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Renal function change after radical cystectomy for urothelial carcinoma patients with a solitary kidney may be independent of urinary diversion type

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Purpose: To compare renal function change by urinary diversion (UD) type (ileal conduit [IC] vs. neobladder [NB]) in patients with a single kidney who underwent radical cystectomy (RC) due to bladder cancer.

Materials and Methods: We evaluated the renal function change in 86 patients with a single kidney who underwent RC between January 1999 and August 2022. Renal function was assessed using serum creatinine, serum estimated glomerular filtration rate (eGFR), eGFR difference value (preoperative and follow-up values), and eGFR difference proportion (eGFR difference value/preoperative eGFR) at 1, 3, 6, 12, 24, 36, 48, and 60 months. In addition, multiple definitions of eGFR decline were evaluated: 10 points, 10%, and 20% decline in eGFR. Cox regression models were used to identify risk factors of eGFR decline-free, recurrence-free, overall, and cancer-specific survival rates.

Results: A total of 54 patients (62.8%) underwent IC, whereas 32 (37.2%) underwent NB. Baseline characteristics were similar between the two groups except for age and body mass index. Renal functions over time by various methods did not differ significantly between the IC and NB groups. Furthermore, eGFR decline-free survival rate using different definitions was similar between the IC and NB groups. Overall survival, recurrence-free survival, and cancer-specific-free survival rates were not different between the IC and NB groups.

Conclusions: UD type (IC vs. NB) did not impact the renal function change of patients with a single kidney who underwent RC. Therefore, patients with a single kidney might be considered to be an indication of NB.

Keywords: Bladder cancer; Kidney function tests; Radical cystectomy; Single kidney; Urinary diversion

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INTRODUCTION

Bladder cancer is the tenth most commonly diagnosed cancer according to the 2020 world statistics for men and women [1]. The national cancer registration statistics of South Korea in 2019 also reported bladder cancer as the tenth most prevalent cancer (5-year survival rate, 87.6%) in South Korea for both sexes, and 72.5% of affected male patients are diagnosed at localized stages [2]. Of the bladder cancers, muscle-invasive bladder cancer has a poor progno-

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sis with high morbidity and mortality, and the standard treatment comprises radical cystectomy (RC) and urinary diversion (UD) [3-5]. Although RC with UD is the treatment of choice, the operation lowers the quality of life because of surgery-related complications and comorbidities [6,7]. In particular, most of the late complications (3 months after RC) are related to UD; therefore, surgeons should consider preoperative factors before determining the UD type [8,9]. Before deciding on the type of diversion, patient age, medical history (including neurological and psychiatric illnesses), performance status, life expectancy, and previous abdominal operation or radiation history are considered [10].

Based on previous studies, complex forms of UD for patients with impaired renal function or a single kidney are not recommended [8,11,12]. However, a previous retrospective study demonstrated that the likelihood of estimated glomerular filtration rate (eGFR) decline did not significantly differ according to UD type in patients with compromised baseline renal function [13]. Many surgeons do not consider a neobladder (NB) when performing RC for patients with a single kidney because of the presumption that NB may further decrease renal function than an ileal conduit (IC). However, there is a lack of evidence. Therefore, we aimed to compare the change in renal function after RC in patients with a single kidney, between the IC and NB groups.

MATERIALS AND METHODS

1. Patients

This retrospective study included 86 patients with a single kidney who underwent RC between January 1999 and August 2022 at Seoul National University Hospital. We included patients with a single kidney who underwent ipsilateral nephrectomy before, concurrently with, or after RC. Those who did not have serum creatinine laboratory results within 90 days before surgery or who underwent cystectomy alone without UD were excluded.

All patients underwent RC using standard techniques: Studer NB. The decision for UD was according to the surgeon's discretion, accounting for the patient's age, comorbidities, disease status, and preferences, as well as the necessity for a negative urethral margin on an intraoperative frozen section.

