



An overview of patients with urothelial bladder cancer over the past two decades: a Surveillance, Epidemiology, and End Results (SEER) study

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Contributions: (I) Conception and design: F Qi, N Yang; (II) Administrative support: None; (III) Provision of study materials or patients: Y Zang, X Li, Y Cheng; (IV) Collection and assembly of data: F Qi, Y Zang, X Li; (V) Data analysis and interpretation: F Qi, Y Cheng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: To explore the overall trends of incidence rate (IR), mortality and survival outcomes of patients with urothelial bladder cancer (UBC) over the past two decades.

Methods: Patients diagnosed with UBC from 1993 to 2012 were extracted from the Surveillance, Epidemiology and End Result (SEER) 18 database. Baseline characteristics and treatment types of included patients were collected retrospectively. Moreover, the age-adjusted IRs and annual percent changes (APCs) were obtained. Afterwards, we calculated the standardized mortality ratios (SMRs) for bladder cancer (BC), cardiovascular disease (CVD) and all-cause mortality by comparing UBC cases with the general population. Finally, survival outcomes of UBC patients were analyzed and compared.

Results: A total of 220,405 UBC patients were identified, including 167,036 (75.79%) male patients and 53,369 (24.21%) female patients, with an average age of 70.84 years old. Most patients were White (89.85%), with older age (71.67%, >65 years old), lower T stage diseases (78.11%, < T2) and lower median household income (55.37%). When compared with patients diagnosed between 1993 and 2002, those diagnosed between 2003 and 2012 had older age (mean: 71.15 *vs.* 70.16 years old, $P < 0.001$), higher proportion of men (76.22% *vs.* 74.83%, $P < 0.001$) and lower median household income (56.69% *vs.* 52.50%, $P < 0.01$). Overall, the IR of UBC increased slightly before 2003 and maintained a stable trend of about 20 per 100,000 person-years after 2003. Additionally, CVD was recognized as an important cause of death (COD) of UBC patients. UBC patients were 44.5 times more likely to die of CVD when compared with the general population. Furthermore, the 3-, 5- and 10-year overall survival (OS) and cancer-specific survival (CSS) rates were 0.709, 0.609 and 0.421, and 0.861, 0.831 and 0.789, respectively. Finally, survival outcomes between patients diagnosed in the two periods (1993–2002 *vs.* 2003–2012) were not significantly different.

Conclusions: The IR of UBC increased slightly before 2003 and remained stable after 2003. UBC patients had higher CVD burden than the general population. Hence, cardiovascular health should be emphasized to reduce mortality after UBC diagnosis. Lastly, survival outcomes of UBC patients in the last two decades showed no significant difference.

Keywords: Incidence; mortality; survival; the Surveillance, Epidemiology and End Result (SEER); urothelial bladder cancer (UBC)

Submitted Mar 02, 2020. Accepted for publication Sep 25, 2020.

doi: 10.21037/atm-20-2108

View this article at: <http://dx.doi.org/10.21037/atm-20-2108>

Introduction

Bladder cancer (BC) is one of the most common malignancies worldwide (1). The estimated global new cases and deaths of BC in 2018 were 549,393 and 199,922, respectively (2). Based on the depth of tumor infiltration, BC is divided into non-muscle invasive BC (NMIBC) and muscle invasive BC (MIBC). About three-fourths of new BC cases are NMIBC at their initial diagnosis (3). Generally, patients with NMIBC have better prognosis than those with MIBC. Previous studies reported that the 5- and 10-year overall survival (OS) rates of MIBC patients were about 50% and 36%, respectively, even with aggressive management (4,5). Moreover, the 5-year OS rate of metastatic diseases was only 15%.

Although the majority of BC patients are non-invasive at initial diagnosis, the possibilities of progression and recurrence in NMIBC patients are very high. Studies (6,7) reported that 10–20% of NMIBC patients progressed to MIBC and approximately 50–70% recurred over time. Therefore, continuous monitoring and surveillance (including regular cystoscopy and intravesical therapy) are essential for NMIBC cases treated with transurethral resection of bladder tumor (TURBt) (8). As a result, BC brings heavy economic and psychological burden to patients.

The incidence rate (IR) of BC in the male population is about three times higher than that in women (9). Generally, BCs are infrequently detected in individuals younger than 40 years old, and the median age at diagnosis ranges from 65 to 74 years old in different studies (5,9). In addition, Lee *et al.* (10) demonstrated that the IR, mortality and survival outcomes of BC were significantly different in patients with different races. The IR of BC in Whites was two times higher than that in African Americans, while the latter had higher tumor stages and worse prognosis.

Urothelial bladder cancer (UBC) is the most common subtype of BC, accounting for 95% of BC cases (11). In this study, we provided a comprehensive overview of UBC patients during the past 20 years (1993–2012) on the basis of the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program. Furthermore, comparisons between patients diagnosed in

the two periods (1993–2002 *vs.* 2003–2012) were made in basic characteristics, IR, mortality and survival outcomes. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-2108>).

Methods

Database

All the original data were downloaded from the SEER database retrospectively. Outcomes of cancer incidence, mortality and long-term follow-up were included in this public and population-based database. SEER 9 was first constructed in 1971 and collected data from 9 registries in Connecticut, Hawaii, New Mexico, Utah, Iowa, San Francisco Oakland (California), Seattle-Puget Sound (Washington), Detroit (Michigan) and Atlanta (Georgia). In 1992, SEER 13 was developed with four additional areas added in [including Alaska Natives, San Jose-Monterey (California), Los Angeles and rural Georgia]. Moreover, SEER 18 was created with five more registries (Greater California, New Jersey, Louisiana, Greater Georgia and Kentucky) at the beginning of the 21st century. Nowadays, with increasing regions participating in this programme, SEER 18 registry accounts for approximately 30% of the total US population. This study was exempt from the Institutional Review Board (IRB) approval because the original data were from a public database. All procedures performed in studies were in accordance with the national research committee and with the Declaration of Helsinki (as revised in 2013).

Patient identification

Patients diagnosed with UBC with positive pathology from 1993 to 2012 were extracted from SEER 18 utilizing the SEER*Stat software. The inclusion criteria were as follows: (I) diagnosed as UBC (C67.0–67.9, International Classification of Diseases for Oncology: 8220–8139) with positive histological confirmation; (II) the latest year of diagnosis was 2012 to ensure a follow-up period of at least 5 years; (III) complete data were available with active

Table 1 SEER stage crosswalk for defining T classification

T classification	Diagnosis years	
	1993–2003, EOD extension, 3rd ed	2004–2012, CS extension
Ta	01, 03, 05	010, 030
Tis	00, 06, 10	060, 100
T1	15, 30	150, 155, 160, 165, 170, 300
≥T2	20–23, 40–85	200–240, 400–810

SEER, Surveillance, Epidemiology, and End Results; CS, collaborative staging; EOD, extent of disease.

follow-up. Furthermore, patients with the type of reporting source being autopsy only or a death certificate were excluded.

Baseline characteristics

We extracted baseline characteristics and treatment types of each patient using the “Case Listing Session” tool of the SEER*Stat software. Variables included age at diagnosis, year of diagnosis, race, sex, marital status, census regions, county level median household income, primary tumor site, tumor grade, histology, TNM stage, extent of disease (EOD), the administration of surgery, radiotherapy and chemotherapy, vital status, cause of death (COD) and survival time.

