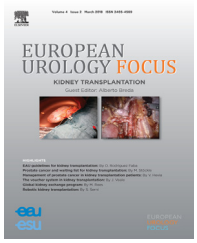
EUROPEAN UROLOGY FOCUS XXX (2019) XXX–XXX

available at www.sciencedirect.com
journal homepage: www.europeanurology.com/eufocus



Bladder Cancer

Sex-specific Differences in the Quality of Treatment of Muscle-invasive Bladder Cancer Do Not Explain the Overall Survival Discrepancy

Marieke J. Krimphove [a,b,c], *Julie Szymaniak* [a,b], *Maya Marchese* [a,b], *Karl H. Tully* [a,b,d], *David D'Andrea* [e], *Matthew Mossanen* [a,b], *Stuart R. Lipsitz* [b,f], *Kerry Kilbridge* [g], *Adam S. Kibel* [a,b], *Luis A. Kluth* [c], *Shahrokh F. Shariat* [e,h], *Quoc-Dien Trinh* [a,b,*]

[a] *Division of Urological Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;* [b] *Center for Surgery and Public Health, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;* [c] *Department of Urology, University Hospital Frankfurt, Frankfurt, Germany;* [d] *Department of Urology, Marien Hospital Herne, Ruhr-University Bochum, Herne, Germany;* [e] *Department of Urology, Medical University of Vienna, Vienna, Austria;* [f] *Department of General Internal Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;* [g] *Department of Medical Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA;* [h] *Institute for Urology and Reproductive Health, Sechenov University, Moscow, Russia*

Article info

Article history:
Accepted June 5, 2019

Associate Editor:
Derya Tilki

Keywords:
Bladder cancer
Health services research
Sex
Quality of care

Abstract

Background: While bladder cancer is less common among women, female sex is associated with worse oncological outcomes.
Objective: To evaluate sex-specific differences in initial presentation and treatment patterns of muscle-invasive bladder cancer.
Design, setting, and participants: A retrospective study using the National Cancer Database to identify individuals diagnosed with muscle-invasive bladder cancer (cT2-T4aN0M0) between 2004 and 2013.
Outcome measurements and statistical analysis: Multivariable logistic regression and negative binomial regression with Bonferroni correction were used to investigate seven treatment measures: care at a high-volume facility, receipt of definitive therapy, delayed treatment, receipt of neoadjuvant or adjuvant chemotherapy, receipt of pelvic lymph node dissection, and number of lymph nodes removed. The secondary outcome was overall survival.
Results and limitations: We identified 27 525 patients, 27.4% of whom were females. Females were diagnosed significantly more often with nonurothelial carcinoma (15.1% vs 9.9%, $p < 0.001$), with squamous carcinoma being the most prevalent variant (46.9%). After Bonferroni correction, there was no difference in six out of seven treatment quality measures. Females were significantly less likely to experience delayed treatment (odds ratio 0.89, 95% confidence interval [CI] 0.84–0.93, $p < 0.001$). Females had significantly worse overall survival compared with males (hazard ratio 1.04, 95% CI 1.00–1.07, $p = 0.030$). Limitations arise from the retrospective design of the study.
Conclusions: Despite little difference in treatment quality measures, female sex is associated with worse overall survival among individuals with muscle-invasive bladder cancer. Our findings suggest that differences in treatment patterns are unlikely to explain the differences in overall survival. Future initiatives should focus on root causes for gender-specific differences in pathological staging and features at diagnosis.
Patient summary: In this study, we did not find differences in the treatment of bladder cancer between men and women that could readily explain why women diagnosed with this disease are more likely to die.

* Corresponding author. Division of Urological Surgery, Brigham and Women's Hospital, 45 Francis St., ASB II–3, Boston, MA 02115, USA. Tel.: +1 617 525 7350; Fax: +1 617 525 6348.
E-mail address: qtrinh@bwh.harvard.edu (Q.-D. Trinh).

https://doi.org/10.1016/j.euf.2019.06.001
2405-4569/

1. Introduction

Bladder cancer is the sixth most common cancer diagnosis in the USA, with 80 470 estimated new cases in 2019 [1], of which only 23% are expected to be females [2]. Despite bladder cancer being less common in females, women are at higher risk of progression and mortality after treatment [3]. Explanations for this striking gap in oncological outcomes may include differences in exposure to risk factors such as smoking, biological differences, and differences in initial evaluation leading to delays in diagnosis and treatment [4,5]. Prior work has focused on epidemiological differences between sexes [6] and differences in pathological features as possible sources of worse outcomes for female patients with bladder cancer [7].

For muscle-invasive bladder cancer (MIBC), an aggressive disease with a devastating prognosis, consistent treatment is crucial for the success of the therapy. Current guidelines recommend neoadjuvant chemotherapy (NAC) in eligible patients, followed by radical cystectomy with pelvic lymph node dissection for clinically localized and locally advanced MIBC [8]. While several quality metrics are known to substantially influence survival from MIBC, little is known about sex-specific differences in these pathways potentially leading to worse outcomes in females compared with males.

Our aim was to investigate sex-specific differences in pathological features at initial presentation, as well as treatment quality measures, including treatment in high- versus low-volume facilities, treatment delay, and differences in treatment pathways along the continuum of MIBC management.

2. Patients and methods

2.1. Data source

We used the National Cancer Database (NCDB) to obtain data from individuals diagnosed with bladder cancer and seen at one of 1500 Commission on Cancer (CoC)-accredited hospitals. The registry, established by the American College of Surgeons, captures around 60% of bladder cancer cases in the USA [9]. Trained data abstractors collect sociodemographic and clinical data, including cancer characteristics and treatment information following standardized methodology.

