Original Study

Sex Does Not Affect Survival: A Propensity Score-Matched Comparison in a Homogenous Contemporary Radical Cystectomy Cohort

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Abstract

To determine whether biological sex affects oncological outcome after radical cystectomy, for muscle-invasive bladder cancer. We performed a retrospective observational cohort study with a propensity score-matched population of 1165 patients. No significant difference was found between sexes regarding overall survival, cancer-specific survival, or recurrence-free-survival. We did not find a significant difference in cancer-related outcomes or overall survival after open radical cystectomy.

Objectives: To determine whether biological sex affects oncological outcome after extended pelvic lymph node dissection, radical cystectomy, and urinary diversion for muscle-invasive bladder cancer, and to identify risk factors impacting outcome. **Patients and Methods:** We performed a single-center, retrospective observational cohort study with prospective data collection with a propensity score matched population. A total of 1165 consecutive patients from 2000 to 2020, (317 women and 848 men) scheduled for open extended pelvic lymph node dissection, radical cystectomy, and urinary diversion for urothelial bladder cancer were included in the final analysis. Overall Survival (OS), Cancer-Specific-Survival (CSS), and Recurrence-Free-survival (RFS) were assessed with multivariable weighted Cox regression analysis as well as with propensity score matched Cox-Regression. **Results:** No significant difference was found between sexes regarding OS (HR 1.18, [0.93-1.49], $P = .16$), CSS (HR 0.87, [0.64-1.18], $P = .38$), or RFS (HR 0.80, [0.59-1.07], $P = .13$). These results were confirmed after propensity score matching: female sex was not associated with inferior OS (HR 1.20, [0.91-1.60], $P = .19$), CSS (HR 1.01, [0.75-1.35], $P = .97$) or RFS (HR 0.98, [0.75-1.27], $P = .86$). **Conclusions:** We did not find a significant difference in cancer-related outcomes or overall survival after extended pelvic lymph node dissection, open radical cystectomy, and urinary diversion for urothelial cancer between males and females even after adjustment with propensity matching score for multiple factors including oncological parameters, smoking status, and renal function.

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Introduction

Bladder cancer is the 10th most common cancer and the 11th most common cause of cancer death worldwide.[1,2] Projections to 2030 suggest, that the incidence of bladder cancer will continue to rise, especially in high and high-middle sociodemographic index countries.[3]

Men have a 3 to 4 times higher risk of being afflicted by bladder cancer and of dying from bladder cancer.[4] Reasons for the higher incidence in men are behavioral risk factors such as smoking and occupational hazards.[5] However, with the rising smoking prevalence among women, increasing trends have been observed in women, whereas in men rates are declining.[6]

There is an increasing focus on biological sex differences and gender-related issues affecting disease-specific outcomes and an extensive body of clinical and epidemiological evidence for variability in cancer associated with sex and gender.[7]

In general, for cancer women have a survival advantage over men,[8] bladder cancer seems to be an exception.[9,10] The underlying reason for this however remains disputed. Potential explanations for this sex difference range from varying exposures to carcinogens, differences in sex-hormone regulation, different pathological tumor

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entities to delayed diagnosis and inferior management in women.[11] Female smokers, for example, seem to not only be at greater risk of developing urothelial bladder cancer[12] but also have a poorer prognosis than male smokers.[13] At the time of diagnosis women present with more advanced disease, are more prone to disease recurrence, have a higher risk of recurrence and have inferior survival.[11]

Radical cystectomy (RC) and pelvic lymph node dissection (PLND) remain the gold standard of treatment for high risk non muscle invasive and muscle invasive bladder cancer.[14] There is conflicting evidence on sex-specific outcome for PLND and RC. Several studies have not shown any differences in margin status, lymph node count post-RC for urothelial bladder cancer, 90-day mortality or perioperative complications between sexes.[15-17] Conversely, others have reported lower PLND rates and higher 90-day mortality and perioperative complications in women.[18,19]

Evidence regarding overall survival, cancer specific survival and recurrence-free survival in women compared to men after RC and PLND remains contradictory with some studies reporting inferior outcome in women[15,16,20,21] whereas others found no difference.[17,22,23]

Here we aim to evaluate sex associated outcome in a homogenous contemporary cohort with urothelial bladder cancer undergoing standardized extended (e)PLND and RC at a single tertiary referral center in Switzerland, including a propensity score matched comparison. By evaluating data from a single center with a longstanding experience in ePLND and RC applying the same standardized approach over decades, we hope to eliminate potential confounders contributing to the multifactorial genesis of differences in sex related health and disease outcome.[24,25]

Patients and Methods

This retrospective observational study, with prospectively collected data, reports a consecutive case series from a single tertiary center and is in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. Ethical approval for this study was provided by the Ethical Committee of the Canton Bern, Switzerland (KEKBE 2016-00660, Chairperson Professor C. Seiler) on June 2nd, 2016, and amended on December 5, 2018. The need for informed consent was waived.

