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ORIGINAL ARTICLE

The influence of neoadjuvant chemoradiation for lower rectal cancer on urinary function

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KEYWORDS
Rectal cancer;
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Summary *Background:* It is unclear whether neoadjuvant chemoradiation for lower rectal cancer causes a deterioration in urinary function. This study aimed to prospectively compare the postoperative urinary function of patients with lower rectal cancer treated by surgery after neoadjuvant chemoradiation with that of patients treated with surgery alone.
Method: Urinary function was assessed before treatment and 1, 3, and 6 months after surgery by calculating the changes in the scores of the seven items of the International Prostatic Symptom Score (incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia) and Quality of life index.
Results: Among 123 patients with lower rectal cancer treated with chemoradiotherapy plus surgery and surgery alone between 2014 and 2016, 29 eligible patients in the surgery after neoadjuvant chemoradiation group and 34 eligible patients in the surgery alone group were analyzed. The changes in each item score at 1, 3, and 6 months after surgery were similar between the two treatment groups. The scores of all items were already recovered at 6 months after surgery, except for weak stream and straining in the Surgery + chemoradiotherapy group and nocturia in the Surgery-alone group.
Conclusion: Neoadjuvant chemoradiotherapy for lower rectal cancer did not affect postoperative urinary function.

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1. Introduction

In Western countries, neoadjuvant chemoradiotherapy (CRT) and total mesorectal excision (TME) with autonomic nerve preservation techniques are considered standard for treating cancer of the mid and lower rectum.[1–3] Urinary function after pelvic surgery has been relatively preserved with the introduction of TME.[4,5] However, deterioration in urinary function is still a major complication. Several reports have shown that 6–14% of patients have severely impaired postoperative urinary function after TME.[6–9]

Neoadjuvant CRT for advanced lower rectal cancer (LRC) is a standard treatment for the reduction of local recurrence.[10–12] However, it was argued that neoadjuvant CRT causes deterioration in urinary function.[13–16] A Chinese group reported that neoadjuvant CRT, in comparison to neoadjuvant chemotherapy, led to significant deterioration in postoperative urinary function of men.[17] However, the Dutch TME trial demonstrated that TME after short-course radiotherapy for rectal cancer did not affect long-term urinary function in contrast to TME alone.[18] Several other studies have reported that deterioration in postoperative urinary and sexual function depends on tumor location; treatment for LRC caused worse postoperative urinary and sexual function than that for upper rectal cancer.[6,19] Further, most studies evaluated postoperative urinary function after three months. Thus, it is still debatable whether neoadjuvant CRT leads to deterioration in postoperative urinary function.

The aim of this study was to elucidate the influence of long-course neoadjuvant CRT on urinary function in patients with LRC who underwent TME. Moreover, we analyzed urinary function at multiple timepoints including before treatment and one month after surgery.

2. Materials and methods

2.1. Patients

We included patients who underwent curative surgery for LRC, defined as adenocarcinoma involving the lower third of the rectum (beyond the peritoneal reflection), between January 2014 and December 2016 at the University of Tokyo Hospital. Patients with recurrence within six months after surgery were excluded. The tumor location was detected via digital rectal examination, colonoscopy, barium enema and pelvic magnetic resonance imaging. All patients underwent surgery according to the principles of TME surgery. Data associated with each patient's demographics, preoperative assessment and treatment, postoperative follow-up, and histology results were collected. Each patient was asked to answer questionnaires of the International Prostatic Symptom Score (IPSS) and Quality of life (QoL) index as later outlined.[20]

The study was approved by the ethics committee of our hospital (reference No. 10046); all patients received written information about the study and signed written consent forms before inclusion in the study.

2.2. Neoadjuvant treatments

Pelvic magnetic resonance imaging, endoscopy, computed tomography, and barium enema were used to evaluate the local spread of the disease. Patients were staged using the TNM Classification of Malignant Tumours, eighth edition.[21] LRC patients with T3 or deeper and any N stage basically underwent neoadjuvant CRT of the pelvis. Neoadjuvant CRT was performed according to the following regimen: 50.4 Gy (1.8 Gy $\times$ 28 fractions) + tegafur–uracil (300 mg/m^2) + leucovorin (75 mg/m^2) $\times$ 28 days during each course of radiotherapy, as described previously.[22] TME surgery was planned 6–10 weeks after completion of CRT.

