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ORIGINAL ARTICLE

The risk factors for urinary dysfunction after autonomic nerve-preserving rectal cancer surgery: a multicenter retrospective study at Yokohama Clinical Oncology Group (YCOG1307)

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Abstract

Aim The aim of this retrospective study was to evaluate the frequency and risk factors of urinary dysfunction after autonomic nerve-preserving surgery for rectal cancer.

Methods This was a retrospective multiinstitution study of 1002 rectal cancer patients conducted between January 2008 and December 2012 in Yokohama Clinical Oncology Group. Patients who had preoperative urinary dysfunction or had not undergone autonomic nerve preservation surgery were excluded. Urinary dysfunction was defined as that with a Clavien-Dindo classification grade ≥ 2. Patient-, tumor-, and surgery-related variables were examined by univariate and multivariate analyses.

Results A total of 887 patients were analyzed. Postoperative urinary dysfunction was observed in 77 patients (8.8%). A multivariate logistic analysis showed that a tumor location in lower rectum (odds ratio [OR] 2.16; 95% confidence interval [CI] 1.15–3.71; $p = 0.02$), tumor diameter ≥ 40 mm (OR 2.07; 95% CI 1.19–4.44; $p < 0.01$), operation time ≥ 240 min (OR 2.07; 95% CI 1.19–4.44; $p < 0.01$), blood loss ≥ 300 ml (OR 2.35; 95% CI 1.12–3.84; $p = 0.02$), and diabetes (OR 3.26; 95% CI 1.80–5.89; $p < 0.01$) were independent risk factors of urinary dysfunction. The incidence of urinary dysfunction exceeded 20% in patients with 3 preoperative predictors (tumor location, tumor diameter, diabetes).

Conclusions This result demonstrated that high-risk patients with more than two risk factors should be informed of the risk of urinary dysfunction.

Trial registration UMIN000033688

Keywords Rectal cancer · Urinary dysfunction · Risk factor · Total mesorectal excision · Lateral lymph node dissection

Introduction

The international standard surgical procedure for rectal cancer is total mesorectal excision (TME) or mesorectal excision (ME), which is resection of the mesorectum with a clear margin from the tumor [1–3]. Postoperative urinary dysfunction is a major complication of rectal cancer surgery and decreases the patients' quality of life (QOL). Since the 1990s, several kinds of nerve-sparing surgery for advanced rectal cancer, which aim to preserve the genitourinary function without compromising radicality, have been developed [4, 5]. Although autonomic nerve-sparing surgery was shown to reduce the risk of urinary dysfunction [6], the incidence of acute urinary retention has been reported to range from 2.5 to 22.3% of patients after rectal surgery because of injury to the pelvic nerves or pelvic plexuses [6–11]. In previous studies, several predictors of acute urinary retention were identified, including male gender [11, 12], old age [8, 11], laparoscopic surgery [13], a low level of anastomosis [9, 14], a longer operative time [6, 8], and a large intraoperative fluid volume [6]. However, there is no clear consensus concerning the risk factors for acute urinary retention. In addition, many previous reports had limitations, including a small sample size [9, 12,

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14] and heterogeneous populations of patients with various diagnoses and surgical procedures [6, 11].

For T3–4 lower rectal cancer, where the lower margin is located at or below the peritoneal reflection, the incidence of lateral pelvic lymph node metastasis is 14–30% [15, 16]. Therefore, in Japan, ME with lateral lymph node dissection (LLND) is the standard procedure for patients with clinical stages II–III advanced lower rectal cancer [17]. To preserve the function of autonomic nerves, nerve-sparing LLND has been developed to obtain good local control with an acceptable QOL [18]. Retrospective studies have reported that the incidence of urinary dysfunction following ME with LLND plus autonomic nerve preservation is comparable to that following TME or ME alone [18–21].

Thus far, no risk classification has yet been made for urinary dysfunction after autonomic nerve-preserving rectal cancer. The aim of this study was to evaluate the frequency and risk factors affecting urinary dysfunction and classify patients by risk factors.

