



Gender effect on the oncologic outcomes of upper urinary tract urothelial carcinoma in Taiwan

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Abstract

Purpose Upper urinary tract urothelial carcinoma (UTUC) is a relatively uncommon malignancy in Western countries, affecting more men than women. By contrast, UTUC is relatively common in Taiwan and diagnosed more often in women than in men. Previous studies regarding the gender effect on cancer behaviour with UTUC have been controversial. Investigation of female predominance of UTUC in Taiwan may help improve UTUC management in Taiwan as well as understand the gender effect on urothelial carcinoma.

Methods Between January 2005 and December 2015, 828 patients with localized UTUC treated with radical nephroureterectomy were enrolled. Cox regression analysis was performed to assess the independent roles of perioperative factors on local recurrence and systemic recurrence.

Results Multivariate analysis revealed the male gender had a trend associated with higher systemic recurrence ($P=0.096$) and independently associated with higher bladder recurrence ($P=0.011$) and cancer-specific mortality ($P=0.014$), even after taking smoking and other established prognostic factors into consideration. Bladder cancer history and multifocal disease are strongly associated with bladder recurrence.

Conclusion Compared with female UTUC patients, male UTUC patients in Taiwan were associated with more bladder recurrences and higher cancer-specific mortality and had a trend associated with more systemic recurrences.

Keywords Upper urinary tract urothelial carcinoma · Nephroureterectomy · Intravesical recurrence · Gender · Prognosis · Risk factor

Abbreviation

UTUC Upper urinary tract urothelial carcinoma

Introduction

Upper urinary tract urothelial carcinoma (UTUC) is a relatively uncommon malignancy in Western countries, with an incidence of approximately two cases per 100,000 people, and accounts for only 5–10% of urinary carcinomas (UC) [1, 2]. In addition, males have higher incidences of UTUC

than females in Western countries. There is a high degree of difference in the epidemiology of UTUC in Western countries and Taiwan, where UTUC patients are predominantly female. According to the Health Promotion Administration of Taiwan, the incidence rate of UTUC in 2016 was 3.61 per 100,000 in males and 4.21 per 100,000 in females. The mortality rate of UTUC in 2016 was 1.36 (16th in males) per 100,000 in males and 1.40 (13th in females) per 100,000 in females. Furthermore, UTUCs represent more than 40% of UCs in Taiwan [3]. Therefore, UTUC is indeed a crucial health problem in Taiwan and its female predominance is unique compared with rest of the world.

Several studies have reported that gender is associated with cancer behaviour of UCs. In T1 urinary bladder UCs, female patients had a higher incidence of recurrence, shorter time to recurrence, and shorter cancer-specific survival [4–6]. In muscle-invasive bladder cancer, survival in female patients was also reported to be shorter than that in males [7]. For upper urinary tract urothelial carcinoma (UTUC), data from previous studies regarding the

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gender effect on cancer behaviour have been sparse and controversial. Hurel et al. reported female gender was a considerable predictor of non-organ-confined disease [8]. A surveillance, epidemiology, and end results analysis conducted by Raman et al. reported that male gender was associated with lower overall survival [9]. Further investigation of the female predominance of UTUC in Taiwan may help improve UTUC management in Taiwan as well as understand the gender effect on urothelial carcinoma. In this study, we analysed the gender effect on oncologic outcomes of UTUC in Taiwan.

Materials and methods

Between January 2005 and December 2015, 905 patients with UTUC were treated by surgical intervention at our institution. We excluded 77 patients who underwent nephron-sparing surgery. Thus, the study included 828 patients with localized UTUC treated at our institution with radical nephroureterectomy. All patients underwent computed tomography (CT) and cystoscopy to determine if they had concurrent bladder disease or distant metastasis. Perioperative and follow-up data, such as age, gender, smoking history, bladder cancer history, bladder recurrence, local recurrence, distant metastasis, and cancer-specific death, were obtained from chart review and the institutional cancer centre registry department. Systemic recurrence was defined as local recurrence and distant metastasis. Local recurrence was defined as ipsilateral retroperitoneal space disease relapse. Distant metastasis was defined as disease relapse outside the urinary tract and ipsilateral retroperitoneal space. Pathological features, including stage, tumour grade, architecture, lymphovascular invasion, concomitant carcinoma in situ, tumour necrosis, and squamous differentiation, were recorded by uropathologists at our institution.

