

Age-specific effect of gender on upper tract urothelial carcinoma outcomes

Jian-Ye Liu · Yong-Hong Li · Zhi-Ling Zhang · Yun-Lin Ye · Zhou-Wei Liu · Kai Yao · Pei Dong · Sheng-Jie Guo · Li-Juan Jiang · Ming-Zhu Zhong · Wei Chen · Hui Han · Zi-Ke Qin · Fang-Jian Zhou

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Abstract The research is to evaluate the age-specific differential effects of gender on outcomes in patients with upper tract urothelial carcinoma (UTUC) treated with radical nephroureterectomy (RNU). Between August 1998 and October 2010, we retrospectively reviewed the data from 285 (67.7 %) men and 136 (32.3 %) women treated with RNU for UTUC at our two institutions. Kaplan–Meier survival estimates the age-specific effect of gender on cancer-specific survival (CSS). Cox proportional hazards regression analyses were used to address the effect of gender on CSS. No significant sex-related differences were found in age and diagnosis, clinicopathologic features, and treatment (all P values >0.05). Women had a 18.7 % increased risk of death from UTUC than men (hazard ratio [HR] 1.187; 95 % confidence interval [95 % CI] 1.017–1.893; $P = 0.021$). The survival disadvantage was only present in patients aged 59 years and older ($P < 0.001$). Conversely, the survival advantage for women was found in women aged 42 to 58 years ($P = 0.011$) and in the age group <42 years

($P = 0.019$). On multivariable Cox regression analyses that adjusted for the effects of clinicopathologic features, the female gender was associated with decreased CSS ($P = 0.036$). In conclusion, the impact of gender on UTUC outcomes after RNU is age-specific. Females who aged 59 years and older experienced worse outcomes than their male counterparts, while women in the age group <42 years and 42–58 years have better outcomes than men. Further research is needed to elucidate the molecular mechanisms underlying the age-specific differential effect of gender on UTUC outcomes.

Keywords Gender · Age groups · Radical nephroureterectomy · Upper tract urothelial carcinoma · Survival

Introduction

Primary upper tract urothelial carcinoma (UTUC) is a rare urologic malignancy, accounting for approximately 5 % of all urothelial tumors [1, 2]. Radical nephroureterectomy (RNU) is the standard treatment for muscle-invasive and high-risk non-muscle-invasive UTUC [3–5]. Overall, UTUC is 2–3 times more common in men than in women in western countries [5, 6]. In addition to the previously well-known differences between men and women regarding the prognosis of patients with bladder urothelial carcinoma (UC) [7–9], reports have also been published about the differences related to the clinical and pathologic characteristics between men and women treated for UTUC [9, 10]. Moreover, and similar to bladder UC, it has been suggested that the stage-adjusted survival of UTUC among women could be worse than that among men [6, 11–13]. Whether these survival differences reflect biologic or

J.-Y. Liu · Y.-H. Li · Z.-L. Zhang · Y.-L. Ye · Z.-W. Liu · K. Yao · P. Dong · S.-J. Guo · L.-J. Jiang · M.-Z. Zhong · H. Han · Z.-K. Qin · F.-J. Zhou
State Key Laboratory of Oncology in South China, Guangzhou 510060, Guangdong, People's Republic of China

J.-Y. Liu · Y.-H. Li · Z.-L. Zhang · Y.-L. Ye · Z.-W. Liu · K. Yao · P. Dong · S.-J. Guo · L.-J. Jiang · M.-Z. Zhong · H. Han · Z.-K. Qin · F.-J. Zhou (✉)
Department of Urology, Sun Yat-sen University Cancer Center, No. 651, Dongfeng Road, East, Guangzhou 510060, Guangdong, People's Republic of China
e-mail: zhoufjsysucc@163.com; zhoufj@sysucc.org.cn

W. Chen
Department of Urology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, Guangdong, People's Republic of China

cultural or both factors remain controversial. If biologic, one potential mechanism to consider would be the possible effect of sex hormones on oncogenic process [14, 15].

