

Long-term Changes in Renal Function, Blood Electrolyte Levels, and Nutritional Indices After Radical Cystectomy and Ileal Conduit in Patients with Bladder Cancer

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Purpose: To assess the long-term changes in renal function, blood electrolyte levels, and nutritional indices after radical cystectomy and ileal conduit in patients with bladder cancer.

Patients and Methods: In 129 patients who underwent radical cystectomy and ileal conduit, we evaluated clinicopathologic features, complications, and the change in the estimated glomerular filtration rate (eGFR) from baseline to 1, 2, 3, 4, 5, and 10 years postoperatively. Two nutritional indices, the geriatric nutritional risk index (GNRI) and prognostic nutrition index (PNI), were calculated with laboratory tests.

Results: In the ileal conduit group, a parastomal hernia was observed in 10% of patients, whereas 13% had an ureteroenteric anastomotic stricture, which was associated with greater decline in the eGFR postoperatively. The first 5 year-decline in the eGFR was 1.74 mL/min/1.73 m²/year. The levels of only potassium showed a significant increase at 1 year postoperatively (mean: 4.34 mEq/L) and remained high compared with the baseline (4.14 mEq/L). Evaluation of the nutritional indices demonstrated that the GNRI, and not PNI, showed a significant, transient increase from 1 to 4 years (range: 108–110) postoperatively compared with the baseline (105).

Conclusion: The first 5 year-decline was much higher than that among Japanese individuals who participated in an annual health examination program. Further research should be performed to identify an appropriate strategy for selecting the suitable type of urinary diversion and postoperative nutritional interventions to improve the clinical outcome of patients with bladder cancer.

Keywords: Urinary Bladder Neoplasms; Cystectomy; Urinary Diversion; Kidney Failure, Chronic; Electrolyte, Nutritional Status

INTRODUCTION

Radical cystectomy (RC), with or without perioperative, systemic chemotherapy, is the standard treatment for selected patients with high-risk, non-muscle invasive bladder cancer (stage Tis or Ta/1) and muscle-invasive urothelial cancer of the bladder (stage \geq T2)^(1,2). RC requires reconstruction of the lower urinary tract, which is called urinary diversion (UD). Although ureterosigmoidostomy was the first widely selected UD, decrease of renal function with time, metabolic acidosis, and the risk of secondary bowel adenocarcinoma were significant disadvantages of this type of surgery and limited its clinical usefulness⁽³⁾. Subsequent advances in technology have provided several reconstructive options and substantial improvements in terms of both functional outcomes and health-related quality of life.

Among the currently available options for UD after RC, ileal conduit is considered the “gold standard” for those with incontinent UD and has remained the major choice for patients with contraindications to continent UD. The latest version of European Association of Urology

guideline recommends offering an orthotopic bladder substitute or ileal conduit diversion to male and female patients lacking any contraindications and who have no tumour in the urethra or at the level of urethral dissection⁽⁴⁾. Ileal conduits are relatively easy and quick to construct, leading to a minimized rate of postoperative complications^(5,6). However, RC and accompanying UD are associated with high risks of perioperative and long-term morbidity and mortality, including subsequent decline in renal function^(7,8). For many years, one of the goals of UD was to protect renal function and restore anatomy, because a high proportion of bladder cancer patients present with impaired renal function⁽⁹⁾. Although several reports have described deterioration of renal function over time after ileal conduit⁽¹⁰⁻¹³⁾, definite conclusions could not be made because of variations in surgical skill and patient backgrounds. There is only limited information regarding long-term complications and changes in blood electrolyte levels and nutritional indices after ileal conduit. In this study, we explored the incidence of complications and post-surgical, chronological changes in blood examination results

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Table 1. Characteristics of 160 patients undergoing radical cystectomy and comparison between urinary diversion.

