

# Risk factors associated with ineligibility of adjuvant cisplatin-based chemotherapy after nephroureterectomy

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**Purpose:** Radical nephroureterectomy (RNU) is a standard treatment for upper urinary tract urothelial carcinoma. However, RNU can result in decreased renal function and cannot be treated with adjuvant chemotherapy. We performed a risk group stratification analysis to determine the preoperative factors that are predictive of diminished renal function after RNU.

**Materials and methods:** We retrospectively evaluated the medical records of all patients who underwent nephroureterectomy for upper urinary tract urothelial carcinoma at the Chang Gung Memorial Hospital from 2001 to 2008. We analyzed the association between perioperative glomerular filtration rate and preoperative parameters including cancer characteristics, serum creatinine level, and kidney size measured on computed tomographic images.

**Results:** A total of 242 patients fulfilled the inclusion criteria. The average decrease in renal function 1 month after RNU was 19.7%. Using 60 mL/min/1.73 m<sup>2</sup> as the eligibility cutoff for cisplatin-based chemotherapy, 42.1% of the population was eligible prior to nephroureterectomy, whereas following surgery only 15.2% remained eligible. Using a cutoff of 45 mL/min/1.73 m<sup>2</sup>, 59.9% of the cohort was eligible for fractionated cisplatin dosing preoperatively, whereas only 32.6% remained above the cutoff postoperatively. The most significant predictors of poor postoperative renal function were body mass index >25 kg/m<sup>2</sup>, age >65 years, contralateral kidney length less than 10 cm, and absence of ipsilateral hydronephrosis.

**Conclusion:** Our results suggest that older age, higher body mass index, smaller contralateral renal length, and absence of ipsilateral hydronephrosis are predictive of decreased renal function after RNU.

**Keywords:** transitional cell, carcinoma, kidney, adjuvant chemotherapy, upper tract urothelial carcinoma

## Introduction

Upper urinary tract (UUT) urothelial carcinoma (UC) is a relatively rare tumor, accounting for only 5%–10% of all renal tumors and 5%–6% of urothelial tumors.<sup>1–3</sup>

Radical nephroureterectomy (RNU) with bladder cuff excision remains the standard treatment of upper-tract urinary urothelial carcinoma.<sup>4</sup> Although RNU with bladder cuff excision is a very effective treatment for organ-confined UUT-UC, it results in less than optimal outcome for patients with nodal and distant metastatic disease.<sup>3,5,6</sup>

The 5-year cancer-specific survival rate has been reported to be >90% for patients with stage pT1 UUT-UC; however, the survival rate for patients with pT3 stage disease is lower than 50%.<sup>7</sup> Adjuvant chemotherapy is an effective treatment modality for the high tumor staging and local advanced urothelial carcinoma.<sup>8</sup> Neoadjuvant chemotherapy before radical cystectomy has been reported to have a survival benefit

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for patients with bladder urothelial carcinoma.<sup>9,10</sup> However, few studies have shown a survival benefit for neoadjuvant chemotherapy before RNU of the UC.<sup>11,12</sup>

Although neoadjuvant chemotherapy before RNU has been performed in more and more patients, it is not the standard procedure yet. Taken together, it is known that radical nephrectomy can result in decreased renal function in patients with renal cell cortical tumors.<sup>13</sup> The same condition has been observed in patients with upper urinary tract urothelial carcinomas after RNU, and that deteriorated renal function may interfere with adjuvant chemotherapy.

We aimed to clarify the relationship between RNU and postoperative renal function in patients with upper urinary tract urothelial carcinoma. We also wanted to find out if there is an adequate predictor for marked post-RNU renal function deterioration.

## Materials and methods

We retrospectively reviewed the medical charts of patients with upper urinary tract urothelial carcinoma who received RNU from 2001 to 2008. Data of interest included patient characteristics (age at surgery, sex, body height, body weight, body mass index [BMI], and underlying disease), cancer characteristics (tumor location, tumor stage based on the seventh edition American Joint Committee on Cancer criteria, pathological grade, and tumor histology), serum creatinine level (pre-operation and 1-month post-operation), and kidney size on computed tomographic images (largest kidney length and width on coronal view, and parenchymal thickness).