2.2. Study population

Individuals diagnosed with bladder cancer between 2004 and 2015 were identified according to World Health Organization ICD-O-3 morphological codes for bladder cancer (ie, C67.0–67.9). We included patients with nonmetastatic localized and locally advanced MIBC (cT2-T4aN0M0) according to the American Joint Committee on Cancer (AJCC), seventh edition. We focused on these patients in order to investigate treatment delivery in patients who require aggressive treatment. We excluded patients with unknown clinical staging information, as well as individuals with missing information on tumor histology or follow-up (includes all patients diagnosed in 2014 and 2015). We further excluded individuals with 0 d elapsed between diagnosis and treatment because they likely did not enter the database upon initial diagnosis (Fig. 1).

2.3. Variables of interest—covariates

Patient-level information included age at diagnosis, race (white, black, other, and unknown), year of diagnosis, and Charlson Deyo Index (CCI; categorized into 0, 1, 2, and ≥3). Cancer-related characteristics comprised stage according to the AJCC (stage II and IIIA), and urothelial versus nonurothelial histology. Treatment variables included radical cystectomy (RC) and RC preceded by NAC, defined as chemotherapy between 180 and 30 d prior to surgery. We restricted the receipt of NAC to 30 d before surgery because the NCDB captures only the first day of treatment and that cutoff allows patients to have received at least one full cycle of NAC. Additional treatment variables included RC followed by adjuvant chemotherapy (AC), defined as chemotherapy within 90 d after surgery; trimodal therapy (TMT), defined as a combination of transurethral resection of the bladder, radiosensitizing chemotherapy, and radiation therapy with

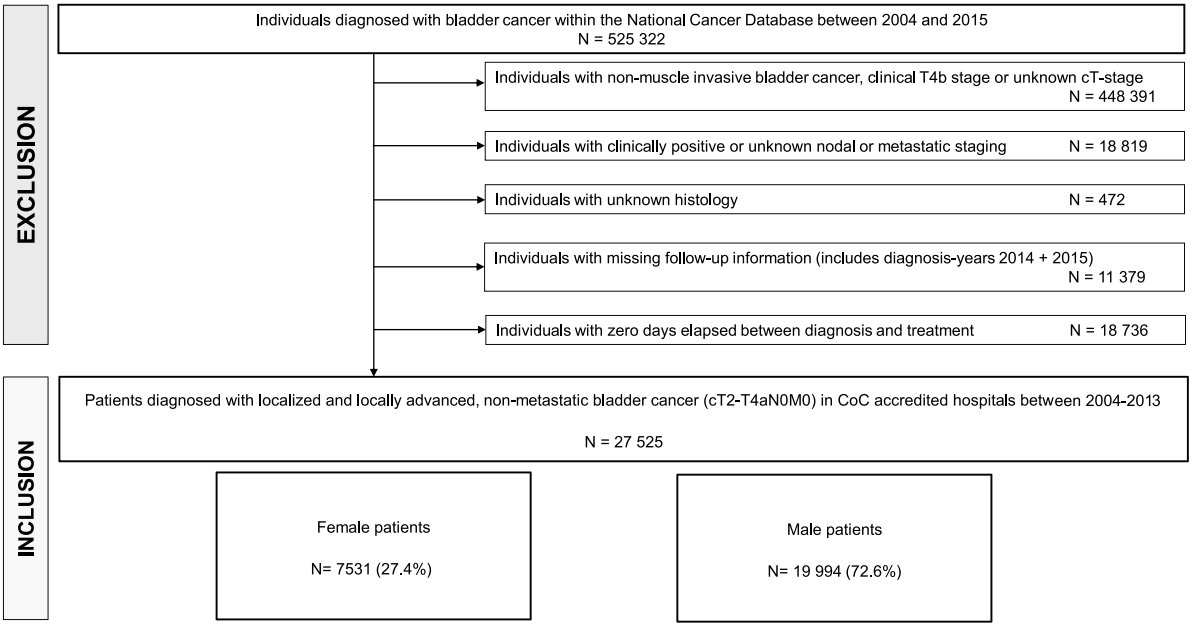


Fig. 1 – Flowchart data selection. CoC = Commission on Cancer.

Please cite this article in press as: Krimphove MJ, et al. Sex-specific Differences in the Quality of Treatment of Muscle-invasive Bladder Cancer Do Not Explain the Overall Survival Discrepancy. Eur Urol Focus (2019), https://doi.org/10.1016/j.euf.2019.06.001

60–65 Gy [10]; chemotherapy or radiation therapy alone; and other. Sociodemographic information contained data on primary insurance carrier (private, Medicaid, Medicare, other government payer [TRICARE, Military, VA, and Indian/Public Health Service], uninsured, and unknown), ZIP code level information on education (high [<13% without high school degree], low [≥13% without high school degree], and unknown), income (high ≥ $48 000 > low, and unknown), and distance to the CoC facility (<12.5 miles, 12.5–49.9 miles, ≥50 miles, and unknown). Facility-level data included county type (metropolitan, urban, rural, or unknown), census geographical region, facility type (academic vs nonacademic program, or other/unknown), and the annual mean facility case volume. To account for caseload variation over the study period, case volume was defined as the mean of the total volume of patients with clinically localized and locally advanced MIBC treated in the given hospital in the year of the patient's diagnosis [11].

