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 has not yet been established in Japan. We conducted a non-randomized phase II study to evaluate the efficacy and safety of preoperative CRT with S-1, a fixed-dose combination of tegafur, gimeracil, and oteracil potassium.

Methods: We conducted a prospective, interventional, 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 a total of 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. The required sample size was calculated to be 30 individuals. The characteristics of the 28 patients included were as follows: cStage (II:12/ III:16), median age of 66 years (range 40–77 years), male/female (20/8), and lesion site (Ra-Rb:3/Rb:23/Rb-P:2).

Results: Preoperative treatment was completed in 27 patients (96%). Treatment abandon was because of diarrhea. Grade 3 or higher adverse events were observed in only two patients (7%). Clinical downstaging was performed in eight patients (29%). Radical resection was achieved in 27 patients (96%), including 19 (68%) who underwent sphincter-preserving surgery. The pCR rate was 11% (three patients). The three-year disease-free survival rate was 79%, and the overall survival was 89%. No local recurrence occurred three years after surgery.

Conclusions: Preoperative CRT with S-1 has an acceptable safety profile, and can potentially contribute to preserving anal function in patients with rectal cancer.

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

Background

Recent advances in chemotherapy have improved the prognosis for patients with colorectal cancer. However, surgical complete resection still determines the prognosis [1]. Apart from 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 patients' quality of life [4]. Research directed toward the treatment of low rectal cancer considering the abovementioned concerns is highly important.

Total mesorectal excision surgery, as proposed by Heald et al. [5], is recognized as the gold standard for rectal cancer treatment. Standard care in western countries is preoperative chemoradiotherapy (CRT) followed by surgery [6]. The rationale behind this approach is provided by large phase III trials, which have demonstrated that neoadjuvant therapy (preoperative adjuvant therapy) reduced the risk of local recurrence [3, 7, 8].

In Japan, the local recurrence rate with surgery alone is a commendable 3–12.6% [9–12], which is comparable to that with neoadjuvant therapy and preoperative CRT in western countries. Surgery including lateral lymph-node dissection [12] followed by adjuvant chemotherapy is recommended in Japan; preoperative CRT can be performed in a limited number of patients, namely those with tumors with a high risk of local recurrence and large pelvic masses or local invasion [1].

Despite the evidence of local control of rectal cancer, preoperative CRT raises several concerns [3, 7, 8] in that it may have adverse effects, particularly concerning postoperative defecation and the effect on anal, urinary, and sexual functions due to radiotherapy [13]. Furthermore, the treatment is complex and costly. Most importantly, there is a concern that local control does not improve overall survival in patients with previous preoperative CRT based on 5-fluorouracil (5-FU) [3, 7, 8]. 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 [14]. Oteracil potassium reduces gastrointestinal toxicity caused by 5-FU [14]. There are reports on S-1 alone producing favorable responses in patients with unresectable advanced or recurrent colorectal cancer [15, 16]. Furthermore, S-1 reportedly has a radiation-sensitizing effect [17]. Therefore, preoperative CRT with S-1 may be safe and sufficiently effective; moreover, combining radiation therapy and oral agents is a simple approach. Our previous phase I study showed that preoperative CRT with S-1 was feasible and well tolerated by patients with low rectal cancer [18]. Therefore, we conducted a phase II study to ensure that preoperative CRT with S-1 would be effective and safe in patients with locally advanced rectal cancer using the doses set in our previous study.

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) [19]. The Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [20] 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 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. 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 [21], and overall survival (OS). The evaluation of downstaging was compared 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 [22], 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 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) [23]; 2. preoperative CT or MRI findings indicative of a cT3-4 clinical stage and any N stage [19]; 3. resectable tumor; 4. no evidence of distant metastasis; 5. aged 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 [24]; 9. can receive therapeutics orally; and 10. those who provided 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. having serious complications; 5. experienced myocardial infarction within the last six months, previous serious medical illness, or allergies to drugs; 6. multiple malignant diseases; 7. requiring treatments for pleural effusion or ascites; 8. having current or previous brain metastases; 9. having

symptoms of watery stool (diarrhea); 10. having fresh bleeding in the digestive organs; 11. circumstances requiring treatment with flucytosine, atazanavir sulfate, and warfarin; 12. evidence of mental disorders that interfere with enrollment in a clinical trial; 13. women who are pregnant or lactating, or who are trying to get pregnant; 14. men who want to have their own children; 15. in the need for systemic administration of corticosteroids; 16. judged unsuitable to participate in this study by physicians.

