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Original article

Survival differences among patients with bladder cancer according to sex: Critical evaluation of radical cystectomy use and delay to treatment

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Abstract

Objective: Sex differences in bladder cancer survival are well known. However, the effect of type of treatment, timing to surgery when rendered, and survival outcomes according to sex have not been extensively examined. Given the relatively low incidence of bladder cancer in females, large multicenter and population-based studies are required to elucidate sex differences in survival. In this study, we sought to characterize the effect of use and timing of radical cystectomy (RC) according to sex and survival outcomes.

Methods: A total of 9,907 patients aged 66 years or older diagnosed with clinical stage II to IV N0M0 bladder cancer from January 1, 2001 to December 31, 2011 from Surveillance, Epidemiology, and End Results-Medicare data were analyzed. We used multivariable regression analyses to identify factors predicting the use and delay of RC. Cox proportional hazards models were used to analyze survival outcomes.

Results: Of the 9,907 patients diagnosed with bladder cancer, 3,256 (32.9%) were females. Women were significantly more likely to undergo RC across all stages compared to their male counterparts (stage II: relative risk [RR] = 1.48, 95% CI: 1.33–1.65, $P < 0.001$; stage III: RR = 1.24, 95% CI: 1.13–1.37, $P < 0.001$; and stage IV: RR = 1.33, 95% CI: 1.19–1.49, $P < 0.001$). Moreover, there was no significant difference in delay to RC according to sex across all clinical stages. Using propensity score matching, women had worse overall (hazard ratio = 1.07; CI: 1.01–1.14; $P = 0.024$), and worse cancer-specific survival (hazard ratio = 1.26; CI: 1.17–1.36, $P < 0.001$) than men.

Conclusion: Sex differences persist with women who are significantly more likely to undergo RC independent of clinical stage. However, women have significantly worse survival than men. Delay from diagnosis to surgery did not account for this decreased survival among women.

Keywords: Bladder cancer; Sex; Differences; Utilization; Radical cystectomy

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1. Introduction

There were an estimated 76,960 new cases and 16,390 deaths from bladder cancer in the United States in 2016, with men accounting for 76.5% of these new cases [1]. Although women are less likely to be diagnosed with bladder cancer, they present with more advanced disease and have worse survival outcomes compared to their male counterparts [2–6]. Moreover, prior studies have shown sex differences in survival following radical cystectomy (RC) [7–11]. The etiology of this sex discrepancy is still largely unknown, with prior studies suggesting inferior process of care measures such as delay to diagnosis among women leading to decreased chance for curative therapy and increased mortality [12]. This theory has been supported by studies attributing hematuria and voiding symptoms to be mistaken for infection, potentially leading to delayed referral to urology with delay in diagnosis of malignancy [13].

Current guidelines for patients with nonmetastatic muscle-invasive bladder cancer recommend neoadjuvant chemotherapy followed by RC with extended pelvic lymphadenectomy [14]. Although underuse of neoadjuvant chemotherapy is well known, RC is significantly underutilized with use relatively unchanged over the past 3 decades, which corroborate similar unchanged survival outcomes among patients with muscle-invasive disease [15]. Moreover, although underutilization of RC is paramount, timing to RC has been strongly associated with survival outcomes [16]. Prior work by Messer et al. [17] identified the female sex as an adverse prognostic factor, independent of clinical and pathological features for patients undergoing RC [18]. However, the effect of type of treatment, timing to surgery when rendered, and survival outcomes according to sex has not been extensively examined [18,19]. Therefore, we provide a population-based assessment to discern whether use of RC differs according to sex, specifically examining the receipt and timing of RC in relation to survival outcomes.

2. Patients and methods

2.1. Data source

Our study used the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Medicare linked database. The dataset contains information on patients with newly diagnosed cancers in 18 US regions that are generalizable to the US population. Bladder cancer identified in the SEER database conformed to the standards of the North American Association of Central Cancer Registries, and case ascertainment in the SEER data was 98% complete [20]. The SEER database contains information on patient demographics, tumor characteristics (stage, grade, and histology), and follow-up information. The Medicare database contains information on inpatient and outpatient claims. The study was deemed exempt by the Institutional Review Board at The University of Texas Medical Branch at Galveston and The University of Texas MD Anderson Cancer Center.

