in the intestine and innervates the internal sphincter muscle. After surgery, the somatic and pudendal nerves are involved in anal function and mainly innervate the external sphincter muscle of the anus. Although their origins are different, examination of these two nerves may be appropriate for assessment of neural degeneration, since neuronal failure of these nerves may cause anal dysfunction. In this study, we evaluated tissue degeneration in the neural range affected by CRT and preoperative chemotherapy, and these results are important for prediction of anal function after surgery.

Various factors can influence anal function and this makes it difficult to predict postoperative anal function before surgery. However, the results of this study suggested that preoperative radiotherapy is the major cause of tissue degeneration around the primary lesion, since almost no tissue degeneration was observed with chemotherapy alone. In another study, we found that neural degeneration was significantly higher in the CRT group and that the neural degeneration and Wexner scores were significantly correlated. Preoperative CRT induced marked neural degeneration around the rectal tumor. The significant correlation between neural degeneration and postoperative anal dysfunction suggests that findings of degeneration may be useful to predict the influence of preoperative CRT on anal function after operation [33]. That is, we examined anal function as part of bowel function, and found that tissue damage was correlated with dysfunction of the anal sphincter. In the current report, we focused on the effects of radiation based on the significantly greater nerve damage observed pathologically in resected specimens in the CRT group compared to the single chemotherapy group. These results suggest that tissue degeneration of the anal sphincter affecting anal function after surgery for colorectal cancer may be mainly caused by radiation. Further studies using a number of cases in detail are necessary to conclude it.

Postoperative maintenance of anal function is important after ISR and further studies are needed to develop a compensatory treatment for maintenance of function (for example, reconstruction of functional muscles) in CRT cases with functional failure. Simultaneous management of therapeutic benefit and anal function is required following ISR, and we intend to examine approaches to maintenance of the benefit of preoperative CRT in a future study. Thus, we are planning to perform a clinical study to establish an approach that combines therapeutic efficacy with maintenance of postoperative anal function for treatment of rectal cancer using preoperative chemotherapy and ISR.

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Postoperative morbidity and mortality after mesorectal excision with and without lateral lymph node dissection for clinical stage II or stage III lower rectal cancer (JCOG0212): results from a multicentre, randomised controlled, non-inferiority trial

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Summary

Background Mesorectal excision is the international standard surgical procedure for lower rectal cancer. However, lateral pelvic lymph node metastasis occasionally occurs in patients with clinical stage II or stage III rectal cancer, and therefore mesorectal excision with lateral lymph node dissection is the standard procedure in Japan. We did a randomised controlled trial to confirm that the results of mesorectal excision alone are not inferior to those of mesorectal excision with lateral lymph node dissection.

Methods This study was undertaken at 33 major hospitals in Japan. Eligibility criteria included histologically proven rectal cancer of clinical stage II or stage III, with the main lesion located in the rectum with the lower margin below the peritoneal reflection, and no lateral pelvic lymph node enlargement. After surgeons had confirmed macroscopic R0 resection by mesorectal excision, patients were intraoperatively randomised to mesorectal excision alone or with lateral lymph node dissection. The groups were balanced by a minimisation method according to clinical N staging (N0 or N1, 2), sex, and institution. Allocated procedure was not masked to investigators or patients. This study is now in the follow-up stage. The primary endpoint is relapse-free survival and will be reported after the primary analysis planned for 2015. Here, we compare operation time, blood loss, postoperative morbidity (grade 3 or 4), and hospital mortality between the two groups. Analysis was by intention-to-treat. This trial is registered with ClinicalTrials.gov, number NCT00190541.

Findings 351 patients were randomly assigned to mesoretcal excision with lateral lymph node dissection and 350 to mesorectal excision alone, between June 11, 2003, and Aug 6, 2010. One patient in the mesorectal excision alone group underwent lateral lymph node dissection, but was analysed in their assigned group. Operation time was significantly longer in the mesorectal excision with lateral lymph node dissection group (median 360 min, IQR 296–429) than in the mesorectal excision alone group (254 min, 210–307, p<0·0001). Blood loss was significantly higher in the mesorectal excision with lateral lymph node dissection group (576 mL, IQR 352–900) than in the mesorectal excision alone group (337 mL, 170–566; p<0·0001). 26 (7%) patients in the mesorectal excision with lateral lymph node dissection group had lateral pelvic lymph node metastasis. Grade 3–4 postoperative complications occurred in 76 (22%) patients in the mesorectal excision with lateral lymph node dissection group and 56 (16%) patients in the mesorectal excision alone group. The most common grade 3 or 4 postoperative complication was anastomotic leakage (18 [6%] patients in the mesorectal excision with lateral lymph node dissection group *vs* 13 [5%] in the mesorectal excision alone group; p=0·46). One patient in the mesorectal excision with lateral lymph node dissection group died of anastomotic leakage followed by sepsis.

Interpretation Mesorectal excision with lateral lymph node dissection required a significantly longer operation time and resulted in significantly greater blood loss than mesorectal excision alone. The primary analysis will help to show whether or not mesorectal excision alone is non-inferior to mesorectal excision with lateral lymph node dissection.

Funding National Cancer Center, Ministry of Health, Labour and Welfare of Japan.

Introduction

Total mesorectal excision or mesorectal excision, in which at least a clear margin of 4 cm of the attached mesorectum distal to the tumour is resected, is the international standard surgical procedure for rectal cancer because it has a lower rate of associated local recurrence and higher rate of patient survival than conventional surgery.[1–3] However, metastasis to lateral pelvic lymph nodes occasionally occurs in patients with clinical stage II or stage III lower rectal cancer, the lower margin of which is located at or below the peritoneal reflection.

The incidence of lateral pelvic lymph node metastasis from lower rectal cancer is about 15%, and mesorectal excision with lateral lymph node dissection has been the

standard procedure for patients with lower rectal cancer in Japan[4-6] since it was introduced in the 1970s. Pelvic autonomic nerve-sparing lateral lymph node dissection has been developed and refined since in the mid-1980s.[7] If metastatic lymph node metastases are not dissected, local or systemic recurrence can develop.[8,9] However, the incidence of local recurrence in patients with rectal cancer who undergo total mesorectal excision or mesorectal excision without lateral lymph node dissection at major hospitals in Europe and North America is reported to be less than 10%.[10-13] Although this incidence is much the same as the rate for patients undergoing standard treatment in major hospitals in Japan,[4-6] comparison is difficult because of differences in the backgrounds of patients.

The difficulty of comparison between different procedures in distinct populations prompted us to assess the survival benefit, local control, operative complications, and sexual and urinary function of patients with rectal cancer undergoing mesorectal excision alone or with lateral lymph node dissection in a randomised controlled trial in major hospitals in Japan. The study aims to determine whether or not mesorectal excision alone is non-inferior to mesorectal excision with lateral lymph node dissection in terms of efficacy. The primary analysis is planned for 2015, and this study is now in the follow-up stage. In this report, we present the data obtained so far for operation time, blood loss, and postoperative morbidity (grade 3 or 4) and mortality. Further analyses of urinary and sexual function are underway and will be reported at a later date.

Methods

Study design and participants

Preoperative inclusion criteria were histologically confirmed adenocarcinoma of clinical stage II or III (as determined by digital rectal examination, CT or MRI, and endoscopy); main lesion of tumour located in the rectum, with the lower tumour margin below peritoneal reflection; no extramesorectal lymph node enlargement (ie, lymph nodes with a short-axis diameter of less than 10 mm shown by CT scan or MRI is not regarded as lymph node enlargement); and no invasion to other organs. Eligible patients were aged between 20 and 75 years with performance status 0 or 1 and no history of chemotherapy, pelvic surgery, or radiation. Intraoperative inclusion criteria were completed mesorectal excision, confirmation that the main lesion of the tumour was located in the rectum, with the lower tumour margin below peritoneal reflection, and macroscopic R0 (ie, no residual tumour) after the mesorectal excision. Exclusion criteria were synchronous or metachronous (within 5 years) malignancies other than carcinoma in situ or mucosal carcinoma, pregnancy or breastfeeding in women, or a psychological disorder or severe mental illness. Patients undergoing treatment with systemic steroids, or with a history of myocardial infarction or unstable angina pectoris within 6 months, or with severe pulmonary emphysema or pulmonary fibrosis were also excluded. The attending physician had the final decision for exclusion.

