

Gender differences in radical nephroureterectomy for upper tract urothelial carcinoma

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Abstract

Purpose Women have been associated with adverse outcomes after radical cystectomy for lower tract urothelial carcinoma. We evaluated the prognostic value of gender in an international cohort of patients treated with radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC).

Methods We retrospectively studied 754 patients treated with RNU for UTUC without neoadjuvant chemotherapy at nine centers located in Asia, Canada, and Europe. Univariable and multivariable Cox regression analyses were used to address recurrence-free (RFS) and cancer-specific survival (CSS) estimates. Median follow-up was 40 months (interquartile range: 18–75).

Results The majority of patients was of men (516, 68.4%). Women were older than men at the time of RNU (median: 69.2 vs. 66.5 years; $P = 0.0003$). Women were less likely to have high-grade disease, undergo lymph node dissection, and to receive adjuvant chemotherapy. Gender was not associated with pathologic stage, lymph node metastasis, lymphovascular invasion, concomitant CIS, tumor architecture, or tumor necrosis. On univariable Cox regression analyses, there was no association between gender and cancer recurrence ($P = 0.76$) or cancer-specific mortality ($P = 0.30$). On multivariable Cox regression analyses that adjusted for the effects of clinicopathologic features, gender was not associated with disease recurrence ($P = 0.47$) or cancer-specific survival ($P = 0.15$).

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Conclusions We found no difference in histopathologic features and outcomes between men and women treated with RNU for UTUC. Nevertheless, epidemiologic and mechanistic molecular studies should be encouraged to design, analyze, and report gender-specific associations to aid in our understanding of gender impact on UTUC incidence, progression, and metastasis.

Keywords Gender · Prognosis · Upper urinary tract · Urothelial carcinoma · Nephroureterectomy

Introduction

Upper urinary tract urothelial carcinoma (UTUC) comprises approximately 5% of all urothelial tumors and 10% of all renal tumors [1]. Radical nephroureterectomy (RNU) with bladder cuff resection and regional lymphadenectomy is regarded as the standard treatment for most patients with UTUC [2]. Epidemiologic studies have shown a difference in the incidence and severity of urothelial carcinoma (UC) between the genders. Lower tract UC such as bladder cancer, for example, affects more men than women, while the prognosis is better in men [1, 3–5]. There is no uniform theory to explain the differential presentation and behavior of bladder cancer between genders. Inequalities in health care, environmental exposure to carcinogens, genetic, anatomical, hormonal, societal, and environmental factors have been suggested as possible explanations [5]. Since lower and upper tract UC share the same biology and UTUC is a relatively uncommon disease, decision regarding UTUC has been made by extrapolation from bladder cancer data. The true impact of gender on incidence and prognosis of patients with UTUC remains, however, poorly investigated. The aim of the current study was to assess the differences between men and women in the histopathologic features at and outcomes after RNU in a large international cohort of patients with UTUC.

Methods

This was an institutional review board–approved study with all participating sites providing the necessary institutional data sharing agreements before initiation of the study. A total of nine academic centers worldwide provided data. A computerized databank was generated for data transfer. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Before final analysis, the database was

frozen, and the final data set was produced for the current analysis.

The database comprised 785 patients treated with RNU with ipsilateral bladder cuff resection between 1987 and 2008. Once excluded, patients who received neoadjuvant chemotherapy ($n = 12$) and patients where the tumor architecture was unknown ($n = 19$), the 754 remaining patients were the subjects of the present analysis.

Surgery was performed by several surgeons according to the standard criteria for RNU, i.e., extrafascial dissection of the kidney with the entire length of ureter and adjacent segment of the bladder cuff. The hilar and regional lymph nodes adjacent to the ipsilateral great vessel generally were resected along with enlarged lymph nodes if abnormal on preoperative computed tomography scans or palpable intraoperatively. Extended lymphadenectomy was not routinely performed.

