

Original article

Renal function outcomes in the early and intermediate phases after radical cystectomy by ileal conduit

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Abstract

Introduction and Objectives: An ileal conduit (IC) is an established option for urinary diversion, despite the fact that early renal impairment (RI) sometimes occurs after surgery. The aim of this study was to investigate the incidence and risk factors of early RI.

Materials and Methods: Thirty-one patients diagnosed with muscle-invasive bladder cancer who underwent RC with IC were analyzed in this study. Early RI was defined as a greater than 25% decrease in estimated glomerular filtration rate (eGFR) over the course of one year after surgery. The incidence and risk factors of early RI were evaluated.

Results: The mean preoperative eGFR of the patients was 69.6 mL/min/1.73 m². Early RI was observed in 7 (22.5%) patients. Multivariate analyses demonstrated that postoperative hydronephrosis was an independent risk factor for early RI ($P=0.018$). The mean intermediate-term eGFR change was -5.1 mL/min/1.73 m² in patients with early RI and was greater than that (-2.9) in patients without early RI, although neither were statistically significantly different.

Conclusion: Renal function after RC with IC decreased immediately over the course of one year, and postoperative hydronephrosis was an independent risk factor for early RI. Renal function had decreased slightly at intermediate-term follow-up with or without early RI.

Key words: renal function, radical cystectomy by ileal conduit, bladder cancer

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Introduction

Radical cystectomy (RC) is the gold standard therapy for muscle-invasive and high-risk bladder cancer¹⁾, although bladder preservation therapy for muscle-invasive bladder cancer (MIBC) has been developed and its good oncological and functional outcomes were recently reported²⁾.

MIBC patients undergoing RC have a high risk of renal impairment^{3–5)} because of advanced age, comorbidities such as diabetes or hypertension, urinary tract infections, preoperative urinary tract obstructions due to disease, and the use of nephrotoxic agents for neo-adjuvant chemotherapy, including cisplatin.

In addition, postoperative events such as acute pyelone-

phritis, postoperative hydronephrosis as a result of anastomosis strictures, and adjuvant chemotherapy worsen renal function in patients after RC with urinary diversion.

After RC, MIBC patients face a potential risk of early renal impairment because of postoperative urinary obstruction or acute pyelonephritis, which often occurs in the acute phase. However, the incidence, severity, and risk factors of early renal impairment after RC have not yet been fully investigated. Furthermore, the impact of early renal impairment on long-term renal function has not yet been clarified.

In this study, we evaluated the severity of the decrease in renal function one year after RC with IC. The incidence and risk factors for early renal impairment after RC were evaluated. The change in intermediate-term renal function from one to five years after RC was assessed and compared in patients with or without early renal impairment.

Materials and Methods

In the study, 56 patients who were diagnosed with locally advanced MIBC and underwent RC at a single institute between 2005 and 2015 were included. This study was approved by the institute's committee on human research. Of these, 45 (80%) patients received ileal conduit urinary

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diversion, and all ileal conduit procedures were performed by Bricker's method⁶. The remaining 11 patients (2 patients with neobladders and 9 patients with ureterostomy) without ileal conduit urinary diversions were excluded. We also excluded 7 patients who died of bladder cancer within 12 months, 5 patients with solitary kidneys, and 2 patients who underwent preoperative hemodialysis. Only the remaining 31 patients were included in the present study.

The clinical data were retrospectively collected from the institute's medical records.

The clinical variables included in this study were age at RC, gender, history of hypertension, history of diabetes mellitus, preoperative estimated glomerular filtration rate (eGFR), clinical T stage, receipt of neoadjuvant chemotherapy, presence of preoperative hydronephrosis, presence of postoperative hydronephrosis, occurrence of postoperative acute pyelonephritis, and receipt of adjuvant or salvage chemotherapy. Serum creatinine level was recorded preoperatively and at one, three, six, and twelve months after RC, and was then annually recorded for up to 5 years. In patients with neoadjuvant chemotherapy, serum creatinine level before chemotherapy was used as preoperative data.

