



## Original article

# The effect of contralateral kidney volume on renal function after radical nephroureterectomy: Implications for eligibility for neoadjuvant chemotherapy for upper tract urothelial cancer

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## Abstract

**Purpose:** We investigated the effect of preoperative contralateral kidney (CK) volume on renal function after radical nephroureterectomy (RNU).

**Methods:** We reviewed 630 patients who underwent RNU between September 1994 and December 2013. Of these 630 patients, 135 patients with advanced upper tract urothelial cancer were ultimately included. Preoperative CK volume was measured from computed tomography images of the venous phase using a specialized volumetric program. Glomerular filtration rate (GFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations and checked preoperatively, 7 days, 1, 3, and 12 months postoperatively.

**Results:** The mean age at surgery was 62.1 (10.1) years and the mean CKD-EPI GFR was 73.8 (75.5) ml/min/1.73 m<sup>2</sup>. After RNU, new-onset CKD was identified in 69 (51.1%) patients. On multivariate logistic regression analysis, high body mass index (95% CI: 1.08–1.51,  $P = 0.005$ ), low preoperative CKD-EPI GFR (95% CI: 0.92–0.98,  $P = 0.037$ ), and low CK volume (95% CI: 0.96–0.99,  $P < 0.001$ ) were associated with new-onset CKD at 1 month after RNU. There was a positive correlation between CK volume and CKD-EPI GFR at 1 month after RNU (Spearman  $\rho = 0.495$ ,  $P < 0.001$ ). When stratified according to CK volume, CK volume less than 150 ml was significantly associated with new-onset CKD after RNU (95% CI: 2.49–26.29,  $P = 0.001$ ).

**Conclusions:** High body mass index, low preoperative CKD-EPI GFR, and low CK volume are significantly associated with new-onset CKD. Therefore, they could be used to identify patients eligible for neoadjuvant chemotherapy in upper tract urothelial cancer. © 2016 Elsevier Inc. All rights reserved.

*Keywords:* Urothelial carcinoma; Nephroureterectomy; Kidney volume; Chronic kidney disease; Chemotherapy

## 1. Introduction

Radical nephroureterectomy (RNU) with bladder cuff excision is the gold standard treatment of upper tract urothelial cancer (UTUC) [1]. With more aggressive tumor characteristics and deferred diagnosis or treatment, however, 34% to 37% of patients already present advanced disease state greater than pathologic stage T3 (pT3) or lymph node involvement or both at the time of RNU [2,3]. As a result, UTUC provides

poor prognosis with a 5-year cancer-specific survival (CSS) reported to be less than 45% in patients with  $\geq$ pT3 [4], and 35% in patients with lymph node involvement [5]. Collectively, these findings indicate that RNU alone is insufficient to treat these patients, and that multimodal treatment strategies should be considered.

To date, although there are insufficient data to provide definite guidelines for the use of perioperative chemotherapy, cisplatin-based chemotherapy is usually recommended in advanced disease, based on the results of studies on muscle-invasive bladder cancer [6,7]. In addition, recent retrospective studies have shown that perioperative chemotherapy has some

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benefits in overall survival and CSS [8,9]. On the contrary, several studies have reported substantial decline of renal function after RNU [2,10]. In these studies, glomerular filtration rates (GFR) were greater than 60 ml/min/1.73 m<sup>2</sup> in 48% to 49% of patients preoperatively, but declined to 19% to 22% of patients after RNU. As the most common side effect of cisplatin-based chemotherapy is nephrotoxicity [11], patients with decreased renal function after RNU would have reduced eligibility for adjuvant chemotherapy. Therefore, predicting changes in renal function after RNU and identifying patients eligible for neoadjuvant chemotherapy (NAC) in UTUC are issues of critical importance.

After RNU, only the contralateral kidney (CK) remains; thus its functioning is essential to maintain postoperative renal function. A significant association between CK volume and postoperative GFR is well documented in patients with renal cell carcinoma [12], but this correlation has not been fully examined in the context of UTUC. Therefore, in this study, we analyzed the association between preoperative CK volume and alterations in renal function over time after RNU to investigate the effect of preoperative CK volume on patient eligibility for NAC for UTUC.

