Original Article

Renal function of bladder cancer patients after urinary diversion by ileal conduit in Rajavithi Hospital

Sittichon Suriyawongkul, Chawawat Gosrisirikul, Vorapot Choonhaklai, Tanet Thaidumrong, Somkiat Pumpaisanchai, Nattapong Wongwattanasatien, Sermsin Sindhubodee, Matchima Huabkong

Division of Urology, Department of Surgery, Rajavithi Hospital, Bangkok, Thailand

Keywords:
Renal function, bladder cancer, urinary diversion, ileal conduit

Abstract

Objectives: Our objectives were to evaluate the long-term renal function after radical cystectomy (RC) and ileal conduit diversion (ICD) and to analyze year-by-year the estimated glomerular filtration rate (eGFR) and morphologic upper urinary tract changes.

Materials and Methods: We retrospectively identified 214 patients who had undergone RC and ICD from 2012 to 2018, with regular postoperative follow-up visits. The eGFR was calculated using the Modification of Diet in Renal Disease equation at baseline and during follow-up. A renal function decrease was defined as a greater than 10 mL/min/1.73 m^2 reduction in the estimated glomerular filtration rate.

Results: The median follow-up period after RC was 24 months (range, 6-60 months). The median eGFR decreased from 64 mL/min/1.73 m^2 (range, 9-125 mL/min/1.73 m^2) to 61.5 mL/min/1.73 m2 (range, 8-125 mL/min/1.73 m^2). A decline in renal function occurred during the first postoperative years (2.74 mL/min/1.73 m^2 and 3.95 mL/min/1.73 m^2 in the first and second year, respectively), with a slight decrease in the subsequent years. The strongest predictor of an eGFR decline was CKD stage 1 or 2 (> 60 mL/min/1.73 m^2). Urinary obstruction was diagnosed in 6 patients (2.8%). Among the patients who underwent prompt interventional treatment, we did not find any association with the eGFR decline.

Conclusion: Patients with urinary ICD have a lifelong risk of chronic kidney disease. Regular monitoring of renal function and the morphologic upper urinary tract will permit early diagnosis and treatment of modifiable factors, avoiding irreversible kidney damage.

Insight Urol 2021;42(1):34-9. doi: 10.52786/isu.a.20

Corresponding author: Sittichon Suriyawongkul
Address: Division of Urology, Department of Surgery, Rajavithi Hospital, Bangkok 10400, Thailand
E-mail: sirgod123@gmail.com
Manuscript received: April 26, 2020
Revision received: March 30, 2021
Accepted after revision: March 31, 2021

Introduction

Chronic kidney disease (CKD) has been identified as an independent risk factor of death, cardiovascular events, and use of specialized healthcare. It is probable that commonly used drugs and surgical intervention can adversely affect several aspects of kidney function.

Although it remains the reference standard treatment of muscle invasive and high-risk urothelial bladder carcinoma, radical cystectomy (RC) is associated with significant risks of perioperative and long-term morbidity and mortality, notably due to renal function impairment. Despite the variety of diversion techniques used, either continent or incontinent, patients undergoing RC have a life-long risk of CKD[1]. Several factors have been identified to explain the renal function decrease, including nonmodifiable parameters such as age, the nephrotoxicity of chemotherapy or medical treatment, chronic hypertension, and diabetes mellitus, and potentially modifiable factors, including mechanical obstruction and urinary tract infection[2].

However, the natural history and long-term follow-up data of renal function decline in patients treated by RC for urothelial bladder cancer have been poorly reported[3,4]. Furthermore, most of the studies have evaluated variation in renal function using serum creatinine as a surrogate value for the estimated glomerular filtration rate (eGFR). Although the reference standard for renal function evaluation is the measured GFR, equations estimating the GFR have been considered to be the better measure of overall kidney function in routine clinical practice. In this study, we analyzed the year-by-year eGFR variations and morphologic upper urinary tract changes in patients who had undergone RC and urinary ICD for urothelial bladder cancer

Materials and Methods

This research was an observational study approved by Rajavithi Hospital Ethics Committee. Data was collected from the medical records of bladder cancer patients which had undergone Radical Cystectomy for localized muscle-invasive bladder cancer in Rajavithi Hospital, from 1 Jan 2012 - 31 December 2018.

Exclusion criteria

- End stage kidney disease which required renal replacement therapy
- Preoperative eGFR < 15 mL/min/1.73 m^2
- Cutaneous ureterostomy
- Ureterosigmoidostomy

The clinical variables evaluated included age, gender, diabetes mellitus, preoperative chronic hypertension, preoperative hydronephrosis, baseline and follow-up eGFR, and receipt of perioperative systemic chemotherapy.