2.2. Ascertainment of study cohort

We restricted our analysis to patients with bladder cancer diagnosed as clinical stage II to IV N0M0 transitional cell or urothelial carcinoma from 2001 through 2011 with claims data available through December 31, 2013. Clinical stage is pathologically confirmed at RC incorporating both clinical stage and pathological stage into a collaborative stage variable using the American Joint Committee on Cancer (AJCC) staging classification system in SEER. We restricted the study sample to subjects who had Medicare fee-for-service coverage and for whom Medicare part A and part B claims data were available 12 months before and 12 months after the date of diagnosis. The final cohort consisted of 9,907 patients (Supplementary Table 1).

2.3. Identification of bladder cancer treatments

Receipt of bladder cancer treatments was determined for 1 year after the date of diagnosis. Subjects who underwent RC were identified based on International Classification of Diseases—Version 9 (ICD-9) and Common Procedural Terminology-4 (CPT-4) codes indicative for RC (Supplementary Table 2). RC used in this study included both open and robot-assisted laparoscopic surgery. Subjects who underwent surgery alone or in combination with radiation or chemotherapy are considered in the RC group. Subjects who received radiation were classified based on diagnosis and procedure codes in Medicare claims that are consistent with ICD-9 and CPT codes specific for radiotherapeutic procedures used to treat bladder cancer (Supplementary Table 2). Among those without RC, we combined subjects who received chemotherapy alone, radiation alone, or combination chemotherapy and radiation into 1 treatment group because bladder-sparing therapeutic protocols for invasive bladder cancer typically combine radiation and chemotherapy [21]. We identified subjects who received chemotherapy based on ICD-9 and CPT-4 codes that are consistent with chemotherapeutic agents commonly used in the management of bladder cancer in the absence of a simultaneous code for RC (Supplementary Table 2).

2.4. Study covariates

Using the SEER database, we obtained age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and non-Hispanic other races), marital status (single, married, and unknown), and SEER region (Northeast, South, Midwest, and West). Urinary symptoms within

1 year before cancer diagnosis were collected and included the following ICD-9 codes grouped into 3 separate categories: irritative urinary symptoms, obstructive urinary symptoms, and hematuria as shown in Supplementary Table 2. We also obtained subject's community socioeconomic characteristics. Census tract–level median household income was divided into quartiles. From the SEER database, we determined cancer diagnosis year, grade, and stage. From claims database, we identified the presence of hydronephrosis, comorbidity score, and treatment method. Level of comorbidity was assessed using the Klabunde modification of the Charlson comorbidity index (CCI) during the year before diagnosis [22]. The Klabunde modification uses comorbid conditions identified by the CCI and incorporates the diagnostic and procedure data contained in Medicare physician part B claims.

2.5. Statistical analysis

Univariate analyses was performed to assess the association of RC with the list of covariates described earlier, using the Pearson chi-square test. We created a multivariable generalized linear model that incorporates stage, treatment method (RC, chemotherapy, and radiation therapy), and sex stratified by stage to evaluate the effect of sex associated with receipt of bladder cancer treatment, and to evaluate the association between sex and delayed RC from the time of diagnosis. In our multivariable analysis, we further classified the timing of RC into 2 groups, less or equal to 12 weeks and longer than 12 weeks, as previous studies have reported inferior overall survival and progression-free survival for patients who received RC more than 84 to 90 days after diagnosis [23–26]. In the sensitivity analysis, we performed propensity score matching. Relative risks (RRs) were reported from these models. Cox proportional hazards models were used to analyze overall and cancer-specific survival outcomes. We used logistic regression analysis to generate probability to match male and female patients using the previously mentioned demographic and clinical covariates as predictors. We then conducted Cox proportional hazards models, and the propensity score–matched cohort was used to analyze overall and cancer-specific survival outcomes. Proportional hazards assumption in Cox Model was tested using proportionality test. All statistical tests were 2-sided, and all analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC). Statistical significance was defined as $P < 0.05$.