Clinical stage was based on the results of digital rectal examination, imaging (CT or MRI), and endoscopy. Clinical stage I rectal tumours and tumours in which the lower margin was located above the peritoneal reflection were not included, because the incidence of lateral pelvic lymph node metastasis in such cases is very low. If lateral pelvic lymph node enlargement was detected by CT or MRI with 5 mm thick sections and the short-axis diameter of the nodes exceeded 10 mm, which is the minimum measurable size in such sections, patients were not included in this study and underwent mesorectal excision with lateral lymph node dissection.

Only surgeons specialising in both procedures from 33 Japanese institutions (listed in the appendix) participated in the study. We obtained written informed consent from all patients before surgery and the protocol was approved by institutional review boards.

See Online for appendix

Randomisation and masking

Randomisation and data handling were done by the JCOG Data Center. After surgeons had confirmed macroscopic R0 resection (ie, no residual tumour) by mesorectal excision and macroscopic absence of lymph node metastasis in the lateral pelvic lymph area, patients were randomised intraoperatively to mesorectal excision alone or with lateral lymph node dissection by phone call to the JCOG Data Center. The groups were balanced by a minimisation method with biased-coin assignment according to clinical N staging by imaging (CT or MRI) and surgical exploration (N0 or N1, 2), sex, and institution. Allocated procedure was not masked to investigators or patients.

Procedures

Mesorectal excision was done by open surgery in accordance with reported methods.[1] Under direct vision with sharp dissection, the rectum was mobilised keeping the plane around the mesorectum, and the attached mesorectum with at least a 4 cm clearance margin distal to the tumour was resected. If the length of the attached mesorectum distal to the tumour was less than 4 cm, the mesorectum was totally resected. The inferior mesenteric artery was ligated at its root. If the blood supply to the distal colon was deemed inadequate as a result of this procedure, preservation of the left colonic artery after lymph node dissection at its root was allowed.

Lateral lymph node dissection was done in accordance with reported methods.[4,5,14] Lateral pelvic lymph nodes include the common iliac node, internal iliac node, external iliac node, obturator node, and middle sacral node. Because metastasis to the external iliac node and middle sacral node in the patients eligible for this study without clinical lateral pelvic lymph node metastasis is rare,[15] dissection of those nodes was not deemed necessary. The other lateral pelvic lymph nodes in the fatty and

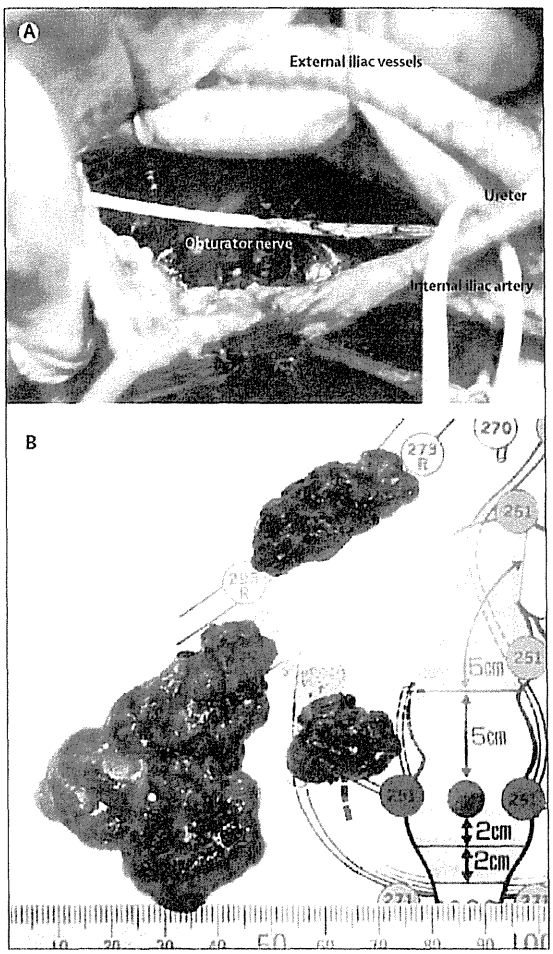

Figure 1: **Lateral lymph node dissection**
(A) The obturator fossa after lateral lymph node dissection, with the dissected fatty and connective tissues (right side). (B) Dissected fatty and connective tissues including lymph nodes.

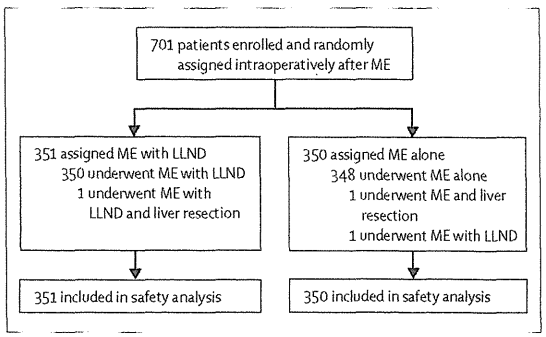

Figure 2: **Trial profile**
We did not collect data for the number of eligible patients before enrolment. ME=mesorectal excision. LLND=lateral lymph node dissection.

connective tissues outside the pelvic plexus, around the common, internal, and oburator fossa were dissected after mesorectal excision (figure 1). All the autonomic nerves were preserved because lymph node metastasis around these nerves is rare in patients without clinical lateral pelvic lymph node metastasis.

For surgical quality control and assurance, intraoperative photographs were taken. In the mesorectal excision alone group, five photos were taken: the site of inferior mesenteric artery ligation, the preserved right and left hypogastric nerves, and the anterior and posterior sides of the resected specimen. In the mesorectal excision with lateral lymph node dissection group, 11 photos were taken: the site of inferior mesenteric artery ligation, the preserved right and left hypogastric nerves, the right and left internal iliac artery, the right and left obturator fossa, the anterior and posterior sides of the resected specimen, and the right and left dissected fatty and connective tissues in the lateral pelvic lymph node area. These photographs were assessed and scored by the committee for quality control and assessment of surgery, and the surgical procedure was discussed and assured according to the score at meetings held twice a year.

Adjuvant chemotherapy with the Roswell Park regimen of intravenous fluorouracil (500 mg/m^2) and L-leucovorin (250 mg/m^2) was given to patients with pathological stage III tumours in both groups. Patients who were stage II did not receive adjuvant chemotherapy.[16] This regimen consisted of three courses of six doses of weekly chemotherapy followed by a 2-week rest. Adjuvant radiotherapy was not used.

Operative methods and pathology results were recorded according to the Japanese Classification of Colon and Rectal Carcinoma (sixth edition)[17] and TNM classification (fifth edition).[18] The primary endpoint was relapse-free survival, and the secondary endpoints were overall survival, local recurrence-free survival, incidence of adverse events, incidence of major adverse events, operation time, blood loss, and incidence of sexual and urinary dysfunction. Operation time, blood loss, and all postoperative morbidities during hospital stay were recorded prospectively on case report forms. Postoperative morbidity was described according to the National Cancer Institute-Common Toxicity Criteria version 2·0. Hospital mortality was defined as postoperative death from any cause within 30 days.

Statistical analysis

We originally estimated that 5-year relapse-free survival after mesorectal excision with lateral lymph node dissection and mesorectal excision alone would be 65%, and the initial sample size was 600 patients, which was determined with one-sided alpha of 0·05, a power of 0·75, and a non-inferiority margin for a hazard ratio (HR) of 1·34. However, we calculated the 5-year relapse-free survival for all randomised patients 5 years after the start of registration, and recorded that it was about 75%. Therefore, the sample size was increased to 700 patients to maintain the required statistical power. Planned accrual and

follow-up were 7 years and 5 years, respectively. Incidences of operative morbidity and mortality were expressed as the number of cases divided by the total number of registered patients. Differences in proportions between groups were assessed with Fisher's exact test. Differences in operation time and blood loss were compared with the Wilcoxon rank sum test. All p values were two-sided, and statistical analysis was done with SAS version 9·1. The data presented in this paper were as of June 12, 2011. Analysis was by intention-to-treat. This trial is registered with ClinicalTrials.gov, number NCT00190541, and UMIN-CTR, number C000000034.

Role of the funding source

The funding sources had no role in the design of the study, collection, analysis, interpretation of the data, writing of the report, or in the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the report for publication.

Results

701 patients were randomly assigned to the mesorectal excision alone group (n=350) or the mesorectal excision with lateral lymph node dissection group (n=351) between June 11, 2003, and Aug 6, 2010 (figure 2). All but three patients received the allocated surgery. Liver metastasis was identified after randomisation in one patient in each group and they underwent hepatic resection after rectal cancer surgery. Lateral lymph node metastasis was strongly suspected after randomisation in one patient allocated to the mesorectal excision alone group and the patient underwent lateral lymph node dissection. These three patients were eligible and included in this analysis. Two patients assigned to the mesorectal excision with lateral lymph node dissection group were found to have clinical stage I disease, despite being reported as clinical stage II or III at enrolment. Two other patients assigned to the same group had synchronous multiple cancers. Three patients (one in the mesorectal excision with lateral lymph node dissection group and two in the mesorectal excision alone group) were judged to have residual tumours before randomisation. We included these seven patients in this analysis, but their data will be excluded from the final survival analysis.