2.4. Main outcome measures

Our aim was to examine the quality of treatment delivery of nonmetastatic localized and locally advanced MIBC. We therefore investigated the following seven quality metrics as our main outcomes of interest: (1) treatment at high- versus low-volume hospitals (hospitals within the top quartile in mean case volume were defined as high-volume hospitals), (2) receipt of definitive treatment (RC with or without NAC and/or AC, or TMT), (3) delayed treatment (>90 d of diagnosis), (4) receipt of NAC in patients who underwent RC, (5) receipt of pelvic lymph node dissection (PLND) in patients who underwent RC, (6) receipt of AC in patients who underwent RC without prior NAC and adverse pathological features (pT3–4 or pN+ or positive surgical margins), and (7) number of lymph nodes removed in patients who underwent RC and PLND with at least one lymph node removed. The secondary outcome of interest was overall survival, defined as the number of months between the date of diagnosis and the date on which the patient was last contacted or died.

2.5. Statistical analysis

First, baseline characteristics of male and female patients were reported using frequencies and proportions for categorical variables, and Pearson's χ^2 test was then used to compare differences in categorical variables. Medians and interquartile ranges were used to describe continuous variables; differences between sexes were assessed using the Mann-Whitney *U* test. In order to describe differences between males and females in presentation at diagnosis, we explored initial presentation of urothelial versus nonurothelial histology, as well as presentation with variant histology. These included micropapillary or sarcomatoid differentiation, squamous cell carcinoma, adenocarcinoma, neuroendocrine differentiation, and other histology according to ICD-O-3 definitions, as previously described [12].

Associations between sex and the first six treatment quality measures were analyzed by fitting multivariable logistic regression models, accounting for the abovementioned covariables. For the last quality metric of lymph node counts, we fitted a negative binomial model because overdispersion occurred with Poisson generalized linear models. To account for unmeasured differences between hospitals, all regression analyses were adjusted for facility-level clustering [13].

All statistical analyses were performed using Stata v.13.0 (StataCorp, College Station, TX, USA). Owing to testing of multiple hypotheses, we adjusted the *p* value according to Bonferroni for the primary outcome (0.05/7 = 0.007), yielding a total type I error rate of 5%. Before conducting the study, we obtained a review board waiver from our institution.

3. Results

3.1. Baseline characteristics of individuals with muscle invasive bladder cancer between 2004 and 2013

Table 1 summarizes the baseline characteristics of 7531 (27.4%) female and 19 994 (72.6%) male individuals diagnosed with clinically localized and locally advanced MIBC. Females were older, were more often of black race, and presented with cT3 disease more frequently (15.4% vs 11.4%, $p < 0.001$) compared with males. Females received treatment more often at facilities closer to home (<12.5 miles: 53.7% vs 48.0%, $p < 0.001$). Female patients had private insurance less often than male patients (24.0% vs 28.6%, $p < 0.001$), and received treatment less often at high-volume facilities (top quartile: 29.0% vs 32.7%, $p < 0.001$).

3.2. Variant histology at diagnosis in patients with cT2-T4aN0M0 disease

We found that significantly more female patients presented with nonurothelial bladder cancer at the time of diagnosis (15.1% vs 9.9%, $p < 0.001$). Of those presenting with variant histology, post hoc pairwise comparisons revealed that females presented significantly more often with squamous cell carcinoma (46.9% vs 28.7%, $p < 0.001$), while men presented more often with neuroendocrine (12.3% vs 21.8%, $p < 0.001$) or micropapillary differentiation (3.8% vs 9.0%, $p < 0.001$) (Fig. 2).

3.3. Quality of treatment

In our adjusted analyses, we found that women were significantly less likely to experience delayed treatment >90 d from diagnosis (odds ratio 0.89, 95% confidence interval [CI] 0.84–0.93, $p < 0.001$). After Bonferroni adjustment, we did not find significant differences between males and females in the receipt of treatment at high- versus low-volume facilities, definitive treatment, the receipt of NAC or PLND in patients who underwent RC, or the receipt of AC in patients who did not have NAC and had adverse pathological features ($p > 0.007$; Table 2 and Fig. 3). The number of lymph nodes removed in patients who underwent RC with PLND did not differ significantly between sexes (incident rate ratio 1.006 lymph nodes, 95% CI 0.98–1.04, $p = 0.713$; Table 3).

3.4. Overall survival

Figure 4 depicts the unadjusted survival of patients with clinically localized and locally advanced disease, stratified by sex. The median follow-up was 72.9 mo; the median overall survival was 27.2 and 35.6 mo for female and male patients, respectively. In the unadjusted and adjusted cox regression models, females had significantly worse overall survival than males (hazard ratio [HR; unadjusted] 1.11, 95% CI 1.08–1.16, $p < 0.001$, and HR (adjusted) 1.04, 95% CI 1.00–1.07, $p = 0.030$; Table 4).

Please cite this article in press as: Krimphove MJ, et al. Sex-specific Differences in the Quality of Treatment of Muscle-invasive Bladder Cancer Do Not Explain the Overall Survival Discrepancy. Eur Urol Focus (2019), https://doi.org/10.1016/j.euf.2019.06.001

Table 1 – Baseline characteristics of male and female patients diagnosed with nonmetastatic clinically localized and locally advanced (cT2-T4aN0M0) bladder cancer between 2004 and 2013 within the National Cancer Database.