Study Population

All patient data from January 1st, 2000, to January 31st, 2020, were collected from a prospectively maintained cystectomy database, which fully complies with the legal requirements of the federal act on research involving human beings. Missing data was retrospectively added from the patients' paper charts and anesthetic records.

Surgical Technique and Perioperative Management

All patients were treated with extended pelvic lymph node dissection, (ePLND) open radical cystectomy (oRC), and urinary diversion (UD). At our institution ePLND and oRC have been performed following the same standardized surgical technique for the last decades as described previously and at least 1 senior urologist was present during surgery.[26] All patients were followed prospectively.

In women, nerve-sparing was performed by dissecting the anterovaginal (11-o'clock or 1-o'clock) wall on the nontumor bearing side, whereas on the tumor bearing side the line of dissection was lateral (9 or 3-o'clock) and the anterior vaginal wall and uterus including the salpinx were removed. The ovaries were left in place and only removed if bleeding occurred or due to extensive adhesions. If the tumor was clearly outside of the region of close proximity to the vagina a reproductive organ-sparing cystectomy was performed.[27] Similarly in men, if deemed oncologically safe a seminal vesicle-sparing approach was taken.[28] The type of UD offered was based on the characteristics of the disease and the patient, the final decision was based on patients' and physicians' preferences. All specimens underwent standard pathologic processing and were staged according to the 1998 TNM classification.[29]

Postoperative Follow-Up

All patients were followed according to a standardized protocol, for the first time after 3 months, then after 6 months. Patients were then followed at 6 monthly intervals for 5 years, yearly intervals up to 10 years and every 2 years thereafter.

Data Collection and Outcome Measures

Collected data included preoperative baseline characteristics including age, sex, body-mass-index (BMI), American Society of Anesthesiologists risk classification score (ASA score), Charlson Comorbidity Index (CCI), smoking status, preoperative hemoglobin value, renal function including creatinine and estimated Glomerular Filtration Rate (eGFR), the existence of preoperative hydronephrosis, and prior abdominal surgery. Surgical factors included duration of surgery, type of UD, intraoperative blood loss, and the need for blood transfusion. Oncological parameters included pathological tumor stage and grade, nodal staging, number of lymph nodes removed, lymphovascular and vascular tumor invasion, carcinoma in situ (CIS), neoadjuvant chemotherapy or adjuvant chemotherapy, and postoperative radiotherapy.

Overall survival (OS), cancer-specific-survival (CSS) and recurrence-free-survival (RFS) were calculated from the time of ORC until the death of any cause, death of bladder cancer or disease recurrence, respectively.

Statistical Analysis

In terms of descriptive summary measures of patient characteristics, continuous variables are examined with the Shapiro-Wilk Normality Test. Fisher's exact and Mann-Whitney-*U*-Tests were used to check whether the resulting data sets would still show significant differences. Data are presented with medians and interquartile ranges (IQR) and categorical variables are presented with counts and percentages.

The outcomes of interest OS, CSS and RFS were assessed with weighted Cox Regression.[30] A weighted multivariate Cox-Regression was performed for each of the 3 outcomes including 24 clinical and oncological parameters. The sample size to estimated parameter ratio for each Cox regression was always higher than $1100/24 = 45.8$ which indicates a very solid base of estimation. This regression requires large (group) data sizes to correctly estimate Hazard Ratios. The group sizes were 69 and more and thus large

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enough to correctly estimate the Hazard Ratios. A weighted multivariate Cox-Regression by Schemper et al. was performed to assess binary outcomes OS, CSS, and RFS. Hazard ratios and their 95% CI were calculated. As the number of male and female patients was unbalanced (845 male, 314 female). Male patients were matched to female patients using the propensity score method (PSM) proposed by Rosenbaum and Rubin.[31] Propensity scores were calculated by performing a logistic regression on the binary parameter gender. After that, propensity scores were matched using the matching algorithm proposed by Sekhon.[32] As the output of the algorithm depends on the order of the input data, data order was resampled 10'000 times and the matching with the lowest total difference in propensity scores was chosen. Fisher's exact and Mann-Whitney-*U*-Tests were used to check whether the resulting data sets would still show significant differences. Then weighted Cox-Regression with Hazard ratios (HR) and their 95% confidence interval (CI) were calculated only for the parameter gender using the matched sample. The parameter sex (male/female) was assessed once as part of a multivariate regression to eliminate statistical confounding and once univariately using a matched sample to reduce bias and increase comparability.

All analyses in this report were performed with the statistics software R, version 4.0.2.[33] *P*-values less than .05 were considered statistically significant.