Table 1 shows the characteristics of all patients. Low anterior resection was done in 568 (81%) of 701 patients. Mesorectal excision with lateral lymph node dissection required a significantly longer operation time and resulted in significantly greater blood loss than did mesorectal excision alone (table 2). Of the 26 patients in the mesorectal excision with lateral lymph node dissection group who had lateral pelvic lymph node metastasis, 11 (42%) were clinical stage II and 15 (58%) were clinical stage III. 19 (73%) had pathological mesorectal lymph node metastasis and seven (27%) had no pathological mesorectal lymph node metastasis. Although more common in the mesorectal excision with lateral lymph node dissection group than with mesorectal excision alone, differences between groups in grade 3 and 4 postoperative complications were not significant (table 3). Anastomotic leakage of all grades,

	ME with LLND (n=351)	ME (n=350)
Sex		
Male	236 (67%)	236 (67%)
Female	115 (33%)	114 (33%)
Age (years)		
Median (IQR)	61 (54–67)	62 (55–68)
Clinical stage		
II	188 (54%)	197 (56%)
III	163 (46%)	153 (44%)
Tumour location*		
Ra	81 (23%)	80 (23%)
Rb	270 (77%)	270 (77%)
Tumour distance from anal verge (cm)†		
Median (IQR)	5·0 (4·0–6·0)	5·0 (3·7–6·0)

ME=mesorectal excision. LLND=lateral lymph node dissection. *Ra=tumour centre located above the peritoneal reflection, Rb=tumour centre located below the peritoneal reflection. †Data for five patients are missing.

Table 1: Characteristics of patients

	ME with LLND (n=351)	ME (n=350)	p value*
Type of surgery			..
Low anterior resection	284 (81%)	284 (81%)	
Abdominoperineal resection	66 (19%)	64 (18%)	
Hartmann's procedure	1 (<1%)	2 (<1%)	
Time (min)			
Median (IQR)	360 (296–429)	254 (210–307)	<0·0001
Blood loss (mL)			
Median (IQR)	576 (352–900)	337 (170–566)	<0·0001
Lateral lymph node metastasis			
Number (%)	26 (7%)	..	..

ME=mesorectal excision. LLND=lateral lymph node dissection. *Wilcoxon rank sum test, two-sided.

Table 2: Operative details

	ME with LLND (n=351)	ME (n=350)	p value*
Any grade 3–4 complication†	76 (22%)	56 (16%)	0·07
Anastomotic leakage‡	18 (6%)	13 (5%)	0·46
Urinary retention	18 (5%)	10 (3%)	0·18
Infection with normal absolute neutrophil count	16 (5%)	17 (5%)	0·86
Haemorrhage with surgery	13 (4%)	5 (1%)	0·09
Wound infection	10 (3%)	8 (2%)	0·81
Pelvic abscess	6 (2%)	2 (<1%)	0·29
Bowel obstruction	4 (1%)	3 (<1%)	1·00
Other§	12 (3%)	9 (3%)	0·66

ME=mesorectal excision. LLND=lateral lymph node dissection. *Fisher's exact test, two-sided. †National Cancer Institute-Common Toxicity Criteria Version 2·0. ‡Denominator is patients with anastomosis (ME with LLND=284, ME=284). §Other=fever, melaena, fistula, thrombosis, urinary frequency.

Table 3: Grade 3–4 postoperative morbidity

which is the major complication after low anterior resection, occurred in 37 (13%) of 284 patients in the mesorectal excision alone group and 32 (11%) of 284 patients in the mesorectal excision with lateral lymph node dissection group (p=0·61). One patient in the mesorectal excision with lateral lymph node dissection group died of anastomotic leakage followed by sepsis. All other patients recovered from surgery and were discharged from hospital.

Discussion

As expected, mesorectal excision with lateral lymph node dissection required a significantly longer operation time and resulted in significantly greater blood loss than did mesorectal excision alone. Although the incidence of grade 3 or grade 4 complications was higher in the mesorectal excision with lateral lymph node dissection group than in the mesorectal excision alone group, these differences were not significant.

In previous reports, the mean difference in intraoperative blood loss between surgical procedures with and without lateral lymph node dissection was more than 500 mL.[19–22] Blood loss might have been less in our study because none of the eligible patients had clinical evidence of lateral pelvic lymph node metastasis. In these patients, lateral lymph node dissection is easier than it is in those with clinical evidence of such metastasis. Also, because expertise with the lateral lymph node procedure is improving, blood loss might have been minimised compared with earlier studies.

The median operation time needed for mesorectal excison with lateral lymph node dissection was longer than that for mesorectal excision alone. This result is attributable to the time needed for lateral lymph node dissection, which is a meticulous procedure, and confirms previous results with regard to the difference in operation time.[20–22]

The incidence of all grade 3 or 4 postoperative complications, apart from infection with a normal absolute neutrophil count, was higher in the mesorectal excision with lateral lymph node dissection group than in the mesorectal excision alone group, but differences were not significant. Results of a previous meta-analysis[19] comparing extended lymphadenectomy including lateral lymph node dissection and conventional surgery for rectal cancer showed that the incidence of perioperative morbidity was higher for extended lymphadenectomy than for conventional surgery. However, one of the major complications, anastomotic leakage of all grades, showed no difference in incidence between the groups. Although we did not collect data for defunctioning stoma, the incidences of anastomotic leakage of all grades in patients who underwent low anterior resection in the mesorectal excision with lateral lymph node dissection group and mesorectal excision alone group were much the same, which suggests that lateral lymph node dissection was not a highly invasive surgical procedure.

Only one patient died from sepsis after anastomotic leakage. The reported mortality after mesorectal excision for rectal cancer surgery in Europe and North America is 1–3%,[11–13,23] and that after mesorectal excision with lateral lymph node dissection in Japan is 1%,[19] which is in line with our results (panel). The low mortality in our study can be attributed to several factors. Only surgeons specialising in both mesorectal excision and lateral lymph node dissection participated in this trial. Second, only patients who were judged to be capable of tolerating lateral lymph node dissection were selected and only high-volume centres for cancer treatment were allowed to enrol patients by the Colorectal Cancer Study Group.

Neoadjuvant chemoradiotherapy for rectal cancer is used worldwide. However, patients undergoing such treatment were not included and adjuvant radiotherapy was not used in our study for two reasons. First, the effectiveness and safety of adjuvant or neoadjuvant chemoradiotherapy for rectal cancer had not been clearly shown when we designed the protocol of this study. Second, adjuvant radiotherapy is not commonly used in Japan because of the lower local recurrence rate and better prognosis for patients in Japan than for those in Europe and North America.

Kim and colleagues[8] showed that lateral pelvic lymph node metastasis is a major cause of local recurrence of rectal cancer. With serial sections from human fetuses and three-dimensional reconstruction, Kusters and colleagues[24] showed that tumour recurrence might arise from lateral pelvic lymph nodes. However, other reports from Europe and North America have not supported these results. Syk and colleagues[25] examined the pattern of local recurrence after total mesorectal excision and concluded that lateral pelvic lymph node metastases are not a major cause of local recurrence. The results of a Dutch trial of total mesorectal excision showed that the rate of lateral site

Panel: Research in context

Systematic review

Total mesorectal excision or mesorectal excision is the international standard surgical procedure for lower rectal cancer.[1] However, lateral pelvic lymph node metastasis occasionally occurs in patients with clinical stage II or stage III rectal cancer, and therefore mesorectal excision with lateral lymph node dissection is the standard procedure in Japan. When metastatic lateral pelvic lymph nodes are not dissected, the patients can have local or systemic recurrence. Although we did not do a systematic search of published work before starting this trial, the reported incidence of local recurrence in rectal cancer patients undergoing mesorectal excision without lateral lymph node dissection at major hospitals in Europe and North America is less than 10%,[10–13] which is much the same as the incidence in patients who undergo mesorectal excision with lateral lymph node dissection at major hospitals in Japan.[4–6] Therefore, we did a randomised controlled trial to determine whether mesorectal excision alone is non-inferior to mesorectal excision with lateral lymph node dissection.

