



# Effects of radical cystectomy, radiotherapy, and chemotherapy on the risk of long-term heart-specific death in bladder cancer patients

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**Background:** At present, the low risk of bladder cancer (BCa)-specific death has allowed for investigation into treatment-related cardiotoxicity. To aid clinicians in selecting appropriate cardiovascular disease screening strategies and interventions, this study explored the heart-specific mortality and prognostic factors of patients with BCa after radical cystectomy (RC), radiotherapy (RT), or chemotherapy (CT), and compared their long-term heart-specific mortality with that of the general male population.

**Methods:** We identified three different treatments for BCa patients from the Surveillance, Epidemiology, and End Results (SEER) database: RC, RT, and CT. Patients were included from 2000 to 2012 and followed through 2015. A cumulative mortality curve and competitive risk regression model were applied to evaluate the prognostic factors of heart-specific mortality, and standardized mortality ratios (SMRs) were calculated.

**Results:** Of 39,500 men, 30.3%, 18.8%, and 50.9% received RC, RT, and CT, respectively. For patients with a survival period of less than 50 months, tumor-specific death exhibited a rapidly increasing trend, which subsequently flatlined. However, the rates heart-specific mortality and other causes exhibited a tendency to increase stably. The heart-specific and all-cause mortality rates of patients in any age group treated with the three abovementioned strategies were higher than those of the general population. The heart-specific mortality of patients with carcinoma in situ treated with RC and CT exceeded their all-cause mortality, while that of other tumor stages did not. The risks of heart-specific [sub-distribution hazard ratio (SHR) =1.38; 95% confidence interval (CI): 1.22–1.57] and tumor-specific (SHR =1.68; 95% CI: 1.60–1.77) deaths in patients who received RT were higher than those of patients who underwent CT.

**Conclusions:** The risks of heart-specific and tumor-specific deaths in patients who received RT were higher than those of the RC and CT groups, especially in patients over 65 years of age who received RT.

**Keywords:** Bladder cancer (BCa); cardiovascular disease; competing risk; Surveillance, Epidemiology, and End Results (SEER)

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## Introduction

Bladder cancer (BCa) is the most common malignant tumor of the urinary system, and its incidence increasing year by year with the growing and ageing population more likely affects older people and men (1,2). Between 1990 and 2016, the number of deaths from BCa increased by 1.6 times {113,414 [95% confidence interval (CI): 110,361–117,066] to 186,199} (3). Many factors are known to be risk factors for BCa, such as exposure to environmental and occupational chemicals and tobacco smoke, but when these risk factors are removed, the mortality rate of BCa patients does not decrease significantly (4-6).

Until recently, BCa treatment had seen little progress. For 30 years, clinicians offered the same, limited range of therapeutics to patients, and the 5-year survival rates were flat (7-9). Further analysis of the causes of death in patients with BCa showed that tumor-specific deaths account for a large proportion, but the proportion of non-tumor-specific deaths is also surprisingly high, especially heart-specific mortality (10). Heart-specific deaths were defined as those with an underlying cause of death in the ICD category of diseases of the heart (e.g., coronary heart disease, heart failure, atrial fibrillation, and myocardial infarction) because this category has been the most inclusive and has had the most consistent definition of heart disease over time.

As increasing age is a natural driver for the incidence of cardiovascular diseases and cardiovascular mortality among the general population, whether the mortality is fully correlated with the death of BCa remains unclear (11). Patients with BCa have received different treatments, and their cardiac death rates are significantly distinct. For instance, radiotherapy (RT) has been shown to increase the mortality of some particular cancers, while chemotherapy (CT) drugs also have exhibited cardiotoxicity (12,13).

At present, the cardiac-specific mortality of BCa patients using different treatments has not been analyzed and compared. In view of the possible treatment-related cardiotoxic effects, we aim to analyze the cardiac-specific mortality of a wide range of BCa patients, including 39,500 BCa patients undergoing surgery, RT, or CT. We present the following article in accordance with the STROBE reporting checklist (available at <https://dx.doi.org/10.21037/tau-21-835>).