The present study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Hospital (approval number: H-2208-173-1354). Informed consent was obtained by all subjects when they were enrolled.

2. Primary outcome

The primary outcome was renal function change after RC, which was measured using creatinine level and eGFR. The eGFR was calculated using the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration and Modification of Diet in Renal Disease (MDRD) study equations. The CKD-EPI equation has been suggested as the most accurate way to quantify eGFR in urology patients [14,15].

To test the consistency of the change in renal function following RC, we used various methods to assess the renal function, including (i) serum creatinine level, (ii) eGFR (CKD-EPI and MDRD), (iii) eGFR difference value (preoperative value–follow-up value), and (iv) eGFR difference proportion (eGFR difference value/preoperative eGFR) at 1, 3, 6, 12, 24, 36, 48, and 60 months [16-19]. Furthermore, eGFR decline was assessed using various definitions: (i) 10 points decline in eGFR, (ii) 10% decline in eGFR, and (iii) 20% decline in eGFR [13,19].

3. Secondary outcome

Secondary outcomes were the eGFR decline-free survival, recurrence-free survival, overall survival, and cancer-specific survival.

4. Statistical analysis

Patients grouped based on UD were compared using a one-way analysis of variance (ANOVA) for continuous variables and a chi-square test for categorical variables. Categorical variables are presented with a number (percentage), and continuous variables with mean value±standard deviation (SD). All p-values were calculated by the chi-square test for categorical variables and the t-test for continuous variables. Serial changes in renal function at each time were compared by independent t-test and two-way repeated ANOVA test between the IC and NB group. Because of the type 1 error possibility from the multiple t-test, we applied the pvalue calculated by Bonferroni's method and performed two-way repeated ANOVA test. Survival-related outcomes (eGFR decline-free, recurrence-free, overall, and cancerspecific survival) stratified by UD were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazard regression models were used to analyze the relationship between clinicopathological factors and survival-related outcomes. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (version 26; IBM Corp.). A two-sided p-value of <0.05 was considered statistically significant.

Table 1. Patient demographics of ileal conduit and neobladder

Parameter -	Total (n=86)		- n valuo
rarameter —	lleal conduit (n=54)	Neobladder (n=32)	- p-value
Age (y)	70.35±9.05	65.63±7.98	0.017*
Sex			0.416
Male	36 (66.7)	24 (75.0)	
Female	18 (33.3)	8 (25.0)	
Body mass index (kg/m ²)	22.36±2.47	23.61±3.10	0.043*
ASA			0.373
1	14 (25.9)	4 (12.5)	
2	34 (63.0)	24 (75.0)	
3	5 (9.3)	4 (12.5)	
4	1 (1.9)	0 (0.0)	
Smoking history			0.578
No	45 (83,3)	28 (87,5)	
Yes	9 (16.7)	4 (12.5)	
Alcohol history			0.649
No	43 (79.6)	24 (75.0)	
Yes	11 (20.4)	8 (25.0)	
OP type		0 (25.0)	0.125
Open	46 (85 2)	28 (87 5)	01120
Lanarosconic	5 (9 3)	0 (0 0)	
Bobotic	3 (5.6)	4 (12 5)	
Cause of penbrectomy	5 (5.6)	(12.5)	0.250
Lipper tract urothelial cell carcinoma	18 (88 9)	27 (84 4)	0.230
Benal cell carcinoma	-0 (00.2) 2 (3 7)	27(0+.+)	
Tuborculosis	1 (1 0)	3 (0,4)	
Others	1 (1.9) 2 (2 7)	2 (5.4) 2 (5.2)	
Nonbrostomy timing	2 (3.7)	2 (0.2)	0.670
Refere systestemy	22 (40 7)	15 (46 0)	0.079
Service Cystectomy	22 (40.7)	1 (2 1)	
Concurrent	3 (5.6)	1 (3.1)	
After cystectomy	21 (38.9)	14 (43.8)	0.465
Variant		22 (22 ()	0.465
No	46 (85.2)	29 (90.6)	
Yes	8 (14.8)	3 (9.4)	
lumor size (cm)	3.02±3.48	2.19±2.93	0.269
Pathologic I stage		- ()	0.396
No tumor	11 (20.4)	7 (21.9)	
Less than T2	21 (38.9)	8 (25.0)	
More than T2	22 (40.7)	17 (53.1)	
Resection margin			>0.999
No	51 (94.4)	31 (96.9)	
Yes	3 (5.6)	1 (3.1)	
Carcinoma <i>in situ</i>			0.379
No	32 (59.3)	22 (68.8)	
Yes	22 (40.7)	10 (31.2)	
Pathologic N stage			0.815
Nx or N0	46 (85.2)	27 (84.4)	
N1	4 (7.4)	4 (12.5)	
N2	3 (5.6)	1 (3.1)	
N3	1 (1.9)	0 (0.0)	