Interpretation

7% of the patients with lower rectal cancer without lateral pelvic lymph node enlargement had lateral pelvic lymph node metastasis. Mesorectal excision with lateral lymph node dissection required a significantly longer operation time and resulted in significantly greater blood loss than mesorectal excision alone. The primary analysis will help to determine whether or not mesorectal excision alone is non-inferior to mesorectal excision with lateral lymph node dissection.

recurrence was only 3% in patients with lower rectal cancer, being much the same as results for patients who underwent lateral lymph node dissection at the National Cancer Center, Tokyo.[26] Analysis of the pattern of local recurrence in our study is very important, and should give a reliable indication of the incidence of lateral pelvic lymph node metastasis. The incidence of such metastasis was 7%, which was lower than the 15% reported in a retrospective multicentre study in Japan,[6] because only patients who had no clinical evidence of lateral pelvic lymph node enlargement were eligible for our study. This result shows that even in patients without clinically evident lateral pelvic lymph node metastasis, such metastasis is sometimes present pathologically.

Our patient population was defined as being lateral pelvic lymph node negative by CT or MRI. Nonetheless, the 7% of patients in the mesorectal excision with lateral lymph node dissection group were found to have lateral pelvic lymph node metastasis after lymph node dissection. Therefore, a similar proportion of patients undergoing mesorectal excision alone probably have such metastasis. If all patients with lateral pelvic lymph node metastasis have local or systemic recurrence, then the relapse rate will be about 7% higher in patients who undergo mesorectal excision alone than in those who also have lateral lymph node dissection. If the results for the primary analysis planned for 2015 show that the upper confidence limit of the HR is less than 1·34, which corresponds to an 8% difference in 5-year relapse-free survival between the groups, then the non-inferiority of mesorectal exicision alone will be confirmed in terms of outcome. If not, mesorectal excision with lateral lymph node dissection should be considered the standard surgical procedure for lower rectal cancer.

Contributors

SFujita, TA, NS, and YM contributed to study design. SFujita, TA, NS, YKi, YKa, MO, SFujii, MS, TY, and YM contributed to data collection, data analysis, and interpretation. JM contributed to statistical analyses. All the authors contributed to writing or review of the report and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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Association between Anal Function and Therapeutic Effect after Preoperative Chemoradiotherapy followed by Intersphincteric Resection

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Key Words
Rectal cancer · Wexner score · Intersphincteric resection · Preoperative chemoradiotherapy · Incontinence

Abstract
Background/Aims: Preoperative chemoradiotherapy (CRT) for rectal cancer improves local control, but can also induce severe anal dysfunction after surgery. The goal of the study was to assess the relationship of the therapeutic effect of CRT with anal function and prognosis after intersphincteric resection (ISR). ***Methods:*** The subjects were 37 patients with lower rectal cancer who underwent ISR with preoperative CRT. The rectal cancer regression grade (RCRG) was quantified based on histologic features of surgical specimens. The relationships of RCRG with anal function (assessed by questionnaire) and incontinence (Wexner score) were examined at 12 months after surgery. ***Results:*** The median Wexner scores at 12 months after stoma closure in RCRG1, -2, and -3 cases were 18.0, 7.5, and 4.5, respectively, and anal function differed significantly among these groups (p = 0.001). Four cases had local recurrence, but 5-year local recurrence rates did not differ significantly among the groups. The 5-year disease-free survival rates were 88.9, 50.8, and 50.0% and the 5-year overall survival rates were 100, 77.3, and 66.7% in RCRG1, -2, and -3 cases, respectively, with no significant differences among the groups. ***Conclusion:*** Postoperative anal function is decreased when the effect of preoperative CRT is strong in patients treated with ISR.

Introduction

Innovative treatment for lower rectal cancer includes preservation of the anus. Low anterior resection with coloanal anastomosis [1] and intersphincteric resection (ISR) [2] are advanced anus-preserving operations for treatment of low rectal cancer with avoidance of colostomy. Anastomoses are made near to or under the dentate line in the anal canal, and the procedures have a tolerable and clinically acceptable local recurrence rate [3, 4].

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Investigations of functional outcome after ISR [5–9] have shown that satisfactory anal function is preserved in most patients, but some have severe dysfunction [9, 10], and conversion to colostomy may be necessary in these cases [6, 10]. Preoperative chemoradiotherapy (CRT) is strongly associated with poor anal function after ISR, and patients with rectal cancer who undergo ISR after preoperative CRT are likely to experience incontinence [11, 12]. Lim et al. [13] reported that a conventionally fractionated 45-Gy dose of preoperative CRT caused poor anorectal function due to damage to the pudendal nerve. Rectal function may also be worsened by radiation-induced proctitis and induction of rectal compliance due to fibrosis of the rectal wall [14, 15]. Direct radiation injury to the internal anal sphincter muscles can also cause anal sphincter dysfunction [16], and we found significantly higher neural degeneration in patients who received preoperative CRT [17].

These findings suggest that preoperative CRT has a negative effect on anal function, but preoperative CRT or radiotherapy is also thought to have the advantage of decreasing local recurrence following ISR [5, 18, 19]. Thus, preoperative CRT is necessary for treatment of rectal cancer and has an important oncological benefit, but this procedure is also the factor with the largest impact on postoperative anal function after ISR. However, despite its apparent importance, there are few reports on the relationship between the therapeutic effect of CRT and anal function after ISR, and there is a need for clarification of this relationship. In this study, we examined this issue based on the prognosis of patients who underwent ISR.

Materials and Methods

Patients

All patients gave informed consent to participate in the study. The study protocol was approved by the institutional review committee in our hospital and the study was performed in compliance with national and international guidelines. Our operative indications for ISR were a tumor edge 5 cm above the anal verge or 3 cm above the dentate line, adenocarcinoma confirmed histologically by preoperative biopsy, and age <76 years [6]. ISR is not indicated in patients with infiltration in the external anal sphincter shown on preoperative MRI. The preoperative stage was determined according to the UICC classification [20].

Surgical Procedure

ISR was performed as described previously [6]. First, dissection was performed by the abdominal approach until total mesorectal excision was complete. The outside layer of the internal sphincter muscle was then exposed and circumferentially divided from the puborectal muscle and the external sphincter. After the abdominal approach was completed, perianal resection was performed. The mucosa and the internal sphincter muscle were incised 1–2 cm distal to the tumor. If the tumor had invaded the external sphincter, ISR plus partial resection of the external sphincter was performed with preservation of at least the subcutaneous part of the external sphincter. The decision whether to create a pouch (either a J-pouch or a transverse coloplasty pouch) was left to the discretion of the surgeon.

Preoperative Therapy

CRT was performed over a 5-week period. A dose of 45 Gy was administered along with intravenous infusion of 5-fluorouracil (250 mg/m^2/day) to increase the efficacy of radiotherapy. Nerve-sparing resection surgery was performed 2 weeks after completion of preoperative CRT [21].

Pathological Evaluation

Hematoxylin and eosin-stained sections of the surgical specimens were used for pathological evaluation. The sections were evaluated by two authors (S.F. and Y.N.), who were blinded to the clinical data. Prior to pathological evaluation, the hematoxylin and eosin-stained sections were examined in low-power magnification fields (10×10). The surgical specimens were examined and the rectal cancer regression grade (RCRG) [22] was quantified based on histologic features as: 1, sterilization or only microscopic foci of adenocarcinoma remaining, with marked fibrosis; 2, marked fibrosis, but macroscopic disease present; or 3, little or no fibrosis with abundant macroscopic disease. If no macroscopic tumor was seen in the pathologic specimen, multiple sections were prepared after blocking the entire region of scarring. Sections were cut at several levels and examined meticulously to identify any residual foci of adenocarcinoma.

Assessment of Anal Function

Functional outcome was assessed using our functional questionnaire [6] and incontinence was evaluated using the continence scale of Jorge and Wexner (Wexner score) [23]. Questionnaires were collected from patients during consultation in the doctor's office after the patient had filled out the questionnaire by themselves at home. Questionnaires to evaluate the Wexner score were given at 12 months after stoma closure. Thus, the relationship between the three RCRG groups and postoperative anal function was examined based on the Wexner score at 12 months after stoma closure. This score reflects postoperative anal function since gradual improvements in Wexner scores are seen from 3 to 6 months and further slight improvements occur between 6 and 12 months [11].

Adjuvant Therapy

Postoperative chemotherapy was offered to patients whose final pathologic specimen was lymph node-positive. Most patients with a stage III tumor (pTNM pathologic classification) received postoperative chemotherapy with 5-fluorouracil and folic acid, tegafur-uracil, or other drugs for 6 months or more.