Materials and methods

Patients

This retrospective multiinstitution study was conducted to evaluate the occurrence and risk factors of urinary dysfunction after autonomic nerve-preserving rectal cancer surgery. The study protocol was approved by the Ethical Advisory Committee of Yokohama City University Graduate School of Medicine and the institutional review board of each participating hospital before the study was initiated. From January 2008 to December 2012, consecutive patients who underwent radical resection of rectal cancer were collected at 13 institutions of the Yokohama Clinical Oncology Group (YCOG) in Japan. The study was registered with the Japanese Clinical Trials Registry as UMIN000033688 (http://www.umin.ac.jp/ctr/index.htm). Patient data were collected from clinical report forms.

The eligibility criteria were (1) rectal cancer located within 12 cm from the anal verge with histologically proven adenocarcinoma or signet-ring cell carcinoma and (2) clinical stage II/III. The exclusion criteria were (1) patients with preoperative urinary dysfunction, (2) autonomic nerve-non-preserving operation cases, and (3) emergent cases.

Surgical procedure

ME was performed by open surgery in accordance with reported methods [9]. Under direct vision with sharp dissection, the rectum was mobilized, maintaining the plane around the mesorectum, and the attached mesorectum with at least a 2-cm clearance distal margin to the tumor was resected. If the length of the attached mesorectum distal to the tumor was less than 2 cm, the mesorectum was totally resected. All pelvic autonomic nerves were preserved as much as possible. Pelvic autonomic nerves include the bilateral lumbar splanchnic nerves, superior hypogastric nerve, hypogastric nerves, and pelvic plexus.

Perioperative management

Urinary dysfunction was defined as Clavien-Dindo classification grade ≥ 2 requiring medication or invasive treatment [22]. The day the urinary catheter was removed after surgery was set at the discretion of the attending physician. The residual urine volume was measured after catheter removal. If residual urine continued to exceed 50 ml over 3 days, medication was prescribed by the physician's judgment.

Statistical analyses

Differences between categorical variables were tested using Pearson's chi-squared test. Differences between continuous variables were tested using the Mann-Whitney *U* test.

Risk factors for urinary dysfunction were primarily evaluated using univariate analyses. Variables that had relevant associations with urinary dysfunction on univariate analyses ($p < 0.05$) were included in a multivariate model. The multivariate analysis was performed using a logistic regression analysis. Statistical analyses were performed using the SPSS statistical software program, version 22.0 (SPSS Inc., Chicago, IL, USA). All tests were 2-sided, and values less than 0.05 were considered statistically significant.

Results

Data from 1002 patients were collected from 13 institutions. Of these, 40 were excluded from the analysis because of preoperative urinary dysfunction, and 75 were excluded because of autonomic nerve-preserving surgery not being performed. The remaining 887 patients were analyzed (Fig. 1).

The patient and tumor characteristics and the operative outcomes of the overall cohort are presented in Table 1. Postoperative urinary dysfunction was observed in 77 patients (8.8%). All patients received medication to relieve urinary symptoms. Sixteen patients (1.8%) were discharged with a catheter or needing clean intermittent self-catheterization. Five patients were free from a catheter or needing clean intermittent self-catheterization within a year. Six patients were needing catheter clean intermittent self-catheterization more than a year. One was dead because of pancreatic cancer 2 years after rectal operation, and self-catheterization was needed to the last. One was performed nephrostomy 4 years after operation

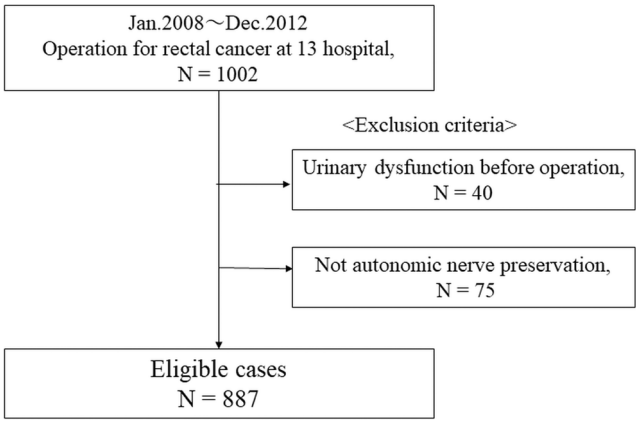

Fig. 1 Outline of patient selection

because of lymph node recurrence. One was performed ileal conduit because of prostatic cancer 2 years after operation. Two was unknown because of lost follow-up.