	Male	Female	Total	*p* value
Age, *n* (%)				<0.001
≤50	950 (4.75)	381 (5.06)	1331 (4.84)	
51–60	3117 (15.6)	983 (13.1)	4100 (14.9)	
61–70	5627 (28.1)	1807 (24.0)	7434 (27.0)	
71–80	6439 (32.2)	2354 (31.3)	8793 (32.0)	
81–90	3861 (19.3)	2006 (26.6)	5867 (21.3)	
Race, *n* (%)				<0.001
White	18 420 (92.1)	6593 (87.5)	25 013 (90.9)	
Black	947 (4.7)	704 (9.4)	1651 (6.0)	
Asian	277 (1.4)	107 (1.4)	384 (1.4)	
Other	138 (0.7)	60 (0.8)	198 (0.7)	
Unknown	212 (1.1)	67 (0.9)	279 (1.0)	
Year of diagnosis, *n* (%)				<0.001
2004	1263 (6.3)	544 (7.2)	1807 (6.6)	
2005	1320 (6.6)	581 (7.7)	1901 (6.9)	
2006	1445 (7.2)	580 (7.7)	2025 (7.4)	
2007	1733 (8.7)	682 (9.1)	2415 (8.8)	
2008	2464 (12.3)	943 (12.5)	3407 (12.4)	
2009	2854 (14.3)	1021 (13.6)	3875 (14.1)	
2010	2150 (10.8)	737 (9.8)	2887 (10.5)	
2011	2115 (10.6)	772 (10.3)	2887 (10.5)	
2012	2260 (11.3)	850 (11.3)	3110 (11.3)	
2013	2390 (12.0)	821 (10.9)	3211 (11.7)	
Charlson Comorbidity Index, *n* (%)				0.119
0	13 729 (68.7)	5258 (69.8)	18 987 (69.0)	
1	4685 (23.4)	1668 (22.2)	6353 (23.1)	
2	1202 (6.0)	471 (6.3)	1673 (6.1)	
≥3	378 (1.9)	134 (1.8)	512 (1.9)	
Histology, *n* (%)				<0.001
Urothelial	18 007 (90.1)	6392 (84.89)	24 399 (88.6)	
Nonurothelial	1987 (9.9)	1139 (15.1)	3126 (11.4)	
cT stage, *n* (%)				<0.001
cT2	16 191 (81.0)	5932 (78.8)	22 123 (80.4)	
cT3	2286 (11.4)	1158 (15.4)	3444 (12.5)	
cT4a	1517 (7.6)	441 (5.9)	1958 (7.1)	
Treatment, *n* (%)				<0.001
Radical cystectomy only	8211 (41.1)	2928 (38.9)	8728 (31.7)	
Neoadjuvant chemotherapy	2576 (12.9)	863 (11.5)	3439 (12.5)	
Adjuvant chemotherapy	1325 (6.6)	458 (6.1)	1783 (6.5)	
Trimodal therapy	479 (2.4)	156 (2.1)	635 (2.3)	
Chemotherapy or radiation only	2990 (15.0)	1246 (16.5)	4236 (15.4)	
Other	4413 (22.1)	1880 (25.0)	6293 (22.9)	
Time to treatment (d), median (IQR)	42 (23–68)	38 (20–62)	41 (22–66)	<0.001
Insurance, *n* (%)				0.0001
Medicaid	725 (3.6)	308 (4.1)	1033 (3.8)	
Medicare	12 515 (62.6)	5108 (67.8)	17 623 (64.0)	
Other government	217 (1.1)	38 (0.5)	255 (0.9)	
Private	5718 (28.6)	1805 (24.0)	7523 (27.3)	
Not insured	528 (2.6)	170 (2.3)	698 (2.5)	
Unknown	291 (1.5)	102 (1.4)	393 (1.4)	
Income[a], *n* (%)				0.418
High	8030 (40.2)	3090 (41.0)	11 120 (40.4)	
Low	11 616 (58.1)	4306 (57.2)	15 922 (57.9)	
Unknown	348 (1.7)	135 (1.8)	483 (1.8)	
Education[a,b], *n* (%)				0.075
High	11 712 (58.6)	4297 (57.1)	16 009 (58.2)	
Low	7947 (39.8)	3099 (41.2)	11 046 (40.1)	
Unknown	335 (1.7)	135 (1.8)	470 (1.7)	
Facility type, *n* (%)				0.058
Academic	8699 (43.7)	3155 (42.2)	11 854 (43.3)	
Nonacademic	11 203 (56.3)	4317 (57.8)	15 520 (56.7)	
Facility location				0.001
Northeast	4574 (22.9)	1826 (24.3)	6400 (23.3)	
South	6489 (32.5)	2367 (31.4)	8856 (32.2)	
Midwest	5563 (27.8)	2140 (28.4)	7703 (28.0)	
West	3276 (16.4)	1139 (15.1)	4415 (16.0)	
Unknown	92 (0.5)	59 (0.8)	151 (0.6)	
County, *n* (%)				0.001
Metro	15 522 (77.6)	6016 (79.9)	21 538 (78.3)	

Please cite this article in press as: Krimphove MJ, et al. Sex-specific Differences in the Quality of Treatment of Muscle-invasive Bladder Cancer Do Not Explain the Overall Survival Discrepancy. Eur Urol Focus (2019), https://doi.org/10.1016/j.euf.2019.06.001

Table 1 (*Continued*)