2.3. Surgical procedures

Surgical procedures included low anterior resection, intersphincteric resection, and abdominoperineal resection, which were performed via the conventional open method, laparoscopic surgery, or robotic surgery. We performed bilateral pelvic wall lymph node dissection when a patient with T3 or deeper LRC did not receive CRT. In patients receiving CRT, we selectively performed lateral pelvic wall lymph nodes dissection, when lateral lymph nodes were suspected of being metastasized before CRT.[23] A protective ileostomy was constructed based on the discretion of the operating surgeons.

2.4. Urinary function

Urinary function was evaluated with the IPSS questionnaire,[24] which includes seven items (incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia), each scored 1 to 5 (a maximum: 35 points), with higher scores indicating more severe urinary dysfunction and poorer QoL. Based on IPSS, urinary function was categorized into 'mild symptom' (IPSS 0–7 points), 'moderate symptom' (IPSS 8–19 points), and 'severe symptom' (IPSS 20–35 points).[23] In this study, patients with 13 points or higher on IPSS, preoperatively, were excluded in accordance with the cut-off in report by Ko et al.[25] Patients completed this questionnaire before surgery ('baseline'), and at 1, 3, and 6 months after surgery. In patients treated with neoadjuvant CRT, the questionnaire before CRT was employed as the baseline. The primary endpoint was to compare the changes in each IPSS score and QoL index between surgery after neoadjuvant CRT and surgery without CRT groups. The secondary endpoints were the changes in IPSS score and QoL index in each group assessed over a period of time postoperatively.

2.5. Statistical analyses

All statistical analyses were conducted using JMP software version 13 (SAS Institute Inc., Cary, NC, USA). Data are presented as means $\pm$ standard errors. The patients' clinical and demographic characteristics were compared using the chi-squared test for categorical variables and Mann–Whitney U-test for continuous variables. The IPSS scores at each time point and the changes from baseline were compared between the two groups using the paired t-test or Student's t-test. $P < 0.05$ was considered statistically significant.

3. Results

A total of 123 patients underwent curative operations for LRC; 63 underwent surgery after neoadjuvant CRT ('Surgery + CRT' group) and 60 underwent surgery without neoadjuvant CRT ('Surgery-alone' group). Of these, 60 were excluded because of refusal (n = 12, 10%), IPSS > 12 preoperatively (n = 18, 15%), loss to follow-up (n = 22, 18%), inadequate description on the questionnaires (n = 7, 6%), and recurrence before 6 month in one patient (1%). Thus, 29 patients in the Surgery + CRT group and 34 patients in the Surgery-alone group were analyzed (Fig. 1).

The demographic and clinical data of the patients are reported in Table 1. The Surgery + CRT group demonstrated more advanced pathological T stages than the Surgery-alone group. The two groups were not significantly different in age, body mass index, diabetes, type of surgery, lateral lymph node dissection, and surgical approach.

First, we compared the changes in each IPSS score and QoL index between the Surgery + CRT group and the Surgery-alone group. The changes in each item score at 1 month from baseline are shown in Table 2. The changes in the Surgery + CRT group were similar to those in the Surgery-alone group. The changes in each item score at 3 months from baseline are shown in Table 3. These changes were similar between the two groups. The changes in each item score at 6 months from baseline were also similar between the two groups (Table 4).

Second, Fig. 2 shows the scores of each of the seven items of IPSS and QoL index according to the treatment approach. The scores of all items were significantly higher in the Surgery + CRT group at 1 month from baseline. However, the scores of all items except for urgency were significantly higher in the Surgery-alone group at 1 month from baseline. The scores of incomplete emptying, frequency, intermittency, weak stream, nocturia and QoL index significantly decreased in the Surgery + CRT group from 1 to 3 months. However, the scores of frequency, weak stream, and QoL index significantly decreased in the Surgery-alone group from 1 to 3 months. The scores of frequency and intermittency significantly decreased in the Surgery-alone group from 3 to 6 months. Compared with the baseline, the scores of urgency and weak stream were still higher at 6 months in the Surgery + CRT group, whereas the score of nocturia was higher at 6 months in the Surgery-alone group.