To our knowledge, a comprehensive evaluation of the age-specific effect of gender on the clinical and pathologic characteristics, as well as the outcomes of patients treated with RNU for UTUC, has not yet been performed. The aim of the present study was to examine the possible contribution of sex hormones to the clinical outcomes in UTUC after RNU, using age as a surrogate for hormone status, in two center UTUC cohorts.

Methods and materials

Patients and surgery

The database comprised of 472 UTUC patients treated with RNU with ipsilateral bladder cuff resection between 1999 and 2010 at our two institutions (Cancer Center and First Affiliated Hospital of Sun Yat-sen University). Once excluded, patients who received neoadjuvant chemotherapy ($n = 16$), have previous radical cystectomy ($n = 6$), established metastasis at diagnosis of UTUC ($n = 10$), and lost to follow-up ($n = 19$), the 421 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. Open RNU was performed in 364 patients (86.5 %), and laparoscopic and retroperitoneoscopic RNU was performed in 57 patients (13.5 %). 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.

Pathological and clinical evaluation

All surgical specimens were processed according to standard pathological procedures, and all slides were re-reviewed by genitourinary pathologists according to identical strict criteria. Pathologists were blinded to clinical outcomes. All specimens were histologically confirmed to be urothelial carcinoma. Tumors were staged according to the 2002 American Joint Committee on Cancer–International Union Against Cancer (AJCC/UICC) TNM classification [16]. Tumor grade was assessed according to the 1998 World Health Organization–International Society of Urologic Pathology consensus classification [17]. Tumor location was defined as either renal pelvic or ureteral based on the location

of the dominant tumor. The dominant lesion was defined as that with the highest pathologic tumor stage (pT). For multifocal tumors at the same stage, the higher grade was selected for main tumor location. Tumor multifocality was defined as the synchronous presence of 2 or more pathologically confirmed tumors in any upper urinary tract location (renal pelvis or ureter). Lymphovascular invasion (LVI) was defined as the unequivocal presence of tumor cells within an endothelium-lined space, with no underlying muscular walls [18]. The selection of the age cut-points as surrogate measures of sex hormone status were based on multiple epidemiologic studies regarding menopause in North America. In these studies, greater than 95 % of women are found to be hormone intact at the age 42, whereas 97 % of women have undergone primary ovarian failure at the age 58 [19]. We used these data to yield 3 epidemiologically based age groups as surrogate measures of hormonal status.

Follow-up regimen

Patients were generally followed up every 3 months during the first 2 years after surgery, every 6 months during years 2–5 and annually thereafter. The follow-up examinations consisted of history taking, physical examination, routine blood evaluation, urinary cytology, chest radiography, cystoscopic evaluation of the bladder, and radiographic evaluation of the contralateral upper urinary tract. Elective bone scans, chest computerized tomography, or magnetic resonance imaging were performed when clinically indicated.

Statistical analysis

Statistical analyses were performed using the statistical software SPSS version 13.0 (SPSS, Inc., Chicago, IL). The chi-squared tests were used to evaluate the association between categorical variables. Differences in variables with a continuous distribution across categories were assessed using the Kruskal–Wallis test. The primary end points were cancer-specific survival (CSS). CSS was defined as the time interval between the date of RNU and the end point, including death or censoring. 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 CSS analyses. Survival probabilities were estimated with Kaplan–Meier method, and the log-rank test was applied to compare survival curves. Univariate and multivariate Cox proportional hazards analyses were used

to assess the relative effect of gender on CSS. Probability values <0.05 were considered significant.

Results

Association of gender with age and clinicopathological characteristics

The present study comprised of 285 (67.7 %) men and 136 (32.3 %) women. The median patient age was 62.0 years (interquartile range, IQR 51.0–70.0). Table 1 shows the association of gender with age and clinicopathologic features. The median age of female and male patients was 62.0 years (IQR 52.0–70.0) and 62.0 years (IQR 48.5–70.0), respectively. No significant sex-related differences were found in age at diagnosis ($P = 0.912$), ECOG performance status ($P = 0.890$), tumor location ($P = 0.783$), tumor focality ($P = 0.506$), type of RNU ($P = 0.858$), lymph node dissection ($P = 0.681$), soft tissue surgical margin ($P = 0.327$), presence of lymphovascular invasion ($P = 0.878$), pathologic stage ($P = 0.294$), tumor grade ($P = 0.271$), the presence of lymph node metastases ($P = 0.083$), or preoperative adjuvant chemotherapy ($P = 0.913$).