In this study, age at diagnosis was divided into six groups, including <35, 35–44, 45–54, 55–64, 65–74 and ≥75 years old. Race was classified into White, Black and Other. Historic stage was categorized into localized, regional and distant. Low and high levels of household income were defined based on the median value. When defining T classification, EOD Extension 3rd edition was applied for patients diagnosed prior to 2003, and collaborative staging (CS) extension was used for patients diagnosed after 2003. A crosswalk for T stage definition is presented in *Table 1*. Additionally, CODs were divided into “died of UBC” and “died of other cause”. We separated cardiovascular disease (CVD) from other causes for deeper discussion due to the relationship between CVD and UBC.

IR trend and annual percent change (APC)

The age-adjusted IRs were obtained utilizing the “Rate Session” tool of the SEER*Stat software. SEER 13 was used to extract the IRs for patients from 1993 to 1999, and SEER 18 was for patients from 2000 to 2012. To make

comparisons between patients diagnosed in the last two decades, we discussed the IRs in the whole population, and further stratified by gender, race and age. Additionally, the APCs were calculated to identify the IRs trends for different populations.

Proportional mortality ratio (PMR)

PMR was defined as the number of deaths due to a specific cause divided by the number of total deaths. In this study, CODs consisted of BC, CVD and other causes. Furthermore, subgroup analyses by clinical variables were conducted, including gender, age at diagnosis, race, T stage, time since diagnosis, median household income, histologic stage and the history of a prior malignancy.

Standardized mortality ratio (SMR)

In this study, we compared the all-cause/CVD mortality of UBC patients with the US population, and defined it as the SMR. SMR was calculated as the observed deaths divided by the expected deaths. It was convenient to obtain the age-specific risks of all-cause/CVD mortality from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (WONDER) Tool (<https://wonder.cdc.gov/>). The expected deaths for different age groups were calculated by multiplying the number of UBC patients in each age category by age-specific crude risk in the general population. Lastly, 95% confidence intervals (CIs) for the SMRs were calculated according to the Boice-Monson method.

Survival outcomes

Kaplan-Meier (KM) analyses were performed to explore the survival outcomes of UBC patients in different periods.

A total 1,477 patients were excluded when calculating the cancer-specific survival (CSS) because of unknown COD. In addition, the 3- and 5-year OS and CSS rates were calculated for further comparisons.

Statistical analysis

The age-adjusted IRs and basic characteristics were obtained based on the 2000 US Standard population using the SEER*Stat software (version 8.3.6; www.seer.cancer.gov/seerstat). Comparisons between UBC patients in the past two decades were performed by Chi-square tests for categorical variables and *t*-tests for continuous variables. The APCs were calculated and generated by Joinpoint Regression Program (<https://surveillance.cancer.gov/joinpoint/>). The entire analyses were performed via SPSS 23.0 software (SPSS Inc., Chicago, IL, USA) and R software (version 3.4.1). Two-sided $P < 0.05$ was considered to be statistically significant.

Results

Basic characteristics

A total of 220,405 UBC patients were identified, including 167,036 males and 53,369 females, with an average age of 70.84 years old (Table 2). Generally, most patients were White (89.85%), with older age (71.67%, >65 years old), lower T stage diseases (78.11%, < T2) and lower median household income (55.37%). When compared with patients diagnosed between 1993 and 2002, those diagnosed between 2003 and 2012 had older age (mean: 71.15 *vs.* 70.16 years old, $P < 0.001$), higher proportion of men (76.22% *vs.* 74.83%, $P < 0.001$) and lower median household income (56.69% *vs.* 52.50%, $P < 0.01$). Furthermore, patients diagnosed between 2003 and 2012 had higher proportion of N0 diseases (93.68% *vs.* 81.26%, $P < 0.001$). When it came to tumor site, there was no obvious difference in the overall trends between patients diagnosed in the two periods. However, significant difference still existed in the internal

Table 2 Description of population-based cohort of patients with urothelial bladder cancer

Variables	Total	1993–2002	2003–2012	P value ¹
N	220,405	69,314	151,091	
Age, year, mean \pm SD	70.84 \pm 12.08	70.16 \pm 12.16	71.15 \pm 12.03	<0.001
<35	1,204 (0.55)	483 (0.70)	721 (0.48)	<0.001
35–44	4,099 (1.86)	1,653 (2.38)	2,446 (1.62)	
45–54	16,526 (7.50)	5,649 (8.15)	10,877 (7.20)	
55–64	40,606 (18.42)	12,214 (17.62)	28,392 (18.79)	
65–74	64,413 (29.22)	21,490 (31.00)	42,923 (28.41)	
\geq 75	93,557 (42.45)	27,825 (40.14)	65,732 (43.50)	
Race, n (%)				<0.001
White	198,035 (89.85)	62,334 (89.93)	135,701 (89.81)	
Black	11,875 (5.39)	3,780 (5.45)	8,095 (5.36)	
Other	9,056 (4.11)	2,965 (4.28)	6,091 (4.03)	
Unknown	1,439 (0.65)	235 (0.34)	1,204 (0.80)	
Sex, n (%)				<0.001
Male	167,036 (75.79)	51,868 (74.83)	115,168 (76.22)	
Female	53,369 (24.21)	17,446 (25.17)	35,923 (23.78)	

Table 2 (continued)

Table 2 (continued)

Variables	Total	1993–2002	2003–2012	P value ¹
Grade, n (%)				<0.001
Grade I	31,428 (14.26)	11,867 (17.12)	19,561 (12.95)	
Grade II	64,916 (29.45)	25,870 (37.32)	39,046 (25.84)	
Grade III	49,409 (22.42)	19,576 (28.24)	29,833 (19.75)	
Grade IV	46,654 (21.17)	7,560 (10.91)	39,094 (25.87)	
Unknown	27,998 (12.70)	4,441 (6.41)	23,557 (15.59)	
Histology, n (%)				<0.001
Localized	171,208 (77.68)	53,523 (77.22)	117,685 (77.89)	
Regional	39,607 (17.97)	12,491 (18.02)	27,116 (17.95)	
Distant	6,663 (3.02)	1,915 (2.76)	4,748 (3.14)	
Unstaged	2,927 (1.33)	1,385 (2.00)	1,542 (1.02)	
T stage, n (%)				<0.001
<T2	172,161 (78.11)	53,611 (77.35)	118,550 (78.46)	
≥T2	44,841 (20.34)	14,295 (20.62)	30,546 (20.22)	
Tx	3,403 (1.54)	1,408 (2.03)	1,995 (1.32)	
Median household income ² , n (%)				<0.001
Low	122,036 (55.37)	36,389 (52.50)	85,647 (56.69)	
High	98,341 (44.62)	32,915 (47.49)	65,426 (43.30)	
Unknown	28 (0.01)	10 (0.01)	18 (0.01)	
Marital status, n (%)				<0.001
Married	134,142 (60.86)	43,745 (63.11)	90,397 (59.83)	
Previous married	51,436 (23.34)	16,411 (23.68)	35,025 (23.18)	
Never married	20,786 (9.43)	6,150 (8.87)	14,636 (9.69)	
Unknown	14,041 (6.37)	3,008 (4.34)	11,033 (7.30)	
With previous primary, n (%)				<0.001
No	166,112 (75.37)	54,558 (78.71)	111,554 (73.83)	
Yes	54,293 (24.63)	14,756 (21.29)	39,537 (26.17)	
Cancer-directed surgery, n (%)				<0.001
No ³	12,067 (5.47)	3,502 (5.05)	8,565 (5.67)	
Yes	207,845 (94.30)	65,711 (94.80)	142,134 (94.07)	
Unknown	493 (0.22)	101 (0.15)	392 (0.26)	

¹, comparison between 1993–2002 and 2003–2012; ², median household income: defined by earnings above the median of the median household income in this sample; ³, including “no surgical procedure”, “needle, or aspiration biopsy” or “Non-cancer directed surgery”. Grade I = well differentiated; Grade II = moderately differentiated; Grade III = poorly differentiated; Grade IV = undifferentiated; anaplastic. UBC, urothelial bladder cancer; SD, standard deviation.

distribution ($P < 0.001$, Table S1).

