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Efficacy and safety of preoperative chemoradiotherapy with S-1 for advanced rectal cancer: a phase II study

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Abstract

Background: Preoperative chemoradiotherapy (CRT) for patients with rectal cancer is not yet established in Japan. We aimed to evaluate the efficacy and safety of preoperative CRT with S-1, a fixed-dose combination of tegafur, gimeracil, and oteracil potassium.

Materials and methods: We conducted a prospective, interventional, non-randomized single-center study. Radiotherapy was administered at a total dose of 45 Gy (1.8 Gy in 25 fractions) for five weeks. S-1 was administered orally for nine weeks (five weeks during and four weeks after radiotherapy) at a dose of 80 mg/m^2/day. The endpoint was the pathological complete response (pCR) rate.

Results: Twenty-eight patients were finally enrolled. The following patient characteristics were recorded: clinical Stage (II: n = 12, III: n = 16), median age (66 years, range 40–77 years), male/female ratio (20/8), and lesion site (Ra-Rb:3/Rb:23/Rb-P:2). Preoperative treatment was completed in 27 patients (96%). Treatment abandonment occurred because of diarrhea. Grade 3 or higher adverse events were observed in one (4%) patient with two events. No serious adverse events occurred in the ≥ 70 years group. The response rate was 68% in all patients and 68% among elderly patients. Radical resection was achieved in all patients,

including 19 (68%) who underwent sphincter-preserving surgery. The pCR rate was 11% (three patients). The five-year disease-free survival rate was 68%, and the overall survival rate was 82%. Local recurrence occurred in only one patient five years after surgery.

Conclusion: Preoperative CRT with S-1 alone may be a safe and acceptable regimen from the perspective of adverse events and oncological outcomes.

Trial registration: UMIN Clinical Trial Registry: UMIN000013598. Registered 1 April 2014, https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000015887

Key words: preoperative CRT; S-1; rectal cancer; pathological complete response; phase II trial

Introduction

Recent advances in chemotherapy have improved the prognosis for patients with colorectal cancer. However, complete surgical resection still determines the prognosis [1]. In addition to the control of distant metastasis, treatment of rectal cancer also involves the control of local recurrence [2, 3] and preservation of anal function to maintain patient quality of life [4]. Research into the treatment of low rectal cancer for both curative resection and preservation of anal function is important.

Total mesorectal excision surgery, as proposed by Heald et al. [5], is recognized as the gold standard for rectal cancer treatment. The standard care in western countries consists of preoperative chemoradiotherapy (CRT) followed by surgery [6, 7]. The rationale for this approach is supported by large phase III trials which have demonstrated that neoadjuvant therapy (preoperative adjuvant therapy) reduced the risk of local recurrence [3, 8, 9]. The anal preservation rate in the CAO/ARO/AIO-94 study was 39% [7, 8]. In Japan, surgical resection is the standard treatment [10], and preoperative CRT has been performed in a limited number of patients [1].

Reports of standard CRT treatment with 5-fluorouracil (5-FU) raise several concerns regarding preoperative CRT despite evidence of local control of rectal cancer [3, 8, 9]. Specifically, there may be adverse effects, including postoperative defecation and effects on anal, urinary, and sexual functions due to radiotherapy [11]. Furthermore, administration of anticancer agents by intravenous drip is more burdensome to the patient than oral administration. Most importantly, local control may not improve overall survival in patients with previous preoperative CRT based on 5-FU [3, 8, 9]. To further improve outcomes, preoperative CRT with novel, advanced anticancer agents should be carefully considered because of efficacy issues and new adverse events.

S-1 is an oral anticancer drug with a fixed-dose combination of tegafur, gimeracil, and oteracil

potassium. The gimeracil in S-1 prevents tegafur from being metabolized to anything other than fluorouracil, thereby increasing the concentration of 5-FU in the body [12]. Oteracil potassium reduces gastrointestinal toxicity caused by 5-FU [12]. There are reports on S-1 alone producing favorable responses in patients with unresectable advanced or recurrent colorectal cancer [13, 14]. Furthermore, S-1 reportedly has a radiation-sensitizing effect [15]. Combining radiation therapy and oral agents is a simple approach and S-1, a prodrug of 5FU, may be a candidate for CRT regimen in Japan [16]. In our previous study, we designed a phase I trial to provide a simple, safe and effective treatment to achieve curative resection and preserve postoperative voiding function in patients with locally advanced rectal cancer, and we demonstrated a feasible prescription dose for preoperative CRT with S-1 [17].
We conducted this phase II study using the doses set in our previous phase I study to evaluate the pCR rate and the efficacy and safety of preoperative CRT with S-1 for patients with locally advanced rectal cancer, including the elderly.