Variables	Total cases	Type of UD			3 group comparison†	P value	
		IC	CU	NB		2 group comparison‡ IC vs CU	2 group comparison‡ IC vs NB
No. of cases	160 (100%)	129 (81%)	23 (14%)	8 (5%)	-	-	-
Sex	Male	127 (79%)	103 (80%)	18 (78%)	7 (88%)	0.84	0.99
	Female	33 (21%)	22 (20%)	5 (22%)	1 (12%)		
ECOG-PS	0	134 (84%)	111 (86%)	20 (87%)	7 (88%)	0.97	0.99
	1–3	26 (16%)	18 (14%)	3 (13%)	1 (12%)		
Charlson Comorbidity Index	0	133 (83%)	108 (83%)	17 (74%)	8 (100%)	0.22	0.25
	1–3	27 (17%)	21 (17%)	6 (26%)	0 (0%)		
Clinical T category	T1/Tis	9 (6%)	7 (5%)	2 (9%)	0 (0%)	0.07	0.69
	T2	71 (44%)	55 (43%)	11 (48%)	5 (63%)		
	T3	45 (28%)	41 (32%)	0 (0%)	2 (25%)		
	T4	35 (22%)	26 (20%)	8 (35%)	1 (12%)		
Clinical N category	N0	146 (91%)	116 (90%)	22 (96%)	8 (100%)	0.44	0.69
	N ≥1	14 (9%)	13 (10%)	1 (4%)	0 (0%)		
Carcinoma in situ	Negative	99 (62%)	82 (64%)	11 (48%)	6 (75%)	0.26	0.17
	Positive	61 (38%)	47 (36%)	12 (52%)	2 (25%)		
Neoadjuvant chemotherapy	No	97 (61%)	71 (55%)	20 (87%)	6 (75%)	0.011	0.46
	Yes	63 (39%)	58 (45%)	3 (13%)	2 (25%)		
Adjuvant chemotherapy	No	134 (84%)	107 (83%)	20 (87%)	7 (88%)	0.85	0.77
	Yes	26 (16%)	22 (17%)	3 (13%)	1 (12%)		
Age at RC	(mean ± SD)	70.0 ± 8.7	69.8 ± 8.3	73.9 ± 10.1	63.3 ± 5.3	0.0013	0.049
BMI (Kg/m ²)	(mean ± SD)	22.5 ± 3.9	22.4 ± 3.7	23.3 ± 5.3	23.2 ± 2.7	0.67	0.99
Serum Creatinine (mg/dL)	(mean ± SD)	1.09 ± 0.95	1.02 ± 0.88	1.55 ± 1.30	0.95 ± 0.36	0.025	0.022
Estimated GFR (mL/min/1.73m ²)	(mean ± SD)	62.0 ± 22.4	64.6 ± 21.9	46.5 ± 20.6	65.7 ± 18.4	0.0022	0.02
PNI	(mean ± SD)	49.8 ± 5.4	49.8 ± 5.3	48.2 ± 5.4	54.8 ± 3.8	0.015	0.88
GNRI	(mean ± SD)	95.3 ± 19.3	95.3 ± 19.9	100.1 ± 11.2	99.7 ± 28.6	0.15	0.99

UD, urinary diversion; IC, ileal conduit; CU, cutaneous ureterostomy; NB, ileal orthotopic neobladder; ECOG-PS, the Eastern Cooperative Oncology Group Performance Status; RC, radical cystectomy; BMI, body mass index; eGFR, estimated glomerular filtration rate; PNI, prognostic nutritional index; GNRI, geriatric nutritional risk index; SD, standard deviation; †, Kruskal-Wallis or Chi-squared test; ‡, post hoc Dunn's test or Fisher's exact test

in patients with ileal conduits and investigated the risk factors of the development of this condition.

PATIENTS AND METHODS

Data collection and follow-up

The ethics committee of the Nara Medical University approved this study, and all participants provided informed consent (reference ID: 1256). The study was conducted in compliance with the study's protocol and in accordance with the provisions of the Declaration of Helsinki (2013).

The medical charts of 182 patients who underwent curative RC between 2000 and 2017 were retrospectively reviewed. Eight patients were excluded because they underwent hemodialysis and did not require any UD procedure, and 14 patients were excluded because they had insufficient follow-up data, leaving 160 (88%) patients for inclusion in this study. Of these, 129 (81%), 23 (14%), and 8 (5%) patients underwent ileal conduit, cutaneous ureterostomy, and ileal orthotopic neobladder, respectively (Figure 1). UD procedure was selected at a physician's discretion. Follow-up was performed according to our institutional protocol⁽¹⁾. Laboratory data, including the serum creatinine, albumin, blood lymphocyte, and blood electrolyte (sodium, potassium, chloride, and calcium) levels, were measured at baseline and follow-up visits at regular intervals after RC and were obtained from the patients' medical charts. The estimated glomerular filtration rate (eGFR)

