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Original Research Article

Renal Dysfunction after Rectal Cancer Surgery: A Long-term Observational Study

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Abstract
Objectives: Despite the high incidence of urinary dysfunction (UD) after rectal surgery, it remains questionable whether UD causes future chronic kidney disease (CKD). This study aimed to clarify the long-term trends in renal function and risk factors for future CKD after rectal resection.
Methods: For comparison, patients who underwent rectal resection (n = 129) and colectomy (n = 127) between 2006 and 2017 were identified. The estimated glomerular filtration rate (eGFR) ratio was calculated as the ratio to the baseline. "eGFR ratio < 0.75 at 3-year" was adopted as a surrogate indicator of future CKD.
Results: eGFR ratio significantly decreased in the rectal cohort compared with the colon cohort at 1.5 years (0.9 vs. 0.95, $p = 0.008$) and at 3 years (0.85 vs. 0.94, $p < 0.001$). Although the preoperative prevalence of CKD was lower in the rectal than the colon cohort (13.9% vs. 23.6%, $p = 0.055$), it was similar at 3 years (29.5% vs. 30.7%). In multivariate analysis, females, and cT4 were independent risk factors for future CKD, but UD itself was not.
Conclusions: Postoperative eGFR significantly decreased after rectal cancer surgery compared to colectomy. The prevalence of CKD more than doubled at 3 years after rectal resection. The female sex and cT4 tumor, instead of the UD, were independent risk factors for future CKD.

Keywords
chronic kidney disease, postoperative complication, rectal cancer, renal dysfunction, urinary dysfunction
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Introduction

Introducing the total mesorectal excision (TME) dramatically improved survival and local control in rectal cancer treatment[1]; additionally, autonomic nerve preservation succeeded in decreasing the risk of urinary dysfunction (UD). Recently, it has been expected that magnified visualization in minimally invasive surgery would achieve precise surgery, potentially leading to the preservation of urinary function[2,3]. However, the incidence of UD after rectal surgery is still high, reportedly 36%-59%[4,5], and remains a major problem. Although the combined resection of the autonomic nervous system for some locally advanced rectal cancers could be a possible reason, another major problem is a surgeon-related factor (i.e., unintentional nerve injury due to technical difficulty, carelessness, or limited skill). Many studies have discussed this issue from technical and anatomical points of view[6,7]. In the era of improving on-

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cologic outcomes after curative rectal resection, avoidance of unintentional UD remains a major surgical challenge.

Chronic kidney disease (CKD) is a global public health problem with a high economic burden on health systems. Additionally, it is a well-known independent risk factor for increased mortality and cerebro-cardiovascular disease development. Although CKD is mainly caused by lifestyle diseases, such as diabetes mellitus, and hypertension, surgeons should recognize that surgical stress and various postoperative complications can lead to CKD[8,9]. Cerebrospinal disease or spinal cord injury reduces bladder capacity. It causes repeated urinary tract infection (UTI), resulting in the triple onset of future CKD and over five times greater incidence of subsequent end-stage renal disease in the general population[10,11].

Similarly, whether UD after rectal surgery can increase the risk of developing future CKD remains a major clinical question. Another simple doubt surrounds the effect of anal preservation on future CKD because UD rarely develops after sphincter-preserving surgery (SPS) than non-SPS[12,13]. However, understanding the influence of postoperative UD and UTI on long-term renal function or the development of future CKD remains a challenge.

This study aimed to clarify the long-term transitions of renal function and the prevalence of CKD after rectal resection and to compare them with those after colectomy. Additionally, risk factors for future CKD after rectal surgery were analyzed, and the impact of postoperative UD on translation into future CKD was explored.

Methods

Patient selection

A retrospective analysis was performed based on information prospectively collected from the Nagoya University Hospital colorectal cancer anonymized database. Figure 1 shows the study flow diagram. As a rectal cohort, 235 stage I-III patients with a rectal adenocarcinoma located within 5 cm from the anal verge who underwent elective surgery with curative intent between April 2006 and April 2017 were selected. Of them, patients who died from any cause, developed recurrence, or were lost to follow-up within the years after surgery were excluded from observing changes in renal function for at least three years. Additionally, patients who previously, or simultaneously underwent urinary diversion or nephrectomy within three years of surgery were excluded. Furthermore, one patient who developed ureteral stenosis due to a common iliac aneurysm and two patients who underwent simultaneous gastrectomy were also excluded. Therefore, the remaining 129 patients were included in the rectal cohort.

In the present study, long-term postoperative renal dysfunction due to the surgery itself is to be evaluated; thus, patients after right-sided colectomy, without involving pelvic manipulation, and is rare to have postoperative dysuria due to the surgery itself, were selected as the comparison group. Two hundred and fifty-seven patients with stage I-III right-sided colonic adenocarcinoma who underwent elective right colectomy with curative intent between January and April during the same period were identified (colon cohort). Patients who died from any cause, developed recurrence, or were lost to follow-up within three years of surgery were excluded. Additionally, patients who had a history of pelvic surgeries (n = 18), underwent simultaneous multivisceral resection (n = 16), and had a history of surgeries or medication for urological disease (n = 11) were also excluded. As a result, the remaining 127 patients were included in the colon cohort.