Effect of age-specific gender on cancer-specific survival

As a group, women demonstrated a 18.7 % worsened CSS compared with men [hazard ratio (HR) 1.187; 95 % confidence interval (95 %CI) 1.017–1.893; $P = 0.021$; Fig. 1]. The survival disadvantage for women was present in patients aged 59 years and older ($P < 0.001$, Fig. 2). The disadvantage, however, was not apparent in patients aged <42 years and 42–58 years. In contrast, the survival advantage for women was present in women aged 42–58 years ($P = 0.011$, Fig. 3) and in the age group <42 years ($P = 0.019$, Fig. 4). When age adjusted into categories corresponding to hormonal status, 5-year CSS for women and men greater than 58 was 40 and 70 %, respectively. For the age 42–58, 5-year CSS for women and men was 71 and 44 %, respectively. For the age less than 42, the 5-year CSS estimates were 82 and 48 % for women and men, respectively.

Univariate and multivariate analysis by gender

To identify the effect of gender on CSS, univariate and multivariate analyses were performed using the Cox regression model (Table 2). In univariate Cox regression analyses,

female was associated with increased risk of cancer-specific mortality (Table 2, $P = 0.021$). Type of RNU ($P = 0.002$), lymph node dissection ($P < 0.001$), soft tissue surgical margin ($P < 0.001$), lymphovascular invasion ($P < 0.001$), tumor grade ($P < 0.001$), pT stage ($P < 0.001$), pN stage ($P < 0.001$), and adjuvant chemotherapy ($P < 0.001$) were also shown to be associated with CSS (Table 2). In multivariate Cox regression analyses, female gender was an independent risk factor for adverse CSS (HR 1.034; 95 % CI 0.739–1.446; $P = 0.036$; Table 2). Of the other variables, lymphovascular invasion ($P = 0.013$), tumor grade ($P = 0.001$), tumor stage ($P < 0.001$), and lymph node status ($P < 0.001$) were also found to be an independent prognostic predictor for CSS (Table 2).

Discussion

Compared with other cancers, there are little data on the impact of gender on stage or grade distribution and outcomes of patients with UTUC. Whether gender differences in UTUC oncological outcome remain controversial because of the contradictory reports [10, 20, 21]. Moreover, no study has analyzed age-specific effect of gender on UTUC outcomes.

Lugghezani et al. reported data from 4,850 patients treated with RNU in the SEER registries. Women were more likely to have advanced pathologic T stage and higher tumor grade at RNU than men [10]. After accounting for the effects of other-cause mortality, stage, grade, and non-cancer characteristics, gender retained its association with cancer-specific mortality. In a large population-based study of bladder UC and UTUC, Mungan et al. found that women presented with a greater primary tumor stage and were more likely to have metastasis [7]. However, recently, two studies reported that women are associated with the same clinical outcome after RNU [20, 21]. Using a large, multicenter data set comprising 1,363 patients from the 12 centers worldwide, the study identified that no significant difference in the clinicopathologic features or prognosis between the women and men [20]. Similarly, in a study including 754 UTUC patients who had undergone RNU, Shariat et al. found that women have the same risk feature in competing risk analyses that adjusted for the effects of standard clinicopathologic [21]. In the present study, no difference in clinicopathologic features between men and women treated with RNU for UTUC; however, the female gender present with more cancer-specific mortality compared with their male counterparts in univariable and multivariable analyses. Moreover, we found that the detrimental effect of the gender on UTUC outcomes was age-specific. The survival disadvantage was only present in patients aged 59 years and older, while women in the age

Table 1 Association of gender with clinical and pathological characteristics in 421 patients treated with RNU for UTUC