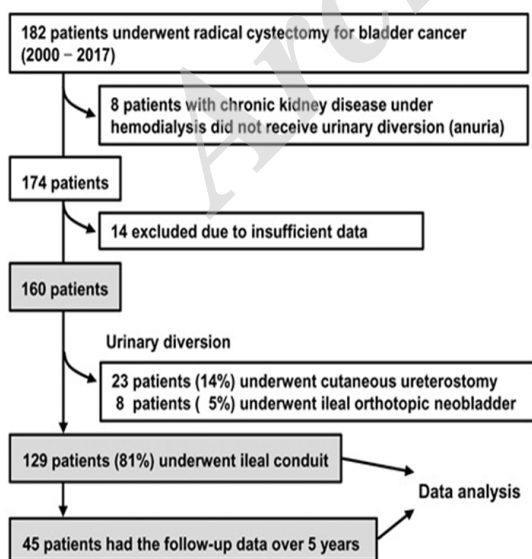


Figure 1. Flow chart for creating the patient dataset.

Table 2. The early and late complications in 129 patients undergoing ileal conduit.

Early or late	Complications	Total	Clavien-Dindo classification			
			I / II	IIIa	IIIb	IV
Early (< 90 days)	Bowel obstruction	32 (25%)	22 (17%)	8 (6%)	2 (2%)	
	Surgical site infection	29 (22%)	13 (10%)	10 (8%)	5 (2%)	1 (1%)
	Pelvic abscess	19 (15%)	1 (1%)	10 (8%)	8 (6%)	
	Ureteroenteric anastomotic stricture	9 (7%)	5 (4%)	4 (3%)		
	Intestinal anastomotic leakage	7 (5%)		7 (5%)		
	Ureteroenteric anastomotic leakage	3 (2%)	1 (1%)	2 (2%)		
Late (> 90 days)	Parastomal hernia	13 (10%)	12 (9%)		1 (1%)	
	Ureteroenteric anastomotic stricture	8 (6%)	2 (2%)	6 (5%)		
	Abdominal incisional hernia	8 (6%)	5 (4%)		3 (2%)	
	Stomal stenosis	3 (2%)	1 (1%)	2 (2%)		

was calculated using the Modification of Diet in Renal Disease Study formula for Japanese patients: $eGFR \text{ mL/min/1.73 m}^2 = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} (\times 0.739 \text{ for women})$ (14). The chronic kidney disease (CKD) stages were defined according to the eGFR (15). The Charlson comorbidity index, which was updated in 2011, was applied for evaluating preoperative comorbidities (16). The stage was assigned according to the 2009 TNM classification of the Union of International Cancer Control.

Calculation of nutrition-based markers

The geriatric nutritional risk index (GNRI) and prognostic nutrition index (PNI) were calculated using laboratory data that were measured during the follow-up period (17). The GNRI score was calculated using the serum albumin levels and ratios of the actual body weight to ideal body weight, which was $22 \times$ the square of height in meters. Thus, $GNRI = 14.89 \times \text{the serum albumin concentration (g/dL)} + 41.7 \times (\text{body weight in kg/ideal body weight})$. The PNI was calculated as $10 \times \text{the serum albumin level (g/dL)} + 0.005 \times \text{the total lymphocyte count (per mm}^3)$. Both indices were reported as continuous variables for the analyses.

RC, lymphadenectomy and UD procedures

Of the 129 patients with ileal conduit, 103 (80%) underwent open RC and 26 (20%) underwent laparoscopic RC. Lymphadenectomy procedures, including removal of the obturator, external iliac, common iliac, and parasacral lymph node chains, were performed basically according to the extended template (18). Regarding the construction of ileal conduits, the terminal ileum was preserved to ensure that bile salts, vitamin B12, and fat-soluble vitamins were adequately maintained (5). A segment of the ileum of approximately 20 cm was isolated and used for UD. The ureters were split and anastomosed to the oral side separately in an open end-to-side manner. The ileal segment of the anal side was anastomosed to the abdominal wall in a nipple-to-stoma manner. Cutaneous ureterostomy was performed by two methods: one ureter was brought across the midline and the two ureters were placed side by side in a double-barrel fashion or the two distal ureteric ends were placed individually. The stoma for cutaneous ureterostomy was created according to the Toyoda method (19). In orthotopic ileal neobladder, ileal construction was performed according to Studer reservoir (20).