Renal estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease equation:

$$\text{eGFR} = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \quad (1)$$

multiplied by 0.742 for female patients and by 1.212 for male patients.<sup>14</sup>

eGFR before and after surgery was compared using serum creatinine drawn closest to 1 month after surgery (range: 4 weeks to 6 weeks after surgery). This timing was selected to best approximate the measured serum creatinine that would affect the delivery of adjuvant chemotherapy. We excluded patients with incomplete medical records, end-stage renal disease under hemodialysis or bilateral disease, and patients who had previously received neoadjuvant chemotherapy or other treatment modalities that could potentially influence renal function.

We used binary logistic regression to assess the correlation of each factor with decreased renal function (45 and 60 mL/min/1.73 m<sup>2</sup>). We also calculated the odds ratio of each predictor of ineligibility for adjuvant chemotherapy after RNU. Multivariate analysis was performed to find the most significant predictors.

All statistical calculations were two-tailed, and  $P < 0.05$  was deemed significant. SPSS version 17 (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis.

## Results

A total of 242 patients fulfilled the criteria for analysis. The median age at surgery was 71 years (range, 42–83 years) and the male-to-female ratio was 1.08 (126 versus 116). Other patient characteristics are listed in Table 1.

The mean eGFR before RNU was 56.9±19.6 mL/min/1.73 m<sup>2</sup>, while mean postoperative eGFR was 45.7±16.6 mL/min/1.73 m<sup>2</sup>. The average renal function decrease

**Table 1** Clinicopathological characteristics of the 242 study patients

Age, years	
Median (range)	71.0 (42–83)
Sex, n (%)	
Male	126 (52)
Female	116 (48)
Body mass index, kg/m <sup>2</sup>	
Median (IQR)	25.10 (13–37)
Primary tumor location, n (%)	
Renal pelvis	152 (63)
Ureteral	90 (37)
Surgical approach, n (%)	
Open	162 (63)
Laparoscopic	80 (22)
Tumor histology, n (%)	
Papillary	17 (6.9)
Infiltrating	225 (93.1)
pT stage, n (%)	
pTa-pTis-pT1	65 (26.8)
pT2	43 (17.8)
pT3	87 (36.1)
pT4	47 (19.3)
Lymph node status, n (%)	
pN0	212 (87.7)
pN+	30 (12.3)
M stage, n (%)	
pM0	232 (96.0)
pM1	10 (4.0)
Contralateral kidney size, cm	
Length, median (range)	10.16 (7.0–12.8)
Width, median (range)	5.1 (3.8–6.9)
Thickness, median (range)	2.0 (1.2–2.3)

**Abbreviations:** IQR, interquartile range; M stage, metastasis stage; pT stage, primary tumor stage.

1 month after RNU was 19.7% and the average renal function decrease 2 years after surgery was 22.1%. Of the 242 patients, 102 (42.1%) had a preoperative eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> and 145 (59.9%) had an eGFR  $\geq 45$  mL/min/1.73 m<sup>2</sup>.

Using 60 mL/min/1.73 m<sup>2</sup> as the eligibility cutoff for cisplatin-based chemotherapy, 42.1% of the population was eligible prior to nephroureterectomy, whereas following surgery only 15.2% remained eligible. Using a cutoff of 45 mL/min/1.73 m<sup>2</sup>, 59.9% of the cohort was eligible for fractionated cisplatin dosing preoperatively, whereas only 32.6% remained above the cutoff postoperatively.

Using 60 mL/min/1.73 m<sup>2</sup> as the cutoff, we analyzed the correlation and odds ratio of possible predictors. The

significant factors were age at operation, BMI, preoperative eGFR, history of hypertension, contralateral kidney size, and ipsilateral hydronephrosis. The detailed data including other factors are listed in Table 2.