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Tab

le 1. Continued				
Parameter	Total (n=86)		n value	
	lleal conduit (n=54)	Neobladder (n=32)	p-value	
Neoadjuvant chemotherapy history			0.755	
No	47 (87.0)	27 (84.4)		
Yes	7 (13.0)	5 (15.6)		
Adjuvant chemotherapy history			>0.999	
No	48 (88.9)	28 (87.5)		
Yes	6 (11 1)	4 (12 5)		

For categorical variables, data are displayed as numbers (raw percentages) and for continuous variables as mean±standard deviation. ASA, American Society of Anaesthesiologists physical status.

Pathologic TNM staging definition was based on American Joint Commission on Cancer (AJCC) staging manual, 8th edition. Neoadjuvant and adjuvant chemotherapy included gemcitabine & cisplatin, gemcitabine & paclitaxel, and atezolizumab.

All p-values were calculated by the chi-square test for categorical variables and the t-test for continuous variables. *p<0.05.



Fig. 1. Post-radical cystectomy eGFR at 1, 3, 6, 12, 24, 36, 48, and 60 months. Renal function change between the ileal conduit and neobladder groups was evaluated by post-operative eGFR using the CKD-EPI equation at 1, 3, 6, 12, 24, 36, 48, and 60 months. There was no significant difference between the two groups in each follow-up time by the t-test and two-way repeated ANOVA test. eGFR, estimated glomerular filtration rate; CKD-EPI equation, Chronic Kidney Disease Epidemiology equation.

RESULTS

In total (n=86), 62.8% (54/86) of patients underwent IC, whereas 37.2% (32/86) underwent NB. Baseline patient characteristics (Table 1) were similar between the two groups, except for age and body mass index (BMI). Patients in the IC group were older than those in the NB group: IC (70.35 ± 9.05) vs. NB (65.63±7.98), p=0.017. BMI was statistically higher in the NB group than in the IC group: IC (22.36±2.47) vs. NB (23.61±3.10), p=0.043. Preoperative renal function, smoking history, operation type (open, laparoscopic, or robotic), previous transurethral resection of the bladder, nephrectomy history, cystectomy pathology, and neoadjuvant/adjuvant chemotherapy and radiation therapy did not differ between the two groups.

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The renal function of the two groups showed no statistical difference in the postoperative creatinine in terms of the mean and SD at 1, 3, 6, 12, 24, 36, 48, and 60 months: p=0.122, 0.401, 0.601, 0.675, 0.102, 0.091, 0.083, and 0.482, respectively. Similar results were observed for the postoperative eGFR (CKD-EPI) in mean±SD at 1, 3, 6, 12, 24, 36, 48, and 60 months (Fig. 1): p=0.674, 0.903, 0.295, 0.873, 0.114, 0.201, 0.211, and 0.758, respectively. The eGFR difference values (mean±SD), compared between the IC and NB groups during the same period, were 0.267, 0.852, 0.946, 0.236, 0.645, 0.778, and 0.706, respectively. The eGFR difference proportion (eGFR difference value/preoperative eGFR; expressed as mean±SD) at 1, 3, 6, 12, 24, 36, 48, and 60 months showed similar results: p=0.144, 0.260, 0.939, 0.643, 0.076, 0.382, 0.434, and 0.895, respectively. No significant difference was observed between the IC and NB groups even after a two-way repeated ANOVA test (absolute eGFR [CKD-EPI], p=0.817; GFR difference, p=0.332; and GFR difference proportion p=0.453).

