



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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Received 6 March 2017; received in revised form 28 April 2017; accepted 28 May 2017

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 NOM0 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. © 2017 Elsevier Inc. All rights reserved.

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

This study was conducted with the support of the Institute for Translational Sciences, University of Texas Medical Branch, United States supported in part by a Clinical and Translational Science Award Mentored Career Development (KL2) Award (KL2TR001441) from the National Center for Advancing Translational Sciences, United States, National Institutes of Health, United States, Comparative Effectiveness Research on Cancer in Texas (CERCIT) (RP140020), and the National Cancer Institute, United States (NCI) (K05 CA134923) (S.B.W.), and in part by the fellowship from University of Texas MD Anderson Cancer Center's Halliburton Employees Foundation (J.H.).

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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

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