



The pattern of bowel dysfunction in patients with rectal cancer following the multimodal treatment: anorectal manometric measurements at before and after chemoradiation therapy, and postoperative 1 year

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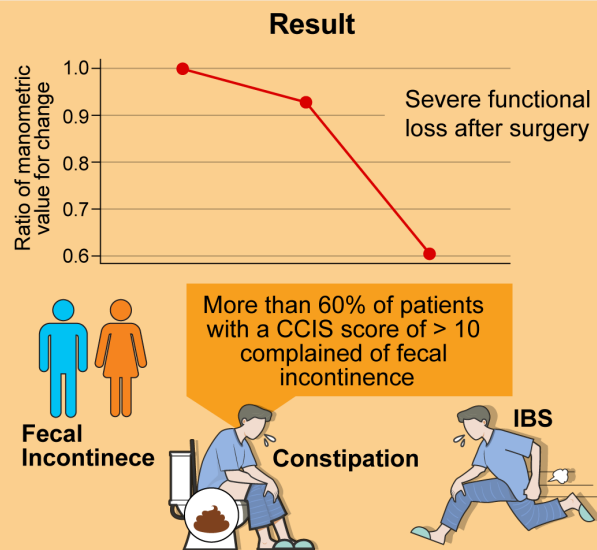
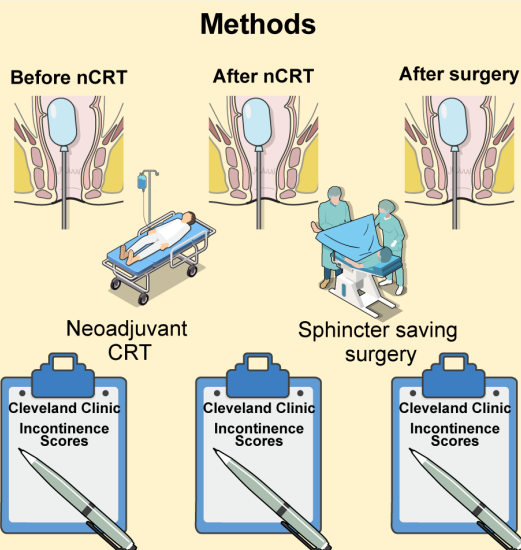
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Graphic Abstract

Purpose

Bowel function assessment with Anorectal manometry and Symptom survey



Conclusion In the course of multimodal treatments, patients should be consulted for poor anorectal function.

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Purpose: Bowel dysfunction commonly occurs in patients with locally advanced rectal cancer treated with a multimodal approach of chemoradiation therapy (CRT) combined with sphincter-preserving rectal resection. This study investigated the decline in anorectal function using sequential anorectal manometric measurements obtained before and after the multimodal treatment as well as at a 1-year follow-up.

Methods: This was a retrospective cohort study conducted in a single center. The study population consisted of patients with locally advanced mid- to low rectal cancer who received the preoperative CRT followed by sphincter-preserving surgery from 2012 to 2016. The anorectal manometric value measured after each treatment modality was compared to demonstrate the degree of decline in anorectal function. A generalized linear model of repeated measures was performed using the manometric values measured pre- and post-CRT, and at 12 months postoperatively.

Results: Overall, 100 patients with 3 consecutive manometric data were included in the final analysis. In the overall cohort study, the mean resting and maximal squeezing pressures showed insignificant decrement post-neoadjuvant CRT. At a 1-year postoperative follow-up, the maximal squeezing pressure significantly decreased. The maximal rectal sensory threshold demonstrated significant reduction consecutively after each following treatment ($P < 0.001$).

Conclusion: The short-term effect of neoadjuvant CRT on the anal sphincters was relatively trivial. The following sphincter-saving surgery resulted in a profound disruption of the anorectal function. Patients with rectal cancer should be consulted on the consequence of multimodal treatment.