Results

We identified 1165 consecutive patients, 848 men and 317 women, who underwent ePLND, oRC and UD for urothelial bladder cancer. Patients with insufficient follow-up (missing data: N = 6) were excluded from the analysis, leaving 1159 patients, 845 men and 314 women for the final analysis.

Clinicopathologic data are presented in Table 2. More women had a BMI < 25 and were nonsmokers than men. Women had a lower CCI and were more likely to have had prior abdominal surgery than men. Intraoperatively women lost less blood but more often needed blood transfusion than men. Women had more advanced pathologic disease and more nodal positivity at the time of surgery. Women also had more lymphovascular and vascular tumor invasion than males. Fewer women received a continent urinary diversion.

There was no significant difference in OS, CSS or RFS between groups in the unmatched overall population (See Figures). On Cox-regression multivariate weighted analyses, female sex was not associated with OS (HR 1.18, [0.93-1.49], $P = .16$), CSS (HR 0.87, [0.64-1.18], $P = .38$) or RFS (HR 0.80, [0.59-1.07], $P = .13$) (Table 3).

Risk factors for OS were age at the time of surgery (HR 1.03; [1.02 - 1.05] for 1 additional year, $P < .0001$), T stage (≥3 having a HR 1.61; [1.29-2.01] times higher than ≤2, $P < .0001$), vascular invasion (HR 1.53; [1.17-2.00] times higher, $P = .002$), lymphovascular invasion (HR 1.33; [1.02-1.74] times higher, $P = .04$), neoadjuvant chemotherapy as well as adjuvant chemotherapy or radiotherapy (HR 1.43, [1.08-1.89] $P = .01$, HR 1.68, $P < .0001$, HR 2.45, [1-92-3.13] $P < .0001$, respectively), number of lymph nodes removed and number of positive lymph nodes (HR 0.98, [0.98-0.99] and 1.07 [1.05-1.09], both $P < .0001$, for 1 additional unit, respectively), ASA Score (3 - 4 having a HR 1.25, [1.01-1.56] times higher than 1 - 2, $P = .04$), smoking history (Yes having a HR 1.34, [1.10-1.63] times higher than No, $P = .004$), CCI (HR 1.06, [1.01-1.11] for 1 additional unit, $P = .02$) and blood transfusion (HR 1.04, [1.00-1.08] for 100 additional mL, $P = .04$).

Table 1 HR for Sex on OSS, CSS, and RFS After Multivariate Weighted Cox Regression

Outcome	Comparison	HR (95%-CI)	*P*-Value
OSS	M (BL) vs. F	1.18 (0.93-1.49)	.16
CSS	M (BL) vs. F	0.87 (0.64-1.18)	.38
RFS	M (BL) vs. F	0.80 (0.59-1.07)	.13

Risk factors for CSS were age at the time of surgery (HR 1.02, [1.00-1.04] for 1 additional year, $P = .02$), T stage (≥3 having a HR 2.03, [1.50-2.73] times higher than ≤2, $P < .0001$), vascular invasion(HR 1.86, [1.37-2.53] times, $P = .003$), neoadjuvant chemotherapy, adjuvant chemotherapy or radiotherapy (HR 1.82, [1.31-2.54] $P = .0004$, HR 3.05, $P < .0001$, and HR 2.96, [2.20-4.00] $P < .0001$, respectively) and number of lymph nodes removed and number of positive lymph nodes (HR 0.99, [0.98-0.99] and 1.05, [1.03-1.08] $P = .002$ and $P < .0001$, for 1 additional node, respectively).

Risk factors for RFS were pathological tumor stage (≥3 having a HR 1.90, [1.46-2.46] times higher than ≤2, $P < .0001$), vascular invasion (HR 1.46, [1.10-1.94] $P = .008$), neoadjuvant chemotherapy, adjuvant chemotherapy or radiotherapy (HR 1.52, [1.13-2.04] $P = .006$, HR 2.56, [1.86-3.52] $P < .0001$, HR 3.08, $P < .0001$, respectively) and number of lymph nodes removed (HR 0.99, [0.98-1.00] $P = .01$, for 1 additional unit.

Matching Analysis

As the number of male and female patients was unbalanced (845 male, 314 female), male patients were 1 to 1 matched to female patients using a special matching algorithm with 24 comparable parameters (matching parameters stated in Table 1 and 2) . This led to a matched sample of 296 male and 296 female patients (Eighteen female patients could not be matched due to incomplete data) (Table 4). There was no significant difference in OS, CSS, or RFS between groups in the matched population (Figure1A-C). On Cox-regression analyses, female sex was not associated with OS (HR 1.20, [0.91-1.60], $P = .19$), CSS (HR 1.01, [0.75-1.35], $P = .97$) or RFS (HR 0.98, [0.75-1.27], $P = .86$).