Variables	Total patients (%) <i>n</i> = 421	Gender		<i>P</i> value
		Male (%) <i>n</i> = 285	Female (%) <i>n</i> = 136	
Age at diagnosis, year, median (IQR)	62.0 (51.0–70.0)	62.0 (52.0–70.0)	62.0 (48.5–70.0)	0.912 ^a
ECOG performance status				0.890 ^b
0	385 (91.4)	261 (91.6)	124 (91.2)	
1 or greater	36 (8.6)	24 (8.4)	12 (8.8)	
Tumor location				0.783 ^b
Renal pelvis	225 (53.4)	151 (53.0)	74 (54.4)	
Ureter	196 (46.6)	134 (47.0)	62 (45.6)	
Tumor focality				0.506 ^b
Unifocal	288 (68.4)	192 (67.3)	96 (70.6)	
Multifocal	133 (31.6)	93 (32.7)	40 (29.4)	
Type of RNU				0.858 ^b
Open	364 (86.5)	247 (86.7)	117 (86.0)	
Laparoscopic/ retroperitoneoscopic	57 (13.5)	38 (13.3)	19 (14.0)	
Lymph node dissection				0.681 ^b
Not performed	223 (53.0)	154 (54.0)	69 (50.7)	
Performed	195 (47.0)	131 (46.0)	64 (49.3)	
Soft tissue surgical margin				0.327 ^b
Negative	385 (91.4)	258 (90.5)	127 (93.4)	
Positive	36 (8.6)	27 (9.5)	9 (6.6)	
Lymphovascular invasion				0.878 ^b
Absent	320 (76.0)	216 (75.8)	104 (76.8)	
Present	101 (24.0)	69 (24.2)	32 (23.2)	
Tumor grade				0.271 ^b
G1	87 (20.7)	63 (22.1)	24 (17.6)	
G2	128 (30.4)	80 (28.1)	48 (35.3)	
G3	206 (48.9)	142 (49.8)	64 (47.1)	
pT Stage				0.294 ^b
pTa/pTis/pT1	157 (37.3)	113 (39.6)	44 (32.4)	
pT2	91 (21.6)	63 (22.1)	28 (20.6)	
pT3	144 (34.2)	89 (31.2)	55 (40.4)	
pT4	29 (6.9)	20 (7.1)	9 (6.6)	
pN Stage				0.083 ^b
pNo/pNx	325 (77.2)	227 (79.6)	98 (72.1)	
pN+	96 (22.8)	58 (20.4)	38 (27.9)	
Adjuvant chemotherapy				0.913 ^b
No	333 (79.1)	225 (78.9)	108 (79.4)	
Yes	88 (20.9)	60 (21.1)	28 (20.6)	

RNU Radical nephroureterectomy, UTUC upper tract urothelial carcinoma, IQR interquartile range

^a Kruskal–Wallis test

^b Chi-square test

group <42 years and 42–58 years have better outcomes than men.

The risk of cancer development is almost certainly related to a combination of environmental and biologic factors although one may predominate in any given situation. The concept of a gender-based survival difference,

premenopausal female experienced better outcomes, and postmenopausal women has worse outcomes than their male counterparts in human cancers is not new, although many of the gender survival differences observed have been previously attributed to social or cultural factors [22]. A notable example of this is seen in patients with lung

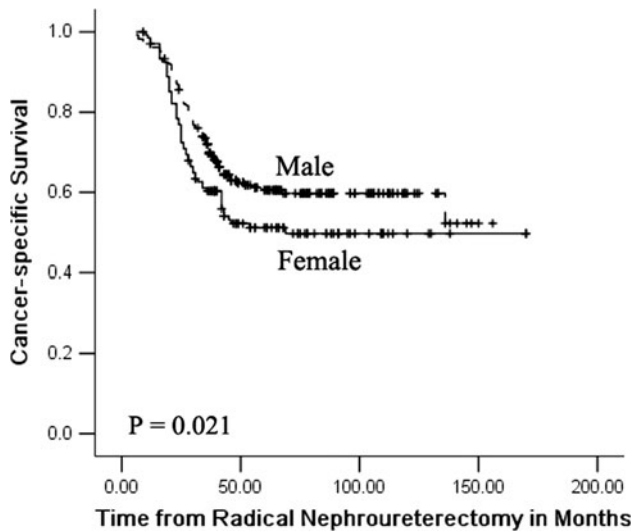


Fig. 1 Kaplan–Meier estimates of cancer-specific survival according to gender in 421 patients treated with radical nephroureterectomy for upper tract urothelial carcinoma