Treatment regimen

The dose of S-1 was 80 mg/m^2/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 rectal cancer patients 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 [25], 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. The median duration of follow-up in this study was 41 months (range, 4–74 months).

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 to 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 [18] were also re-enrolled for the current analysis. DFS and OS were evaluated using the Kaplan–Meier method with the statistical analysis software “EZR” [26].

Patient characteristics

Thirty patients were enrolled; however, two patients were deemed ineligible. One patient was due for a re-evaluation of wall-depth cT2 [19], and another patient was due for irradiation above the prescribed radiation dose; they were excluded from this study (Fig. 2).

Results

The clinicopathological findings of the 28 patients enrolled in the study are presented in Table 1. There were 20 men and eight women. Their median age was 66 (range, 44–70) 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 patient had diarrhea symptoms due to preoperative CRT treatment, which therefore had to be discontinued after three courses. Subsequently, this patient was scheduled for surgery. Thus, preoperative treatment was completed in 27/28 patients, with a completion rate of 96%. Table 1 shows the background information and surgical procedures for the 28 patients, including the patient who did not complete CRT. The procedures performed on the patients were as follows: super low anterior resection (sLAR, 21%), transanal total mesorectal excision (taTME, 21%), intersphincteric resection (ISR, 25%), 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 27 patients (96%). The histological types were differentiated carcinomas in 25 patients (89%) and mucinous carcinomas in three patients (11%). 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.

Table 1

Clinicopathological findings in the 28 patients eligible for analysis

Characteristic	Number of patients (n=28)
Age (years, median) (range)	66 (40-77)
Sex, n (%)	
Male	20 (71)
Female	8 (29)
PS	
0	13 (46)
1	15 (54)
Tumor location[a] , n (%)	
Ra-Rb	3 (11)
Rb	23 (82)
Rb-P	2 (7)
Tumor size (cm, median) (range)	4.3 (1.9–10.4)
cT factor[b] , n (%)	
cT3	19 (48)
cT4a	4 (14)
cT4b	5 (18)
cStage[b] , n (%)	
II	12 (43)
III	16 (57)
Operations, n (%), (number of laparoscopic procedures)	

PS ECOG performance status; *sLAR* super low anterior resection; *taTME* transanal total mesorectal excision; *ISR* intersphincteric resection; *APR* abdominoperineal resection; *TPE* total pelvic exenteration; *Tub* tubular adenocarcinoma; *Muc* mucinous adenocarcinoma; *Ra*, the segment of rectum from the height of the inferior border of the second sacral vertebra to the peritoneal reflection; *Rb*, rectum located below the peritoneal reflection; *Ra-Rb*, the location in Ra to Rb, with Ra as the main; *Rb-P*, the location in Rb to anal canal, with Rb as the main

[a] According to the Japanese Classification of Colorectal Carcinoma (Second English edition)

[b] According to the tumor, node, metastasis classification system (UICC 6th edition)

sLAR	6 (21), (6)
taTME	6 (21), (4)
ISR	7 (25), (7)
APR	6 (21), (3)
TPE	3 (11), (0)
Sphincter preserving resection	19 (68)
Histology	
Tub 1, 2	25 (89)
Muc	3 (11)

PS ECOG performance status; *sLAR* super low anterior resection; *taTME* transanal total mesorectal excision; *ISR* intersphincteric resection; *APR* abdominoperineal resection; *TPE* total pelvic exenteration; *Tub* tubular adenocarcinoma; *Muc* mucinous adenocarcinoma; *Ra*, the segment of rectum from the height of the inferior border of the second sacral vertebra to the peritoneal reflection; *Rb*, rectum located below the peritoneal reflection; *Ra-Rb*, the location in Ra to Rb, with Ra as the main; *Rb-P*, the location in Rb to anal canal, with Rb as the main