Discussion

The lifetime probability of being diagnosed with cancer (including sex-specific cancers) is approximately equal for men and women[34] (40% vs. 39%, respectively). At shared anatomic sites (excluding sex-specific cancers), the burden of cancer is significantly higher among men than among women, with men having a greater than 2-fold higher risk for most cancers than women.[35] A recent comprehensive analysis of sex differences in the risk of 21 cancer anatomic sites within a large US cohort, found that apart from thyroid and gallbladder cancers, men had a higher risk of cancer than women at most shared anatomic sites, including rectum, kidney, gastric cardia, biliary tract, skin, liver, orophar-

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Table 2 Clinicopathologic Features of 1159 Patients Treated by Radical Cystectomy for Muscle-Invasive Bladder Cancer Stratified by Sex

	All	Female	Male	*P*-Value
Patient characteristics				
n	1159	314	845	
Age (y)	69.0 (62.1-75.8)	69.3 (60.7-76.8)	68.9 (62.7-75.6)	.91
BMI				
<25	478 (41.2%)	166 (52.9%)	312 (36.9%)	
≥25	681 (58.8%)	148 (47.1%)	533 (63.1%)	<.0001
Smoker				
No	478 (41.2%)	174 (55.4%)	304 (36.0%)	
Yes	681 (58.8%)	140 (44.6%)	541 (64.0%)	<.0001
ASA score				
1-2	610 (52.6%)	175 (55.7%)	435 (51.5%)	
3-4	549 (47.4%)	139 (44.3%)	410 (48.5%)	.21
Charlson score	4 (1-6)	3 (0-5)	4 (2-6)	<.0001
GFR preoperative (n = 1159)	72.9 (56.2-91.6)	70.1 (5.3-8.9)	74 (5.8-9.2)	.01
Hydronephrosis (n = 1159)				
No	926 (79.9%)	244 (77.7%)	682 (80.7%)	
Yes	233 (20.1%)	70 (22.3%)	163 (19.3%)	.28
Prior abdominal surgery				
No	725 (62.6%)	163 (51.9%)	562 (66.5%)	
Yes	434 (37.4%)	151 (48.1%)	283 (33.5%)	<.0001
Intraoperative data				
Total Blood Loss	1000 (700-1495)	820 (600-1200)	1100 (800-1500)	<.0001
OP Duration (hours)	6.5 (5.8-7.1)	6.3 (5.6-6.9)	6.5 (5.9-7.2)	.0007
Ec Transfusion (mL)	0 (0-0)	0.0 (0.0-2.8)	0.0 (0.0-0.0)	.003
Urinary diversion				
Continent	641 (55.3%)	138 (43.9%)	503 (59.5%)	
Incontinent	518 (44.7%)	176 (56.1%)	342 (40.5%)	<.0001
Oncological parameters				
pT (Tumor)				
≤pT2				
T0/Ta/Tx	**680 (58.7%)**	**159 (50.6%)**	**521 (61.7%)**	
T1	139 (12.0%)	25 (8.0%)	114 (13.5%)	
T2	179 (15.4%)	39 (12.4%)	140 (16.6%)	
≥pT3 :	362 (31.2%)	95 (30.3%)	267 (31.6%)	
T3	**479 (41.3%)**	**155 (49.4%)**	**324 (38.3%)**	**.0007**
T4	384 (33.1%)	127 (40.4%)	257 (30.4%)	
pN stage	95 (8.2%)	28 (9.0%)	67 (7.9%)	
pN0	838 (72.3%)	212 (67.5%)	626 (74.1%)	
pN+	321 (27.7%)	102 (32.5%)	219 (25.9%)	.03
pG (grade)				
2	69 (6.0%)	15 (4.8%)	54 (5.4%)	
3	1090 (94.0%)	299 (95.2%)	791 (93.6%)	.33
pVI (vascular invasion)				
No	903 (79.7%)	226 (73.6%)	677 (82.0%)	
Yes	230 (20.3%)	81 (26.4%)	149 (18.0%)	.003

(*continued on next page*)

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Table 2 (*continued*)

	All	Female	Male	*P*-Value
pLVI (lymphovascular invasion)				
No	886 (79.4%)	218 (72.4%)	668 (82.0%)	
Yes	230 (20.6%)	83 (27.6%)	147 (18.0%)	.0006
Concomitant Cis				
No	515 (44.4%)	148 (47.1%)	367 (43.4%)	
Yes	644 (55.6%)	166 (52.9%)	478 (56.6%)	.29
LN count, median (IQR)	31 (23-41)	31 (23-41)	32 (23-41)	.63
LN count (positive) median (IQR)	0 (0-1)	0 (0-1)	0 (0-0)	.02
Neoadjuvant chemotherapy				
No	957 (82.6%)	261 (83.1%)	96 (82.4%)	
Yes	202 (17.4%)	53 (16.9%)	149 (17.6%)	.79
Adjuvant chemotherapy				
No	897 (77.4%)	235 (74.8%)	662 (78.3%)	
Yes	262 (22.6%)	79 (25.2%)	183 (21.7%)	.21
Postop. radiotherapy				
No	1014 (87.5%)	273 (86.9%)	741 (87.7%)	
Yes	145 (12.5%)	41 (13.1%)	104 (12.3%)	.76