This study was approved by the Nagoya University Hospital Institutional Review Board (#2020-0103). Written consent has been obtained from all patients.

Treatment

In the rectal cohort, all patients underwent TME, or more extended surgery using an open or minimally invasive approach. Unilateral or partial combined resection of the autonomic nervous system and/or adjacent organs was performed if necessary for R0 resection. According to the Japanese guidelines, lateral lymph node dissection was selectively indicated for stage II/III low rectal cancer[14]. The operative procedure was divided into two groups according to sphincter preservation. The SPS group included patients with anterior resection with the double stapling technique and intersphincteric resection with transanal hand-sewn anastomosis, whereas those with abdominoperineal resection and Hartmann's procedure with a permanent colostomy, causing posterior tilting of the urinary bladder into the deep pelvis, were classified in the non-SPS group. In the SPS group, diverting ileostomy was performed as appropriate, which was reversed 3-4 months after surgery or after administration of adjuvant chemotherapy. Neoadjuvant chemotherapy was given for some stage II/III patients as a part of our clinical trial or daily practice[15,16], whereas preoperative chemoradiotherapy (CRT) was indicated for limited patients when the radial margin was involved after neoadjuvant chemotherapy[17].

In the colon cohort, open, or laparoscopic right colectomy with lymphadenectomy was performed. In both cohorts, adjuvant chemotherapy was recommended for stage III or high-risk stage II patients. The decision regarding the treatment strategy was made in the multidisciplinary conference for the most part.

The patients were followed-up with routine blood tests, including serum creatinine every 3-6 months and computed tomography every 6-12 months up to 5 years.

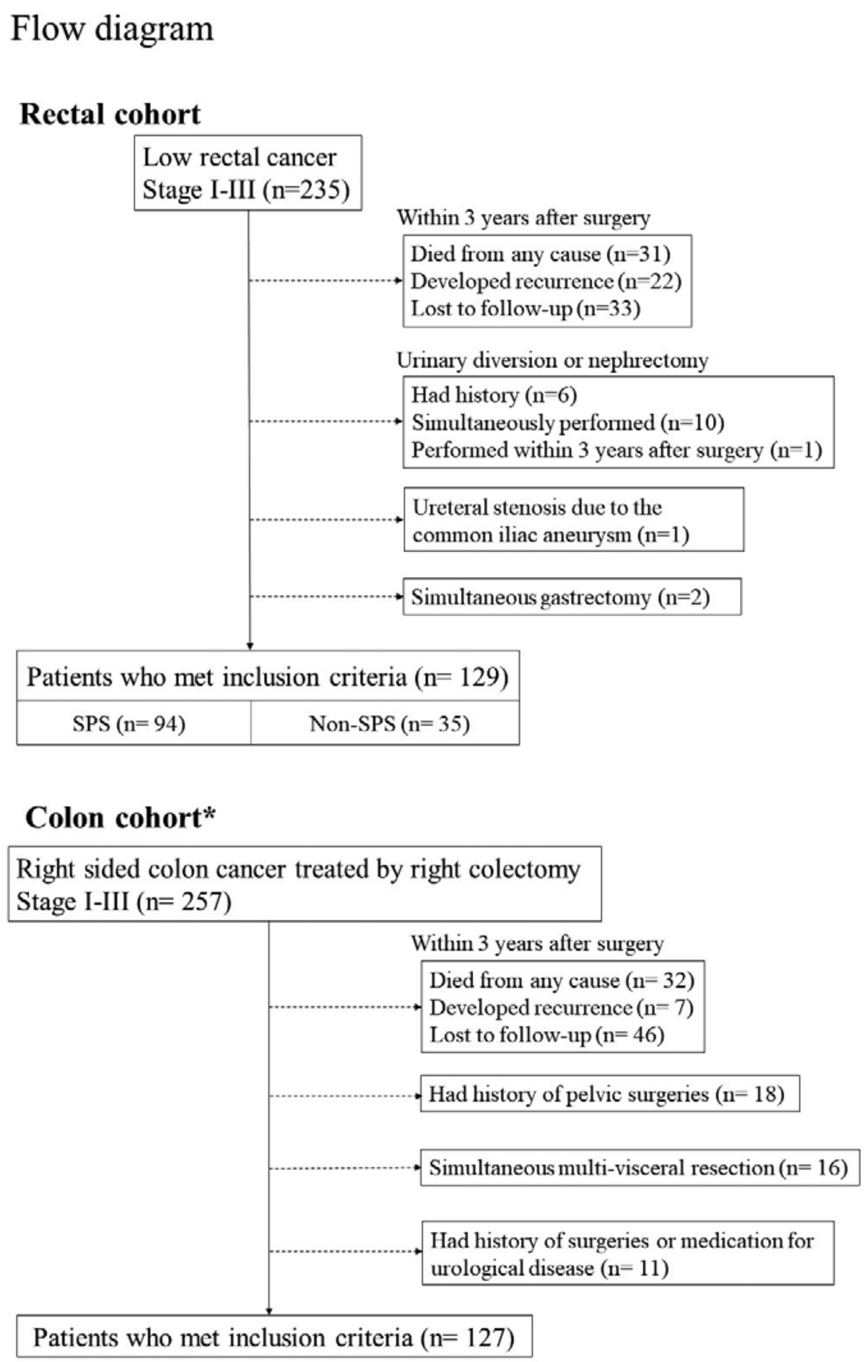

Figure 1.
Flow diagram. *Patients who underwent colectomy between January and April. SPS; sphincter-preserving surgery