Our institutional follow-up protocol, which was performed in this study, is postoperative fibre cystoscopy and renal echo every 3 months during the first 2 years, every 6 months during the third year, and then every year during the follow-up period. CT was performed annually to assess local or regional recurrence of the tumour and lymph node status. SPSS version 21 software was used for all statistical analyses. Chi-square tests and two-sample *t* tests were used for intergroup comparisons, and the Kaplan–Meier test was used for time-to-event analysis. Multivariate Cox regression analysis was used to assess the independent roles of perioperative factors on intravesical events. Any parameters with statistically significant association were adopted for further multivariate analysis. A *P* value of < 0.05 was considered statistically significant.

Results

As shown in Table 1, this study included 382 male patients (46.1%) and 446 female patients (53.9%). No significant differences in age, follow-up duration, bladder cancer history, distribution of tumour location, tumour necrosis, squamous differentiation, and adjuvant chemotherapy was observed between the sexes. Male patients were significantly more likely to smoke ($P < 0.001$), were less likely to have chronic kidney disease ($P < 0.001$), and experienced greater lymphovascular invasion ($P = 0.022$) compared with female patients. Regarding oncologic outcomes, a higher incidence of bladder recurrence ($P = 0.001$) and systemic recurrence ($P = 0.004$) as well as a greater

Table 1 Patient characteristics

	Female	Male	<i>p</i> value
No	446	382	
Follow up duration (months)	33.8 ± 19.4	35.9 ± 19.3	0.119
Age	67.2 ± 10.8	66.5 ± 10.7	0.350
Bladder cancer history	110 (24.7)	112 (29.3%)	0.132
Smoking	17 (3.8%)	102 (26.7%)	< 0.001
CKD stage			< 0.001
I	13 (2.9%)	7 (1.8%)	
II	81 (18.2%)	65 (17.0%)	
III	157 (35.2%)	194 (50.8%)	
IV	62 (13.9%)	43 (11.3%)	
V	133 (29.8%)	73 (19.1%)	
Stage			0.088
0*	129 (28.9%)	92 (24.1%)	
1	109 (24.4%)	86 (22.5%)	
2	77 (17.3%)	66 (17.3%)	
3	106 (23.8%)	99 (25.9%)	
4	25 (5.6%)	39 (10.2%)	
Renal pelvis	190 (42.6%)	161 (42.1%)	0.895
Ureter	133 (29.8%)	121 (31.7%)	0.564
Renal pelvis and ureter	123 (27.6%)	100 (26.2%)	0.651
High grade	410 (91.9%)	350 (91.6%)	0.873
Papillary	340 (76.2%)	287 (75.3%)	0.762
Lymphovascular invasion	86 (19.3%)	99 (25.9%)	0.022
Carcinoma in situ	175 (39.2%)	148 (38.8%)	0.908
Tumor necrosis	148 (32.0%)	137 (35.9%)	0.418
Squamous differentiation	120 (26.9%)	121 (31.7%)	0.132
Adjuvant chemotherapy	23 (5.2%)	32 (8.4%)	0.064
5-Year bladder recurrence	115 (25.8%)	126 (33.0%)	0.001
5-Year systemic recurrence	88 (19.7%)	111 (29.1%)	0.004
5-Year cancer specific mortality	44 (9.9%)	72 (18.8%)	< 0.001

CKD chronic kidney disease, LVI lymphovascular invasion, CIS carcinoma in situ, TN tumor necrosis

cancer-specific mortality rate ($P=0.001$) were observed in male patients (Fig. 1).