Data shown as median (25th-75th percentiles) or percentages and *P*-values as of Mann-Whitney-U and Fisherś-Exact tests, depending on distribution. Only full datasets are included in all tables.

ynx, bladder, larynx, noncardia gastric, and esophageal adenocarcinoma. Even after adjustment for a wide range of risk factors and carcinogenic exposure the male predominance remained implicating sex-related biologic mechanisms as the major determinants for the male-female difference in the risk of cancer.[8] However urothelial bladder cancer is the only cancer, where men had a survival benefit in a population based study from the Surveillance Epidemiology and End Results (SEER) database.[36] Krimphove et al. analyzed data from the National Cancer Data base to investigate sex-specific differences in pathological features at presentation as well as treatment quality measures and concluded that once the diagnosis of muscle invasive bladder cancer is established the sex gap in survival is marginal, independent of comorbidities, pathological stages, histological features and treatment patterns.[9]

In this Swiss cohort with urothelial bladder cancer from a tertiary referral center with longstanding expertise in ePLND and oRC with UD, we did not find a significant difference in oncological outcome between males and females with urothelial bladder cancer. Both in the complete cohort and after adjustment with propensity matching score for multiple factors including oncological parameters (eg, TNM, neoadjuvant or adjuvant treatment etc.), smoking status, BMI, ASA score, Charlson score and renal function no clinically significant difference in outcome between males and females was found. Positive margins were comparable to existing literature with a total of 10 women and 27 men (3.1% overall) being reported as R1.[37] The factor "sex" did not affect cancer-related outcomes in our UBC patients.

Women presented with more advanced disease (eg, tumor stage, positive lymph nodes), which despite being a risk factor for survival outcome after RC[38] did not result in inferior survival in women in our unmatched cohort. Most multi center and population based studies evaluating outcome after RC consistently report inferior outcome in women,[15,16,20,39,40] including a recent systematic review and meta-analysis.[21] In contrast single center studies from other large volume centers found no difference in oncological outcome between men and women.[17,23]

Soave, in a German population observed no difference in tumor stage at presentation between sexes,[17] whereas in Pichler et al.'s cohort women had more advanced tumor stages in line with our findings.[23] In 1 other single center study a nonmatched cohort showed more advanced disease at cystectomy and superior outcome in men in a nonmatched cohort, with no difference after matching.[22]

These discrepancies may partly be explained by the fact that mainly population-based studies tend to rely on rudimentary information on pathologic features and patient management and assess outcome in centers with different treatment standards. Single center studies, including this study, on the other hand report outcome after a standardized treatment approach and patient management. Data from large volume centers with extensive surgical experience and a well standardized approach to ePLND and RC may reflect a more comparable treatment in men and women, and an increased urologist's female RC volume. This supports the notion of centralization leading to more experience in performing this highly morbid procedure.

Women seem to have an advantage following chemotherapy, which may equalize the preoperative disparity in stage and consequently outcome.[41,42] In our cohort approx. Twenty percent of both men and women received neoadjuvant chemotherapy, which initially was mostly given in the presence of risk factors, such

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Figure 1 Comparison of the clinical outcomes OSS (A), CSS (B) and RFS (C) stratified by sex (female and male) in the matched cohort (Kaplan–Meier curves). (A) OSS matched population, (B) CSS matched population, and (C) Kaplan–Meier curve RFS matched population.