The eGFR was calculated based on a formula by the Japanese Society of Nephrology ($eGFR [mL/min/1.73 m^2] = 194 \times \text{serum creatinine}^{-1.094} \times \text{Age}^{-0.287} [\times 0.739 \text{ if female}]^7$).

The lowest eGFR over the course of one year after RC was collected and the decrease was compared to preoperative eGFR was calculated. Early renal impairment was defined as a greater than 25% decrease from the lowest eGFR^{8,9}.

Intermediate term eGFR changes were evaluated annually from one to five years after RC in patients with or without early renal impairment.

Univariate and multivariate logistic regression analyses were conducted to evaluate the risk factors of early renal impairment using the clinical variables described above. Intermediate-term eGFR changes were compared using Fisher's exact test. All analyses were carried out using JMP version 11.2.0 (SAS Institute, Cary, NC, USA). A *P* value <0.05 was considered statistically significant.

Results

The median follow-up period was after 57 (12 to 184) months. Patient characteristics are shown in Table 1. In this cohort, 26 (83.9%) patients were male, and the median age was 70 years old. Twelve (38.7%) patients with hypertension required medication, and only one patient had diabetes mellitus. The median (mean) preoperative eGFR was 67.9 (69.6) mL/min/1.73 m², and 8 (25.8%) patients had preoperative chronic kidney disease with stages greater than 3 (eGFR <60 mL/min/1.73 m²).

A total of 19 (61.3%) patients received neoadjuvant chemotherapy with gemcitabine and cisplatin.

Table 1 Patients' characteristics

| | n=31 |
|---|------------------|
| Age (years) | 70 (51–79) |
| Male gender | 26 (83.9) |
| Preoperative eGFR, mL/min/1.73 m ² | 67.9 (40.1–95.4) |
| Preoperative eGFR < 60 mL/min/1.73 m ² | 8 (25.8) |
| Diabetes mellitus | 1 (3.2) |
| Hypertension | 12 (38.7) |
| Preoperative hydronephrosis | 7 (22.6) |
| Postoperative hydronephrosis | 10 (32.3) |
| Postoperative acute pyelonephritis | 2 (6.5) |
| Clinical T stage | |
| T2 | 24 (77.4) |
| T3 | 7 (22.6) |
| Neoadjuvant chemotherapy | 19 (61.3) |
| Adjuvant chemotherapy | 3 (9.7) |

Continuous variables were expressed as medians (range) and categorical variables were expressed as numbers (%).

Preoperative hydronephrosis due to disease was observed in 7 (22.6%) patients. Three patients recovered from it after urinary diversion. The remaining 4 patients did not, and 3 of them required a ureteral stent or percutaneous nephrostomy replacement.

Six patients newly developed hydronephrosis after urinary diversion. Thus, 10 patients experienced postoperative hydronephrosis. One of these six patients required percutaneous nephrostomy due to acute pyelonephritis.

Only 3 patients received adjuvant or salvage chemotherapy including cisplatin, while postoperative acute nephritis was observed in 2 patients.

Early renal impairment

The median (mean) lowest eGFR over the course of one year after RC with an ileal conduit was 60.5 (60.8) mL/min/1.73 m², which decreased by 8.8 mL/min/1.73 m² (–11.5%) compared to the preoperative eGFR.

Early renal impairment was observed in 7 (22.5%) patients.