3. Results

Patient demographics are summarized in Table 1. Of the 9,907 patients diagnosed with bladder cancer, 3,256 (32.9%) were females. Although there was no significant difference in bladder cancer diagnosis over the study period, women were older, nonwhite race/ethnicity, unmarried, had fewer comorbidities, and presented with more advanced disease than men (all $P < 0.001$). Men were more likely to present with hematuria and obstructive urinary symptoms, whereas women were more likely to present with irritative urinary symptoms (all $P < 0.001$). Overall, 2,738 of the total patients in this study underwent RC, 1,038 (31.9%) of them were females ($P < 0.001$) (Fig. 1).

We analyzed predictors for receipt of RC stratified by stage and sex as shown in Table 2. Patients who received neoadjuvant chemotherapy were more likely to have delayed RC across all stages ($P < 0.01$). Women were significantly more likely to undergo RC across all stages compared to their male counterparts (stage II: RR = 1.48, 95% CI: 1.33–1.65, $P < 0.001$; stage III: RR = 1.24, 95% CI: 1.13–1.37, $P < 0.001$; and stage IV: RR = 1.33, 95% CI: 1.19–1.49, $P < 0.001$). Moreover, there was no significant difference in delay to RC according to sex across all clinical stages.

The overall and cancer-specific survival estimates for all patients with bladder cancer according to stage and sex are presented in Table 3. Overall survival for all patients (hazard ratio [HR] = 1.07; 95% CI: 1.02–1.12; $P = 0.010$) and those with stage IV disease (HR = 1.19; 95% CI: 1.08–1.30; $P < 0.001$) was significantly worse for women than men (Fig. 2). Moreover, women had worse cancer-specific survival when compared to men for all stages (HR = 1.27; 95% CI: 1.19–1.35; $P < 0.001$) and specifically among those diagnosed with stage II (HR = 1.20; CI: 1.09–1.32; $P < 0.001$), stage III (HR = 1.45; CI: 1.24–1.70; $P < 0.001$), and stage IV (HR = 1.29; CI: 1.16–1.43; $P < 0.001$) (Fig. 3). Using propensity score matching (Supplementary Table 3), women had worse overall (HR = 1.07; CI: 1.01–1.14; $P = 0.024$) and cancer-specific survival (HR = 1.26; CI: 1.17–1.36; $P < 0.001$) than men.

Adjusted HR of delayed RC for overall survival and cancer-specific survival stratified by sex were performed (Supplementary Table 4). There was no significant difference in overall or cancer-specific survivals noted. As an attempt to control for further unknown confounders, we analyzed noncancer survival by treatment (rather than all-cause survival). We noticed an effect of RC on the cancer-specific but not the noncancer survival ($P = 0.207$).

4. Discussion

Men are more likely to be diagnosed with bladder cancer; however, women have increased bladder cancer-specific mortality [1–6,27]. Our study used a large population-based cancer registry to critically examine sex differences in survival taking into account known predictors for survival as well as treatments including receipt and timing of RC. Our research confirms that although women have decreased incidence and increased bladder

Table 1
Patient demographic and clinical characteristics

Characteristic	Total	Male		Female		*P* value
		No.	%	No.	%	
Year of diagnosis						0.058
2001	815	561	8.4	254	7.8	
2002	920	579	8.7	341	10.5	
2003	883	596	9.0	287	8.8	
2004	971	637	9.6	334	10.3	
2005	992	665	10.0	327	10.0	
2006	942	623	9.4	319	9.8	
2007	906	610	9.2	296	9.1	
2008	908	599	9.0	309	9.5	
2009	848	584	8.8	264	8.1	
2010	866	589	8.9	277	8.5	
2011	856	608	9.1	248	7.6	
Age group						<0.001
66–69	1,333	988	14.9	345	10.6	
70–74	1,942	1,364	20.5	578	17.8	
75–79	2,405	1,615	24.3	790	24.3	
80+	4,227	2,684	40.4	1,543	47.4	
Race/ethnicity						<0.001
White	8,564	5,863	88.2	2,701	83.0	
Black	604	292	4.4	312	9.6	
Hispanics	279	194	2.9	85	2.6	
Other	460	302	4.5	158	4.9	
Marital status						<0.001
Single	1,440	918	13.8	522	16.0	
Married	5,420	4,394	66.1	1,026	31.5	
Unknown	3,047	1,339	20.1	1,708	52.5	
Rural area						0.108
No	9,691	6,495	97.7	3,196	98.2	
Yes	216	156	23	60	1.8	
Census region						0.016
West	3,907	2,694	40.5	1,213	37.3	
Northeast	2,354	1,540	23.2	814	25.0	
Midwest	1,139	761	11.4	378	11.6	
South	2,507	1,656	24.9	851	26.1	
Median household income, $						0.511
≤23,364	2,808	1,882	28.3	926	28.4	
23,365–31,906	2,523	1,701	25.6	822	25.2	
31,907–41,719	2,344	1,595	24.0	749	23.0	
≥41,720	2,232	1,473	22.1	759	23.3	
Stage						0.007
II	5,220	3,578	53.8	1,642	50.4	
III	1,889	1,241	18.7	648	19.9	
IV	2,798	1,832	27.5	966	29.7	
Hydronephosis						<0.001
No	8,866	6,018	90.5	2,848	87.5	
Yes	1,041	633	9.5	408	12.5	
Grade						0.182
Low	625	439	6.6	186	5.7	
High	8,754	5,866	88.2	2,888	88.7	
Unknown	528	346	5.2	182	5.6	
Comorbidity score						0.001
0	5,361	3,527	53.0	1,834	56.3	
1	2,415	1,615	24.3	800	24.6	
2	1,083	767	11.5	316	9.7	
3+	1,048	742	11.2	306	9.4	
Radical cystectomy						<0.001
No	7,169	4,951	74.4	2,218	68.1	
Yes	2,738	1,700	25.6	1,038	31.9	
Treatment						<0.001
No curative treatment	4,405	3,036	45.6	1,369	42.0	