Surgical technique

All patients underwent pelvic lymphadenectomy before RC was performed. An ileal segment 15 to 20 cm long was isolated approximately 15 cm proximal to the ileocecal valve. The ureters were split and anastomosed separately in the ileal segment. Ureteroileal anastomoses were performed using either the direct implantation Bricker (23%) or the Wallace technique (77%). The ureteral catheter was brought directly through the ileal segment and secured to the abdominal skin. The ileal segment was oriented in the isoperistaltic direction and anastomosed to the abdominal wall in a nipple-tostoma fashion. The ureteral catheters were removed on the 13^{th} or 14^{th} day postoperative.

Patient follow-up data and data collection

The patients were followed up regularly at our department or their local hospital at 1, 3, and 6 months, and annually thereafter. At each visit, the patients' blood pressure, complete blood count, and serum creatinine, were determined and urine culture was completed. Renal ultrasonography or abdominopelvic computed tomography were performed alternatively every 6 months for 2 years and annually thereafter. The radiologists diagnosed hydronephrosis by measuring the anteroposterior diameter of the renal pelvis. The images of the upper urinary tract were compared with previous images to determine the presence of any radiologic changes. We focused our evaluation on postoperative complications, including mechanical urinary obstruction, urinary tract infection, and urolithiasis. Urinary tract obstruction was documented in patients with hydronephrosis secondary to ureteroileal stricture and/or stomal obstruction. In these instances patients underwent repeat surgery, and the obstruction resolved. The designation of recurrent urinary tract infection was determined by bacteriuria of % 10^5 colony-forming units lasting ≥ 3 months per year, whether or not symptomatic.

Pyelonephritis was defined as a febrile episode with a positive urine culture after excluding any other cause for the fever.

Renal function evaluation

The GFR was the primary outcome measured. It was calculated using the Modification of Diet in Renal Disease (MDRD) equation[5].

GFR (mL/min/1.73 m^2) = 175 × (serum creatinine) - 1.154 × (age) - 0.203 × (0.742, if female)

To be consistent with previous studies, decreased renal function was defined as a reduction in the GFR > 10 mL/min/1.73 m^2 after surgery[3]. To evaluate the factors associated with an eGFR decrease, we compared the preoperative values with those obtained at the subsequent postoperative visits. The CKD stage was also used to classify renal function. Similar to the method in a recent analysis we compared the preoperative eGFR with the values obtained at the subsequent postoperative visits. At the 1-year postoperative point, we evaluated serum creatinine, measured 9 to 18 months postoperatively. In addition, we accounted for all subsequent values obtained within each subsequent year.

Statistical analysis

Continuous, normally distributed and non-normal distributed variables are reported as the median and range. Univariate statistical analyses were performed with a Student's t test for quantitative variables and Fisher's exact test for qualitative variables. Linear regression analysis was used to test the liaison between the quantitative variables. For all statistical analyses, a 2-sided p-value < 0.05 was considered statistically significant. All data were analyzed using the Statistical Package for Social Sciences, version 25.0 (SPSS, Chicago, IL).

Results

Patient characteristics

The clinicopathologic features of the patients at surgery are reported in Table 1. All 214 patients with serum creatinine measurements available at baseline and regular follow-up visits after surgery, were evaluated. The median follow-up period after RC for patients alive at the last visit was 24 months (range, 6-60 months). The overall survival rate was 80% at 5 years. Median patient age was 63 years (range, 27-87 years), and the gender ratio was 3 : 1. Of the 214 patients, 70 (31%) received platinum-based chemotherapy. Postoperative complications included ureteroenteric stricture (n = 1), recurrent urinary tract infection (n = 2), and urolithiasis (n = 3)

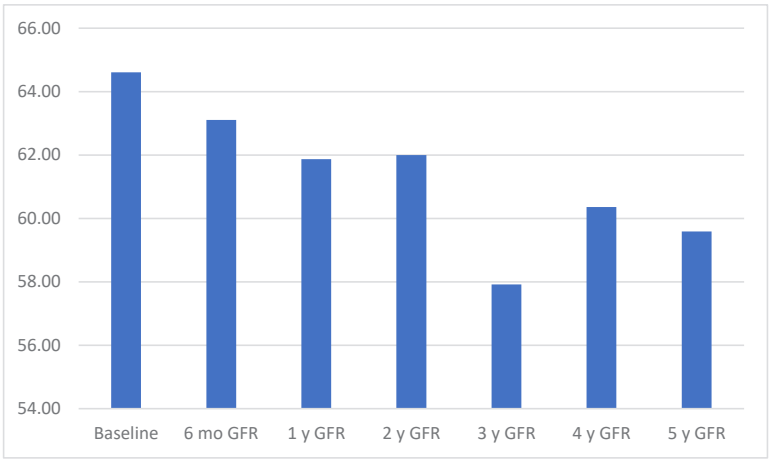
Changes in eGFR

The median estimated glomerular filtration rate (eGFR) significantly decreased from 64 mL/min/1.73 m^2 to 61.5 mL/min/1.73 m^2 (p = 0.008) between preoperative and final F/U.