[a] According to the Japanese Classification of Colorectal Carcinoma (Second English edition)

[b] According to the tumor, node, metastasis classification system (UICC 6th edition)

Adverse events

Adverse events during preoperative CRT are listed in Table 2. In all grades, adverse events included anemia, hypoalbuminemia, diarrhea, leukopenia, transaminitis, and general fatigue in 71%, 68%, 46%, 39%, 29%, 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. Grade 3 adverse events occurred in only two patients (7%), with diarrhea or hypoalbuminemia occurring in 8%. No grade 4 adverse events were observed. Postoperative adverse events are listed in Table 3. Grade 3 adverse events 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.

Table 2
Adverse events associated with preoperative chemoradiotherapy in advanced rectal cancer patients (n = 28)

Adverse event	G1	G2	G3	G4	Total (%)	≤G2 (%)	G3 + 4 (%)
Diarrhea	6	6	1	0	13 (46)	7 (25)	1 (4)
Constipation	1	0	0	0	1 (4)	0 (0)	0 (0)
Melena	2	0	0	0	2 (7)	0 (0)	0 (0)
Anal pain	1	0	0	0	1 (4)	0 (0)	0 (0)
Anal discomfort	3	0	0	0	3 (11)	0 (0)	0 (0)
Stomatitis	1	0	0	0	1 (4)	0 (0)	0 (0)
Stomachache	3	0	0	0	3 (11)	0 (0)	0 (0)
Nausea	4	0	0	0	4 (14)	0 (0)	0 (0)
Anorexia	5	1	0	0	6 (21)	1 (4)	0 (0)
General fatigue	7	0	0	0	7 (25)	0 (0)	0 (0)
Weight loss	2	0	0	0	2 (7)	0 (0)	0 (0)
Buttocks skin pain	6	1	0	0	7 (25)	1 (4)	0 (0)
Buttocks dermatitis	1	4	0	0	5 (18)	4 (14)	0 (0)
Increased urination frequency	3	0	0	0	3 (11)	0 (0)	0 (0)
Painful urination	1	0	0	0	1 (4)	0 (0)	0 (0)
Residual urine	3	0	0	0	3 (11)	0 (0)	0 (0)
Hand-foot syndrome	0	0	0	0	0 (0)	0 (0)	0 (0)
Hyponatremia	0	1	0	0	1 (4)	1 (4)	0 (0)
Hyperkalemia	2	0	0	0	2 (7)	0 (0)	0 (0)
Hypoalbuminemia	16	2	1	0	19 (68)	3 (11)	1 (4)
Hyperbilirubinemia	0	1	0	0	1 (4)	1 (4)	0 (0)
Hypercreatininemia	0	0	0	0	0 (0)	0 (0)	0 (0)
Transaminitis	7	1	0	0	8 (29)	1 (4)	0 (0)
Leukopenia	5	6	0	0	11 (39)	6 (21)	0 (0)

Adverse event	G1	G2	G3	G4	Total (%)	≤G2 (%)	G3 + 4 (%)
Neutropenia	8	0	0	0	8 (29)	0 (0)	0 (0)
Anemia	12	8	0	0	20 (71)	8 (29)	0 (0)
Thrombocytopenia	4	0	0	0	4 (14)	0 (0)	0 (0)

Table 3
Postoperative complications in advanced 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 (9)	1 (5)
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 (0)
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)

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 4. The preoperative downstaging rate was 29% (8/28). According to the RECIST, four patients (14%) had CR, 15 patients (53%) had PR, eight patients (29%) had SD, and one patient (4%) had PD. The clinical response rate (percentage of CR + PR) according to the RECIST was 68% (19/28). 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%.