Statistical Analysis

Patients were divided into three groups: RCRG1, -2, and -3. Overall survival (OS) and disease-free survival (DFS) were calculated using the Kaplan-Meier method. Time to final follow-up, treatment failure, or death was measured from the date of proctec-

Table 1. Background data based on RCRG

	RCRG1	RCRG2	RCRG3
Patients, n (%)	9 (24)	22 (59)	6 (16)
Median age, years (range)	54 (37–66)	58 (39–72)	58 (27–72)
Gender, M:F	6:3	17:5	5:1
Median AV, cm	3.8 (2–5.0)	3.2 (0–5.0)	3.7 (2.0–5.0)
Operative procedure, n (%)			
Total ISR	2 (22)	10 (45)	2 (33)
Subtotal ISR	7 (78)	10 (45)	3 (50)
Partial ISR	0 (0)	2 (9)	1 (17)
PESR	2 (22)	6 (27)	1 (17)
Clinical/pathology stage, n (%)			
I	2 (22)/9 (100)	4 (18)/11 (50)	2 (33)/3 (50)
II	6 (67)/0 (0)	7 (32)/2 (9)	2 (33)/0 (0)
IIIa	0 (0)/0 (0)	5 (23)/4 (18)	0 (0)/1 (17)
IIIb	1 (11)/0 (0)	5 (23)/4 (18)	1 (17)/1 (17)
IV	0 (0)/0 (0)	1 (5)/1 (5)	1 (17)/1 (17)
Postoperative complications, n (%)	3 (33)	5 (27)	1 (17)
Anastomotic leakage	1 (11)	3 (14)	1 (17)
Pelvic abscess	2 (22)	3 (14)	1 (17)

Clinical stage: the timing of clinical assessment was performed before CRT. AV = Anal verge.

tomy. Local recurrence was evaluated using a cumulative local relapse-free survival curve. Assessment of recurrence and survival was performed in patients with microscopically curative surgery. Differences between curves were evaluated by log-rank test. Comparison of the Wexner scores between the three RCRG groups was performed by a Kruskal-Wallis test. All statistical analyses were performed using SPSS for Windows, v.13.0 J (SPSS-Japan Inc., Tokyo, Japan). A p value of <0.05 was considered to be significant.

Results

Between 2001 and 2006, 120 patients underwent ISR for very low rectal cancer at the National Cancer Center Hospital East (NCCHE), Chiba, Japan. ISR was indicated for lesions located less than 5 cm from the anal verge. For ISR cases from 2002 to 2004, CRT was performed for all patients who gave consent. Among these cases, pathological findings regarding the effect of CRT and postoperative anal function were investigated in 37 patients. A diverting stoma was constructed in each patient and the stoma was finally closed in all patients.

The clinical characteristics of the 37 patients are shown in table 1. Age, gender ratio, anal verge distance, and operative procedure did not differ significantly among the three RCRG groups. The clinical stage was I or II in 62% of the cases, mainly because of downstaging by CRT. Total and subtotal ISR were performed in many of these cases. There were no significant differences in clinical stage among the three RCRG groups. All RCRG1 cases were of pathological stage I, and so there was a significant difference in pathological stage among the three RCRG groups. Many of the CRT cases were stage I or II and total ISR was performed in some of these cases. In this study, RCRG1 cases all showed a complete response.

Postoperative complications occurred in 9 subjects [24%; anastomotic leakage in 5 (11%) and pelvic abscess in 6 (16%)]. There was no significant difference in the rate of postoperative complications among the three RCRG groups. The average time between the primary operation and closure of the stoma was 227 days (range: 80–665), with no significant differences in this time among the three RCRG groups.

Association with Anal Function at 12 Months after Surgery

No patient had a Wexner score of ≥2 preoperatively and none had problems with preoperative anal function. The median Wexner scores at 12 months after stoma closure were 18.0, 7.5, and 4.5 in the RCRG1, -2, and -3 groups, respectively. A higher Wexner score indicates

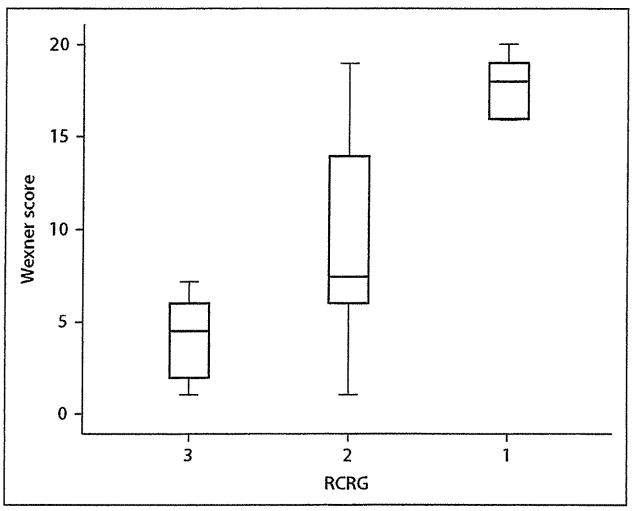

Fig. 1. Relationship between RCRG and anal function at 12 months after surgery. The median Wexner scores at 12 months after stoma closure in the RCRG1, -2, and -3 groups were 18.0, 7.5, and 4.5, respectively, with anal function differing significantly among the three groups (p = 0.001 by Kruskal-Wallis test).

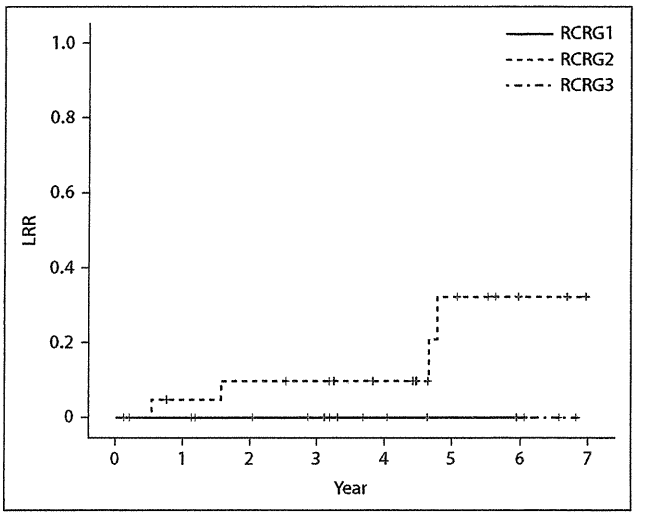

Fig. 2. Cumulative local recurrence rates (LRR) in the RCRG1, -2, and -3 groups. Local recurrence occurred in 4 patients, all of whom were RCRG2 cases. The 5-year local recurrence rates did not differ significantly among the three groups (RCRG1: 0%; RCRG2: 33.3%; RCRG3: 0%).

greater anal dysfunction. Based on these scores, anal function differed significantly among the three groups (p = 0.001 by Kruskal-Wallis test; fig. 1).

Therapeutic Prognosis

The median observation period for all subjects was 74 months, and the 3-year and 5-year survival rates were 83 and 81%, respectively. For cases at pathological stages I, II, III, and IV, the 5-year OS rates were 86, 93, 67, and 50%, respectively, and the 5-year DFS rates were 75, 80, 40, and 0%, respectively.

Local Recurrence

Local recurrence, including regional lymph node metastasis, was observed in 4 cases, all of which were in the RCRG2 group. All 4 cases were also at pathologic stage III. The 5-year local recurrence rates did not differ significantly among the three RCRG groups (fig. 2).

Survival

During follow-up, 11 of 37 patients developed recurrence: 1, 7, and 3 in the RCRG1, 2-, and -3 groups, respectively. The 5-year DFS rates were 88.9, 50.8, and 50.0% in the respective groups, with no significant differences among the three groups (p = 0.32 for RCRG1 vs. RCRG2, p = 0.60 for RCRG2 vs. RCRG3, and p = 0.114 for RCRG1 vs. RCRG3; log-rank test; fig. 3). The 5-year OS rates were 100, 77.3, and 66.7% in the RCRG1, -2, and -3 groups, respectively (fig. 4). A tendency for improved OS was found in the RCRG3 group (p = 0.12 for RCRG1 vs. RCRG2, p = 0.93 for RCRG2 vs. RCRG3, and p = 0.07 for RCRG1 vs. RCRG3), but there were no significant differences in OS among the three groups. The absence of significant findings for these data may be due to the small numbers of patients in the three groups.