Table 1
Continued

Characteristic	Total	Male		Female		*P* value
		No.	%	No.	%	
Radical cystectomy alone	365	224	3.4	141	4.3	
Radical cystectomy with LDS	2,373	1,476	22.2	897	27.5	
Radiation therapy or chemotherapy or both	2,764	1,915	28.8	849	26.1	
Neoadjuvant chemotherapy						0.784
No	9,513	6,389	96.1	3,124	95.9	
Yes	394	262	3.9	132	4.1	
Hematuria						<0.001
No	3,672	2,385	35.9	1,287	39.5	
Yes	6,235	4,266	64.1	1,969	60.5	
Irritative symptoms						<0.001
No	7,726	5,299	79.7	2,427	74.5	
Yes	2,181	1,352	20.3	829	25.5	
Obstructive symptoms						<0.001
No	8,606	5,587	84.0	3,019	92.7	
Yes	1,301	1,064	16.0	237	7.3	

LDS = lymph node dissection.

cancer–specific mortality, these differences in survival cannot be explained by RC use, delay to surgery, or adverse clinical and pathological determinants, or all of these.

First, women presented with more advanced disease, which is consistent with prior studies. Moreover, there was no significant difference in diagnosis according to sex during the study period. Although we did not account for delay to diagnosis of urinary symptoms (i.e., hematuria) in diagnosing bladder cancer, we found women diagnosed to be older, non-Hispanic black race/ethnicity, and unmarried. These determinants, in addition to advanced stage of disease, have been previously associated with decreased survival among patients with bladder cancer [21,28]. Other studies have found that women present with more advanced stage for cystectomy, and stage for stage, do worse. However, 1 study found that when matched 1:1 with males receiving cystectomy, taking in to account stage, grade, p53 status, chemotherapy use, hydronephrosis, and time to cystectomy, there was no difference [29]. In the present study, using propensity score matching analyses to control for these and other determinants, we showed a persistent decreased overall and cancer-specific survival among women when compared to men. As an attempt to control for further unknown confounders, we analyzed noncancer survival by treatment (rather than all-cause survival). We noticed an effect of treatment on the cancer-specific but not the noncancer survival, thus confirming the association between treatment and cancer-specific survival cannot be explained by other unknown confounders [30]. Although we certainly understand such analytic methods cannot control for all potential confounders, these data suggest that advanced-stage disease at presentation may not account for the survival difference according to sex [4]. Moreover, advanced stage disease such as stage IV is not necessarily the same for men and women. In the case of extension to the genital system in women, surgery can be easily proposed and performed, whereas it is more complicated in the case of rectal or parietal involvement in men. This is a major bias to discuss in order to consider when interpreting the survival difference according to sex in patients with stage IV cancer.

