Long-Term Renal Function Outcomes in Bladder Cancer After Radical Cystectomy

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Purpose: To evaluate postoperative renal function and risk factors for the loss of renal function in patients who had undergone radical cystectomy.

Materials and Methods: A retrospective single institutional study evaluated 70 patients, including 54 men and 16 women who underwent radical cystectomy. The median follow-up period was 34.5 months (range, 12 to 228 months). In this cohort, four types of urinary diversions were studied, including ileal neobladder (n = 24), ileocecal neobladder (n = 12), ileal conduit (n = 25), and cutaneous ureterostomy (n = 9). Postoperative changes in renal function were reviewed, and the estimated serum creatinine-based glomerular filtration rate (eGFR) was calculated. The variables analyzed were age, a prior history of hypertension or diabetes mellitus, pre-operative renal function, type of urinary diversion, the postoperative occurrence of acute pyelonephritis, and the presence of chemotherapy.

Results: The mean eGFR was 74.6 (range, 15.2 to 155.1) mL/min/1.73 m^2 before surgery and 63.6 (range, 8.7 to 111.5) mL/min/1.73 m^2 at the last follow-up. The 10-year renal deterioration-free interval was 63.8%. Multivariate analysis showed that a postoperative episode of acute pyelonephritis [Odds Ratio (OR), 3.21; 95% Confidence Interval (CI), 1.14 to 9.02; $P = .03$] and the presence of chemotherapy (OR, 3.27; 95% CI, 1.33 to 8.01; $P = .01$) were significant adverse factors.

Conclusion: Twenty-four (34.2%) patients demonstrated reduced renal function during the follow-up period. Postoperative episodes of acute pyelonephritis and the presence of chemotherapy were found to be significant adverse factors.

Keywords: urinary bladder neoplasms, urinary diversion, follow-up studies, treatment outcome, cystectomy

INTRODUCTION

Urinary diversion is inevitable during radical cystectomy (RC) in patients with muscle-invasive and high-grade non-muscle invasive bladder cancer. One of the most important requirements for any substitution of the bladder is that it should not jeopardize the function of the upper urinary tract. To achieve long-term upper urinary tract safety, a variety of reconstruction techniques have been discussed.[1]

However, there have been few publications describing the long-term renal function outcomes of the patients with bladder cancer who have undergone RC. Comparing renal function results between different studies is hampered due to differences in patients' characteristics, the definitions of renal function, and surgical techniques. Currently, the estimated serum creatinine-based glomerular filtration rate (eGFR) is considered to be the better measure of overall kidney function, and it is widely used to evaluate postoperative renal function after partial nephrectomy and renal transplantation.[2,3]

In the present study, we evaluated postoperative renal function and the risk factors for the loss of renal function in patients who had undergone RC in a single institution.

MATERIALS AND METHODS

A total of 149 patients who had undergone RC between 1988 and 2008 were identified. All data were obtained in accordance with the privacy protection policy of our institution. Of these patients, 79 (53%) were excluded from the study because of the following reasons: less than 12 months follow-up (46 patients), simultaneous nephrectomy or nephroureterectomy (25 patients), resection of the entire urinary tract (1 patient), the necessity of dialysis during the postoperative course (1 patient), and insufficient data (6 patients). As a result, of the 149 patients, 70 patients (54 men and 16 women) were included in the present study.

In this cohort, four types of urinary diversions were compared: cutaneous ureterostomy (n = 9), ileal conduit (n = 25), ileal neobladder (n = 24), and ileocecal neobladder (n = 12). Before the selection of the urinary diversion, a thorough evaluation of the patients' baseline renal function, including their 24-hour creatinine clearance was performed. Impaired renal function (serum creatinine level >2 mg/dL) usually precludes continent urinary diversions as it leads to an inability to compensate for metabolic disturbances.[4,5] The indications for the selection of urinary diversion were dependent on the patient's age, comorbidity, and prior abdominal surgery.

The patients that underwent the ileocecal neobladder procedure received a cutaneous continent reservoir (8 patients) or an orthotopic neobladder (4 patients). The advantages of the ileocecal reservoir are its large initial volume and its ileocecal valve, which can be reinforced to ensure that urinary reflux into the ureter is prevented. The ileocecal neobladder procedure has not been performed in our institution since 1995 as it causes hypochloremic metabolic disturbance and vitamin B_{12} deficiency.