Table 4
Response to treatment and pathological findings (n = 28)

Finding	Number of patients (%)
Response[a]	
Complete response	4 (14)
Partial response	15 (53)
Stable disease	8 (29)
Progressive disease	1 (4)
Downstaging (c > yc[b])	8 (29)
Pathological curability[c]	
R0	27 (96)
R1	0 (0)
R2	1 (4)
Pathological response	
Non-pCR	25 (89)
pCR	3 (11)

pCR pathological complete response

[a]According to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

[b] Notation used to compare stages. Stages were denoted as “c,” and “yc,” to distinguish between before CRT and after CRT, respectively.

[c] R0, no distant metastasis and no residual tumor; R1, microscopic residual tumor at resection lines; R2, macroscopic residual tumor.

Received benefit from preoperative CRT

Sphincter-preserving resection was achieved in 19 patients (68%). Among the 25 patients with Rb and Rb-P lesions, 14 (56%) had anal preservation. Before CRT, 4/9 patients (44%) 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 (Table 5).

Table 5
Received benefit from preoperative CRT with S-1

Received benefit	n (%)
Improvement of anal pain	7/7 (100)
Improvement of melena	12/12 (100)
Sphincter-preserving surgery	
Rb and Rb-P	14/25 (56)
Rb/cT4 and Rb-P/cT4	4/9 (44)
CRT chemoradiotherapy;	
Rb, rectum located below the peritoneal reflection; *Rb-P*, rectum (Rb) to anal canal, and *cT4*, tumor wall invasion beyond the serosa before CRT	

Long-term prognosis

Four patients (11%) had a recurrence within three years after surgery. There were no local recurrences. Distant metastases were found in three patients with pulmonary metastasis and one patient with aortic lymph node metastasis. Three patients died within three years after surgery. There was only one tumor-related death, which was in a patient with PD who received preoperative CRT. The two other deaths were not tumor related. The three-year DFS was 79%, and the three-year OS was 89% (Fig. 3).

Discussion

The purpose of this study was to evaluate 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 [18].

First, we evaluated the safety of preoperative CRT with S-1. In a similar phase II study reported by Inomata et al. [21], 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 to be 10.8% [21], which is comparable to the 7% found in our study. Therefore, preoperative CRT with S-1 can be performed safely at our recommended dose. Based on the high completion rate, compliance with S-1 medication can also be judged acceptable. The occurrence of skin problems on the buttocks due to radiation were also considered acceptable because of their low grade. However, because of the high incidence of diarrhea symptoms characteristic of S-1 adverse events, such symptoms must be monitored closely to ensure that they 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 [21, 27]. This finding, although not an endpoint, might be considered reduction in clinical symptoms with CRT treatment.

Next, we evaluated the effect of preoperative CRT with S-1. Tumor shrinkage due to preoperative treatment may contribute to improved curative surgery [28, 29], and it can also be expected to be associated with improved anal function preservation [30, 31]. Similar studies using S-1 have reported pCR rates of 22.2% [27] and 10.8% [21], although there were slight differences in the regimen. These results are comparable to the treatment effects in our study. Among patients with Rb and Rb-P lesions, 56% were able to achieve anal preservation. Among them, 4/9 patients (44%) with cT4 cancer achieved anal preservation. This suggests that preoperative CRT may contribute to anal preservation. Traditionally, we have been working on anal function preservation surgery with laparoscopic-ISR and -taTME, which precedes the transanal procedure [32–34]. In the present study, these techniques were performed in approximately half of the patients. Proficiency in this technique may have been one of the factors that led to the 68% overall anal preservation.

In a report by Hiratsuka et al. [35] on long-term prognosis, the rates of local recurrence, lung metastasis, and liver metastasis were 13.5%, 16.2%, and 2.7%, respectively. In the present study, although the observation period was only 3 years, the recurrence after surgery was well controlled, with only three patients (11%) experiencing lung metastasis. In particular, local recurrence was well controlled as we observed no local recurrence, which is better than the 13.5% reported by Hiratsuka et al. This may be due to the additional 4 weeks of S-1 treatment after radiotherapy; however, the exact reason is unclear. The frequency of distant metastases in our study was comparable to that in their study.