Management and definition of postoperative urinary tract complications

Intra- and postoperative analgesics were intravenously administered, and no patient underwent epidural anesthesia. The urinary catheter was removed on postoperative Days 1-3. For patients with difficulty emptying their bladder, the urinary catheter was reinserted and removed a few days later for re-evaluation. For patients whose residual urine volume exceeded 50 ml, clean intermittent self-catheterization (CIC) was introduced several times daily. CIC was continued until the residual urine volume was reduced to 50 ml or less. Simultaneously, medications, such as alpha-1 blockers, and cholinergic drugs, were given to patients with difficulty emptying their bladder.

In the present study, UD was defined as the reinsertion of a urinary catheter and/or introduction of CIC postoperatively and was further divided into two types according to onset time: early UD during hospitalization and prolonged UD after discharge. UTI was clinically diagnosed based on symptoms and/or urine sediment or culture and was treated with antibiotics. UTI during the initial hospitalization was defined as an early UTI, whereas that requiring unexpected readmission was regarded as a late UTI.

Evaluation of renal function

As an index of renal function, the estimated glomerular filtration rate (eGFR) was adopted, which was calculated according to the Japanese Society of Nephrology and Pharmacotherapy using the following formula[18]:

eGFR (mL/min/1.73 m^2) = 194 × $age^{-0.287}$ × serum creatinine $(mg/dL)^{-1.094}$ (× 0.739, in females)

The eGFR was obtained at the following points: preoperatively as a baseline and every six months after surgery. The eGFR ratio was calculated as the ratio to the baseline at each point. CKD was defined as an eGFR of less than 60 mL/min/1.73 m^2 according to the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines[19].

CKD is the final stage of progressive renal dysfunction, and long-term follow-up is often indispensable for the diagnosis; therefore, it is essential to predict high risk in patients and prevent them from reaching CKD. Meanwhile, an eGFR reduction of 25% or more within three years was generally accepted as a predictive factor for end-stage CKD or cardiovascular death[20-22]. In this study, an eGFR ratio < 0.75 at three years was adopted as a surrogate indicator of future CKD after surgery, and risk factors for this surrogate point were analyzed.

Postoperative acute kidney injury (AKI) is a common complication after major abdominal surgery and reportedly increases the risk of future CKD[23,24]. AKI was defined as follows: serum creatinine level increased by ≥ 0.3 mg/dL or > 50% or more within 48 h after surgery[25].

Statistical analysis

Where appropriate, comparisons were made using Fisher's exact test or the Mann-Whitney U test. First, a mixed-effects model for repeated measures estimated the mean of the eGFR or eGFR ratio at each point. Then, changes in the linear trend of the eGFR ratio over time (i.e., whether it was significantly different from 0) were examined using a linear growth model that allowed the intercept and slope of the eGFR ratio change over time to vary by subject and included age as a continuous variable. Differences in the slopes of the eGFR ratio change over time according to the cohort were examined by the statistical significance (p < 0.05) of the product term of the grouping variable with the month as a continuous variable in the growth model. To select potential risk factors for future CKD, multivariate logistic regression analyses analyzed the variables with a p-value of 0.05 or less in the univariate analyses. A *p*-value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software version 26.0 (IBM Japan Ltd., Tokyo, Japan) and the SAS software program version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The baseline characteristics and perioperative results were quite different between the rectal and colon cohorts (Table 1). Briefly, patients in the former cohort had a younger age, more frequent neoadjuvant chemotherapy, longer operative time, more intraoperative blood loss, and a longer postoperative hospital stay than those in the latter cohort. Additionally, postoperative UTI, early, and prolonged UD, ileus, and unexpected readmission were seen more frequently in the rectal cohort than in the colon cohort. Among the 129 patients in the rectal cohort, 94 (72.9%) underwent SPS, whereas non-SPS was performed in the remaining 35 (27.1%). Patients in the non-SPS group had hypertension more frequently, more blood loss, and a longer postoperative hospital stay than those in the SPS group. In the SPS group, 58 patients (61.7%) underwent diverting ileostomy.

Regarding postoperative complications, early UD more frequently developed in the non-SPS group than in the SPS group (31.4% vs. 10.6%, $p = 0.007$). In the rectal cohort, 12 patients underwent unilateral (n = 10) or partial (n = 2) combined resection of the pelvic plexus. The eGFR declined more than 25% within three years after surgery was found in half of the patients with unilateral complete resection but was not seen in two patients with unilateral partial resection.