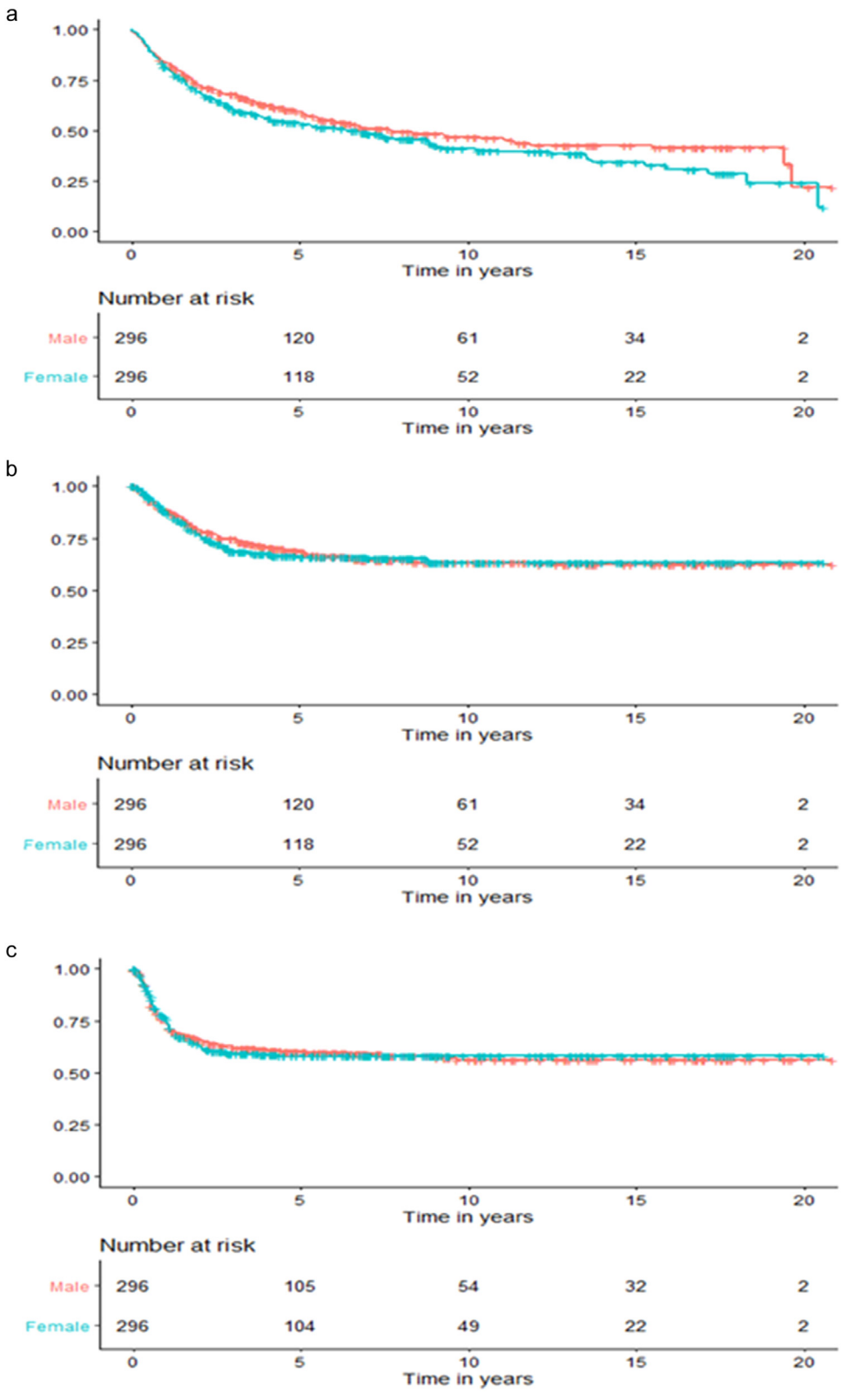

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Table 3 Summary of Hazard Ratios With 95%-CI for outcomes OS, CSS, and RFS

