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The Influence of Neoadjuvant Chemoradiation for Middle and Lower Rectal Cancer on Anorectal Function

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Abstract. *Background/Aim: To date, there is no clear understanding whether preoperative long-course chemoradiotherapy combined with surgery for rectal cancer is detrimental to anorectal function. The purpose of this study was to clarify the influence of preoperative chemoradiotherapy and surgery for middle and lower rectal cancer on postoperative anorectal function. Patients and Methods: Data of 113 patients with middle or lower rectal cancer treated with preoperative chemoradiotherapy plus surgery or surgery alone between January 2013 and December 2016 were analyzed. A total of 84 and 29 patients underwent low anterior resection and intersphincteric resection, respectively. In patients with T3 or deeper and with any N stage cancer below peritoneal reflection, surgery plus lateral lymph node dissection or preoperative radiation (total: 50.4 Gy/28 fractions) to the pelvis with chemoradiotherapy plus surgery was treated. Anorectal function was assessed prior to treatment and 6 and 12 months postoperatively. Specifically, maximum resting pressure and maximum squeezing pressures were measured. The Wexner score was recorded prior to treatment and 12 months postoperatively. Results: maximum resting pressure and maximum squeezing pressure decreased post-surgery in both groups. Maximum resting pressure and maximum squeezing pressure at 12 months and the Wexner score at 12 months post-surgery were comparable among patients treated with chemoradiotherapy plus surgery and those treated with surgery alone. Conclusion: Preoperative chemoradiotherapy did not clearly impair postoperative anorectal function in patients who underwent low anterior resection and intersphincteric resection.*

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Anorectal function following pelvic surgery is relatively preserved following the introduction of total mesorectal excision (TME). However, several reports have shown an impaired postoperative anorectal function in 30% to 76% of patients following TME, with or without preoperative chemoradiotherapy (CRT) (1-4).

Currently, preoperative CRT is considered the gold standard treatment for reducing local recurrence of advanced middle and low rectal cancer (5-7). Several studies reported an increased risk of postoperative anorectal dysfunction following preoperative CRT (8-12). Numerous past studies utilized questionnaires to evaluate anorectal functions such as Wexner continence score (13), St. Mark's score (14), and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (15). However, to date, there is still a limited number of reports on anorectal function assessment *via* manometric approach in such patients (16-18). Moreover, small number of patients, single arm, or measurements at only 1-2 timepoints represent limitations in these studies (16-18).

The purpose of this study was to clarify the influence of preoperative CRT and surgery for middle and lower rectal cancer on postoperative anorectal function *via* manometric and questionnaire approaches.

Patients and Methods

Patients. We examined consecutive patients who underwent curative surgery for middle or low rectal cancer at the University of Tokyo Hospital between January 2013 and December 2016. The patients were followed-up for at least 1 year postoperatively. Tumor location was determined with the following approaches: Digital rectal examination, endoscopy, barium enema, with/without pelvic magnetic resonance imaging. All patients were treated by low anterior resection (LAR) or intersphincteric resection (ISR) following TME surgery principles as mentioned below (19). We excluded tumors that involved the anal canal from the analysis. For each patient, we collected data associated with their demographics, preoperative assessment and therapies, postoperative follow-up, and histological outcomes.

The study obtained approval from the Ethics Committee of the University of Tokyo (reference no. 10046). The study was conducted in accordance to Declaration of Helsinki for human research.

Neoadjuvant treatment. Patients were staged according to the eighth edition of the American Joint Committee on Cancer Staging Manual (20). Patients with stage T3 or deeper and with N0 or deeper cancer below the peritoneal reflection were treated with surgery plus lateral lymph node dissection (LLND) or preoperative CRT plus surgery. Specifically, preoperative CRT was administered with the following regimen: 50.4 Gy (1.8 Gy × 28 fractions) to the pelvis concomitant with oral tegafur-uracil (300 mg/m^2) and leucovorin (75 mg/m^2) for 28 days as previously described (21). Regarding the radiation method, planning computed tomographic images were acquired with 2-mm slice thickness. A three-dimensional conformal technique was used with planning computed tomography. The entire pelvis was treated with the four-field technique and uniform planning target volume margins of 5 mm in the lateral, anteroposterior, and cranio-caudal directions were applied. The TME surgical operation was performed 6-10 weeks following CRT completion.

Surgical procedures. Surgical procedures included LAR and ISR. These were completed *via* conventional open approach, laparoscopic surgery, or robotic surgery. The selection of LAR or ISR procedure was based on whether the tumor was located within 2 cm of the upper border of the anal canal. The anastomotic technique was performed employing the double-stapling technique or the handsewn technique in LAR cases. In contrast, anastomoses were made using the handsewn technique in all ISR cases. We performed bilateral pelvic wall lymph node dissection in patients with T3 or deeper low rectal cancer below the peritoneal reflection unless they did not undergo CRT. On the contrary, in patients receiving CRT, we performed LLND selectively when lateral lymph nodes were suspected of metastasizing prior to CRT (22). In LAR cases, a diverting stoma was constructed at the discretion of the operating surgeons. On the other hand, a diverting stoma was constructed in all ISR cases.