## Methods

### *Data sources*

The comprehensive demographic and cancer-specific information were obtained from the Surveillance, Epidemiology, and End Results (SEER) database. The cause of death was assigned according to the tenth revision of the International Classification of Diseases (ICD-10). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### *Patient selection*

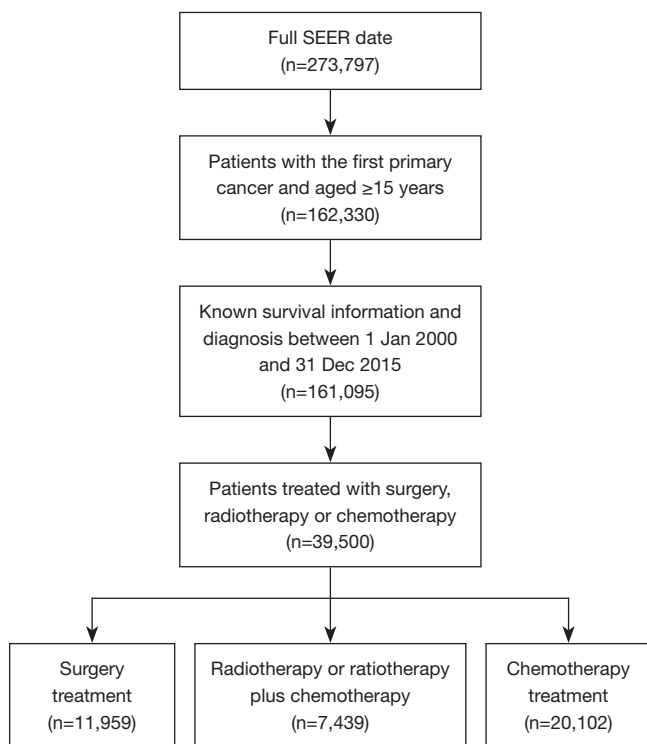
The current analysis was limited to men over the age of 15 who were diagnosed with primary malignant BCa between 1 January 2000 and 31 December 2012. Patients with unknown treatment, unknown survival outcome, and lack of mortality data were excluded. The follow-up period ended on the 31 December 2015.

### *Study variables*

Definitions and information regarding variables such as age at diagnosis, year of diagnosis, marital status, and ethnicity, tumor histopathological type, cancer stage, tumor grade, and treatment [radical cystectomy (RC), RT, or CT] was obtained from the SEER database. Patients were stratified by treatment (RC, RT/RT + CT, and CT) age at diagnosis (<50, 50–64, 65–74, or ≥75 y), and year of diagnosis (year 2000–2005 or 2006–2012).

### *Statistical analysis*

The composition ratio was used to describe the baseline characteristic distribution, and the chi-squared test was used to evaluate the comparison of composition ratios. A competitive risk model was used to estimate the BCa-specific crude cumulative mortality and heart-specific crude cumulative mortality of BCa patients, and to plot the crude cumulative mortality curve. The Fine-Gray competitive risk model was used to adjust for the confounding effects of clinical features, and to evaluate the risk of BCa-specific death and heart-specific death in patients undergoing RC, RT, or CT. Cox proportional hazards regression was used to



**Figure 1** Illustration of the patient selection process. SEER, Surveillance, Epidemiology, and End Results.

evaluate the risk of all-cause mortality. In the groupings of this study, RC included those who received RC alone, RC combined with CT, and RC combined with RT.

To compare mortality between the patients with BCa and the general population, mortality in those with BCa was further stratified according to age and stage, and standardized mortality ratios (SMRs) were estimated using the all-cause mortality and heart-specific mortality of the general population. The cause specific SMR was the ratio of the total number of deaths observed to the expected number of deaths for a specific age reference.

The age-specific mortality of the general male population in the United States was obtained from Wide-ranging Online Data for Epidemiologic Research (WONDER), an epidemiological internet-based database maintained by Centers for Disease Control and Prevention (CDC) (14). Statistical analysis was performed and figures were prepared using Stata/MP, version 14.0 and R software package.  $P < 0.05$  (two-sided) was considered to be statistically significant.

## Results

### Patients characteristics

Among the 273,797 BCa cases recorded in SEER database, 162,330 (59.3%) patients were first primary cancer and aged over 15 years old. Of these patients, 161,095 (99.3%) were diagnosed with BCa and had full survival data between January 1st 2000 and December 31st 2015. Among these patients, 39,500 (24.5%) were treated with surgery, RT, or CT and were eligible for inclusion in this study (Figure 1).

We compared the basic clinical data of the three groups of patients with BCa undergoing RC (30.3%), CT (50.9%), or RT or both (18.8%) (Table 1). The majority of patients were married (59.8, 49.2, and 61.3, respectively), white (87.5, 85.2, and 88.2, respectively), and diagnosed between 2006 and 2012 (64.4, 65.5, and 84.8, respectively).

The age distribution was as follows: patients younger than 50 years old contributed the smallest part, while the 50–64, 65–74, and  $\geq 75$  years age groups were relatively even. Patients aged  $< 50$ , 50–64, and 65–74 years were more likely to receive RC (7.9%, 36.3%, and 32.5%, respectively), although this was only marginally higher than patients administered CT (6.4%, 30.6%, and 31%, respectively). However, as for men aged  $\geq 75$  years, the majority was treated with RT/RT + CT (58.1%).