Change in eGFR and prevalence of CKD

Table 2 summarizes the eGFR value and ratio and prevalence of CKD at baseline, 1.5 years, and 3 years after surgery. The baseline eGFR value was significantly higher in the rectal cohort than in the colon cohort (82.7 vs. 73.5 mL/min/1.73 m^2, $p < 0.001$); however, the eGFR ratio was significantly lower in the rectal cohort than in the colon cohort at 1.5 years (0.9 vs. 0.95, $p = 0.008$) and at 3 years (0.85 vs. 0.94, $p < 0.001$). Moreover, although the initial prevalence of CKD was lower in the rectal cohort than in the colon cohort (13.9% vs. 23.6%, $p = 0.055$), it was similar at 3 years after surgery (29.5% vs. 30.7%, $p = 0.892$).

In the rectal cohort, the prevalence of CKD was similar before surgery between patients who underwent SPS and non-SPS; however, it increased at 3 years in the non-SPS group compared with the SPS group (42.9% vs. 24.5%, $p = 0.052$).

Table 1. Patient's Background and Treatment Outcomes According to Surgical Procedures.

		Rectal resection			Right colectomy	
	Total	SPS	non-SPS			
Variables	N = 129	N= 94	N = 35	*p* value*	N = 127	*p*-value**
Backgrounds						
Age, years, median (range)	63 (29–89)	63 (33–89)	69 (29–88)	0.067	68 (34–92)	0.001
Gender				0.321		0.08
Male	75 (58.1)	52 (55.3)	23 (65.7)		59 (46.5)	
Female	54 (41.9)	42 (44.7)	12 (34.3)		68 (53.5)	
Hypertension	43 (33.3)	26 (27.7)	17 (48.6)	0.035	42 (33.1)	1
Diabetes mellitus	15 (11.6)	9 (9.6)	6 (17.1)	0.233	21 (16.5)	0.285
Preoperative CKD	18 (14)	13 (13.8)	5 (14.3)	1	30 (23.6)	0.055
Clinical staging						
cT4	22 (17.1)	16 (17)	6 (17.1)	1	14 (11)	0.208
cN+	52 (40.3)	35 (37.2)	17 (48.6)	0.313	43 (33.9)	0.303
Preoperative treatment						
Neoadjuvant chemotherapy	49 (38)	35 (37.2)	14 (40)	0.839	0	<0.001
Preoperative irradiation	1 (0.8)	0	1 (2.9)	0.271	0	1
Surgical results						
Operative approaches				0.379		0.344
Open	36 (27.9)	24 (25.5)	12 (34.3)		43 (33.9)	
Minimally invasive approach	93 (72.1)	70 (74.5)	23 (65.7)		84 (66.1)	
Operative time, min, median (range)	380 (143–966)	362 (143–966)	404 (189–890)	0.421	199 (100–379)	<0.001
Blood loss, ml, median (range)	86 (0–4396)	44 (0–1370)	149 (5–4396)	0.001	36 (0–904)	<0.001
Lateral lymph node dissection	53 (41.1)	35 (37.2)	18 (51.4)	0.163	—	—
Combined resection of adjacent organs and/or pelvic plexus	12 (9.3)	7 (7.4)	5 (14.3)	0.305	4 (3.1)	0.068
Curability				1.000		0.498
R0	127 (98.4)	92 (97.9)	35 (100)		127 (100)	
R1	2 (1.6)	2 (2.1)	0		0	
Postoperative hospital stay, days, median (range)	17 (10–72)	16 (10–67)	22 (12–72)	<0.001	10 (6–57)	<0.001
Complications						
During hospitalization						
Major complications	14 (10.9)	12 (12.8)	2 (5.7)	0.349	6 (4.7)	0.101
Early urinary tract infection	10 (7.8)	7 (7.4)	3 (8.6)	1	1 (0.8)	0.01
Early urinary dysfunction	21 (16.3)	10 (10.6)	11 (31.4)	0.007	0	<0.001
Postoperative AKI	21 (16.3)	14 (14.9)	7 (20)	0.592	13 (10.2)	0.197
Ileus	26 (20.2)	19 (20.2)	7 (20)	1	5 (3.9)	<0.001
Prolonged urinary dysfunction	10 (7.8)	5 (5.3)	5 (14.3)	0.133	0	0.002
Unexpected readmission	25 (19.4)	17 (18.1)	8 (22.9)	0.618	7 (5.5)	0.001
Late urinary tract infection	3 (2.3)	3 (3.2)	0	0.562	1 (0.8)	0.622
Small bowel obstruction	15 (11.6)	9 (9.6)	6 (17.1)	0.233	5 (3.9)	0.034
Postoperative treatment						
Adjuvant chemotherapy	48 (37.2)	39 (41.5)	9 (25.7)	0.107	34 (26.8)	0.082
eGFR -25% at 3 years	23 (17.8)	17 (18.1)	6 (17.1)	1	7 (5.5)	0.003

Values in parentheses are percentages unless indicated otherwise. * SPS vs. non-SPS, ** rectal resection vs. right colectomy.
SPS, sphincter-preserving surgery; CKD, chronic kidney disease; AKI, acute kidney injury

Semiannual serial changes in the modified eGFR ratio were evaluated using the random growth model method for three years after surgery. The eGFR ratios significantly decreased after rectal resection compared with colectomy (p < 0.001) (Figure 2A), whereas they were parallel in the non-SPS and SPS groups (p = 0.683) (Figure 2B).

