The Impact of Sex Differences on Renal Function Outcomes After Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma: A Retrospective Study

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Abstract

Background: Upper tract urothelial carcinoma (UTUC) is a relatively rare type of urothelial carcinoma. Additionally, only few reports have examined the sex differences in patients with UTUC. Therefore, the present study aimed to identify the sex factors affecting renal function in patients with UTUC.

Methods: Patients who underwent radical nephroureterectomy for non-metastatic UTUC between 2000 and 2013 were retrospectively reviewed and divided into two groups by sex. The Kaplan–Meier method was applied to evaluate the effects of sex on survival, whereas for the other clinicopathological parameters, hazard ratios were evaluated using the Cox regression model. The analyses were also performed in patients with different chronic kidney disease (CKD) stages.

Results: A total of 368 patients were included, 147 men and 221 women. Female patients had a higher rate of anemia, advanced CKD stage, and dialysis. Male patients predominantly had a higher rate of smoking. The Kaplan–Meier analysis revealed no differences between sexes on metastasis-free survival (MFS) and cancer-specific survival. Multivariate analysis confirmed that ureteral tumors, advanced pathological tumor stage, and adjuvant chemotherapy indicated significantly worse survival outcomes in both sexes. However, only female patients with advanced CKD showed poorer MFS. After adjusting for renal function, the analysis found men had worse MFS.

Conclusions: The female sex is significantly associated with a higher prevalence of advanced CKD among patients with UTUC in Taiwan. The impact of sex differences on renal function needs to be considered when evaluating survival.

Highlights

- No significant effect regarding sex was observed for cancer-specific survival
- Female patients showed a higher rate of anemia, advanced chronic kidney disease stage, and dialysis
- Sex differences in renal function are important in assessing survival outcomes of upper tract urothelial carcinoma
- After adjusting for renal function, women were found to have better metastasis-free survival than men

Background

Urothelial carcinoma (UC) is the most common malignancy of the urinary tract that includes UC of the urinary bladder (UBUC) and upper urinary tract (UTUC). UBUC is a major UC, with an estimated 90–95% new UC cases, whereas UTUC comprises 5–10% of all UC. Increasing evidence suggests UTUC should be considered a different disease entity from UBUC even though both are urothelial in origin [1, 2]. The optimal management of UTUC differs from UBUC, ranging from surgical intervention, postoperative instillation therapy, postoperative surveillance, and medical management [1]. Until now, the standard treatment for invasive, non-metastatic UTUC remains radical nephroureterectomy (RNU) with bladder cuff excision. However, unlike UBUC, a high risk of disease recurrence and progression are reported in UTUC, especially in the advanced stage [3].

Several large studies focused on sex-associated outcomes in UTUC. In an analysis of 4,850 UTUC cases, Lughezzani et al. [4] reported women were more likely to have more advanced pathologic T stage and higher tumor grade at RNU than men. However, after adjusting for confounding factors, no statistically significant differences in survival were found between the sexes. Milojevic et al. [5] identified the effects of sex differences on Balkan endemic-related UTUC
and found that sex could not predict the outcomes. Hurel et al. [6] showed that the female sex was an independent factor for predicting final non-organ-confined disease ($p = 0.007$) but not of survival. Xylinas et al. [7] developed nomograms built on a retrospective analysis of 1,839 patients with UTUC and found that men had a higher risk of intravesical recurrence than women. A Taiwanese study noted no differences between the sexes in the clinicopathological characteristics of UBUC; however, female patients with bladder cancer were more prone to have more advanced UTUC and renal impairment than male patients [8]. Li et al. [9] observed that male patients with renal insufficiency have a higher possibility of bladder tumor recurrence after RNU. Nevertheless, the effects of sex in UTUC have still not been established by a global consensus.

In Taiwan, the prevalence and incidence of chronic kidney disease (CKD) are higher compared with those in other countries [10]. Previous reports have shown that the female sex had a higher prevalence of proteinuria and renal impairment than the male sex [10, 11]. Chen et al. [12] used the Taiwan Longitudinal Health Insurance Database to demonstrate that CKD is a significant factor associated with UTUC. To our knowledge, few reports have analyzed the relationship between sex differences in renal function and their prognosis in Asia. The aim of the present study was to identify the sex-related factors affecting renal function in patients with UTUC who underwent RNU.