IR trend and APC

Overall, the IR of UBC increased slightly before 2003 and maintained a stable trend of about 20 per 100,000 person-years after 2003. Among the male population, this trend was consistent with that in the whole population. The overall IR had been stable in the past 20 years in the female population,

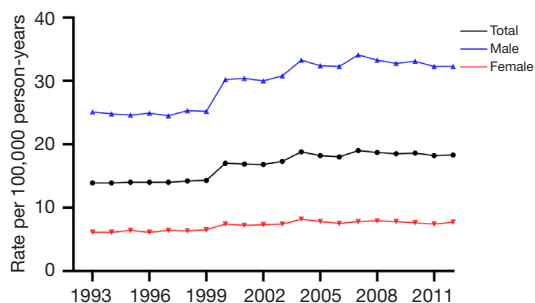


Figure 1 Incidence rates of urothelial bladder cancer in the general population, male and female from 1993 to 2012.

maintaining around 8.0 per 100,000 person-years (Figure 1).

Overall, the IR increased with the increasing of age. However, for patients under 75 years old, the IR of UBC had been stable in all age groups in the last two decades. For patients over 75 years old, the IR increased slightly before 2003, and maintained stable after 2003 (140/100,000, Figure 2). As for race categorization, the IRs of Blacks and others remained at about 11.0 and 8.0 per 100,000 person-years respectively. The IR of Whites increased slightly before 2003 and remained at about 20.0 per 100,000 person-years after 2003. For further race-age classification, the IRs of Blacks and others were relatively stable at all age groups. For Whites, the IR trends in all age groups were similar to those in the whole population (Figure 3).

Moreover, subsequent analyses by sex showed the similar IR trends with the whole population. However, in female Blacks and others, the IR in people aged over 65 years old fluctuated greatly, which was mainly because of the small number of cases in this population (Figure 4).

As shown in Figure 5, the Joinpoint regression figures indicate that the APCs before 2004 in different populations were statistically significant. The APC before 2004 was 2.95,

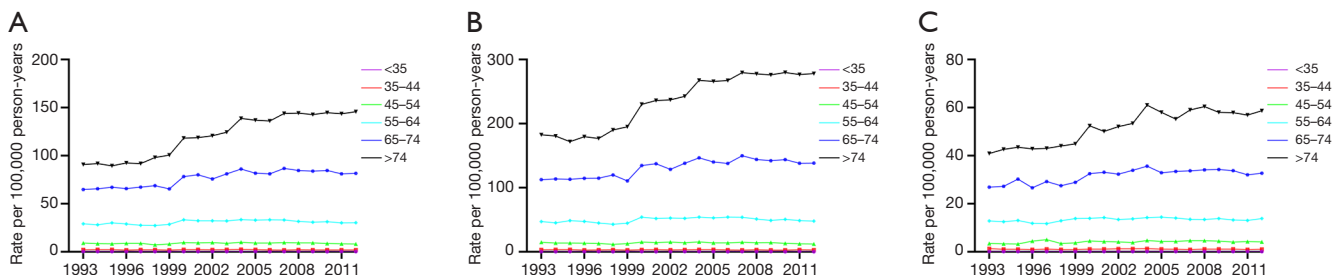


Figure 2 Incidence rates of urothelial bladder cancer in the general population (A), male (B) and female (C) stratified by age from 1993 to 2012.

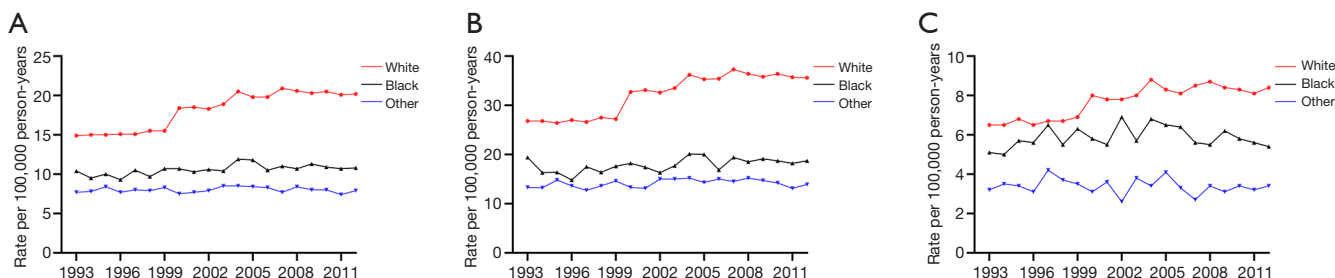


Figure 3 Incidence rates of urothelial bladder cancer in the general population (A), male (B) and female (C) stratified by race from 1993 to 2012.

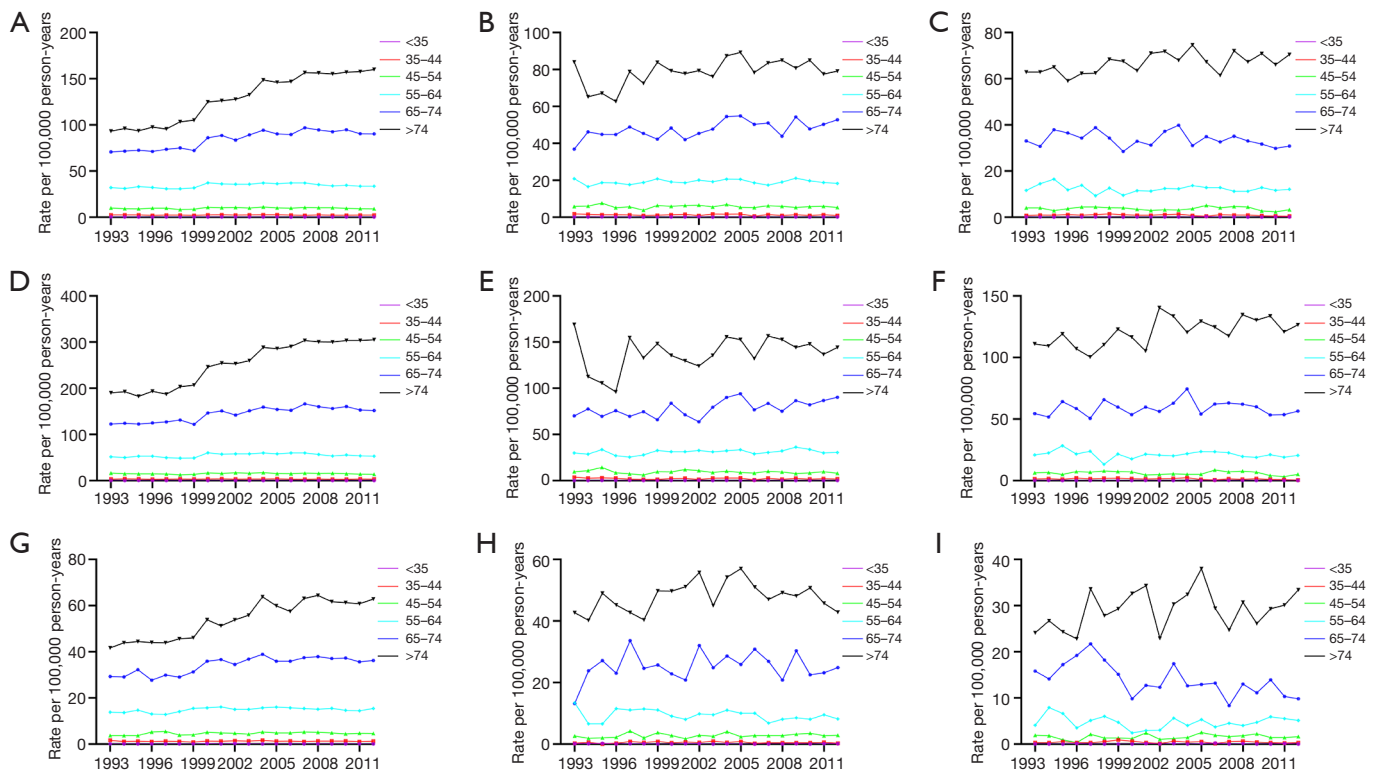


Figure 4 Incidence rates of urothelial bladder cancer in the general population (A,B,C), male (D,E,F) and female (G,H,I) stratified by race-age (A, D and G for White; B, E and H for Black; C, F and I for Other) from 1993 to 2012.