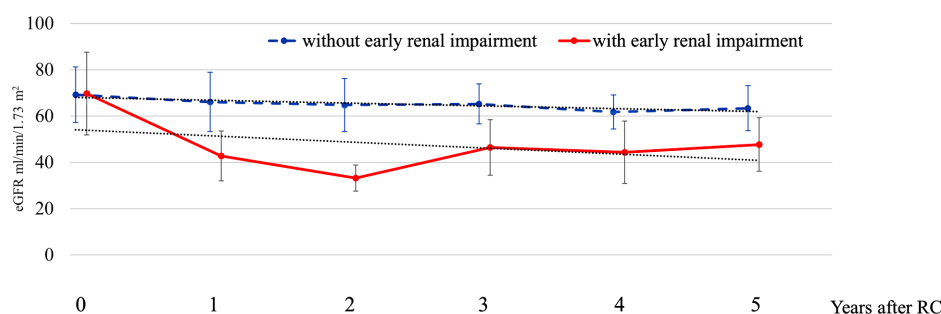
Table 2 shows the univariate and multivariate analyses for the risk factors of early renal impairment. Postoperative hydronephrosis and male gender were associated with early renal impairment in univariate analysis but the presence of preoperative low eGFR was not. In multivariate analysis, postoperative hydronephrosis was an independent risk factor for early renal impairment (*P*=0.018). Diabetes, adjuvant or salvage chemotherapy, and acute pyelonephritis were not included in analyses because of their small sample sizes.

Intermediate-term eGFR change

The mean eGFR change from one year to up to five years after RC was –3.5 mL/min/1.73 m² in the total cohort. Fig-

Table 2 Risk factors for early renal impairment

| Variables | Univariate | | Multivariate | |
|------------------------------|--------------|---------|--------------|---------|
| | Hazard ratio | P value | Hazard ratio | P value |
| Age ≥ 70 years | 1.98 | 0.417 | – | – |
| Male gender | 2.28 | 0.048 | 1.56 | 0.054 |
| Hypertension | 1.19 | 0.806 | – | – |
| Preoperative eGFR < 60 | 1.90 | 0.407 | – | – |
| Neoadjuvant chemotherapy | 1.69 | 0.523 | – | – |
| Preoperative hydronephrosis | 1.06 | 0.959 | – | – |
| Postoperative hydronephrosis | 6.45 | 0.014 | 5.94 | 0.018 |



| | 0 | 1 | 2 | 3 | 4 | 5 |
|---|----|----|----|----|----|----|
| Number of patients at risk without early renal impairment | 24 | 24 | 20 | 18 | 13 | 13 |
| with early renal impairment | 7 | 7 | 3 | 3 | 3 | 2 |

Figure 1 The intermediate-term eGFR changes in patients with or without early renal impairment.

Figure 1 shows the intermediate-term eGFR change in patients with or without early renal impairment. The mean eGFR change was $-5.1 \text{ mL/min/1.73 m}^2$ in patients with early renal impairment, and $-2.9 \text{ mL/min/1.73 m}^2$ in patients without early renal impairment.

There was no statistically significant difference in the mean intermediate-term eGFR change between the two groups ($P=0.154$).

Discussion

Early renal impairment

In this study, eGFR decreased immediately over the course of one year after RC with an ileal conduit, with the mean early decrease from preoperative eGFR being $8.8 \text{ mL/min/1.73 m}^2$ (-11.5%).

This immediate decrease in renal function after RC has been described in several studies. Rouanne et al. showed a similar eGFR decrease ($-9 \text{ mL/min/1.73 m}^2$) in the first year after RC with an ileal conduit similar to that in our study¹⁰.

This early eGFR decrease over the course of one year occurred in a similar proportion (-9.5 to 12%) of patients who underwent another urinary diversion, including a neobladder^{8,11}.

Early renal impairment was observed in 22.5% patients in this cohort, and postoperative hydronephrosis was an independent risk factor for early renal impairment.

Makino et al. also reported that early renal impairment defined as a greater than 25% decrease in eGFR was observed in 20% of patients after RC, and that urinary obstruction (ureteroenteric stricture) was the sole risk factor of early renal impairment⁸.

A study has shown a relationship between postoperative grade and duration of hydronephrosis as well as renal function after urinary diversion, wherein they found that postoperative transient hydronephrosis had no significant influence on renal function one year after urinary diversion¹¹.

If severe postoperative hydronephrosis has only newly occurred, it can cause acute renal failure or urinary tract infections. Therefore, such severe postoperative hydrone-

phrosis must be treated immediately by ureteral stent replacement or percutaneous nephrostomy so that the hydronephrosis improves.

