Survival Differences Among Bladder Cancer Patients According to Gender: Critical Evaluation of Radical Cystectomy Use and Delay to Treatment

Stephen B. Williams[1], **Jinhai Huo**[2], **Tamer Dafashy**[1], **Cameron Ghaffary**[1], **Jacques G. Baillargeon**[3], **Edwin E. Morales**[4], **Simon P. Kim**[5], **Yong-Fang Kuo**[6], **Eduardo Orihuela**[1], **Douglas S. Tyler**[7], **Stephen J. Freedland**[8], **Ashish M. Kamat**[9]

[1]Division of Urology, The University of Texas Medical Branch at Galveston, Galveston, TX

[2]Department of Health Services Research, The University of Texas MD Anderson Cancer Center, Houston, TX

[3]Department of Medicine, Division of Epidemiology, Sealy Center on Aging, The University of Texas Medical Branch at Galveston, Galveston, TX

[4]The Department of Urology, The University of Texas Health Science Center at San Antonio

[5]Department of Urology, Case Western Reserve University, Cleveland, OH

[6]Department of Medicine, Division of Biostatistics, Sealy Center on Aging, Sealy Center on Aging, The University of Texas Medical Branch at Galveston, Galveston, TX

[7]Department of Surgery, The University of Texas Medical Branch at Galveston, Galveston, TX

[8]Department of Urology, Cedars Sinai Medical Center, Los Angeles, CA

[9]Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, TX

Abstract

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

Methods: A total of 9,907 patients aged 66 years or older diagnosed with clinical stage II-IV N0M0 bladder cancer from January 1, 2001 to December 31, 2011 from SEER-Medicare data

Corresponding author: Stephen B. Williams, MD, The University of Texas Medical Branch, Division of Urology, 301 University Blvd, Galveston, TX 77555, P: 409-747-7333, F: 409-772-0088, stbwilli@utmb.edu.

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 female. Women were significantly more likely to undergo RC across all stages compared to their male counterparts (Stage II: Relative Risk (RR) 1.48, 95% Confidence Interval (CI) = 1.33-1.65, P < 0.001; Stage III: RR 1.24, 95% CI = 1.13-1.37, p<0.001; 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 gender across all clinical stages. Using propensity score matching, women had worse overall (HR 1.07, CI 1.01-1.14, p=0.024), and worse cancer-specific survival (HR 1.26, CI 1.17-1.36, p<0.001) than men, respectively.

Conclusion: Gender differences persist with women 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.

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 gender differences in survival following radical cystectomy [7-11]. The etiology of this gender 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 non-metastatic muscle-invasive bladder cancer recommend neoadjuvant chemotherapy followed by radical cystectomy (RC) with extended pelvic lymphadenectomy [14]. While 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, while underutilization of RC is paramount, timing to RC has been strongly associated with survival outcomes [16]. Prior work by Messer et al. identified the female gender as an adverse prognostic factor, independent of clinical and pathological features for patients undergoing RC [17, 18]. However, the impact of type of treatment, timing to surgery when rendered and survival outcomes according to gender has not been extensively examined [18, 19]. Therefore, we provide a population-based assessment in order to discern whether utilization of RC differs according to gender, specifically examining the receipt and timing of RC in relation to survival outcomes.

PATIENTS AND METHODS

Data Source

Our study utilized 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, 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.

Ascertainment of Study Cohort

We restricted our analysis to patients with bladder cancer diagnosed as clinical stage II-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 radical cystectomy incorporating both clinical stage and pathological stage into a collaborative stage variable using the 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).

Identification of Bladder Cancer Treatments

Receipt of bladder cancer treatments was determined for one year after 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 utilized 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 on the basis of 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 one 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 bladder cancer in the absence of a simultaneous code for RC (Supplementary Table 2).

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 one year before cancer diagnosis were collected and included the following ICD-9 codes grouped in 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 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 utilizes comorbid conditions identified by the CCI and incorporates the diagnostic and procedure data contained in Medicare physician Part B claims.

Statistical Analysis

Univariate analyses was performed to assess the association of RC with the list of covariates described above, using the Pearson chi-square test. We created a multivariable generalized linear model that incorporates stage, treatment method (RC, chemotherapy, and radiation therapy), and gender stratified by stage to evaluate the effect of gender associated with receipt of bladder cancer treatment, and to evaluate the association between gender and delayed RC from time of diagnosis. In the our multivariable analysis, we further classified the timing of RC into two groups, less or equal to 12 weeks and longer than 12 weeks, since previous studies have reported inferior overall survival and progression-free survival for patients who received RC more than 84–90 days after diagnosis. [23-26]. In the sensitivity analysis, we performed propensity score matching. Relative risks 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 in the propensity score matched cohort were 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 $p < 0.05$.