Patients with tumor grades III and IV accounted for 73.8%. Of these, RC-treated patients accounted for 39.6% (grade III) and 38.8% (grade IV), RT/RT + CT-treated patients accounted for 25% (grade III) and 21.4% (grade IV), and CT-treated patients accounted for 35.4% (grade III), 39.8% (grade IV). Meanwhile, patients with tumor grade II were mainly administered CT (80.2%).

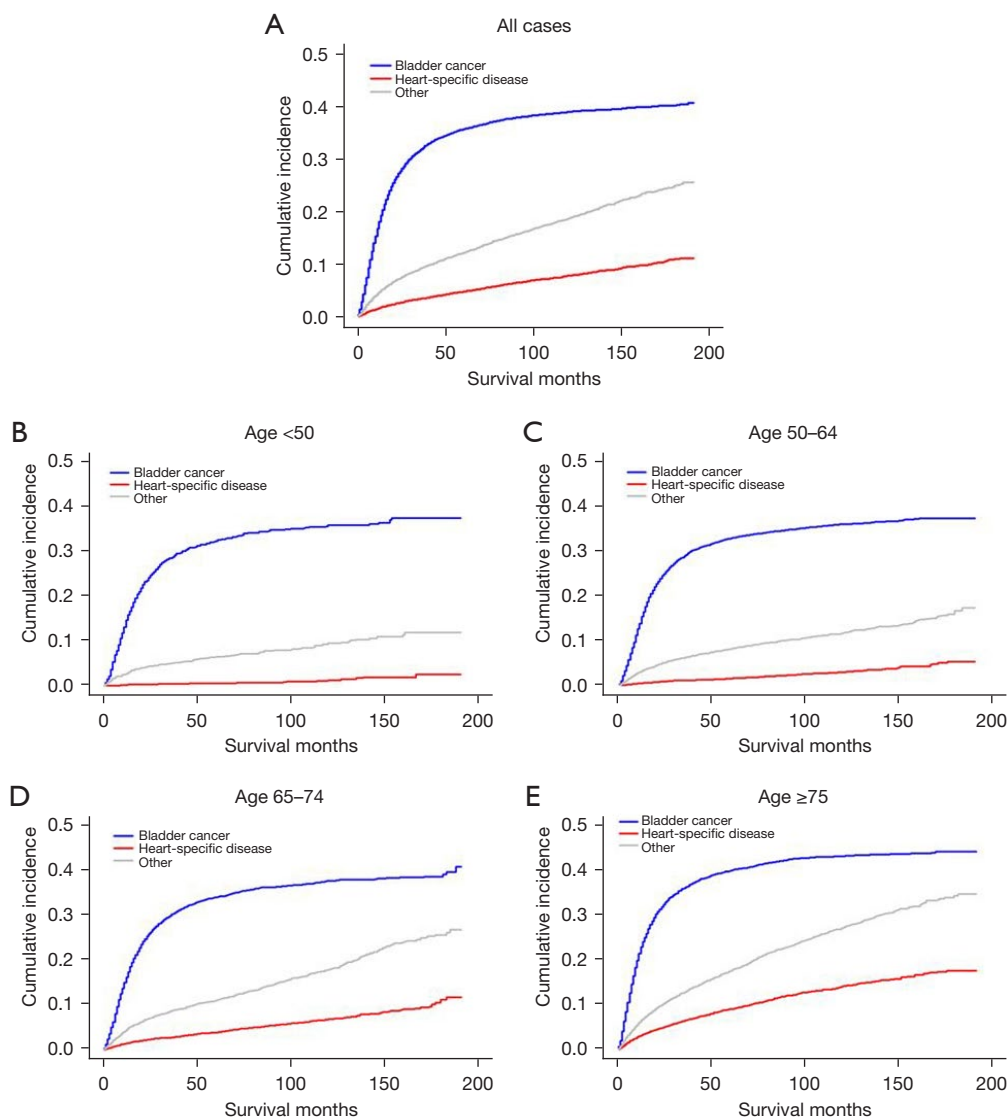
### Cumulative mortality

We compared the cumulative mortality in patients with BCa in terms of three different causes of mortality: tumor-specific death, diseases of the heart, and other causes. Among all patients, the cumulative incidence of BCa was the highest, which was nearly four times the figure for diseases of the heart and twice the figure of other causes in patients who survived 50–200 months after diagnosis. Specifically, for patients with a survival period of less than 50 months, tumor-specific death exhibited a rapidly increasing trend, which subsequently flatlined. However, compared to tumor-specific mortality, However, the rates heart-specific