**Methods**

**Patients**

Patients who underwent either open or laparoscopic RNU with bladder cuff excision for non-metastatic UTUC at Kaohsiung Medical University Hospital, Kaohsiung, Taiwan between 2000 and 2013 were included in the study. The present study was approved by the review board of our institution (KMUH-IRB-20120138). Patients were divided into two groups by sex. Clinical parameters including demographic characteristics, pathological features, oncologic follow-up, and the cause leading to mortality were retrospectively collected. Patients with neoadjuvant chemotherapy or radiotherapy, concurrent muscle-invasive bladder tumor, acute blood disorders, bone marrow diseases, and incomplete clinical information were excluded. Tumor stage was evaluated according to the 2002 American Joint Committee Cancer TNM system. All cases were reviewed by two pathologists and re-classified as low or high grade using the 2004 World Health Organization grading system. Renal function was evaluated using the estimated glomerular filtration rate based on the Chronic Kidney Disease Epidemiology Collaboration creatinine-based formula [13].

**Postoperative follow-up**

After the operation, outpatient clinics were arranged every 3 months in the first 2 years and every 6 months in the subsequent 2 years. From the fifth year, annual follow-ups were arranged in patients with no evidence of disease. Detailed history taking, physical examination, urine cytology, cystoscopy, and serial imaging survey were performed following the surveillance guidelines. Metastatic progression was defined as tumor recurrence at the operation site, regional lymph nodes, and distant organs. Tumors occurring in the bladder or contralateral upper urinary tract were considered metachronous and not categorized as disease progression. Adjuvant chemotherapy and radiation therapy were administered in 71 and 30 patients, respectively, according to pathological stage, performance status, renal function, and consent to treatment.

**Statistical analysis**

Differences between categorical parameters were assessed using the $\chi^2$ or Fisher’s exact test. The Kaplan–Meier method was applied to estimate the effects of sex on metastasis-free survival (MFS) and cancer-specific survival
Survival rates were recorded from the day of RNU to metastatic progression, cancer-specific death, or the latest visit. Survival curves were compared using a log-rank test. Only prognostic factors that were statistically significant in univariate analysis were included in the multivariate Cox proportional hazard model to identify independent predictors for MFS and CSS. Statistical significance was set at $p < 0.05$. SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

**Results**

Overall, we included 368 patients, 147 (39.9%) men and 221 (60.1%) women, in the current study. Table 1 shows the patients’ clinical and pathologic profiles. The mean ± standard deviation age of patients who underwent RNU was 66.8 ± 10.6 years. The mean follow-up after surgery was 41.7 ± 31.7 months (40.4 ± 30.2 months among men and 42.5 ± 32.7 months among women). No difference in follow-up time was observed between the two groups.
| Demographics and clinicopathological characteristics of 368 patients with UTUC | Male | Female | p value |
|---|---|---|---|
| n = 368 | n = 147 | n = 221 |
| Age (years) | | | |
| Mean ± SD | 66.8 ± 10.6 | 66.2 ± 11.9 | 67.2 ± 9.7 | 0.438 |
| Smoking | 72 (19.6) | 66 (44.9) | 6 (2.7) | < 0.001 |
| BMI (kg/m²) | | | |
| Mean ± SD | 23.7 ± 3.9 | 23.8 ± 3.7 | 23.6 ± 4.1 | 0.654 |
| Anemia | | | |
| Yes | 240 (65.2) | 87 (59.2) | 153 (69.2) | 0.047 |
| ECOG score | | | 0.174 |
| 0, 1 | 328 (89.1) | 135 (91.8) | 193 (87.3) |
| 2, 3 | 40 (10.9) | 12 (8.2) | 28 (12.7) |
| CKD stage | | | 0.017 |
| Stage 1 | 30 (8.2) | 9 (6.1) | 21 (9.5) |
| Stage 2 | 89 (24.2) | 40 (27.2) | 49 (22.2) |
| Stage 3 | 146 (39.7) | 68 (46.3) | 78 (35.3) |
| Stage 4 | 33 (9.0) | 13 (8.8) | 20 (9.0) |
| Stage 5 | 70 (19.0) | 17 (11.6) | 53 (24.0) |
| Advanced CKD (stage 4, 5) | | | 0.008 |
| Yes | 103 (28.0) | 30 (20.4) | 73 (33.0) |
| Dialysis | | | < 0.001 |
| Yes | 63 (17.1) | 12 (8.2) | 51 (23.1) |
| Type of operation | | | 0.144 |
| Open | 221 (60.1) | 95 (64.6) | 126 (57.0) |
| Laparoscopic | 147 (39.9) | 52 (35.4) | 95 (43.0) |
| Tumor location | | | 0.689 |
| Pyelocaliceal | 142 (38.6) | 53 (36.1) | 89 (40.3) |
| Ureteral | 161 (43.8) | 66 (44.9) | 95 (43.0) |
| Both | 65 (17.7) | 28 (19.0) | 37 (16.7) |