Figure 1 shows the median eGFR evolution from baseline to event analysis. At 5 years postoperative, median GFR deceased 2.74 mL/min/1.73 m^2 in the first year before decreasing slowly in the subsequent years.

Table 1. Demographic data.

Patient characteristics (N = 214)	n (%)
Patients	214 (100)
Age (years)	
- Median	63
- Range	27-87
Gender	
- Male	161 (75)
- Female	53 (25)
Comorbidity	
- Chronic hypertension	89 (42)
- Diabetes mellitus	36 (17)
Preoperative hydronephrosis	93 (44)
Adjuvant chemotherapy	53 (25)
Neoadjuvant chemotherapy	14 (7)
Years followed up (mean±sd)	2.04 (1.36)
Type of anastomosis	
- Wallace	164 (76.6)
- Bricker	50 (23.4)
Preoperative eGFR (mL/min/1.73 m^2)	
- Median	64
- Range	8-125
Patients with eGFR > 90 mL/min/1.73 m^2	37 (17)
Patients with eGFR 60-90 mL/min/1.73 m^2	89 (42)
Patients with eGFR 30-59 mL/min/1.73 m^2	68 (32)
Patients with eGFR < 30 mL/min/1.73 m^2	20 (9)
Pathologic stage	
pT1	58 (27)
pT2	60 (28)
pT3	58 (27)
pT4	37 (17)
pN+	57 (26)



N=214		Baseline	6 mo GFR	1 y GFR	2 y GFR	3 y GFR	4 y GFR	5 y GFR
n	Valid	214	213	196	112	60	33	22
	Missing	0	1	18	102	154	181	192
Mean GFR (mL/min/1.75 m^2)		64.61	63.10	61.87	62.00	57.92	60.36	59.59

Figure 1. Change in median estimated glomerular filtration rate (eGFR) after radical cystectomy across the postoperative period.

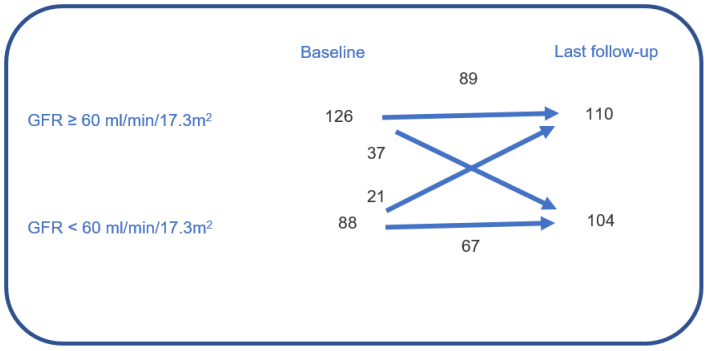


Figure 2. Chronic kidney disease (CKD) stage in patients with ileal conduit diversion before surgery and at last follow-up visit.

Figure 2 shows the evolution of CKD stage from baseline to the last follow-up visit. At baseline, 126 out of 214 patients (58%) had normal renal function (eGFR > 60 mL/min/1.75 m^2) and 88 (42%) had CKD stage 3, defined as an eGFR of < 60 mL/min/1.73 m^2. Of the 126 patients with a normal preoperative eGFR, new-onset stage 3 CKD was detected postoperatively in 37 (17%). In contrast, in 21 of 88 patients (26%) with a preoperative eGFR of > 15 but < 60 mL/min/1.73 m^2 the functional capacity of their kidneys improved.

Factors influencing renal function

The variables associated with renal function deterioration are reported in Table 2 and Table 3. A normal preoperative eGFR at baseline (> 60 mL/min/1.73 m^2) was independently associated with worse renal outcome in both univariate and multivariate analysis ($p < 0.001$). However, preoperative hydronephrosis was associated with worse renal outcome only in the univariate analysis.

Diabetes (n = 22), chronic hypertension (n = 57), gender, age, pathological stage, type of anastomosis and adjuvant chemotherapy were not associated with a poor renal function outcome ($p > 0.05$).

Discussion

The standard treatment of muscle invasive bladder cancer is radical surgery with urinary diversion and chemotherapy[8]. Ileal conduit is the type of urinary diversion that is most frequently used in Rajavithi Hospital. Decreased renal function has been noted in most patients during long-term follow-up after urinary diversion. However, long-term data evaluating the risk factors associated with worsening renal function

Table 2. Univariate analysis of clinicopathologic variables and complications associated with renal function deterioration.