Table 5 shows the total IPSS score in the two treatment groups at 6 months. The frequency of 'moderate symptom' did not differ between the Surgery + CRT and Surgery-alone groups (27.6% vs 17.6%, $P = 0.35$). There were no patients with 'severe symptom' in the two treatment groups at 6 months.

4. Discussion

In this prospective observational study, we assessed the influence of long-course neoadjuvant CRT for LRC on urinary function by comparing surgery plus CRT with surgery alone. Past studies on IPSS reported that urinary function was markedly impaired at 3 months after surgery.[17,26] However, to our knowledge, short-term urinary function in LRC treated with surgery after neoadjuvant CRT or surgery alone has not been evaluated. We demonstrated that all items of IPSS at 1 month after surgery were markedly higher than at 3 months, regardless of treatment.

Previous studies and this study on urinary function regarding perioperative radiotherapy are summarized in Table 6. As shown, treatments, the timing, and methods of evaluating urinary function vary from study to study. Urinary function was evaluated at multiple time points by Lange et al., Luca et al., and Huang et al.[17,26,27] The subjects, CRT type, and evaluation method for urinary function

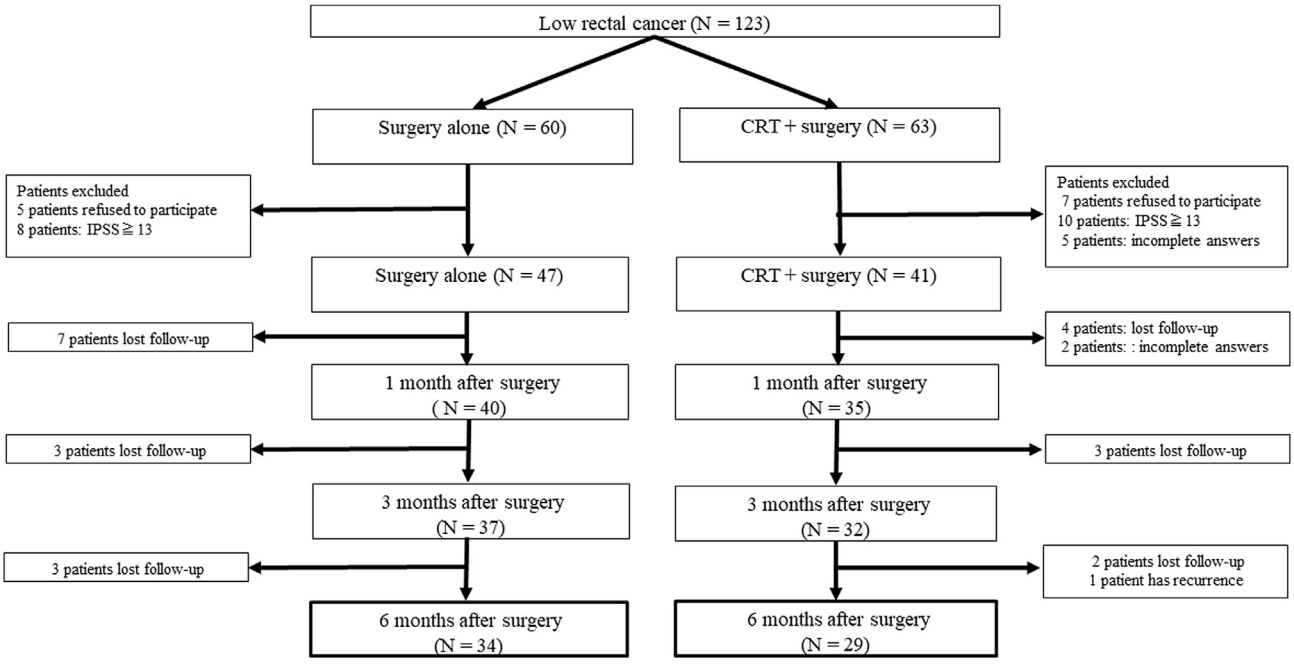

Figure 1 Flow diagram of the prospective study.

Table 1 Demographics, tumor characteristics, and treatment (n = 63).