Assessment of anal function. In the manometric approach for anal function, a one-channel catheter (GMMS-100R-SI instrument; Star Medical, Tokyo, Japan) was inserted into the rectum in the left decubitus position. We measured the maximum resting pressure (MRP) and maximum squeezing pressure (MSP) using the rapid pull-through technique. MSP was measured in increments above the resting pressure. We excluded patients with outlying manometric data, such as preoperative MSP less than 70 mmHg, and postoperative MRP or MSP more than twice as high as preoperatively. Measurements were carried out at the following timepoints: Before treatment (baseline), and at 6 and 12 months postoperatively. Manometric data at each timepoint are presented as ratios of the baseline values.

The score of Jorge and Wexner (Wexner score) was used to evaluate anal incontinence (13). The higher the score, the more severe the anal incontinence, ranging from 0 to 20. Wexner score was evaluated before treatment (baseline) and 12 months postoperatively, and their difference was analyzed. We excluded patients who did not undergo stomal closure at 12 months post-surgery. The frequency of daily bowel movement was queried at 12 months postoperatively.

Statistical analyses. Date have been provided as the mean±standard error. Patient demographics and tumor characteristics were compared using chi-square test for categorical variables or Mann–Whitney *U*-test for continuous variables. The MRP, MSP, Wexner score, and frequency of daily bowel movement were compared between the two groups using Mann–Whitney *U*-test. All statistical analyses were performed by the use of JMP software version 14 (SAS Institute Inc., Cary, NC, USA). Values of $p<0.05$ were considered statistically significant.

Results

We selected 168 patients with middle or lower rectal cancer. They were treated with preoperative chemoradiotherapy plus surgery or surgery alone. A total of 123 and 45 patients underwent LAR and ISR, respectively.

Effects of preoperative CRT in LAR cases. A total of 83 patients underwent LAR without neoadjuvant CRT, whereas 40 patients underwent LAR after neoadjuvant CRT. Of the 123 LAR cases, 39 patients were excluded. Exclusion criteria were as follows: Refusal in 19 (15%), lost to follow-up in 16 (13%), and outlying manometric data in four (3%). Thus, finally 58 patients in the group treated with surgery alone and 26 patients in the CRT plus surgery group were analyzed (Figure 1).

Table I outlines the patient demographics, tumor characteristics, and treatment data. The distance between the lower edge of tumor and the anal verge in the CRT plus surgery group was shorter than that in the surgery alone group by 2.2 cm ($p<0.0001$). More advanced clinical and pathological T-stages were observed in the CRT plus surgery group. A diverting stoma was more frequently created in the CRT plus surgery group (73% *vs*. 43%, respectively; $p=0.011$). No significant difference was observed between the two groups in other parameters (*i.e*. age, gender, body mass index, clinical and pathological N-stage, adjuvant chemotherapy, LLND, surgical approaches, and anastomotic technique).

MRP and MSP values before treatment were similar in the group treated with surgery alone group and the CRT plus surgery group (MRP: 58.3±2.8 *vs*. 50.1±4.2, $p=0.11$; MSP: 218.0±13.1 *vs*. 203.9±19.6 $p=0.55$). Figure 2 shows the changes from baseline in MRP and MSP at 6 and 12 months post-surgery in both groups. Between baseline and 6 months, MRP decreased by 21% in that treated with surgery alone ($p<0.0001$) and by 22% in the CRT plus surgery group ($p<0.0001$). No difference was observed in MRP at 6 and 12 months between the two groups ($p=0.97$ and $p=0.24$, Figure 2A). Between baseline and 6 months, MSP decreased by 12% in the group treated with surgery alone ($p=0.003$) and by 21% in that treated with CRT plus surgery ($p<0.0001$). Additionally, MSP did not differ at 6 and 12 months between the two groups ($p=0.19$ and $p=0.062$, respectively, Figure