RESULTS

Patient demographics are summarized in Table 1. Of the 9,907 patients diagnosed with bladder cancer 3,256 (32.9%) were female. While there was no significant difference in bladder cancer diagnosis over the study period, women were older, non–Caucasian 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, while women more 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 female ($p < 0.001$) (Figure 1).

We analyzed predictors for receipt of radical cystectomy stratified by stage and gender 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: Relative Risk (RR) 1.48, 95% Confidence Interval (CI) = 1.33-1.65, P < 0.001; Stage III: RR 1.24, 95% CI = 1.13-1.37, p<0.001; 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 gender across all clinical stages.

The overall and cancer-specific survival estimates for all bladder cancer patients according to stage and gender 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 (Figure 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) (Figure 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, respectively.

Adjusted hazard ratios of delayed RC for overall survival and cancer-specific survival stratified by gender 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 non-cancer survival by treatment (rather than all-cause survival). We noticed an effect of RC on the cancer-specific but not the non-cancer survival (p=0.207).

DISCUSSION

Men are more likely to be diagnosed with bladder cancer, however, women have increased bladder cancer-specific mortality [1-6, 27]. Our study utilized a large population-based cancer registry to critically examine gender 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 cancer-specific mortality, these differences in survival cannot be explained by RC use, delay to surgery and/or adverse clinical and pathological determinants.

First, women presented with more advanced disease which is consistent with prior studies. Moreover, there was no significant difference in diagnosis according to gender during the study period. While we did not account for delay to diagnosis of urinary symptoms (i.e. hematuria) to diagnosis of 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 bladder cancer patients [21, 28]. Other studies have found that women present with more advanced stage for cystectomy and stage for stage, do worse. However, one 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 non-cancer survival by treatment (rather than all-cause survival). We noticed an effect of treatment on the cancer-specific but not the non-cancer survival thus confirming the association between treatment and cancer-specific survival cannot be explained other unknown confounders [30]. While we certainly understand such analytic methods cannot control for all potential confounders, these data suggest advanced stage disease at presentation may not account for the survival difference according to gender [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 gender in patients with stage IV cancer.

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, while 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 and 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 comorbidities observed (i.e. CCI   2) among women which could influence the decision to pursue surgery. In the present study, female patients with decreased comorbidities may need less preoperative evaluations, consultations and studies which may expedite timing to surgery. Moreover, advanced stage at presentation may prompt providers to act more aggressively. However, it should also be mentioned that use of RC was low regardless of gender. Despite these longstanding guidelines, radical cystectomy is markedly underused; only 19-21% of patients age 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 decrease 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 gender [32]. Moreover, a plausible etiology for the known survival discrepancy pertains to prior the androgen receptor (AR) axis. The AR 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 bladder cancer patients may result in the increased incidence among men. However, Daugherty et al. have shown that cumulative exposure to estrogen and progestin is protective against bladder cancer incidence [35]. The decreased production of estrogen and progesterone as observed in post-menopausal women and effects

on biological aggressiveness of bladder cancer remains to be determined. From the present study we found process of care determinants (i.e. RC use and delay to treatment) were not associated with gender differences in survival which suggests further research discerning biological aggressiveness of bladder cancer according to gender is needed.

While our findings are clinically relevant, they must be interpreted within the context of the study design. First, patients utilized in this study are older and thus we cannot comment on our findings in relation to gender for younger patients. However, a majority of patients with bladder cancer are diagnosed in their sixth decade of life and therefore we provide a contemporary analysis of the gender differences in survival. Second, there is evidence supporting the use of neoadjuvant chemotherapy to significantly downstage and improved survival benefit at radical cystectomy [36]. In the present analysis, the use of perioperative chemotherapy was not accounted for due to the low utilization rates with no difference in use according to gender observed (data not shown) in the present cohort. Prior research by Booth et al. has shown that approximately 4% of patients with muscle-invasive bladder cancer receive neoadjuvant chemotherapy, thus potentially limiting this as a significant unmeasured confounding variable [37]. 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 gender 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 non-cancer survival. Thus, the current data provide a robust, generalizable assessment of gender differences in survival at the population-based level.