Average hemoglobin A1c was 7.2 present in diabetes patients. Sixteen patients (15.7%) used insulin, 71 patients (69.6%) took oral drugs, 7 patients (6.9%) was untreated, and 9 patients (8.8%) was unknown in diabetes patients.

Findings of the univariate and multivariate analyses

The univariate analysis showed that the tumor location (in the lower rectum, with the tumor center below the peritoneal reflection) ($p < 0.01$), tumor diameter (≥ 40 mm) ($p < 0.01$), lateral lymph node dissection performed ($p < 0.01$), anastomosis ($p < 0.01$), operation time (≥ 240 min) ($p < 0.01$), blood loss (≥ 300 ml) ($p < 0.01$), and diabetes diagnosis (present) ($p < 0.01$) were associated with a higher incidence of urinary dysfunction (Table 2).

A multivariate logistic analysis showed that the tumor location (lower rectum) (odds ratio [OR] 2.16; 95% confidence interval [CI] 1.15–3.71; $p = 0.02$), tumor diameter (≥ 40 mm) (OR 2.07; 95% CI 1.19–4.44; $p < 0.01$), operation time (≥ 240 min) (OR 2.07; 95% CI 1.19–4.44; $p < 0.01$), blood loss (≥ 300 ml) (OR 2.35; 95% CI 1.12–3.84; $p = 0.02$), and diabetes (OR 3.26; 95% CI 1.80–5.89; $p < 0.01$) were independent risk factors of urinary dysfunction (Table 3).

We showed the preoperative risk factors of urinary dysfunction to be a tumor location in the lower rectum, a tumor diameter ≥ 40 mm, and diabetes. When the patients were divided into groups according to how many of the 3 preoperative independent predictors were present, the occurrence rate of urinary dysfunction was 1.6% (2/124), 5.0% (21/416), 15.0% (48/321), and 22.6% (6/27) in patients with 0, 1, 2, and all 3 predictors, respectively. The more accompanying the independent predictors are, the higher the incidence of urinary dysfunction (Fig. 2).

Discussion

We analyzed a total of 887 patients who underwent elective autonomic nerve-preserving surgery for rectal cancer. Postoperative urinary dysfunction was diagnosed in 77 patients (8.8%). A multivariate analysis showed that tumor location (lower rectum), tumor diameter (≥ 40 mm), operation time (≥ 240 min), blood loss (≥ 300 ml), and diabetes diagnosis (present) were independent risk factors for postoperative urinary dysfunction. Unlike previous studies that had significant limitations, particularly with respect to the small sample size and heterogeneous patient populations, our study included a relatively large sample size. Therefore, our results are expected to be more reliable than those of previous studies.

In our study, urinary dysfunction was defined as that with a Clavien-Dindo classification grade ≥ 2 requiring medication or invasive treatment. Urinary dysfunction occurred in 77 patients (8.8%). Although the definition of postoperative urinary dysfunction was different from that used in our study, acute urinary retention has been reported to occur in 2.5–22.3% of patients after rectal surgery [6–11]. The incidence of urinary dysfunction in this study was within the ranges reported by previous studies. In this study, all operation was performed skilled colorectal surgeons. The disparity between institutions was little because the incidence of urinary dysfunction was 3.3–13.7% which was equivalent to previous reports (2.5–22.3%). So, there was no heterogeneity of treatment results across centers.

Tumor location in the lower rectum and tumor diameter ≥ 40 mm were significantly associated with an increased incidence of urinary dysfunction according to a multivariate logistic analysis. Consistent with the present study, it was reported that a low level of anastomosis increased postoperative urinary dysfunction [9, 14]. This suggests that surgical procedures of ME below the peritoneal reflection might increase the risk of injuring the autonomic nerves. The S4 pelvic nerve and neuro-vascular bundle are thought to be important for the urinary function [4, 23, 24] and are sometimes injured when dissection planes should be beyond usual mesorectal planes due to tumor expansion. Same as tumor diameter, large tumors are difficult to keep good sight and tension and tends to injure S4 pelvic nerve and neuro-vascular bundle.