Keywords: Rectal neoplasms; Fecal incontinence; Manometry; Combined modality therapy; Proctectomy

INTRODUCTION

Multimodal treatment of chemoradiation therapy (CRT) combined with radical rectal resection has been the gold standard for treatment of locally advanced rectal cancer, improving the oncologic outcome and sphincter-saving rate of patients with rectal cancer [1–3]. However, clinicians and surgical oncologists frequently encounter patients with ample loss of anorectal, sexual, and urinary functions after the treatment. Severe functional anorectal disorders after low anterior resection (LAR), termed LAR syndrome (LARS), have been recognized as an important factor associated with poor quality of life [4, 5].

The major LARS was estimated to occur in up to 41% of patients following radical rectal resection [6]. The risk factors to increase the major LARS include old age, diverting stoma, anastomotic leakage, radiotherapy, and tumor location close to the anal canal [6, 7]. Several studies reported decline in anorectal function from the multimodal treatment, using different scoring systems and questionnaires as reported by patients [6, 8, 9]. Although bowel dysfunction after rectal cancer treatment is widely reported, only a limited number of studies with small sample sizes have provided objective data for anorectal function obtained from anorectal manometry [7, 10, 11]. Herein, this study aims to demonstrate the manometric changes in patients with mid- to low rectal cancer throughout multimodal treatment of preoperative CRT, followed by total mesorectal excision (TME) and evaluate the degree of functional loss by different treatment modalities.

METHODS

On the basis of a standardized database constructed from patient records, data of the cohort study were extracted. Patients with rectal cancer who underwent sphincter-saving surgery post-CRT from 2012 to 2016 were studied retrospectively. This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of St. Vincent's Hospital, The Catholic University of Korea (No. VC19RESI0169). The need for informed consent was waived because of the retrospective design and because the analysis used anonymous clinical data and involved no additional procedure besides routine practices in a clinical setting, presenting no risk of harm to the patients.

Patients with histologically proven rectal cancer were included in the analysis. The flow chart of inclusion and exclusion criteria is shown in Fig. 1. Patients who underwent non-sphincter-saving surgery including Hartmann's procedure or abdominoperineal resection, local excision, palliative bypass surgery, and subtotal or total colectomy were excluded. Patients with a tumor located 12 cm above the anal verge and those who received no CRT or received postoperative CRT were excluded. Patients with anastomotic leakage, defined according to the International Study Group of Rectal Cancer [12], were also excluded. Among remaining patients, the patients with all 3 manometric data gathered pre- and post-CRT and at 1-year postoperatively were only included in this study. Following the pathologic confirmation of rectal cancer, patients were assessed for locoregional disease by using magnetic resonance imaging (MRI) and transrectal ultrasonography. The abdominopelvic and chest computed tomography (CT) was used