Materials and methods

Protocol

The current study was conducted in a single center as an interventional, single-arm, phase II trial. The enrollment period was between April 2014 and November 2017. The study protocol was approved by the Ethics Committee of Toho University Omori Medical Center (approval numbers/approval date: no.25-216/27 November 2013, no.27-251/18 February 2015), and written informed consent was obtained from all registered patients. This study was registered in the UMIN Clinical Trials Registry as UMIN000013598 (further details can be accessed at https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000015887). Cancer staging was based on the tumor, node, metastasis (TNM) classification system (Union for International Cancer Control, 6th edition) [18]. The Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [19] were used to assess tumor response to preoperative treatment using computed tomography (CT) or magnetic resonance imaging (MRI). Tumor response to preoperative treatment was defined as: complete response (CR), complete disappearance of the target lesion; partial response (PR), at least 30% reduction in target lesion; progressive disease (PD), 20% increase in the target lesion and absolute increase of 5 mm or more and/or appearance of new lesions; stable disease (SD), a state of neither PR nor PD. We used the Common Terminology Criteria for Adverse Events v4.0 to grade adverse events. Adverse events of preoperative CRT were evaluated by the physicians involved in this study at the start of each course.

Endpoints

The pathological complete response (pCR) rate was the primary endpoint of this study. The endpoint was not set for a high pCR rate but rather with the aim of presenting objective tumor shrinkage performance for the CRT regimen. Secondary endpoints included the treatment completion rate, downstaging rate, curative resection rate, anal sphincter preservation rate, safety, local recurrence rates, disease-free survival (DFS), histological efficacy [20], and overall survival (OS). The evaluation of downstaging was conducted by comparing the stage before and after CRT. The stage was denoted by a prefix, indicating clinical findings at diagnosis with "c," clinical findings after preoperative treatment (i.e., yield of treatment) with "yc,"; the descriptions follow the TNM classification system and Japanese guideline for classification of colorectal cancer [21], which have been used in Japan since 2013 (http://www.jsccr.jp/whatsnew/kiyaku8.html). R0 resection was defined as "no distant metastasis and no residual tumor." Local recurrence was defined as an anastomotic and pelvic recurrence.

Inclusion criteria

The inclusion criteria were the following: 1. histologically confirmed rectum adenocarcinoma (i.e., in Ra, which is the segment of the rectum from the height of the inferior border of the second sacral vertebra to the peritoneal reflection; Rb, which is the segment of the rectum located below the peritoneal reflection; or P, which is the anal canal; Ra-Rb, the notation is the location in Ra to Rb, with Ra as the main; Rb-P, the notation is the location in Rb to P, with Rb as the main; not in the rectosigmoid [Rs], which is the segment from the height of the sacral promontory to the inferior border of the second sacral vertebra) [22]; 2. preoperative CT or MRI findings indicative of a cT3-4 clinical stage and any N stage [18]; 3. resectable tumor; 4. no evidence of distant metastasis; 5. age 20–80 years; 6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; 7. no prior antitumor therapy; 8. adequate organ function according to laboratory findings (white blood cell count ≥ 4,000/mm^3 and ≤ 12,000/mm^3, neutrophil count ≥ 2,000/mm^3, platelet count ≥ 100,000/mm^3, hemoglobin ≥ 9.0 g/dL, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase ≤ upper limit of normal × 2.5, serum total bilirubin ≤ 1.5 mg/dL, serum creatinine ≤ N (upper limit of normal range), creatinine clearance ≥ 50 mL/min/body as calculated using the Cockcroft-Gault equation [23]; 9. patients able to receive treatment orally; and 10. provision of written informed consent.

Exclusion criteria

Patients were excluded from the study on the basis of the following 16 exclusion criteria: 1. unable to receive chemotherapy containing S-1; 2. history of radiotherapy in the pelvis; 3. clinically significant infections; 4. serious complications; 5. myocardial infarction within the last six months, previous serious medical illness, or allergies to drugs; 6. multiple malignant diseases; 7. treatment required for pleural effusion or ascites; 8. current or previous brain metastases; 9. symptoms of watery stool (diarrhea); 10. fresh bleeding in the digestive organs; 11. requirement for treatment with flucytosine, atazanavir sulfate, and warfarin; 12. evidence of mental disorders that interfere with enrollment in a clinical trial; 13. pregnancy or lactation and women who were trying to get pregnant; 14. men who wanted to have their own children; 15. in the need for systemic administration of corticosteroids; 16. patients considered unsuitable to participate in this study by physicians.