As shown in Table 2, using multivariate Cox regression analyses, male gender was found to be independently associated with bladder recurrence ($P=0.011$) and cancer-specific mortality ($P=0.014$). However, it only revealed a trend for systemic recurrence ($P=0.096$). Locally advanced stage (stage > 2) was the most significant and independent factor associated with systemic recurrence and cancer-specific mortality (both $P < 0.001$), but not urinary bladder recurrence. In addition, nodal positive disease and nonpapillary tumour architecture were also significantly associated with systemic recurrence ($P < 0.001$ and 0.023) and cancer-specific mortality ($P=0.028$ and 0.005). Regarding bladder recurrence, other independently associated factors included smoking history ($P=0.035$), previous bladder cancer history ($P < 0.001$), multifocal disease ($P < 0.001$), and high-grade disease ($P=0.044$).

Discussion

In Western countries, UTUC is a relatively rare malignancy and more prevalent in men. In the United States, the incidence of UTUC is 0.7–1.1 per 100,000 over the last 30 years with a male-to-female ratio of 1.7–1 [10]. The incidence of UTUC was 2.45 per 100,000 in men and 1.25 per 100,000 in women from 1999 through 2003 in Denmark [11]. In Asian countries other than Taiwan, the epidemiology of this condition appears similar. According to the 2015 annual cancer report of Korea, the incidence of renal pelvis UC was 0.3 per 100,000 in men and 0.1 per 100,000 in women. The incidence of ureter UC was 0.3 per 100,000 in men and 0.2 per 100,000 in women [12]. In Japan, the male-to-female ratio of UTUC incidence was found to be 2:1 [13]. Therefore, because UTUC is more prevalent in Taiwan and with a unique female predominance, we conducted this study to analyse the gender effect on oncologic outcomes of UTUC in Taiwan.

Bladder recurrence after radical nephroureterectomy for UTUC was reported in 30–50% of patients. Level 1 evidence has been reported wherein a single postoperative administration of intravesical mitomycin C reduced postoperative intravesical recurrence. However, only a small minority of patients receive adjuvant administration of intravesical mitomycin C due to the concern of cost and side effects [14]. In our study, the 5-year bladder recurrence rate was 29.1%. We also identified that bladder cancer history and multifocal disease were both strong associated factors for bladder recurrence. This is compatible with previous studies and further proves the credibility of this study. Both factors indicated that urothelial cancerization is an important feature in clinical practice and