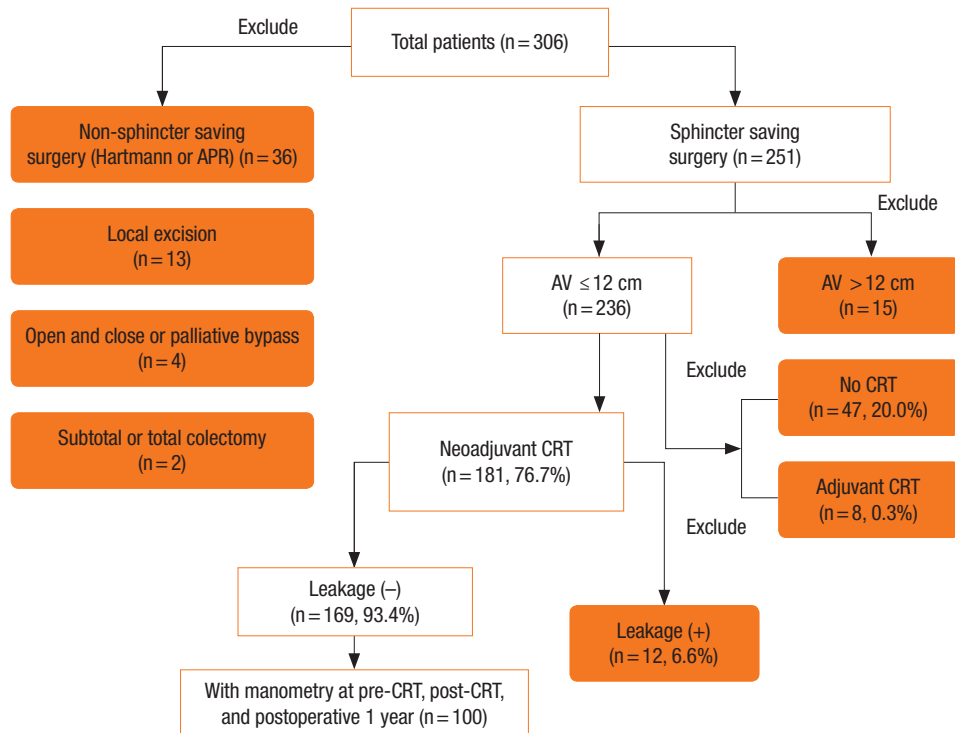


Fig. 1. The flow chart of inclusion and exclusion criteria of the study. APR, abdominal perineal resection; AV, anal verge; CRT, chemoradiation therapy.

to evaluate for systemic disease. Rigid proctoscopy was performed to measure the distance from the anal verge to the distal margin of tumor. Preoperative CRT was given to patients with clinical stage (c) T3 or clinically node-positive disease. Two types of CRT, either short-course or long-course, were offered to the patients depending on their preference and eligibility. The eligibility criteria were as follows: (1) histologically confirmed cancer; (2) tumor distal margin is located ≤ 8 cm from the anal verge; (3) cT3-4N0-2 classification as determined by MRI and/or endorectal ultrasonography; (4) no evidence of distant metastasis; (5) Karnofsky performance score of ≥ 70 ; and (6) adequate bone marrow, liver, and renal functions (leukocyte count, $> 4,000/\text{mm}^3$; hemoglobin level, > 10 g/dL; platelet count, $> 100,000/\text{mm}^3$; serum bilirubin level, < 1.5 mg/dL; serum transaminase level, < 2.5 times the upper normal limit; and serum creatinine level, < 1.5 mg/dL) [13]. Patients who satisfied the eligibility criteria received short-course CRT, while the others underwent long-course CRT. For long-course treatment, a regimen of 5-fluorouracil (5-FU), 2 cycles of intravenous 5-FU (400 mg/m^2) at 1 hour before radiotherapy, and intravenous leucovorin (20 mg/m^2) before each dose of 5-FU on days 1–5 and 29–33 were delivered concurrently with radiation of 45–50 Gy in 25–28 fractions to the pelvis. In short-course CRT, capecitabine, a dose of 825 mg/m^2 twice daily from days 1–12, was delivered concurrently with radiation of 33 Gy in 10 fractions for 2 weeks. In all patients, TME was performed at

6–8 weeks post-CRT, irrespective of long- or short-course CRT. A temporary diverting stoma, such as loop ileostomy or transverse loop colostomy, was created during TME in all patients. The diverting stoma was closed at 12–14 weeks post-index operation after confirming that the anastomosis was intact by colonoscopy and abdominopelvic CT.

Anorectal manometry was performed with a manual pull-through technique using conventional manometry with a water-perfusion system that used an 8-channel microtip catheter (Mui Scientific). Manometric data included mean resting pressure (MRP), maximum squeezing pressure (MSP), percentage of asymmetry of resting and squeezing the sphincter, length of the high-pressure zone at resting and squeezing the sphincter, recto-anal inhibitory reflex, maximal rectal sensory threshold (MRST), and rectal compliance (RC). Patients were questioned using the Cleveland Clinic Incontinence Scores (CCIS) to assess symptoms and severity of fecal incontinence [14]. Patient-reported scores were documented with anorectal manometry. A specialized nurse practitioner with > 10 years of experience in the manometry procedure performed the procedures and managed the data.

