Original article

**Longitudinal change in renal function after nephroureterectomy in patients with upper tract urothelial carcinoma**

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**A B S T R A C T**

**Aims:** Chronic kidney disease is a significant risk factor for several comorbidities and death. The longitudinal change in renal function after nephroureterectomy in patients with upper tract urothelial carcinomas and the risk of developing chronic kidney disease (CKD) was investigated.

**Materials and methods:** This retrospective study included 186 patients who underwent unilateral nephroureterectomy between 1997 and 2001. Creatinine data prior to and after the surgery were collected and the estimated Glomerular Filtration Rate (eGFR) were calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

**Results:** The cohort of 186 patients included 87 men and 99 women with a mean age of 67.2 years. Preoperative mean eGFR was 41.97 mL/minute/1.73 m\textsuperscript{2}. Eighty six percent of the patients’ preoperative eGFR were <60 mL/minute/1.73 m\textsuperscript{2}. The mean eGFR was 35.85 mL/minute/1.73 m\textsuperscript{2} at the end of the 5-year follow up. For the 26 patients with preoperative normal renal function, 17 patients (65.4%) had new chronic kidney diseases. Ten patients (5.4%) required hemodialysis at the end of the study.

**Conclusion:** In this study, it was found that the average renal function of the patients with upper tract urothelial carcinoma is not as good as the general population. More than half of the normal renal function patients have new onset chronic kidney disease after surgery. For preventing further deterioration of renal function, the implication of partial nephrectomy or segmental ureterectomy for selected patients with localized urothelial carcinoma should be re-examined. Besides, neoadjuvant chemotherapy should be considered for those who are not good candidates for local treatment.

**1. Introduction**

Chronic kidney disease is a significant risk factor for several comorbidities and death.\textsuperscript{1} There have been several reports suggesting that the incidence rate of chronic kidney disease is as high as 26% after radical nephrectomy in patients with renal cell carcinoma.\textsuperscript{2} Therefore, current guidelines recommend nephron-sparing surgery as the standard treatment for early-stage renal cell carcinoma.\textsuperscript{3,4} By contrast, radical nephroureterectomy (NUx) with bladder cuff excision remains a standard treatment in upper tract urothelial carcinoma (UTUC).\textsuperscript{5,6}

Compared with renal cell carcinoma, UTUC often results in obstructive uropathy rather than massive nephron loss. As the mechanism of renal function deterioration is different, it was proposed that long-term renal function change after renal surgery in patients with urothelial may be different from those who have renal cell carcinoma. However, to the best of our knowledge, few reports have discussed the prevalence of chronic kidney disease in patients who had received NUx because of UTUC.

The longitudinal change in renal function after NUx in patients with UTUCs was investigated and the new onset chronic kidney diseases in this patient group were examined. The findings are discussed in terms of the implications of nephron-sparing surgery.

**2. Materials and methods**

**2.1. Patient selection**

After obtaining the approval of the Institutional Review Board of Chang-Gung Memorial Hospital, clinical data on patients with
UTUC treated with unilateral NUx at Chang-Gung Memorial Hospital, Guishan Township, Taiwan between 1997 and 2001 were retrospectively reviewed. Of the 312 patients who received NUx, those with dialysis-dependent status and a solitary kidney prior to the surgery were excluded, and our analysis was limited to patients with no known renal parenchymal disease. A total of 186 patients were enrolled for the final analysis.

2.2. Statistical analysis

Preoperative evaluation of the patients included medical history, physical examination, laboratory studies (including serum creatinine level), urine routine analysis, chest X-ray, electrocardiogram, and abdominal computed tomography or magnetic resonance imaging. Tumor size was measured using the longest diameter of the tumor. Pathological staging was based on the 2009 American Joint Committee on Cancer 7th edition TNM staging system. The baseline and follow-up data of patients were obtained from the Institutional Review Board and medical records.

Perioperative renal function was evaluated using the serum creatinine level and the estimated glomerular filtration rate (eGFR). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Serum creatinine level was checked prior to and after surgery and during follow-up in the outpatient department.