Treatment regimen

The dose of S-1 was 80 mg/m2/day. S-1 was administered orally, twice daily along with radiation therapy on days 1–5, 8–12, 15–19, 22–26, and 29–33. On days 36–40, 43–47, 50–54, and 57–61, S-1 was administered twice daily without radiotherapy. Radiation therapy consisted of 1.8 Gy/day on days 1–5, 8–12, 15–19, 22–26, and 29–33 (total dose of 45 Gy in 25 fractions) (Fig. 1). Resection in patients with rectal cancer with D3 lymph node dissection was performed within 2–3 weeks after completion of S-1 therapy. Postoperative treatment for one year consisted of starting oral administration of tegafur-uracil (300 mg/m^2/day) and leucovorin (75 mg/body/day), following a cycle of four weeks of oral administration and one week of no medication [24], within 4–6 weeks postoperatively.

Follow-up

Blood tests, including the tumor markers carcinoembryonic antigen and carbohydrate antigen 19-9, were performed once a month for one year after surgery. Imaging studies were performed every six months postoperatively using CT or abdominal ultrasonography.

Study design and statistical methods

Using an expected CR rate of 20% and a threshold CR rate of 5%, the number of patients required for a one-sided $\alpha = 0.1$ and $\beta = 0.1$ was calculated to be 28. The target number of patients was set at 30, with consideration given to ineligible cases. As approved by the Ethics

Committee of Toho University Omori Medical Center (approval number: 25-216, 27-251), patients who participated in the previous phase I trial [17] were also re-enrolled for the current analysis. DFS and OS were evaluated using the Kaplan–Meier method with the statistical analysis software “EZR” [25].

Enrolled patients

Thirty patients were enrolled; however, two patients were deemed ineligible: one due to a re-evaluation of wall-depth cT2 [18], and the other patient due to irradiation above the prescribed radiation dose; both patients were excluded from this study.

Results

The 28 patients who were eligible for the analysis included 20 men and eight women. Patient median age was 66 years (range 40–77 years). The clinical findings at diagnosis (before treatment) were as follows: 13 patients (46%) had an ECOG PS of 0 and 15 (54%) had an ECOG PS of 1; the lesion site was Ra-Rb, Rb, and Rb-P in three (11%), 23 (82%), and two (7%) patients, respectively; the cT factor was cT3, cT4a, and cT4b in 19 (68%), four (14%), and five (18%) patients, respectively; and the lesions in 12 (43%) and 16 (57%) patients were classified as cStages II and III, respectively. One (4%) patient had diarrhea symptoms due to preoperative CRT treatment so treatment was discontinued after three courses. Subsequently, this patient was scheduled for surgery. Therefore, preoperative treatment was completed in 27/28 patients, with a completion rate of 96%. The surgical procedures performed were as follows: super low anterior resection (sLAR, 21%), transanal total mesorectal excision (taTME, 21%), intersphincteric resection (ISR, 26%), abdominoperineal resection (APR, 21%), and total pelvic exenteration (TPE, 11%). Laparoscopic surgery and open surgery were performed in 20 (71%) and eight patients (29%), respectively. Radical surgery was performed in all patients. The histological types were differentiated carcinomas in 25 (89%) patients and mucinous carcinomas in three (11%) patients. The only patient who failed to complete CRT treatment was a 52-year-old woman with PS0, Rb lesion site, clinical stage III, and a pathological diagnosis of well-differentiated adenocarcinoma before treatment.

Adverse events

Adverse events during preoperative CRT are listed in Table 1. In all grades, adverse events included anemia, hypoalbuminemia, diarrhea, leukopenia, transaminitis, and general fatigue in 68%, 68%, 46%, 39%, 32%, and 25% of the patients, respectively. Buttock pain and

buttock dermatitis occurred in 25% and 18% of the patients, respectively. Most adverse events that occurred in patients were grade 1 or 2. Two Grade 3 adverse events, diarrhea and hypoalbuminemia, occurred in one 52-year-old patient (4%). No grade 4 adverse events were observed. Furthermore, no G3 or greater adverse events were observed in the ≥ 70 years patient group, although there was no difference in the PS0/1 rate between the ≥ 70 years and < 70 years patient groups. Adverse events of G2 or greater occurred in 7 out of 9 (78%) patients in the ≥70 years group and 11 out of 19 (58%) patients in the <70 years group, although this difference was not significant (p = 0.42, Fisher's exact test) and CRT was performed equally in both groups. G2 or greater adverse events of diarrhea were observed in 2 (22%) patients in the ≥ 70 years patient group and 5 (26%) patients in the < 70 years patient group, respectively. Anemia occurred in 4 (44%) patients in the ≥ 70 years patient group and in 5 (26%) patients in the < 70 years group, although the difference was not significant (p = 0.41).
Postoperative adverse events with Grade 3 included hypoalbuminemia in 7% and intestinal leakage, ileus, anemia, and hypercreatininemia in 4% of the patients. No grade 4 adverse events were observed during the postoperative period.