	OSS	CSS	RFS
Patient Characteristics			
Sex (Male vs. Female)	1.18 (0.93-1.49)	0.87 (0.64-1.18)	0.80 (0.59-1.07)
Age (+ 1 y)	1.03[c] (1.02-1.05)	1.02* (1.00-1.04)	1.01 (0.99-1.02)
BMI (< 25 vs. ≥ 25)	1.21 (0.99-1.48)	0.93 (0.72-1.19)	1.04 (0.83-1.30)
Smoker (No vs. Yes)	1.34[b] (1.10-1.63)	1.15 (0.87-1.52)	0.96 (0.76-1.22)
ASA Score (1 - 2 vs. 3 - 4)	1.25[a] (1.01-1.56)	1.04 (0.77-1.42)	0.97 (0.74-1.27)
Charlson Score (Score + 1)	1.06[a] (1.01-1.11)	1.03 (0.97-1.10)	1.02 (0.96-1.08)
Preop. renal function (GFR + 10 mL/min)	0.97 (0.94 -1.01)	0.97 (0.92-1.02)	0.98 (0.93-1.02)
Hydronephrosis (No vs. Yes)	0.98 (0.78-1.24)	1.24 (0.94-1.63)	1.01 (0.77-1.32)
Prior abdominal surgery (No vs. Yes)	0.89 (0.74-1.07)	0.96 (0.76-1.27)	1.06 (0.84-1.34)
Intraoperative data			
Urinary Diversion°	1.03 (0.79-1.33)	1.05[c] (1.03-1.08)	1.03 (1.00-1.05)
Blood Loss (+ 100mL)	0.99 (0.97-1.01)	0.99 (0.96-1.02)	0.99 (0.96-1.01)
Duration of surgery (+ 1h)	0.97 (0.87-1.07)	0.88 (0.75-1.02)	0.91 (0.81-1.03)
Blood transfusion (+ 100mL)	1.04[a] (1.00-1.08)	1.02 (0.97-1.08)	1.02 (0.98-1.07)
Oncological Parameters			
Tumor stage (≤pT2 vs. ≥pT3)	1.61[c] (1.29-2.01)	2.03[c] (1.50-2.73)	1.90[c] (1.46-2.46)
Nodal stage (N0 vs. N+)	1.05 (0.81-1.35)	1.20 (0.87-1.64)	1.10 (0.82-1.47)
G-Path (2 vs. 3)	1.06 (0.71-1.58)	0.86 (0.48-1.54)	1.17 (0.65-2.10)
pVI (No vs. Yes)	1.53[b] (1.17-2.00)	1.86[b] (1.37-2.53)	1.46[b] (1.10-1.94)
pLVI (No vs. Yes)	1.33[a] (1.02-1.74)	1.16 (0.85-1.57)	1.17 (0.86-1.58)
concomitant Cis (No vs. Yes)	0.85 (0.70-1.04)	0.87 (0.68-1.10)	1.11 (0.89-1.38)
LN count (+ 1)	0.98[c] (0.98-0.99)	1.82[b] (1.31-2.54)	1.52[b] (1.13-2.04)
LN count (positive) (+ 1)	1.07[c] (1.05-1.09)	3.05[c] (2.17-4.30)	2.56[c] (1.86-3.52)
Neoadjuvant Chemotherapy (No vs. Yes)	1.43[a] (1.08-1.89)	2.96[c] (2.20-4.00)	3.08[c] (2.32-4.08)
Adjuvant Chemotherapy (No vs. Yes)	1.68[c] (1.32-2.13)	0.99 (0.70-1.39)	1.18 (0.87-1.59)
Postoperative Radiotherapy (No vs. Yes)	2.45[c]s (1.92-3.13)	0.99[b] (0.98-0.99)	0.99[a] (0.98-1.00)

For binary parameters, the first-mentioned group is the baseline group and the second-mentioned group the comparison group.
Coding for significances.
[a] $P \leq .05$.
[b] $P < .01$.
[c] $P < .0001$.

as hydronephrosis or radiologic suspicion of lymph node metastasis. In Mitra's cohort 44.5% of men and 35.3% of women presented with ≤ pT1, whereas in our series the corresponding percentages are 30% and 20%, respectively. Patients with non-muscle invasive BC would not have received neoadjuvant therapy, potentially reducing the survival advantage gained by neoadjuvant therapy in women and thus minimizing the survival benefit in men in our cohort in contrast to Mitra et al's. In our cohort, only eleven men and 3 women achieved ypT0 after neoadjuvant chemotherapy.

Overall, in our series, women were less likely to smoke or have a history of smoking, more likely to have a BMI < 25 and more likely to have had prior abdominal surgery. In agreement with other studies, women were found to have a more advanced pathological disease stage and were more likely to have node positive disease.[25] Despite these observations, we could not find a significant difference in OSS, CSS or RFS after surgery. The hazard ratio for OS was slightly higher for women before and after matching, whereas for CS and RFS it was lower before matching and increased slightly after matching. We had a very solid base of estimation as the sample size to estimated parameter ratio for each Cox regression was always higher than 42 (1100/26 = 42.3). This should grant highly accurate results.

There are multiple potential explanations for contradictory findings between studies. The unbalanced and unmatched study designs of some studies can lead to a multitude of biases. The fact that other high volume single center studies report similar outcomes, highlights the value studies from centers of excellence offer. A homogenous series, high caseload, and expertise in all aspects of management in patients undergoing RC and UD is imperative to achieve optimal patient management. Even though these studies may not reflect outcomes throughout the population, they do show what is possible in a specialized setting with standardized procedures. Other biological factors, such as potential sex dependent patient management, genetic, anatomic (thinner bladder wall and faster tumor invasion, more advanced disease stage and surgical complications), and hormonal (hormones and hormonal receptors) differences, although still discussed contentiously may prove to have

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Table 4 Descriptive Summary of Covariates by Sex (Female n = 296 and Matched Male n = 296) After Matching