	Male	Female	Total	*p* value
Urban	3263 (16.3)	1097 (14.6)	4360 (15.8)	
Rural	448 (2.2)	155 (2.1)	603 (2.2)	
Unknown	761 (3.8)	263 (3.5)	1024 (3.7)	
Distance (mile), *n* (%)				<0.001
<12.5	9600 (48.0)	4047 (53.7)	13 647 (49.6)	
12.5–49.9	6449 (32.3)	2173 (28.9)	8622 (31.3)	
≥50	3623 (18.1)	1175 (15.6)	4798 (17.4)	
Unknown	322 (1.6)	136 (1.8)	458 (1.7)	
Caseload quartile[c], *n* (%)				<0.001
1st	4190 (21.0)	1661 (22.1)	5851 (21.3)	
2nd	4394 (22.0)	1814 (24.1)	6208 (22.6)	
3rd	4864 (24.3)	1874 (24.9)	6738 (24.5)	
4th	6546 (32.7)	2182 (29.0)	8728 (31.7)	

IQR = interquartile range.
[a] ZIP code–level variable.
[b] Percentage of residents in home county with no high school degree from 2012 American County Survey Data.
[c] Facility caseload was calculated as the mean of the total volume of patients with clinically localized and locally advanced muscle-invasive bladder cancer treated in the given hospital in the year of the patient's diagnosis (cases/yr: first quartile: 1–4.6; second quartile: 4.6–7.2; third quartile: 7.2–13.2; fourth quartile: 13.3–51.1).

4. Discussion

The survival gap between men and women for bladder cancer is well documented. Such findings are surprising given that females generally have better disease-specific survival than males for the majority of cancers affecting both sexes [14–16]. Several explanations have been proposed, most of which revolve around evidence suggesting that women are diagnosed with more aggressive disease, due to either biology or presentation of disease. However, once diagnosed with MIBC, there are relatively few data on sex-specific differences in presentation and treatment patterns, and how these differences may affect oncological outcomes.

Our study confirms the survival disadvantage for females, although the difference may not be as striking as previously reported [17]. We found that females presenting with MIBC were 4% more likely to die than men. Prior work has repeatedly shown that females are at a higher risk of cancer-specific mortality following RC [7,18–20]. However, more recent literature challenges this hypothesis: when accounting for confounders, including comorbidities, pathological stages, histological features, and treatment patterns, the sex survival gap diminishes or even disappears [4,21,22]. What is more, Andreassen et al [23] recently showed that a less favorable prognosis for women with bladder cancer is present only in the first 2 years after diagnosis, and that it is partly attributable to more advanced stage at diagnosis. It is possible that the variation in observed outcomes between the studies arise from differences in study design, sample size, and treatment patterns prior to RC. Our findings suggest that once the diagnosis of MIBC disease is established, the sex gap in survival is narrow.

To further understand the small survival gap between sexes, we examined differences in treatment quality metrics among individuals diagnosed with MIBC. We found no differences in six out of the seven treatment quality measures. Male and female individuals were equally likely to receive treatment at high-volume facilities, receive definitive treatment, receive NAC when undergoing RC, receive AC after RC if adverse features were present, and receive PLND at RC. There was also no difference in the number of lymph

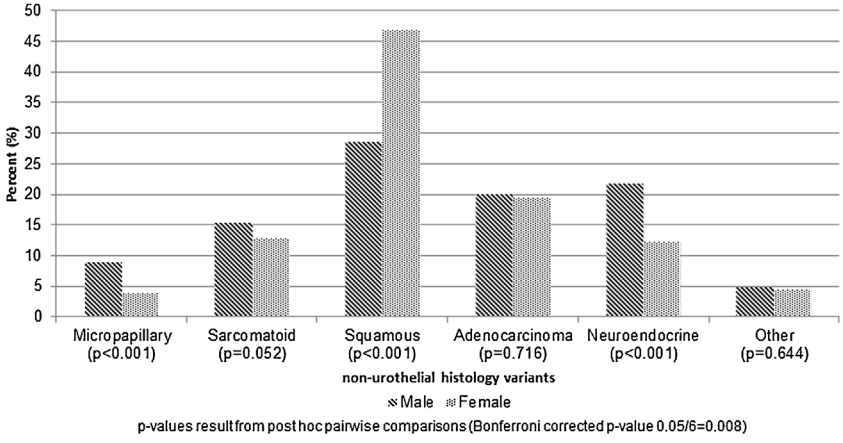


Fig. 2 – Distribution of variant histologies in male and female patients with nonurothelial bladder cancer.

Please cite this article in press as: Krimphove MJ, et al. Sex-specific Differences in the Quality of Treatment of Muscle-invasive Bladder Cancer Do Not Explain the Overall Survival Discrepancy. Eur Urol Focus (2019), https://doi.org/10.1016/j.euf.2019.06.001

Table 2 – Multivariable logistic regression predicting six treatment quality measures in male and female patients diagnosed with nonmetastatic localized and locally advanced muscle-invasive bladder cancer.