Preoperative CRT has been performed with an anticancer agent in addition to S-1. The pCR rates in preoperative CRT with S-1 plus irinotecan have been reported to be 34.7% [36] and 24% [37] in two studies. A pCR rate of 22.9% [38] was reported for preoperative CRT with S-1 plus oxaliplatin. All of these reports revealed higher levels of tumor control than those obtained in studies using CRT with S-1 alone; however, the incidence of side effects in these reports was higher than 15%, which is problematic. A recent multicenter study of preoperative CRT with S-1 plus oxaliplatin, which employed a total dose of 50.4 Gy but ensured treatment compliance by chemotherapy gaps, reported a pCR rate of 27.3%, and 11.1% of the patients showed grade 3 adverse events [39]. Regarding long-term prognosis, the 3-year DFS in the pCR and non-pCR groups were 92% and 58%, respectively, with a significantly better prognosis reported in the pCR group. However, the 3-year DFS for all patients was 67.5%, which did not improve the overall prognosis. All recurrences were distant metastases. These results indicate that while local recurrence is well controlled, the strong tumor-suppressive effect of preoperative CRT is not reflected in the overall prognosis.

There have been no phase III studies on preoperative CRT with S-1 so far. The 3-year OS in our phase II study on CRT with S-1, was 89%, whereas 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 to be 94.3% [40], and 93% [39], 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% [41]. The OS in preoperative CRT with two agents might be slightly better than with one agent in phase II studies. However, in the phase III trial ACCORD [42], which is a study on preoperative CRT with capecitabine plus oxaliplatin, the three-year OS was reported to be

88.3%, and there was no prognostic benefit found 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. Further studies are needed to determine whether the tumor-suppressive effect of preoperative CRT for lower rectal cancer leads to anal preservation and contributes to improved prognosis.

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

Conclusions

Preoperative CRT with S-1 has an acceptable safety profile and the potential to contribute to preserving anal function in patients with rectal cancer.

Abbreviations

5-FU: 5-fluorouracil; APR: abdominoperineal resection; CR: complete response; CRT: chemoradiotherapy; CT: computed tomography; DFS: disease-free survival; ECOG: Eastern Cooperative Oncology Group; ISR: intersphincteric resection; MRI: magnetic resonance imaging; OS: overall survival; pCR: pathological complete response; PD: progressive disease; PR: partial response; PS: performance status; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease; taTME: transanal total mesorectal excision; TNM: tumor, node, metastasis; TPE: total pelvic exenteration

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Toho University Graduate School of Medicine (approval number 25-216, 27-251), and written informed consent was obtained from all registered patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to the data is confidential patients' data but are available from the corresponding author on reasonable request.

Competing interests

Kimihiko Funahashi 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 declare no conflicts of interest associated with the present study.

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Authors' contributions

MU performed the analysis. KF contributed to the study conception and design. MU, KF, TK, SK, KY, YM, TK, and YN performed the surgical treatment. MU, KF, TK, and SK administered chemotherapy and checked for side effects. AT planned and performed the radiation therapy. All authors have read and approved the final manuscript.