**Table 1** Basic characteristics at diagnosis of patients with BCa in the RC, RT/RT + CT, or CT treatment groups

Characteristics	RC	RT/RT + CT	CT	P value
Subjects, n (%)	11,959 (30.3)	7,439 (18.8)	20,102 (50.9)	
Marital status, n (%)				<0.001
Married	7,154 (59.8)	3,662 (49.2)	12,323 (61.3)	
Widowed/divorced	2,848 (23.8)	2,581 (34.7)	4,365 (21.7)	
Single	1,508 (12.6)	888 (11.9)	2,506 (12.5)	
Unknown	449 (3.8)	308 (4.1)	908 (4.5)	
Age, n (%)				<0.001
<50	945 (7.9)	242 (3.3)	1,292 (6.4)	
50–64	4,338 (36.3)	1,209 (16.3)	6,156 (30.6)	
65–74	3,887 (32.5)	1,664 (22.4)	6,230 (31.0)	
≥75	2,789 (23.3)	4,324 (58.1)	6,424 (32.0)	
Year of diagnosis, n (%)				
2000–2005	4,263 (32.6)	2,570 (34.5)	3,055 (15.2)	
2006–2012	7,696 (64.4)	4,869 (65.5)	17,047 (84.8)	<0.001
Race, n (%)				<0.001
White	10,465 (87.5)	6,339 (85.2)	17,720 (88.2)	
Black	813 (6.8)	721 (9.7)	1,186 (5.9)	
Other	655 (5.5)	369 (5.0)	1,050 (5.2)	
Unknown	26 (0.2)	10 (0.1)	146 (0.7)	
Grade, n (%)				<0.001
I	117 (1.0)	99 (1.3)	1,921 (9.6)	
II	698 (5.8)	391 (5.3)	4,403 (21.9)	
III	4,128 (34.5)	2,606 (35.0)	3,699 (18.4)	
IV	6,405 (53.6)	3,532 (47.5)	6,565 (32.7)	
Unknown	611 (5.1)	811 (10.9)	3,514 (17.5)	
Stage, n (%)				<0.001
<i>In situ</i>	193 (1.6)	102 (1.4)	9,462 (47.1)	
Local	4,775 (39.9)	4,310 (57.9)	7,136 (35.5)	
Regional	5,992 (50.1)	1,366 (18.4)	1,245 (6.2)	
Distant	911 (7.6)	1,528 (20.5)	2,044 (10.2)	
Unknown	88 (0.7)	133 (1.8)	215 (1.1)	
Cause of death, n (%)				<0.001
Alive	5,314 (44.4)	1,567 (21.1)	13,367 (66.5)	
BCa	4,566 (38.2)	3,983 (53.5)	3,861 (19.2)	
Heart-specific disease	490 (4.1)	590 (7.9)	879 (4.4)	
Other	1,589 (13.3)	1,299 (17.5)	1,995 (9.9)	

BCa, bladder cancer; RC, radical cystectomy; RT, radiotherapy; CT, chemotherapy.



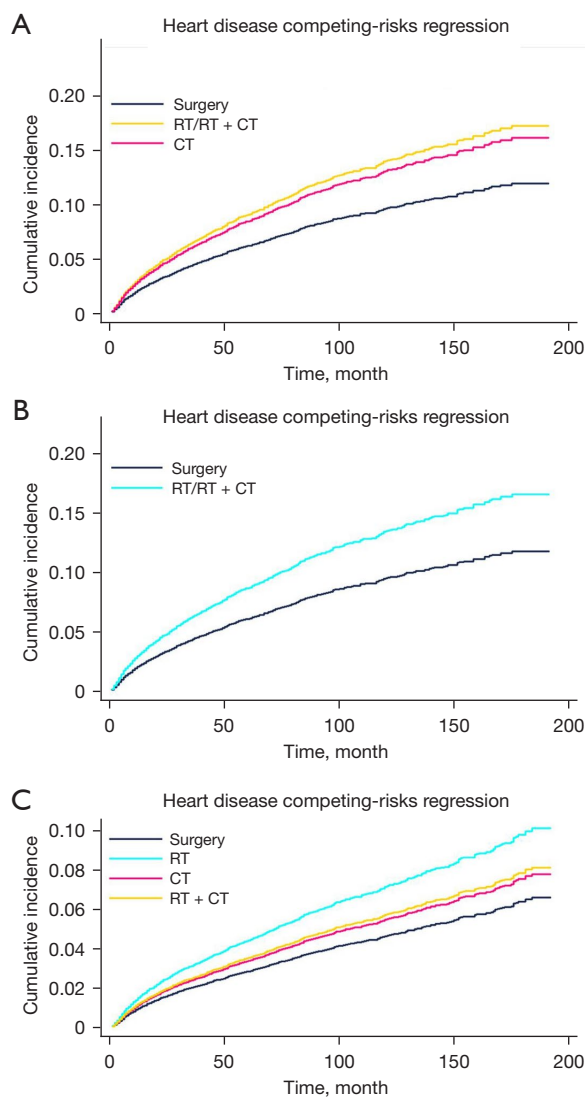
**Figure 2** Multivariable adjusted cumulative incidence function curve of patients with BCa. (A) Cause-specific mortality of the overall BCa population. (B-E) Heart-specific and BCa mortality rates by age at diagnosis: (B) <50 y; (C) 50–64 y; (D) 65–74 y; and (E)  $\geq 75$  y. BCa, bladder cancer.