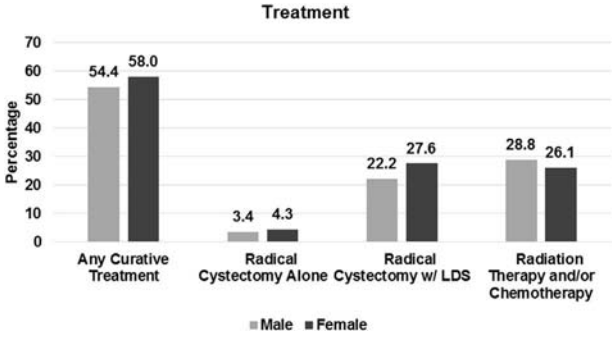


Fig. 1. Treatments according to sex. LDS = lymph node dissection.

Second, when compared to men, we observed women to have worse overall survival among all patients and in those with stage IV disease. In propensity score matching analyses, women had worse overall and cancer-specific survival when compared to men. Thus, although we cannot control for all potential confounders, when we attempted to do so using propensity score matching, women have significantly worse survival than men. Age and comorbidity are likely determinants for overall survival; however, dietary intake and lifestyle are integral predictors for cancer—overall as well as cancer-specific survival [7,31].

Third, women had increased use of treatments, specifically RC, with no significant difference in delay to surgery. One plausible explanation for the increased use of treatments and more specifically RC, could be the fewer

Table 2
Multivariable model on predictors of receipt of radical cystectomy and receipt of delayed radical cystectomy stratified by stage

Sex	No. (%)	Receipt of radical cystectomy				No. (%)	Receipt of delayed radical cystectomy			
		RR	95% CI		*P* value		RR	95% CI		*P* value
Stage II										
Male	643 (18.0)	1.00				283 (7.9)	1.00			
Female	381 (23.2)	1.48	1.33	1.65	<0.001	169 (10.3)	0.99	0.94	1.05	0.744
Stage III										
Male	541 (43.6)	1.00				180 (14.5)	1.00			
Female	330 (50.9)	1.24	1.13	1.37	<0.001	105 (16.2)	0.99	0.94	1.03	0.513
Stage IV										
Male	516 (28.2)	1.00				196 (10.7)	1.00			
Female	327 (33.9)	1.33	1.19	1.49	<0.001	96 (9.9)	0.96	0.90	1.02	0.181

Predictors in the model: year of diagnosis, age, race/ethnicity, marital status, rural area, census region, median income, tumor grade, stage, hydronephrosis, hematuria, irritative or obstructive symptom, and comorbidity score.

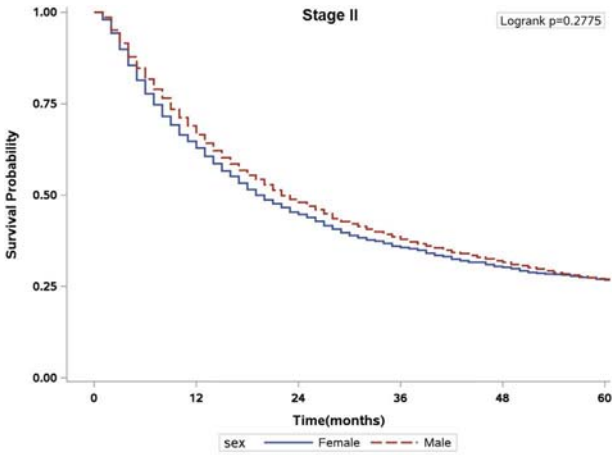
comorbidities observed (i.e., CCI $\geq$ 2) among women that could influence the decision to pursue surgery. In this study, female patients with decreased comorbidities may need less preoperative evaluations, consultations, and studies that may expedite timing to surgery. Moreover, advanced stage at presentation may prompt providers to act more aggressively. However, it should also be mentioned that the use of RC was low regardless of sex. Despite these longstanding guidelines, RC is markedly underused; only 19% to 21% of patients 66 years of age and older with muscle-invasive disease are offered this potentially curative surgery [15,21]. In the present study, despite the relative increased use of a potentially curable surgery with no increased delay to treatment (we even noted decreased delay to surgery among patients with stage IV disease), women have worse cancer-specific survival. Prior research concerning the biological aggressiveness of bladder cancer according to subtype of muscle-invasive disease may help elucidate the biological underpinnings of carcinogenesis according to sex [32]. Moreover, a plausible etiology for the known survival discrepancy pertains to prior androgen receptor axis. The androgen receptor axis activates a number of known downstream oncogenes such as the epithelial growth factor receptor (EGFR/ERBB2) pathway and the increased β-catenin signaling [33,34]. It is possible that increased circulating serum concentrations of androgen in male patients with bladder cancer may result in the increased incidence among men. However, Daugherty et al. [35] have shown that cumulative exposure to estrogen and progestin is protective against bladder cancer incidence. The decreased production of estrogen and progesterone as observed in postmenopausal women and effects on biological aggressiveness of bladder cancer remain to be determined. From the present study, we found that process of care determinants (i.e., RC use and delay to treatment) were not associated with sex differences in survival, which suggests that further research discerning biological aggressiveness of bladder cancer according to sex is needed.