SD, standard deviation; BMI, body mass index; CKD, chronic kidney disease; ECOG, Eastern Cooperative Oncology Group; UTUC, upper tract urothelial carcinoma.
Female patients had a higher risk of preoperative anemia ($p = 0.047$) than male patients. Advanced CKD, which was defined as CKD in stage 4 or 5 in this study, was significantly associated with the female sex ($p = 0.008$). Therefore, a higher dialysis rate was also noted among female patients ($p < 0.001$). Male patients had a higher rate of smoking ($p < 0.001$).

**MFS and CSS**

Ninety-six patients (26.1%) underwent disease progression (45 women and 51 men). The respective overall 3- and 5-year MFS rates were 74.5% and 70.6%. Kaplan–Meier analysis indicated that MFS rates were not significantly influenced by sex ($p = 0.093$; Fig. 1a).
Sixty-seven patients (18.2%) had cancer-specific mortality during follow-up (38 women and 29 men). The respective overall 3- and 5-year CSS rates were 82.4% and 77.4%. Similarly, sex did not exhibit a significant effect on CSS ($p = 0.492$; Fig. 1b).

**MFS and CSS in men**

In male patients, the respective 3- and 5-year MFS rates were 70.9% and 63.8%. Univariate analysis showed that ureteral tumors ($p = 0.029$), advanced pathological stage ($p < 0.001$), lymph node invasion ($p = 0.001$), high tumor grade ($p = 0.016$), and adjuvant chemotherapy ($p < 0.001$) were associated with worse MFS (Table 2). Ureteral tumors ($p = 0.019$), advanced pathological tumor stage ($p < 0.001$), and adjuvant chemotherapy ($p = 0.038$) were independent risk factors for lower MFS in multivariate analysis.
Table 2
Univariate and multivariate analyses predicting MFS and CSS in male patients with UTUC after RNU

| Characteristics                      | MFS          |         | CSS          |         |
|--------------------------------------|--------------|---------|--------------|---------|
|                                      | (n = 147)    | Univariate | Multivariate | Univariate | Multivariate |
|                                      | p            | p       | p            | p       |
|                                      | analysis     | analysis | analysis     | analysis |
|                                      | HR (95% CI)  | HR (95% CI) | HR (95% CI) | HR (95% CI) |
| Age (years)                          |              |         |              |         |
| Over 65 years                        | 0.88 (0.43–1.78) | 0.712 | 1.04 (0.46–2.38) | 0.923 |
| BMI (kg/m²)                          |              |         |              |         |
| Over 27 kg/m²                        | 1.25 (0.51–3.07) | 0.625 | 0.96 (0.33–2.81) | 0.944 |
| ECOG score                           |              |         |              |         |
| 2, 3 versus 0, 1                     | 1.32 (0.38–4.67) | 0.660 | 1.40 (0.35–5.53) | 0.632 |
| CKD stage                            |              |         |              |         |
| Stage 2 versus stage 1               | 3.85 (0.44–34.10) | 0.199 | 1.70 (0.18–15.83) | 0.639 |
| Stage 3 versus stage 1               | 4.09 (0.48–34.71) | 0.167 | 2.46 (0.29–21.20) | 0.399 |
| Stage 4 versus stage 1               | 6.86 (0.66–71.72) | 0.083 | 3.56 (0.33–38.78) | 0.279 |
| Stage 5 versus stage 1               | 1.07 (0.08–13.66) | 0.960 | 2.00 (0.11–35.71) | 0.634 |
| Advanced CKD (stage 4, 5)            | 1.26 (0.52–3.13) | 0.599 | 1.29 (0.45–3.72) | 0.637 |
| Type of operation                    |              |         |              |         |
| Laparoscopy versus open              | 0.88 (0.42–1.84) | 0.731 | 0.60 (0.36–1.01) | 0.585 |
| Tumor location                       |              |         |              |         |
| Ureteral versus pyelocaliceal        | 2.48 (1.09–5.68) | **0.029** | 4.17 (1.27–13.71) | **0.019** |
|                                      |              |         | 2.94 (1.07–8.05) | **0.031** |
|                                      |              |         | 3.01 (1.03–8.79) | **0.043** |
| Pathologic T stage |  |  |  |  |  |  |  |  |  |  |  |
|-------------------|---|---|---|---|---|---|---|---|---|---|---|
| pT2 versus pTa/pTis/pT1 | 2.29 (0.70–7.49) | 0.163 | 1.16 (0.20–6.76) | 0.185 | 1.21 (0.25–5.75) | 0.811 | 1.24 (0.23–6.68) | 0.836 |
| pT3 versus pTa/pTis/pT1 | 8.40 (2.85–24.74) | 0.001 | 1.79 (0.92–3.47) | 0.177 | 5.54 (1.70–18.02) | 0.002 | 1.79 (0.92–3.47) | 0.303 |
| pT4 versus pTa/pTis/pT1 | 25.20 (3.96–160.19) | 0.001 | 2.62 (1.46–4.71) | 0.001 | 17.92 (3.08–104.12) | 0.004 | 2.62 (1.46–4.71) | 0.004 |