Response to treatment after CRT

Clinical response (downstaging: c > yc) as assessed by CT before and after CRT using RECIST, and pathological curability are presented in Table 2. The preoperative downstaging rate was 29% (8/28). According to the RECIST, four (14%) patients had clinical CR, 15 (53%) patients had PR, 8 (29%) patients had SD, and 1 (4%) patient had PD. The clinical response rate (percentage of CR + PR) according to the RECIST was 68% (19/28). The clinical response rate was 67% (6 of 9 patients) in the ≥ 70 years group and 68% (13 of 19 patients) in the < 70 years group. This difference was not significant (p = 0.99). All patients with surgical curative-A were evaluated for pathological R0; pCR was observed in three patients. The pCR rate as the endpoint in this study was 11%.

Received benefit from preoperative CRT

Sphincter-preserving resection was achieved in 19 (68%) patients. Among the 25 patients with Rb and Rb-P lesions, 14 (56%) had anal preservation. Before CRT, 4/9 (44%) patients with cT4 cancer, assuming APR or TPE, were able to achieve anal preservation. Although seven patients had anal pain and 12 patients had melena before CRT, all patients had relief of symptoms after CRT.

Long-term prognosis

Of 28 patients enrolled in this study, four (14%) patients had a recurrence within three years after surgery, and 6 (21%) patients had a recurrence within five years after surgery. One (4%) patient with local recurrence was observed five years after surgery. Distant metastases were found in four (14%) patients with pulmonary metastasis and one (4%) patient with aortic lymph node metastasis. Five (18%) patients died within five years after surgery. Three tumor-related deaths were in patients with PD who received preoperative CRT, pulmonary metastasis, and local recurrence. The two remaining deaths were not tumor-related. The three-year and five-year DFS were 75% and 68%, respectively, and the three-year and five-year OS were 86% and 82%, respectively (Fig. 2).

Discussion

The purpose of this study was to evaluate as degree of the pCR rate and the efficacy and safety of preoperative CRT with S-1 for locally advanced rectal cancer at the recommended dose determined in a previous phase I study [17].

In recent years, the idea that surgery is not necessary for cases in which clinical complete response (cCR) has been achieved, that is, the Watch and Wait strategy [26], has been proposed. To increase the CR rate, preoperative CRT following systemic chemotherapy, referred to as total neoadjuvant therapy (TNT), has been developed, although this strategy has not yet been established. In the phase II trial CAO/ARO/AIO-12, while the pCR rate was 30% in TNT using FOLFOX, the incidence of grade 3 or higher adverse events was high at 27% [27]. In Japan, surgical resection based on lateral lymph node dissection in the pelvis is the standard treatment [10], and preoperative CRT has been performed in selective patients [1]. However, it is necessary to focus on surgical treatment using preoperative treatment such as CRT and TNT.

First, similar studies using CRT with S-1 alone have reported pCR rates of 10.8% to 22.2% [16,20,28], although there were slight differences among the studies in the regimen used. The pCR rate in our study using CRT with S-1 alone was 11%, which was not higher than that previously reported using CRT with 2 agents, S-1 plus irinotecan or S-1plus oxaliplatin [30-31], although this was the expected favorable level of pCR rate using CRT with a single agent [32].

Second, we evaluated the safety of preoperative CRT with S-1. In a similar phase II study reported by Inomata et al. [20], in which S-1 was administered at the same dose as in our study, the incidence of adverse events was reported to be acceptable. Grade 3 or higher

adverse events were reported in 13.5% of patients [20], which is comparable to the 7% rate (two events) observed in our study. Imano et al. [16] reported 18.5% of ≥ Grade 3 side effects, which may have been due to the slightly higher radiation dose of 50.4G. Although the preoperative CRT with S-1 plus irinotecan or oxaliplatin revealed higher levels of tumor control than those achieved using CRT with S-1 alone, the incidence of side effects in these reports was higher than 15%, which may be problematic. Furthermore, in our study, CRT was safely administered with no increased incidence of side effects in the ≥ 70 years group, although the response rates in the two groups were similar. Therefore, preoperative CRT with S-1 could be performed safely at our recommended dose. Based on the high completion rate, compliance with S-1 medication is acceptable. The occurrence of skin problems on the buttocks due to radiation were also considered acceptable because these complications were low grade. However, even if the patient's CCr value is within the safe range of S-1, the incidence of mild diarrhea symptoms characteristic of S-1 adverse events tends to be high. Therefore, side effects must be monitored closely to ensure that particularly diarrhea symptoms do not interfere with continued treatment. Our study showed an unexpectedly favorable effect of preoperative CRT on patient symptoms, including reduction in anal pain and improvement of melena, which has not been reported previously [20, 28]. This finding, although not an endpoint, may be considered a reduction in clinical symptoms with CRT treatment.