All the patients underwent RC and urinary diversion, and the basic technique was identical regardless of the operator. In the continent urinary diversion group, the ureters were anastomosed with the LeDuc-Camey technique (9 patients) or Chimney technique (15 patients). Recently, the Chimney technique has mainly been used for the ureter implantation in our group because anti-reflux mechanisms are not always necessary in low pressure reservoir.

After the surgery, the patients were followed-up for metastasis and urinary obstruction with routine blood tests, a radiological chest examination, and a computed tomography scan of the abdomen and pelvis every 3 to 6 months for the first 2 to 3 years and every 6 to 12 months thereafter. Bone scans were carried out when symptoms appeared.

Postoperative changes in renal function were examined, and eGFR was calculated using the standard Japanese formula (eGFR = 194 × age-0.287 × creatinine-1.094 mL/min/1.73 m^2 [× 0.739 if female]), which was developed by the Japanese Society of Nephrology.[6] Renal deterioration was defined as a greater than 25% decrease in eGFR compared to pre-operative renal function.[7,8]

The variables analyzed were age, gender, a prior history of hypertension or diabetes mellitus, pre-operative renal function, type of urinary diversion, the presence of chemotherapy, and the repeated postoperative episode of acute pyelonephritis (APN). Pyelonephritis was defined as a positive urine culture (bacteriuria of $>10^5$ colony-forming units) and the presence of flank pain or tenderness with fever (>38 °C axillary).

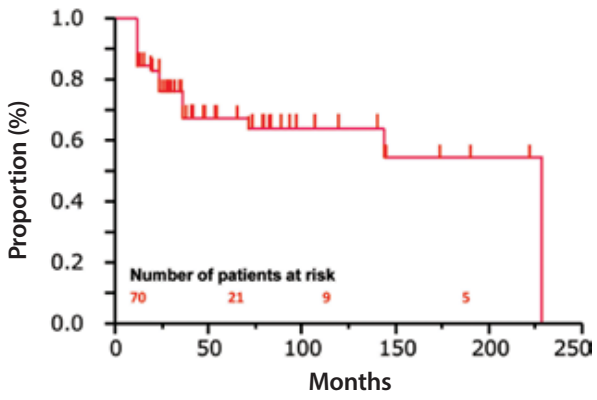

Figure 1. Kaplan–Meier curve of the renal deterioration-free interval of all the patients.
The 10-year renal deterioration-free interval was 63.8%.

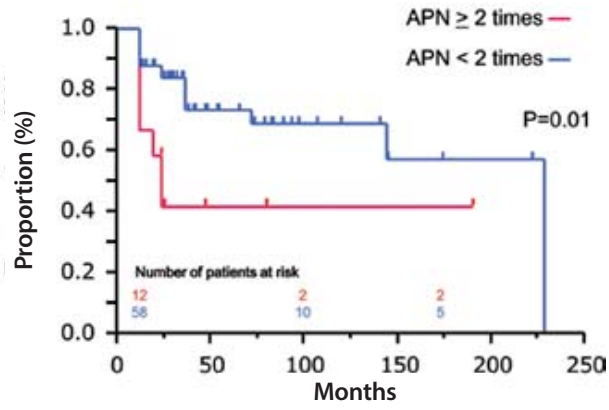

Figure 2. Kaplan–Meier curve of the renal deterioration-free interval by the repeated acute pyelonephritis episode in univariate Log-Rank analysis.

Hypertension was defined as pre-operative systolic and diastolic blood pressure measurements of >140 and >90 mmHg, respectively. Patients with diabetes mellitus were defined as those who met the relevant diagnostic criteria and required glycemic control.

The renal deterioration-free interval (as defined above) was estimated using the Kaplan-Meier method, and distributions were compared using the Log-Rank test. Multivariate analyses were performed using the Cox proportional hazards model. All calculations were performed using commercially available statistical software (StatView 5.0, SAS Institute, Cary, North Carolina, USA). *P* values less than .05 were considered significant.

RESULTS

The median age of the patients was 63.5 years (range, 25 to 88 years). The median follow-up period was 34.5 months (range, 12 to 228 months). The median postoperative follow-up period was 39 months (range, 13 to 85 months) for cutaneous ureterostomy, 47 months (range, 12 to 223 months) for the ileal conduit, 33 months (range, 16 to 130 months) for the ileal neobladder, and 129 months (range, 14 to 243 months) for the ileocecal neobladder. The median eGFR was 74.6 mL/min/1.73 m^2 (range, 15.2 to 155.1 mL/min/1.73 m^2) before the surgery and 63.6 mL/min/1.73 m^2 (range, 8.7 to 111.5 mL/min/1.73 m^2) at the last follow-up. The 10-year renal deterioration-free interval was 63.8% (Figure 1).