Evaluation of postoperative complications

Complications after RC were objectively evaluated according to the Clavien-Dindo classification system (21). Early and late complications were defined as complica-

tions occurring within 90 days of RC and 90 days after RC, respectively. Parastomal hernia is defined as any protrusion in the vicinity of the urostoma with the patient straining in a supine and an erect position (22).

Statistical analyses

The clinicopathological characteristics of the patients in this study were compared using the Kruskal-Wallis test, following the post hoc test (Dunn test), Chi-squared test, and Fisher's exact test, as appropriate. Continuous variables are expressed in means \pm standard deviations and shown in line charts. The normality was checked by Shapiro-Wilk test. The Student t-test, Mann-Whitney U test, paired t-test, or Wilcoxon's signed-rank test was used, as appropriate. The cumulative rate of complications was drawn using the Kaplan-Meier plot. The linear regression analysis was used to calculate the annual eGFR decrement. IBM SPSS version 21 (SPSS Inc., Chicago, IL, USA) and PRISM software version 7.00 (GraphPad Software, Inc., San Diego, CA, USA) were used for statistical analyses and data plotting, respectively. Statistical significance was set at $P < 0.05$, and all reported P -values were two-sided.

In the paired t -test for long-term changes in continuous values, power analysis using G*Power (version 3.1.9.2) was performed a priori, and showed that a sample of 34 patients was required to detect a between-group difference given an effect size of 0.50, a power of 0.80 and an alpha of 0.05.

RESULTS

Patient characteristics

The clinicopathological characteristics of the 160 patients undergoing RC and UD are listed in **Table 1**. The median follow-up period after RC was 44.1 months. During the follow-up period, 49 patients died (31%), including 35 with recurrent disease (22%). Other causes of death were acute myocardial infarction in two patients, pneumonia in two, panperitonitis due to intestinal perforation in two, other malignancy in two, chronic kidney disease in one, urinary tract infection in one, heart failure in one, and unknown in three, respectively. Sixty-nine patients (39%) received two to three cycles of platinum-based neoadjuvant chemotherapy and 26 patients (16%) received two to three cycles of platinum-based adjuvant chemotherapy. Almost half of the patients undergoing ileal conduit received neoadjuvant chemotherapy, whereas only 13% of patients undergoing cutaneous ureterostomy received neoadjuvant chemotherapy ($P = 0.005$). Forty-one (32%) of the 129 patients undergoing ileal conduit had stage T3

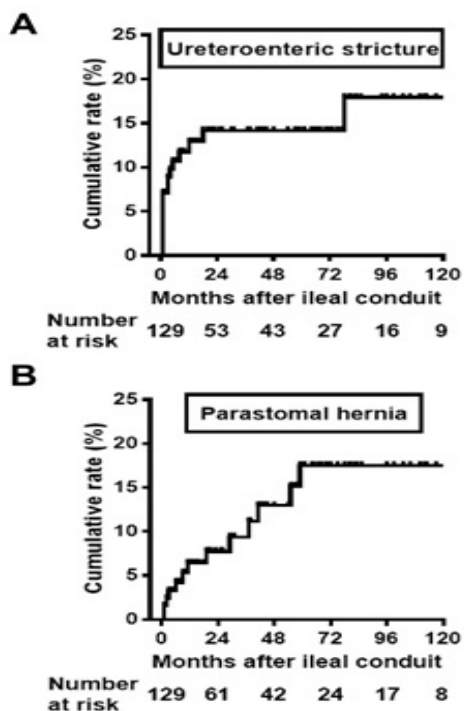


Figure 2. Kaplan-Meier plots for calculating the cumulative incidence of complications. (A) ureteroenteric stricture and (B) parastomal hernia. The numbers at risk are shown.

disease, whereas no patients with stage T3 disease underwent cutaneous ureterostomy ($P = 0.018$). Patients undergoing ileal conduit were younger than those who underwent cutaneous ureterostomy, but older than those who underwent orthotopic neobladder. The eGFR in patients with cutaneous ureterostomy was lower than that in those with ileal conduit ($P = 0.02$). However, sex, performance status, the Charlson comorbidity index, clinical N category, presence of carcinoma in situ, and adjuvant chemotherapy were not associated with the selected type of UD.