Third, we evaluated the effect of preoperative CRT with S-1. Tumor shrinkage due to preoperative treatment may allow improved curative surgery [33, 34], and this could also be expected to be associated with improved anal function preservation [35, 36]. Among patients with Rb and Rb-P lesions, 56% were able to achieve anal preservation. Of these, 44% of the patients with cT4 cancer achieved anal preservation. This suggests that preoperative CRT may contribute to anal preservation. The standard approach has been anal function preservation surgery with laparoscopic-ISR and taTME, which precedes the transanal procedure [37–39]. In the present study, these techniques were performed in approximately 46% of the patients. Proficiency in this technique may have been one of the factors that led to the 68% overall anal preservation rate.

In a report of CRT with S-1 by Hiratsuka et al. [40] on long-term prognosis, the rates of local recurrence, lung metastasis, and liver metastasis were 13.5%, 16.2%, and 2.7%, respectively. In a report by Imano [16], the rates of local recurrence, lung metastasis, liver metastasis, and distant lymph node metastasis were 11.1%, 16.7%, 7.4%, and 3.7%, respectively. In the present study, the distant metastasis rate five years after surgery was 18% (5/28), which was

similar to that previously reported [16, 40]. And it was the same tendency that lung metastases were most common in 4 out of 5 patients. The local recurrence was well controlled in this study as we observed one local recurrence (4%) at five years postoperatively, which is better than that previously reported [16, 40]. Our regimen was a study designed before the TNT regimen was announced. The low rate of local recurrence may be explained by the additional 4 weeks of S-1 treatment after radiotherapy as consolidation chemotherapy[41]; however, the exact reason for our findings of well local control is unclear. The frequency of distant metastases in our study was comparable to that in their studies [16, 40].

Finally, to date, there have been no phase III studies on preoperative CRT with S-1. A 5-year OS in CRT with S-1 alone was reported in two previous similar studies using CRT with S-1 alone, which at 74.7% and 72.8% [16, 40], is comparable to the 82% rate in our study. The 3-year OS in our phase II study on CRT with S-1, was 86%, while the 3-year OS in other phase II studies on preoperative CRT with two agents, S-1 plus irinotecan and S-1 plus oxaliplatin, was reported as 94.3% [42], and 93% [43], respectively. Moreover, the 3-year OS in a phase II study on preoperative CRT with capecitabine plus irinotecan, was also reported to be 93.6% [44]. The OS in preoperative CRT with two agents may be slightly better than with one agent in phase II studies. However, in the phase III trial ACCORD [45], which is a study on preoperative CRT with capecitabine plus oxaliplatin, the 3-year OS was 88.3% and no prognostic benefit was identified in the capecitabine plus oxaliplatin group compared to the capecitabine alone group. Therefore, it may not be that preoperative CRT with two agents is more likely to contribute to OS prolongation. The preoperative CRT that actually improves life expectancy has not yet been established, although we consider that CRT using oral anticancer drugs may be a simple and safe treatment option. Further studies are needed to determine whether the tumor-suppressive strength of preoperative CRT for lower rectal cancer results in anal preservation and improved prognosis.

This study was limited by the fact that it was a non-randomized, single-center study. Therefore, a multicenter, randomized clinical trial on a larger number of patients is required.

Conclusions

Using preoperative CRT with S-1 alone, we had a favorable pCR rate of 11%. Also, preoperative CRT with S-1 alone had an acceptable safety profile even for elderly patients and enabled rectal cancer surgery aimed at preserving the anal sphincter muscle. Our results suggest that preoperative CRT with S-1 alone may be acceptable from the perspective of adverse events and oncological outcomes.

Conflict of interests

K.F. received research grants from Taiho Pharmaceutical Co., Ltd., Tokyo, Japan; Yakult Honcha Co., Ltd., Tokyo, Japan; Eisai Co., Ltd., Tokyo, Japan; and Chugai Pharmaceutical Co., Ltd., Tokyo, Japan. The other authors have no conflicts of interest associated with the present study.

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None declared.

Authors' contributions

M.U. performed the analysis. K.F. contributed to the study's conception and design. M.U. and K.F. participated interpretation of data. T.K., S.K., Y.M., and K.Y. participated in the collection of data. YN participated in the collection of literature. A.K. revised critically the manuscript. AT planned and performed the radiation therapy. All authors have read and approved the final manuscript.