| Lymph node invasion |  |  |  |  |  |  |  |  |  |  |  |
|---------------------|---|---|---|---|---|---|---|---|---|---|---|
| Yes versus no       | 4.16 (1.80–9.61) | 0.001 | 1.20 (0.41–3.51) | 0.747 | 3.18 (1.30–7.80) | 0.009 | 1.19 (0.29–2.45) | 0.747 |

| Grade               |  |  |  |  |  |  |  |  |  |  |  |
|---------------------|---|---|---|---|---|---|---|---|---|---|---|
| High versus low     | 2.98 (1.11–8.01) | 0.016 | 1.18 (0.19–3.75) | 0.831 | 2.70 (0.76–9.62) | 0.113 |

| Adjuvant chemotherapy |  |  |  |  |  |  |  |  |  |  |  |
|-----------------------|---|---|---|---|---|---|---|---|---|---|---|
| Yes versus no         | 16.08 (6.32–40.89) | 0.001 | 2.81 (1.06–7.44) | 0.038 | 5.58 (2.32–13.44) | 0.001 | 2.81 (1.01–7.44) | 0.038 |

| Anemia                |  |  |  |  |  |  |  |  |  |  |  |
|-----------------------|---|---|---|---|---|---|---|---|---|---|---|
| Anemia versus no anemia | 1.38 (0.67–2.84) | 0.389 | 1.69 (0.71–4.02) | 0.232 |

**MFS**, metastasis-free survival; **CSS**, cancer-specific survival; **HR**, hazard ratio; **CI**, confidence interval; **BMI**, body mass index; **CKD**, chronic kidney disease; **ECOG**, Eastern Cooperative Oncology Group; **UTUC**, upper tract urothelial carcinoma.

The respective 3- and 5-year CSS rates for the male group were 80.5% and 74.9%. Prognostic factors in univariate analysis for CSS were almost identical to those for MFS (except tumor grade). Multivariate analysis showed that patients with ureteral tumors ($p = 0.043$), advanced pathological tumor stage ($p = 0.004$), and adjuvant chemotherapy ($p = 0.038$) indicated significantly worse outcomes (Table 2).