mortality and other causes exhibited a tendency to increase stably. This suggests that there will be a continuous rise in the number in patients who live longer (Figure 2A).

We also explored the data of patients by the different age groups, 50–64, 65–74, and  $\geq 75$  years, and found that the composition and changing trend of the causes of death in all age groups were similar to that of the entire population. Nevertheless, for older patients (65–74 and  $\geq 75$  years), the number of heart-specific deaths was significantly increased, especially in patients with a relatively long survival period

(longer than 50 months) (Figure 2B–2E).

The lowest mortality belonged to patients that received surgery and any of the other treatment strategies after BCa diagnosis (Figure 3A, 3B). The percentage of those who underwent RT/RT + CT outnumbered that of patients who chose CT only (Figure 3A). By further analyzing the various treatment methods separately, two treatment methods that included RT exhibited the top two mortality rates, followed by CT, with surgery still maintaining a low mortality rate (Figure 3C).



**Figure 3** The heart-specific competing-risks regression of patients with BCa undergoing RC, RT or CT. BCa patients were grouped as follows: (A) RC, RT/RT + CT, and CT; (B) RC and RT/RT + CT/CT; (C) RC, RT, CT, and RT + CT. BCa, bladder cancer; RC, radical cystectomy; RT, radiotherapy; CT, chemotherapy.

### Mortality compared with the general population

The heart-specific and all-cause mortality rates of patients with BCa undergoing RC, RT, or CT were standardized by age and cancer stage relative to the general population (Table 2). Overall, the heart-specific and all-cause mortality rates of patients of any age groups treated with the three aforementioned strategies were higher than those of general population. The all-cause mortality of patients was

generally five times (or higher) than that of heart-specific mortality. Along with increasing age, the all-cause mortality rate of BCa patients exhibited a continuous downward trend. However, the heart-specific mortality of patients who received RC or CT fluctuated around SMR 2, while that of patients who underwent RT showed an initially increasing trend that subsequently decreased, reaching a peak in the 65–70 age group (SMR =7.53; 95% CI: 5.46–10.39).

We also grouped the patients according to tumor stages, and found that the heart-specific mortality of patients with carcinoma *in situ* treated by RC and CT exceeded their all-cause mortality, while that of other stages did not. The all-cause mortality rate of patients with distant tumor metastasis was the highest among all patients, regardless of treatment (RC: SMR =32.17, 95% CI: 29.78–34.75; RT/RT + CT: SMR =45.25, 95% CI: 42.67–47.99; CT: SMR =38.74, 95% CI: 36.83–40.74).

### Relative risk model for specific causes

We established a Fine-Gray model of competitive risk to explore the internal logic of the prognostic factors of heart disease or BCa mortality in patients receiving RC, RT, or CT (Table 3). Taking 5 years as a time period, the risk of heart-specific death increased from 2.32 (50–64 years) to 10.72 ( $\geq 75$  years) with the increase in the patient's age. This trend was consistent with that of the risk of tumor-specific death in patients, where patients over 75 years of age had a higher risk of dying from tumors [sub-distribution hazard ratio (SHR) =1.39; 95% CI: 1.28–1.50]. Patients with BCa diagnosed between 2006 and 2012 (SHR =0.59; 95% CI: 0.54–0.65) had a significantly lower risk of heart-specific death than those diagnosed in 2000–2005. Compared with other tumor stages, patients with distant metastasis had the lowest risk of heart-specific death (SHR =0.37; 95% CI: 0.29–0.47), but their risk of tumor-specific death, which gradually increased with tumor progression, was several times higher than that of the other stages (SHR =48.79; 95% CI: 41.91–56.79).