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Table 1. Adverse events associated with preoperative chemoradiotherapy in advanced rectal cancer patients (n = 28)

Adverse event																		
	G1	**G2**	**G3**	**G4**	**All grade** (n = 28)	**%**	**≥ G2**	**%**	**G3 + 4**	**%**	**All grade < 70 years** (n = 19)	**%**	**All grade ≥ 70 years (n = 9)**	**%**	**≥ G2 < 70 years (n = 19)**	**%**	**≥ G2 ≥ 70 years (n = 9)**	**%**
Diarrhea	6	6	**1**	0	13	46	7	25	1	4	9	47	4	44	5 (1)	26	2	22
Constipation	1	0	0	0	1	4	0	0	0	0	0	0	1	11	0	0	0	0
Melena	2	0	0	0	2	7	0	0	0	0	1	5	1	11	0	0	0	0
Anal pain	1	0	0	0	1	4	0	0	0	0	1	5	0	0	0	0	0	0
Anal discomfort	3	0	0	0	3	11	0	0	0	0	3	16	0	0	0	0	0	0
Stomatitis	1	0	0	0	1	4	0	0	0	0	0	0	1	11	0	0	0	0
Stomachache	3	0	0	0	3	11	0	0	0	0	2	11	1	11	0	0	0	0
Nausea	4	0	0	0	4	14	0	0	0	0	4	21	0	0	0	0	0	0
Anorexia	5	1	0	0	6	21	1	4	0	0	3	16	2	22	0	0	1	11
General fatigue	7	0	0	0	7	25	0	0	0	0	4	21	3	33	0	0	0	0

Weight loss	2	0	0	0	2	7	0	0	0	0	0	0	2	22	0	0	0	0
Buttocks skin pain	6	1	0	0	7	25	1	4	0	0	3	16	4	44	0	0	1	11
Buttocks dermatitis	1	4	0	0	5	18	4	14	0	0	3	16	2	22	2	11	2	22
Increased urination frequency	3	0	0	0	3	11	0	0	0	0	2	11	0	0	0	0	0	0
Painful urination	2	0	0	0	2	7	0	0	0	0	1	5	1	11	0	0	0	0
Residual urine	3	0	0	0	3	11	0	0	0	0	1	5	1	11	0	0	0	0
Hand-foot syndrome	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hyponatremia	0	1	0	0	1	4	1	4	0	0	0	0	1	11	0	0	1	11
Hyperkalemia	2	0	0	0	2	7	0	0	0	0	2	11	0	0	0	0	0	0
Hypoalbuminemia	16	2	**1**	0	19	68	3	11	1	4	10	53	9	100	2(1)	11	1	11
Hyperbilirubinemia	0	1	0	0	1	4	1	4	0	0	0	0	1	11	0	0	2	22
Hypercreatininemia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Transaminitis	9	0	0	0	9	32	0	0	0	0	8	42	1	11	0	0	0	0
Leukopenia	5	6	0	0	11	39	6	21	0	0	9	47	2	22	5	26	1	11

Neutropenia	8	0	0	0	8	29	0	0	0	0	6	32	2	22	0	0	0	0
Anemia	10	9	0	0	19	68	9	32	0	0	12	63	7	78	5	26	4	44
Thrombocytopenia	4	0	0	0	4	14	0	0	0	0	1	5	3	33	0	0	0	0
Number of patients with adverse events	10	17	1	0	28	100	18	64	1	4	19	100	9	100	11	58	7	78

The number in () is the number of patients with Grade 3 of adverse events.

Table 2. Response to treatment and pathological findings (n = 28)

Finding	**Number of patients**					
	Total (n = 28)	**%**	**< 70 years (n = 19)**	**%**	**≥ 70 years (n = 9)**	**%**
Gender (male/female)	20/8		12/7		8/1	
Median age, range (year)	66, 40–77		60, 40–69		75, 71–77	
cStage II/III	12/16		7/12		5/4	
Location site						
Ra-Rb		3	2		1	
Rb		23	16		7	
Rb-P		2	1		1	
Downstaging (c > yc)**						
Down*	8	29	6	32	2	22
Stable	19	67	12	63	7	78
Progress	1	4	1	5	0	0
Downstaging (c > yp)**						
Down*	16	57	11	58	5	56
Stable	11	39	7	37	4	44
Progress	1	4	1	5	0	0
Response***						
Complete response*	4	14	4	21	0	0
Partial response	15	53#	9	47	6	67
Stable disease	8	29	5	27#	3	33
Progressive disease	1	4	1	5	0	0
Pathological curability***						
R0	28	100	19	100	9	100
R1	0	0	0	0	0	0
R2	0	0	0	0	0	0
Pathological response						