Early and late complications

Both early and late complications were observed after RC and ileal conduit. The incidence of complications, expressed as numbers and percentages, is summarized in **Table 2**. The most frequent complication was bowel obstruction (32 patients, 25%), which sometimes required an indwelling ileus tube or surgical intervention, such as synectenterotomy. Ureteroenteric anastomotic stricture, ureteroenteric anastomotic leakage, parastomal hernia, and stomal stenosis were complications that were specific to ileal conduit. Among 17 patients presenting with an ureteroenteric stricture, bilateral strictures were observed in 5, while the remaining 12 had a unilateral stricture. Regarding stoma-related, late complications during the follow-up period, parastomal hernia was observed in 13 patients, one of whom underwent repair surgery using mesh. Among the patients presenting with complications, the median time from ileal conduit to the diagnosis of ureteroenteric stricture and parastomal hernia was 29 and 11 months, respectively (**Figure 2**). Three patients (2%) had stomal steno-

sis; however, none had prolapse of the stoma.

Baseline and postoperative change in renal function

The baseline eGFR of the 129 patients undergoing ileal conduit was 64.6 ± 21.9 mL/min/1.73 m². The CKD stage was G1 in 9 (7%), G2 in 54 (42%), G3a in 34 (26%), G3b in 14 (11%), and G4 in 5 (4%) patients. The detailed 5-year follow-up data of 45 (35%) of these 129 patients were available and subjected to the analyses of the change in renal function over time. In these 45 patients, the CKD stage was G1 in 4 (9%), G2 in 19 (42%), G3a in 15 (33%), G3b in 6 (13%), and G4 in 1 (2%) patient, and this distribution was not statistically different from that of the remaining 84 of patients ($P=0.81$). The change in the eGFR after surgery was plotted on line graphs (**Figure 3A**). The mean eGFR was 72.6 at baseline, 71.9 at 1 year, 69.3 at 2 years, 66.7 at 3 years, 64.6 at 4 years, 63.9 at 5 years, and 62.1 at 10 years postoperatively. The first 5-year decrease in the eGFR was 8.7, and the next 5-year decrease was 2.2. During the first 5 years postoperatively, the eGFR decrease rate was 1.74 per year. From 5 to 10 years postoperatively, the eGFR decrease rate was only 0.55 per year. During the first 5 years following ileal conduit, the eGFR decline rate was 1.74 per year (**Figure 3A**). Along with the creatinine level and eGFR, the blood urea nitrogen (BUN) level was used to evaluate renal function and help diagnose renal disease. The BUN level significantly increased until 1 year postoperatively and did not continue to rise, and was not concordant with our observation of the eGFR (**Figure 3B**). The postoperative decrease rate of the eGFR was compared between patients with an ureteroenteric stricture and those without (**Figure 3C**). Patients with an ureteroenteric stricture had slightly higher decrease in the eGFR than did those without, although there was no significant difference. A similar analysis showed that perioperative chemotherapy (neoadjuvant or adjuvant) did not affect the decrease rate of the eGFR after ileal conduit (**Figure 3D**).

The CKD stage of the 45 selected patients at baseline, 3 years, and 5 years is shown in **Figure 3E**. The number of patients with stage G1/G2 decreased, whereas that of patients with stage G3/G4 increased over time. Hemodialysis was required for two patients (4%) (CKD stage 5D) during the follow-up period. One of these patients was 53-year-old woman with an eGFR of 23.8 at the baseline examination and the second was 78-year-old man with an eGFR of 42.4 at baseline.

Postoperative changes in blood electrolyte levels and nutritional indices

The change in blood electrolyte levels and nutritional indices from baseline to 10 years after ileal conduit was plotted on line graphs (**Figures 4A-F**). Among the four blood electrolytes that were tested, only potassium showed a significant increase at 1 year postoperatively, and its level remained high compared to that at baseline (**Figure 4B**). An evaluation of the nutritional indices demonstrated that the GNRI showed a significant, transient increase from 1 to 4 years postoperatively (**Figures 4F, G**). In contrast, the PNI did not change postoperatively (**Figure 4H**).