Table 1 shows the patients' characteristics stratified according to the type of diversion. Both cutaneous diversion and ileal conduit tended to be performed in older patients who had complication of renal insufficiency and hypertension. Furthermore, surgical intervention, including balloon ureteral dilation, was needed to improve the ureteral obstruction for 7 patients who had deteriorating renal function during the outpatient follow-up.

Univariate Log-Rank analysis demonstrated a significant relationship between renal deterioration with the repeated APN episode (Figure 2; $P = .01$) and the presence of chemotherapy ($P = .02$). The frequency of APN after RC varied as follows: 11 patients suffered from one APN, 8 patients from two APN, 2 patients from three APN, and 2 patients from more than four APN. On the other hand, there was no significant difference in the frequency of APN events among the four types of urinary diversion.

The peri-operative chemotherapy regimens used in the current series were one to two cycles of methotrexate, vinblastine, adriamycin, and cisplatin (MVAC, n = 5), two or three cycles of methotrexate, epirubicin, and cisplatin (MEC, n = 12), three to six cycles of paclitaxel, ifosfamide, and nedaplatin (PIN, n = 2), seven to fifteen cycles of combination chemotherapy, including MEC and PIN (n = 2), and five cy-

Table 1. Characteristics of patients stratified according to the type of urinary diversion that they underwent.

Variables	Cutaneous ureterostomy	Ileal conduit	Ileal neobladder	Ileocecal neobladder	*P*
Patients, n	9	25	24	12	
Age, >75/<75 y	5/4	5/20	1/23	0/12	*<.01*
Gender, male/female	6/3	20/5	19/5	9/3	.86
Pre-operative eGFR,* >60/<60 mL/min/1.73 m^2	3/6	21/4	21/3	12/0	*.01*
Chemotherapy, +/-	3/6	8/17	6/18	5/7	.78
Acute pyelonephritis, >2/<2 times	2/7	2/23	7/17	1/11	.19
Ureteral obstruction,+/-	1/8	5/20	0/24	1/11	.14
Diabetes mellitus,+/-	3/6	3/22	3/21	0/12	.16
Hypertension, +/-	4/5	9/16	2/22	1/11	*.03*

*eGFR indicates estimated serum creatinine-based glomerular filtration rate.

cles of paclitaxel and carboplatin (n = 1). In the cisplatin-including chemotherapy group, 10 (52%) patients out of 19 showed renal deterioration compared to 0 (0%) subjects out of 3 in the other chemotherapy group. On the other hand, there were no significant differences in renal deterioration among chemotherapy courses.

Multivariate analysis showed that the postoperative repeated episode of APN [Odds Ratio (OR), 3.21; 95% Confidence Interval (CI), 1.14 to 9.02; *P* = .03] and the presence of chemotherapy (OR, 3.27; 95% CI, 1.33 to 8.01; *P* = .01) were significant adverse factors. On the other hand, age, gender, pre-operative eGFR, the type of urinary diversion, diabetes mellitus, and hypertension did not affect the patients' renal function outcomes (Table 2).

DISCUSSION

Urinary diversion is mandatory for patients undergoing RC. Long-term follow-up of postoperative renal function is critical for evaluating urologic reconstructive procedures. However, comparison of long-term renal function results is difficult because selection of a particular urinary diversion procedure is subject to the patient's characteristics. Furthermore, the parameters used to define the upper urinary tract deterioration are not always the same among reports.[7-9]

This study shows that 34.2% of patients who underwent urinary diversion procedures experienced renal deterioration during the follow-up period, as defined by a greater than 25% decrease in eGFR. With regard to the ileal conduit diversion group, 29% of patients developed renal deterioration. This result is comparable to the results of a previous study in which 18% to 29% of patients revealed worsening renal function during a median follow-up period of 8 years.[8,10]