Pathologic evaluation

All surgical specimens were processed according to standard pathologic procedures at each institution. Tumors were staged according to the American Joint Committee on Cancer—Union Internationale Contre le Cancer (UICC) TNM classification. Tumor grading was assessed according to the 1998 WHO/International Society of Urologic Pathology (ISUP) consensus classification. Tumor architecture was defined based on the predominant feature [6]. LVI was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls [7, 8]. Tumor necrosis was defined as the presence of microscopic coagulative necrosis, whereas the presence of necrosis on gross examination was not included [9]. The extent of tumor necrosis was assessed in a semi-quantitative manner at low magnification (reduced from $\times 40$). Tumor necrosis was recorded as absent or focally present (0–10% of tumor area) or extensively present (more than 10% of the tumor area) based on the histological evaluation of all available tumor blocks.

Follow-up regimen

Patients were generally observed every 3–4 months for the first year after RNU, every 6 months from the second through the fifth years, and annually thereafter. Follow-up consisted of a history, physical examination, routine blood work and serum chemistry studies, urinary cytology, chest radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper urinary tract. Elective bone scans, chest computed tomography, and magnetic resonance imaging were performed when clinically indicated.

Table 1 Association of gender with clinical and pathologic characteristics in 785 patients treated with radical nephroureterectomy with ipsilateral bladder cuff resection for upper tract urothelial carcinoma

	No. of patients (%)	Gender		<i>P</i>
		Male (%)	Female (%)	
Stage				0.79 ^a
Ta	162 (21.5)	117 (22.7)	45 (18.9)	
Tis	9 (1.2)	6 (1.2)	3 (1.3)	
T1	187 (24.8)	121 (23.5)	66 (27.7)	
T2	142 (18.8)	95 (18.4)	47 (19.8)	
T3	211 (28)	145 (28.1)	66 (27.7)	
T4	43 (5.7)	32 (6.2)	11 (4.6)	
Grade				0.02
Low	138 (18.3)	83 (16.1)	55 (23.1)	
High	616 (81.7)	433 (83.9)	183 (76.9)	
Regional lymph nodes				0.14
N0	131 (17.4)	97 (18.8)	34 (14.3)	
Nx	574 (76.1)	382 (74.0)	192 (80.7)	
N+	49 (6.5)	37 (7.2)	12 (5.0)	
Lymph node dissection				0.047
Yes	180 (76.1)	192 (33.3)	46 (25.6)	
No	574 (23.9)	382 (66.6)	134 (74.4)	
Tumor architecture				0.75
Papillary	604 (80.1)	415 (80.4)	189 (79.4)	
Sessile	150 (19.9)	101 (19.6)	49 (20.6)	
Lymphovascular invasion				0.42
Absent	608 (80.6)	412 (67.8)	104 (71.2)	
Present	146 (19.4)	196 (32.2)	42 (28.8)	
Concomitant CIS				0.48
Absent	659 (87.4)	454 (88)	205 (86.1)	
Present	95 (12.6)	62 (12)	33 (13.9)	
Necrosis				0.72
Absent	589 (78.1)	405 (78.4)	184 (77.3)	
Present	165 (21.9)	111 (21.5)	54 (22.7)	
Location				0.58
Renal Pelvis	402 (59.4)	271 (67.4)	191 (69.5)	
Ureter	275 (40.6)	131 (32.6)	84 (30.5)	
Surgical modality				0.77
Open	684 (90.7)	467 (90.5)	217 (91.2)	
Laparoscopic	70 (9.3)	49 (9.5)	21 (8.8)	
Adjuvant chemotherapy				0.05
No	680 (91.5)	458 (90.2)	222 (94.5)	
Yes	63 (8.5)	50 (9.8)	13 (5.5)	

^a Test for trend

Disease recurrence was defined as local failure in the operative site, regional lymph nodes, or distant metastasis. Bladder recurrences were not considered in the analysis of recurrence-free survival rate. Cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or by death certificates alone. Most patients who were identified as having died of UTUC had progressive, widely disseminated metastases at the time

of death. Patients who died in the perioperative period (i.e., death within 30 days of surgery) were censored at the time of death for UTUC-specific survival analyses.