Clinicopathological characteristic	Surgery alone (n = 34)	CRT + surgery (n = 29)	*P*
Age (years), median (range)	63.5 (44–88)	66 (42–81)	0.58
Sex, n (%)			0.28
Male	19 (56)	20 (69)	
Female	15 (44)	9 (31)	
BMI (mean ± SD), kg/m^2	23.4 ± 3.8	23.3 ± 3.5	0.87
Diabetes, n (%)			0.51
Yes	2 (6)	3 (10)	
No	32 (94)	26 (90)	
Type of surgery, n (%)			0.44
LAR	23 (68)	20 (69)	
APR	2 (6)	4 (14)	
ISR	9 (26)	5 (17)	
T stage, n (%)			<0.001[a]
pTx	0 (0)	7 (24)	
pT1	16 (47)	2 (7)	
pT2	11 (32)	7 (24)	
pT3	4 (12)	12 (42)	
pT4	3 (9)	1 (3)	
Lateral lymph Node dissection, n (%)	8 (24)	8 (28)	0.94
Surgical approach, n (%)			0.10
Open	0 (0)	2 (7)	
Laparoscopic	22 (65)	22 (76)	
Robot	12 (35)	5 (17)	

CRT: chemoradiotherapy, BMI: body mass index, SD: standard deviation, LAR: low anterior resection, APR: abdominoperineal resection, ISR: intersphincteric resection, p: pathological, Tx: no residual tumor.
[a] *P* value is significant.

Table 2 Comparison of changes at one month after surgery from the baseline on urinary function in the surgery after chemoradiation and surgery alone groups.

Variables	Mean change in surgery alone group (n = 34)	Mean change in CRT + surgery group (n = 29)	*P*
Incomplete emptying	0.41 ± 0.23	0.55 ± 0.18	0.54
Frequency	0.5 ± 0.25	0.62 ± 0.22	0.72
Intermittency	0.47 ± 0.26	0.76 ± 0.32	0.48
Urgency	0.03 ± 0.25	0.28 ± 0.14	0.41
Weak stream	1.24 ± 0.33	1.24 ± 0.33	0.99
Straining	0.56 ± 0.24	0.5 ± 0.18	0.85
Nocturia	0.46 ± 0.17	0.65 ± 0.23	0.48
Quality of life	0.94 ± 0.29	0.79 ± 0.36	0.74

CRT: chemoradiotherapy.

Table 3 Comparison of changes at three months after surgery from the baseline on urinary function in the surgery after CRT and surgery alone groups.

Variables	Mean change in surgery alone group (n = 34)	Mean change in CRT + surgery group (n = 29)	*P*
Incomplete emptying	0.24 ± 0.21	0.07 ± 0.18	0.55
Frequency	0 ± 0.17	0 ± 0.13	1.00
Intermittency	0.12 ± 0.18	0.31 ± 0.22	0.49
Urgency	−0.09 ± 0.20	0.28 ± 0.18	0.18
Weak stream	0.35 ± 0.31	0.55 ± 0.27	0.63
Straining	0.21 ± 0.08	0.24 ± 0.15	0.83
Nocturia	0.29 ± 0.13	0.05 ± 0.19	0.28
Quality of life	0.03 ± 0.25	−0.14 ± 0.32	0.67

CRT: chemoradiotherapy.

in the study by Morino et al.[8] were similar to those in our study. they reported that long-course CRT before laparoscopic surgery in male patients with rectal cancer did not affect postoperative urinary function at 12 months after surgery.[8] However, it was retrospective and assessment was only conducted once after surgery.

Whether CRT disturbs postoperative urinary function is a big concern in the treatment of LRC. As shown in Table 6, six of the nine studies concluded that radiotherapy or CRT did not affect postoperative urinary function, and the other three reported that radiotherapy or CRT raised a risk of postoperative incontinence. Among them, Pollack et al. analyzed the Stockholm I and II trials conducted in 1980s; the former trial applied two-portal technique through which the urinary bladder may be damaged more than the four-portal technique.[13] Bruheim et al. did not assess preoperative urinary function.[15] In the study of Huang et al.,[17] the mean value of total IPSS score before surgery was as high as 6.1–6.9 points. Therefore, patients with impaired urinary function before treatment were included in that study.[17] In contrast, our study compared a surgery plus CRT group with a surgery alone group, and we excluded patients

Table 4 Comparison of changes at six months after surgery from the baseline on urinary function between surgery after CRT group and surgery alone group.