Discussion

Abdominoperineal ISR with coloanal anastomosis is an extreme form of rectal resection [2, 3, 5–10, 12, 18, 24–29], and recent efforts have focused on increasing the rate of sphincter preservation. In our previous report [28], the median follow-up periods were 40 months in patients treated with ISR and 57 months in those that underwent abdominoperineal resection, the respective 5-year local relapse-free survival rates were 83 and 80%, and the 5-year DFS rates were 69 and 63%, respectively. Acceptable oncologic results were obtained with ISR in patients with very low rectal cancer located within 5 cm of the anal verge. Thus, the use of ISR can reduce the number of abdominoperineal resection procedures with-

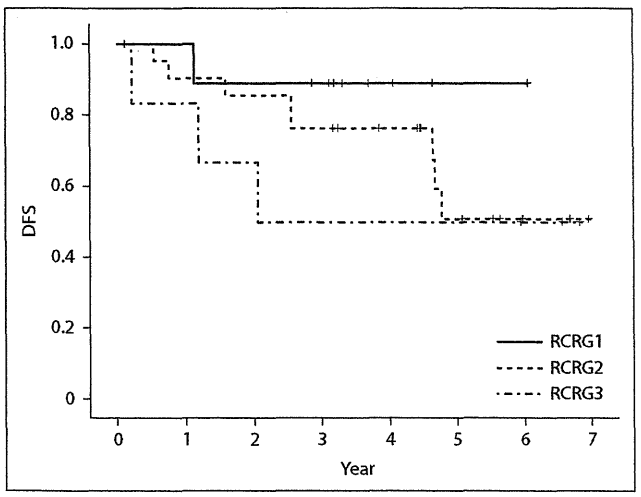

Fig. 3. DFS in the RCRG1, -2, and -3 groups. During follow-up, 11 of 37 patients developed recurrence: 1 RCRG1 case, 7 RCRG2 cases, and 3 RCRG3 cases. There were no significant differences in DFS among the three groups by log-rank test. Five-year DFS = RCRG1: 88.9%; RCRG2: 50.8%; RCRG3: 50.0%.

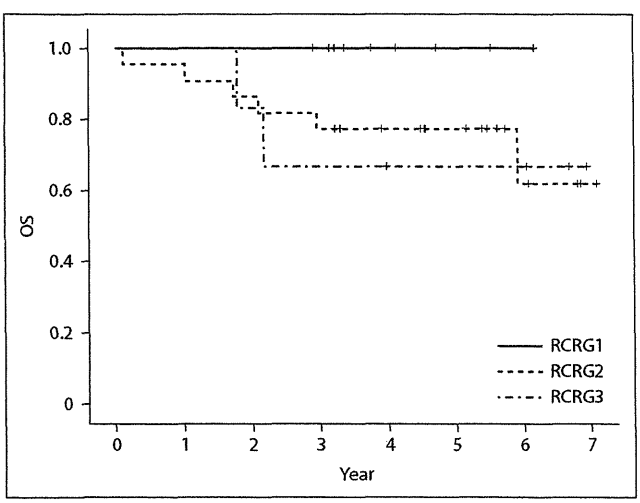

Fig. 4. OS in the RCRG1, -2, and -3 groups. The 5-year OS rates were 100, 77.3, and 66.7% in RCRG1, -2, and -3 cases, respectively, with no significant differences among the three groups.

out compromising local recurrence and survival. In addition, most patients who underwent ISR had acceptable anal function in the series of Schiessel et al. [27], our previous report [28], and other studies [7, 8, 26], although there are few studies of long-term anal function after ISR.

Our analysis showed that preoperative CRT had a negative effect on anal function, regardless of the surgical method [11]. Functional results after ISR are significantly altered by preoperative radiotherapy [12] and preoperative CRT has a negative effect on anal function immediately after surgery for rectal cancer, even in cases with no ISR [30–33]. Many cases were of pathological stages I and II due to downstaging by CRT, but total ISR was performed in some of these cases. This approach was used because we were unable to judge the position of the tumor edge on the anal side before preoperative CRT, which prevented maintenance of a clear distal margin. However, this had no influence on the analysis of the Wexner score because the comparison of this score with anal dysfunction was performed only within the CRT cases. Moreover, of the factors investigated, preoperative CRT had the greatest effect on anal dysfunction after ISR, and total ISR was more strongly associated with anal dysfunction than either subtotal or partial ISR. Therefore, a negative effect of preoperative CRT on anal function was found regardless of the extent of internal sphincter muscle preservation. This suggests that it may be important to examine degeneration around the internal sphincter muscle for prediction of anal dysfunction.

The results of this study showed that postoperative anal function decreased when the effect of preoperative CRT was high in patients who underwent ISR. The cause of the negative effect of conventionally fractionated CRT on anorectal function is unclear. Lim et al. [13] suggested that poor anorectal function after preoperative CRT was due to damage to the pudendal nerve, and rectal function may also be worsened by radiation-induced proctitis and reduced rectal compliance [14, 15]. Moreover, anal sphincter dysfunction may be caused by direct radiation injury to the internal anal sphincter muscles [16].

In another study, we found that neural degeneration was significantly higher in the CRT group and that neural degeneration and Wexner scores were significantly correlated [17]. We examined neural degeneration using a scoring system for function (we refer to this as the NFS system) and found that preoperative CRT induced marked neural degeneration around the rectal tumor. The significant correlation between neural degeneration and postoperative anal dysfunction suggests that findings of neural degeneration may be useful for prediction of the influence of preoperative CRT on anal dysfunction after surgery [17]. In the current study, patients in whom CRT had a strong therapeutic effect (RCRG1 group) may have had higher incidences of neural degeneration and fibrosis, which then had a negative effect on anal function. Further accumulation of cases in which CRT had a strong therapeutic effect will allow evalu-

ation of the relationship between tissue degeneration (NFS system) and postoperative anal function (Wexner score).

In our patients, surgery was performed within 2–3 weeks after completion of preoperative CRT and the histological changes occurred during this period. In a report [34], surgery was performed 6–8 weeks after CRT for some cases to avoid acute-phase disorders. A delay of surgery until 6–8 weeks after CRT may increase the probability of reaching RCRG1 and tissue injury can also be clearly observed by examining removed samples. In addition, anal function improved with the postoperative course in some cases, suggesting that nerves and tissue including muscle can regenerate, with a resultant improvement in anal function. However, an investigation of anal function after ISR in patients who underwent surgery at our hospital suggested that functional recovery is unlikely in cases with unfavorable function at 6–12 months after surgery [11]. Since CRT-induced early-phase tissue degeneration is associated with anal function at 12 months after surgery, as found in this study, tissue degeneration early after CRT may have a long-term effect on anal function.

Radiotherapy before surgery for rectal cancer can contribute to a decrease in postoperative local redevelopment [35–37], but it is unclear if radiotherapy contributes to OS. Comparison of the prognosis of the 37 patients who received preoperative CRT in this study with that of 21 patients who received ISR alone in another study showed 5-year OS of 81 and 84%, respectively ($p = 0.6$, log-rank test), 5-year DFS of 69 and 67%, respectively ($p = 0.6$, log-rank test), and 5-year local DFS of 78 and 82%, respectively ($p = 0.7$, log-rank test), with no significant differences between the two groups. This suggests that CRT does not contribute to the prognosis in all patients. However, the prognosis of the RCRG1 group in this study suggested a tendency for favorable survival in this group during the follow-up period, and redevelopment occurred in only 1 patient. There have been several studies on the prediction of the effects of preoperative CRT using biomarkers, but there is no current method for prediction of RCRG1 with high sensitivity. Development of such a method could allow CRT to be performed beneficially even though anal function might be damaged. However, our results suggest that performance of CRT is not appropriate for all patients who undergo ISR for preservation of anal function.

Various factors may influence anal function and this makes it difficult to predict postoperative anal function before surgery. However, the results of this study showed a significant correlation between RCRG class and Wexner score. Postoperative anal function is important after ISR and there is a need to develop a compensatory treatment for maintenance of function (e.g. reconstruction of functional muscles) for CRT cases with functional failure. A preoperative examination with high sensitivity is also required to select potential RCRG1 cases before CRT is performed since the prognosis of RCRG1 cases may be favorable. The results of the current study showed that postoperative anal function after ISR decreased in patients in whom the effect of preoperative CRT was high. However, OS in these cases may be higher, which suggests that preoperative CRT might have conflicting effects in ISR.