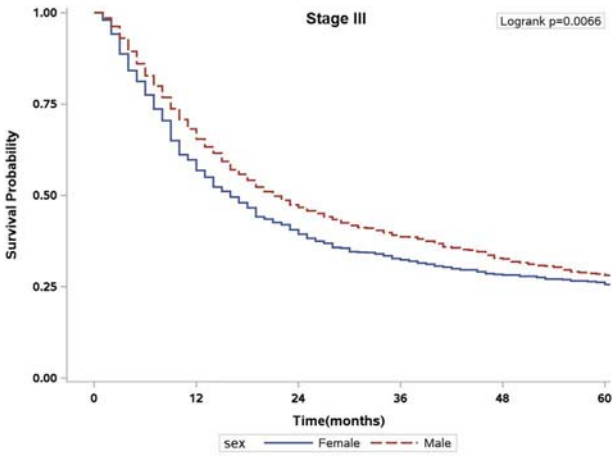
Although our findings are clinically relevant, they must be interpreted within the context of the study design. First, patients used in this study are older, and thus we cannot comment on our findings in relation to sex for younger patients. However, most patients with bladder cancer are diagnosed in their sixth decade of life, and therefore we provide a contemporary analysis of the sex differences in survival. Second, there is evidence supporting the use of neoadjuvant chemotherapy to significantly downstage and improve survival benefit at RC [36]. In the present analysis, the use of perioperative chemotherapy was not accounted for owing to the low usage rates with no difference in use according to sex observed (data not shown) in the present cohort. Prior research by Booth et al. [37] has shown that approximately 4% of patients with muscle-invasive bladder cancer receive neoadjuvant chemotherapy, thus potentially

Table 3
Hazard ratios of overall survival and cancer-specific survival in patients diagnosed with bladder cancer

	Overall survival				Cancer-specific survival			
	HR	95% CI		*P*	HR	95% CI		*P*
Sex								
Male	1.00				1.00			
Female (all patients)	1.07	1.02	1.12	0.010	1.27	1.19	1.35	<0.001
Female (stage II)	0.98	0.91	1.05	0.531	1.20	1.09	1.32	<0.001
Female (stage III)	1.12	0.99	1.26	0.071	1.45	1.24	1.70	<0.001
Female (stage IV)	1.19	1.08	1.30	<0.001	1.29	1.16	1.43	<0.001

Predictors in the model: treatment, year of diagnosis, age, race/ethnicity, marital status, rural area, census region, median income, tumor grade, stage, neoadjuvant chemotherapy, hydronephrosis, and comorbidity score.