Variables	Mean change in surgery alone group (n = 34)	Mean change in CRT + surgery group (n = 29)	*P*
Incomplete emptying	0.05 ± 0.19	0.03 ± 0.16	0.92
Frequency	−0.35 ± 0.21	0.03 ± 0.18	0.17
Intermittency	−0.08 ± 0.12	0.21 ± 0.18	0.17
Urgency	−0.09 ± 0.16	0.28 ± 0.15	0.10
Weak stream	0 ± 0.29	0.41 ± 0.21	0.26
Straining	0.21 ± 0.16	0.28 ± 0.16	0.76
Nocturia	0.38 ± 0.17	0.26 ± 0.24	0.67
Quality of life	−0.12 ± 0.22	−0.5 ± 0.25	0.26

CRT: chemoradiotherapy.

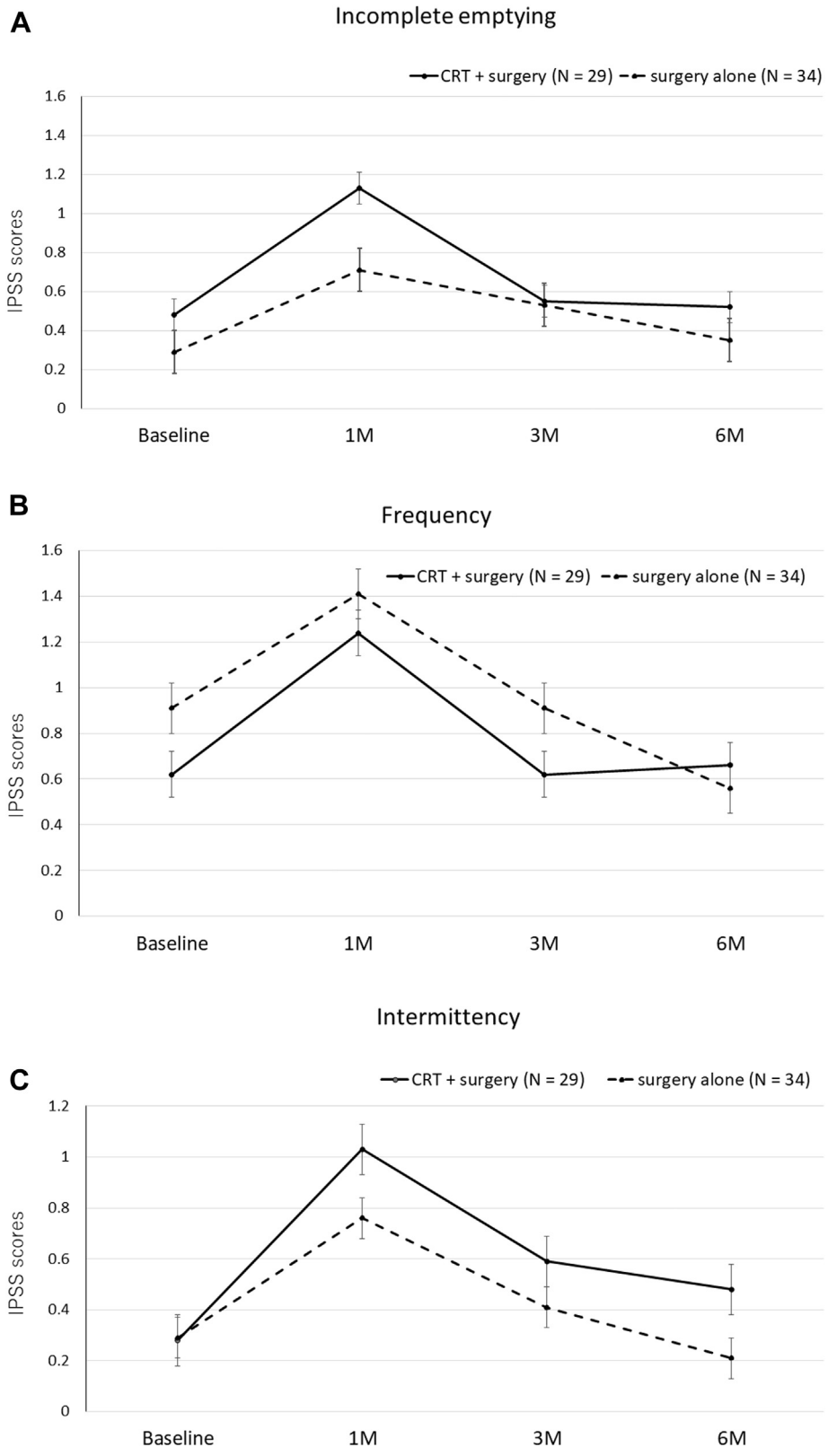

Figure 2 A—H The scores of the seven items of International Prostatic Symptom Score (IPSS) and Quality of life index from before surgery to six months after surgery. A, Incomplete emptying; B, Frequency; C, Intermittency; D, Urgency; E, Weak stream; F, Straining; G, Nocturia; H, Quality of life. CRT, chemoradiotherapy; M, month.

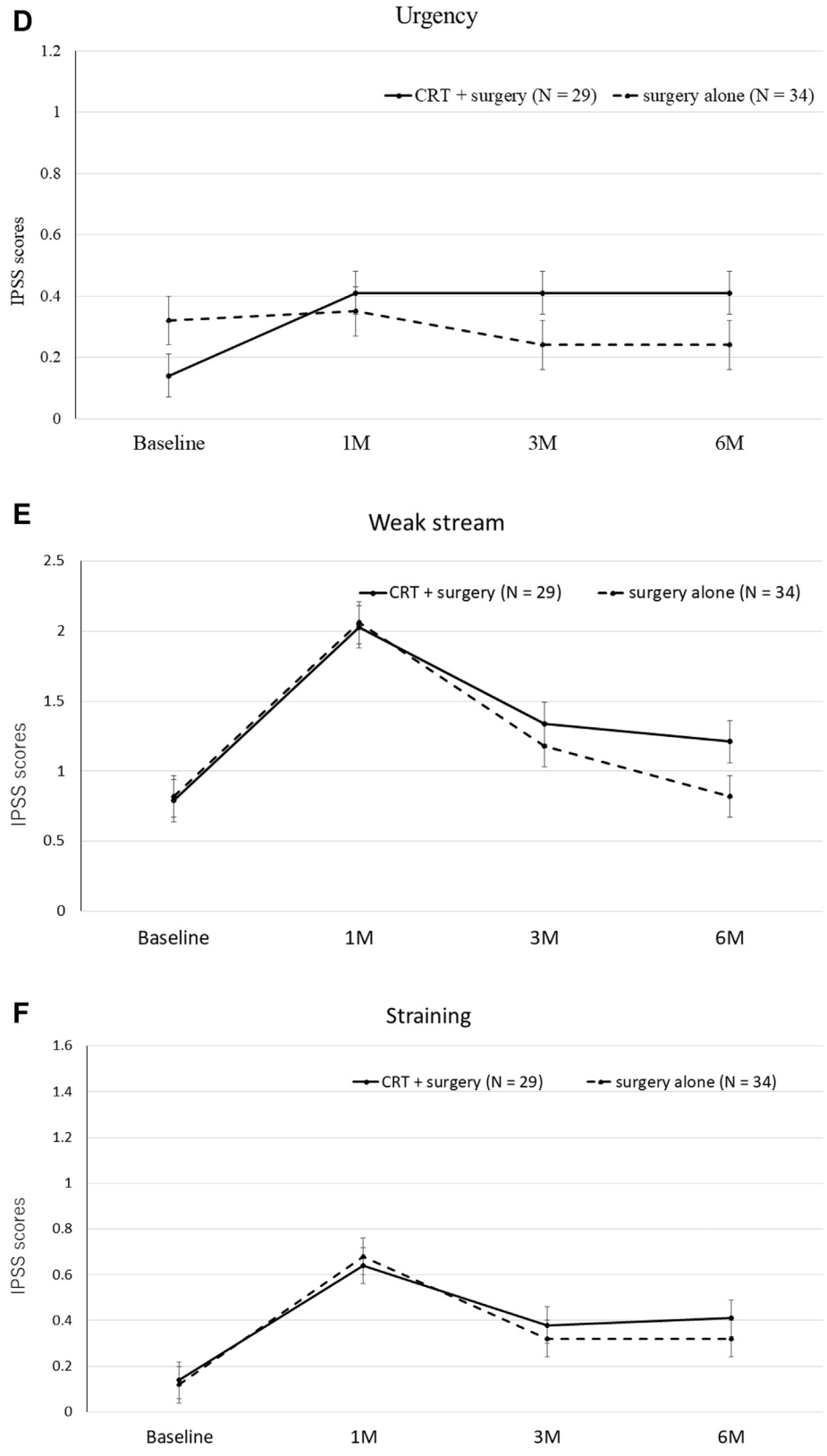

Figure 2 (*continued*).

