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ARTICLE

The association between gender, stage and prognosis in bladder cancer patients undergoing radical cystectomy

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ABSTRACT

Objective: The incidence of bladder cancer is three times as high in men compared to women. Moreover, women are generally diagnosed with a more severe tumor stage and have poorer prognosis. This study aimed to examine the association between gender, stage, and prognosis among a subgroup of bladder cancer patients treated with radical cystectomy.

Patients and methods: A total of 460 patients (131 women, 329 men) with bladder cancer undergoing radical cystectomy at Aarhus University Hospital in 2015–2018 were retrospectively selected for this study and followed until 2021 at the latest. Correlations between gender, patient and tumor characteristics and oncological outcomes were analyzed by the Chi-squared test. By the use of multiple linear regression, we adjusted for age, comorbidity and the proportion of organ-confined and non-organ-confined disease at diagnosis.

Results: Female patients were found to be younger and less comorbid than male patients. A higher proportion of patients with muscle-invasive bladder cancer and non-organ-confined disease at the time of cystectomy was observed among female patients. Recurrence of cancer occurred 3.4 (0.1–6.7) months earlier in female patients, and they had a 47% higher cancer-specific mortality (RR = 1.47 (1.04–2.1)) compared to male patients. In the adjusted analysis, the association of an earlier recurrence in female patients remained.

Conclusion: This study verifies that gender disparities exist among bladder cancer patients, even after adjusting for age, comorbidity and for the proportion of organ-confined and non-organ-confined disease at cystectomy. Further investigations are required to investigate the etiology of this observed difference between sexes.

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Introduction

The age-standardized incidence of bladder cancer (BC) is approximately 73 per 100,000 per year in Denmark [1]. The average age at time of diagnosis is 70 years [2]. Men are diagnosed with BC three times more frequently than women. However, women tend to have a more severe tumor stage at the time of diagnosis as well as a poorer prognosis in terms of higher risks of cancer recurrence, progression and post-treatment mortality [3]. Well-established risk factors for BC development include advanced age, tobacco smoking and exposure to occupational and environmental factors such as aromatic amines and benzene chemicals. Radical cystectomy (RC) with lymph node dissection is the primary treatment for patients with localized, non-metastatic muscle-invasive BC (MIBC) and high risk non-muscle-invasive bladder cancer (NMIBC) [2]. Moreover, neoadjuvant chemotherapy (NAC) is an integral part of RC in patients with MIBC.

Former studies have examined the impact of gender on BC presentation and development and have suggested several possible biological and epidemiological explanations for the observed gender disparity. One explanation is that the occurrence of hematuria in female patients is often initially considered as a result of other conditions such as urinary infections, menstruation, etc. [3]. This will lead to a delay in BC diagnosis and could be a part of the explanation as to why female patients tend to have more advanced tumors at the time of diagnosis.

The presence of sex steroid hormones and their receptors might also be an important factor in the pathogenesis of BC, and gender differences in this hormone axis could potentially explain part of the observed disparities [4,5]. Other possible mechanisms are low exposure to estrogen and a disparity in the expression of some hepatic metabolic enzymes [3,4]. The impact of gender on BC presentation and development remains yet to be fully understood as gender disparities persist even after adjusting for well-established risk factors.

The objective of this study was, therefore, to examine the impact of gender on stage at diagnosis and prognosis among BC patients treated with RC.

Patients and methods

All patients with MIBC or high-risk NMIBC treated with RC at a single university hospital, Aarhus University Hospital, in

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Denmark in the period from 1 January 2015 to 31 December 2018 were retrospectively selected for this study. Patients were followed until their latest contact at the treating center within the year of 2021, unless recurrence of cancer, death or immigration occurred prior to this. In accordance with the Danish national guidelines, the patients were offered follow-up with CT-scans of the thorax and abdomen at least 4, 12 and 24 months after RC [2]. Data were collected from the patients' medical records and kept in a local quality registry. The data provide information regarding the patients' gender, age, tumor stage, smoking habits/history, comorbidities as well as their status on recurrence of cancer and cause of death, if any. In this study, the outcome measures comprised of different adverse oncological outcomes, among these the risk of and time till recurrence, the overall risk of death as well as the risk of BC-specific death (cancer-specific mortality (CSM)). An adjusted analysis was performed taking age and comorbidity (crude CCI) into account and the data in this specific analysis were also stratified based on the patients' severity of disease at cystectomy in terms of organ-confined (OC) and non-organ-confined (non-OC) disease, respectively. Non-OC disease was defined as tumor stage of T3–T4 and/or a positive nodal status. This stratification was performed to determine whether gender had an impact on BC prognosis regardless of the tumor stage at diagnosis.