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Figures

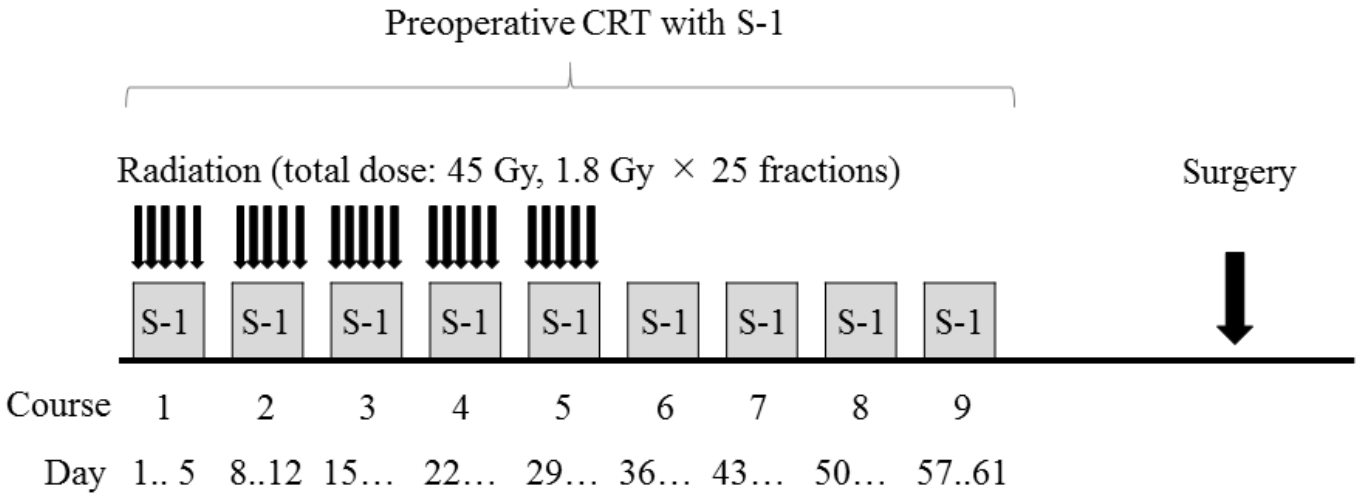

Figure 1

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 course with S-1. The dose of S-1 was 80 mg/m2/day, and the total dose of radiation was 45 Gy (1.8 Gy x 25 fractions). Gy Gray