CONCLUSIONS

Gender differences in survival persist despite women 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 inherent characteristics of tumor biology likely impact gender differences in survival. These findings support further research to discern the biological underpinnings of bladder carcinogenesis according to gender.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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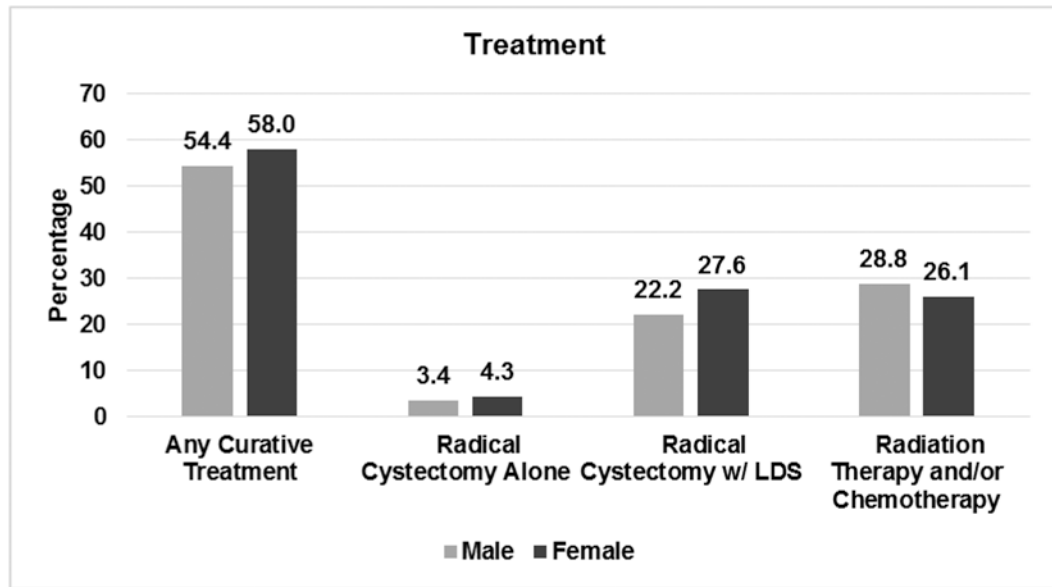
Figure 1.
Treatments according to gender
LDS: Lymph node dissection
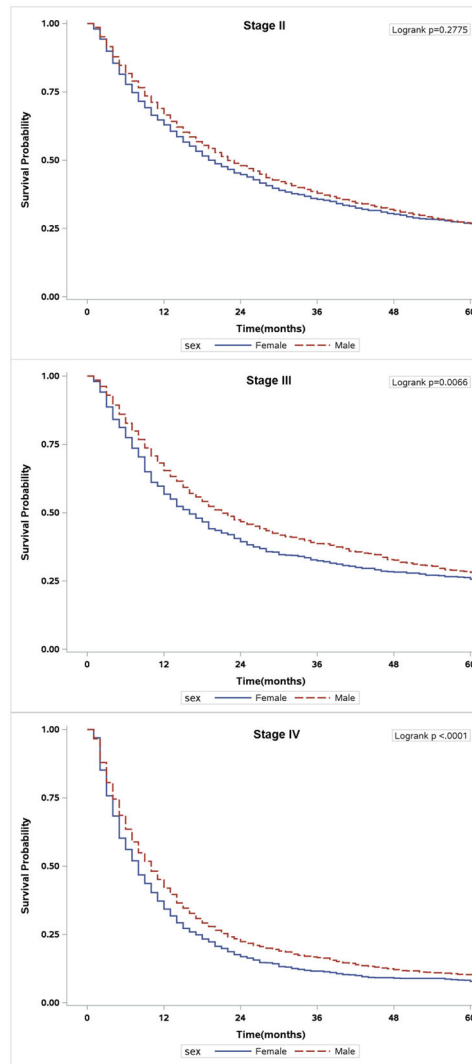
Figure 2.
Unadjusted overall survival of patients stratified by sex. A) Stage II patients. B) Stage III patients. C) Stage IV patients.
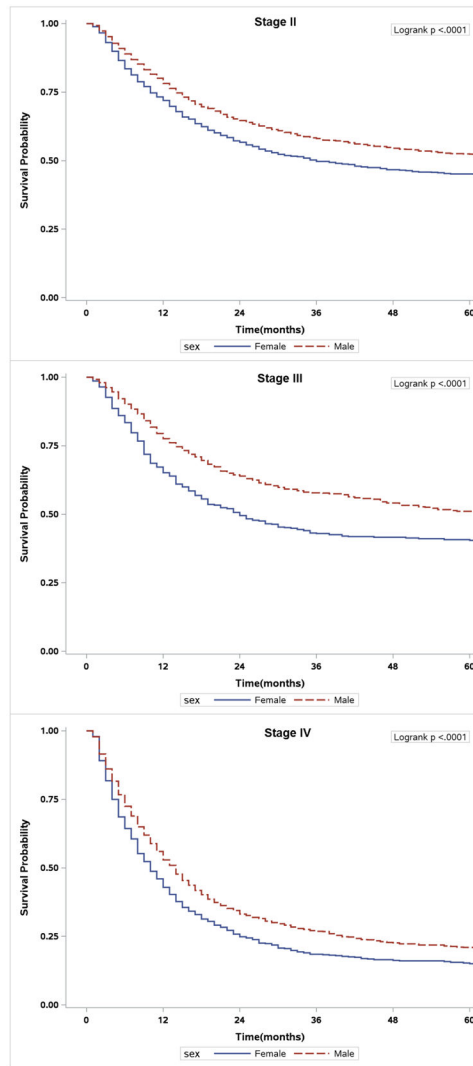
Figure 3.
Unadjusted cancer-specific survival of patients stratified by sex. A) Stage II patients. B)
Stage III patients. C) Stage IV patients.