The longitudinal change in renal function after surgery was investigated, and possible risk factors for postoperative new onset chronic kidney disease were analyzed, which was defined as an eGFR level <60 mL/min/1.73 m².

Preoperative and postoperative mean eGFR for all patients were compared using the paired t test. In addition, preoperative and postoperative incidence of eGFR <60 mL/min/1.73 m² was analyzed. The Chi-square test was used to evaluate the diversity between the groups. All statistical calculations were two tailed, and p < 0.05 was deemed significant. All statistical analysis was performed using SPSS software (version 20; SPSS Inc., Chicago, IL, USA).

3. Results

Table 1 lists demographic, tumor staging, and renal function data for the 186 patients enrolled in the analysis. Patients with UTUC were predisposed to have bad baseline renal function, as evidenced by the mean preoperative serum creatinine level (1.65 mg/dL) and mean preoperative eGFR (41.97 mL/min/1.73 m²). Most patients (n = 160, 86.0%) had a preoperative eGFR of <60 mL/min/1.73 m². Mean eGFR immediately after NUx was significantly lower than mean preoperative eGFR (41.97 mL/min/1.73 m² vs. 35.21 mL/min/1.73 m², p < 0.001). During postoperative Years 1–5, the mean eGFR varied between 31.69 mL/min/1.73 m² and 35.85 mL/min/1.73 m² (Fig. 1), but there was no significant change in eGFR during follow-up. These results indicate that the patient’s renal function deteriorated immediately after the surgery, but stabilized during follow-up.

In this study’s database, 160 (86.0%) of the 186 patients had preoperative chronic kidney disease. This result was consistent with that of previous literature, which has reported that these patients’ renal function tends to be worse compared with that of the general population. A previous study reported that the prevalence of clinically recognized CKD is 9.83%. This could explain the reason for impaired functions of the unaffected kidney prior to the surgery. An analysis of the relationship between preoperative chronic kidney disease and other comorbidities such as diabetes, hypertension, and coronary artery disease was attempted. However, we could not detect the trend of the relationship. This may be because of the small sample size. Besides medical comorbidities, aristolochic acid had been reported to be another factor that would impair the function of the unaffected kidney prior to the surgery. Owing to the limitation of this retrospective study, we were unable to collect adequate data for analysis. By contrast to previous studies, which only recorded postoperative serum creatinine levels once, this report followed the longitudinal change of these patients’ renal function. It was observed that the patients’ renal function deteriorated immediately after surgery. However, no further renal function deterioration was observed in the following years.

The distribution of each chronic kidney disease stage is shown in Fig. 2. During the 5-year follow-up, 19 of the 26 patients (73.1%) with normal preoperative renal function developed chronic kidney disease after the surgery. For the 186 patients who underwent NUx,

![Fig. 1. Mean eGFR over time. Renal function change in the first 5 postoperative years.](image-url)
the 5-year cancer-specific survival and overall survival rate were 90.2% and 82.6%, respectively (Fig. 3A and B). The comparison between tumor location and perioperative renal function change is listed in Table 2. There is a trend that ureter tumors had poor renal outcome after the surgery. However, no statistical significance is observed.

In this study series, after the 5-year follow-up, 10 patients (5.4%) required hemodialysis after the surgery. Eight patients were female and the mean age at operation was 63 years. The mean preoperative eGFR was 12.87 mL/minute/1.73 m² and the mean time to dialysis was 2.77 years (Fig. 3C).

4. Discussion

The study’s database includes the renal outcome of patients who retained a solitary kidney after receiving a unilateral
nephroureterectomy to treat UTUC. The general belief was that most people could lead a normal life with only one kidney; however, this viewpoint has been evolving since Rosenthal et al first introduced the concept of nephron-sparing surgery in 1984. In addition, a decrease in nephron number has been shown to correlate with the progressive impairment of renal function and hypertension. In the following years, several urologists reported that nephron-sparing surgery led to a better renal outcome than radical nephrectomy in treating renal cell carcinoma. However, the role of nephron-sparing surgery in treating urothelial carcinoma remains undetermined. To the best of our knowledge, there are few papers that have discussed this issue. Lane et al collected a cohort of 336 patients and analyzed their perioperative change in renal function. In their study, the patients’ mean preoperative eGFR, which was 61.7 mL/minute/1.73 m², deteriorated to 47.9 mL/minute/1.73 m² after surgery. However, they only collected postoperative serum creatinine data for 3 months, rather than collecting longitudinal data. In addition, this research group used the abbreviated Modification in Diet and Renal Disease (MDRD) study equation to calculate eGFR. This equation has limited usefulness because it systematically underestimates measured GFR at higher values. The Chronic Kidney Disease Epidemiology Collaboration research group proposed another equation in 2009, which yields higher eGFR at lower creatinine levels.