Using 45 mL/min/1.73 m<sup>2</sup> as the cutoff, the significant predictors were BMI, preoperative serum creatinine level, preoperative eGFR, tumor stage, contralateral kidney size, and ipsilateral hydronephrosis. Other factors and detailed results are listed in Table 3.

We performed multivariate analyses to define the most significant predictors. We found that patients with younger age, lower BMI, larger contralateral renal length, and ipsilateral hydronephrosis were more likely to remain

**Table 2** Clinicopathological characteristics of 102 patients who met the eligibility cutoff of 60 mL/min/1.73 m<sup>2</sup> for cisplatin-based chemotherapy

Characteristics	Total (n=102)	(n=37) eGFR $\geq 60$ mL/min	(n=65) eGFR <60 mL/min	Sig	OR	95% CI for OR	
Age (years), mean $\pm$ SD	65.82 $\pm$ 10.9	63.0 $\pm$ 13.2	67.43 $\pm$ 9.02	0.001	1.068	1.027	1.112
Sex, n							
Male	57	26	31	0.029	2.592	1.101	6.103
Female	45	11	34				
BMI (kg/m <sup>2</sup> ), mean $\pm$ SD	24.7 $\pm$ 4.5	21.56 $\pm$ 4.79	26.47 $\pm$ 3.25	<0.001	1.581	1.261	1.981
Preoperative Scr (mg/dL), mean $\pm$ SD	0.99 $\pm$ 0.16	0.96 $\pm$ 0.19	1.00 $\pm$ 0.15	0.236	4.645	0.366	58.984
Preoperative eGFR (mL/min/1.73 m <sup>2</sup> ), mean $\pm$ SD	71.97 $\pm$ 11.3	79.78 $\pm$ 13.5	68.84 $\pm$ 6.7	<0.001	0.892	0.845	0.942
History of diabetes, n							
Yes	22	6	16	0.325	1.687	0.596	4.776
No	80	31	49				
History of HT, n							
Yes	33	6	27	0.011	3.671	1.345	10.017
No	69	31	38				
Tumor characteristics							
Tumor histology, n							
Papillary	6	4	2	0.133	3.818	0.664	21.947
Infiltrating	96	33	63				
Tumor side, n							
Left	74	21	30	0.304	0.653	0.29	1.472
Right	71	16	35				
Tumor stage, n							
T1+Ta	23	8	15	0.741	0.938	0.641	1.372
T2	20	4	16				
T3	33	16	17				
T4	26	9	17				
Node status, n							
N0	91	30	61	0.056	0.281	0.076	1.035
N+	11	7	4				
Contralateral kidney size (cm), mean $\pm$ SD							
Length	10.50 $\pm$ 1.1	11.21 $\pm$ 0.89	10.1 $\pm$ 1.0	<0.001	0.342	0.212	0.553
Width	5.13 $\pm$ 1.12	5.59 $\pm$ 0.7	4.86 $\pm$ 1.24	0.003	0.448	0.265	0.756
Thickness	0.71 $\pm$ 0.09	0.75 $\pm$ 0.08	0.69 $\pm$ 0.09	0.002	0	0	0.05
Hydronephrosis, n							
Yes	77	34	43	0.007	0.172	0.048	0.625
No	25	3	22				

**Abbreviations:** BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HT, hypertension; OR, odds ratio; Scr, serum creatinine level; SD, standard deviation; Sig, P-value.

**Table 3** Clinicopathological characteristics of 145 patients who met the eligibility cutoff of 45 mL/min/1.73 m<sup>2</sup> for cisplatin-based chemotherapy