**MFS and CSS in women**
In female patients, the 3- and 5-year MFS rates were 76.9% and 75.3%, respectively. Univariate analysis showed that advanced CKD stage \((p = 0.008)\), multifocal tumors \((p = 0.006)\), advanced pathological stage \((p < 0.001)\), lymph node invasion \((p = 0.001)\), high tumor grade \((p < 0.001)\), and adjuvant chemotherapy \((p < 0.001)\) were associated with worse MFS (Table 3). Advanced CKD stage \((p = 0.030)\), advanced pathological tumor stage \((p = 0.003)\), and adjuvant chemotherapy \((p < 0.001)\) were independent risk factors for lower MFS in multivariate analysis.
| Characteristics | MFS (n = 221) | CSS | Univariate p | Multivariate p | Univariate p | Multivariate p |
|-----------------|---------------|-----|--------------|----------------|--------------|----------------|
| Age (years)     |               |     |              |                |              |                |
| Over 65 years   | 0.99          |     | 0.980        |                | 1.56         | 0.253          |
|                 | (0.52–1.90)   |     |              |                | (0.73–3.33)  |                |
| BMI (kg/m²)     |               |     |              |                |              |                |
| Over 27 kg/m²   | 0.91          |     | 0.818        |                | 0.535        | 0.259          |
|                 | (0.39–2.13)   |     |              |                | (0.18–1.61)  |                |
| ECOG score      |               |     |              |                |              |                |
| 2, 3 versus 0, 1| 1.44          |     | 0.483        |                | 1.05         | 0.921          |
|                 | (0.52–4.00)   |     |              |                | (0.37–2.97)  |                |
| CKD stage       |               |     |              |                |              |                |
| Stage 2 versus 1| 1.70          |     | 0.403        |                | 0.71         | 0.616          |
|                 | (0.49–5.95)   |     |              |                | (0.18–2.74)  |                |
| Stage 3 versus 1| 1.89          |     | 0.290        |                | 1.18         | 0.785          |
|                 | (0.57–6.21)   |     |              |                | (0.35–3.99)  |                |
| Stage 4 versus 1| 2.06          |     | 0.009        |                | 1.06         | 0.939          |
|                 | (1.03–6.98)   |     |              |                | (0.23–4.98)  |                |
| Stage 5 versus 1| 2.92          |     | 0.004        |                | 1.84         | 0.381          |
|                 | (1.01–7.43)   |     |              |                | (0.46–7.35)  |                |
| Advanced CKD     |               |     |              |                |              |                |
| (stage 4, 5)    | 2.81          |     | 0.008        |                | 1.47         | 0.333          |
|                 | (1.28–6.17)   |     |              |                | (0.67–3.22)  |                |
| Type of operation|               |     |              |                |              |                |
| Laparoscopy      | 1.12          |     | 0.728        |                | 0.64         | 0.230          |
| versus open     | (0.59–2.10)   |     |              |                | (0.31–1.33)  |                |
| Tumor location  |               |     |              |                |              |                |
| Ureteral versus | 1.90          |     | 0.088        |                | 1.83         | 0.118          |
| pyelocaliceal   | (0.90–4.00)   |     |              |                | (0.77–4.35)  |                |
|                 | 2.95 (1.22–7.14) |     | 0.003        |                | 2.92 (1.16–7.41) | 0.025 |
| Comparison                  | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value |
|-----------------------------|-------------|---------|-------------|---------|-------------|---------|-------------|---------|
| Both versus ureteral        | 2.08 (0.92–4.69) | 0.076   | 1.02 (0.56–1.84) | 0.868   | 1.56 (0.65–3.71) | 0.314   | 1.06 (0.63–1.79) | 0.884   |
| Both versus pyelocaliceal   | 3.95 (1.66–9.39) | 0.001   | 1.56 (0.48–5.03) | 0.389   | 4.60 (1.68–12.64) | 0.002   | 1.60 (0.47–5.41) | 0.399   |
| Pathologic T stage          |             |         |             |         |             |         |             |         |
| pT2 versus pTa/pTis/pT1     | 2.28 (0.82–6.29) | 0.254   | 1.61 (0.46–5.60) | 0.546   | 2.31 (0.73–7.26) | 0.362   | 3.01 (0.89–10.18) | 0.466   |
| pT3 versus pTa/pTis/pT1     | 10.16 (4.12–25.03) | <0.001  | 1.87 (1.06–3.29) | 0.022   | 7.97 (2.93–21.72) | <0.001  | 2.36 (1.39–4.00) | 0.024   |
| pT4 versus pTa/pTis/pT1     | 17.06 (4.84–60.20) | <0.001  | 2.18 (1.37–3.48) | 0.003   | 13.56 (3.67–50.16) | <0.001  | 3.55 (1.87–6.75) | 0.001   |
| Lymph node invasion         |             |         |             |         |             |         |             |         |
| Yes versus no               | 3.32 (1.62–6.81) | 0.001   | 1.32 (0.52–3.36) | 0.557   | 2.76 (1.27–6.02) | 0.009   | 1.12 (0.44–2.84) | 0.812   |
| Grade                       |             |         |             |         |             |         |             |         |
| High versus low             | 10.20 (2.39–43.48) | <0.001  | 4.20 (0.81–21.74) | 0.088   | 6.76 (1.57–29.41) | 0.004   | 2.46 (0.50–12.20) | 0.271   |
| Adjuvant chemotherapy       |             |         |             |         |             |         |             |         |
| Yes versus no               | 12.66 (5.68–18.28) | <0.001  | 11.41 (4.46–29.17) | <0.001  | 4.77 (2.17–10.50) | <0.001  | 3.29 (1.42–7.66) | 0.006   |
| Anemia                      |             |         |             |         |             |         |             |         |
| Anemia versus no anemia     | 0.96 (0.49–1.89) | 0.915   | 1.53 (0.68–3.44) | 0.298   |               |         |             |         |

MFS, metastasis-free survival; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index; CKD, chronic kidney disease; ECOG, Eastern Cooperative Oncology Group; UTUC, upper tract urothelial carcinoma.

