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Gender and Mortality after Radical Cystectomy: Competing Risk Analysis

Ulrike Heberling^a Rainer Koch^b Matthias Hübler^c Gustavo B. Baretton^d
Oliver W. Hakenberg^e Manfred P. Wirth^a Michael Froehner^a

^aDepartments of Urology, Dresden, Germany; ^bDepartments of Medical Statistics and Biometry, Dresden, Germany;

^cDepartments of Anesthesiology, Dresden, Germany; ^dDepartments of Pathology, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; ^eDepartment of Urology, University of Rostock, Rostock, Germany

Keywords

Urologic neoplasms · Gender · Comorbidity · Bladder · Cystectomy · Competing risk analysis · Proportional hazards model

Abstract

Background: Data on the impact of gender on mortality after radical cystectomy is conflicting. We investigated a large single center sample with long-term follow-up in order to determine the relationship between gender and outcome.

Patients and Methods: A total of 1,184 consecutive patients who underwent radical cystectomy for high risk superficial or muscle-invasive urothelial or undifferentiated bladder cancer between 1993 and 2015 were stratified by gender. Demographic data was compared using Mann-Whitney U test, chi-square test, or Fisher exact test. Cox proportional hazard models were used for the analysis of competing risks and logit models were used for the prediction of the receipt of adjuvant cisplatin-based chemotherapy. **Results:** Female patients were older, healthier, less frequently current smokers and had more extravesical tumors. In the multivariate analyses, female gender was an independent predictor of (lower) non-bladder cancer (competing) mortality (hazards

ratio [HR] 0.68, 95% CI 0.49–0.95, $p = 0.0248$) but no predictor of bladder cancer-specific mortality (HR in the full model 1.20, 95% CI 0.94–1.54, $p = 0.15$). Gender was no predictor of the receipt of adjuvant cisplatin-based chemotherapy. **Conclusions:** Female gender was associated with an increased risk of extravesical disease but was no independent predictor of bladder cancer-specific mortality. Anatomical differences might be a plausible explanation for these observations.

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Introduction

Data on the impact of gender on mortality after radical cystectomy is conflicting. Female patients have been found to harbor a higher mortality risk after radical cystectomy [1–3]. The reasons for this phenomenon are discussed controversially [1]. Other authors, however, did not observe gender-related outcome differences [4–6]. We investigated a large single center sample with long-term follow-up in order to identify gender-related differences in prognostic parameters and in the mortality risk from bladder cancer and from competing causes.

Table 1. Demographic data of the study sample. Tumor stages are given as the cystectomy and lymph node dissection specimen tumor stages according to the 2017 TNM classification [7]. Patients initially classified as pT3a according to the 1992 TNM classification (invasion of deep bladder detrusor muscle) were reclassified as pT2 according the current classification

Parameter	Overall, <i>n</i> (%)	Males, <i>n</i> (%)	Females, <i>n</i> (%)	<i>p</i> value*
Sample size	1,184 (100)	929 (78.5)	255 (21.5)	–
Follow-up, censored patients, years, mean	7.34	7.32	7.43	0.28
BMI, kg/m ² , mean	27.0	27.0	26.9	0.23
Age, years, mean	68.7	68.0	71.1	<0.0001
Mean number of removed lymph nodes**	17.4	17.6	16.5	0.11
Extravesical disease (pT3–4 [7])	500 (42.2)	366 (39.4)	134 (52.5)	0.0002
Positive lymph nodes (pN1–3 [7])	308 (26.0)	239 (26.3)	69 (28.0)	0.59
Extravesical disease and positive lymph nodes (pT3–4 and pN1–3 [7])	232 (19.6)	173 (18.6)	59 (23.1)	0.11
Extravesical disease or positive lymph nodes (pT3–4 or pN1–3 [7])	576 (48.6)	432 (46.5)	144 (56.5)	0.0048
ASA classes 3–4	493 (41.6)	383 (41.2)	110 (43.1)	0.58
CCS classes 2–4	131 (11.1)	107 (11.5)	24 (9.4)	0.34
NYHA classes 2–4	211 (17.8)	162 (17.4)	49 (19.2)	0.51
Charlson score 2 or higher	449 (37.9)	365 (39.3)	84 (32.9)	0.06
Charlson score 2 or higher and ASA classes 3–4	305 (25.8)	247 (26.6)	58 (22.7)	0.21
Diabetes mellitus	288 (24.3)	234 (25.2)	54 (21.2)	0.19
Diabetes mellitus with end organ damage	149 (12.6)	129 (13.9)	20 (7.8)	0.0100
Chronic lung disease	218 (18.4)	192 (20.7)	26 (10.2)	0.0001
History of myocardial infarction	86 (7.3)	73 (7.9)	13 (5.1)	0.13
Cerebrovascular disease	65 (5.5)	56 (6.0)	9 (3.5)	0.12
Peripheral vascular disease	129 (11.0)	111 (11.9)	18 (7.1)	0.0264
Any neoadjuvant chemotherapy	55 (4.6)	47 (5.1)	8 (3.1)	0.20
Adjuvant cisplatin-based chemotherapy	258 (21.8)	202 (21.8)	56 (22.0)	0.97
Current smokers	327 (27.6)	288 (31.0)	39 (15.3)	<0.0001
Continent urinary diversion	390 (32.9)	363 (39.1)	27 (10.6)	<0.0001
90-Day mortality	50 (4.2)	35 (3.8)	15 (5.9)	0.14
Deaths from any cause	650 (54.9)	508 (54.7)	142 (55.7)	0.78
Deaths from non-cancer causes	205 (17.3)	164 (17.7)	41 (16.1)	0.78
Deaths from bladder cancer	372 (31.4)	278 (29.9)	94 (36.9)	0.0345
Deaths from second cancers	66 (5.6)	60 (6.5)***	6 (2.4)****	0.0114
Deaths from unknown causes	7 (0.6)	6 (0.6)	1 (0.4)	1.00