We attempted to determine the group of patients that would experience a poor renal outcome. There were no significant preoperative conditions that could be used to predict renal outcome. As for the 10 patients who required hemodialysis after the surgery, significant predisposing factors (Table 3) were not observed. However, it was observed that patients whose renal function

![Fig. 3. Survival of patients with upper tract urothelial carcinoma who had received nephroureterectomy and bladder cuff excision: (A) overall survival; (B) cancer-specific survival; (C) survival curve of freedom from hemodialysis. The overall and cancer-specific survival was calculated. The 5-year overall and cancer-specific rates are 82.6% and 90.2% respectively. A total of 10 patients became hemodialysis-dependent at the time of data collection. Cum – cumulative.]

<table>
<thead>
<tr>
<th>Tumor location (n)</th>
<th>Mean eGFR (mL/min/1.73 m²)</th>
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<tbody>
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<td></td>
<td>PreOP</td>
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<td>Renal pelvis (104)</td>
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<td>Renal calyces (20)</td>
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<td>Ureter (5)</td>
<td>44.64</td>
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<tr>
<td>Multifocal (57)</td>
<td>41.34</td>
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worsened immediately after surgery tended to have a worse 5-year renal outcome compared with other patients. Therefore, careful observation of this group of patients is suggested.

The mainstream treatment for UTUC is nephroureterectomy and bladder cuff excision.\(^5\)\(^6\) In this observation, the renal function will be damaged even if the patient still has a healthy kidney. Therefore, these results indicated that maybe radical surgery is an overtreatment for all patients with upper tract urothelial carcinoma. As the enrolled patients’ preoperative overall renal function was normal and no significant cortex thinning was observed, the split renal function test is not routinely performed. If nephron-sparing surgery is taken into consideration, split renal function tests, such as MAG3 renal scan, may play an important role in decision-making when treating early-staged upper tract urothelial carcinoma. However, the data is not sufficient for adequate analysis due to the limitation of a retrospective study. In previous studies, Lane et al\(^10\) observed that 52% of the patients with UTUC had chronic kidney disease at the time of diagnosis and experienced a median 21% relative reduction in renal function after receiving NUx. The chronic kidney disease prevalence rate significantly increased to 78% after the surgery. As renal function deteriorated, these patients were unable to tolerate full-dose cisplatin-based chemotherapy. As a result, they suggest that neoadjuvant chemotherapy should be considered while treating patients with UTUC.\(^10\)

There are a few limitations in this study. First, this was a single-center retrospective review; therefore, some cases were lost to follow-up over time. As a result, the patients’ survival rate may not have been accurately estimated. In addition, the adjuvant therapy protocols varied and cannot offer a better illustration of oncological outcome. Further prospective observation is needed to evaluate the detailed condition of these patients’ natural history. The cohort concluded the renal function change in the patients who received NUx was because of upper tract urothelial carcinoma. This report is different from that of the other studies, which only recorded one creatinine data after the surgery, because a temporal change of the patients’ renal function was offered. During the 5-year follow-up, most of the patients’ renal function worsened. Considering the possible comorbidities, which may be induced by poor renal function, local ablative treatment or partial nephrectomy in selected patients should be considered. As for those patients who are not suitable for local treatment, neoadjuvant chemotherapy should be considered as an alternative treatment.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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Acknowledgments

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References


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Table 3

Preoperative factors associated with postoperative hemodialysis-dependent status.

<table>
<thead>
<tr>
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