Risk factor analysis for future renal dysfunction

In univariate analyses, female sex, cT4 tumor, neoadjuvant chemotherapy, combined resection of the pelvic plexus

Table 2. Change in Renal Function According to Surgical Procedures.

	Rectal resection				Right colectomy	
	Total	SPS	non-SPS			
	n = 129	n = 94	n = 35	*p*-value*	n = 127	*p* value**
Preoperative (baseline)						
eGFR, mL/min/1.73 m^2	82.7 (31.6–139.3)	83.5 (41.7–137.7)	78.7 (31.6–139.3)	0.438	73.5 (31.3–355.6)	<0.001
CKD (<60)	18 (13.9)	13 (13.8)	5 (14.3)	1	30 (23.6)	0.055
At 1.5 years						
eGFR, mL/min/1.73 m^2	74.4 (31.3–117.4)	75 (38.4–117.4)	65.5 (31.3–112.8)	0.282	69.4 (30.2–287.3)	0.004
eGFR ratio	0.9 (0.62–1.23)	0.91 (0.63–1.23)	0.89 (0.62–1.17)	0.412	0.95 (0.68–1.26)	0.008
CKD (<60)	29 (22.5)	18 (19.1)	11 (31.4)	0.158	37 (29.1)	0.254
At 3 years						
eGFR, mL/min/1.73 m^2	70.7 (34–116.7)	71.4 (34–110.5)	67.3 (35.4–116.7)	0.591	67.3 (22.8–260.1)	0.034
eGFR ratio	0.85 (0.58–1.29)	0.85 (0.64–1.24)	0.87 (0.58–1.29)	0.607	0.94 (0.55–1.34)	<0.001
CKD (<60)	38 (29.5)	23 (24.5)	15 (42.9)	0.052	39 (30.7)	0.892

Values in parentheses are percentages unless indicated otherwise. * SPS vs. non-SPS, ** rectal resection vs. right colectomy.
eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease

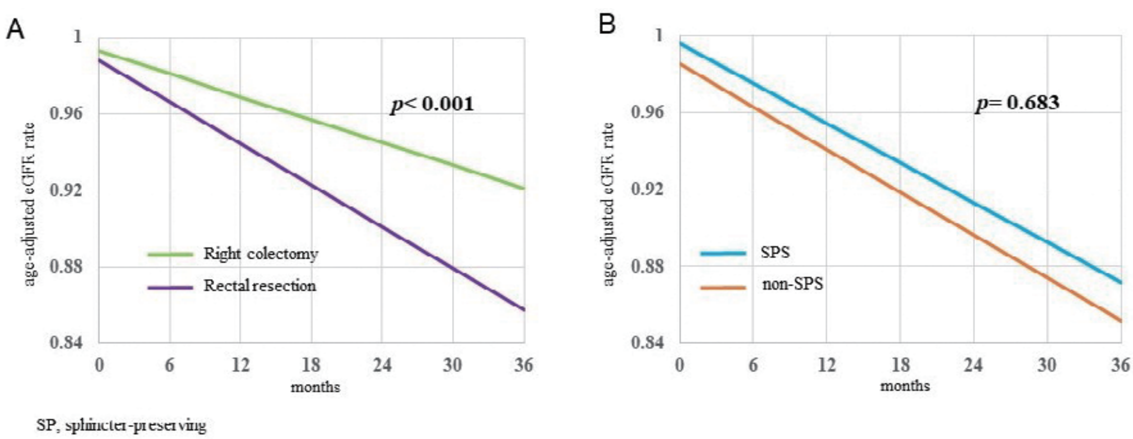

Figure 2.
Semiannual serial changes in the modified eGFR ratio using the random growth model method over three years after surgery. A: Comparison of changes in the eGFR ratio between rectal resection and right colectomy; B: Comparison of changes in the eGFR ratio between the non-SPS and SPS groups. SPS; sphincter-preserving surgery

and/or adjacent organs, and early UD were identified as potential risk factors for an eGFR ratio < 0.75 at three years after rectal surgery (Table 3). In the multivariate analysis, including potential variables with a *p*-value of 0.05 or less in univariate analyses, female sex (odds ratio: 4.2, p = 0.013) and cT4 tumor (odds ratio: 5.88, p = 0.038) were independent risk factors for future CKD, whereas early UD was not (Table 3).

Discussion

Despite the high incidence of UD after rectal cancer surgery, there is a limited investigation about the long-term trend in renal function and the relationship between postoperative UD and the subsequent incidence of future CKD. This study demonstrated three key findings: first, postoperative renal function significantly worsened after rectal resection compared to colectomy, despite heterogeneous backgrounds, including age, and initial eGFR; second, renal function after rectal surgery gradually deteriorated with a reduction in the eGFR value by 15% and with a doubled prevalence of CKD at three years; third, female sex and cT4 stage were independent risk factors for an eGFR ratio < 0.75 at three years in rectal surgery, suggesting a potential risk for future end-stage CKD; however, the occurrence of UD or UTI was not risk factors.