Fig. 2 shows the time-to-event analysis for eGFR declinefree survival, determined postoperatively as 10 points decline in eGFR, compared to the preoperative value. The log-rank p-value between the IC and NB groups showed no statistical difference at 0.108. Other definitions of eGFR decline-free survival, using postoperative 10% or 20% decline in eGFR compared to preoperative values, are presented in Fig. 2. No significant differences were observed in the 10% or 20% decline in eGFR decline-free survival definitions: 10% decline (p=0.067) and 20% decline (p=0.151). Similar results were observed in the eGFR of MDRD; there were no significantly different results between the IC and NB groups when compared with the previously mentioned eGFR decline-free survival definitions.



Fig. 2. Post-radical cystectomy eGFR decline-free survival. Multiple definitions of eGFR decline were used: 10 points, 10%, and 20% decline in eGFR using the CKD-EPI equation. (A) eGFR decline free survival, which is defined as GFR difference value (GFR DV=preoperative value–follow-up value) >10 points, showed no significant difference between the ileal conduit and neobladder groups. Estimated GFR decline-free survival that used GFR difference proportion (GFR DP=eGFR difference value/preoperative eGFR) >10% (B) and >20% (C) also presented no statistical difference. eGFR, estimated glomerular filtration rate; CKD-EPI equation, Chronic Kidney Disease Epidemiology equation; DV, difference value; DP, difference proportion; IC, ileal conduit.



Fig. 3. Recurrence-free survival, overall survival, cancer-specific survival. Recurrence-free survival (A) and overall survival (B) showed no significant difference according to urinary diversion type. Cancer-specific survival (C) showed a significant difference (p-value=0.036). However, urinary diversion type was not a significant factor in multivariate analysis. IC, ileal conduit.

Endpoints other than renal function considered in our study were recurrence-free survival, overall survival, and cancer-specific survival. The median follow-up until urothelial cell carcinoma recurrence after RC was 235 months (interquartile range 7.0–48.0 mo), and the median follow-up until survival after RC was 35.8 months (interquartile range 165–70.2 mo). Recurrence-free and overall survival were not affected by the UD type: the log-rank p-values were 0.202 and 0.086, respectively (Fig. 3). However, cancer-specific survival was statistically different according to UD type (Fig. 3); NB had better cancer-specific survival than IC (log-rank pvalue 0.036). Multivariable analysis was also performed for cancer-specific survival. However, the hazard ratio of the UD type was not significant (hazard ratio 0.087, 95% confidence interval 0.009–1.383, p=0.109) (Table 2).

DISCUSSION

In this single-center study, we aimed to determine the effect of UD on renal function in patients with a single kidney who underwent RC for urothelial cell carcinoma. We cautiously suggest that the diversion type has no impact on renal function, survival, and recurrence.

We considered various factors for evaluating renal function. Absolute and relative comparisons were performed using the serum creatinine level, MDRD eGFR, and CKD-EPI eGFR. A previous study reported that the CKD-EPI equation was better than the MDRD equation for a wide range of GFR, especially elevated GFR [14]. In addition, the CKD-EPI equation showed enhanced precision, better accuracy, and less bias than the MDRD equation regarding the measured and calculated GFR [14]. In a previous study, the CKD-EPI eGFR equation demonstrated the greatest precision and ac-