In general, renal function is favorably preserved after continent urinary diversion compared with that after conduit urinary diversion,[10] and the incidence of renal deterioration after continent urinary diversion has been reported to range from 7.4% to 16%.[11,12] In our study, 43.7% of patients who underwent continent urinary diversion experienced renal impairment, and this rate was moderately higher than that described in a previous report. However, these reports concentrated on serial serum creatinine measurements as an indicator of renal functional deterioration, which is a poor indicator of early renal impairment.[13]

Fontaine and colleagues evaluated GFR pre-operatively in patients who underwent reconstruction of the lower urinary tract using a bowel segment, and followed them for at least 10 years. In their study, 80% of patients displayed no change in their renal function, while 20% suffered from renal deterioration of more than 20% GFR loss.[14] Therefore, the upper urinary tract deterioration rate that we observed during our 10-year study period is comparable to that of the previous report.

Chemotherapy prior to or after RC was found to be a significant predictor of renal deterioration in our series. The MVAC

Table 2. Results of multivariate analysis.*

Variable	Hazard Ratio (95% CI)	*P*
Age, every 10 years	1.17 (0.78 to 1.76)	.44
Gender, female	1.40 (0.45 to 4.29)	.56
Pre-operative eGFR,< 60 mL/min/1.73 m^2	0.77 (0.24 to 2.44)	.66
Urinary diversion (Compared to Ileal neobladder)		.39
Cutaneous ureterostomy	0.30 (0.05 to 1.78)	
Ileal conduit	1.00 (0.32 to 3.15)	
Ileocecal neobladder	0.45 (0.10 to 2.01)	
Chemotherapy	3.27 (1.33 to 8.01)	*.01*
Acute pyelonephritis,>2 times	3.21 (1.14 to 9.02)	*.03*
Diabetes mellitus	1.78 (0.48 to 6.57)	.39
Hypertension	0.40 (0.10 to 1.59)	.19

*CI indicates confidence interval; and eGFR estimated serum creatinine-based glomerular filtration rate.

is the standard chemotherapy regimen for metastatic urothelial cancer.[15,16] In Japan, the MEC is a relatively frequent choice, based on a prospective randomized trial showing an approximately equivalent response rate and incidence of adverse effects compared to the MVAC.[17] We use the PIN, which is a new combination therapy as salvage therapy after standard cisplatin-based chemotherapy.[18] Cisplatin is a potent chemotherapy agent that is used to treat a broad spectrum of malignancies, but it causes renal tubular dysfunction and a cumulative impairment of renal function, as manifested by a decline in the GFR.[19]

More than three courses of chemotherapy were administered to 16 (73%) of the 22 patients who received chemotherapy. In cases involving relapse or metastasis, patients often receive multiple courses of salvage chemotherapy, which can aggravate renal function. In our series, 4 (18%) of 22 patients underwent 3 to 15 cycles of chemotherapy. Despite the nephrotoxicity of chemotherapy, it is necessary to use multimodal treatment strategies incorporating peri-operative chemotherapy with surgery to optimize patient's outcomes. When chemotherapy is employed, it is necessary to take the patient's laboratory data into account and prevent nephrotoxicity by forced hydration and diuresis.[20]

Our results confirm that repeated APN after RC was a prevalent risk factor for renal deterioration. Samuel and associates reported that recurrent APN was significantly more common in patients who experienced a deterioration of GFR.[8] Our study also showed that 7 (29%) out of 24 patients whose renal function deteriorated experienced repeated APN, which was an independent adverse factor for renal deterioration. Among the patients who experienced APN (n = 23), a total of 48% patients suffered from it in 1 month after RC. Such peri-operative episode of APN might be prevented by antibiotic prophylaxis, and we recently recommend the temporal peri-operative use of antibiotics. On the other hand, APN in our series, was not associated with post renal obstruction, which requires surgical intervention (P = .52). It is essential to maintain optimal control of APN in patients with urinary diversions.

Finally, we found that the incidence of upper urinary tract deterioration is not significantly different among the four types of urinary diversion. The limitations of this study include its retrospective design, small patient population in each type of urinary diversion, various patients' characteristics, and the different follow-up periods between the four urinary diversions. Furthermore, different surgeons performed the procedures. However, even with these limitations, our findings show that repeated APN and peri-operative chemotherapy were prognostic parameters for renal deterioration.

CONCLUSION

Twenty-four (34.2%) patients who underwent RC demon-

strated deterioration of renal function during the follow-up period. On the other hand, there was no significant difference in renal deterioration among the four types of urinary diversion. We identified two important potentially variables that should be considered in the follow-up of patients with urinary diversion, ie, the postoperative episode of repeated APN and the presence of chemotherapy. These factors were significant predictors of a decrease in postoperative renal function.