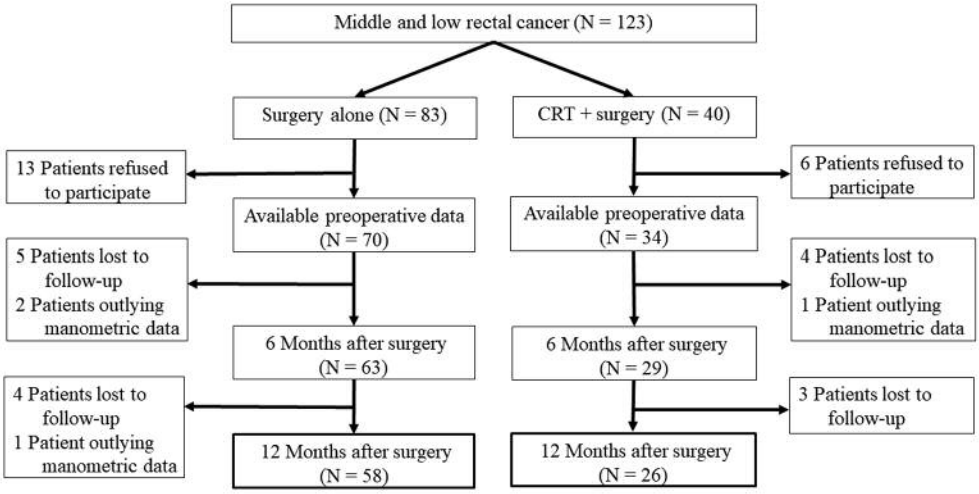

Figure 1. *Flow diagram of the prospective study in low anterior resection cases.*

2B). We did not observe the recovery of MRP and MSP from 6 to 12 months post-surgery in the two groups.

When analyzing the Wexner score, two patients in each group were further excluded from the analysis due to the presence of a protective stoma 1 year after LAR. Thus, finally we analyzed 56 patients in the group treated with surgery alone and 24 in that treated with CRT plus surgery. The baseline Wexner score was similar in the groups (1.8±0.4 *vs*. 2.8±0.6, respectively; p=0.17). Figure 3 shows the comparison of the change in the Wexner score between baseline and 12 months. The Wexner score increased postoperatively in both groups. We did not observe a significant intergroup difference (p=0.54). The frequency of daily bowel movement at 12 months postoperatively in the CRT plus surgery group was higher than that in the group treated with surgery alone (4.3±0.7 *vs*. 7.3±1.1, respectively; p=0.019).

Effects of preoperative CRT in ISR cases. A total of 24 patients underwent ISR without preoperative CRT and 21 patients underwent ISR after preoperative CRT. Of the 45 ISR cases, 16 patients were excluded. Exclusion criteria were as follows: refusal in seven (16%), lost to follow-up in seven (16%) and outlying manometrics in two (4%). Finally, we analyzed 14 patients in the group treated with surgery alone and 15 in the group treated with CRT and surgery (Figure 4).

Table II describes patient demographics, tumor characteristics, and treatment data. We noted older age in the CRT plus surgery group. The clinical T-stage in the CRT plus surgery group was more advanced than that in the group treated with surgery alone (p=0.0008). The pathological N-stage was more advanced in the group treated with surgery alone (p=0.030). Of note, no significant difference in other parameters between the two groups was observed (*i.e*. gender, body mass index, tumor location from the anal verge, clinical N-stage, pathological T-stage, adjuvant chemotherapy, LLND, surgical approaches, anastomotic technique, and diverting stoma rate).

MRP and MSP values before treatment were similar in the two groups. Figure 5 shows MRP and MSP changes at 6 and 12 months post-surgery from the baseline in the two groups. We found that MRP decreased between baseline and 6 months by 22% in the group treated with surgery alone (p<0.0001) and by 43% in the CRT plus surgery group (p<0.0001). Of note, MRP did not differ at 6 and 12 months between the two groups (p=0.055 and p=0.78, Figure 5A). We observed that MSP decreased between baseline and 6 months by 11% in that treated with surgery alone (p=0.006) and by 33% in the CRT plus surgery group (p<0.0001). Additionally, MSP in the CRT plus surgery group was lower than that in the surgery alone group at 6 months post-surgery (p=0.027, Figure 5B), but no significant difference was observed between the two groups at 12 months post-surgery (p=0.33, Figure 5B). MRP and MSP recovery from 6 to 12 months post-surgery was not observed in the two groups.

Three patients in the group treated with surgery alone and four in the CRT plus surgery group were further excluded from the analysis of the Wexner score due to the presence of stoma 1 year after ISR. Thus, we finally analyzed 11 patients in the group treated with surgery alone group and 11 patients in the CRT plus surgery group. The baseline Wexner score was similar in the two groups (1.0±1.0 *vs*. 3.1±1.0, respectively; p=0.14). The Wexner score increased postoperatively in both groups (6.1±1.6 *vs*. 8.4±1.6,

Table I. *Demographics, tumor characteristics, and treatment in patients who underwent low anterior resection (n=84).*