Statistical analysis

The Fisher's exact test and the chi-square test were used to evaluate the association between categorical variables.

Table 2 Univariable and multivariable Cox regression analyses of gender targeting disease recurrence in 785 patients treated with radical nephroureterectomy with ipsilateral bladder cuff resection for upper tract urothelial carcinoma ($n = 179$ recurrences)

Parameter	Univariable analyses			Multivariable analysis		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Gender ^a	0.95	0.7–1.3	0.76	0.87	0.6–1.3	0.47
Stage			<0.0001			<0.0001
Ta/Tis	1	–	–	1	–	–
T1	1.1	0.5–2.1	0.82	0.74	0.3–1.7	0.49
T2	3.1	1.7–5.6	0.0003	2.3	1.1–4.6	0.02
T3	5.9	3.4–10.2	<0.0001	2.6	1.3–5.3	0.007
T4	33.8	18.1–63.3	<0.0001	8.7	3.6–20.8	<0.0001
Grade	3.1	1.7–5.4	0.0001	1.2	0.6–2.5	0.62
Lymph node status			<0.0001			0.20
N0	1	–	–	1	–	–
Nx	0.9	0.6–1.3	0.58	1.1	0.7–1.7	0.77
N+	5.6	3.4–9.3	<0.0001	1.7	0.9–3.2	0.11
Adjuvant chemotherapy	6.2	4.4–8.7	<0.0001	3.5	2.2–5.4	<0.0001
Lymphovascular invasion	4.0	3–5.5	<0.0001	1.9	1.3–2.8	0.0006
Sessile tumor architecture	2.9	2.1–4.0	<0.0001	1.7	1.2–2.6	0.006
Concomitant CIS	2.2	1.5–3.1	<0.0001	2.5	1.7–3.8	<0.0001
Ureteral tumor location	1.34	0.97–1.9	0.08	1.5	1.04–2.1	0.03

^a Male is the referent category

Differences in variables with a continuous distribution across dichotomous categories were assessed using the Mann–Whitney U test. The Kaplan–Meier method was used to calculate survival functions, and differences were assessed with the log rank statistic. Univariable and multivariable Cox regression models addressed time to recurrence and cancer-specific mortality after RNU. Statistical significance in this study was set as $P \leq 0.05$. All reported *P* values were two-sided. Analyses were performed with SAS version 9.2 (SAS Institute Inc, Cary, NC).

Results

Association of gender with clinical and pathologic features

The mean patient age was 68 years (interquartile range: 61–75; range: 32–92). The majority of patients was of men (516, 68.4%) and had high-grade disease (616, 81.7%). Women were older than men at the time of RNU (median: 69.2 vs. 66.5 years; $P = 0.0003$). Table 1 shows the association of gender with clinical and pathologic features. Women were less likely to have high-grade disease, undergo lymph node dissection, and to receive adjuvant chemotherapy. Gender was not associated with pathologic stage, lymph node metastasis, lymphovascular invasion, concomitant CIS, tumor architecture, or tumor necrosis.

Association of gender with clinical outcomes

The median follow-up duration for all patients was 34 months (interquartile range: 16–65; range: 1–271). On follow-up, 250 patients had died, of which 151 had died of UTUC. Overall, 179 patients developed disease recurrence. The median follow-up for patients who were alive at last follow-up was 40 months (interquartile range: 18–75, range: 1–271). The 2- and 5-year recurrence-free survival estimates were 80% (SE: 1.6) and 73% (SE: 1.9), respectively. The 2- and 5-year cancer-specific survival estimates were 85% (SE: 1.4) and 75% (SE: 1.9), respectively.