Table 2. Univariate and multivariate analysis for cancer-specific survival

Davameter	Univariate		Multivariate		
Parameter	OR (95% CI)	p-value	OR (95% CI)	p-value	
Age	1.045 (0.994–1.099)	0.081			
Sex	2.112 (0.920-4.845)	0.078			
Body weight	0.925 (0.881–0.971)	0.002*			
Height	0.921 (0.878–0.966)	0.001*			
Body mass index	0.874 (0.727–1.050)	0.150			
Smoking	0.913 (0.270-3.087)	0.883			
Alcohol	0.737 (0.271-2.000)	0.549			
OP type (ref: open)					
Laparoscopic	0.909 (0.121–6.834)	0.926			
Robotic	0.842 (0.112–6.304)	0.867			
Diversion type (ref: ileal conduit)	0.296 (0.088–0.998)	0.050	0.304 (0.087-1.063)	0.062	
Transurethral resection of bladder					
Carcinoma <i>in situ</i> (+)	0.604 (0.923–1.533)	0.289			
Lymphovascular invasion (+)	8.402 (1.792–39.380)	0.007*			
Variant (+)	3.208 (1.182-8.702)	0.022*			
Nephrectomy					
Cause of nephrectomy (ref: urothelial cell carcinoma)					
Renal cell carcinoma	2.023 (0.269–15.229)	0.494			
Tuberculosis	0	0.988			
Othersª	0	0.988			
Timing of nephrectomy (ref: before cystectomy)					
Concurrent cystectomy	0.670 (0.085-5.307)	0.704			
After cystectomy	0.786 (0.303-2.040)	0.620			
Radical cystectomy					
Tumor size(cm)	1.014 (0.821–1.252)	0.899			
Pathologic T stage (ref: no tumor)					
<t2< td=""><td>0.536 (0.237–1.209)</td><td>0.133</td><td>3.704 (0.971–14.129)</td><td>0.055</td></t2<>	0.536 (0.237–1.209)	0.133	3.704 (0.971–14.129)	0.055	
≥T2	1.246 (0.674–2.301)	0.483	1.426 (0.332–6.124)	0.633	
Resection margin	1.839 (0.241–14.041)	0.557			
Carcinoma <i>in situ</i> (+)	1.356 (0.591–3.114)	0.472			
Lymphovascular invasion (+)	2.708 (1.112–6.595)	0.028*			
Variant (+)	2.483 (0.977–6.309)	0.056	2.740 (0.878-8.550)	0.083	
Pathologic N stage (+) (ref: pN0)	6.023 (2.200–16.492)	<0.001*	9.277 (2.562–33.596)	0.001*	
LN dissection (+)	0.254 (0.072–0.904)	0.034*			
Ratio of positive LN ^b	12.510 (1.716–91.168)	0.013*			
Neoadjuvant chemotherapy	0.789 (0.184–3.388)	0.750			
Adjuvant Chemotherapy	1.750 (0.585–5.238)	0.317			

LN, lymph node; OR, odds ratio; Cl, confidence interval.

^a:Others: infection, inflammation, and congenital disease.

^b:Ratio of positive LN: positive LN/total resected LN.

Univariate analysis and multivariate analysis results were obtained using Cox proportional hazards model for cancer specific survival. Multivariate analysis was done with age, sex, body mass index, smoking history, urinary diversion type, transurethral resection of the bladder (pathologic presence of lymphovascular invasion, variant pathology), radical cystectomy (pathologic T stage, lymphovascular invasion, variant pathology, resection margin, pathologic N stage), neoadjuvant chemotherapy, and adjuvant chemotherapy.

*p<0.05.

curacy, and the least bias among four formulas for comparing renal function before and after nephrectomy: Cockcroft-Gault, Modification of Diet in Renal Disease Study, reexpressed Modification of Diet in Renal Disease Study, and Chronic Kidney Disease-Epidemiology Study equations [15]. Recently published studies comparing the renal function of patients who underwent cystectomy also used the CKD-EPI equation for assessing renal function decline [17,20].