Clinicopathological characteristic		Surgery alone (n=58)	CRT+ surgery (n=26)	*p*-Value
Age, years	Mean±SE	62.8±1.4	63.1±2.1	0.91
Gender, n (%)	Male	35 (61)	19 (73)	0.25
	Female	23 (39)	7 (27)	
BMI, kg/m^2	Mean±SE	23.2±0.5	23±0.7	0.81
Tumor location from AV, cm	Mean±SE	7.8±0.3	5.6±0.5	**<0.0001**
cT-stage, n (%)	cT1	17 (29)	0 (0)	**0.0015**
	cT2	10 (17)	1 (4)	
	cT3	27 (47)	23 (88)	
	cT4	4 (7)	2 (8)	
cN-stage, n (%)	cN0	43 (74)	18 (69)	0.59
	cN1	13 (22)	5 (19)	
	cN2	1 (2)	1 (4)	
cLLN metastasis, n (%)	Yes	1 (2)	2 (8)	
pT-stage, n (%)	(y)pTx	0 (0)	7 (27)	**<0.0001**
	(y)pT1	16 (28)	2 (8)	
	(y)pT2	14 (24)	2 (8)	
	(y)pT3	24 (41)	14 (54)	
	(y)pT4	4 (7)	1 (4)	
pN-stage, n (%)	(y)pN0	31 (53)	19 (72)	0.24
	(y)pN1	19 (33)	5 (20)	
	(y)pN2	8 (14)	2 (8)	
LLN dissection, n (%)	Yes	11 (19)	4 (15)	0.69
Surgical approach, n (%)	Open	1 (2)	2 (8)	0.091
	Laparoscopic	31 (45)	18 (69)	
	Robotic	26 (53)	6 (23)	
Anastomotic technique, n (%)	DST	51 (88)	21 (81)	0.39
	Handsewn	7 (12)	5 (19)	
With diverting stoma, n (%)	After surgery	25 (43)	19 (73)	**0.011**
	At 6 months	13 (22)	9 (35)	0.25
	At 12 months	2 (4)	2 (8)	0.42
Adjuvant chemotherapy, n (%)	Yes	29 (50)	9 (35)	0.19

CRT: Chemoradiation; SE: standard error; BMI: body mass index; AV: anal verge; c: clinical; p: pathological; LLN: lateral lymph node; DST: double stapling technique. Bold values show significance.

respectively; p=0.33). No significant intergroup difference was observed in the change in Wexner score between baseline and 12 months (p=0.93, Figure 6). The frequency of daily bowel movement did not differ in the two groups (5.3±1.2 *vs*. 5.1±1.1, respectively; p=0.91).

Discussion

In this prospective observational study, we evaluated the influence of long-course preoperative CRT in patients with middle and lower rectal cancer on anorectal function. To this end, we compared the group treated with surgery alone and that treated with CRT plus surgery. It has been shown by numerous studies on anorectal function that preoperative CRT can impair postoperative anorectal function (2, 10, 11, 23-25). However, in several of these reports, enrolled patients had upper rectal cancer. Moreover, postoperative anorectal function was evaluated exclusively with a questionnaire. In contrast, we compared postoperative anorectal function between patients with and without preoperative CRT who underwent LAR or ISR. Furthermore, in the present study, both manometric data and the Wexner score were measured at multiple timepoints.

Table III summarizes both previous and our results as to anorectal function evaluated by manometry in patients treated with perioperative radiotherapy. Depending on the study, there are differences in terms of timing, anorectal function evaluation methods, and treatment. About a half of the studies concluded that preoperative CRT did not impair postoperative anorectal function. The remaining reported that radiotherapy or CRT increased the risk of postoperative incontinence. However, such findings have limitations. Specifically, Nardi *et al*. evaluated anorectal function only in patients treated by preoperative CRT (24). Inhat *et al*. evaluated anorectal function at only one postoperative timepoint (18). Gervaz *et al*. reported that postoperative MRP in the CRT plus surgery group decreased more compared with the group treated with surgery alone, whereas