The risks of heart-specific (SHR =1.38; 95% CI: 1.22–1.57) and tumor-specific deaths (SHR =1.68; 95% CI: 1.60–1.77) in patients who received RT were higher than those of patients who underwent CT. The stratified study based on different ages showed that the risk of heart-specific death in patients over 65 years of age who received RT treatment was higher than that of patients who received other treatments (Table 4). Similarly, patients over 75 years of age who underwent RT had a relatively higher risk of

**Table 2** The heart-specific and all-cause mortality rates of patients with BCa undergoing RC, RT, or CT were standardized by age and cancer stage relative to the general population

Group	SMR heart-specific (95% CI)			SMR overall (95% CI)		
	RC	RT/RT + CT	CT	RC	RT/RT + CT	CT
<b>Age</b>						
50–54	2.72 (1.41, 5.22)	4.49 (1.12, 17.97)	1.27 (0.53, 3.06)	24.42 (22.13, 26.93)	76.56 (65.81, 89.06)	14.04 (12.46, 15.81)
55–59	2.92 (1.94, 4.39)	2.54 (0.82, 7.88)	1.76 (1.09, 2.83)	16.55 (15.3, 17.91)	49.9 (44.38, 56.1)	10.72 (9.82, 11.71)
60–64	2.6 (1.91, 3.54)	4.36 (2.41, 7.87)	2.35 (1.76, 3.15)	12.22 (11.43, 13.07)	31.05 (28, 34.44)	7.41 (6.86, 8)
65–69	2.75 (2.16, 3.5)	7.53 (5.46, 10.39)	1.88 (1.46, 2.41)	9.21 (8.66, 9.79)	21.72 (19.88, 23.72)	5.28 (4.92, 5.66)
70–74	2.18 (1.74, 2.73)	6.44 (4.98, 8.33)	1.79 (1.45, 2.21)	6.62 (6.23, 7.03)	15.57 (14.42, 16.82)	3.93 (3.67, 4.19)
75–79	1.91 (1.56, 2.33)	4.33 (3.49, 5.38)	2 (1.71, 2.35)	4.54 (4.27, 4.84)	10.86 (10.18, 11.58)	2.93 (2.76, 3.12)
80–85	1.63 (1.35, 1.98)	3.44 (2.92, 4.04)	1.54 (1.33, 1.79)	3.35 (3.13, 3.58)	6.64 (6.27, 7.03)	2.25 (2.12, 2.4)
<b>Stage</b>						
<i>In situ</i>	2.93 (1.67, 5.16)	2.69 (1.21, 5.98)	1.35 (1.18, 1.54)	2.48 (1.85, 3.32)	3.63 (2.61, 5.06)	1.07 (1, 1.15)
Local	1.65 (1.42, 1.92)	4.41 (3.9, 4.99)	2.14 (1.89, 2.43)	3.31 (3.14, 3.48)	8.26 (7.91, 8.63)	3.9 (3.73, 4.08)
Regional	2.51 (2.19, 2.88)	3.5 (2.63, 4.64)	3.12 (2.25, 4.33)	9.71 (9.4, 10.03)	13.4 (12.5, 14.36)	14.9 (13.88, 16)
Distant	3.56 (2.18, 5.8)	5.53 (3.89, 7.86)	3.4 (2.38, 4.86)	32.17 (29.78, 34.75)	45.25 (42.67, 47.99)	38.74 (36.83, 40.74)
Unknown	1.19 (0.3, 4.75)	3.5 (1.46, 8.41)	1.85 (0.83, 4.11)	7.14 (5.46, 9.35)	12.33 (9.85, 15.44)	7.33 (6.05, 8.88)
Total	2.08 (1.89, 2.29)	4.27 (3.84, 4.75)	1.79 (1.64, 1.94)	6.68 (6.51, 6.85)	11.75 (11.39, 12.12)	3.86 (3.76, 3.97)

BCa, bladder cancer; RC, radical cystectomy; RT, radiotherapy; CT, chemotherapy; SMR, standardized mortality ratio; CI, confidence interval.

tumor-specific death (SHR =1.62; 95% CI: 1.50–1.75).

## Discussion

In this study, which was based on mega data and a large sample of patients, we analyzed the long-term heart-specific mortality of BCa patients. Overall, the results of the study showed that the heart-specific mortality rate in BCa patients diagnosed in recent years was significantly lower than that of patients diagnosed in earlier years. This may be related to the improvement of the precision of surgery, RT, and CT as well as the quality of comprehensive management of tumors, which has fewer complications and side effects. At the same time, the treatment of cardiovascular diseases and the ability to respond to cardiovascular events have been improved, which has also effectively reduced heart-specific deaths.