CONFLICT OF INTEREST

None declared.

REFERENCES

1 Hautmann RE, Abol-Enein H, Hafez K, et al. Urinary diversion. Urology. 2007;69:17-49.

2 Lane BR, Poggio ED, Herts BR, et al. Renal function assessment in the era of chronic kidney disease: Renewed emphasis on renal function centered patient care. J Urol. 2009;182:435-43; discussion 443.

3 Gera M, Slezak JM, Rule AD, et al. Assessment of changes in kidney allograft function using creatinine-based estimates of glomerular filtration rate. Am J Transplant. 2007;7:880-7.

4 Koch MO, McDougal WS, Thompson CO Mechanisms of solute transport following urinary diversion through intestinal segments: An experimental study with rats. J Urol. 1991;146:1390-4.

5 Koch MO, McDougal WS, Flora MD Urease and the acidosis of urinary intestinal diversion. J Urol. 1991;146:458-62.

6 Matsuo S, Imai E, Horio M, et al. Revised equations for estimated gfr from serum creatinine in japan. Am J Kidney Dis. 2009;53:982-92.

7 Hautmann RE Urinary diversion: Ileal conduit to neobladder. J Urol. 2003;169:834-42.

8 Samuel JD, Bhatt RI, Montague RJ, et al. The natural history of postoperative renal function in patients undergoing ileal conduit diversion for cancer measured using serial isotopic glomerular filtration rate and 99m technetium-mercaptoacetyltriglycine renography. J Urol. 2006;176:2518-22; discussion 2522.

9 Akerlund S, Delin K, Kock NG, et al. Renal function and upper urinary tract configuration following urinary diversion to a continent ileal reservoir (kock pouch): A prospective 5 to 11-year followup after reservoir construction. J Urol. 1989;142:964-8.

10 Kristjansson A, Bajc M, Wallin L, et al. Renal function up to 16 years after conduit (refluxing or anti-reflux anastomosis) or continent urinary diversion. 2. Renal scarring and location of bacteriuria. Br J Urol. 1995;76:546-50.

11 Thoeny HC, Sonnenschein MJ, Madersbacher S, et al. Is ileal orthotopic bladder substitution with an afferent tubular segment detrimental to the upper urinary tract in the long term? J Urol. 2002;168:2030-4; discussion 2034.

12 Wiesner C, Pahernik S, Stein R, et al. Long-term follow-up of submucosal tunnel and serosa-lined extramural tunnel ureter implantation in ileocaecal continent cutaneous urinary diversion (mainz pouch i). BJU Int. 2007;100:633-7.

13 Kristjansson A, Mansson W Renal function in the setting of urinary diversion. World J Urol. 2004;22:172-7.

14 Fontaine E, Leaver R, Woodhouse CR The effect of intestinal urinary reservoirs on renal function: A 10-year follow-up. BJU Int. 2000;86:195-8.

15 Sternberg CN, Yagoda A, Scher HI, et al. M-vac (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. J Urol. 1988;139:461-9.

16 Sternberg CN The treatment of advanced bladder cancer. Ann Oncol. 1995;6:113-26.

17 Kuroda M, Kotake T, Akaza H, et al. Efficacy of dose-intensified mec (methotrexate, epirubicin and cisplatin) chemotherapy for advanced urothelial carcinoma: A prospective randomized trial comparing mec and m-vac (methotrexate, vinblastine, doxorubicin and cisplatin). Japanese urothelial cancer research group. Jpn J Clin Oncol. 1998;28:497-501.

18 Shinohara N, Harabayashi T, Suzuki S, et al. Salvage chemotherapy with paclitaxel, ifosfamide, and nedaplatin in patients with urothelial cancer who had received prior cisplatin-based therapy. Cancer Chemother Pharmacol. 2006;58:402-7.

19 Gonzales-Vitale JC, Hayes DM, Cvitkovic E, et al. The renal pathology in clinical trials of cis-platinum (ii) diamminedichloride. Cancer. 1977;39:1362-71.

20 Cvitkovic E, Spaulding J, Bethune V, et al. Improvement of cis-dichlorodiammineplatinum (nsc 119875): Therapeutic index in an animal model. Cancer. 1977;39:1357-61.