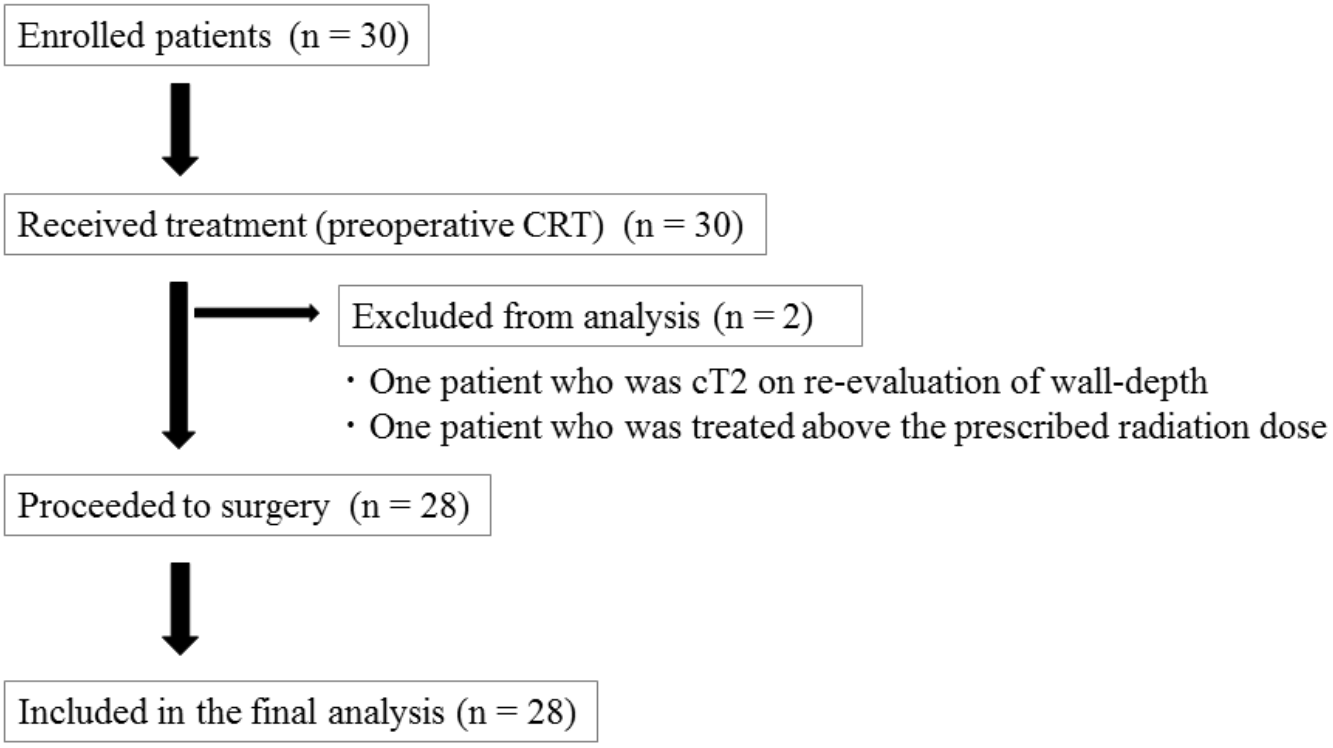

Figure 2

Flowchart of patient enrollment in the current study CRT chemoradiotherapy; cT2, tumor invasion to, but not beyond, the muscularis propria before surgery

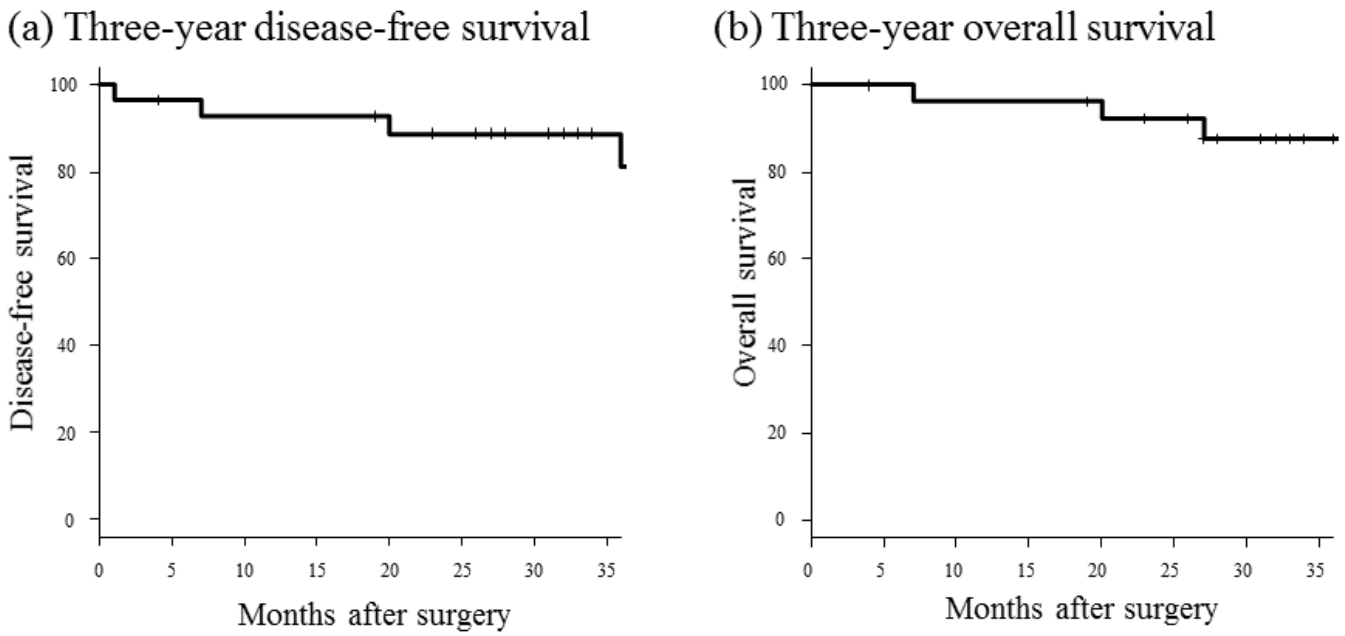

Figure 3

Three-year disease-free survival (a) overall survival (b) in postoperative advanced rectal cancer patients who received preoperative CRT with S-1

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