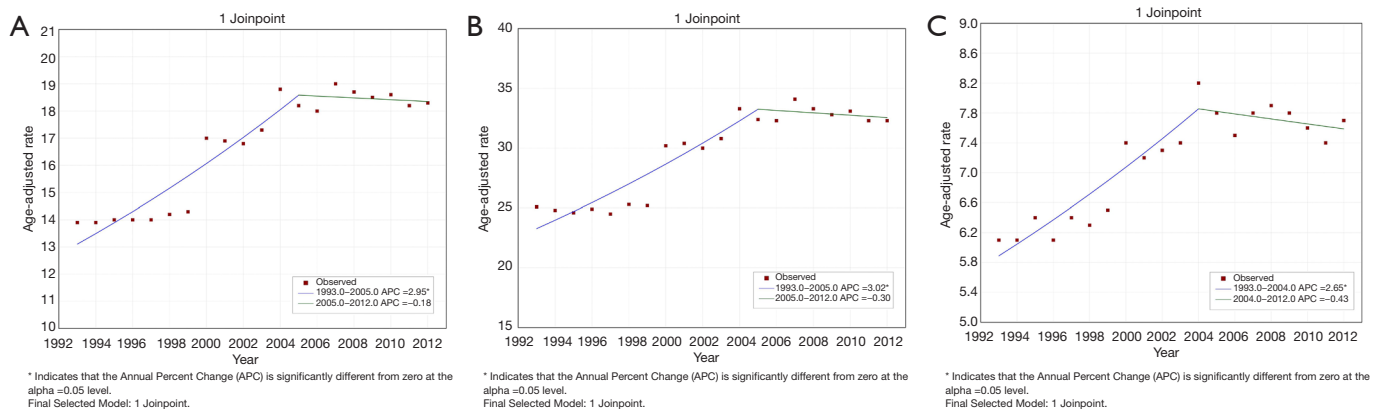


Figure 5 Annual percentage change curves for different populations: the general population (A), male (B) and female (C).

3.02 and 2.65 for the whole, male and female populations, respectively (all $P < 0.05$).

Proportional mortality ratio

A total of 131,585 UBC patients died up to the last follow-

up (December 31, 2017). Among them, 39,030 patients died of BC, 30,881 patients died of CVD, and the remaining patients died of other causes (data not tabled). The PMRs of each COD are shown in *Figure 6A*, and further stratified by age at diagnosis (*Figure 6B*), gender (*Figure 6C*), race (*Figure 6D*), median household income (*Figure 6E*), the

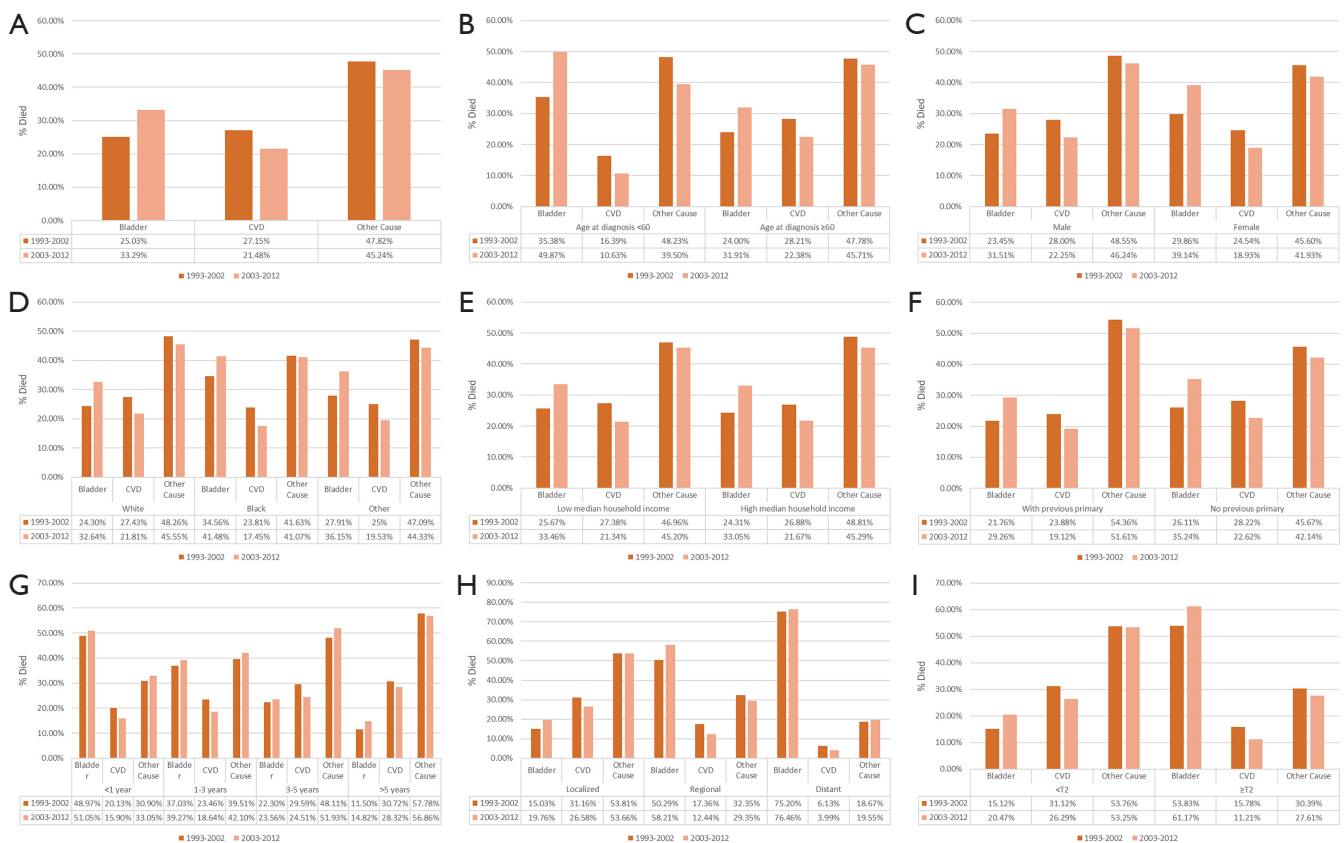


Figure 6 Proportional mortality ratios for general population (A), and further stratified by age at diagnosis (B), gender (C), race (D), median household income (E), previous primary malignancy (F), time since diagnosis (G), historic stage (H), and T stage (I).

history of a prior malignancy (Figure 6F), time to diagnosis (Figure 6G), histological type (Figure 6H) and T stage (Figure 6I).