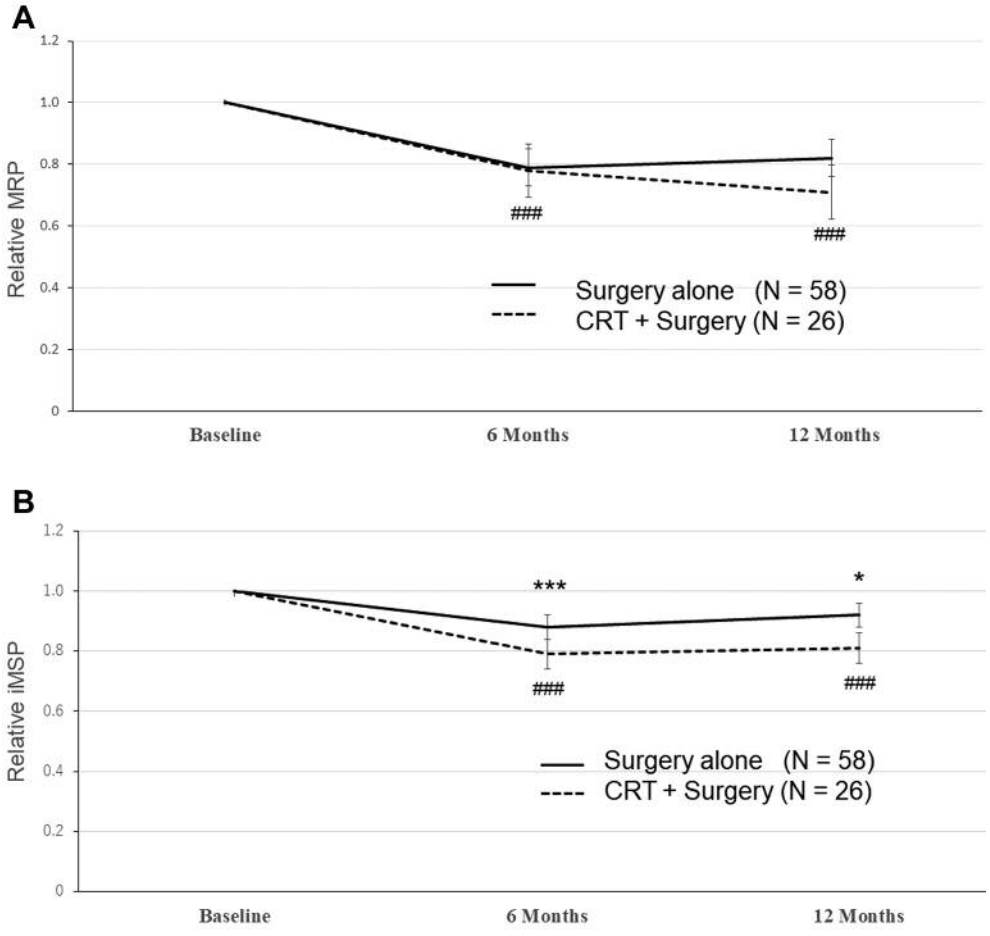

Figure 2. *Changes in maximum resting pressure (MRP; A) and incremental maximum squeezing pressure (iMSP; B) at 6 and 12 months after low anterior resection from baseline in the group treated with surgery alone and that treated with chemoradiotherapy (CRT) plus surgery. MRP did not differ significantly between the two groups at 6 months (p=0.97) and 12 months (p=0.24). iMSP did not differ significantly between the two groups at 6 months (p=0.19) and 12 months (p=0.62). Significantly different from baseline at ***p<0.0001 and *p<0.04 for surgery alone, and ###p<0.0001 for CRT plus surgery.*

they did not find a difference in MSP between the two groups (25). However, tumor location and anastomosis level in the CRT plus surgery group were lower than in that which underwent surgery alone. Of note, Ammann *et al*. (17) and Canda *et al*. (26) used a CRT regimen and evaluation methods for anorectal function which resembled those in our study. Additionally, Ammann *et al*. reported that postoperative MRP in the CRT plus surgery group decreased more than in the group treated with surgery alone (17). However, the authors did not determine the timing of postoperative analysis, with an interquartile range of 149-405 days. Of note, Canda *et al*. reported similar results. However, in their study cohort, tumor location in the CRT plus surgery group was significantly lower than that in the group treated with surgery alone (26).

We noted the anorectal function for LAR and ISR to mitigate the influence of the level of anastomosis. We

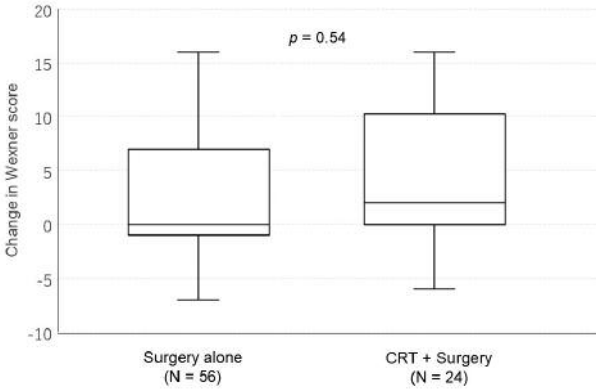

Figure 3. *Difference between preoperative and postoperative Wexner scores in the low anterior resection group treated with surgery alone and that treated with chemoradiotherapy (CRT) plus surgery. Bars are the range of scores. Boxes are the range from 1st quartile to 3rd quartile. Lines are median.*