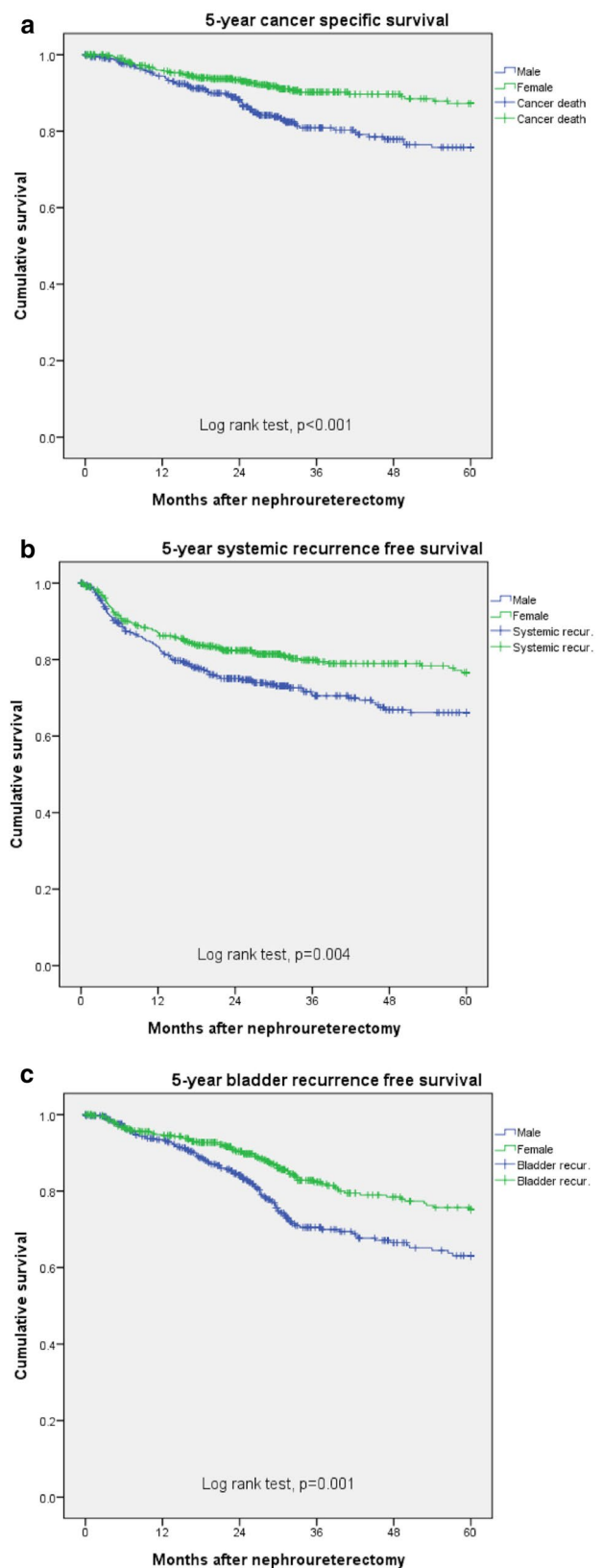


Fig. 1 Kaplan–Meier curves demonstrating survival in males and females undergoing nephroureterectomy for UTUC: **a** cancer specific survival; **b** systemic recurrence free survival; **c** bladder recurrence free survival

Table 2 Cox regression multivariate analysis for UTUC oncologic outcome

	Bladder recurrence		Systemic recurrence		Cancer specific mortality	
	UV	MV	UV	MV	UV	MV
SG > 2	0.509		<0.001	<0.001, HR = 3.66, 95% CI = 2.50–5.37	<0.001	<0.001, HR = 5.16, 95% CI = 2.97–8.97
Male	0.001	0.011, HR = 1.53, 95% CI = 1.10–2.13	0.005	0.096	0.001	0.014, HR = 1.65, 95% CI = 1.11–2.46
Smoking	0.005	0.035, HR = 1.54, 95% CI = 1.03–2.30	0.267		0.149	
CKD > 3	0.132		<0.001	0.030, HR = 0.689, 95% CI = 0.49–0.97	0.013	0.269
Age	0.159		0.182		0.045	0.011, HR = 1.03, 95% CI = 1.01–1.05
ACT	0.294		<0.001	0.230	<0.001	0.387
BCH	<0.001	<0.001, HR = 3.09, 95% CI = 2.27–4.22	0.993		0.488	
NP	0.898		<0.001	<0.001, HR = 2.24, 95% CI = 1.43–3.50	<0.001	0.028, HR = 1.94, 95% CI = 1.07–3.50
MT	<0.001	<0.001, HR = 1.87, 95% CI = 1.35–2.60	0.041	0.074	0.005	0.019, HR = 1.64, 95% CI = 1.09–2.46
HG	0.014	<0.044, HR = 2.22, 95% CI = 1.02–4.80	<0.001	0.103	0.009	0.649
Non-PA	0.805		<0.001	0.023, HR = 1.44, 95% CI = 1.05–1.97	<0.001	0.005, HR = 1.80, 95% CI = 1.20–2.72
LVI	0.262		<0.001	0.010, HR = 1.56, 95% CI = 1.11–2.17	<0.001	0.112
SD	0.047	0.035, HR = 0.67, 95% CI = 0.46–0.97	0.044	0.993	0.037	0.804
CIS	0.028	0.912	0.925		0.297	
TN	0.762		0.001	0.564	0.002	0.885

