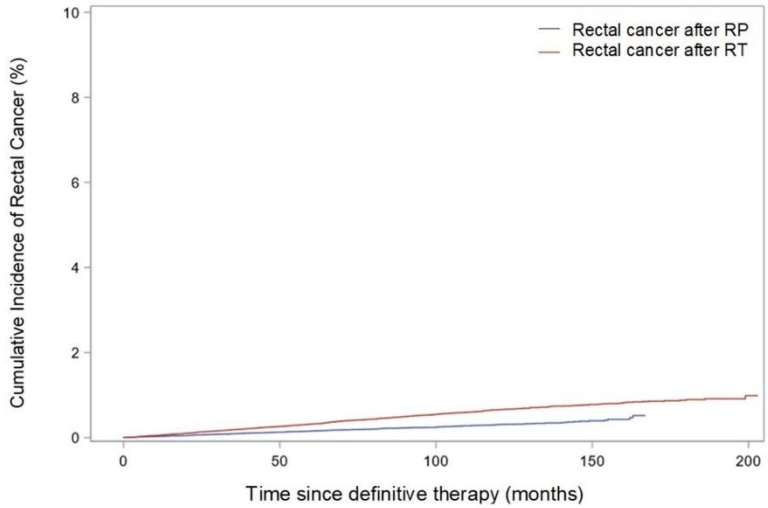

Figure 3. Cumulative incidence function of death from bladder cancer. RP: radical prostatectomy; RT: radiation therapy.

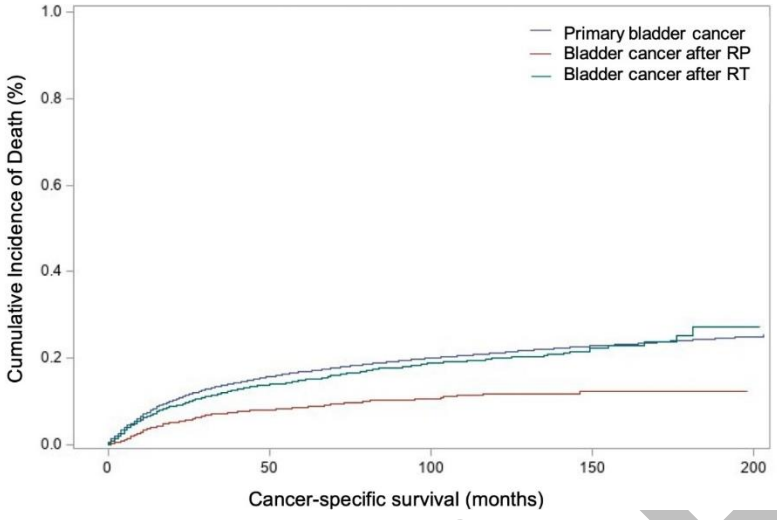

Figure 4. Cumulative incidence function of death from rectal cancer. RP: radical prostatectomy; RT: radiation therapy.