The 3- and 5-year CSS rates for the female group were 83.7% and 79.1%, respectively. Prognostic factors in univariate analysis for CSS revealed that ureter tumors (p = 0.013), advanced pathological stage (p < 0.001), lymph node invasion (p = 0.009), high tumor grade (p = 0.004), and adjuvant chemotherapy (p < 0.001) were associated with poor CSS (Table 3). Multivariate analysis showed that patients with ureteral tumors (p = 0.025), advanced pathological tumor stage (p = 0.001), and adjuvant chemotherapy (p = 0.006) predicted significantly worse outcomes (Table 3).

**Sex differences**
No differences were found between the sexes in MFS ($p = 0.093$; Fig. 1a) and CSS ($p = 0.731$; Fig. 1b). The Kaplan–Meier analysis revealed that advanced CKD was associated with worse MFS ($p = 0.031$; Fig. 1c) but not CSS ($p = 0.109$; Fig. 1d). We found that women had a higher rate of advanced CKD in our study cohort. Multivariate analysis revealed that advanced CKD was an independent predictor of MFS in women. After adjusting for CKD status, we noted that men had worse MFS (log-rank test, $p = 0.019$; Fig. 1e). No differences were found in CSS even after adjusting for renal function (log-rank test, $p = 0.492$; Fig. 1f). This close association between advanced CKD and MFS was only observed in women. Men had a higher rate of smoking, which did not impact the MFS (log-rank test, $p = 0.962$; Additional file 1: Fig. 1a) and CSS (log-rank test, $p = 0.616$; Additional file 1: Fig. 1b).

**Discussion**

The worldwide incidence of UTUC is less common in women [3–7]. However, an epidemiological study in Taiwan showed a higher prevalence of UTUC in women than in men [9, 11, 12, 14, 15]. The Taiwan Cancer Registry Annual Report [15] in 2018 also revealed that the crude incidence rate was higher in women (male-to-female ratio = 1:1.3). Clearly, the sex-based distributions of UTUC in Taiwan differ from those in other regions in the world. Chen et al. [16] attribute the progressive increase in the high incidence of UTUC, especially among women, in part to the systematic replacement of traditionally used Chinese herbs with aristolochic acid based on aristolactam-DNA adducts and TP53 mutations, which are identical to those observed in UTUC associated with Balkan endemic nephropathy. A previous report indicated a higher incidence of using alternative therapies for special conditions in women. One of the culturally based reasons is that women consume special nourishment and diets involving herbal medicines daily for at least 1 month after each pregnancy [14]. The exposure to aristolochic acid contributes significantly to the high incidence of UTUC in women in Taiwan. Another study showed a higher proportion of pT3 and advanced-grade UTUC reported in women undergoing nephroureterectomy [4]. The diagnosis of metastatic UTUC was also higher in women [6]. Male patients with UTUC thus have better pathologic outcomes than female patients for the same disease, which may be explained by inequalities in health care between the sexes. A trend toward a more inferior quality of care for women might be an additional possible cause of the sex inequalities [17]. However, no differences were observed between the sexes in CSS in most studies [4–7, 9].

Preoperative CKD was reported as an independent risk factor for higher renal and urothelial cancer rates, but not for prostate, colorectal, lung, breast, or all cancers combined [18]. A national cohort study showed that CKD, the female sex, age, hematuria, bladder cancer history, and end-stage renal disease were significantly associated with UTUC [12]. A study from Japan on UBUC oncologic outcomes in patients with CKD showed that these patients presented with more aggressive cancer behaviors leading to disease progression and recurrence [19]. In our study cohort, the incidence of advanced pT stage (T3, T4) tumor in patients with advanced CKD was 40.0%, which is significantly higher than that in patients with non-advanced CKD (19.4%; $p = 0.001$). Preoperative CKD was also associated with higher metastatic features in survival analysis. Several studies have proven an association between CKD and cancer outcomes related to the effects of chronic inflammation, oxidative stress, and uremia-related immune deficiency [20–23]. The immune deficiency may increase the risk of cancer, especially virus-associated cancers [20].