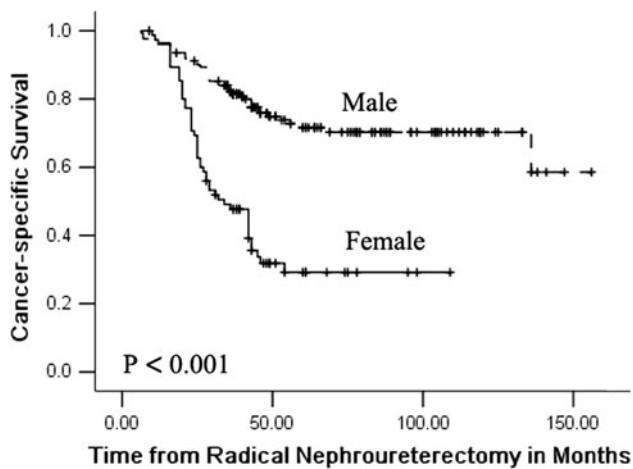


Fig. 2 Kaplan–Meier estimates of cancer-specific survival according to gender in 421 patients aged 58 years and higher

cancer, where disproportionate numbers of men suffering from the disease in the past have now been replaced with women in near-equal rates as the social norms changed in the mid-twentieth century to include women as smokers [22]. Even this, however, is confounded by the improved survival of premenopausal women in certain populations as seen in particular clinical trials [23]. A significant body of evidence supporting the biologic, and perhaps hormone-related, foundation of gender-associated cancer survivorship, however, counters the cultural model [24]. In urological oncology, this has been most commonly seen with urothelial carcinoma. A recent meta-analysis, for example, estimated there to be a 49 % increased relative

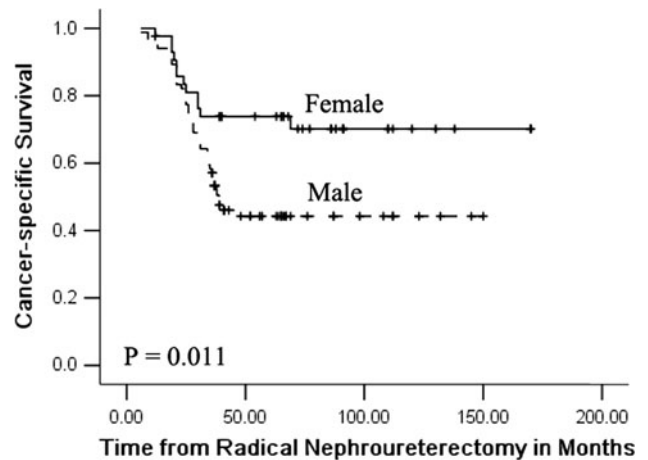


Fig. 3 Kaplan–Meier estimates of cancer-specific survival according to gender in 421 patients aged 42–58 years

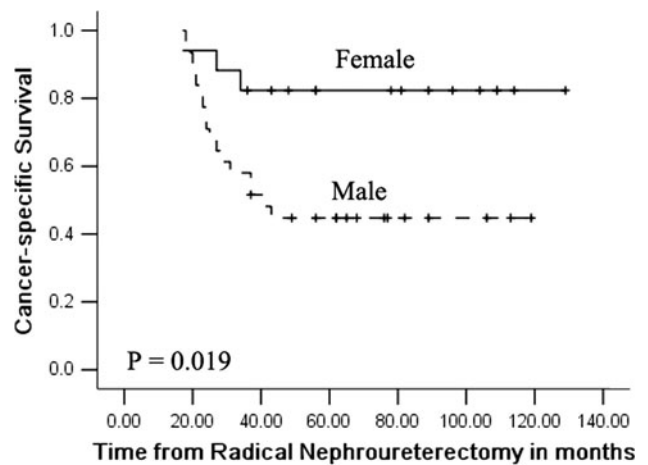


Fig. 4 Kaplan–Meier estimates of cancer-specific survival according to gender in 421 patients under age 42 years

risk of developing bladder cancer in women who underwent early menopause [25].