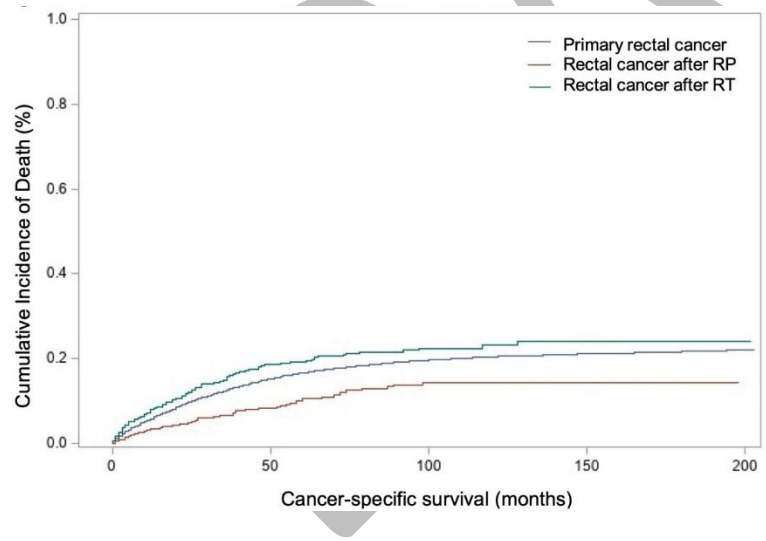

Table 1. Baseline clinical and demographic characteristics of prostate cancer patients treated with primary surgery or primary radiation		
	Primary surgery n=198 184	**Primary radiotherapy n=190 536**
Age (mean±SD)	60.7±8.3	68.3±13.0
Year of diagnosis (median)	2005	2004
Race (n, %)		
White	163 752 (83.2)	146 993 (77.9)
Black	24 229 (12.3)	30 689 (16.3)
Other	8736 (4.4)	11 044 (5.8)
Marital status		
Married	154 860 (82.1)	134 372 (76.3)
Not married	33 852 (17.9)	41 685 (23.7)
Prostate cancer clinical tumor (T) stage		
0	2 (0)	2 (0)
1	670 (0.4)	28 982 (18.0)
2	128 386 (79.2)	119 299 (74.2)
3	32 968 (20.4)	12 477 (7.8)

SD: standard deviation.

Table 2. Multivariable analysis using Fine-Gray subdistribution hazard and cause-specific hazard model for development of secondary bladder and rectal cancer after primary treatment for prostate cancer				
	Fine-Gray subdistribution hazard ratio (95% CI)	**p**	**Cause-specific hazard ratio (95% CI)**	**p**
Secondary bladder cancer				
Treatment (reference group: surgery)				
Radiation	2.12 (1.98, 2.28)	<0.001	2.53 (2.36, 2.71)	<0.001
Age (per 1 year increase)	1.006 (1.005, 1.008)	<0.001	1.006 (1.006, 1.007)	<0.001
Year of diagnosis (per 1 year increase)	0.97 (0.96, 9.98)	<0.001	0.99 (0.98, 1.00)	0.06
Race (reference group: White)				
Black	0.58 (0.52, 0.65)	<0.001	0.58 (0.51, 0.65)	<0.001
Other	0.56 (0.47, 0.67)	<0.001	0.55 (0.46, 0.66)	<0.001
Marital status (reference group: married)				
Unmarried	0.88 (0.81, 0.96)	0.004	0.93 (0.85, 1.01)	0.08
Secondary rectal cancer				
Treatment (reference group: surgery)				
Radiation	1.94 (1.69, 2.24)	<0.001	2.24 (1.96, 2.56)	<0.001
Age (per 1 year increase)	1.002 (0.997, 1.007)	0.38	1.005 (1.002, 1.008)	<0.001
Year of diagnosis (per 1 year increase)	0.94 (0.92, 0.96)	<0.001	0.96 (0.94, 0.97)	<0.001
Race (reference group: White)				
Black	1.07 (0.89, 1.28)	0.46	1.07 (0.90, 1.28)	0.44
Other	1.19 (0.93, 1.53)	0.17	1.17 (0.91, 1.50)	0.22
Marital status (reference group: married)				
Unmarried	0.92 (0.78, 1.08)	0.32	1.04 (0.88, 1.21)	0.66

CI: confidence interval.

Table 3. Multivariable analysis using Fine-Gray subdistribution hazard and cause-specific hazard models for development of secondary bladder and rectal cancer after primary treatment for prostate cancer with radiotherapy subgroups.				
	Hazard ratio using Fine-Gray subdistribution model (95% CI)	**p**	**Hazard ratio using cause-specific hazard model (95% CI)**	**p**
Secondary bladder cancer				
Treatment (reference group: pre-2003 radiation)				
Surgery	0.43 (0.40, 0.46)	<0.001	0.38 (0.36, 0.41)	<0.001
Post-2003 radiation	0.80 (0.74 0.87)	<0.001	0.92 (0.85. 1.01)	0.09
Age (per 1year increase)	1.006 (1.005, 1.008)	<0.001	1.007 (1.006, 1.007)	<0.001
Race (reference group: White)				
Black	0.58 (0.52, 0.65)	<0.001	0.58 (0.51, 0.65)	<0.001
Other	0.56 (0.47, 0.67)	<0.001	0.55 (0.46, 0.66)	<0.001
Marital status (reference group: married)				
Unmarried	0.88 (0.81, 0.96)	0.0035	0.93 (0.85, 1.01)	0.08
Secondary rectal cancer				
Treatment (reference group: pre-2003 radiation)				
Surgery	0.43 (0.37, 0.50)	<0.001	0.40 (0.34, 0.45)	<0.001
Post-2003 rZadiation	0.69 (0.58, 0.82)	<0.001	0.78 (0.66, 0.94)	0.007
Age (per 1 year increase)	1.002 (0.998, 1007)	0.30	1.005 (1.003, 1.008)	<0.001
Race (reference group: White)				
Black	1.07 (0.89, 1.28)	0.47	1.07 (0.90, 1.28)	0.45
Other	1.12 (0.93, 1.54)	0.15	1.18 (0.91, 1.50)	0.21
Marital status (reference group: married)				
Unmarried	0.92 (0.78, 1.08)	0.28	1.04 (0.89, 1.22)	0.64