who preoperatively scored 13 points or higher on the IPSS. Therefore, we consider that neoadjuvant CRT essentially does not affect urinary function in LRC patients.

Our results suggested that surgery is an important factor for impaired urinary function. In this regard, Lange et al. in the Dutch TME trial reviewed their patients' surgical records

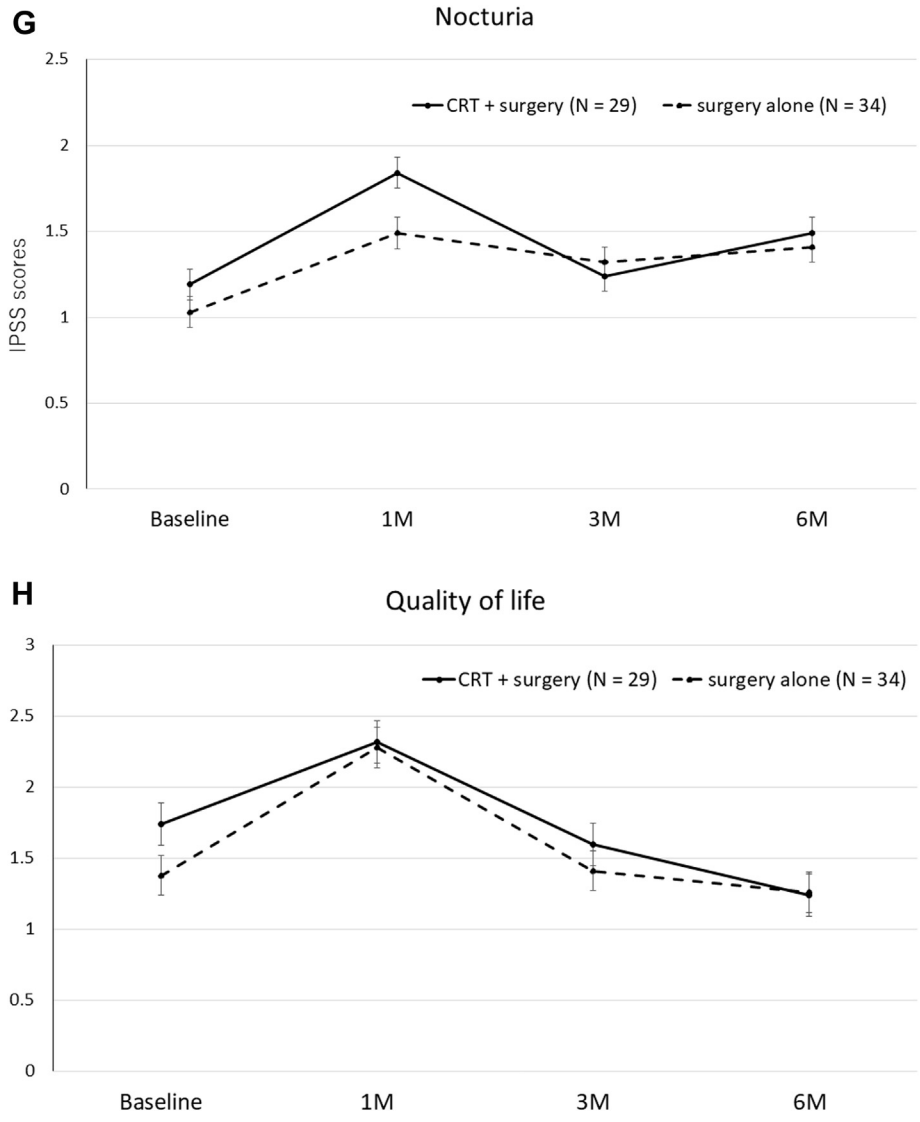

Figure 2 (*continued*).

and speculated that the risk of dysuria after TME seemed attributable to intraoperative surgical damage to the sacral splanchnic nerves and inferior hypogastric plexus.[26] Pollack et al. also stated that surgical damage to autonomic nerves itself would affect urinary incontinence.[13] In accordance with the previous notions, temporary impairment in each IPSS item score was observed after surgery regardless of preoperative CRT in our study.