As a routine diagnostic workup before and after neoadjuvant CRT, patients diagnosed with rectal cancer underwent anorectal manometry for functional assessment. Patients were reassessed for anorectal function at 1-year post-index surgery.

Data collection and statistical analysis

Patients' data were collected retrospectively, and we constructed a standardized database that included patient demographics, body mass index, American Society of Anesthesiologists physical status classification, tumor location, neoadjuvant therapy, operative characteristics, pathologic TNM stage, and manometric data of resting and squeezing pressures and RC. Patient-reported CCIS scores were grouped as 0 points, 1–10 points, and 10–20 points at each time.

To determine whether the anorectal function changed over time with neoadjuvant CRT followed by TME, a generalized linear model of repeated measures was created using the manometric values measured pre- and post-CRT and at 12 months postoperatively. The Greenhouse-Geisser correction was used to correct possible violated sphericity. The paired-sample t-test was used to make post hoc comparisons. A P-value of <0.05 was considered statistically significant. For multiple testing, Bonferroni correction was used.

The effect of multimodal treatment was estimated by the ratio of the manometric value, which was calculated by dividing the value obtained immediately post-CRT and at 1-year post-index surgery by the initial value obtained pre-CRT [15]. A generalized linear model of repeated measures was applied to the ratio of manometric values. The same statistical analysis was used to determine differences between the subgroups. All statistical analyses were performed using IBM SPSS ver. 26.0 (IBM Corp).

RESULTS

Table 1 demonstrates patient demographics and characteristics (mean age, 63 years [range, 38–82 years]; 58 male and 42 female). The tumor was located < 6 cm from the anal verge in 50 patients and 6 cm above it in 51 patients. Long-course CRT with 5-FU was given to 91 patients, while 10 received short-course CRT with capecitabine. For the anastomotic technique, an end-to-end stapler for colorectal anastomosis was used in 83 patients. Coloanal anastomosis via the handsewn method was conducted in 18 patients.

The manometric value measured after each treatment is shown in Table 2. In the overall cohort, the absolute value of MRP is not reduced after preoperative CRT but decreased after radical rectal resection although not statistically significant. The relative change by the ratio, shown in Table 3, showed no statistical significance throughout treatment either. The preoperative MRP was slightly higher in male patients than in female patients. Comparatively, regarding relative changes of MRP, male patients presented a significant reduction after the surgery ($P=0.039$), but this remained unchanged in female patients. The relative change of the MRP showed a significant reduction in patients with handsewn anastomosis compared to patients with stapled anastomosis at 1 year after surgery ($P=0.030$).

The MSP demonstrated minimal reduction after preoperative

Table 1. Patient demographics

| Characteristic | Data |
|--------------------------------------|-------------|
| No. of patients | 169 |
| Age (yr) | 63.4 ± 10.3 |
| Sex | |
| Male | 97 (57.4) |
| Female | 72 (42.6) |
| Body mass index (kg/m ²) | 22.8 ± 4.8 |
| ASA PS classification | |
| I | 60 (35.5) |
| II | 104 (61.5) |
| III | 5 (3.0) |
| Tumor location (cm) | |
| ≤ 6 | 82 (48.5) |
| 6 > and ≤ 12 | 87 (51.5) |
| RT type | |
| Short-course | 16 (9.5) |
| Long-course | 153 (90.5) |
| Operation | |
| Lap | 156 (92.3) |
| Robot | 6 (3.6) |
| Open | 6 (3.6) |
| Conversion | 1 (0.6) |
| Anastomosis | |
| Handsewn | 34 (20.1) |
| Stapled | 135 (79.9) |
| Pathologic stage (yp) | |
| TIS/CR | 24 (14.2) |
| I | 44 (26.0) |
| II | 44 (26.0) |
| III | 52 (30.8) |
| IV | 5 (3.0) |

Values are presented as number only, mean ± standard deviation, or number (%). ASA, American Society of Anesthesiologists; PS, physical status; RT, radiation therapy; TIS, tumor *in situ*; CR, complete response.