In total, data on 464 patients were retrieved from the database. Four patients were excluded because of missing or incorrect data in the medical records, resulting in a total of 460 patients included in the analyses. The data retrieval for the project was approved by the Danish Patient Safety Authority (permission no. 3–3013–2584/1). Patient acceptance for registrations was waived through this approval.

Statistical analysis

Statistical measures such as mean values, differences, risk ratios (RR) and odds ratios (OR) were calculated and chi-squared tests were performed to test for associations between gender and several clinical and pathological characteristics as well as different adverse oncological outcomes. In this study, the 95% confidence intervals (95% CI) are presented rather than the associated *p*-values. The estimates in the adjusted analysis (Table 4) were calculated using multiple linear regression in R, a statistics program.

Results

Clinical and pathological characteristics

A total of 460 patients were included, with 131 women (28%) and 329 men (72%). Clinical and pathological characteristics of these patients are summarized in Table 1. Female patients were significantly younger than male patients, with an average age of 69 (67.5–70.9) years compared to 71 (70.1–72.1) years. The proportions of current, previous and never smokers did not differ between sexes. Comorbidity was significantly higher in male patients compared to female patients based on both ASA-score and Charlson Comorbidity Index (CCI), both the crude and age-adjusted CCI. A significant gender difference was observed in the distribution of NMIBC and MIBC in the specimens from cystectomy. Thus, 46% (37–55%) of female patients had MIBC at the time of RC compared to only 32% (27–37%) of the male patients. The same disparity was observed regarding the proportion of non-OC disease at RC, with 37% (29–46%) in female patients and 30% (25–35%) in male patients.

Associations between gender and oncological outcomes

Mean follow-up time was 20.6 (18.3–23.0) months for female patients and 22.4 (20.8–23.9) months for male patients (Table 2). During follow-up, 41 (31%) female patients and 82 (25%) male patients experienced a recurrence of cancer in terms of either local recurrence in the bladder and/or occurrence of metastases. The mean time to recurrence was 7.2 months for female patients and 10.6 months for male patients, giving a difference of 3.4 (0.1–6.7) months (Table 2), and this difference remained the same when we adjusted for age and comorbidity (Table 4). In the stratified analysis, female patients still experienced recurrence earlier than male patients, regardless of their tumor stage at diagnosis, as the difference in the OC-group and non-OC group was 5.9 and 1.3 months, respectively (Table 4).

In total, 43 (33%) female patients and 118 (36%) male patients died during follow-up (Table 3). There was no association between gender and the overall risk of dying. Death occurred on average 5.0 (–0.3–10.3) months earlier in female patients, and they had a 47% higher risk of dying due to BC (RR = 1.47 (1.04–2.1)) than male patients. On the contrary, a higher proportion of male patients died due to other reasons than their BC diagnosis (13% vs. 3%). The association of a higher cancer-specific mortality (CSM) in female patients remained in the adjusted analysis (OR = 1.68 (1.04–2.72), Table 4). When stratifying for the type of disease at diagnosis, female patients still had a higher CSM in the non-OC group, though the association diminished in the OC-group (Table 4).

Discussion

In this study, 460 BC patients treated with RC were included. Female patients were found to be younger and with more severe tumor stage at the time of diagnosis compared to male patients. On the contrary, male patients were more comorbid. Our results showed that recurrence occurred earlier in female patients with a mean difference of 3.4 months. Moreover, female patients had a 47% higher CSM than male patients.