On univariable Cox regression analysis, there was no association between gender and cancer recurrence (HR: 0.95, $P = 0.76$) (Table 2). The 3-year recurrence-free survival for men was 75% (SE: 2) when compared to 77% (SE: 3) for women (log rank $P = 0.76$; Fig. 1a).

On multivariable Cox regression analysis that adjusted for the effects of stage, grade, lymph node status, lymphovascular invasion, concomitant CIS, tumor architecture, tumor location, and adjuvant chemotherapy, gender was not associated with disease recurrence (HR: 0.87, $P = 0.47$) (Table 3). The statistical significance of results did not change when patients who received adjuvant chemotherapy were excluded (HR: 0.85, $P = 0.46$), when patients with metastasis to lymph nodes were excluded (HR: 0.83, $P = 0.37$), or when both were excluded (HR: 0.8, $P = 0.37$).

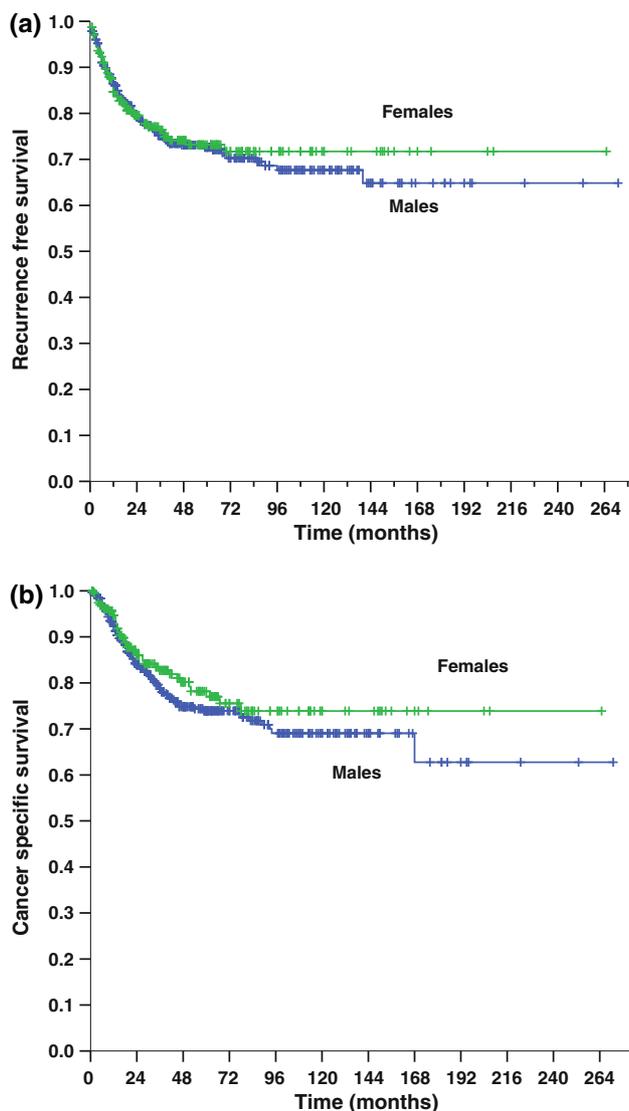


Fig. 1 Kaplan–Meier curves of **a** recurrence-free survival and **b** cancer-specific survival stratified by gender in 785 patients treated with radical nephroureterectomy with ipsilateral bladder cuff resection for upper tract urothelial carcinoma

On univariable Cox regression analysis, gender was not associated with cancer-specific mortality (HR: 0.83, $P = 0.30$) (Tables 3). The 3-year cancer-specific survival for men was 80% (SE: 2) when compared to 83% (SE: 3) for women (log rank $P = 0.30$) (Fig. 1b).