To determine renal function decline, our study referred to previous journals and combined various definitions using different values and ratios [13,16-24]. The follow-up duration and interval were different between previous studies; we followed up the renal function after cystectomy for 5 years. Other studies defined the renal function decline by comparing the assessment and preoperative periods using only one episode [13,18,19,22]. We questioned this definition and determined that renal function decline should be used when there were two or more consecutive episodes. A one-time renal function decline may be a temporary event or may improve later. Moreover, considering the short survival time of patients with a single kidney, advanced renal function values from serum creatinine and eGFR (CKD-EPI and MDRD equations) may result from over-hydration at the time of death or a cachexic state [25]. In such cases, serum cystatin C may be helpful because it is not affected by muscle mass and hydration [26]. In addition to the several definitions of renal function decline, there are several laboratory tests that depend on a patient's medical condition.

Previous studies have reported a significant relationship between renal function decline and neoadjuvant chemotherapy [18], higher preoperative eGFR [20], and urinary tract obstruction (ureteroenteric or enterourethral stricture) [13,19,24]. Another study reported similar complications of NB and IC, which contrasts the popular view that IC is simple and safe [24]. If urinary tract obstruction is managed timeously after NB, renal function may not be considered a contraindication. Therefore, indications of NB should be expanded in the future because the surgical outcomes of NB and IC do not differ.

This study had several limitations. First, there was a limited sample size, and the study was retrospective. For more statistically significant results, a large-scale, multicenter, prospective study is required in the future. Second, all patients who underwent nephrectomy before, concurrently with, or after RC were included in our analysis. A previous study reported that nephrectomy was a significant risk factor for the progression of chronic kidney disease and renal function decline after nephrectomy [27]. In our study, 37 patients underwent nephrectomy before cystectomy, 4 underwent RC concurrently with nephrectomy, and 35 underwent nephrectomy after cystectomy. Although the different timings of nephrectomy did not influence renal function change in the IC and NB groups, a sophisticated study that unifies nephrectomy timing should be conducted in the future. Third, the causes of nephrectomy varied in our study. Although most cases were caused by upper tract urothelial cell carcinoma, some patients underwent nephrectomy due to kidney cancer or tuberculosis 2 patients had kidney cancer, 4 had tuberculosis, and 4 had an infection or congenital diseases. Patients with upper tract urothelial cell carcinoma are more vulnerable to bladder carcinoma (22%-47%) or contralateral upper tract recurrence (5%) [28-30]. Although our study results showed that the cause of nephrectomy was not statistically related to our primary endpoint, further studies with a large number of participants are needed to determine the association with nephrectomy.

Our study presents patients data who underwent RC and simultaneously had a single kidney, a patient population difficult to recruit. Furthermore, the study findings are applicable to a variety of nephrectomy timings and causes, and can contribute to various indications of RC.

CONCLUSIONS

Among several factors for choosing UD type, a single kidney was thought to be a contraindication for NB formation. However, our study showed that UD type (IC vs. NB) when undergoing RC did not impact postoperative renal function change to a single kidney patients. Accordingly, patients with a single kidney might be considered to be an indication of NB. Our study has strength in that various renal function parameters and renal function decline definitions were used for comparing postoperative renal function decline between IC and NB groups. Our study is meaningful that it can be a starting point to expand NB indication even to a single kidney patients.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Gyeong Hun Kim, Chang Wook Jeong, Cheol Kwak, and Ja Hyeon Ku. Data acquisition: Gyeong Hun Kim, Hyeong Dong Yuk, Chang Wook Jeong, and Ja Hyeon Ku. Statistical analysis: Gyeong Hun Kim. Data analysis and interpretation: Gyeong Hun Kim, Hyeong Dong Yuk, and Ja Hyeon Ku. Drafting of the manuscript: Gyeong Hun Kim. Critical revision of the manuscript: Ja Hyeon Ku. Administrative, technical, or material support: Chang Wook Jeong, Cheol Kwak, and Ja Hyeon Ku.

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Supervision: Ja Hyeon Ku. Approval of the final manuscript: all authors.

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