UV univariate analysis, MV multivariate analysis, SG stage, CKD chronic kidney disease, ACT adjuvant chemotherapy, BCH bladder cancer history, NP nodal positive, MT multifocal tumor, HG high grade, Non-PA non-papillary, LVI lymphovascular invasion, SD squamous differentiation, CIS carcinoma in situ, TN tumor necrosis

that such high-risk patient should be closely monitored or intensively treated with intravesical prevention [15]. In addition, both Tanaka et al. and Xylinas et al. reported that male gender was also strongly associated with intravesical recurrence [14, 16]. The results were similar to our observation that male patients were also found to have a higher risk of intravesical recurrence in Taiwan. This finding improved our clinical decision making regarding cystoscopic follow-up and postoperative intravesical chemotherapy instillation. However, some bladder cancer studies reported female gender to be associated with an increased risk of recurrence in primary T1 high-grade disease [5]. Though UTUC and UBC are similar in histology, the clinical cancer behaviour is different between the two [17]. The aetiology of bladder recurrence of UTUC is much more complicated because of urothelial field cancerization and intraluminal cancer cells seeding from the upper tract to the urinary bladder [18, 19]. Identification of bladder recurrence patterns between UTUC and UBC is worth

further investigation. In regards to distant UTUC recurrence, the mechanism includes the epithelial mesenchymal transition of cancer cells [20, 21]. Such recurrence outside the urinary tract is difficult to manage by endoscopic or surgical intervention. Male patients in this study tended to have poorer oncologic and survival outcomes, whereas previous studies reported higher mortality rates in female than in male patients [1].

Gender-related behavioural dimorphism, such as cigarette smoking, UV radiation exposure, and HPV infection, was thought to be associated with the relatively poor oncologic outcomes of male UTUC patients [22, 23]. However, the gender effect is still borderline associated with systemic recurrence and independently associated with cancer-specific mortality under multivariate analysis by taking smoking and other established prognostic factors into consideration. A previous study also reported that even in the absence of exposure to cigarettes or occupational hazards, the gender-related risk persisted [24].

With similar disease staging between genders as well as taking smoking and other established prognostic factors into consideration, gender differences in metabolic detoxification of carcinogens and hormonal effects may also explain the difference in oncological outcomes between genders. The hormonal effect on cancer is commonly seen in ovarian, lung, and colorectal cancer [25–30]. Previous studies have increasingly evidenced that UC is potentially an endocrine-related cancer. Hormone receptors, including androgen receptor (AR), oestrogen receptor (OR), progesterone receptor (PR), and glucocorticoid receptor (GR), were found to be expressed on upper urinary tract urothelial carcinoma cells without appreciable differences of expression levels between women and men. Kashiwagi et al. reported that in male tumours, the expression of AR and PR tended to be higher and lower, respectively [31, 32]. Additionally, hormonal receptors were also reported to be associated with oncologic outcomes of UCs [33, 34]. In addition, Liu et al. reported higher cancer-specific survival for women aged less than 59 years, whereas women aged 59 years or older had lower survival rates than men. This finding may support the concept that premenopausal women have more favourable oncologic outcomes, whereas postmenopausal women have less favourable oncologic outcome than men [35]. Previous studies have also revealed that gender difference in metabolism of carcinogens, such as the enzyme uridine 5'-diphosphoglucuronosyltransferase, which are involved in aromatic amine metabolism, may explain differences in tumour behaviour of UTUCs between genders [36]. Further research investigating possible molecular-level factors that may be related to cancer behaviour is warranted.

The strength of this study is the large number of patients included. However, this study is limited by its retrospective and single population design. The unique predominantly female UTUC population may have led to collection bias, and the data may need further validation from other predominantly UTUC populations. The comorbidity evaluated in this study included chronic kidney disease only. Other comorbidities might also influence the analysis, especially for survival outcomes. In addition, we did not retrospectively collect the data about potential risk factor to UTUC such as occupational exposure and analgesic drug use. The reported median time to bladder recurrence is 10 months [37]. Most extraurinary tract recurrences are identified within 2 years [38]. In this study, the average follow-up duration in male and female populations was 33.8 and 35.9 months. This was sufficient time to observe cancer-related outcomes and provide a preliminary report on the gender effect on UTUC.

Conclusions

For UTUC patients in Taiwan, men are associated with more bladder recurrence and systemic recurrence and have higher cancer-specific mortality compared with women.

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