CRT, but it significantly decreased post-TME ($P<0.001$). The relative change of the MSP presented a similar pattern ($P<0.001$). The MSP was significantly higher in male patients than in female patients in all 3 measurements ($P<0.001$). The MSP in both groups with stapled and handsewn anastomoses significantly decreased post-rectal resection ($P=0.006$ and $P<0.001$, respectively).

The MRST significantly decreased after each treatment ($P<0.001$). The relative change of the MRST indicated significant reduction consecutively after each treatment ($P<0.001$), shown in

Table 2. Anorectal manometric values measured at each time period

| Variable | Pre-CRT | Post-CRT | Postoperative 1 year | P-value |
|----------------------|----------------|----------------|----------------------|---------|
| Overall cohort | | | | |
| MRP (mmHg) | 56.56 ± 3.75 | 54.08 ± 3.16 | 44.95 ± 4.27 | 0.067 |
| MSP (mmHg) | 261.49 ± 12.72 | 251.29 ± 13.60 | 197.25 ± 11.20 | <0.001 |
| MRST (mL) | 165.50 ± 6.48 | 133.90 ± 5.11 | 87.27 ± 6.15 | <0.001 |
| RC (mL/mmHg) | 0.845 ± 0.072 | 0.742 ± 0.058 | 0.704 ± 0.104 | 0.210 |
| Stapled anastomosis | | | | |
| MRP (mmHg) | 56.36 ± 4.15 | 52.95 ± 3.50 | 47.90 ± 4.69 | 0.340 |
| MSP (mmHg) | 260.94 ± 30.13 | 254.54 ± 15.07 | 206.17 ± 12.25 | <0.001 |
| MRST (mL) | 166.14 ± 7.24 | 130.24 ± 5.19 | 75.63 ± 5.52 | <0.001 |
| RC (mL/mmHg) | 0.832 ± 0.08 | 0.704 ± 0.06 | 0.614 ± 0.08 | 0.170 |
| Handsewn anastomosis | | | | |
| MRP (mmHg) | 58.38 ± 8.87 | 59.23 ± 7.46 | 31.54 ± 10.01 | 0.007 |
| MSP (mmHg) | 264.94 ± 30.13 | 236.47 ± 32.17 | 156.59 ± 26.15 | 0.006 |
| MRST (mL) | 167.22 ± 14.7 | 154.44 ± 15.28 | 141.11 ± 18.14 | 0.480 |
| RC (mL/mmHg) | 0.907 ± 0.170 | 0.917 ± 0.136 | 1.115 ± 0.242 | 0.670 |

Values are presented as mean ± standard deviation.

CRT, chemoradiation therapy; MRP, mean resting pressure; MSP, maximal squeezing pressure; MRST, maximum rectal sensory threshold; RC, rectal compliance.

Table 3. The mean ratio of anorectal manometry in the overall cohort and the subgroups