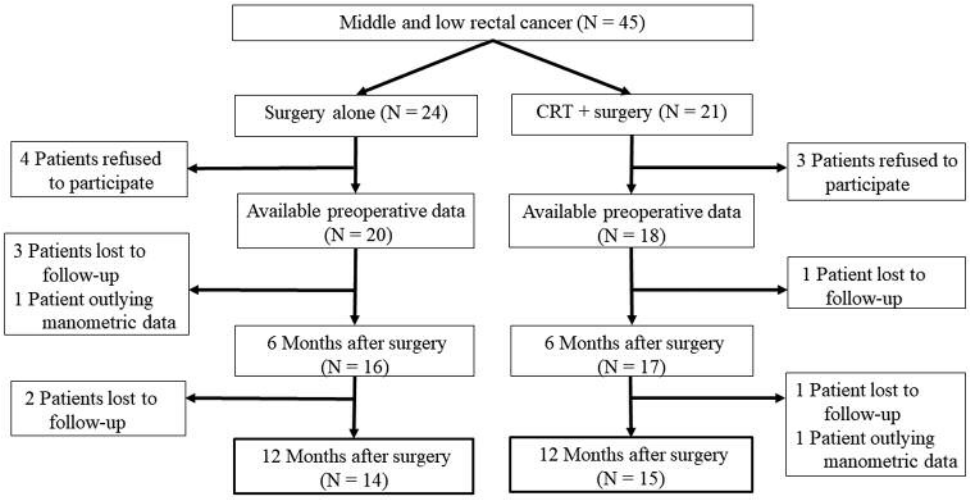

Figure 4. *Flow diagram of the prospective study in intersphincteric resection cases.*

Table II. *Demographics, tumor characteristics, and treatment in patients who underwent intersphincteric resection (n=29).*

Clinicopathological characteristic		Surgery alone (n=14)	CRT+ surgery (n=15)	*p*-Value
Age, years	Mean±SE	54.1±2.8	62.3±2.7	**0.048**
Gender, n (%)	Male	7 (50)	11 (73)	0.19
	Female	7 (50)	4 (27)	
BMI, kg/m^2	Mean±SE	23±0.8	21.1±0.8	0.13
Tumor location from AV, cm	Mean±SE	3.3±0.3	3.3±0.3	0.86
cT-stage, n (%)	cT1	6 (43)	0 (0)	**0.0008**
	cT2	5 (36)	2 (13)	
	cT3	3 (21)	12 (80)	
	cT4	0 (0)	1 (7)	
cN-stage, n (%)	cN0	11 (79)	7 (47)	0.074
	cN1	0 (0)	4 (27)	
	cN2	0 (0)	1 (7)	
cLLN metastasis, n (%)	Yes	3 (21)	3 (20)	
pT-stage, n (%)	(y)pTx	0 (0)	3 (20)	0.11
	(y)pT1	10 (71)	5 (33)	
	(y)pT2	2 (14)	2 (14)	
	(y)pT3	2 (14)	5 (33)	
	(y)pT4	0 (0)	0 (0)	
pN-stage, n (%)	(y)pN0	8 (57)	11 (73)	**0.030**
	(y)pN1	6 (43)	1 (7)	
	(y)pN2	0 (0)	3 (20)	
LLN dissection, n (%)	Yes	4 (29)	3 (20)	0.59
Surgical approach, n (%)	Open	0 (0)	0 (0)	0.86
	Laparoscopic	7 (50)	8 (53)	
	Robotic	7 (50)	7 (47)	
Anastomotic technique, n (%)	Handsewn	14 (100)	15 (100)	>0.99
With diverting stoma, n (%)	After surgery	14 (100)	15 (100)	>0.99
	At 6 months	9 (64)	12 (80)	0.34
	At 12 months	3 (21)	4 (27)	0.74
Adjuvant chemotherapy, n (%)	Yes	7 (50)	9 (6)	0.59

CRT: Chemoradiation; SE: standard error; BMI: body mass index; AV: anal verge; c: clinical; p: pathological; LLN: lateral lymph node. Bold values show significance.