Similar to previous reports[12,13], this study showed that early UD developed more frequently after non-SPS than SPS. Additionally, CKD remarkably occurred three years after non-SPS. This finding could be attributed to the postop-

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Table 3. Univariate and Multivariate Analyses of Risk Factors for “eGFR Ratio <0.75 at Three Years” after Rectal Resection (n= 129).

Variables	n	(%)	Univariate			Multivariate		
			OR	95% CI	*p* value	OR	95 % CI	*p* value
Age								
<70 years	86	66.7	1					
≥70 years	43	33.3	1.08	0.42–2.79	0.871			
Gender								
Male	75	58.1	1			1		
Female	54	41.9	3.22	1.25–8.28	0.015	4.18	1.34–12.99	0.014
Hypertension								
No	86	66.7	1					
Yes	43	33.3	0.85	0.32–2.26	0.745			
Preoperative CKD (eGFR <60)								
No	111	86	1					
Yes	18	14	0.54	0.11–2.51	0.428			
cT4								
No	107	82.9	1			1		
Yes	22	17.1	7.92	2.83–22.16	<0.001	5.93	1.1–31.83	0.038
cN+								
No	77	59.7	1			1		
Yes	52	40.3	2.23	0.9–5.57	0.085	0.94	0.27–3.28	0.921
Neoadjuvant chemotherapy								
No	80	62	1			1		
Yes	49	38	5.06	1.9–13.46	0.001	3.17	0.84–11.91	0.088
Sphincter preserving surgery								
No	35	27.1	1					
Yes	94	72.9	1.07	0.38–2.97	0.901			
Operative approach								
Open	36	27.9	1					
Minimally invasive approach	93	72.1	1.49	0.51–4.36	0.469			
Lateral lymph node dissection								
No	76	58.9	1					
Yes	53	41.1	1.73	0.7–4.28	0.236			
Combined resection of adjacent organs and/or pelvic plexus								
No	117	90.7	1			1		
Yes	12	9.3	8.84	2.5–31.25	0.001	0.57	0.07–4.92	0.61
Major complications								
No	115	89.1	1					
Yes	14	10.9	0.33	0.04–2.62	0.291			
Early urinary dysfunction								
No	108	83.7	1			1		
Yes	21	16.3	3.82	1.35–10.75	0.011	1.89	0.28–12.77	0.513
Early urinary tract infection								
No	119	92.2	1					
Yes	10	7.8	2.12	0.51–8.91	0.304			
Postoperative AKI								
No	108	83.7	1					
Yes	21	16.3	2.14	0.73–6.3	0.167			
Prolonged urinary dysfunction								
No	119	92.2	1			1		
Yes	10	7.8	3.51	0.9–13.63	0.07	1.91	0.22–16.32	0.555

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury erative backbend of the urinary bladder without supporting tissue around the urethra. Moreover, several pudendal nerve branches are frequently injured or removed in non-SPS[26-28]. Interestingly, the eGFR reduction rate was comparable between the groups. A simple cause was that the baseline eGFR value was lower in the non-SPS group due to the higher median age than the SPS group, resulting in greater development of CKD after non-SPS. Another possible reason was appropriate medical interventions, such as introducing CIC, and/or oral medication, which could control UD during discharge in more than half of the patients who developed early UD. Postoperative UD is not always linked to future renal dysfunction. We should recognize that persistent residual urine could cause repeated UTIs and lead to future CKD[29]. Another interesting hypothesis is that the presence of incontinence could reduce the residual urine after non-SPS, leading to a reduction in future CKD. Regarding UD at one year after non-SPS, it was reported that incontinence became predominant over difficulty emptying the bladder[12].

Although healthy middle- and old-aged men have significantly worse renal function than women[30], it is unclear why the female sex has a higher risk factor for future CKD than the male counterpart. Deepak et al. reported that some male patients had a fair amount of residual urine after laparoscopic TME, despite having no subjective symptoms (i.e., subclinical UD)[31]. Such a phenomenon should frequently occurs in females[12,32]. The urethral structure varies greatly, depending on sex. Female patients might partially resolve the difficulty emptying the bladder by urinary straining[32,33]; however, as a harmful result, subclinical residual urine, and associated repeated UTI might cause a long-term persistent decline in renal function. Additionally, CIC's technical and anatomical difficulties in females might cause insufficient or abandoned CIC[12]. The relationship between female subclinical UD and changes in renal function over time is an important subject for further study.

Another risk factor is the cT4 tumor instead of the UD. In this study, cT4 tumors were strongly associated with combined resection of the pelvic plexus and/or adjacent organs. It is well-known that the extent of autonomic nerve preservation is associated with the risk of developing urinary dysfunction. However, even partial resection of the pelvic plexus has been reported to reduce bladder contractility and compliance, increasing clinical and subclinical UD[32]. Indeed, the incidence of patients with more than 50 ml residual urine reached up to nearly 50% one month after rectal resection combined with partial autonomic nerves[33]. This might be why T4 remains a risk factor for future end-stage CKD. Clarification of the relationship between the extent of autonomic nerve preservation and future renal function needs further study.