On multivariable Cox regression analysis that adjusted for the effects of stage, grade, lymph node status, lymphovascular invasion, concomitant CIS, tumor architecture, tumor location, and adjuvant chemotherapy, gender was not associated with cancer-specific survival (HR 0.73, $P = 0.15$) (Table 3). The statistical significance of results did not change when patients who received adjuvant chemotherapy were excluded (HR: 0.7, $P = 0.15$), when patients with positive nodes were excluded (HR: 0.67,

$P = 0.08$), or when both were excluded (HR: 0.65, $P = 0.11$).

Comment

We found no difference in histopathologic features and outcomes between men and women treated with RNU for UTUC. This is in agreement with the study of Fernandez et al. [10] who assessed a large dataset of 1,363 patients treated with RNU. This is in contrast to lower tract urothelial carcinoma. While men are ~3–4 times more likely to develop bladder urothelial carcinoma than women, women present with more advanced disease and have worse survival [5]. Recently, two studies reported that women are associated with worse clinical outcome after radical cystectomy for bladder cancer. Using a large, multicenter data set comprising 3,357 patients (673 women, 20%), the first study identified woman as a poor risk feature in competing risk analyses that adjusted for the effects of standard clinicopathologic characteristics [3]. Using data from 4,850 patients treated with RNU in the SEER registries, Lugghezani et al. found that women were more likely to have advanced pathologic T stage and higher tumor grade at RNU than men [11]. After accounting for the effects of other-cause mortality, stage, grade, and non-cancer characteristics, gender retained its association with bladder cancer-specific mortality. This disparity among genders is proposed to be the result of a differential exposure to carcinogens (i.e., tobacco and chemicals) as well as reflective of genetic, anatomic, hormonal, societal, and environmental factors. While gender inequalities exist among radical cystectomy patients [5], they do not among RNU patients. This suggests that there is no difference in the biological behavior of UTUC between men and women once treated with RNU. Epidemiologic and mechanistic molecular studies should be encouraged to design, analyze, and report gender-specific associations to aid in our understanding of gender differences in UTUC incidence.

There are several important limitations to our study. First and foremost are the limitations inherent to retrospective analyses. Another limitation is that we did not review all pathologic specimens. Moreover, we excluded all patients treated with preoperative chemotherapy potentially creating a bias. Furthermore, the population in this study underwent surgery by multiple surgeons and had specimens evaluated by multiple pathologists. This could be construed as strength in turn, as it is reflective of real-world practice making the conclusions of the study more generalizable. Finally, the study period spans more than 21 years, and the data in the present study may not represent current practice patterns, considering that diagnostic tools, surgical techniques, perioperative care, indication for surgery,

Table 3 Univariable and multivariable Cox regression analyses of gender targeting cancer-specific survival in 785 patients treated with radical nephroureterectomy with ipsilateral bladder cuff resection for upper tract urothelial carcinoma ($n = 151$ cancer-specific deaths)

Parameter	Univariable analyses			Multivariable analysis		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Gender ^a	0.83	0.6–1.2	0.3	0.73	0.5–1.1	0.15
Stage			<0.0001			<0.0001
Ta/Tis	1	–	–	1	–	–
T1	1.0	0.5–2.3	0.9	0.8	0.3–2.1	0.70
T2	3.3	1.6–6.6	0.001	2.1	0.9–4.6	0.07
T3	7.4	3.9–13.9	<0.0001	2.9	1.3–6.2	0.007
T4	45.5	22.4–92.4	<0.0001	9.2	3.5–24.6	<0.0001
Grade	3.6	1.9–7.1	0.0002	1.0	0.5–2.1	0.96
Lymph node status			<0.0001			0.30
N0	1	–	–	1	–	–
Nx	1.0	0.6–1.6	0.96	1.4	0.8–2.4	0.24
N+	6.5	3.7–11.5	<0.0001	1.8	0.8–3.7	0.13
Adjuvant chemotherapy	6.4	4.4–9.2	<0.0001	3.4	2.1–5.4	<0.0001
Lymphovascular invasion	4.8	3.4–6.6	<0.0001	2.2	1.5–3.3	<0.0001
Sessile tumor architecture	3.3	2.4–4.6	<0.0001	1.9	1.3–3.0	0.003
Concomitant CIS	2.0	1.3–2.9	0.0007	2.2	1.4–3.5	0.0005
Ureteral tumor location	1.25	0.9–1.8	0.22	1.4	0.97–2.0	0.08

^a Male is the referent category

administration of perioperative chemotherapy, regimen of chemotherapy, and follow-up protocols might have changed over time. However, 39% of the patients in the study were treated in the 1990s and 56% in the year 2000 or thereafter.