| Variable | CRT ^a | CRT + surgery ^b | dF | F | P-value |
|----------|------------------|----------------------------|-------|--------|---------|
| Overall | | | | | |
| MRP | 1.114 ± 0.066 | 0.981 ± 0.068 | 0.525 | 2.182 | 0.120 |
| MSP | 1.010 ± 0.041 | 0.836 ± 0.043 | 0.961 | 10.971 | <0.001 |
| MRST | 0.928 ± 0.067 | 0.604 ± 0.048 | 5.100 | 24.497 | <0.001 |
| RC | 1.141 ± 0.119 | 1.309 ± 0.298 | 4.240 | 0.974 | 0.340 |
| MRP | | | 1.080 | 4.869 | 0.030 |
| Handsewn | 1.018 ± 0.157 | 0.667 ± 0.157 | | | |
| Stapled | 1.136 ± 0.074 | 1.050 ± 0.074 | | | |
| MSP | | | 0.181 | 2.096 | 0.130 |
| Handsewn | 0.874 ± 0.097 | 0.664 ± 0.101 | | | |
| Stapled | 1.040 ± 0.045 | 0.874 ± 0.047 | | | |
| MRST | | | 1.112 | 5.315 | 0.009 |
| Handsewn | 0.991 ± 0.159 | 0.987 ± 0.104 | | | |
| Stapled | 0.914 ± 0.075 | 0.520 ± 0.049 | | | |
| RC | | | 4.317 | 0.992 | 0.330 |
| Handsewn | 1.521 ± 0.282 | 1.934 ± 0.702 | | | |
| Stapled | 1.117 ± 0.132 | 1.172 ± 0.329 | | | |

Values are presented as mean ± standard deviation.

CRT, chemoradiation therapy; dF, degree of freedom; MRP, mean resting pressure; MSP, maximal squeezing pressure; MRST, maximum rectal sensory threshold; RC, rectal compliance.

^aThe ratio of each manometric value was calculated by dividing the value obtained immediately after CRT by the initial value obtained before CRT. ^bThe ratio of each manometric value was calculated by dividing the value obtained at year post-index surgery by the initial value obtained before CRT.

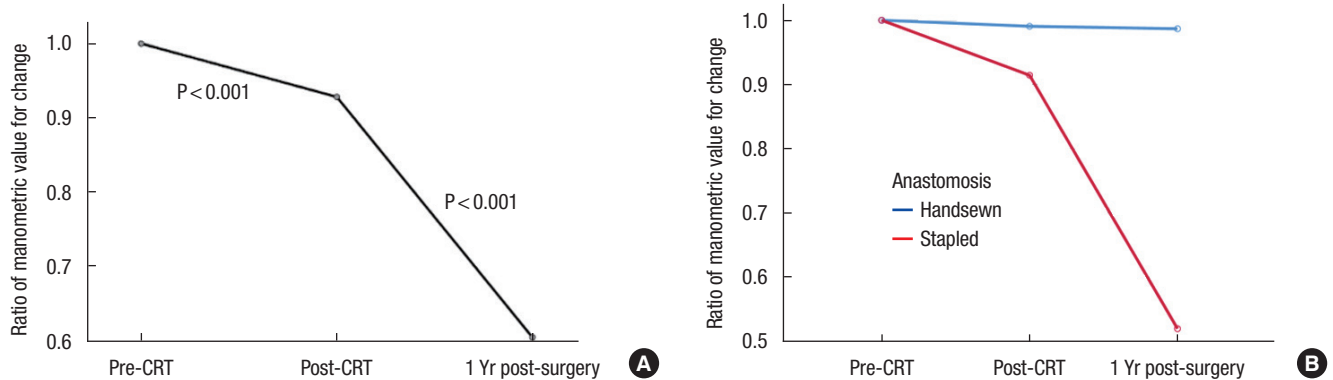


Fig. 2. (A) Overall manometric change. (B) Manometric change by anastomosis. CRT, chemoradiation therapy.

Fig. 2A. Both sexes showed a similar pattern of reduction. A comparison of the MRST in patients with different anastomoses demonstrated that the MRST was worse in patients with a stapled anastomosis postsurgery than in those with handsewn anastomosis ($P < 0.001$), as shown in Fig. 2B.

The mean value of RC decreased throughout treatment, although the change was statistically insignificant. Both sexes demonstrated inconsiderable change of RC ($P = 0.885$). RC in patients with handsewn anastomosis seemed ameliorated postsurgery. Contrarily, patients with stapled anastomosis showed a reduction in RC after each treatment, although the change was statistically insignificant ($P = 0.331$).