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	1333	988	14.9	345	10.6	
70-74	1942	1364	20.5	578	17.8	
75-79	2405	1615	24.3	790	24.3	
80+	4227	2684	40.4	1543	47.4	
Race/ethnicity						<0.001
White	8564	5863	88.2	2701	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	1440	918	13.8	522	16.0	
Married	5420	4394	66.1	1026	31.5	
Unknown	3047	1339	20.1	1708	52.5	
Rural area						0.1088
No	9691	6495	97.7	3196	98.2	
Yes	216	156	2.3	60	1.8	
Census Region						0.016
West	3907	2694	40.5	1213	37.3	
Northeast	2354	1540	23.2	814	25.0	
Midwest	1139	761	11.4	378	11.6	
South	2507	1656	24.9	851	26.1	
Median Household Income, $						0.511
23,364	2808	1882	28.3	926	28.4	
23,365–31,906	2523	1701	25.6	822	25.2	
31,907–41,719	2344	1595	24.0	749	23.0	

Characteristic	Total	Male No.	Male %	Female No.	Female %	p-value
41,720	2232	1473	22.1	759	23.3	
Stage						0.007
II	5220	3578	53.8	1642	50.4	
III	1889	1241	18.7	648	19.9	
IV	2798	1832	27.5	966	29.7	
Hydronephosis						<0.001
No	8866	6018	90.5	2848	87.5	
Yes	1041	633	9.5	408	12.5	
Grade						0.182
Low	625	439	6.6	186	5.7	
High	8754	5866	88.2	2888	88.7	
Unknown	528	346	5.2	182	5.6	
Comorbidity Score						0.001
0	5361	3527	53.0	1834	56.3	
1	2415	1615	24.3	800	24.6	
2	1083	767	11.5	316	9.7	
3+	1048	742	11.2	306	9.4	
Radical Cystectomy						<0.001
No	7169	4951	74.4	2218	68.1	
Yes	2738	1700	25.6	1038	31.9	
Treatment						<0.001
No curative treatment	4405	3036	45.6	1369	42.0	
Radical Cystectomy Alone	365	224	3.4	141	4.3	
Radical Cystectomy w/ LDS	2373	1476	22.2	897	27.5	
Radiation Therapy and/or Chemotherapy	2764	1915	28.8	849	26.1	
Neoadjuvant chemotherapy						0.784
No	9513	6389	96.1	3124	95.9	
Yes	394	262	3.9	132	4.1	
Hematuria						<0.001
No	3672	2385	35.9	1287	39.5	
Yes	6235	4266	64.1	1969	60.5	
Irritative Symptoms						<0.001
No	7726	5299	79.7	2427	74.5	
Yes	2181	1352	20.3	829	25.5	
Obstructive Symptoms						<0.001
No	8606	5587	84.0	3019	92.7	
Yes	1301	1064	16.0	237	7.3	

Table 2.

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

Sex	Receipt of Radical Cystectomy					Receipt of Delayed Radical Cystectomy				
	No. (Percent)	RR	95% CI		P-value	No. (Percent)	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	<.001	169 (10.3)	0.99	0.94	1.05	0.744
Stage III		1.00								
Male	541 (43.6)					180 (14.5)	1.00			
Female	330 (50.9)	1.24	1.13	1.37	<.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	<.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.

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**
Gender						
Male	1.00			1.00		
Female (All patients)	1.07	1.02 1.12	0.010	1.27	1.19 1.35	<.001
Female (Stage II)	0.98	0.91 1.05	0.531	1.20	1.09 1.32	<.001
Female (Stage III)	1.12	0.99 1.26	0.071	1.45	1.24 1.70	<.001
Female (Stage IV)	1.19	1.08 1.30	<.001	1.29	1.16 1.43	<.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.