Conclusions

Although UTUC is more common in male patients, the results of the present study have confirmed that no significant difference was found in the major clinicopathologic features and prognosis between the women and men undergoing RNU for UTUC. Epidemiologic and mechanistic molecular studies should be encouraged to design, analyze, and report gender-specific associations to aid in our understanding of gender differences in UTUC incidence.

Conflict of interest The authors declare that they have no conflict of interest in the manuscript.

References

- Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ (2009) Cancer statistics, 2009. *CA Cancer J Clin* 59:225–249
- Margulis V, Shariat SF, Matin SF et al (2009) Outcomes of radical nephroureterectomy: a series from the upper tract urothelial carcinoma collaboration. *Cancer* 15:1224–1233
- Svatek RS, Shariat SF, Dinney C et al (2009) Evidence-based gender related outcomes after radical cystectomy: results of a large multicenter study. *J Urol* 181:629 [abstract]
- Jeldres C, Isbarn H, Capitanio U et al (2009) Gender is an important predictor of cancer-specific survival in patients with urothelial carcinoma after radical cystectomy. *J Urol* 181:635 [abstract]
- Shariat SF, Sfakianos JP, Droller MJ, Karakiewicz PI, Meryn S, Bochner BH (2010) The effect of age, gender on bladder cancer: a critical review of the literature. *BJU Int* 105:300–308
- Remzi M, Haitel A, Margulis V et al (2009) Tumour architecture is an independent predictor of outcomes after nephroureterectomy: a multi-institutional analysis of 1363 patients. *BJU Int* 103:307–311
- Kikuchi E, Margulis V, Karakiewicz PI et al (2009) Lymphovascular invasion predicts clinical outcomes in patients with node-negative upper tract urothelial carcinoma. *J Clin Oncol* 27:612–618
- Novara G, Matsumoto K, Kassouf W, Walton TJ, Fritsche HM, Bastian PJ, Martínez-Salamanca JJ, Seitz C, Lemberger RJ, Burger M, El-Hakim A, Baba S, Martignoni G, Gupta A, Karakiewicz PI, Ficarra V, Shariat SF (2010) Prognostic role of lymphovascular invasion in patients with urothelial carcinoma of the upper urinary tract: an international validation study. *Eur Urol* 57(6):1064–1071
- Zigeuner R, Shariat SF, Margulis V, Karakiewicz PI, Roscigno M, Weizer A, Kikuchi E, Remzi M, Raman JD, Bolenz C, Bensalah K, Capitanio U, Koppie TM, Kassouf W, Sircar K, Patard JJ, Fernández MI, Wood CG, Montorsi F, Ströbel P, Wheat JC, Haitel A, Oya M, Guo CC, Ng C, Chade DC, Sagalowsky A, Langner C (2010) Tumour necrosis is an indicator of aggressive biology in patients with urothelial carcinoma of the upper urinary tract. *Eur Urol* 57(4):551–734
- Fernandez MI, Shariat SF, Margulis V et al (2009) Evidence-based sex-related outcomes after radical nephroureterectomy for upper tract urothelial carcinoma: results of large multicenter study. *Urology* 73:142–146
- Lughezzani G, Sun M, Perrotte P et al (2010) Gender-related differences in patients with stage I to III upper tract urothelial carcinoma: results from the surveillance, epidemiology, end results database. *Urology* 75:321–327