Our study had several limitations. One limitation of our results was analyzed retrospectively, although it is unlikely that large prospective randomized trials could be performed owing to the low incidence of this malignancy. Another limitation of our study is the unavailability of true hormonal status of the subjects. Although we believe that the use of age as a surrogate for menopausal status is reasonably reliable, age of menopause for an individual can vary widely across the world based on differences in genetics, nutrition, and other environmental factors. Additionally, the relationship of UTUC diagnosis with the presence of other concomitant conditions that might affect the hormonal status of women is unknown.

Table 2 Univariable and multivariable Cox regression analyses of gender targeting CSS in 421 patients treated with RNU for UTUC

Parameters	Univariable analysis		Multivariable analysis	
	HR (95 % CI)	<i>P</i> value	HR (95 % CI)	<i>P</i> value
Age at diagnosis	1.003 (0.991–1.016)	0.600	1.004 (0.991–1.018)	0.527
ECOG performance status				
0	1	0.220	1	0.865
1 or greater	1.369 (0.829–2.260)		0.954 (0.558–1.632)	
Tumor location				
Renal pelvis	1	0.933	1	0.793
Ureter	1.013 (0.749–1.369)		1.044 (0.755–1.444)	
Tumor focality				
Unifocal	1	0.797	1	0.464
Multifocal	0.959 (0.694–1.324)		0.879 (0.624–1.240)	
Type of RNU				
Open	1	0.002	1	0.398
Laparoscopic/retroperitoneoscopic	0.383 (0.208–0.707)		0.759 (0.401–1.437)	
Lymph node dissection				
Not performed	1	<0.001	1	0.897
Performed	3.258 (2.361–4.497)		0.971 (0.622–1.516)	
Soft tissue surgical margin				
Negative	1	<0.001	1	0.475
Positive	3.387 (2.252–5.095)		1.299 (0.634–2.662)	
Lymphovascular invasion				
Absent	1	<0.001	1	0.013
Present	3.621 (2.667–4.914)		1.160 (0.818–1.645)	
Tumor grade				
G1	1	<0.001	1	0.001
G2	2.754 (1.420–5.342)		1.210 (0.602–2.429)	
G3	6.482 (3.490–12.040)		2.336 (1.200–4.545)	
pT Stage				
pTa/pTis/pT1	1	<0.001	1	<0.001
pT2	2.876 (1.560–5.300)		2.282 (1.213–4.291)	
pT3	10.310 (6.151–17.280)		5.606 (3.107–10.115)	
pT4	22.657 (12.196–42.092)		6.518 (2.580–16.466)	
pN Stage				
pNo/pNx	1	<0.001	1	<0.001
pN+	9.296 (6.711–12.877)		4.735 (2.932–7.646)	
Adjuvant chemotherapy				
No	1	<0.001	1	0.104
Yes	3.788 (2.767–5.186)		0.707 (0.465–1.074)	
Gender				
Male	1	0.021	1	0.036
Female	1.187 (1.017–1.893)		1.034 (0.739–1.446)	

RNU Radical nephroureterectomy, UTUC upper tract urothelial carcinoma, CSS cancer-specific survival, HR hazard rate, CI confidence interval

Conclusions

In conclusion, the present study suggests that gender was an independent prognostic factor for UTUC treated by RNU. Moreover, the impact of gender on UTUC outcome

was age-specific. Females who aged 59 years and older experienced worse outcomes than their male counterparts, while women in the age group <42 years and 42–58 years have better outcomes than men. The role of gender-specific hormones in the survival of UTUC needs to be further

studied. If a true beneficial effect of hormone status on UTUC does exist, then the potential for therapy targeting the endocrine axis would also need to be investigated.

Conflict of interest All authors have no any financial disclosures and conflict of interest.

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