	Female Patients	Male Patients	*P*-Value
Patients characteristics			
Age	69.0 (60.5-76.6)	70.0 (63.6-76.2)	.31
BMI <25 vs. ≥25	159 (53.7%) / 137 (46.3%)	142 (48.0%) / 154 (52.0%)	.19
Smoker No vs. Yes	160 (54.1%) / 136 (45.9%)	146 (49.3%) / 150 (50.7%)	.29
ASA Score 1 - 2 vs. 3-4	167 (56.4%) / 129 (43.6%)	164 (55.4%) / 132 (44.6%)	.87
CCI	3 (0-5)	3 (0-5)	.32
GFR preoperative (mL/min)	70.5 (52.5-88.5)	71.4 (53.1-90.0)	.57
Hydronephrosis No vs. Yes	228 (77.0%) / 68 (23.0%)	241 (81.4%) / 55 (18.6%)	.22
Prior abdominal surgery No vs. Yes	153 (51.7%) / 143 (48.3%)	159 (53.7%) / 137 (46.3%)	.68
Intraoperative data			
Urinary Diversion			
Continent	131 (44.3%)	138 (46.6%)	
Incontinent	165 (55.7%)	158 (53.4%)	.62
Blood Loss (mL)	800 (600-1200)	900 (700- 1200)	.19
Duration of surgery (h)	6.3 (5.7-6.9)	6.3 (5.7-7.1)	.43
Blood transfusion (mL)	0 (0-275)	0 (0-0)	.17
Oncologic Parameters			
pT ≤pT2 vs. ≥pT3	152 (51.4%) / 144 (48.6%)	169 (57.1%) / 127 (42.9%)	.19
pN pN0 vs. pN+	202 (68.2%) / 94 (31.8%)	216 (73.0%) / 80 (27.0%)	.24
Grade 2 vs. 3	13 (4.4%) / 283 (95.6%)	16 (5.4%) / 280 (94.6%)	.7
pVI No vs. Yes	215 (72.6%) / 81 (27.4%)	224 (75.7%) / 72 (24.3%)	.45
pLVI No vs. Yes	214 (72.3%) / 82 (27.7%)	225 (76.0%) / 71 (24.0%)	.35
Cis No vs. Yes	137 (46.3%) / 159 (53.7%)	134 (45.3%) / 162 (54.7%)	.87
Neoadj. chemotherapy No vs. Yes	246 (83.1%) / 50 (16.9%)	246 (83.1%) / 50 (16.9%)	1
Adj. chemotherapy No vs. Yes	223 (75.3%) / 73 (24.7%)	230 (77.7%) / 66 (22.3%)	.56
Postop. radiotherapy No vs. Yes	259 (87.5%) / 37 (12.5%)	263 (88.9%) / 33 (11.1%)	.7
Lymph nodes total	31 (23-40)	32 (24-40)	.6
Lymph nodes positive	0 (0-1)	0 (0-1)	.3

Data are shown as median (25th-75th percentiles) or percentages and *P*-values as of Mann-Whitney-*U* and Fisher's-Exact tests, depending on the distribution.

an impact on the observed differences in outcome and warrant further evaluation.[43]

Our results support prior evidence suggesting, that outcome after ePLND, RC and UD in matched cohorts are not affected by differences in sex.

Strengths and Limitations

A strength of this study is the inclusion of a large sequential population from a high caseload single center of excellence for RC and UD with standardized perioperative management and surgery over decades and long-term standardized follow-up. In addition, patient data were prospectively entered into the database and the rate of incomplete data was low (6%). The high number of patients included and events allowed to accurately estimate and reveal risk factors.

This study has various limitations: There is a potential bias from unmeasured risk factors in this retrospective case series with prospectively assessed data and some missing values. Despite the use of multiple regression analysis and risk adjustment, the potential for residual confounding factors cannot be completely eliminated. The "single centeredness" of this study could be considered a limitation. On the other hand, thanks to our very standardized approach and long-term patient follow-up, we are comparing a large series of patients treated according to the same standards independent of sex, avoiding the contamination of diverse treatment and patient management strategies inherent to retrospective multi center studies.

Conclusion

We did not find a clinically significant difference in cancer related outcome and overall survival after extended pelvic lymph node dissection, radical cystectomy, and urinary diversion for urothelial cancer between males and females even after adjustment with propensity matching score for multiple factors including oncological parameters, smoking status, and renal function.

Clinical Practice Points

- Radical cystectomy (RC) and pelvic lymph node dissection (PLND) remain the gold standard of treatment for high-risk non-muscle invasive and muscle-invasive bladder cancer. To date, there

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is conflicting evidence on sex-specific outcomes for PLND and RC.
- Our results support prior evidence suggesting, that outcomes after ePLND, RC, and UD in matched cohorts are not affected by differences in sex. Based on our data, we could prove that highly morbid procedures performed in high-volume centers can eliminate sex-based outcome discrepancies.

Disclosure

All authors have no conflict of interest and nothing to disclose.

CRediT authorship contribution statement

Fabian P. Stangl: Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **Oliver D. Buehler:** Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Patrick Y. Wuethrich:** Conceptualization, Supervision, Validation, Writing – original draft. **Marc A. Furrer:** Data curation, Formal analysis. **Fiona C. Burkhard:** Conceptualization, Supervision, Validation, Resources, Project administration, Writing – original draft, Writing – review & editing.

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