The results of this study are consistent with other studies examining the impact of gender on oncological outcomes in BC patients treated with RC. Thus, Heberling et al. [6] found female patients to be less comorbid and more likely to have extravesical tumors ($\geq$ T3) similarly to our findings presented in Table 1. Likewise, Rosiello et al. [7] found female gender to be an independent predictor of non-OC disease at the time of RC (OR = 1.23, $p < 0.001$). An explanation as to why

Table 1. Patients' clinical and pathological characteristics.

	Women ($n = 131$)		Men ($n = 329$)	
	Amount/mean	Proportion (95% CI)	Amount/mean	Proportion (95% CI)
Age (mean–years)	69.18	(67.52–70.85)	71.13	(70.14–72.12)
Smoking status				
Currently smoking	37	28.2% (20.7–36.8%)	99	30.1% (25.2–35.4%)
Previously smoking	60	45.8% (37.1–54.7%)	173	52.6% (47.0–58.1%)
Never smoking	34	26.0% (18.7–34.3%)	57	17.3% (13.4–21.9%)
BMI (mean)	26.31	(25.41–27.20)	26.59	(26.14–27.03)
ASA-score (mean)	2.09	(1.98–2.20)	2.25	(2.19–2.32)
Charlson Comorbidty Index (mean)				
Crude	0.66	(0.50–0.83)	1.27	(1.11–1.43)
Adjusted for age	2.97	(2.72–3.21)	3.76	(3.57–3.95)
Urinary diversion				
Ileal conduit	125	95.4% (90.3–98.3%)	314	95.4% (92.6–97.4%)
Other	6		15	
Tumor stage (TURB)[a]				
$\leq$ T1	41	31.3% (23.5–40.0%)	122	37.1% (31.9–42.6%)
$\geq$ T2	86	65.6% (56.9–73.7%)	201	61.1% (55.6–66.4%)
Not specified	4	3.1%	6	1.8%
Tumor stage (RC)[b]				
NMIBC ($\leq$ T1)	68	51.9% (43.0–60.7%)	222	67.5% (62.4–72.5%)
MIBC ($\geq$ T2)	60	45.8% (37.1–54.7%)	105	31.9% (26.9–37.3%)
Not specified	3	2.3%	2	0.6%
Nodal status				
Positive (N+)	17	13.0% (7.7–20.0%)	46	14.0% (10.4–18.2%)
Negative	114	87.0%	283	86.0%
Type of disease (RC)[b]				
OC	79	60.3% (51.4–68.7%)	229	69.6% (64.3–74.5%)
Non-OC	49	37.4% (29.1–46.3%)	99	30.1% (25.2–35.4%)
Not specified	3	2.3%	1	0.3%
Histological type				
TCC	118	90.1% (83.6–94.6%)	309	93.9% (90.8–96.3%)
SCC	10	7.6% (3.7–13.6%)	6	1.8% (0.7–3.9%)
Other	2	1.5%	8	2.4%
Not specified	1	0.8%	6	1.8%
MIBC patients treated with NAC				
Did receive NAC	16	26.7% (16.1–39.7%)	29	27.6% (19.3–37.2%)
Did not receive NAC	44	73.3%	76	72.4%

[a]Based on the specimen from TURB.
[b]Based on the specimen from RC.
Abbreviations: RC: radical cystectomy; NMIBC: non-muscle-invasive bladder cancer: which means tumor stage $\leq$ T1; MIBC: muscle-invasive bladder cancer: which means tumor stage $\geq$ T2; OC: organ-confined disease, which means tumor stage $\leq$ T2 without any lymph node or distant metastases; non-OC: non-organ confined disease, which means tumor stage of T3–T4 and/or a positive nodal status (N+); NAC: neoadjuvant chemotherapy.

female patients are found to be less comorbid could be that females tend to have more frequent doctor appointments due to a greater awareness of symptoms and increased focus on health. The risk of being comorbid increases with age, and the fact that the female patients in this study are less comorbid could partly be due to their younger age compared to the male patients (69 vs. 71 years). However, the female patients in both Heberling et al. [6] and Rosiello et al. [7] were significantly older than the male patients.