pCR*	3	11	3	16	0	0
non-pCR	25	89	16	84	9	100

*A 52-year-old patient with G3 adverse events was a responder who was included in downstaged, clinical complete response, and pathological complete response. **notation used to compare stages; Stages were denoted as “c”, “yc”, and “yp” to distinguish between before chemotherapy (CRT), after CRT, and at the time of pathological diagnosis post-CRT, respectively. ***: using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; R0: no distant metastasis and no residual tumor, R1: microscopic residual tumor at resection lines, R2: macroscopic residual tumor. #: Value adjusted to make total 100%.

Figure 1. Treatment schedule of preoperative chemoradiotherapy (CRT). A total of nine courses of S-1 was administered, consisting of one course per week with five treatment days followed by two days of rest. Radiotherapy was administered during the first 5 courses with S-1. The dose of S-1 was 80 mg/m^2/day, and the total dose of radiation was 45 Gy (1.8 Gy x 25 fractions). Gy — Gray

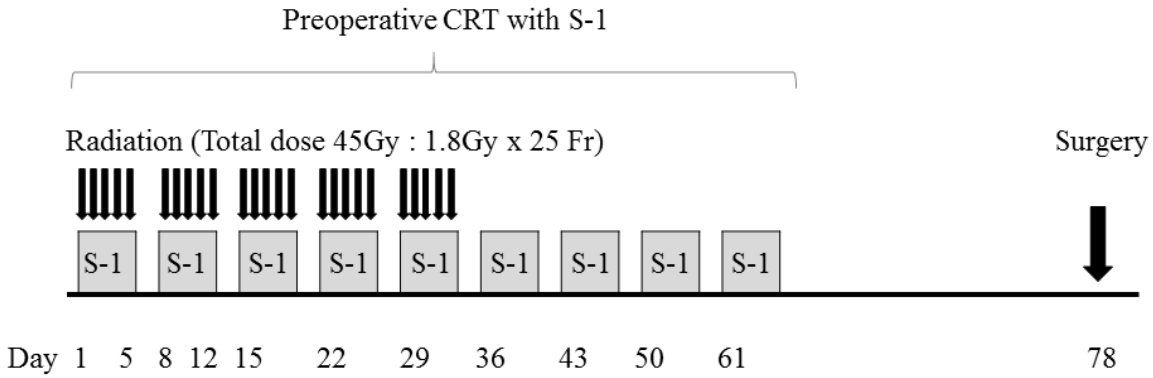
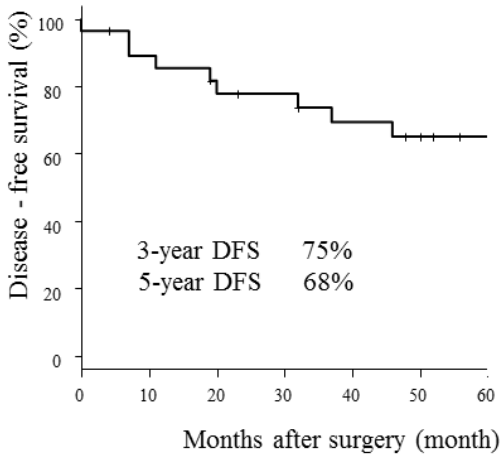
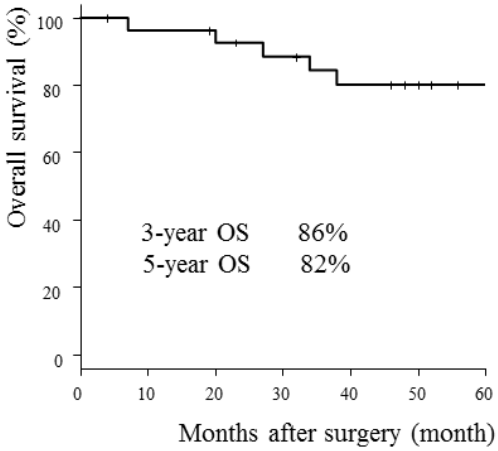


Figure 2. Five-year disease-free survival (**A**) overall survival (**B**) in postoperative patients with advanced rectal cancer who underwent preoperative chemotherapy (CRT) with S-1

a. The 5-year disease-free survival



b. The 5-year overall survival



Supplementary File

Figure S1.