Blood loss ≥ 300 ml and operation time ≥ 240 min were also significantly associated with an increased incidence of urinary dysfunction in the multivariate logistic analysis. In ME procedures, the area at greatest risk of intraoperative bleeding occurring is around the neuro-vascular bundle. Lange showed that blood loss was a risk factor for long-term difficulty with bladder emptying after rectal surgery in a Dutch trial [25]. Consistent with the present study, it was reported that a longer operative time increased the rate of postoperative urinary dysfunction [6, 8], as a longer operation

Table 1 Patients' characteristics

Variables		*N* = 887	Percent
Gender	Male	580	65.4
	Female	307	34.6
Age (year)	< 75	649	73.2
	≥ 75	238	26.8
BMI (kg/m^2)	< 25	722	71.9
	≥ 25	160	18.1
ASA	I	295	33.3
	II	531	59.8
	III	53	6.0
	Unknown	8	0.9
Diabetes	Yes	102	11.5
	No	785	88.5
Tumor location	Upper rectum	468	52.8
	Lower rectum	419	47.2
Tumor size (mm)	< 40	272	30.7
	≥ 40	615	69.3
Preoperative therapy	Performed	27	3.0
	Not performed	860	97.0
Surgical approach	Open	696	78.5
	Laparoscopic	191	21.5
Surgical procedure	LAR	632	71.2
	ISR	29	3.3
	Rectal amputation	175	19.7
	Hartmann's operation	47	5.3
	Combined resection of uterus or part of bladder or vagina	4	0.5
LLND	Performed	158	17.8
	Not performed	729	82.2
Operation time (min)	< 240	479	54.0
	≥ 240	408	46.0
Blood loss (ml)	< 300	515	58.1
	≥ 300	372	41.9
Pathological stage (UICC)	0/I/II	426	48.0
	III	440	49.6
	IV	21	2.4
Postoperative urinary dysfunction		77	8.8

BMI body mass index, *ASA* American Society of Anesthesiologists, *LAR* low anterior resection, *ISR* intersphincteric resection, *LLND* lateral lymph node dissection

time is related to greater procedural complexity, which may increase the risk of nerve damage and hinder postoperative recovery [6, 8].

Diabetes was significantly associated with an increased incidence of urinary dysfunction in the multivariate logistic analysis. Urologic complications, including diabetic bladder dysfunction, are plausibly the most common complications, collectively affecting well over 50% of diabetic individuals [26]. Diabetic bladder dysfunction is characterized by an increased bladder capacity caused by decreased bladder sensation which is dominated by the autonomic nerve [27]. We believe that diabetes patients' autonomic nerves are extremely sensitive and therefore easily affected by surgical invasion.

In the present study, LLND was not associated with an increased incidence of urinary dysfunction in the multivariate logistic analysis. A meta-analysis including 3 studies with 264 patients showed that LLND was associated with an increased incidence of urinary dysfunction [28–32]. A recent Japanese study (JCOG0212) demonstrated that autonomic nerve-preserving LLND did not increase the risk of early urinary dysfunction [33]. Compared with past meta-analysis report based on retrospective studies with limitation of influence of

Table 2 Univariate analysis of urinary dysfunction

Variables		UD (−) $N = 810$	UD (+) $N = 77$	p value
Gender	Male	527	53	0.51
	Female	283	24	
Age (year)	< 75	599	50	0.09
	≥ 75	211	27	
BMI (kg/m^2)	< 25	661	61	0.53
	≥ 25	144	16	
Diabetes	Yes	83	19	< 0.01
	No	727	58	
Tumor location	Upper rectum	442	26	< 0.01
	Lower rectum	368	51	
Tumor size (mm)	< 40	260	12	< 0.01
	≥ 40	550	65	
Preoperative therapy	Performed	22	5	0.06
	Not performed	788	72	
Surgical procedure	Open	633	63	0.45
	Laparoscopic	177	14	
LLND	Performed	133	25	<0.01
	Not performed	677	52	
Anastomosis	Performed	610	48	0.01
	Not performed	200	29	
Operation time (min)	< 240	452	27	< 0.01
	≥ 240	358	50	
Blood loss (ml)	< 300	490	25	< 0.01
	≥ 300	320	52	

UD urinary dysfunction, *BMI* body mass index, *LLND* lateral lymph node dissection

preoperative radiotherapy, Japanese study was a randomized trial with no influence of preoperative radiotherapy. In addition, the quality of autonomic nerve-preserving LLND was ensured by intraoperative photographs in JCOG0212 study [34]. In our study, autonomic nerve-preserving LLND is not associated with urinary dysfunction because of almost no influence of preoperative radiotherapy and secure autonomic nerve preservation.