Both Messer et al. [8] and Kluth et al. [9] found female patients to be associated with a significantly higher risk of cancer recurrence with an HR = 1.16 ($p = 0.03$) and HR = 1.12 ($p = 0.02$), respectively. We found that recurrence of cancer occurred significantly earlier in female patients compared to male patients with a mean difference of 3.4 months. A larger proportion of current/previous smokers among female patients would probably increase the risk of getting recurrence and facilitate an earlier onset. In our study, male patients were slightly over-represented in the 'current' and 'previous' smoking group, though we did not find patient smoking status to differ significantly between sexes. Both Messer et al. [8] and Kluth et al. [9] did not have any information regarding patient smoking status, so we cannot rule out this hypothesis.

Other studies' results on gender disparities in relation to the CSM are conflicting. Nevertheless, several studies found female gender to be associated with a higher risk of death due to BC, similar to our results [7–9]. Rosiello et al. [7] found that female patients with non-OC disease were associated with a higher CSM after RC than male patients with non-OC disease, though this association did not remain significant when solely looking at the patients with OC disease, which is similar to our findings presented in Table 4. One potential explanation for female patients to have a higher CSM is that female patients are less comorbid, hence male patients might die due to other reasons (e.g., cardiovascular diseases) before their BC diagnosis reaches a terminal stage. Supporting this hypothesis, we found male patients to have a higher risk of dying due to other reasons than their BC diagnosis, though the overall risk of dying did not differ significantly between sex. Williams et al. [10] found female patients to have a poorer cancer-specific survival rate than

Table 2. Associations between gender and recurrence of cancer.

	Women ($n = 131$)	Men ($n = 329$)	Estimate
Time of follow-up[a] (months)			
Median	24	24	
Mean (95% CI)	20.62 (18.3–23.0)	22.35 (20.8–23.9)	
Number of patients with recurrence	41	82	
Risk of recurrence (%) 95% CI	31.3% (23.5–40.0%)	24.9% (20.3–30.0%)	RR = 1.26 (0.92–1.72)
Time to recurrence (months)			
Median	4	8	
Mean (95% CI)	7.2 (4.5–9.8)	10.6 (8.6–12.5)	Diff. = 3.4 (0.1–6.7)
Type of cancer recurrence[b]			
Local	25	37	
Local lymph nodes	9	15	
Distant lymph nodes	8	22	
Liver	4	17	
Lung	13	28	
Bone	5	14	
CNS	2	4	
Skin	1	3	
Other	9	12	

[a]The time of follow-up determined by the date of their latest contact at Aarhus University Hospital within the year of 2021, unless recurrence, death or immigration occurred prior to this.
[b]The patients had recurrence of cancer in terms of recurrence locally in the bladder and/or metastases.

Table 3. Associations between gender and mortality.

	Women ($n = 131$)	Men ($n = 329$)	Estimate
Number of deaths	43	118	
Risk of death (overall - %)	32.8% (24.9–41.6%)	35.9% (30.7–41.3%)	RR = 0.92 (0.69–1.22)
95% CI			
Time to death (months)			
Median	12	17.5	
Mean (95% CI)	16.2 (12.1–20.4)	21.2 (17.9–24.5)	Diff = 5.0 (–0.3–10.3)
Cause of death			
Amount (proportion, %)			
BC	37 (28.2%)	63 (19.2%)	
Other reasons	4 (3.1%)	43 (13.1%)	
Unknown	2	12	
Risk of BC-specific death (CSM), 95% CI	28.2% (20.7–36.8%)	19.2% (15.0–23.8%)	RR = 1.47 (1.04–2.10)

Abbreviation: BC: bladder cancer; CSM: cancer-specific mortality.

Table 4. Adjusted[a] analysis for associations between gender and oncological outcomes.