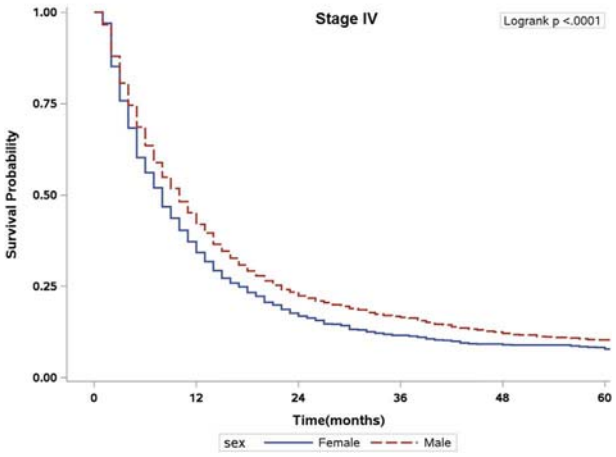
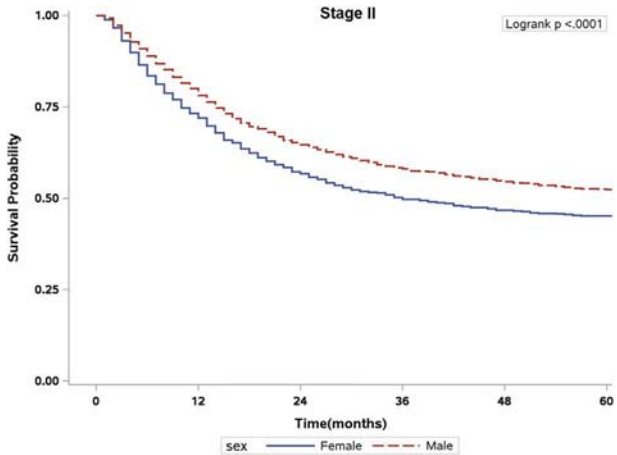
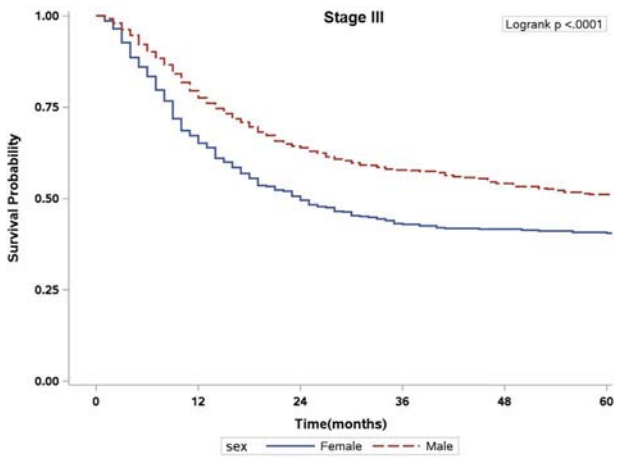


Fig. 2. Unadjusted overall survival of patients stratified by sex: (A) stage II patients, (B) stage III patients, and (C) stage IV patients.





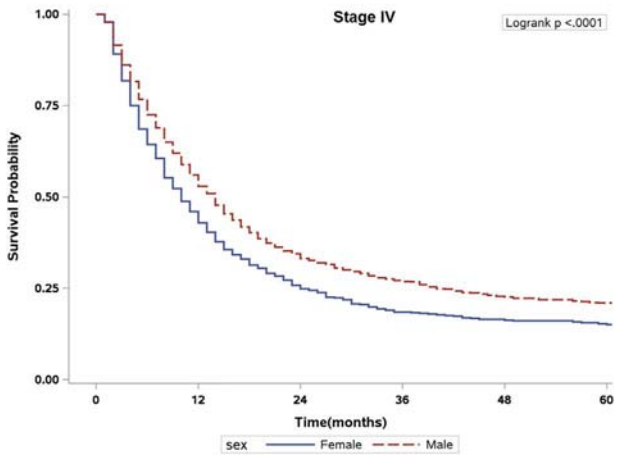


Fig. 3. Unadjusted cancer-specific survival of patients stratified by sex: (A) stage II patients, (B) stage III patients, and (C) stage IV patients.

limiting this as a significant unmeasured confounding variable. Third, we understand inherent limitations in using cancer registry data, and in particular, the inability to control for unknown confounders. We acknowledge the heterogeneity in staging according to sex as well as inherent staging limitations of using cancer registries. We attempted to control for potential confounders using propensity score matching. In addition, we determined an effect of treatment on the cancer-specific but not the noncancer survival. Thus, the current data provide a robust, generalizable assessment of sex differences in survival at the population-based level.

5. Conclusions

Sex differences in survival persist despite women who are significantly more likely to undergo treatment including

RC. These findings were independent of clinical stage. Delay from diagnosis to surgery did not account for the decreased cancer-specific survival among women, suggesting that inherent characteristics of tumor biology likely affect sex differences in survival. These findings support further research to discern the biological underpinnings of bladder carcinogenesis according to sex.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.urolonc.2017.05.022.

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