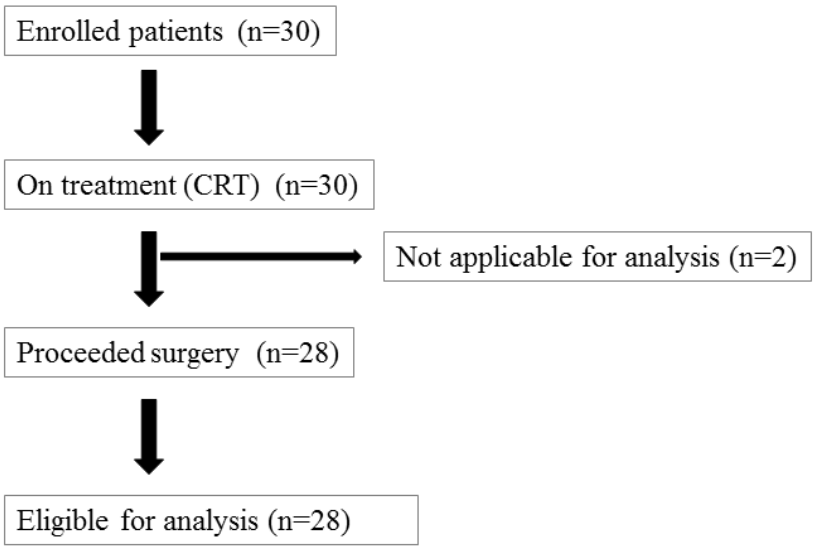

Enrolled patients (n=30)
On treatment (CRT) (n=30)
Not applicable for analysis (n=2)
Proceeded surgery (n=28)
Eligible for analysis (n=28)

Table S1.

Clinicopathological findings in 28 eligible patients for analysis

Characteristic		Number of patients (n=28)	%
Age (Years)	Median	66	
	Range	40-77	
Gender	Male	20	71
	Female	8	29
PS	0	13	46
	1	15	54
Tunor location*	Ra	3	11
	Rb	23	82
	Rbp	2	7
Tumor size (cm)	Median	4.3	
	Range	1.9-10.4	
cT factor*	cT3	19	68
	cT4a	4	14
	cT4b	5	18
cStage*	II	12	43
	III	16	57
Operations	sLAR	6 (6/0)	21
(number of Lap/Open)	taTME	6 (4/2)	21
	ISR	7 (7/0)	25
	APR	6 (3/3)	21
	TPE	3 (0/3)	11
Surgical curability**	A	27	96
	B	0	0
	C	1	4
Histology	Tub 1,2	25	89
	Muc	3	11

PS : performance status, sLAR : super low anterior resection,

taTME : transanal total mesorectal excision, ISR : intersphincteric resection,

APR : abdominoperineal resection, TPE : total pelvic exenteration,

Lap : laparoscopic surgery, Open : open abdominal surgery,

Tub : tubular adenocarcinoma, Muc : mucinous adenocarcinoma

*: using the tumor-node-metastasis (TNM) classification system (UICC 6th edition)

**: A; no residual tumor, C; macroscopic residual tumor, B; neither A nor C

Table S2.

Received benefit for preoperative chemoradiotherapy with S-1

Recived benefit	Number of patients (n)	%
Improvement of anal pain	7/7	100
Improvement of melena	12/12	100
Sphincgter presurving surgery		
Ra~Rbp	20/28	71
Rb~Rbp	14/25	56
Rb~Rbp/cT4	4/9	44

Ra: rectum located above the peritoneal reflection, Rb: rectum located below the peritoneal reflection, and Rbp: rectum (Rb) to anal canal, cT4: tumor wall invasion beyond the serosa before CRT

Table S3.

Postoperative complications
in advanced low rectal cancer patients (n = 28)

Postoperative complication	total number	G1	G2	G3	G4	total	%	G2≦	%	G3+4	%
retroperitoneal space infection	28	1	3	0	0	4	14	3	11	0	0
intestinal leakage	22	1	1	1	0	3	14	2	7	1	4
urological leakage	3	1	0	0	0	1	33	0	0	0	0
ileus	28	0	0	1	0	1	4	1	4	1	4
pneumoderma	20	1	0	0	0	1	5	0	0	0	0
high-output stoma	17	1	0	0	0	1	6	0	0	0	0
hypoalbuminemia	28	10	15	2	0	27	96	17	61	2	7
hyperbilirubinemia	28	2	2	0	0	4	14	2	7	0	0
hypercreatininemia	28	0	0	1	0	1	4	1	4	1	4
transaminitis	28	4	0	0	0	4	14	0	0	0	0
leukopenia	28	2	0	0	0	2	7	0	0	0	0
anemia	28	15	7	1	0	23	82	8	29	1	4
thrombocytopenia	28	4	0	0	0	4	14	0	0	0	0