Several steps can be taken to prevent future CKD after rectal cancer surgery. First, residual urine volume should be measured over the long term. It has been reported that the residual urine volume gradually increases or remains high, even after several years after rectal surgery[4,12,31,34,35]. Evaluation of residual urine only during hospitalization might be insufficient; therefore, establishing a simple, and noninvasive measuring method that can be performed at home is eagerly awaited. Second, education should be provided on sufficient and sustainable CIC for high-risk patients[36]. In our cohort, three patients required CIC for more than one year; however, certain CICs 4-5 times a day can avoid the subsequent decrease in eGFR. This might be why early or prolonged UD was not a risk factor for future CKD in the multivariate analysis.

The single-center design, small sample size, and retrospective nature are limitations in the present study. Moreover, the lack of data and definition regarding the subclinical UD and UTI should be considered a limitation. Detecting and managing them are pressing problems for preventing future CKD. Adding a urinalysis to the routine blood tests at the regular follow-up may help detect subclinical UTI. Although the serum creatine-based eGFR value could be easily measured, it might not have reflected genuine renal function. When severe loss of muscular volume developed after surgery, the eGFR value could have been overestimated, resulting in an underestimation of renal dysfunction[37].

Moreover, although preoperative CRT is a robust risk factor for postoperative UD[38], our cohort included only one CRT patient. The impact of CRT was not evaluated in this study. That is rather favorable for confirming the impact of rectal resection itself; meanwhile, the effect of preoperative CRT on future renal function remains unclear, and further investigation in a multicenter study with many cases is needed.

In conclusion, postoperative eGFR significantly decreased after rectal cancer surgery compared to colectomy. The prevalence of CKD more than doubled at 3 years after rectal resection. Female sex and cT4 tumor were independent risk factors for future renal dysfunction, but postoperative UD was not. However, UD might not be accurately evaluated, and further development of residual urine measurement is needed.

Conflicts of Interest
There are no conflicts of interest.

Author Contributions
All authors contributed to the study's conception and design. Masanori Sando and Kay Uehara performed material preparation and data collection. Masanori Sando, Yuanying Li, and Hiroshi Yatsuya performed the analysis. Masanori Sando wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. All

authors read and approved the final manuscript.

Approval by Institutional Review Board (IRB)

This study was approved by the Nagoya University Hospital Institutional Review Board (#2020-0103).