* *p* values are given for Mann-Whitney U test for quantitative variables, chi-square test or Fisher exact test for binary variables.

** Patients without a known number of removed lymph nodes were excluded for the calculation of the mean value.

*** Most common types: lung, gastric or duodenal, lymphoma/leukemia/plasmocytoma, hepatocellular, cholangiocellular, or gall bladder.

**** Lung (*n* = 2), pancreas (*n* = 2), leukemia, tongue.

CCS, classification of angina pectoris of the Canadian Cardiovascular Society; NYHA, classification of cardiac insufficiency of the New York Heart Association; ASA, American Society Association physical status classification; TNM, tumor node metastasis; BMI, body mass index.

Patients and Methods

Study Sample

The study sample consisted of 1,184 patients who consecutive-ly underwent radical cystectomy for high risk superficial or muscle-invasive urothelial or undifferentiated bladder cancer at our institution between 1993 and 2015. Institutional review board approval was obtained. The patients were stratified into males and females.

Data Collection

Tumor-related and patient-related data were obtained from patient charts. Demographic data is shown in Table 1. Follow-up information and data on the receipt of adjuvant cisplatin-based chemotherapy were obtained from patient charts, office urologists, general practitioners, the local tumor registry, local authorities, health insurances, the patients themselves, or their relatives. Deaths from all causes were considered events concerning overall mortality. Deaths from uncontrolled bladder cancer were consid-

ered events concerning bladder cancer-specific mortality. Deaths from other causes or from unknown causes were considered events concerning (competing) non-bladder cancer mortality. Further analogous analyses were performed with deaths from uncontrolled second cancers and deaths from non-cancer causes as endpoints.

Statistical Analysis

Demographic data were compared using Mann-Whitney U test, chi-square test, or Fisher exact test. Kaplan-Meier curves were used for the analysis of overall mortality whereas competing risk analysis was used for the analysis of individual causes of death. Univariate comparisons of mortality curves were done with the log-rank test (overall mortality) and the Pepe Mori test (competing risk analyses), respectively. Cox proportional hazard models were used for the analysis of competing risks and logit models were used for the prediction of the receipt of adjuvant cisplatin-based chemotherapy. The analyses were performed with the Statistical Analysis Systems version 9.4 statistical package (SAS Institute, Cary, NC, USA).

Results

In the current study, female patients were older, healthier, less frequently current smokers and had more frequently extravesical tumors, compared with their male counterparts (Table 1). In the univariate analysis, overall mortality did not differ between females and males (10-year rates 61.0 vs. 59.1%, $p = 0.35$; Fig. 1). Female patients had, however, a higher bladder cancer-specific mortality (10-year rates 41.5 vs. 34.1%, $p = 0.0067$; Fig. 2). Whereas there was no detectable relationship between gender and non-cancer mortality, female gender was associated with a trend toward lower second cancer mortality (10-year rates 2.9 vs. 7.0%, $p = 0.17$; Fig. 2). After stratification by the local tumor extent (bladder confined versus extravesical), bladder cancer-specific mortality was virtually identical in females and males with bladder confined tumors, whereas there was still some trend toward increased bladder cancer-specific mortality in females in patients with extravesical or lymph node-positive disease (Fig. 3).