DISCUSSION

In this single-center study, we reported the postoperative complications and changes over time in various laboratory examination results after RC and ileal con-

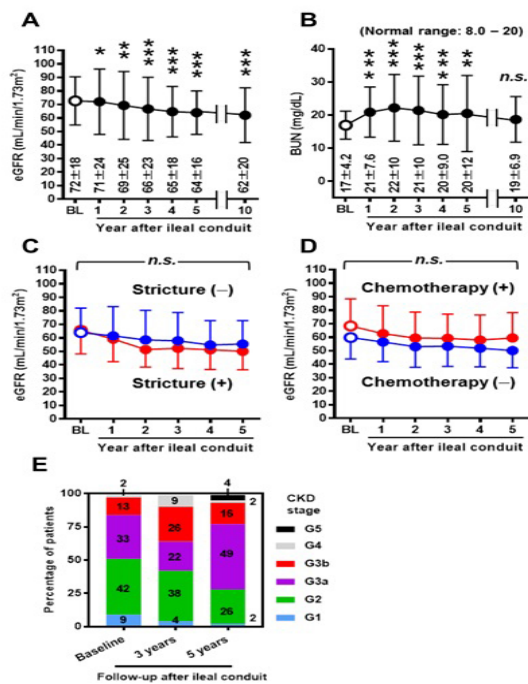


Figure 3. Change over time in the renal function after radical cystectomy and ileal conduit. A and B: The change over time in the eGFR and BUN was shown and plotted with means \pm standard deviations. Values at each postoperative time point (1, 2, 3, 4, 5, and 10 years) were compared with values at baseline using the paired t-test or Wilcoxon's signed-rank test as appropriate. n.s.: not significant; *, $P < 0.05$; **, $P < 0.01$; and ***, $P < 0.001$. The data from 21 patients are available for 10-year study. C and D: Comparison of changes in the eGFR postoperatively according to ureteroenteric strictures and perioperative platinum-based chemotherapy. The data of patients with an ureteroenteric stricture (red) and those without (blue) were compared at each time point using the Mann-Whitney U -test. n.s.: not significant (B). The data of patients who received perioperative platinum-based chemotherapy (red) and those who did not (blue) were compared as well (C). D: The distribution of patients according to the CKD stage is shown as a bar plot for the baseline, 3-year postoperative, and 5-year postoperative values. eGFR: estimated glomerular filtration rate; BUN: blood urea nitrogen; CKD: chronic kidney disease

duit. Invasive bladder cancer has aggressive features and requires intensive interventions, such as RC and UD. To improve a patient's quality of life, long-term management of complications and changes after surgery has become essential. Substantial variability exists in the incidence of early and late complications after UD (3,7,8). The types and rates of complications depend on the selected UD, and these complications can be classified roughly into three types: bowel anastomosis-related, reservoir/conduit-related, and ureteroenteric anastomosis-related (23). In the present study, we focused on two postoperative complications: parastomal hernia and ureteroenteric stricture. A parastomal hernia occurs when the edges of the stoma come away from the muscle, allowing abdominal contents such as a section of the bowel or omentum to come out(22). Shimko et al. performed a large study of 1,057 patients with a median follow-up of 9.2 years and observed parastomal hernias in 14% of the patients (8), which was similar to the result of our cohort (10%). A

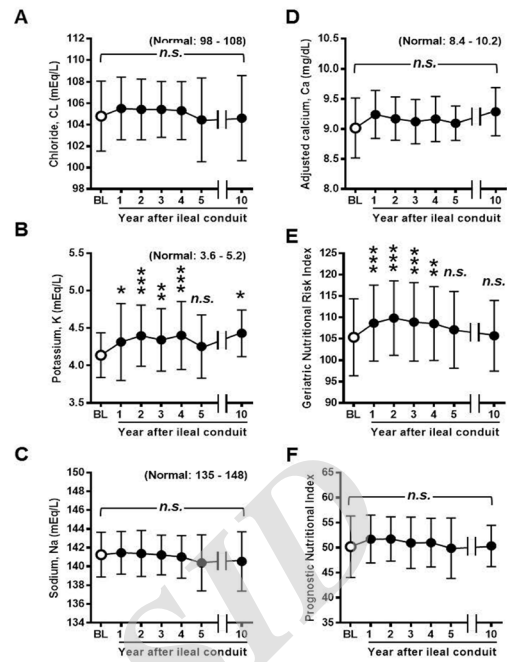


Figure 4. Time course of change in the blood electrolytes and nutrition index after radical and ileal conduit

symptomatic parastomal hernia leads to poor quality of life. While the hernias of most patients can be managed conservatively with stomal support, including an abdominal support belt, surgical intervention is required if there is incarceration or strangulation of the hernia, or other complications.