For BCa, awareness of hematuria as the major presenting symptom is paramount, and early diagnosis with individualized treatment and follow-up is key to a successful outcome. In terms of BCa surgical treatment,

with the increased popularity of robotic surgery in recent years, numerous studies have compared the perioperative results and long-term progression-free survival of robot-assisted RC (RARC) and RC (15,16). The results have demonstrated that RARC is technically feasible, provides the same perioperative and oncological results compared with RC, and has the potential advantage of being more refined (17). Increased development may further shorten the operation time and reduce the increase in the patient's heart load caused by anesthesia (18). However, RARC also has high costs. The development of the technique can bring about better treatment.

A general analysis has shown that older patients have a higher potential for death due to cardiac-specific causes. At present, the influence of age on the risk of cardiovascular disease cannot be ruled out. The significant enhancement of medical oncology treatment, especially the clinical application of immunotherapy, enables patients to achieve a longer survival period, combined with the risk factors of degenerative changes in aging patients. Therefore, we further stratified our assessment based on age and tried to

**Table 3** All-cause, heart-related, and bladder-related mortality of patients by demographic and clinical characteristics at diagnosis

Group	All causes		Heart-specific disease		BCa	
	HR	P value	SHR	P value	SHR	P value
<b>Marital</b>						
Married	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
Widowed/divorced	1.26 (1.22, 1.30)	<0.001	1.16 (1.05, 1.28)	0.004	1.18 (1.13, 1.23)	<0.001
Single	1.27 (1.22, 1.33)	<0.001	1.14 (0.97, 1.34)	0.104	1.16 (1.10, 1.23)	<0.001
Unknown	1.11 (1.03, 1.20)	0.006	0.95 (0.75, 1.21)	0.691	1.14 (1.03, 1.25)	0.01
<b>Age</b>						
<50	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
50–64	1.24 (1.15, 1.33)	<0.001	2.32 (1.50, 3.60)	<0.001	1.08 (1.00, 1.17)	0.056
65–74	1.63 (1.52, 1.75)	<0.001	5.40 (3.52, 8.27)	<0.001	1.16 (1.07, 1.26)	<0.001
≥75	2.45 (2.28, 2.63)	<0.001	10.72 (7.01, 16.38)	<0.001	1.39 (1.28, 1.50)	<0.001
<b>Year of diagnosis</b>						
2000–2005	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
2006–2012	0.87 (0.84, 0.90)	<0.001	0.59 (0.54, 0.65)	<0.001	0.83 (0.80, 0.86)	<0.001
<b>Race</b>						
White	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
Black	1.14 (1.08, 1.20)	<0.001	0.92 (0.76, 1.12)	0.424	1.16 (1.09, 1.24)	<0.001
Other	0.83 (0.78, 0.89)	<0.001	0.65 (0.51, 0.83)	0.001	0.87 (0.80, 0.95)	0.002
Unknown	0.27 (0.16, 0.46)	<0.001	0.36 (0.09, 1.43)	0.146	0.40 (0.23, 0.68)	0.001
<b>Grading</b>						
I	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
II	1.23 (1.10, 1.37)	<0.001	1.24 (0.98, 1.57)	0.071	1.22 (1.02, 1.45)	0.027
III	1.52 (1.38, 1.69)	<0.001	1.13 (0.90, 1.43)	0.298	1.73 (1.47, 2.03)	<0.001
IV	1.40 (1.27, 1.55)	<0.001	1.06 (0.84, 1.34)	0.644	1.65 (1.41, 1.94)	<0.001
Unknown	1.49 (1.34, 1.66)	<0.001	1.15 (0.90, 1.48)	0.266	1.53 (1.29, 1.81)	<0.001
<b>Stage</b>						
<i>In situ</i>	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
Local	2.86 (2.68, 3.05)	<0.001	1.02 (0.89, 1.18)	0.749	10.57 (9.10, 12.29)	<0.001
Regional	6.12 (5.70, 6.56)	<0.001	0.77 (0.64, 0.93)	0.005	24.89 (21.34, 29.03)	<0.001
Distant	14.30 (13.34, 15.32)	<0.001	0.37 (0.29, 0.47)	<0.001	48.79 (41.91, 56.79)	<0.001
Unknown	4.55 (3.99, 5.18)	<0.001	0.63 (0.40, 0.99)	0.047	18.47 (15.06, 22.65)	<0.001
<b>Treatment</b>						
RC	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
RT/RT + CT	1.93 (1.85, 2.00)	<0.001	1.38 (1.22, 1.57)	<0.001	1.68 (1.60, 1.77)	<0.001
CT	1.21 (1.16, 1.26)	<0.001	1.18 (1.04, 1.35)	0.013	1.17 (1.11, 1.22)	<0.001

BCa, bladder cancer; HR, hazard ratio; SHR, sub-distribution hazard ratio; RC, radical cystectomy; RT, radiotherapy; CT, chemotherapy.