In the multivariable analyses, female gender was an independent predictor of (lower) competing mortality (hazards ratio [HR] 0.68, 95% CI 0.49–0.95, $p = 0.0248$) but no predictor of bladder cancer-specific mortality (HR in the full model 1.20, 95% CI 0.94–1.54, $p = 0.15$; Table 2). Concerning second cancer mortality, female gender narrowly missed the significance level in the multivariable analysis as a predictor of (lower) mortality (HR 0.43, 95% CI 0.18–1.04, $p = 0.06$; Table 2). Nevertheless, lower competing mortality in females was largely contributable

Fig. 1. Cumulative overall mortality after radical cystectomy stratified by gender. The p value is given for the log-rank test.

to a lower incidence of fatal second cancers (Table 1; Fig. 2). Multivariable logit models predicting the probability of receipt of adjuvant cisplatin-based chemotherapy are shown in Table 3. The impact of gender was negligible compared with that of tumor-related variables, age and comorbidity (Table 3).

Discussion

In this study, female gender was associated with an increased risk of extravesical disease. The resulting increased bladder cancer-specific mortality risk in the univariate analysis disappeared after controlling for stage and other possible confounders.

In contrast to a comparable multicenter study [3], there was a more pronounced overweight of locally advanced tumor stages (extravesical disease: 39.4% in males vs. 52.5% in females in the current study, Table 1 vs. pT3–4: 43.0% in males and 46.5% in females [3]). On the other hand, in this study, female gender was no independent predictor of bladder cancer-specific mortality. In the cited multicenter study, with a HR of 1.17 in the multivariable analysis, the impact of gender was relatively small compared with that of tumor stage-related variables [3]. It is conceivable that gender-related effects not attributable to the confounders (Table 2) were too small to become demonstrable in our single center study. Patient recruitment in the cited study [3] started in 1971 and adjuvant chemotherapy was (in contrast to the current study; Table 2) not associated with improved survival [3]. A

Fig. 2. Cumulative mortality from bladder cancer, non-bladder cancer (competing) causes overall, non-cancer causes and second cancers, respectively, stratified by gender. p values are given for the Pepe Mori test.

Fig. 3. Bladder cancer-specific mortality analyzed separately in patients with bladder confined primary tumors (<pT3 [7]), extravesical primary tumors (pT3–4 [7]), and positive lymph nodes (pN1–3 [7]), respectively, stratified by gender. p values are given for the Pepe Mori test.

somewhat greater age difference between males and females (1 year [3] vs. 3.1 years in this study) and a less favorable stage distribution in females are further demographic differences between the current and the cited study [3]. A similar difference between females and males concerning the presence of extravesical disease (T3–4, 58.7 vs. 47.2% [8]) as in the current study was observed in

a recent multicenter study from Austria [7], whereas in a Canadian multicenter study that observed narrowly identical mortality rates lower differences (T3–4 in females 61 vs. 58% in males [6]) were found. In one multicenter study, a lower 90-day mortality rate was observed in females [9], a finding that was not confirmed in our study (Table 1).

Table 2. Optimal multivariable models for the endpoints overall mortality, bladder cancer-specific mortality, non-bladder cancer (competing) mortality overall, non-cancer mortality, and second cancer mortality. Beside the variables identified as independent predictors of overall mortality, the following three variables (that were not significantly associated with this endpoint) were included in these multivariable analyses: gender (female vs. male), smoking status (current smokers vs. none-smokers, former smokers, or unknown smoking status), and BMI (as a continuous variable, per unit increase)