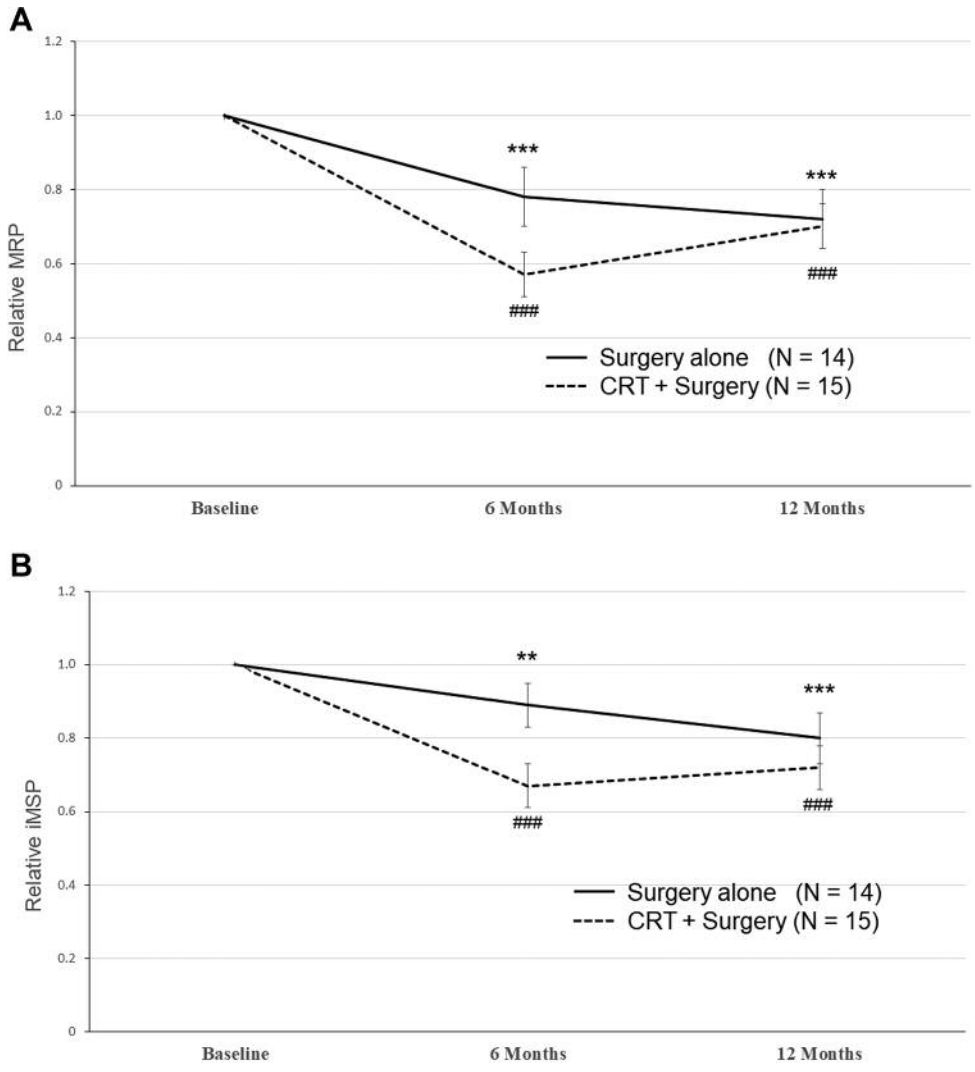

Figure 5. *Changes in maximum resting pressure (MRP; A) and incremental maximum squeezing pressure (MSP; B) at 6 and 12 months after intersphincteric resection from baseline in the group treated with surgery alone and that treated with chemoradiotherapy (CRT) plus surgery. MRP did not differ significantly between the two groups at 6 months (p=0.055) and 12 months (p=0.78). iMSP was significantly lower in the CRT plus surgery group at 6 months (p=0.027) but was not different at 12 months (p=0.33). Significantly different from baseline at ***p<0.0001 and **p<0.006 for surgery alone, and ###p<0.0001 for CRT plus surgery.*

found that the anorectal function was impaired after LAR and ISR regardless of preoperative CRT. Notably, postoperative anorectal function in the CRT plus surgery group, with the tumor location being lower, did not differ from that in the group treated with surgery alone in LAR cases. In a study performed by Kushwaha *et al*., the authors reported that radiotherapy did not affect MRP and MSP at 6 weeks and 6 months post-treatment completion in patients with prostate or bladder cancer (27). Similarly, Jang *et al*. concluded that anorectal function at 4-7 weeks post-CRT completion was unchanged from pretreatment in patients with middle and lower rectal cancer (28). However, several studies have reported that rectal surgery itself impairs anal manometric data. Specifically, Kitaguchi *et al*. reported that regardless of preoperative CRT, a significant decrease of MRP and MSP was observed after ISR (by 35% and 10%, respectively) (29). Our findings are in line with such results. It has been suggested that physical deformity and denervation-induced pressure disproportion of the anal canal may reduce anorectal function analyzed by three-dimensional manometry even in LAR (30). Current progress in radiation technology is prominent. At our

Table III. *Characteristics of articles on anorectal manometry regarding perioperative radiotherapy.*