In patients diagnosed between 2003 and 2012, the proportion of BC-specific deaths increased and CVD-specific deaths decreased when compared with patients diagnosed between 1993 and 2002. As shown in Figure 6B, the largest increase in BC-specific deaths was detected in patients younger than 60 years old. When compared with patients over 60 years old, the proportion of BC-specific deaths was higher and the proportion of CVD-specific deaths was lower in patients younger than 60 years old. Furthermore, as the time to diagnosis increased, the proportion of BC-specific deaths was decreasing, while the proportions of CVD/other causes-specific deaths was increasing. Conversely, as the histological level progressed (localized vs. regional vs. distant), the proportion of BC-specific deaths increased significantly, while the proportion of CVD/other causes-

specific deaths decreased significantly. Furthermore, Blacks were more likely to die of BC than other races. However, no significant difference was found in the subgroup analyses by gender, the history of a prior malignancy and the median household income.

SMR

The SMR analysis was limited to patients diagnosed between 1999 and 2012 due to that fact that data on WONDER online databases were recorded only from 1999 to 2017. Comparisons between the general population and UBC cases in the age-specific risks of BC, CVD and all-cause mortality are presented in Table 3. UBC patients had higher BC, CVD and all-cause mortality than the general population. Similarly, higher mortality could be seen in both male and female populations. Overall, UBC patients were 3,905.6 times (95% CI: 3,864.3–3,947.4) more likely to die of BC, 44.5 times (95% CI: 43.9–45.0) more likely

Table 3 Standardized mortality ratios of cardiovascular disease, bladder cancer and all-cause mortality, by age and gender, 1999–2012

Age	Observed deaths	Number of UBC cases	Crude risk ¹	Expected deaths	SMR (95% CI)
CVD mortality ² , n=24,608					
<35 years	5	989	4.5	0.0	112.3 (48.0–263.0)
35–44 years	34	3,368	35.5	1.2	28.4 (20.4–39.7)
45–54 years	350	14,347	107.6	15.4	22.7 (20.4–25.2)
55–64 years	1,799	35,823	259.8	93.1	19.3 (18.5–20.2)
65–74 years	5,573	55,342	652.8	361.3	15.4 (15.0–15.8)
≥75 years	16,847	83,242	3,219.0	2,679.6	6.3 (6.2–6.4)
Male	19,491	146,748	278.3	408.4	47.7 (47.1–48.4)
Female	5,117	46,383	294.3	136.5	37.5 (36.5–38.5)
Overall	24,608	193,131	286.4	553.1	44.5 (43.9–45.0)
All-cause mortality, n=108,359					
<35 years	62	989	78.6	0.8	79.8 (62.2–102.2)
35–44 years	551	3,368	189.7	6.4	86.2 (79.3–93.7)
45–54 years	3,409	14,347	421.2	60.4	56.4 (54.6–58.3)
55–64 years	12,085	35,823	898.0	321.7	37.6 (36.9–38.2)
65–74 years	28,171	55,342	2,081.4	1,151.9	24.5 (24.2–24.7)
≥75 years	64,081	83,242	7,759.0	6,458.7	9.9 (9.8–10.0)
Male	82,784	146,748	829.5	1,217.3	68.0 (67.5–68.5)
Female	25,575	46,383	818.1	379.5	67.4 (66.6–68.2)
Overall	108,359	193,131	823.7	1,590.8	68.1 (67.7–68.5)
Bladder cancer mortality, n=33,943					
<35 years	28	989	0.0	0.0	26,2232.9 (181,437.9–379,006.3)
35–44 years	316	3,368	0.2	0.0	46,912.1 (42,016.9–52,377.6)
45–54 years	1,674	14,347	1.3	0.2	8,975.3 (8,555.6–9,415.7)
55–64 years	4,773	35,823	4.8	1.7	2,775.8 (2,698.2–2,855.7)
65–74 years	8,482	55,342	14.7	8.1	1,042.6 (1,020.7–1,065.0)
≥75 years	18,670	83,242	47.0	39.1	477.2 (470.4–484.1)
Male	24,475	146,748	6.4	9.4	2,606.0 (2,573.5–2,638.8)
Female	9,468	46,383	2.7	1.3	7,560.2 (7,409.5–7,714.1)
Overall	33,943	193,131	4.5	8.7	3,905.6 (3,864.3–3,947.4)

¹, crude risk was calculated based on the US population (per 100,000); ², CVD mortality includes: diseases of heart (ICD 10 = 100–109, 111, 113, 120–151), hypertension without heart disease (ICD 10 = 110, 112), cerebrovascular diseases (ICD 10 = 160–169), atherosclerosis (ICD 10 = 170), aortic aneurysm (ICD 10 = 171), other diseases of arteries, arterioles and capillaries (ICD 10 = 172–178). SMR, standardized mortality ratio; CVD, cardiovascular disease; UBC, urothelial bladder cancer; CI, confidence interval; ICD, International Classification of Diseases.

Table 4 Survival probabilities of 3-, 5- and 10-year overall survival of urothelial bladder cancer patients, further stratified by age, gender and T stage

Variables	1993–2012	1993–2002	2003–2012
3-year OS	0.709 (0.707–0.711)	0.710 (0.707–0.714)	0.708 (0.706–0.710)
<60 years	0.870 (0.867–0.874)	0.881 (0.876–0.887)	0.865 (0.861–0.869)
≥60 years	0.674 (0.672–0.676)	0.671 (0.667–0.675)	0.676 (0.673–0.678)
Male	0.715 (0.712–0.717)	0.720 (0.716–0.723)	0.712 (0.710–0.715)
Female	0.690 (0.686–0.694)	0.683 (0.676–0.690)	0.694 (0.689–0.699)
<T2	0.802 (0.800–0.804)	0.805 (0.802–0.808)	0.800 (0.798–0.802)
≥T2	0.365 (0.360–0.369)	0.366 (0.359–0.374)	0.364 (0.359–0.369)
5-year OS	0.609 (0.607–0.611)	0.609 (0.605–0.613)	0.608 (0.606–0.611)
<60 years	0.830 (0.827–0.834)	0.841 (0.834–0.847)	0.825 (0.820–0.830)
≥60 years	0.561 (0.559–0.564)	0.556 (0.551–0.560)	0.564 (0.561–0.567)
Male	0.610 (0.607–0.612)	0.613 (0.609–0.617)	0.608 (0.606–0.611)
Female	0.605 (0.601–0.609)	0.596 (0.589–0.604)	0.609 (0.604–0.614)
<T2	0.696 (0.694–0.698)	0.698 (0.694–0.702)	0.695 (0.693–0.698)
≥T2	0.284 (0.280–0.288)	0.285 (0.278–0.293)	0.284 (0.279–0.289)
10-year OS	0.421 (0.419–0.423)	0.421 (0.417–0.425)	0.421 (0.418–0.424)
<60 years	0.747 (0.743–0.752)	0.755 (0.748–0.763)	0.745 (0.739–0.751)
≥60 years	0.3520 (0.348–0.353)	0.344 (0.341–0.349)	0.354 (0.350–0.357)
Male	0.417 (0.415–0.420)	0.420 (0.415–0.424)	0.417 (0.413–0.420)
Female	0.433 (0.428–0.437)	0.426 (0.418–0.433)	0.436 (0.430–0.433)
<T2	0.487 (0.484–0.489)	0.488 (0.484–0.493)	0.486 (0.483–0.490)
≥T2	0.180 (0.176–0.184)	0.179 (0.173–0.185)	0.180 (0.176–0.186)

Data were HR (95% CI). Note: 3,403 patients were excluded due to the unknown T stage when stratified by T stage. OS, overall survival; UBC, urothelial bladder cancer; HR, hazard ratio; CI, confidence interval.

to die of CVD and 68.1 times (95% CI: 67.7–68.5) more likely to die of all causes when compared with the general population.