## 2. Materials and methods

### 2.1. Patients

After receiving approval from the Institutional Review Board of Samsung Medical Center, we retrospectively reviewed a prospectively maintained database of 630 patients who underwent RNU for UTUC between September 1994 and December 2013. Of 630 patients, as adjuvant chemotherapy is not recommended in patient with T2 or less, we identified 271 (43%) patients with advanced pathologic results (defined as pathologic stage greater than T3 or lymph node involvement or both). Of these patients, we excluded patients without preoperative computed tomography (CT) scans of the venous phase or delay phase ( $n = 61$ ) or measurement of serum creatinine levels or all of these ( $n = 7$ ) at any time points after RNU. We also excluded patients with preoperative Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) GFR less than 60 ml/min/1.73 m<sup>2</sup> ( $n = 68$ ), because we chose this value as a possible cut-off for eligibility for full dose cisplatin-based NAC. Ultimately, 135 patients with preoperative enhanced CT, serum creatinine level measurements at any time points, and CKD-EPI GFR  $\geq 60$  ml/min/1.73 m<sup>2</sup> were included in this study. No patients had any history of nephrotoxic chemotherapy preoperatively.

### 2.2. Data collection

Clinicopathological characteristics of patients, including age at surgery, sex, comorbidities such as hypertension and

diabetes mellitus, body mass index (BMI), smoking history, American Society of Anesthesiologists (ASA) score, operation side, and tumor location were obtained from medical records at the time of surgery. To identify changes in renal function over time, serum creatinine levels were measured preoperatively, 7 days, 1 month, 3 months, and 12 months after RNU. We calculated GFR using the CKD-EPI equations in consideration of age, sex, and serum creatinine level [13]. CKD was defined as when the calculated CKD-EPI GFR decreased to less than 60 ml/min/1.73 m<sup>2</sup> at 1 month after RNU [14]. We divided patients into 2 groups according to occurrence of new-onset CKD after RNU and analyzed serial changes of CKD-EPI GFR.

To measure CK volume, we used preoperative CT images performed within 1 month of surgery. CT scans were performed using the standard clinical abdomen-pelvic image protocol taken in 5 mm thickness with a 64-multidetector CT scanner (GE Medical Systems, Milwaukee, WI). Renal parenchyma was considered as normal functioning tissues not containing the pelvocalyceal system, blood vessels, renal sinus fat tissue, or renal cysts when enhanced on CT scans. Three-dimensional (3D) kidney volume was estimated using a specialized volumetric software program, Xelis (Infinit, Seoul, South Korea), on CT images of a preoperative venous phase [15]. We delineated the boundaries of the enhancing renal parenchyma with a threshold of 50 HU. The specialized volumetric program then calculated CK volumes automatically by creating 3D reconstructions.

### 2.3. Statistical analysis

Continuous and categorical variables were expressed as mean (standard deviation, range) and absolute values (percentage). An independent *t*-test and chi-square test or Fisher's exact test were used to compare clinicopathological characteristics between the 2 groups. Multivariate logistic regression analysis was performed to identify predictors associated with new-onset CKD after RNU. Spearman's rank correlation was performed to confirm the correlation between CK volume and CKD-EPI GFR at 1 month after RNU. To further analyze the effect of CK volume on new-onset CKD, multivariate logistic regression analysis was performed by adjusting for predictors associated with new-onset CKD after RNU. All statistical analyses were performed with IBM SPSS version 20.0 (IBM Corp. Armonk, NY). Two-tailed  $P < 0.05$  were considered statistically significant.

## 3. Results

The baseline clinicopathological characteristics of 135 patients who underwent RNU are presented in Table 1. Among the 135 total patients, the mean age at surgery was 62.1 (10.1, 33.0–86.0) years and 92 (68.1%) patients were

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