	Decrease in renal function	No decrease in renal function	Odds ratio	P-value
Gender n (%)			0.66	0.235
Male	101 (72.7)	60 (80.0)		
Female	38 (27.3)	15 (20.0)		
Age (years) Mean±SD	62.2(10.95)	64.3 (10.19)		0.24
Preoperative GFR n (%)			3.96	< 0.001
> 60 mL/min/1.73 m²	59 (78.7)	67 (48.2)		
< 60 mL/min/1.73 m²	16 (21.3%)	72 (51.8)		
Diabetes mellitus n (%)	22 (15.8)	14 (18.7)	0.82	0.596
Hypertension n (%)	57 (41.00)	32 (42.70)	0.93	0.814
Preoperative hydronephrosis n (%)	22 29.3	72 51.8	0.37	0.002
pT stage (≥ pT2 vs pT1 stage) n (%)			0.52	0.034
pT1	27 (36.0)	31 (22.5)		
≥ pT2	48 (64.0)	107 (77.5)		
Type of anastomosis n (%)			0.52	0.034
Wallace	59 (78.7)	105 (75.5)		
Bricker	16 (21.3)	34 (24.5)		
Adjuvant chemotherapy n (%)	37 (26.60)	16 (21.30)	1.34	0.393

Table 3. Multivariate analysis of clinicopathologic variables and complications associated with deterioration in renal function.

	HR	Lower	Upper	P-value
Gender	1.039	1.005	1.074	0.025
Age	0.616	0.292	1.298	0.203
Preoperative eGFR > 60 mL/min/1.73 m²	5.871	2.614	13.188	< 0.001
DM	1.588	0.653	3.864	0.308
HT	1.098	0.541	2.229	0.796
Preoperative hydronephrosis	0.930	0.449	1.927	0.846
pT stage (> pT2 vs pT1 stage)	0.682	0.332	1.401	0.298
Type of anastomosis	0.961	0.455	2.027	0.916
Adjuvant chemotherapy	0.982	0.460	2.100	0.963

in patients with urinary diversion are lacking.

Eisenberg et al reported the first study evaluating renal function decrease-free survival with long-term follow up in a large cohort of patients treated by RC and urinary diversion. They reported that the renal function decline approached 49% and 72% at 5 and 10 years after urinary diversion, respectively. They found a statistically significant association between older age, higher preoperative eGFR, chronic hypertension, postoperative hydronephrosis, ureteroenteric anastomotic stricture, and pyelonephritis and an increased risk of subsequent decreased renal function[3].

Jin et al found renal function decrease in 25% of patients after RC at a minimum of a 10-year follow-up period. The incidence of urinary tract obstruction was significant and that diabetes and hypertension were contributing factors associated with renal function deterioration in patients with incontinent diversion[4].

Osawa et al, reported that 34.2% of their patients had reduced renal function after the mid-term follow-up period after RC[6].

Mathieu Rouanne et al, found the overall rate of renal function had decreased by 51% at 5 years after urinary diversion by ileal conduit. They considered a significant annual decline in GFR of > 1 mL/min/1.73 m^2. They found that a normal preoperative eGFR > 60 mL/min/1.73 m^2 was associated with decreased renal function postoperatively. However, neither chronic hypertension nor diabetes mellitus was associated with the eGFR decline[7].

In our study, we noted that the overall rate of renal function had decreased after surgery. We considered as significant a decline in GFR of > 10 mL/min/1.73 m^2 because we could not monitor the year-by-year eGFR. We found normal preoperative eGFR > 60 mL/min/1.73 m^2 and no preoperative hydronephrosis were associated with decreased renal function postoperatively. This situation can be explained as relative improvement due to the regression of preoperative hydronephrosis in patients with preoperative eGFR < 60 mL/min/1.73 m^2. Diabetes, chronic hypertension, gender, age, pathological stage, type of anastomosis and adjuvant chemotherapy were not associated with a poor renal function outcome.

Our study is limited by its retrospective, nonrandomized design. We further acknowledge the potential for underestimating renal related postoperative complications, given the tertiary referral nature of our center, since patients frequently undergo follow up locally. Additionally, excluding patients from analysis when they did not have long term RF data available may have introduced selection bias. Those on whom RF data were and were not recorded in our registry may have had clinically relevant clinicopathological differences that would have impacted an RF decrease and we could not examine the effects of medical or surgical intervention for renal related complications.

eGFR is not the gold standard measures of inulin clearance or creatinine clearance under diuretic conditions. It has limited accuracy in measuring serum creatinine in patients after UD due to creatinine reabsorption.

Conclusion

Most patients experienced a decrease in RF during long-term follow up after RC. The long-term renal function in patients with an ileal conduit urinary tract can be adversely affected by both diversion and non- diversion-related factors. These data emphasize the importance of continuing to monitor eGFR after RC and identifying and treating renal related complications early to limit renal function deterioration to prevent irreversible kidney damage.

Conflict of Interest

The authors declare no conflict of interest.

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