	Odds ratio	95% Confidence interval	*p* value
Treatment at high- vs low-volume hospital			
Male	Reference		
Female	0.89	0.82–0.97	0.010
Receipt of definitive treatment			
Male	Reference		
Female	0.96	0.91–1.03	0.290
Delayed treatment			
Male	Reference		
Female	0.89	0.84–0.93	<0.001*
Receipt of NAC in patients who underwent radical cystectomy			
Male	Reference		
Female	1.03	0.94–1.13	0.544
Receipt of pelvic lymph node dissection in patients who underwent radical cystectomy			
Male	Reference		
Female	0.91	0.80–1.04	0.160
Receipt of adjuvant chemotherapy in patients with adverse pathological features who underwent radical cystectomy and no neoadjuvant chemotherapy			
Male	Reference		
Female	0.95	0.82–1.10	0.483

NAC = neoadjuvant chemotherapy.
All models were controlled for age, race, year of diagnosis, Charlson Comorbidity Index, insurance, income, education, county, distance to the hospital, facility type and location, histology, clinical T stage, and mean case volume quartile.
* $p < 0.007$, based on a Bonferroni corrected α to yield a total permissible type I error rate of 0.05 for the study.

Table 3 – Multivariable negative binomial generalized regression predicting the difference in the number of lymph nodes removed in female versus male patients who underwent radical cystectomy with pelvic lymph node dissection for nonmetastatic localized and locally advanced muscle-invasive bladder cancer.

	IRR	95% Confidence interval	*p* value
Male	Reference		
Female	1.006	0.98–1.04	0.713

IRR = incident rate ratio.
The model was controlled for age, race, year of diagnosis, Charlson Comorbidity Index, insurance, income, education, county, distance to the hospital, facility type and location, histology, clinical T stage, and mean case volume quartile.

nodes removed according to sex. In contrast, we identified a quality metric where females fared better: female patients were less likely to experience delayed treatment, irrespective of the type of definitive treatment. Timely treatment in an aggressive disease such as MIBC is crucial: Gore et al [24] showed that delayed cystectomy of >12 wk adversely affected survival significantly [24]. Taken together, our results suggest that differences in treatment patterns are unlikely to be the root cause in the differences in MIBC outcomes.

Interestingly, we found that women presented more often with nonurothelial carcinoma as well as a higher clinical tumor stage at diagnosis, corroborating work from prior studies [7,25]. Underlying reasons include differences in biology and in diagnostic evaluation: women experience significantly longer delays between presentation with hematuria and diagnosis of bladder cancer [26]. Of those with nonurothelial carcinoma, women significantly more often had squamous cell carcinoma, a subgroup known to be associated with worse outcomes [27]. NAC is the standard of care for MIBC patients [8], as it has demonstrated a substantial survival benefit compared with RC alone [28]. However, response to NAC is worse in squamous cell carcinoma patients [29], limiting the treatment options for this histological variant. On the contrary, men presented more often with neuroendocrine differentiation, representing a variant of bladder cancer with a more favorable prognosis and a better response to NAC [12]. Varying histology may thus play a role in differences in bladder cancer outcomes.

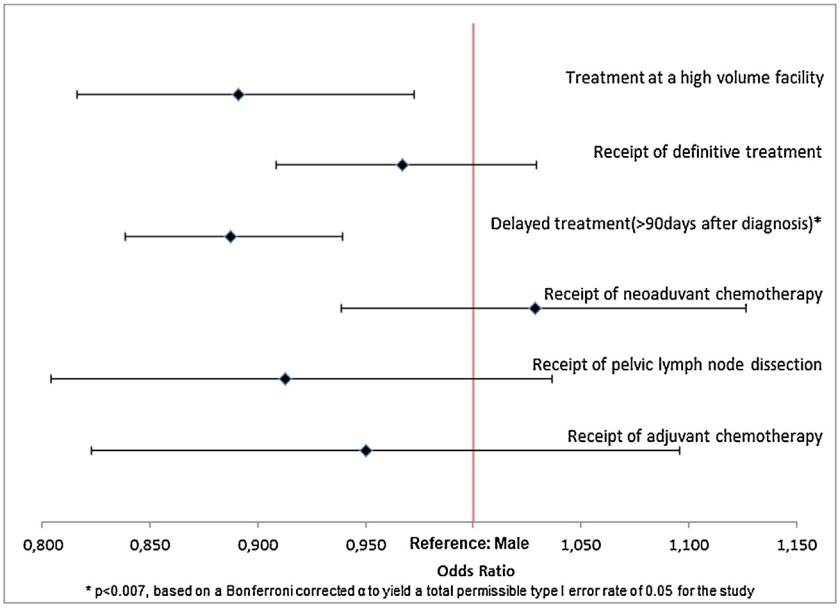


Fig. 3 – Forest plot depicting odds ratios of multivariable logistic regression analyses of six different treatment quality measures.

Please cite this article in press as: Krimphove MJ, et al. Sex-specific Differences in the Quality of Treatment of Muscle-invasive Bladder Cancer Do Not Explain the Overall Survival Discrepancy. Eur Urol Focus (2019), https://doi.org/10.1016/j.euf.2019.06.001

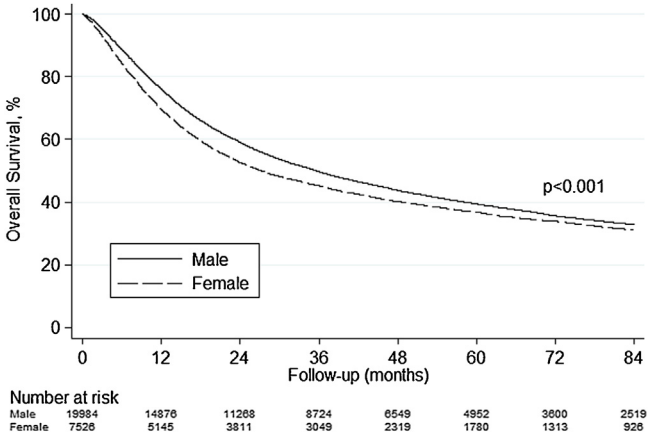


Fig. 4 – Kaplan-Meier survival curves depicting unadjusted overall survival in male and female patients with clinically localized and locally advanced (cT2-T4aN0M0) bladder cancer between 2004 and 2013 within the National Cancer Database.