Because many patients with muscle-invasive urothelial cancer of the bladder have baseline renal impairment to some degree (partially owing to high age)(9,24), protecting renal function and the upper urinary tract after UD is one of the main clinical concerns. According to previous reports, more than half of the patients undergoing RC and UD experienced deterioration of renal function, regardless of the type of UD (13,25). Several risk factors, such as hypertension, diabetes mellitus, high age, baseline eGFR, postoperative acute pyelonephritis, and the type of UD, contribute to a decrease in the postoperative eGFR(10-13). We demonstrated that a ureteroenteric stricture could be associated with a decrease in the postoperative eGFR, although it did not reach statistical significance. Eisenberg et al. revealed that there was an association between ureteroenteric strictures and a decrease of more than 10 ml/min/1.73 m² in the eGFR in a multivariate analysis of 1,241 patients undergoing ileal conduit. According to a survey of the decline in renal function over 10 years in 120,727 participants aged 40 years or older, the average rate of eGFR decline was 0.36 per year (26). During the first 5 years following ileal conduit, the eGFR decline rate was 1.74 per year (Figure 3A), which was much higher than that of individuals who participated in an annual health examination program in Japan (0.36 per year).

A previous study reports metabolic acidosis rates of 14.8% at 1 month and 10.0% at 1 year after ileal conduit⁽²⁷⁾. A significant association between renal function and the development of metabolic acidosis was observed, and it was especially strong in the early postoperative period. The majority of patients present with clinically insignificant acidosis, but in some cases, acidosis can provoke bone demineralization and other complications. Bowel segment maintains its absorptive function and enables many substances such as urine, ammonia, hydrogen, and chloride to be reabsorbed into the blood flow. This results in metabolic, hyperchloremic acidosis and an increased load of nitrogen compounds, especially when the colonic part is used for UD. Acid-base imbalance is usually treated with sodium citrate, sodium bicarbonate, nicotinic acid, or chlorpromazine⁽²⁸⁾. Electrolyte disorders are more common in patients undergoing continent UD than in those with incontinent UD. When the ileum is used for UD, hypokalemia with coexisting acidosis is typical and problematic⁽²⁹⁾. Among our cohort, no patients experienced clinically symptomatic acidemia, hyperchloremic acidosis, hypokalemia, or hypocalcemia.

We previously reported that the PNI value showed transient deterioration at 1 and 3 months after RC, with a return to baseline values at 6 months⁽³⁰⁾. In the current study, we evaluated long-term postoperative changes in two nutritional indices. Although the PNI did not show any postoperative change, the GNRI value showed a significant, transient increase from 1 to 4 years postoperatively. The PNI was invented to predict the risk of complications after gastrointestinal surgery, and the GNRI was established to predict the risk of morbidity and mortality in hospitalized elderly patients. Few studies have addressed the nutritional status of patients undergoing RC and UD. The accuracy and utility of established nutritional indices such as the PNI, GNRI, and controlling nutritional status index should be confirmed using a larger cohort of patients.

The present study has several limitations. The first is its retrospective nature, with a potential selection bias; for example, some patients were excluded because their data were insufficient. There were missing data regarding the comorbidities including diabetic mellitus and hypertension, which could be potential risk factors for the decline in renal function. Third, this study includes only 45 patients in the subanalysis, which is considered to be a relatively low sample size.

CONCLUSIONS

We explored the long-term complications and change in renal function, blood electrolyte levels, and nutritional indices after RC and ileal conduit. Further studies should be performed to identify an appropriate strategy for selecting a suitable type of UD and postoperative nutritional interventions to improve the clinical outcome of surgery in these patients.

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