Simultaneous management of the therapeutic benefit of CRT and anal function is required following ISR, and we plan to examine approaches to this problem in a future study. For example, preoperative chemotherapy alone may be appropriate based on the improvement of colorectal cancer observed with this approach. If preoperative chemotherapy is effective for downstaging, local control, and inhibition of distant metastasis, as seen for preoperative CRT, this chemotherapy may be the most appropriate preoperative therapy for ISR, with a focus placed on postoperative anal function. We often confront a dilemma regarding the therapeutic effects of preoperative CRT and preservation of anal function in ISR, but we consider it important both to use an appropriate surgical method after preoperative CRT and to select the most appropriate preoperative therapy for ISR.

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Disclosure Statement

None of the authors have a conflict of interest regarding the work in the study.

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CASE REPORT

Rectoseminal vesicle fistula as a rare complication after low anterior resection: a report of three cases

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Abstract A rectoseminal vesicle fistula is a rare complication after a low anterior resection for rectal cancer, usually developing in the outpatient postoperative period with pneumaturia, fever, scrotal swelling or testicular pain. A diagnostic water-soluble contrast enema, cystography and computed tomography reveal a tract from the rectum to the seminal vesicle. Anastomotic leakage is thought to be partially responsible for the formation of such tracts. This report presents three cases of rectoseminal vesicle fistula, and the presumed course of the disease and optimal treatment options are discussed.

Keywords Colon fistula · Seminal vesicle · Urinary fistula

Introduction

The complications of end-to-end anastomosis for lower rectal cancer include anastomotic leakage, rectovaginal fistula, intrapelvic abscess and stenosis. A rectoseminal vesicle fistula is rare. Three patients developed rectoseminal vesicle fistula and were treated over a period of 19 years. This report reviews and summarizes similar previously reported cases, while focusing on the presumed course of the disease, diagnostic procedures and treatment options.

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Patient 1

A 73-year-old male was admitted to the surgical department for treatment of rectal cancer 7 cm from the anal verge. Colonoscopy revealed a type 2 tumor of the rectum and the histopathological examination of a specimen obtained by colonoscopy revealed adenocarcinoma. Laboratory tests were normal. The preoperative staging was T3N0M0. The patient did not receive any neoadjuvant therapy.

A low anterior resection was performed with an end-to-end anastomosis. Microscopic examination of the specimen revealed well-differentiated adenocarcinoma of the rectum with adequate resection margins and no metastases in the 12 resected lymph nodes. This was a T3N0M0 tumor, according to World Health Organization (WHO) classification.

The immediate postoperative course was uneventful. The discharge from the intrapelvic drain was noted to be purulent on postoperative day 7. A water-soluble contrast enema demonstrated minor anastomotic leakage on day 14. The patient was treated conservatively with intrapelvic drainage and antibiotics. Oral diet was resumed on postoperative day 24 and the patient was discharged on day 29. He was readmitted on postoperative day 37 with acute left testicular pain, fever and pneumaturia. A vasogram followed by fistulography demonstrated a fistula from the seminal vesicle to the rectum via the anastomotic site (Fig. 1).

Computed tomography revealed air bubbles located between the rectum and seminal vesicle. Anastomotic leakage followed by coloseminal vesicle fistula after low anterior resection was diagnosed. The leakage was locally restricted, without any sign of generalized peritonitis, and was successfully treated using only urethral catheterization

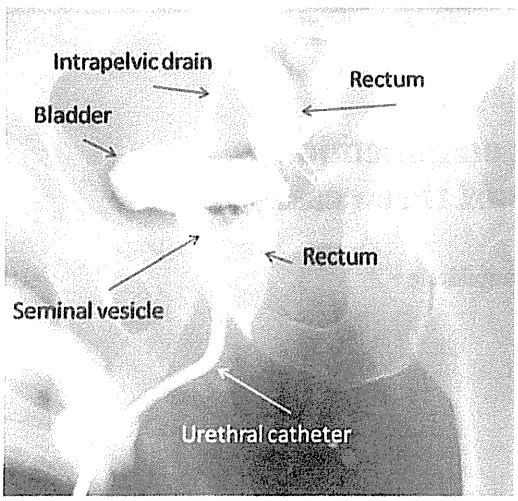

Fig. 1 A vasogram followed by fistelography demonstrating fistula from the seminal vesicle to the rectum via the anastomotic site. 136 × 128 mm (150 × 150 DPI)

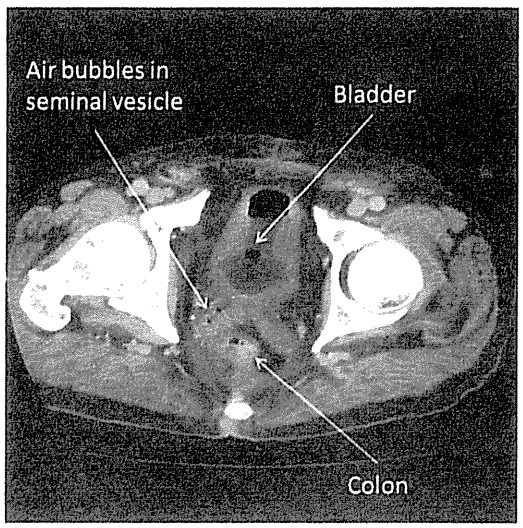

Fig. 2 CT showing air bubbles in and around the seminal vesicle. This slice is 1 cm above the anastomotic site. 125 × 125 mm (150 × 150 DPI)

and antibiotics with oral diet. The fistula had successfully healed by postoperative day 62, or 25 days after readmission.

Distant metastases were found 17 months after the first operation. The patient underwent partial hepatectomy and pulmonary resection for metastases from rectal cancer. He is doing well without local recurrence at 4 years after the first operation.

Patient 2

A 76-year-old male was admitted to the surgical department for treatment of rectal cancer 7 cm from the anal verge. Colonoscopy revealed a type 2 tumor of the rectum and the histopathological examination of a colonoscopic specimen led to a diagnosis of adenocarcinoma. Laboratory tests yielded normal results. The preoperative stage was T3N1M0. The patient's medical history included diabetes mellitus, hypertension, angina pectoris and pulmonary hypertension. The patient did not receive any neoadjuvant therapy.

A low anterior resection was performed with end-to-end anastomosis. A microscopic examination of the specimen revealed moderately differentiated adenocarcinoma of the rectum with adequate resection margins and lymph node metastasis in one of the 12 resected nodes. This was a T3N1M0 tumor.

The patient accidentally removed the urethral catheter while the balloon was still inflated on postoperative day 7. No apparent damage was observed in the urethra at that time. He was discharged on postoperative day 11. He presented to the emergency department 1 month after first discharge with acute testicular pain, pneumaturia and a swollen scrotum. A water-soluble contrast enema demonstrated a fistula between the anastomotic site and a seminal vesicle. CT revealed air bubbles around the seminal vesicle and a series of abscesses from the seminal vesicle to the scrotum (Fig. 2). Conservative therapy with antibiotics and urethral catheterization was attempted which failed, so diverting transverse colostomy was performed on postoperative day 50 (day 39 after readmission). Healing of the fistula was confirmed at another hospital and stoma closure was eventually performed, about 14 months after the first operation.

The patient was treated for pulmonary metastases with oral tegafur-uracil. He has survived 3 years and 10 months since the first operation without local recurrence.

Patient 3

A 49-year-old male was admitted to the surgical department for treatment of a huge rectal cancer. Colonoscopy revealed a type 3 tumor of the rectum and a histopathological examination led to a diagnosis of adenocarcinoma. Computed tomography (CT) and magnetic resonance imaging demonstrated the tumor and adjacent abscess forming a mass 10 cm in diameter, with infiltration into the right seminal vesicle. The C-reactive protein level was elevated to 7.1 mg/dl. Pelvic incisional drainage was performed prior to the radical operation. Preoperative staging was T4N2M0.