**Table 4** All-cause, heart-related, and bladder-related mortality in patients with BCa who underwent RC, RT/RT + CT, or CT at diagnosis, analyzed by age and treatment subgroup

Age	Variables	All causes		Heart-specific disease		BCa	
		HR	P value	SHR	P value	SHR	P value
<50	Treatment						
	RC						
	RT/RT + CT	2.15 (1.78, 2.60)	<0.001	1.62 (0.52, 5.12)	0.407	1.89 (1.50, 2.39)	<0.001
	CT	1.39 (1.18, 1.64)	<0.001	1.26 (0.52, 3.09)	0.609	1.34 (1.12, 1.61)	0.002
50–64	Treatment						
	RC						
	RT/RT + CT	1.84 (1.69, 2.00)	<0.001	1.29 (0.83, 2.00)	0.261	1.67 (1.51, 1.86)	<0.001
	CT	1.27 (1.18, 1.37)	<0.001	1.00 (0.69, 1.46)	0.981	1.26 (1.16, 1.38)	<0.001
65–74	Treatment						
	RC						
	RT/RT + CT	1.90 (1.76, 2.05)	<0.001	1.59 (1.25, 2.02)	<0.001	1.57 (1.43, 1.73)	<0.001
	CT	1.17 (1.09, 1.26)	<0.001	1.00 (0.79, 1.27)	0.995	1.20 (1.09, 1.31)	<0.001
≥75	Treatment						
	RC						
	RT/RT + CT	1.98 (1.86, 2.10)	<0.001	1.49 (1.25, 1.77)	<0.001	1.62 (1.50, 1.75)	<0.001
	CT	1.17 (1.10, 1.26)	<0.001	1.38 (1.15, 1.66)	0.001	1.01 (0.93, 1.11)	0.754

BCa, bladder cancer; RC, radical cystectomy; RT, radiotherapy; CT, chemotherapy; HR, hazard ratio; SHR, sub-distribution hazard ratio.

eliminate the problems of aging and degeneration caused by age itself. For patients over 65 years who received RT, the heart-specific mortality rate was significantly higher than that of the RC and CT groups. Meanwhile, the heart-specific mortality risk of the other age groups who received any of the three treatments was not significant different to that of the general population.

Radiation-induced heart disease (RIHD) is a unifying term used to describe all cardiac complications related to RT. The pathophysiological process of RIHD mainly includes DNA damage caused by radiation and oxidative stress, which ultimately leads to endothelial damage (19). RT may accelerate the process of atherosclerosis, venous thromboembolism, early coronary artery disease, valvular heart disease, and heart failure (20). In recent years, the rapid development of cytotoxic CT, molecular targeted inhibitors, and immune checkpoint therapy (target cytotoxic T lymphocyte antigen 4, programmed cell death-1, and PD-ligand 1) are mostly directed at signal transduction pathways and immune regulation. These methods have

limited long-term cardiovascular toxicity data due to their short application life (21,22).

Cardiotoxicity is a potential complication of various tumor treatments. The ESMO clinical practice guidelines are the result of a multidisciplinary review of cardiology and oncology. Its ultimate goal is to provide strict standard recommendations for the prevention, evaluation, monitoring and management of cardiotoxicity risks during anti-cancer treatment (23). In principle, the risk-benefit ratio of drugs must be explained according to the nature and severity of the disease.

The establishment of the prognostic risk model suggested that risk stratification and pre-treatment screening will be included in the diagnosis and treatment of BCa patients, which can detect and predict the effects that can reduce the risk of cardiac-specific death and benefit patients. This analytical model showed that patients in different tumor stages have different courses of progression, and those with distant metastases have a low risk of heart-specific death. This result needs to be analyzed with survival time and

other factors. Analyze the prognostic risk of patients using a single factor is unscientific.

At present, there is a lack of guidelines for the management of RT-related cardiac complications in BCa patients.

However, the model in this paper has certain limitations because it does not consider important information, such as RT type, strategy, dose, CT plan, time, etc. Also, some patients who died of unknown causes were included, and the specific types of cardiac-specific deaths were not discussed. The general information in the SEER database was not sufficient, and we cannot rule out whether it had a specific effect.

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