Survival outcome

We calculated the 3-, 5- and 10-year OS and CSS of the whole population, and further stratified by gender, T stage, age at diagnosis. The 3-, 5- and 10-year rates for OS and CSS were 0.709, 0.609 and 0.421, and 0.861, 0.831 and 0.789, respectively (Tables 4,5). Figure 7A reveals that there was no significant difference between patients diagnosed in the two periods in OS ($P=0.7319$). However, significant difference was detected in the comparison of CSS

(Figure 7B, $P<0.001$). Moreover, comparisons stratified by clinical characteristics are shown in Figures S1,S2. For patients diagnosed in the two periods (1993–2002 vs. 2003–2012), the probabilities were 0.710 and 0.708 for 3-year OS, 0.609 and 0.608 for 5-year OS, and 0.421 and 0.421 for 10-year OS, respectively (Table 4). As for CSS, the probabilities were 0.865 and 0.858 for 3-year CSS, 0.836 and 0.829 for 5-year CSS, and 0.796 and 0.786 for 10-year CSS (Table 5). Therefore, the actual differences between patients diagnosed in the two periods were not obvious.

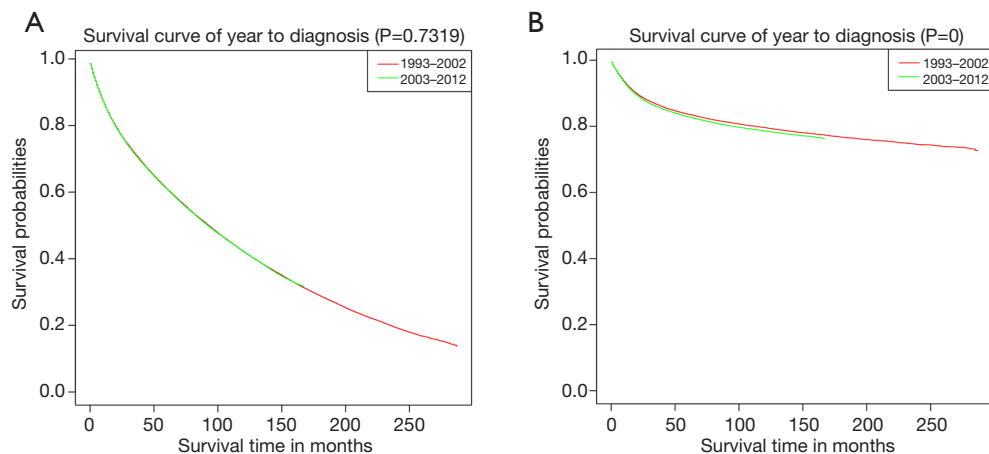
Discussion

Generally, most UBC patients had older age, lower median

Table 5 Survival probabilities of 3-, 5- and 10-year cancer-specific survival of urothelial bladder cancer patients, further stratified by age, gender and T stage

Variables	1993–2012	1993–2002	2003–2012
3-year CSS	0.861 (0.859–0.862)	0.865 (0.863–0.868)	0.858 (0.857–0.860)
<60 years	0.916 (0.913–0.918)	0.925 (0.921–0.930)	0.911 (0.907–0.914)
≥60 years	0.848 (0.846–0.850)	0.851 (0.847–0.854)	0.847 (0.845–0.849)
Male	0.872 (0.870–0.873)	0.880 (0.877–0.883)	0.868 (0.866–0.870)
Female	0.826 (0.823–0.829)	0.823 (0.817–0.829)	0.828 (0.823–0.832)
< T2	0.945 (0.944–0.946)	0.951 (0.949–0.953)	0.943 (0.941–0.944)
≥ T2	0.515 (0.510–0.520)	0.520 (0.511–0.529)	0.513 (0.507–0.519)
5-year CSS	0.831 (0.830–0.833)	0.836 (0.833–0.839)	0.829 (0.827–0.831)
<60 years	0.899 (0.896–0.902)	0.907 (0.902–0.912)	0.895 (0.891–0.898)
≥60 years	0.815 (0.813–0.817)	0.818 (0.815–0.822)	0.814 (0.812–0.816)
Male	0.841 (0.839–0.843)	0.850 (0.846–0.853)	0.838 (0.835–0.840)
Female	0.800 (0.796–0.803)	0.797 (0.790–0.803)	0.801 (0.797–0.805)
< T2	0.921 (0.920–0.923)	0.928 (0.925–0.930)	0.918 (0.917–0.920)
≥ T2	0.460 (0.454–0.465)	0.464 (0.455–0.474)	0.457 (0.451–0.464)
10-year CSS	0.789 (0.787–0.791)	0.796 (0.793–0.799)	0.786 (0.784–0.789)
<60 years	0.876 (0.872–0.879)	0.884 (0.878–0.889)	0.872 (0.868–0.877)
≥60 years	0.767 (0.764–0.769)	0.771 (0.767–0.775)	0.764 (0.761–0.767)
Male	0.798 (0.795–0.800)	0.807 (0.803–0.811)	0.793 (0.790–0.796)
Female	0.764 (0.760–0.768)	0.763 (0.756–0.770)	0.763 (0.758–0.769)
< T2	0.881 (0.879–0.882)	0.888 (0.885–0.891)	0.877 (0.874–0.879)
≥ T2	0.412 (0.406–0.417)	0.418 (0.409–0.428)	0.409 (0.402–0.416)

Data were HR (95% CI). Note: 1,477 cases were excluded due to the unknown cause of death; 3,379 patients were excluded due to the unknown T stage when stratified by T stage. CSS, cancer-specific survival; UBC, urothelial bladder cancer; CI, confidence interval.

**Figure 7** Kaplan-Meier curves of overall survival (A) and cancer-specific survival (B) for urothelial bladder cancer patients in different time periods.

household income and lower T stage. When compared with patients diagnosed between 1993 and 2002, those diagnosed between 2003 and 2012 had older age, higher proportion of men and lower median household income. The IRs of UBC had a slight upward trend before 2003, and remained stable after 2003. In this study, CVD was considered to be an important COD. In patients diagnosed between 2003 and 2012, the proportion of BC-specific deaths increased when compared with that in patients diagnosed between 1993 and 2002. Additionally, the 3-, 5- and 10-year probabilities for OS were 0.709, 0.609 and 0.421, and 0.861, 0.831 and 0.789 for CSS. Lastly, actual differences in survival outcomes between patients in the two periods were not obvious.

The median age at diagnosis of enrolled patients was 72.0 years old. The male-to-female ratio and the NMIBC-to-MIBC ratio were both about 3:1. Basic characteristics of UBC patients in this study were broadly consistent with those of previous studies (5,12-14). Moreover, older age at diagnosis, higher proportion of non-invasive diseases and N0 stage diseases were found in patients diagnosed between 2003 and 2012. First of all, it suggested that the tumor burden caused by BC was decreasing due to the rapid development of medicine and economy. In addition, we found that the proportion of people who chose surgery reduced slightly over time. We attributed this to the fact that more and more treatment alternatives have been provided for UBC patients, including molecular targeted drugs (15,16), neoadjuvant chemotherapy (17,18), immunotherapy (19,20) and so on.