A low anterior resection of the tumor with the bilateral seminal vesicles and diverting ileostomy were performed with end-to-end anastomosis. A microscopic examination of the specimen revealed moderately differentiated

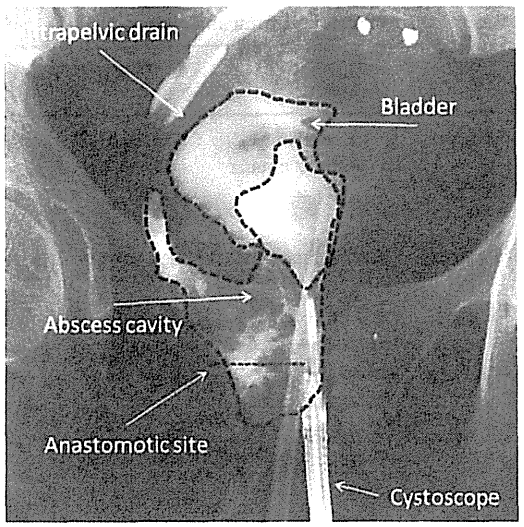

Fig. 3 A vasogram under cystoscope control demonstrates fistula from the ejaculatory duct to the anastomotic site via an abscess cavity. 137 × 137 mm (150 × 150 DPI)

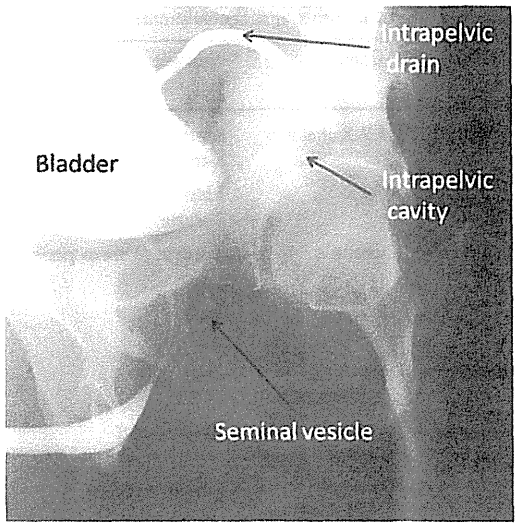

Fig. 4 Retrograde cystourethrography shows fistulous communication between the seminal vesicle and intrapelvic cavity. This represents seminal vesicle fistula after concomitant resection of rectum and seminal vesicle. 125 × 125 mm (150 × 150 DPI)

adenocarcinoma of the rectum with adequate resection margins and no metastases in any of the 44 resected lymph nodes. This was a T3N0M0 tumor.

The patient displayed fever and fecaluria on postoperative day 10. CT revealed anastomotic leakage surrounded by a cavity filled with pus and an increased air–water level. A vasogram under cystoscopic control demonstrated a fistula from the ejaculatory duct to the anastomotic site via an abscess cavity (Fig. 3). He was diagnosed with anastomotic leakage followed by creation of a fistula between the anastomotic site and the excision site of the seminal vesicles. The patient was effectively treated using lavage from an intrapelvic drainage tube and urethral catheterization with a saline flush. The abscess cavity gradually contracted and disappeared, but the fistula remained refractory. Gracilis muscle flap closure was attempted but proved unsuccessful. Additional abdominal rectus muscle flap closure achieved an improvement of the fistula.

The patient finally underwent total pelvic exenteration for intrapelvic recurrence along with intention to treat urinary division after 2 years and 6 months. He has survived 3 years since the first operation.

Discussion

Abscess formation around the seminal vesicle is infrequently encountered in patients without apparent anastomotic leakage that have undergone concomitant resection of the rectum and seminal vesicle (Fig. 4). The usual clinical course is cloudy discharge from the pelvic drain, fever, and relatively normal results of laboratory tests, other organ function and general status. A water enema of the anastomotic site subsequently reveals no leakage. Cutting off the root of the seminal vesicle without ligation causes a seminal vesicle fistula and local collection of pus. Simply leaving the fistula open may be adequate as long as the fever is controlled by antibiotics. The patient usually recovers from the fistula within several weeks. The prophylactic approach includes a ligation of the base of the resected seminal vesicle.

This report presented three cases of rectoseminal vesicle fistula after low anterior resection. Low anterior resection has been performed at this institution since 1992, with more than 1100 patients treated. Three patients developed rectoseminal vesicle fistula and were treated over a 19 years period. Coloseminal vesicle fistula is particularly uncommon. The causes or origin of such fistulae include inflammatory bowel disease, low anterior resection, prostatectomy, radiation proctitis, and sigmoid colon diverticula [1–3]. Only 10 cases of seminal vesicle fistula were found among the reported postsurgical intervention cases [3–9] (Table 1).

Minor leakage was demonstrated on postoperative day 14 in the first case, and was conservatively treated using only a drainage tube. Mild residual inflammation might have adversely influenced the fragile seminal vesicle wall. Outpatient follow-up on postoperative day 37 revealed a fistula to the seminal vesicle. Denonvilliers' fascia, which is located between the rectal anterior wall and the seminal vesicle beneath the level of the peritoneal reflection, may be removed when performing total mesorectum excision [10]. Denonvilliers' fascia is a very strong tissue that divides the urinary tract and rectum. Infectious material

Table 1 Clinical features, diagnostic examinations, and treatment of patients with postoperative coloseminal vesicle fistula

Author	Cause	Symptoms	Urine passage	Onset	Diagnostic examination	Initial treatment	Radical treatment
Goldman [4]	LAR leakage	Pneumaturia, bacteriuria testicular pain,	No	1 month	Water-soluble contrast enema	Cutaneous vasotomy	None
Kollmogen [5]	APR	Urethral discharge, fever, dysuria	No	10 days	Sinography	Antibiotics, drainage	None
Carlin [6]	Crohn's	Discharge from perineal sinus	No	15 years	CT sinography	N.S.	None
	AR	None	No	2 months	CT with rectal contrast enema	Drainage	APR
Calder [7]	Open prostatectomy	N.S.	N.S.	N.S.	Water-soluble contrast enema	N.S.	N.S.
Celebrezze [8]	Prostatic brachytherapy	Rectal ulcer	Yes	2 years	N.S.	Mucosal flap	Diversion
	Prostatic brachytherapy	Rectal bleeding	Yes	15 months	N.S.	Mucosal flap	Colostomy
Kawasaki [9]	LAR leakage	Dysuria	No	2 weeks	Water-soluble contrast enema	Conservative	Colostomy
Our cases	LAR leakage	Pneumaturia, testicular pain, fever	No	1 month	CT and vesiculography	Urinary catheter	None
	AR	Pneumaturia, testicular pain, scrotal swelling	No	2 weeks	CT and contrast enema	Urinary catheter, antibiotics	Colostomy
	LAR leakage	Fecaluria, fever, scrotal swelling	Yes	1 week	CT and vasogram	Urinary catheter, antibiotics	Muscle flap

LAR low anterior resection, *AR* anterior resection, *APR* abdominoperineal resection, *N.S.* not stated

may cause local tissue destruction and the formation of a fistula if this septum is resected.

The second case showed no evidence of anastomotic leakage during the postoperative course. Latent anastomotic leakage may have been present or the fragile seminal vesicle wall may have eventually collapsed, allowing passage between the seminal vesicle and anastomotic site in the outpatient follow-up period. Accidental catheter removal may have adversely affected the urinary tract, with injury of the ejaculatory duct and seminal vesicle causing fistula to the rectum. However, a seminal vesicle fistula is rarely observed in cases with accidental removal of a urethral catheter.

The third case required resection of a huge T4 mass, including the bilateral seminal vesicles. A Retzius cavity approach was selected due to the size of the tumor occupying the pelvic cavity, and the bases of the seminal vesicles were difficult to identify for ligation. Anastomotic leakage caused the abscess formed by leakage to increase in size around the remnant rectum, and become a seed of inflammation, leading to a fistula into the unclosed ejaculatory duct.

Rectoseminal vesicle fistula formation in all three cases appeared to be due to a combination of resection of Denonvilliers' fascia or the seminal vesicle itself and anastomotic leakage.

Many investigators have evaluated the safety of the double stapled technique and its role in rectal cancer surgery. They concluded that the double stapling technique is an equivalent or even superior type of intervention with respect to speed, sterility and anastomosis safety, while also associate with fewer complications [11–20]. However, Kosugi et al. [21] reported that the incidence of rectovaginal fistula was higher in patients who were anastomosed by the double stapled technique or had concomitant resection of the vaginal wall. The current surgical reports and postoperative examinations proved no direct relationship between the double stapled technique and fistulae. However, these reports concerning rectovaginal fistula [21–23] emphasize that the double stapled technique might cause rectoseminal vesicle fistula when frustrating distal anastomosis is carelessly performed.

No diverting stoma was constructed in the first two cases. The first case recovered conservatively, but the other was treated with transverse colostomy. The third case required the construction of a diverting ileostomy, but it failed. These cases suggest that a diverting stoma cannot always prevent leakage or the formation of rectoseminal vesicle fistula. Several studies have shown the absence of a diverting stoma to be a risk factor for leakage after LAR [24–29], whereas others did not [30]. Anastomotic failure and the completion of rectoseminal vesicle fistula are thought to be influenced by an infectious environment, the viscosity of the discharge and the rectum-cavity urinary tract pressure gradient. Whether diverting the fecal stream

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