Newly postoperative low-grade hydronephrosis not requiring urgent treatment has been observed and can remain, however, which could explain early renal impairment after RC with urinary diversion.

Severe preoperative hydronephrosis due to bladder cancer can be improved by urinary diversion, but some patients do not completely recover if the duration of ureteral dilation was prolonged. Thus, the continuance of pre- and post-low-grade hydronephrosis can also worsen renal function in the early phase after RC.

Postoperative hydronephrosis newly developed in 19% of patients in this study, and all new hydronephrosis cases were due to ureteroenteric strictures. In previous studies, ureteroenteric strictures were also observed in a certain proportion of patients (12 to 15%) after undergoing RC with urinary diversion other than ileal conduits^{3,8}.

In this study, 4 of 10 patients with postoperative hydronephrosis underwent ureteral stent replacement or percutaneous nephrostomy to improve their hydronephrosis. Two patients recovered their renal function while the remaining two experienced early renal impairment.

Postoperative hydronephrosis occurs at a certain rate after RC with any urinary diversion and is one of the main reasons for early renal impairment. This is, however, a modifiable and curative factor. Surgeons should make every effort to carry out precise surgical anastomosis in urinary diversion. The appropriate timing for the treatment of postoperative hydronephrosis after RC should also be investigated and clarified.

Intermediate-term renal function

Following an immediate decrease in the first year, eGFR decreased slightly after RC with an ileal conduit.

The intermediate-term eGFR decrease was greater in patients with early renal impairment than in those without early renal impairment, though no statistically significant difference was found.

Several studies have investigated the risk factors for renal impairment after RC in the intermediate to long term^{3,4,8,9}. Hatakeyama *et al.* showed that postoperative hydronephrosis, as well as older age, preoperative eGFR, and cutaneous ureterostomy, were risk factors for stage 3b chronic kidney disease five years after RC¹².

During the long-term follow-up of ten years, urinary obstruction was reported to be a risk factor for decreased renal function after RC with an ileal conduit, as well as diabetes or hypertension⁴.

Therefore, the continuance of hydronephrosis or urinary obstruction after urinary diversion could be an important risk factor for both early- and late-phase decreases in renal function.

In this study, the mean eGFR change was greater in patients with early renal impairment compared to those without early renal impairment during the intermediate term. However, early renal impairment did not influence intermediate-term renal function. To clarify the impact of hydronephrosis and early renal impairment on long-term renal function, further investigations with more patients having long-term follow-ups are warranted. Clinicians must continue to pay careful attention to renal function after RC during long-term follow-ups with patients, especially those with hydronephrosis or early renal impairment.

Our study was limited by its retrospective design and small number of patients.

Although diabetes has a considerable effect on renal function, we did not evaluate the association between diabetes and renal function after RC since there was only one patient with diabetes included in this study.

Although the impact of postoperative hydronephrosis on renal function can vary with the grade of hydronephrosis, the grade of hydronephrosis was not evaluated in this study.

Further studies that consider the comorbidity and severity of hydronephrosis are needed to clarify renal impairment after urinary diversion.

Renal function after RC with an ileal conduit was affected by both urinary diversion and non-diversion-related factors. For various reasons, patients undergoing RC have a risk of acute and chronic renal impairment. One such urinary diversion-related factor—hydronephrosis—is the most important risk factor for renal impairment.

Precise surgical procedures to avoid postoperative hydronephrosis and to ensure appropriate treatment for postoperative hydronephrosis may be crucial facets in preserving renal function.

Conclusion

Renal function after RC with an ileal conduit decreased immediately over the course of the first year, with postoperative hydronephrosis being an independent risk factor for acute decreases in renal function. Renal function had decreased slightly over the following five years with or without early renal impairment.

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Author Contributions: Motohiro Fujiwara: Acquisition of data, analysis of data and drafting of the manuscript; Naoko Kawamura: Conception, design and statistical analysis; Tetsuo Okuno: Supervision.

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