CI: confidence interval.

Table 4. Multivariable analysis using Fine-Gray subdistribution hazard and cause-specific hazard models for bladder and rectal cancer-specific survival				
	Hazard ratio using Fine-Gray model (95% CI)	**p**	**Hazard ratio using cause-specific hazard model (95% CI)**	**p**
Bladder cancer-specific survival				
Primary vs. secondary bladder cancer (reference: primary bladder cancer)				
Secondary bladder cancer after surgery	0.73 (0.63, 0.85)	<0.001	0.69 (0.60, 0.81)	<0.001
Secondary bladder cancer after RT	0.91 (0.83, 0.999)	0.048	0.97 (0.89, 1.06)	0.52
Age (per 1 year increase)	1.024 (1.022, 1.025)	<0.001	1.041 (1.040, 1.042)	<0.001
Year of diagnosis (per 1 year increase)	0.98 (0.98, 0.99)	<0.001	0.996 (0.993, 0.998)	0.002
Race (reference group: White)				
Black	1.17 (1.11, 1.24)	<0.001	1.31 (1.25, 1.38)	<0.001
Other	0.89 (0.84, 0.95)	0.0004	0.86 (0.81, 0.91)	<0.001
Marital status (reference group: married)				
Unmarried	1.21 (1.18, 1.24)	<0.001	1.35 (1.31, 1.38)	<0.001
Bladder cancer stage (reference group: stage 0)				
1	2.83 (2.73, 2.94)	<0.001	2.97 (2.86, 3.08)	<0.001
2	8.38 (8.08, 8.69)	<0.001	10.1 (9.77, 10.5)	<0.001
3	10.7 (10.2, 11.2)	<0.001	13.2 (12.6, 13.8)	<0.001
4	25.0 (24.1, 26.0)	<0.001	40.7 (39.2, 42.3)	<0.001
Rectal cancer-specific survival				
Primary vs. secondary rectal cancer (reference: primary rectal cancer)				
Secondary rectal cancer after surgery	0.79 (0.61, 1.03)	0.08	0.72 (0.55, 0.93)	0.01
Secondary rectal cancer after RT	1.02 (0.86, 1.19)	0.86	1.06 (0.91, 1.24)	0.45
Age (per 1 year increase)	1.005 (1.004, 1.007)	<0.001	1.02 (1.018. 1.021)	<0.001
Year of diagnosis (per 1 year increase)	0.99 (0.98, 0.99)	<0.001	0.995 (0.991, 0.999)	0.03
Race (reference group: White)				
Black	1.11 (1.04, 1.17)	0.001	1.25 (1.18, 1.32)	<0.001
Other	1.06 (1.002, 1.13)	0.04	1.04 (0.98, 1.10)	0.25

Marital status (reference group: married)				
Unmarried	1.27 (1.22, 1.31)	<0.001	1.46 (1.41, 1.51)	<0.001
Rectal cancer stage (reference group: stage 0)				
1	2.86 (2.45, 3.34)	<0.001	2.86 (2.45, 3.34)	<0.001
2	6.14 (5.27, 7.14)	<0.001	6.58 (5.65, 7.66)	<0.001
3	7.68 (6.60, 8.93)	<0.001	8.74 (7.51, 10.2)	<0.001
4	19.3 (16.6, 22.4)	<0.001	40.9 (35.2, 47.6)	<0.001

CI: confidence interval.