Ninety percent of patients reported no symptoms of incontinence pre- and post-CRT. Only 6 patients remained nonsymptomatic for fecal incontinence at 1-year post-index surgery. More than 60% of patients with a CCIS score of > 10 complained of fecal incontinence. Eight patients who experienced fecal incontinence before any treatment claimed improvement of symptoms post-CRT. The same set of patients complained of worsening of incontinence with a CCIS score of > 10 posttreatment. Six patients who experienced no fecal incontinence before any treatment had newly developed incontinent symptoms post-CRT. They presented either a similar degree of fecal incontinence or worsening of symptoms at 1-year post-CRT and surgery.

DISCUSSION

On the basis of an objective measurement using anorectal manometry, this study delineated the deterioration of anorectal function throughout multimodal treatment for locally advanced rectal cancer. With a considerable sample size, it attempted to objectify the relative decrement of anorectal function in sequence, showing the effect of CRT followed by TME. The alteration of CCIS reported by the patients supported the debilitation of anorectal function that correlated with consecutive manometric measurements.

A slight decrease of the MRP and MSP after preoperative CRT

reflected that CRT does not significantly affect the anal sphincters within the short period, approximately 6 to 8 weeks between CRT and radical rectal resection. The CCIS score reported by most patients also demonstrated no new onset of incontinent symptoms post-CRT, supporting the manometric findings pre- and post-CRT. However, neoadjuvant CRT had a significant deleterious effect on the MRST. In this study, change in the MRST immediately after CRT showed a decrease in statistical significance. This finding is in accordance with that in previous studies on anorectal function post-CRT in patients with rectal cancer [11, 16–18]. To explain the reduced MRST post-CRT, Song et al. [18] investigated the acute inflammation and edema caused by radiation exposure to the rectum. A recent study investigating radiation-induced injury to the rectal wall after neoadjuvant CRT for rectal cancer revealed that the morphological distortion, inflammation, fibrosis of mucosa and submucosa, and sclerosis of submucosal vessels were noticeably dominant [19]. These changes in tissues lead to a change in the pressure and volume maintained between the anal sphincter complex and rectal wall, probably resulting in the MRST reduction.

In conjunction with the MRST, RC calculated by the MRST over the MSP is affected by radiation therapy. However, the RC value relative to the change in either volume or pressure may not accurately demonstrate alteration of the rectum and sphincter muscle complex, because individual patients may have different degrees of inflammatory change, tumor response, or degree of fibrosis depending on their responses to CRT. Therefore, it would be challenging to use RC as an accurate indicator for changes in anorectal function. To assess RC accurately, a new technique or tool is required, such as ultrasound-based elastography, to measure the degree of stiffness and fibrosis in the rectum and pelvis.

The effect of radiotherapy on anal sphincters is not well explained due to varying, sometimes contradictory, reports of manometric parameters pre- and post-CRT in different studies. The manometric data from a small number of patients with mid- to low rectal cancer reported a significant reduction in anal resting and squeezing pressures measured immediately after CRT [11,

17]. Contrarily, a recent study evaluating the change of anorectal function in patients with low rectal cancer demonstrated an increased anal resting pressure and slightly decreased squeezing pressure measured shortly after neoadjuvant CRT [16]. Such a variation can be explained partly by different techniques in anorectal manometry. The pull-through method used in this study has established data on anal pressure [20, 21]. However, the values measured in different patient groups were known to vary [22]. We attempted to overcome such difficulty by using a single examiner with sufficient experience using conventional manometry. Furthermore, by using the ratio of subsequent measurements over the initial value, the degree of change in each patient was calculated rather than comparing the absolute value of manometric data.