References

1. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet. 1986 Jun; 1(8496): 1479-82.
2. Yamaoka Y, Kagawa H, Shiomi A, et al. Robotic-assisted surgery may be a useful approach to protect urinary function in the modern era of diverse surgical approaches for rectal cancer. Surg Endosc. 2021 Jun; 35(3): 1317-23.
3. Fleming CA, Cullinane C, Lynch N, et al. Urogenital function following robotic and laparoscopic rectal cancer surgery: meta-analysis. Br J Surg. 2021 Feb; 108(2): 128-37.
4. Lange MM, Maas CP, Marijnen CA, et al. Urinary dysfunction after rectal cancer treatment is mainly caused by surgery. Br J Surg. 2008 Aug; 95(8): 1020-8.
5. Ito M, Kobayashi A, Fujita S, et al. Urinary dysfunction after rectal cancer surgery: results from a randomized trial comparing mesorectal excision with and without lateral lymph node dissection for clinical stage II or III lower rectal cancer (Japan Clinical Oncology Group Study, JCOG0212). Eur J Surg Oncol. 2018 Apr; 44(4): 463-8.
6. Junginger T, Kneist W, Heintz A. Influence of identification and preservation of pelvic autonomic nerves in rectal cancer surgery on bladder dysfunction after total mesorectal excision. Dis Colon Rectum. 2003 May; 46(5): 621-8.
7. Hollabaugh RS, Jr., Steiner MS, Sellers KD, et al. Neuroanatomy of the pelvis: implications for colonic and rectal resection. Dis Colon Rectum. 2000 Oct; 43(10): 1390-7.
8. Ostermann M, Cennamo A, Meersch M, et al. A narrative review of the impact of surgery and anaesthesia on acute kidney injury. Anaesthesia. 2020 Jan; 75 (Suppl 1): e121-33.
9. Sando M, Uehara K, Li Y, et al. Pelvic exenteration associated with future renal dysfunction. Surg Today. 2020 Dec; 50(12): 1601-9.
10. Sung BM, Oh DJ, Choi MH, et al. Chronic kidney disease in neurogenic bladder. Nephrology (Carlton). 2018 Mar; 23(3): 231-6.
11. Lawrenson R, Wyndaele JJ, Vlachonikolis I, et al. Renal failure in patients with neurogenic lower urinary tract dysfunction. Neuroepidemiology. 2001; 20(2): 138-43.
12. Karlsson L, Bock D, Asplund D, et al. Urinary dysfunction in patients with rectal cancer: a prospective cohort study. Colorectal Dis. 2020; 22(1): 18-28.
13. Havenga K, Enker WE, McDermott K, et al. Male and female sexual and urinary function after total mesorectal excision with autonomic nerve preservation for carcinoma of the rectum. J Am Coll Surg. 1996 Jun; 182(6): 495-502.
14. Hashiguchi Y, Muro K, Saito Y, et al. Japanese society for cancer of the colon and rectum. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol. 2020 Jan; 25(1): 1-42.
15. Kamiya T, Uehara K, Nakayama G, et al. Early results of multicenter phase II trial of perioperative oxaliplatin and capecitabine without radiotherapy for high-risk rectal cancer: Corona I study. Eur J Surg Oncol. 2016 Jun; 42(6): 829-35.
16. Hattori N, Nakayama G, Uehara K, et al. Phase II study of capecitabine plus oxaliplatin (CapOX) as adjuvant chemotherapy for locally advanced rectal cancer (Corona II). Int J Clin Oncol. 2020 Jan; 25(1): 118-25.
17. Ore AS, Dombek GE, Cordova-Cassia CA, et al. Omission of or poor response to preoperative chemoradiotherapy impacts radial margin positivity rates in locally advanced rectal cancer. Dis Colon Rectum. 2021 Jun; 64(6): 669-76.
18. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009 Jun; 53(6): 982-92.
19. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002; 39(2 Suppl 1): S1-266.
20. Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA. 2014 Jun; 311(24): 2518-31.
21. Kanda E, Usui T, Kashihara N, et al. Importance of glomerular filtration rate change as surrogate endpoint for the future incidence of end-stage renal disease in general Japanese population: community-based cohort study. Clin Exp Nephrol. 2018 Apr; 22(2): 318-27.
22. Matsushita K, Selvin E, Bash LD, et al. Change in estimated GFR associates with coronary heart disease and mortality. J Am Soc Nephrol. 2009 Dec; 20(12): 2617-24.
23. Ozrazgat-Baslanti T, Thottakkara P, Huber M, et al. Acute and chronic kidney disease and cardiovascular mortality after major surgery. Ann Surg. 2016 Dec; 264(6): 987-96.
24. Prowle JR, Forni LG, Bell M, et al. Postoperative acute kidney injury in adult non-cardiac surgery: joint consensus report of the Acute Disease Quality Initiative and PeriOperative Quality Initiative. Nat Rev Nephrol. 2021 Sep; 17(9): 605-18.
25. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012; 120(4): c179-84.
26. Kontturi M, Larmi TK, Tuononen S. Bladder dysfunction and its manifestations following abdominoperineal extirpation of the rectum. Ann Surg. 1974 Feb; 179(2): 179-82.
27. Daniels IR, Woodward S, Taylor FG, et al. Female urogenital dysfunction following total mesorectal excision for rectal cancer. World J Surg Oncol. 2006 Dec; 4: 1-4.
28. Moriya Y. Function preservation in rectal cancer surgery. Int J Clin Oncol. 2006 Oct; 11(5): 339-43.
29. Yamasaki T, Naganuma T, Iguchi T, et al. Association between chronic kidney disease and small residual urine volumes in patients with benign prostatic hyperplasia. Nephrology (Carlton). 2011Mar; 16(3): 335-9.
30. Imai E, Horio M, Yamagata K, et al. Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. Hypertens Res. 2008 Mar; 31(3): 433-41.
31. George D, Pramil K, Kamalesh NP, et al. Sexual and urinary dysfunction following laparoscopic total mesorectal excision in male patients: a prospective study. J Minim Access Surg. 2018 Apr; 14(2): 111-7.
32. Ameda K, Kakizaki H, Koyanagi T, et al. The long-term voiding function and sexual function after pelvic nerve-sparing radical surgery for rectal cancer. Int J Urol. 2005 Mar; 12(3): 256-63.
33. Akasu T, Sugihara K, Moriya Y. Male urinary and sexual functions after mesorectal excision alone or in combination with ex-

tended lateral pelvic lymph node dissection for rectal cancer. Ann Surg Oncol. 2009 Oct; 16(10): 2779-86.

34. Varpe P, Huhtinen H, Rantala A, et al. Quality of life after surgery for rectal cancer with special reference to pelvic floor dysfunction. Colorectal Dis. 2011 Apr; 13(4): 399-405.

35. Ledebo A, Bock D, Prytz M, et al. Urogenital function 3 years after abdominoperineal excision for rectal cancer. Colorectal Dis. 2018 Jun; 20(6): O123-o34.

36. Matsuoka N, Moriya Y, Akasu T, et al. Long-term outcome of urinary function after extended lymphadenectomy in patients with distal rectal cancer. Eur J Surg Oncol. 2001 Mar; 27(2): 165-9.

37. Chuah LL, Miras AD, Perry LM, et al. Measurement of glomerular filtration rate in patients undergoing obesity surgery. BMC Nephrol. 2018 Dec; 19(1): 383.

38. Bregendahl S, Emmertsen KJ, Lindegaard JC, et al. Urinary and sexual dysfunction in women after resection with and without preoperative radiotherapy for rectal cancer: a population-based cross-sectional study. Colorectal Dis. 2015 Jan; 17(1): 26-37.