	Total	Organ-confined disease (OC)[b]	Non-organ-confined disease (non-OC)[b]
OR of recurrence[c]	OR = 1.42 (0.9–2.25)	OR = 0.82 (0.35–1.91)	OR = 1.35 (0.64–2.85)
Difference in mean time to recurrence (months)	Diff. = 3.4 (–0.1–6.9)	Diff. = 5.9 (–3.4–15.2)	Diff. = 1.3 (–2.2–4.9)
OR of death	OR = 1.0 (0.64–1.56)	OR = 0.56 (0.26–1.18)	OR = 0.91 (0.43–1.96)
OR of BC-specific death	OR = 1.68 (1.04–2.72)	OR = 0.87 (0.35–2.15)	OR = 1.77 (0.84–3.75)
Difference in mean time to death (months)	Diff. = 4.9 (–1.4–11.2)	Diff. = 8.8 (–4.4–22.0)	Diff. = 1.3 (–2.1–4.9)

[a]Adjusted for gender, age and comorbidity (CCI).
[b]The data is stratified in relation to the patients' tumor stage at the time of RC in terms of organ-confined disease (OC) and non-organ-confined disease (non-OC).
[c]The estimates (ORs and differences) in this table are based on male patients being the reference group and are all followed by a 95%-CI.
Three women and one man were excluded from this table as their status of disease at RC (OC vs. non-OC) was not specified.

male patients with an HR = 1.26 ($p < 0.001$), consistent with our results (HR = 1.82 (1.06–3.15), table not shown), though our survival rates were limited to a time period including only the first year following RC. Contrary to Williams et al. [10], we did not find female patients to be associated with a worse overall survival rate than male patients. The similar overall survival rates between sex in our study (table not shown) might be due to a higher proportion of comorbidity and other causes of death than BC among male patients counterbalancing the significantly higher CSM in female patients.

Strengths and limitations

Only four patients (three men, one woman) were excluded from the original dataset, making selection bias less likely to affect our results. However, we only included BC patients treated with RC in this study, which may serve as a limitation. For instance, one may think that female patients with a long diagnostic delay were diagnosed with metastatic disease for which reason they were never treated with RC. It is therefore possible that there is a group of female patients with severe adverse oncological outcomes who were never

included in this study, diminishing the effect size of the observed gender differences.

Data on the patients were retrieved from electronic medical reports and are assumedly more reliable than, e.g., self-administered questionnaires. The study population of 460 patients is a potential limitation of the study as other studies examining similar hypotheses have larger sample sizes. This relatively small study population affects the effect sizes of this study as the results are associated with more uncertainty due to the wider confidence intervals.

One major strength is that we were able to adjust for the patients' severity of BC disease in terms of OC vs. non-OC disease. As we found female patients to be associated with a significantly higher proportion of non-OC BC, it is reasonable to think that this higher proportion of severe BC-cases among female patients could affect the associations observed between gender and different oncological outcomes. Yet, we found that recurrence of cancer occurred earlier in female patients than male patients regardless of their tumor stage at the time of RC, and female patients with non-OC disease still had a higher CSM like the one observed for all the female patients. We were also able to adjust for the patients' smoking status (table not shown), an important risk factor in BC development [11], which yielded similar results as the unadjusted CSM signifying smoking status as a minor confounder to our results. However, we cannot rule out the likelihood of residual confounding affecting our study as we do not have any information on, e.g., the patients' socioeconomic and educational status, and information regarding this would be preferable to obtain in future studies.

The patients were treated with RC between 2015 and 2018 and followed until the end of 2021 at the latest. In this study, the total 1-year cancer-specific survival rate was found to be 90% (table not shown), which is very similar to previous findings in Denmark [12]. This strengthens the validation of this study's results and makes them generalizable to all BC patients treated with RC in Denmark.

These results support the hypothesis that a gender disparity exists among BC patients, though further investigations are required to properly explain this disparity and before a potential implementation of a new way of handling BC patients in Denmark and other similar countries. If future studies establish that female patients with BC are at higher risk of adverse oncological outcomes, it would be reasonable with gender specific changes in the diagnostic guideline for BC. For instance, female patients might be offered more frequent cystoscopies and earlier intervention with RC.

Conclusion

In this study, female patients were significantly younger and had a more severe tumor stage at the time of RC, whereas male patients were more comorbid. Recurrence of cancer occurred significantly earlier in female patients and they had a higher CSM compared to male patients. The association of an earlier onset of cancer recurrence and a higher CSM in female patients remained when we adjusted for age and comorbidity, and when stratifying for the proportion of OC and non-OC disease at the time of RC recurrence still occurred earlier in female patients. Therefore, this study supports the hypothesis that a gender disparity exists among BC patients undergoing radical treatment.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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