The steep reduction of both the MRP and MSP at the 1-year follow-up indicated that severe dysfunction of the anorectal sphincter muscle inevitably occurs after the multimodal treatment. Here, >90% of patients complained of newly developed incontinent symptoms or experienced worsening of symptoms, indicating an apparent functional loss. Although this study cannot speculate the sole effect of CRT, previous studies comparing patients who received both radiotherapy and surgery to those who underwent surgery only also demonstrated worse functional outcome in patients who received the multimodal treatment [10, 17, 23]. The cumulative effect of CRT and TME was anticipated to disturb the anorectal function profoundly.

Interestingly, functional outcomes differed between the 2 different anastomotic methods. Patients with stapled anastomosis demonstrated a significant reduction of the MSP and MRST postsurgery. In patients with handsewn anastomosis, both the MRP and MSP significantly decreased. However, the MRST in patients with handsewn anastomosis showed no significant change. The metal composite of the anastomotic ring partly explained the significantly lower MRST in patients with stapled anastomosis. As stapler use resulted in the anastomotic ring being composed of metal fixed in the tissue, the anastomotic ring may limit the distensibility of the constructed neorectum.

Although relative change in anal pressure showed no statistical significance in the 2 different anastomotic groups, the ratio of the MSP in patients with handsewn anastomosis was lower at both periods: post-CRT and postsurgery. Neoadjuvant CRT may have a negative impact on patients with handsewn anastomosis, not on those with stapled anastomosis. The patients with a distal margin of rectal cancer located <5 cm from the anal verge were exposed to booster radiation in the anal canal. Although all patients received the same total radiation dose, additional radiation exposure cannot be avoided in patients with low rectal cancer. The squeezing pressure of patients with low rectal cancer demonstrated a considerable decrease in the slope post-CRT. Radiation seemed to negatively affect the anal sphincters, in accordance with results of previous reports by De Nardi et al. [11] and Kusunoki et al. [24]. This evidence suggests that high-dose radiother-

apy focused on the anal canal may cause significant anal sphincter dysfunction in the short term.

The anal pressure in healthy adults differs with sex [25]. Previous studies on average values of anorectal manometry in healthy adults demonstrated that the squeezing pressure was significantly higher in males than in females [25–27]. This study also revealed that before any treatment, male patients presented with a higher MRP and MSP than female patients. Male patients showed a more significant decrement of the MRP post-TME. Considering that males have a narrow pelvis and long anal canal [28], disruption of the anatomic structure of the pelvic floor and shortening of the anal canal due to TME may have a more remarkable influence in males than in females. As there is no sex-related difference in the CCIS score, the change in anorectal manometric values does not precisely demonstrate the functional difference. Further study on sexual differences in developing bowel dysfunction is necessary.

This study has several limitations. First, the retrospective nature of the study places the selection bias. With careful selection of the inclusion and exclusion criteria, we attempted to overcome the selection bias. Second, this study demonstrated no different anorectal function by age. When the analyses were performed with age adjustment, a significant difference was still not observed. A similar and larger cohort study is necessary to verify the impact of age. Additionally, the study cohort includes patients with multiple risk factors for a major LARS, including CRT and a diverting stoma. Thus, the functional outcome shown in this study is anticipated worse than that of patients with fewer risk factors. Third, this study did not demonstrate the anorectal function of patients in whom neoadjuvant CRT was omitted or those without a diverting stoma. Lastly, bowel dysfunction symptoms were limited to fecal incontinence symptoms, as indicated by CCIS scores. MRST or RC reduction may be reflected by symptoms of urgency or frequency instead of incontinence. LARS could reflect fecal urgency or frequency; however, data on LARS were not available in this study.

The anorectal function is profoundly disrupted by TME following neoadjuvant CRT, as demonstrated in the abrupt reduction of anal pressure and the MRST. Clinicians and surgical oncologists should consult patients with rectal cancer regarding the anticipated functional loss before preceding the multimodal treatment.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conceptualization: all authors; Data curation: all authors; Writing—original draft: all authors; Writing—review & editing: all authors. All authors read and approved the final manuscript.

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