Characteristics	Total (n=145)	(n=102) eGFR ≥45 mL/min	(n=43) eGFR <45 mL/min	Sig	OR	95% CI for OR	
Age (years), mean ± SD	66.9±10.1	66.82±10.8	68.0±10.0	0.754	1.006	0.971	1.042
Sex, n							
Male	74 (51.0)	47 (67.1)	27	0.068	0.506	0.244	1.052
Female	71 (49.0)	55 (66.2)	16				
BMI, kg/m <sup>2</sup> , mean ± SD	24.51±4.54	23.48±4.40	26.97±3.90	<0.001	1.243	1.111	1.391
Scr, mg/dL, mean ± SD	1.06±0.193	1.00±0.166	1.19±0.19	<0.001	493.082	36.913	6,586.62
eGFR, mL/min, mean ± SD	66.59±13.5	69.59±14.0	59.48±8.83	<0.001	0.927	0.892	0.962
History of diabetes, n							
Yes	35	28	7	0.156	0.514	0.205	1.288
No	110	74	36				
History of HT, n							
Yes	61	45	16	0.442	0.751	0.361	1.56
No	84	57	27				
Tumor characteristics							
Tumor histology, n							
Papillary	10	6	4	0.462	0.609	0.163	2.278
Infiltrating	135	96	39				
Tumor side, n							
Left	74	51	23	0.701	1.15	0.563	2.348
Right	71	51	20				
Tumor stage, n							
T1+Ta	38	14	24	<0.001	0.335	0.222	0.505
T2	25	20	5				
T3	48	34	14				
T4	34	34	0				
Node status, n							
N0	134	95	39	0.614	1.392	0.386	5.025
N+	11	7	4				
Contralateral kidney size (cm), mean ± SD							
Length	10.42±0.99	10.6±1.06	9.9±0.56	<0.001	0.399	0.241	0.66
Width	5.12±1.00	5.4±0.82	4.57±1.17	<0.001	0.386	0.229	0.651
Thickness	0.70±0.09	0.73±0.09	0.64±0.76	<0.001	0.001	0	0.002
Hydronephrosis, n							
Yes	107	83	24	0.002	0.289	0.132	0.632
No	38	19	19				

**Abbreviations:** BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HT, hypertension; OR, odds ratio; Scr, serum creatinine level; SD, standard deviation; Sig, *P*-value.

eligible for full-dose cisplatin-based chemotherapy after the surgery. When an eGFR value of 45 mL/min/1.73 m<sup>2</sup> was used as the cutoff point, we found that all of those variables, with the exception of age, remained significant predictors (Table 4).

Receiver operating characteristic curve analysis revealed that BMI >25 kg/m<sup>2</sup>, age >65 years, and contralateral kidney length <10 cm were the most significant predictors of poor postoperative renal function.

## Discussion

The prognosis of upper urinary tract urothelial cell carcinoma has been shown to be significantly related to tumor stage.<sup>15</sup>

Margulis et al reported that the 5-year survival rates of patients with positive lymph nodes were 35.3% for patients with pT2 disease, 74.7% for patients with pT3 disease, and 54% for those with pT4 disease.<sup>7</sup> Of the patients with upper urinary tract urothelial carcinoma, patients with pathologic stage T2 or higher accounted for more than half of the evaluated patients.<sup>7</sup> Based on the abovementioned evidence, RNU alone may be sufficient for localized upper urinary tract urothelial carcinoma. For patients with locally advanced disease or high tumor staging and suspicious metastatic disease, multimodal therapy may be required for better outcome.

There are conflicting data regarding the efficacy of adjuvant chemotherapy for locally advanced disease and

**Table 4** Multivariate analysis of preoperative variables for disease-specific survival

	P-value	OR	(95% CI for OR)	
<b>Post-eGFR&lt;60</b>				
Age	0.007	1.987	1.204	3.279
BMI	0.005	10.392	2.046	52.788
Preoperative eGFR	0.002	0.554	0.385	0.798
Contralateral renal length	0.012	0.012	0.000	0.386
Hydronephrosis	0.011	0.000	0.000	0.065
<b>Post-eGFR&lt;45</b>				
BMI	<0.001	1.493259	1.243	1.793
Preoperative eGFR	<0.001	0.8396842	0.769	0.916
Contralateral renal length	0.064	0.346669	0.113	1.063
Contralateral renal width	0.010	0.3749981	0.178	0.788
Contralateral renal thickness	0.055	0.1191959	0.014	1.050
Hydronephrosis	<0.001	0.0476294	0.010	0.235