Table 4 – Multivariable Cox regression predicting overall survival in patients diagnosed with clinically localized and locally advanced muscle-invasive bladder cancer.

	Hazard ratio	95% Confidence interval	*p* value
Male	Reference		
Female	1.04	1.00–1.07	0.030

The model was controlled for age, race, year of diagnosis, Charlson Comorbidity Index, treatment, insurance, income, education, county, distance to the hospital, facility type and location, histology, clinical T stage, and mean case volume quartile.

However, it must be considered that nonurothelial variants occur in only a small subgroup of patients.

Limitations to this study include unmeasured confounding, which is inherent to all retrospective observational studies. Generally, based on previous literature, these confounders tend to favor the female sex (eg, comorbidities are likely to be under-reported in males)—which would likely lead to *greater* differences than what was observed in this study. In addition, we were not able to account for differences in sex-specific biological and behavioral risk factors, including smoking or exposure to industrial chemicals. Furthermore, we used data from the NCDB, representing a hospital-based registry with information on patients seen in CoC-accredited hospitals only. Thus, our results may not be generalizable to the greater population. Additionally, the NCDB does not capture individual agents and the length of chemotherapy. It is therefore possible that patients did not receive all or full cycles of chemotherapy as recommended in current guidelines. However, by restricting the last possible starting day of NAC to 30 d before surgery, most patients likely received at least one full cycle of chemotherapy. Finally, our survival analysis is limited to overall survival, as the NCDB does not capture cancer-specific survival data. Despite these limitations, our study provides a comprehensive analysis of sex-specific treatment quality measures in the management of MIBC.

5. Conclusions

In a retrospective cohort of >23 000 patients with MIBC, we found that females presented with worse pathological features at diagnosis. However, there were no differences in six out of seven treatment quality metrics between men and women presenting with MIBC, and in one quality measure, women fared better than men. The marginal difference in overall survival between men and women is therefore unlikely to be driven by treatment inequities between sexes. Future initiatives should focus on identifying root causes for sex-specific differences in pathological staging and features at diagnosis.

***Author contributions*:** Quoc-Dien Trinh and Marieke Johanna Krimphove had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Krimphove, Szymaniak, Marchese, Tully, D'Andrea, Shariat, Trinh.
Acquisition of data: Trinh.
Analysis and interpretation of data: Krimphove, Szymaniak, Marchese, Tully, Lipsitz, Trinh.
Drafting of the manuscript: Krimphove, Szymaniak, Marchese, Tully.
Critical revision of the manuscript for important intellectual content: Marchese, D'Andrea, Mossanen, Kilbridge, Kibel, Kluth, Shariat, Trinh.
Statistical analysis: Krimphove, Marchese, Lipsitz.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Mossanen, Kilbridge, Kibel, Kluth, Shariat, Trinh.
Other: None.

***Financial disclosures*:** Quoc-Dien Trinh certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Quoc-Dien Trinh reports personal fees from Astellas, Bayer, Janssen, Insightec, and Intuitive Surgical. Shahrokh F. Shariat reports personal fees from Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Cepheid, Ferring, Ipsen, Jansen, Lilly, MSD, Olympus, Pfizer, Pierre Fabre, Roche, Sanochemia, Sanofi, and Wolff, all outside the submitted work; and has been issued patents for "Method to determine prognosis after therapy for prostate cancer," "Methods to determine prognosis after therapy for bladder cancer," "Prognostic methods for patients with prostatic disease," and "Soluble fas urinary marker for the detection of bladder transitional cell carcinoma." Adam S. Kibel reports consulting fees from Sanofi, Dendreon, Tokai, and Profound.

***Funding/Support and role of the sponsor*:** Quoc-Dien Trinh is supported by the Brigham Research Institute Fund to Sustain Research Excellence, the Bruce A. Beal and Robert L. Beal Surgical Fellowship, the Genentech Bio-Oncology Career Development Award from the Conquer Cancer Foundation of the American Society of Clinical Oncology, a Health Services Research pilot test grant from the Henry M Jackson Foundation for the Advancement of Military Medicine, and the Clay Hamlin Young Investigator Award from the Prostate Cancer Foundation. David F. Friedlander is supported by a National Institutes of Health T32 training grant. The NCDB is a joint project of the CoC of the American College of

Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of deidentified data used herein; they have not been verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin (69):2019;7–34.
[2] Shariat SF, Sfakianos JP, Droller MJ, Karakiewicz PI, Meryn S, Bochner BH. The effect of age and gender on bladder cancer: a critical review of the literature. BJU Int 2010;105:300–8.
[3] Uhlig A, Seif Amir Hosseini A, Simon J, et al. Gender specific differences in disease-free, cancer specific and overall survival after radical cystectomy for bladder cancer: a systematic review and meta-analysis. J Urol 2018;200:48–60.
[4] Soave A, Dahlem R, Hansen J, et al. Gender-specific outcomes of bladder cancer patients: a stage-specific analysis in a contemporary, homogenous radical cystectomy cohort. Eur J Surg Oncol 2015;41:368–77.
[5] Dobruch J, Daneshmand S, Fisch M, et al. Gender and bladder cancer: a collaborative review of etiology, biology, and outcomes. Eur Urol 2016;69:300–10.
[6] Donsky H, Coyle S, Scosyrev E, Messing EM. Sex differences in incidence and mortality of bladder and kidney cancers: national estimates from 49 countries. Urol Oncol Semin Orig Invest 2014;32(40):e23–31.
[7] Kluth LA, Rieken M, Xylinas E, et al. Gender-specific differences in clinicopathologic outcomes following radical cystectomy: an international multi-institutional study of more than 8000 patients. Eur Urol 2014;66:913–9.
[8] Witjes J, Bruins M, Compérat E. EAU guidelines on muscle-invasive and metastatic bladder cancer. European Association of Urology; 2018. https://uroweb.org/wp-content/uploads/EAU-Guidelines-Muscle-invasive-and-Metastatic-Bladder-Cancer-Guidelines-2016
[9] Lerro CC, Robbins AS, Phillips JL, Stewart AK. Comparison of cases captured in the national cancer data base with those in population-based central cancer registries. Ann Surg Oncol 2013;20:1759–65.
[10] Seisen T, Sun M, Lipsitz SR, et al. Comparative effectiveness of trimodal therapy versus radical cystectomy for localized muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2017;72:483–7.
[11] Rosen JE, Hancock JG, Kim AW, Detterbeck FC, Boffa DJ. Predictors of mortality after surgical management of lung cancer in the National Cancer Database. Ann Thorac Surg 2014;98:1953–60.
[12] Vetterlein MW, Wankowicz SAM, Seisen T, et al. Neoadjuvant chemotherapy prior to radical cystectomy for muscle-invasive bladder cancer with variant histology. Cancer 2017;123:4346–55.
[13] Donner A, Donald A. Analysis of data arising from a stratified design with the cluster as unit of randomization. Stat Med 1987;6:43–52.
[14] Ellison LF. Differences in cancer survival in Canada by sex. Health Rep 2016;27:19–27.
[15] Cook MB, McGlynn KA, Devesa SS, Freedman ND, Anderson WF. Sex disparities in cancer mortality and survival. Cancer Epidemiol Biomarkers Prev 2011;20:1629–37.
[16] Micheli A, Ciampichini R, Oberaigner W, et al. The advantage of women in cancer survival: an analysis of EUROCARE-4 data. Eur J Cancer 2009;45:1017–27.
[17] Williams SB, Huo J, Dafashy TJ, et al. Survival differences among patients with bladder cancer according to sex: critical evaluation of radical cystectomy use and delay to treatment. Urol Oncol 2017;35 (Oct. (10)):602, e601-602 e609.
[18] Messer JC, Shariat SF, Dinney CP, et al. Female gender is associated with a worse survival after radical cystectomy for urothelial carcinoma of the bladder: a competing risk analysis. Urology 2014;83:863–7.
[19] Otto W, May M, Fritsche H-M, et al. Analysis of sex differences in cancer-specific survival and perioperative mortality following radical cystectomy: results of a large German multicenter study of nearly 2500 patients with urothelial carcinoma of the bladder. Gender Med 2012;9:481–9.
[20] May M, Bastian PJ, Brookman-May S, et al. Gender-specific differences in cancer-specific survival after radical cystectomy for patients with urothelial carcinoma of the urinary bladder in pathologic tumor stage T4a. Urol Oncol 2013;31:1141–7.
[21] Kaushik D, Frank I, Eisenberg MS, et al. Gender-specific survival following radical cystectomy for pT4 bladder cancer. World J Urol 2014;32:1433–9.
[22] Mitra AP, Skinner EC, Schuckman AK, Quinn DI, Dorff TB, Daneshmand S. Effect of gender on outcomes following radical cystectomy for urothelial carcinoma of the bladder: a critical analysis of 1,994 patients. Urol Oncol 2014;32(52):e51–9.
[23] Andreassen BK, Grimsrud TK, Haug ES. Bladder cancer survival: women better off in the long run. Eur J Cancer 2018;95:52–8.
[24] Gore JL, Lai J, Setodji CM, Litwin MS, Saigal CS. Mortality increases when radical cystectomy is delayed more than 12 weeks: results from a Surveillance, Epidemiology, and End Results-Medicare analysis. Cancer 2009;115:988–96.
[25] Heberling U, Koch R, Hübler M, et al. Gender and mortality after radical cystectomy: competing risk analysis. Urol Int 2018;101:293–9.
[26] Cohn JA, Vekhter B, Lyttle C, Steinberg GD, Large MC. Sex disparities in diagnosis of bladder cancer after initial presentation with hematuria: a nationwide claims-based investigation. Cancer 2014;120:555–61.
[27] Matulay JT, Woldu SL, Lim A, et al. The impact of squamous histology on survival in patients with muscle-invasive bladder cancer. Urol Oncol 2019;37, 353.e17–24.
[28] Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859–66.
[29] Dotson A, May A, Davaro F, Raza SJ, Siddiqui S, Hamilton Z. Squamous cell carcinoma of the bladder: poor response to neoadjuvant chemotherapy. Int J Clin Oncol 2019;24:706–11.

Please cite this article in press as: Krimphove MJ, et al. Sex-specific Differences in the Quality of Treatment of Muscle-invasive Bladder Cancer Do Not Explain the Overall Survival Discrepancy. Eur Urol Focus (2019), https://doi.org/10.1016/j.euf.2019.06.001