Table 3 Multivariate analysis of urinary dysfunction

Variables	Odds ratio	95% CI	p value
Diabetes, yes	3.26	1.80–5.89	< 0.01
Tumor location, lower rectum	2.16	1.15–3.71	0.02
Tumor size (mm), ≥ 40	2.07	1.19–4.44	< 0.01
LLND, performed	1.78	0.59–5.43	0.31
Anastomosis, performed	1.24	0.69–2.21	0.85
Operation time (min), ≥ 240	2.35	1.12–3.84	0.02
Blood loss (ml), ≥ 300	2.35	1.31–4.57	0.01

CI confidence interval, *LLND* lateral lymph node dissection

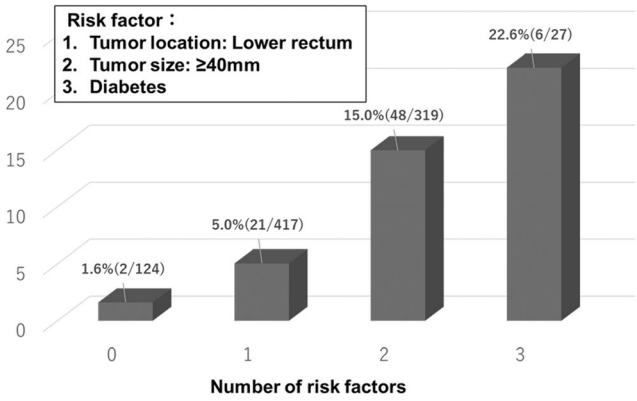

Fig. 2 Relationship between the rate of urinary dysfunction after rectal cancer surgery and the number of risk factors

There are several limitations associated with our study. First, this was a retrospective study. Second, there is currently no consensus concerning the definition of acute urinary dysfunction, and the definition of urinary dysfunction varies. Some studies have defined it based on the residual urine volume [4, 33], some based on the International Prostate Symptom Score (IPSS) [35, 36], and others based on the frequency of urination [28]. This has resulted in wide variation in the rate of urinary dysfunction among studies. Third, almost no patients had undergone preoperative treatment such as chemotherapy or chemoradiotherapy in the present study. Only a very small population (1.5%) had received preoperative radiotherapy. In Japan, straightforward TME with LLND is the standard treatment for locally advanced rectal cancer [17]. Radiotherapy is also thought to affect the urinary function. Two randomized multicenter studies on preoperative radiotherapy plus surgery versus surgery alone for rectal cancer demonstrated worse effects of preoperative radiotherapy on the urinary function [37, 38]. Because preoperative treatment was often performed in previous reports, we cannot simply compare the present results with previous ones.

In conclusion, we identified the preoperative risk factors of urinary dysfunction as tumor location (lower rectum), tumor size (≥ 40 mm), and diabetes. Risk stratification for urinary dysfunction after rectal cancer surgery can be achieved using the independent predictors clarified in this study. This result showed that high-risk patients who have more than two risk factors should be informed of the risk of urinary dysfunction.

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Author contributions JW and MO contributed to the study design. All of the authors contributed to the data collection, data analysis, and interpretation. JW and KN contributed to the statistical analyses. All of the authors contributed to the writing or review of the report and approved the final version.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Approval of the research protocol The study protocol was approved by the Ethical Advisory Committee of Yokohama City University Graduate School of Medicine and the institutional review board of each participating hospital before the study was initiated.

Registry and the Registration No. of the Study: This study was registered with the Japanese Clinical Trials Registry as UMIN000033688 (http://www.umin.ac.jp/ctr/index.htm).

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