Authors, year (Ref)	Country	Study design	Sample size	Groups analyzed	Time of assessment	Items of manometry	Findings
Birnbaum *et al.* 1992, (32)	USA	Prospective	20	Preop. CRT	Before CRT, 1 month after CRT	MRP, MSP, RST	No difference
Gervaz *et al.* 2001, (25)	USA	Prospective	42	Preop. CRT and postop. CRT *vs.*	Before CRT, before stomal surgery alone	MRP, MSP, RST closure	Impaired anorectal function in preop. CRT
Ammann *et al.* 2003, (17)	Austria	Prospective	50	Preop. CRT *vs.* surgery alone	Before CRT, 12 months after surgery	MRP, MSP, RAIR, RST	Impaired anorectal function in preop. CRT
Pietsch *et al.* 2007, (33)	Germany	Prospective	39	Preop. CRT *vs.* surgery alone	Before CRT, 3-6 months after stomal closure	MRP, MSP, HPZ	No difference
Canda *et al.* 2009, (26)	Turkey	Prospective	41	Preop. CRT *vs.* surgery alone	Before CRT, after CRT, median of 13.9 months after surgery	MRP, MSP, RAIR, RST	Impaired anorectal function in preop. CRT
Jang *et al.* 2010, (28)	Korea	Prospective	80	Preop. CRT	Before CRT, after CRT	MRP, MSP, HPZ, RAIR, RST	No difference
Kye *et al.* 2013, (16)	Korea	Prospective	30	Preop. CRT	Before CRT, after CRT	MRP, MSP, HPZ, RAIR, RST	No difference
Nardi *et al.* 2017, (24)	UK	Prospective	39	preop. CRT	Before CRT, after CRT, 12 months after stomal closure	MRP, MSP, RST	Impaired anorectal function in preop. CRT
Ihnat *et al.* 2018, (18)	Czech Republic	Prospective	65	Preop. RT and postop. RT *vs.* surgery alone	12 months after surgery	MRP, MSP, RAIR, RST	Impaired anorectal function in preop. RT
Our study	Japan	Prospective	113	Preop. CRT *vs.* surgery alone	Before CRT, 6 months, 12 months after surgery	MRP, MSP	No difference

Preop.: Preoperative; postop.: postoperative; CRT: chemoradiotherapy; RT: radiotherapy; MRP: maximum resting pressure; MSP: maximum squeezing pressure; HPZ: high pressure zone; RAIR: recto-anal inhibitory reflex; RST: rectal sensory threshold.

Institute, a three-dimensional conformal technique with planning by thin-slice images was applied in order to avoid unnecessary irradiation. Intensity-modulated radiation therapy has gradually replaced four-field box radiotherapy for rectal cancer in western countries (31). In the future, a more improved radiation technique will ensure sparing the anal canal.

The anastomosis level in the CRT plus surgery group was expected to be lower than that in the group treated with surgery alone because of the difference in the tumor location in LAR cases. Moreover, a diverting stoma in the CRT plus surgery group was more frequently created than that in the surgery alone group. Consequently, the period of disuse of the bowel distal to the stoma in the was longer in the CRT plus surgery group at 12 months after surgery. We consider that these factors would chiefly result in an increased frequency of daily bowel movement.

Our analysis has several limitations. Firstly, it was a single-center study and had a small sample size. There were biases in age, tumor-related factors, and diverting stoma between the two groups. Manometric data after rectal surgery were evaluated regardless of diverting stoma in both groups. The follow-up period was not sufficiently long to evaluate the long-term effects of surgery and

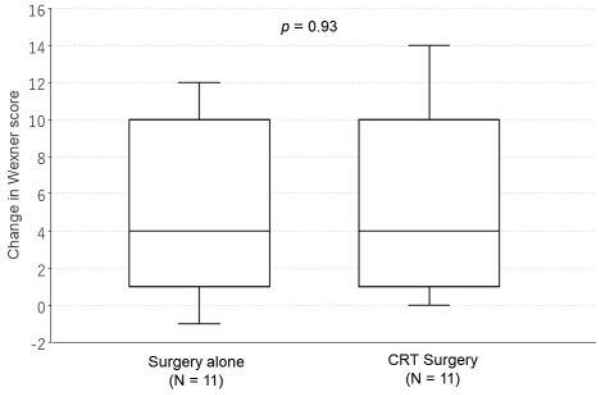

Figure 6. *Difference between the preoperative and postoperative Wexner scores in the group treated with surgery alone and that treated with chemoradiotherapy (CRT) plus surgery. Boxes are the interquartile range, lines are the median and bars are the range of scores.*

neoadjuvant CRT on anorectal function. Finally, we did not compare anorectal function after CRT (pre-surgery) with the baseline before CRT. This is due to the fact that not all patients of the CRT plus surgery group were evaluated at this timepoint.

In conclusion, neoadjuvant CRT in patients with middle and low rectal cancer did not clearly impair postoperative anorectal function at 12 months post-surgery. A larger number of patients and a longer observation period are required to analyze the late effects on anorectal function.

Conflicts of Interest

None of the Authors has conflicts of interest that would influence this work.

Authors' Contributions

Y.H., H.N., K.K., K.H., T.T., T.N., K.S., M.K., S.E., K.M., H.S., and S.I. contributed to the conception, design, or acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for significant intellectual content; and approved the final version for publication.

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