Category	HR	95% CI	p value
<i>Endpoint overall mortality</i>			
Age (continuous variable, per year increase)	1.02	1.01–1.03	<0.0001
Charlson score (continuous variable, per unit increase)	1.12	1.07–1.16	<0.0001
ASA classes 3–4 (versus 1–2)	1.54	1.29–1.88	<0.0001
Extravesical disease (pT3–4 [7]; versus bladder confined disease, <pT3 [7])	2.21	1.85–2.63	<0.0001
Positive lymph nodes (pN1–3 [7]; versus negative lymph nodes or unknown, pN0-x [7])	2.66	2.17–3.27	<0.0001
Number of removed lymph nodes <17 or unknown (versus 17 or more*)	1.22	1.04–1.43	0.0126
Any neoadjuvant chemotherapy (versus none)	1.81	1.31–2.50	0.0014
Adjuvant cisplatin-based chemotherapy (versus none or unknown)	0.52	0.42–0.65	<0.0001
<i>Endpoint bladder cancer-specific mortality</i>			
Extravesical disease (pT3–4 [7]; versus bladder confined disease, <pT3 [7])	2.55	2.00–3.24	<0.0001
Positive lymph nodes (pN1–3 [7]; versus negative lymph nodes or unknown, pN0-x [7])	3.41	2.63–4.42	<0.0001
Any neoadjuvant chemotherapy (versus none)	2.38	1.60–3.53	<0.0001
Adjuvant cisplatin-based chemotherapy (versus none or unknown)	0.71	0.54–0.92	0.0103
<i>Endpoint non-bladder cancer (competing) mortality overall</i>			
Age (continuous variable, per year increase):	1.05	1.04–1.07	<0.0001
Charlson score (continuous variable, per unit increase)	1.16	1.09–1.24	<0.0001
ASA classes 3–4 (versus 1–2)	1.64	1.24–2.15	0.0248
Positive lymph nodes (pN1–3 [7]; versus negative lymph nodes or unknown, pN0-x [7])	0.44	0.31–0.62	<0.0001
Number of removed lymph nodes <17 or unknown (versus 17 or more*)	0.74	0.58–0.94	0.0156
Current smokers (versus none-smoker, former smoker or unknown)	1.60	1.24–2.08	0.0004
Gender female (versus male)	0.68	0.49–0.95	0.0248
<i>Endpoint non-cancer mortality</i>			
Age (continuous variable, per year increase)	1.06	1.06–1.08	<0.0001
Charlson score (continuous variable, per unit increase)	1.13	1.06–1.21	<0.0001
ASA classes 3–4 (versus 1–2)	2.02	1.48–2.75	<0.0001
Positive lymph nodes (versus negative lymph nodes or unknown)	0.43	0.29–0.63	<0.0001
Current smokers (versus none-smokers, former smokers or unknown)	1.40	1.02–1.92	0.0393
<i>Endpoint second cancer mortality</i>			
BMI (continuous variable, per unit increase)	0.95	0.90–1.00	0.0463
Charlson score (continuous variable, per unit increase)	1.21	1.09–1.35	0.0004
Positive lymph nodes (pN1–3 [7]; versus negative lymph nodes or unknown, pN0-x [7])	0.48	0.25–0.95	0.0340
Current smokers (versus none-smoker, former smoker or unknown)	1.95	1.19–3.19	0.0082

* Stratified by the median number or removed lymph nodes; In the full model, the HR for the endpoint bladder cancer-specific mortality for 17 or more removed lymph nodes was 0.94 (95% CI 0.76–1.16, $p = 0.56$).

In the full models, the following HRs for female gender were observed: endpoint overall mortality: 0.98 (95% CI 0.81–1.18, $p = 0.80$); endpoint bladder cancer-specific mortality: 1.20 (95% CI 0.94–1.54, $p = 0.15$); endpoint non-bladder cancer (competing) mortality overall: 0.69 (95% CI 0.49–0.96, $p = 0.0300$); endpoint non-cancer mortality: 0.82 (95% CI 0.58–1.18, $p = 0.30$); endpoint second cancer mortality: 0.43 (95% CI 0.18–1.04, $p = 0.06$).

ASA, American society association physical status classification; HR, hazard ratio; BMI, body mass index.

Whereas in 2 multicenter studies which started patient recruitment in 1971 [3] and 1979 [10] higher bladder cancer-specific mortality after radical cystectomy was observed in females, a multicenter study enrolling patients between 1994 and 2008 did not find measurable

gender-related mortality differences [6]. Several possible explanations have been discussed for the overweight of more advanced tumor stages and for the adverse outcome in females with bladder cancer [1]. Beside a delayed diagnosis in females, hormonal differences and

Table 3. Full and optimal multivariable logit models predicting the application of adjuvant cisplatin-based chemotherapy. Beside the impact of the plausible predictors, that of gender was negligible in these models