Subsequently, we analyzed the main CODs of UBC patients. We found that CVD was one of the most important CODs. Many previous studies have investigated the relationship between cancer survivors and CVD. In a population-based cohort study (21) on the basis of the multiple linked UK electronic health records databases, conclusions could be drawn that the medium-term to long-term risk for CVD in survivors of most cancer types was higher than that in the general population. Felix *et al.* (22) demonstrated that female patients with endometrial cancer had higher CVD burden. Usually, women with endometrial cancer may experience excess CVD in any age category, especially in younger age groups. Furthermore, Bosco *et al.* (23) reported that androgen deprivation therapy for prostate cancer patients could increase the risk of CVD.

Many previous studies (24-28) have explored the critical role of smoking in the development and progression of BC. Hou *et al.* (29) found that former and current smoking

status could increase the risk of recurrence and mortality in patients with BC. Masaoka and his teammates (30) declared that smoking was a persuasive risk factor for BC in Japanese. Other factors such as obesity (31-33), and diabetes (34-36) were also considered to be related to the occurrence and development of BC. Coincidentally, these factors are highly recognized to be tightly associated with the risk of CVD, which could well explain the higher proportion of CVD mortality in UBC patients.

In addition, we found that survival outcomes of UBC patients did not change significantly over the past 20 years. Nowadays, with the fast development of technology and medicine, increasing management manners for UBC have been emerged, including robot-assisted technology in surgery, the advent of molecular targeted drugs and immunotherapy. In theory, the mentioned above could extremely improve the prognosis of UBC patients. However, ideal survival improvement was not detected in this study. Jahnson *et al.* (37) performed a study based on the Swedish National Registry of Urinary Bladder Cancer (SNRUBC) to explore the changes in cancer characteristics, management and survival outcomes of BC patients over a period of 15 years (1997–2001 *vs.* 2002–2006 *vs.* 2007–2011). They found that the proportion of non-muscle invasive diseases increased over time, and the management became more aggressive for all cancer stages. Despite these, survival outcomes exhibited no significant differences over time. It was probable that many patients in advanced stages with extravesical involvement would only benefit little in survival outcomes (38,39). Additionally, cystectomy is a palliative treatment for many patients due to the older age, higher comorbidity or advanced stages (37). On the contrary, Engholm *et al.* (40) investigated the 5-year relative survival of patients with BC diagnosed in the Nordic countries between 1964 and 2003, and found that the relative survival of BC patients improved significantly over time.

Nevertheless, several limitations should not be ignored in our study. Firstly, the absence of related information regarding to the risk factors (such as socio-economic, lifestyle, and dietary changes) made it difficult to investigate a direct interpretation of the role over time. Secondly, it was a descriptive and retrospective study, leading to unavoidable sources of bias and variations. Additionally, data on tumor stages or size were limited, causing a potential bias during the analysis procedure. Although the SEER database has its own defects, it covers approximately 30% of the US population. However, it is one of the best databases to

investigate the incidence, mortality and survival outcomes of cancer patients.

In conclusion, incidence of UBC increased slightly before 2003 and maintained a stable trend of about 20 per 100,000 person-years after 2003. Patients with UBC were with higher CVD burden than the general population. Moreover, comparisons between patients in the last two decades showed no obvious changes in survival outcomes. Further studies to identify suitable CVD screening strategies and interventions in this population are warranted.

Acknowledgments

Funding: This study was supported by the National Natural Science Foundation of China (No. 81702520), the Medical Research Project of Jiangsu Provincial Health and Family Planning Commission (No. H2018052), the Research Project of Jiangsu Cancer Hospital (No. ZN201602), and the young talents program of Jiangsu Cancer Hospital (No. 2017YQL-04).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/atm-20-2108>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm-20-2108>). XL serves as an unpaid Section Editor of *Annals of Translational Medicine* from Oct 2019 to Sep 2020. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies were in accordance with the national research committee and with the Declaration of Helsinki (as revised in 2013). This study was exempt from Institutional Review Board (IRB) approval because the original data were from a public database.

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Cite this article as: Zang Y, Li X, Cheng Y, Qi F, Yang N. An overview of patients with urothelial bladder cancer over the past two decades: a Surveillance, Epidemiology, and End Results (SEER) study. *Ann Transl Med* 2020;8(23):1587. doi: 10.21037/atm-20-2108

Table S1 Additional information on urothelial bladder cancer patients included in the study

Variables	Total	1993–2002	2003–2012	P value ¹
N	220,405	69,314	151,091	
Tumor site, n (%)				<0.001
Trigone	14,035 (6.37)	4,340 (6.26)t	9,695 (6.42)	
Dome	7,613 (3.45)	2,488 (3.59)	5,125 (3.39)	
Lateral wall	45,181 (20.50)	14,355 (20.71)	30,826 (20.40)	
Anterior wall	4,383 (1.99)	1,302 (1.88)	3,081 (2.04)	
Posterior wall	20,788 (9.43)	6,535 (9.43)	14,253 (9.43)	
Bladder neck	7,082 (3.21)	2,326 (3.36)	4,756 (3.15)	
Ureteric orifice	9,920 (4.50)	3,548 (5.12)	6,372 (4.22)	
Urachus	34 (0.02)	12 (0.02)	22 (0.01)	
Overlapping lesion	24,067 (10.92)	8,247 (11.90)	15,820 (10.47)	
Bladder, NOS	87,302 (39.61)	26,161 (37.74)	61,141 (40.47)	
T stage, n (%)				<0.001
T0	29 (0.01)	0 (0.00)	29 (0.02)	
Ta	102,913 (46.69)	29,398 (42.41)	73,515 (48.66)	
Tis	16,444 (7.46)	7,898 (11.39)	8,546 (5.66)	
T1	52,775 (23.94)	16,315 (23.54)	36,469 (24.14)	
≥T2	44,841 (20.34)	14,295 (20.62)	30,546 (20.22)	
Tx	3,403 (1.54)	1,408 (2.03)	1,995 (1.32)	
N stage, n (%)				<0.001
N0	197,876 (89.78)	56,327 (81.26)	141,549 (93.68)	
N1	2,984 (1.35)	332 (0.48)	2,652 (1.76)	
N2	2,574 (1.17)	454 (0.65)	2,120 (1.40)	
N3	161 (0.07)	42 (0.06)	119 (0.08)	
Nx	16,810 (7.63)	12,159 (17.54)	4,651 (3.08)	
M stage, n (%)				<0.001
M0	210,840 (95.66)	66,276 (95.62)	144,564 (95.68)	
M1	5,788 (2.63)	1,641 (2.37)	4,147 (2.74)	
Mx	3,777 (1.71)	1,397 (2.02)	2,380 (1.58)	
Census region, n (%)				<0.001
Alaska	109 (0.05)	40 (0.06)	69 (0.05)	
East	88,375 (40.10)	24,982 (36.04)	63,393 (41.96)	
Northern Plains	22,801 (10.35)	8,619 (12.43)	14,182 (9.39)	
Pacific Coast	98,395 (44.64)	30,940 (44.64)	67,455 (44.65)	
Southwest	10,725 (4.87)	4,733 (6.83)	5,992 (3.97)	

¹, comparison between 1993–2002 and 2003–2012. UBC, urothelial bladder cancer; NOS, not otherwise specified.