**Abbreviations:** BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

metastatic disease. Hellenthal et al and Vassilakopoulou et al reported that systemic adjuvant chemotherapy is not beneficial.<sup>16,17</sup> As for neoadjuvant chemotherapy, Matin et al and Rajput et al reported that systemic neoadjuvant chemotherapy could achieve a complete remission (pT0) rate of 15%,<sup>11,12</sup> and some studies have also reported that neoadjuvant chemotherapy improves overall survival.<sup>10,11,16,17</sup> Considering the established effect of neoadjuvant chemotherapy in bladder urothelial cell carcinoma, cisplatin-based chemotherapy may be more effective than neoadjuvant therapy for upper urinary tract urothelial cell carcinoma.<sup>10,17</sup>

On the other hand, cisplatin-based chemotherapy requires adequate renal function, which may decrease after RNU.<sup>18–23</sup> Thus, neoadjuvant cisplatin-based chemotherapy might be a more appropriate treatment for patients with locally advanced or metastatic upper urinary tract urothelial cell carcinoma.

In our study, we set the cutoff points for renal function as an eGFR of 60 mL/min/1.73 m<sup>2</sup> and 45 mL/min/1.73 m<sup>2</sup>. An eGFR value of 60 mL/min/1.73 m<sup>2</sup> is used to define eligibility for full-dose cisplatin therapy and also represents the transition into stage III chronic kidney disease, while 45 mL/min/1.73 m<sup>2</sup> may be a compromise between the eGFR of 40 mL/min/1.73 m<sup>2</sup> that was used as the lower limit to exclude patients for reduced-dose cisplatin by Hussain et al and the eGFR of 50–55 mL/min/1.73 m<sup>2</sup> that has been used in several European studies to qualify patients as ineligible for cisplatin.<sup>23,24</sup>

According to our findings as well as those published previously, 37%–49% of patients had a preoperative eGFR of more than 60 mL/min/1.73 m<sup>2</sup>, making them eligible for full-dose cisplatin-based chemotherapy. The percentage decreased

to 19% after RNU. At a cutoff of 45 mL/min/1.73 m<sup>2</sup>, the number of patients eligible for cisplatin-based chemotherapy decreased from 60%–80% to 33%–55%.<sup>23–26</sup>

A number of studies have reported similar findings, namely that a decrease in postoperative eGFR may hinder the use of neoadjuvant chemotherapy and possibly result in poor outcome. Neoadjuvant chemotherapy, therefore, should be prompted in select high-risk patients who may experience significant renal function deterioration after the operation.

In our study, we found that patients >65 years, patients with a BMI >25 kg/m<sup>2</sup>, patients with a contralateral kidney length <10 cm, and patients without ipsilateral hydronephrosis are at significant risk of decreased renal function after surgery. In that group, patients with a disease stage of T2 or higher and patients with metastatic disease should undergo neoadjuvant chemotherapy rather than adjuvant chemotherapy.

It is assumed that in elderly patients and patients with higher BMI, the remnant kidney may barely support the physical need, making it easy to fail under stress.

Besides, in the patients who had unilateral disease and suffered from obstructive uropathy before RNU, the other healthier kidney accounted for more renal function. This means that the post-RNU renal function would be closer to the pre-RNU renal function. That is why we found that patients with ipsilateral hydronephrosis and larger contralateral kidney would had less renal function loss after the surgery.

Our study is limited by its retrospective nature and by the small number of patients included for analysis. In addition, renal size or cortical thickness does not accurately represent the renal function of the remnant kidney. Renograms may

offer more information. A prospective study with a larger sample size is needed to confirm our findings.

## Conclusion

In our study, only some of the patients with upper urinary tract urothelial cell carcinoma were eligible for cisplatin-based chemotherapy, and this proportion decreased significantly after RNU. To increase survival outcome, patients of advanced age, those with higher BMI values, patients with smaller contralateral renal length, and patients without evidence of ipsilateral hydronephrosis are likely to develop renal insufficiency after surgery and should be treated with neoadjuvant chemotherapy.

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## Disclosure

The authors report no conflicts of interest in this work.

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