Category	Full model			Optimal model		
	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value
Age: (continuous variable, per year increase)	0.93	0.91–0.95	<0.0001	0.93	0.91–0.95	<0.0001
Charlson score: (continuous variable, per unit increase)	0.80	0.70–0.91	0.0006	0.78	0.70–0.89	<0.0001
ASA class: (3–4 vs. 1–2)	0.85	0.55–1.31	0.47			
Extravesical disease (pT3–4 [7]): (yes vs. no)	6.20	4.13–9.30	<0.0001	6.03	4.03–9.01	<0.0001
Positive lymph nodes (pN1–3 [7]): (yes vs. no or unknown)	12.83	8.64–19.05	<0.0001	12.38	8.41–18.22	<0.0001
Number of removed lymph nodes: (<17 or unknown vs. 17 or more*)	0.69	0.48–0.99	0.0460	0.69	0.48–0.99	0.0453
Any neoadjuvant chemotherapy: (yes vs. no)	0.89	0.42–1.92	0.77			
Adjuvant cisplatin-based chemotherapy: (yes vs. no)	Variable not included into this analysis					
Gender: (female vs. male)	0.79	0.50–1.23	0.29			
Smoking status: (current smokers vs. others**)	0.75	0.49–1.16	0.20			
Body mass index: (continuous variable, per unit increase)	0.90	0.95–1.03	0.65			

* Stratified by the median number or removed lymph nodes.

** None-smokers, former smokers, or unknown smoking status.

differences in treatment have been blamed [1, 3, 9, 10]. Since gender-related outcome differences seemed to diminish in more recent times, some authors speculated on time-dependent differences in awareness or access to treatment in females [9]. In the current study, there was a higher incidence of extravesical disease in females (52.5 vs. 39.4%) without a relevant difference in the incidence of lymph node metastases (28.0 vs. 26.3%) and a virtually identical outcome of males and females with bladder confined primary tumor (Fig. 3). These observations might fit to the hypothesis that anatomical differences (a thicker bladder wall in males that needs to be crossed by the tumor in order to reach adjacent structures and major intrinsic differences in pelvic anatomy that may influence tumor spread [11–13]) might explain the mortality differences between males and females after radical cystectomy. Anatomical differences might also explain the fact that a higher mortality in females with bladder cancer contrasts to a lower mortality in females seen in a great variety of other cancers [14].

The results of this study do not support the hypothesis that female candidates for radical cystectomy should undergo more intense treatment and follow-up [2] since the stage-adjusted mortality rates did not differ meaningfully (Table 2; Fig. 2). Encouraging more patients with extravesical or lymph node-positive disease to undergo adjuvant cisplatin-based chemotherapy irrespective of gender might be a more promising approach to decrease bladder-cancer specific mortality (Table 2).

The 21.8% rate of administration of adjuvant cisplatin-based chemotherapy in the current study was narrowly identical with the rates observed in multicenter studies [3, 6]. This rate contrasts with 48.9% high risk patients with either extravesical or lymph node-positive disease who could be candidates for such treatment (Table 1). In this study, gender was no predictor of the administration of adjuvant cisplatin-based chemotherapy (Table 3). It is, therefore, unlikely that differences in its use contributed meaningfully to gender-related mortality differences.

With more patients available for analysis, the current study stabilized the results of earlier analyses, that is, the association of the number of removed lymph nodes (stratified by the median) with overall, competing but not with bladder cancer-specific mortality [15], the association of adjuvant cisplatin-based chemotherapy with overall, disease-specific but not with competing mortality [16] now reaching the significance level for the latter endpoint and the association of current smoking with competing but not bladder cancer-specific and overall mortality [17] (data shown in Table 2). Since most fatal second cancers in this study (Table 1) are known to be associated with smoking [18], the differing prevalence of smoking among females and males (Table 1) might explain the trend toward lower mortality from second cancers in females in this study.

This study has limitations and strengths. Although the sample size is relatively large for a single center study, multicenter studies are able to investigate considerably

larger samples in order to identify small effects and to perform subgroup analyses. On the other hand, in this series, follow-up was substantially longer than in comparable studies [3, 4, 9, 10]. Whereas only crude stratifications were available to adjust for tumor-related parameters, in contrast to other studies [3, 4, 9, 10] relatively detailed data were available to control for comorbidity and the causes of death were classified in detail allowing competing risk analyses for different causes of death. It may, however, not be ruled out that unmeasured confounders influenced the results. Finally, the fact that treatment and patient selection might have changed during the relatively long recruitment period is another possible limitation of this study.

Conclusion

Female gender was associated with an increased risk of extravesical disease. The resulting increased bladder cancer-specific mortality risk in the univariate analysis disappeared after controlling for stage and other possible confounders in the multivariable analysis. Anatomical differences might be a plausible explanation for these observations.

Disclosure Statement

The authors declare no conflict of interest.

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