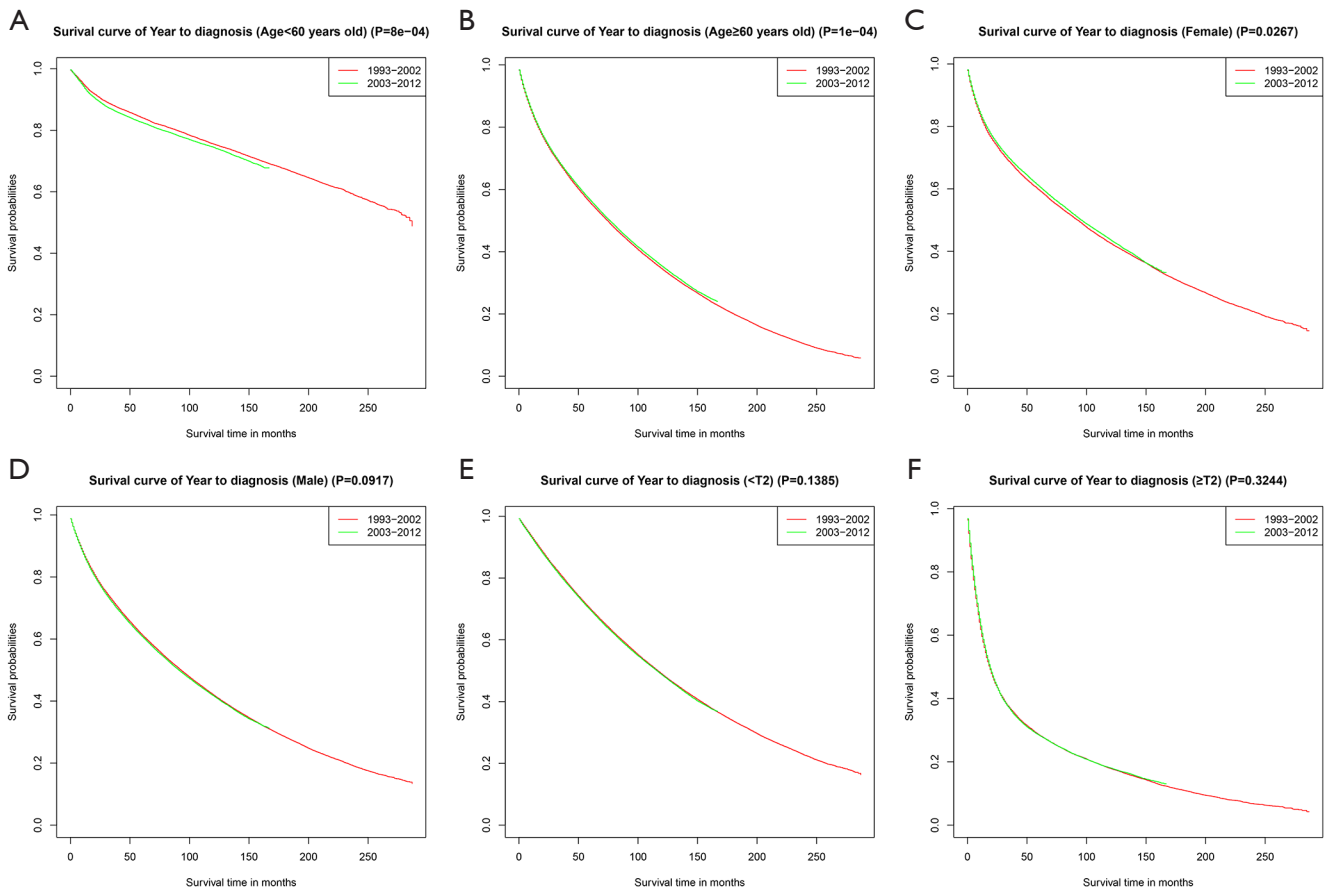


Figure S1 Kaplan-Meier curves of overall survival for urothelial bladder cancer patients in different time periods, stratified by age (A,B), gender (C,D) and T stage (E,F).

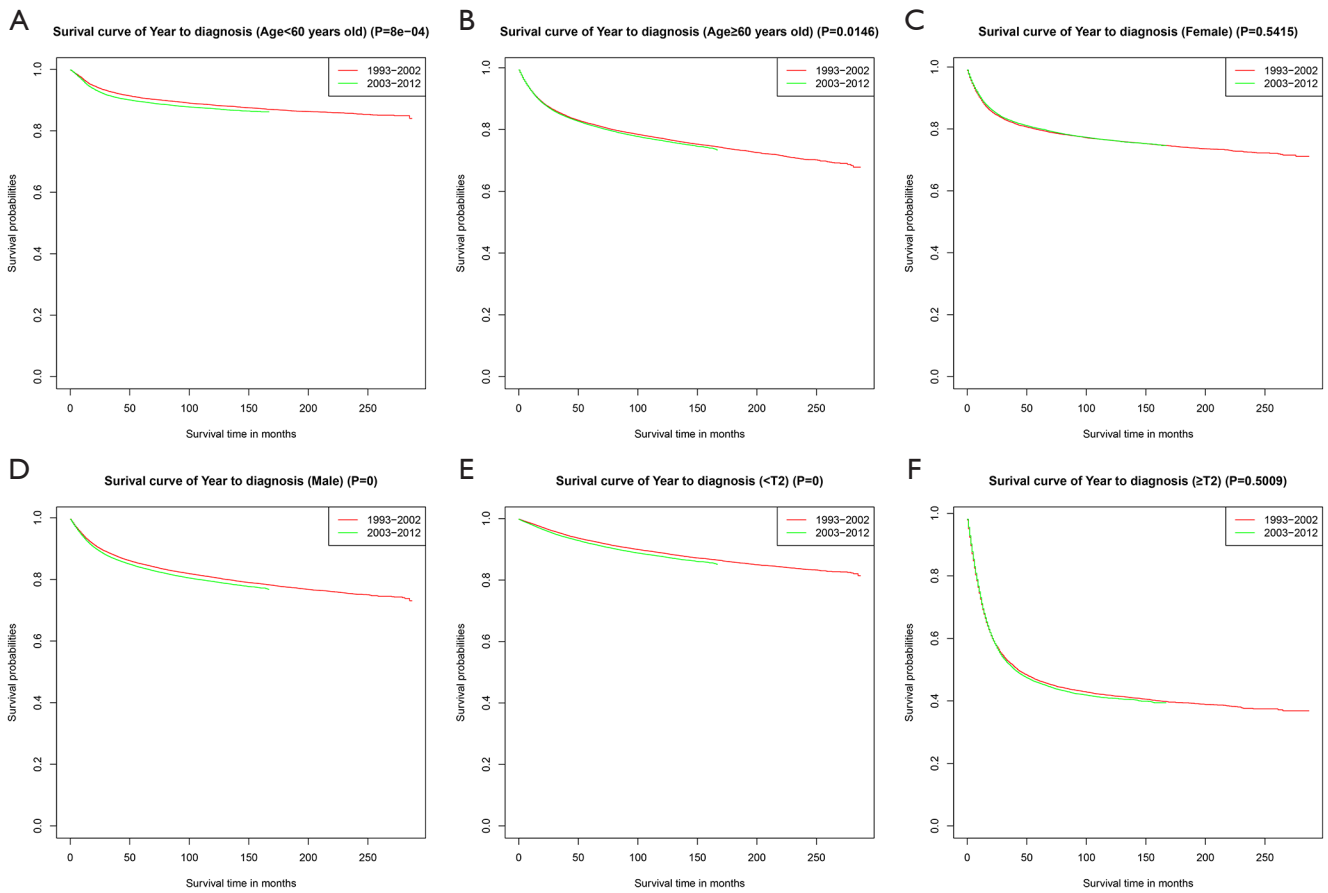


Figure S2 Kaplan-Meier curves of cancer-specific survival for urothelial bladder cancer patients in different time periods, stratified by age (A,B), gender (C,D) and T stage (E,F).