Our study has several limitations. First, this was a single-center study with a small sample size. Second, the initial baseline scores of each item of IPSS in the Surgery + CRT and Surgery-alone groups were not equal. Additionally, the follow-up period was not long enough to observe the long-term effects of surgery with or without neoadjuvant CRT on urinary function. The scores of weak stream, straining, and nocturia require further evaluation in order to assess whether these can be fully recovered in the long-term postoperative period.

In conclusion, neoadjuvant CRT for LRC did not affect postoperative urinary function which was evaluated 1—6 months after surgery. Overall, postoperative urinary function was better at 3 months than at 1 month. No patient had severe urinary dysfunction after surgery at 6 months, regardless of CRT. A longer observation period with a larger number of patients is needed to analyze the long-term effects of surgery plus neoadjuvant CRT on urinary function.

Table 5 Total IPSS between surgery after CRT group and surgery alone group at six months after surgery.

IPSS n (%)	Surgery alone group (n = 34)	CRT + surgery group (n = 29)	*P*
Mild (0—7 points)	28 (82.4)	21 (72.4)	0.35
Moderate (8—19 points)	6 (17.6)	8 (27.6)	
Severe (20—35 points)	0	0	

IPSS: International Prostate Symptom Score, CRT: chemoradiotherapy.

Table 6 Characteristics of articles on questionnaires of urinary function regarding perioperative radiotherapy.

Study (year) (country)	Study design	Sample size	Groups analyzed	Short/long course radiotherapy	Time of assessment	Items of questionnaires	Impact of RT/CRT
Birgisson et al[28] (2005) (Sweden)	Retrospective	1146	preop. CRT vs surgery alone	Short	6M-	Incontinence	ND
Pollach et al[13] (2006) (USA)	RCT	139	preop. RT vs surgery alone	Short	180M (mean)	Incontinence; IE	Incontinence: impaired Incomplete emptying: ND
Lange et al[26] (2008) (Netherlands)	RCT univariate analysis	785	preop. CRT, surgery alone	Short	baseline, 3M, 6M, 12M, 18M, 24M, 60M	Incontinence; IE	ND
Morino et al[8] (2009) (Italy)	Retrospective multivariate analysis	50	preop. CRT, surgery alone	Long	baseline, 12M	IPSS	ND
Bruheim et al[15] (2010) (Norway)	Prospective	492	preop. RT/CRT and postop. RT/CRT vs surgery alone	Long	24M-	Incontinence; Dysuria; Hematuria; Urgency	Incontinence: impaired Dysuria: ND Hematuria: ND Urgency: ND
Varpe et al[16] (2011) (Finland)	Prospective	69	preop. RT/CRT, surgery alone	Short and long	baseline, 12M	IE; Urgency; Straining; Pain	ND
Contin et al[29] (2013) (Germany)	Prospective multivariate analysis	263	preop. CRT, preop. RT, surgery alone	Short and long	51M (mean)	ICIQ	ND
Luca et al[27] (2013) (Italy)	Prospective univariate analysis	74	preop. CRT, surgery alone	Not specified	baseline, 1M, 6M, 12M	Incontinence	ND
Huang et al[17] (2016) (China)	Prospective	97	preop. CRT vs preop. CT	Long	baseline, 3M, 6M, 12M	IPSS	Impaired urinary function in preop. CRT
Our study (Japan)	Prospective	63	preop. CRT vs surgery alone	Long	baseline, 1M, 3M, 6M	IPSS	ND

preop.: preoperative, CRT: chemoradiotherapy, M: months, ND: no difference, IE: incomplete emptying, RCT: randomized control study, postop.: postoperative, IPSS: International Prostate Symptom Score, RT: radiotherapy, ICIQ: International Consultation on Incontinence Questionnaire, CT: chemotherapy.

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Conflicts of interest

The authors declare that they have no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2018.11.004.

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