As the tumor continues to grow in UTUC, the cancer cells can create a physical obstruction that may put pressure on the urinary tract, subsequently leading to nephron and kidney dysfunction [24]. Some reports believed that renal impairment mechanisms differ between the sexes [12, 19]. A recent report by Schneider et al. [25] showed that the availability of nitric oxide in renal circulation is greater in female patients with type 2 diabetes, which is associated with reduced levels of oxidative stress in women. Another study demonstrated significant sex differences in renal vascular function in patients with CKD [26]. Although the effects are canceled out by age, younger women (< 55
years) exhibit both better endothelium-dependent and endothelium-independent dilation than men of the same age. Convincing evidence has shown that renal endothelial dilatory function can predict susceptibility to renal damage [27]. Therefore, the sex differences observed in our data may be due to lower oxidative stress and better renal vascular function in women.

In the present study, two major differences between the sexes were identified: the high prevalence of CKD and dialysis in women and the high smoking rate in men.

In Taiwan, women use more traditional Chinese medicine treatments than men [28]. These treatments include herbal medicines, acupuncture, moxibustion, and other therapies, which are all covered by the national health insurance system [28]. Sex differences persisted across the age groups. The regular consumption of herbal medicines in Taiwan is very common. Previous studies have reported a high national prevalence of UC in the country, which is associated with the use of carcinogenic remedies containing aristolochic acid [14, 16]. Moreover, Taiwanese women have a higher tendency to self-medicate than men and are higher users of healthcare services in general [28]. The high prevalence and low awareness of CKD in Taiwan have also been reported [29]. The need to advocate more strongly for CKD prevention and education for both physicians and the populace is urgently needed.

Unlike previous studies, we demonstrated that the female sex was not an unfavorable prognostic factor for UTUC. Considering the higher rate of CKD among women with UTUC, we hypothesized that CKD status may also influence previous results. Few reports have demonstrated the difference in CKD rates between the sexes. In this study, we showed that after adjusting for CKD status, women had better metastasis outcomes. Other potential contributing factors to the unique presentations of female cases need further identification and investigation in Taiwan. Theories elucidating the differences in incidence, severity, and prognosis of UTUC between the sexes have not been established. Differences between sexes in carcinogenic exposures, routes of entry, or enzymatic processing of environmental substances may account for the clinical discrepancies.

This study had several limitations. First, this was a retrospective analysis of a single-center series. Second, the enrolled patients were treated by different surgeons over a 13-year period. Third, we could not exclude all possible factors that potentially contributed to CKD. Thus, in order to eliminate the confounders, we took CKD stages into consideration and determine the effects on UTUC outcomes. However, further meta-analysis is needed to compare our findings with those of other published reports with larger populations.

Conclusions

This study found that women had no inferior surgical outcomes than men in RNU but tended to have poorer MFS with advanced CKD. Conversely, advanced CKD did not influence MFS in men. However, after adjusting for renal function, women were found to have better MFS than men. Thus, sex differences in renal function are an important factor in considering the outcomes in UTUC in clinical practice.

Declarations

*Ethics approval and consent to participate:* The present study was approved by the review board of our institution (KMUH-IRB-20120138). All patients signed the informed consent form.

*Consent for publication:* Not applicable
Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interest.

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Authors’ contributions: Conception: W.-J.W. and T.-M.C.; Design of the work: C.-C.L., T.-M.C., and Y.-M.L.; Acquisition and analysis: C.-C.L., T.-M.C., and Y.-M.L.; Writing and editing: C.-C.L. and T.-M.C.; Supervision: W.-J.W., H.W.C., and Y.-H.C.T.-M.C., C.-C.L., and Y.-M.L. analyzed and interpreted the patient data. W.-J. W., H.-W.C., and Y.-H.C. designed the work of the study. T.-M.C. was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1
Kaplan–Meier estimates of survival in patients with UTUC based on sex. a, MFS. b, CSS. Kaplan–Meier estimates of survival in patients with UTUC based on renal function. c, MFS. d, CSS. Kaplan–Meier estimates of survival in patients with UTUC based on sex after adjusting the renal function. e, MFS. f, CSS.

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