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Long-term outcomes of neoadjuvant-synchronous S-1 plus radiotherapy for locally advanced rectal cancer: a multi-institutional prospective phase II study

Takahiro Hiratsuka[1)], Tsuyoshi Etoh[1)], Takao Hara[1)], Tomonori Akagi[1)], Koichiro Tahara[2)], Toshifumi Matsumoto[3)], Tadashi Ogawa[4)], Kyuzo Fujii[5)], Akio Shiromizu[6)], Hidefumi Shiroshita[1)] and Masafumi Inomata[1)]

1) Department of Gastroenterological and Pediatric Surgery, Oita University Faculty of Medicine, Oita, Japan
2) Department of Surgery, National Hospital Organization Oita Medical Center, Oita, Japan
3) Department of Gastroenterological Surgery, National Hospital Organization Beppu Medical Center, Beppu, Japan
4) Department of Surgery, Oita Prefectural Hospital, Bunyo, Japan
5) Department of Surgery, Nakatsu Municipal Hospital, Nakatsu, Japan
6) Department of Surgery, Oita Red Cross Hospital, Oita, Japan

Abstract:

Objectives: This study aimed to evaluate the long-term outcomes of neoadjuvant chemoradiotherapy with S-1 in patients with locally advanced rectal cancer. Methods: A multi-institutional, prospective, phase II trial was conducted between April 2009 and August 2011. The study enrolled 37 patients with histologically proven rectal carcinoma (T3-4 N0-3 M0) who underwent neoadjuvant chemoradiotherapy with S-1. Total mesorectal excision with D3 lymphadenectomy was performed 4-8 weeks after completion of neoadjuvant chemoradiotherapy with S-1 in 36 patients. We then analyzed late adverse events, overall survival, and disease-free survival. Results: The median patient age was 59 years (range: 32-79 years); there were 24 men and 13 women. Ten patients had Stage II disease, and 27 had Stage III disease. Severe late adverse events occurred in 7 patients (18.9%). The 5-year disease-free survival was 66.7%, and the 5-year overall survival was 74.7%. The median follow-up period was 57 months. Local recurrences developed in 5 patients (13.5%), and distant metastases developed in 8 (21.6%). Conclusion: Neoadjuvant-synchronous chemoradiotherapy with S-1 for locally advanced rectal cancer is feasible in terms of adverse events and long-term outcomes. (UMIN Clinical Trial Registry: UMIN000003396)

Keywords:

neoadjuvant chemoradiotherapy, rectal cancer, S-1

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Introduction

Colorectal cancer (CRC) was the third highest cause of cancer-related deaths in Japan in 2013[1)], and the death rate is predicted to rise in the future. Therefore, studies aimed at improving treatment outcomes in patients with rectal cancer are critical.

The standard therapies for locally advanced rectal cancer in Japan and Western countries differ. The standard therapy in Japan is surgery and adjuvant chemotherapy[2)], whereas that in Western countries is neoadjuvant chemoradiotherapy (CRT) followed by surgery; the latter approach may decrease the local recurrence rate but does not improve overall survival[3,4)]. Even though neoadjuvant CRT may improve the local control rate, it has not been established as a standard treatment in Japan because of its questionable efficacy and side effects.

To date, a number of clinical trials have demonstrated the

Corresponding author: Takahiro Hiratsuka, htakahiru@oita-u.ac.jp
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efficacy of including 5-fluorouracil (5-FU) with CRT, either as monotherapy or in combination with oxaliplatin or capecitabine[5-7]. S-1 markedly increases the sensitivity of CRC cells (even 5-FU-resistant cells) to radiotherapy[8]. Moreover, the metabolite of S-1, soteracil potassium, antagonizes orotate phosphoribosyltransferase, which inhibits 5-fluoronucleosides (the active metabolites) generated from 5-FU, leading to reduced toxicity of 5-FU[8]. Sato et al. reported good outcomes, with increased rates of completing treatment (86.6%) and pathological complete response (pCR; 34.7%), in a phase II trial of neoadjuvant preoperative CRT with S-1 plus irinotecan and radiation in patients with locally advanced rectal cancer[9]. We also conducted a phase II trial to evaluate neoadjuvant-synchronous S-1 with radiotherapy for locally advanced rectal cancer and demonstrated its short-term safety[10]. There are only a few reports on the short-term outcomes of neoadjuvant CRT using S-1 for locally advanced rectal cancer, and long-term outcomes for patients receiving this regimen remain unknown. Therefore, the purpose of this study was to evaluate the long-term outcomes of neoadjuvant CRT with S-1 for locally advanced rectal cancer.

Methods

Patients

The design of this multi-institutional, prospective, phase II study, referred to as the OITA TRIAL 1, has been described previously[11]. This was an open trial conducted in 17 specialized centers in Oita, Japan, that provided their own radiotherapy and chemotherapy as well as surgical therapy results. The study protocol was approved by the Oita University Clinical Trial Review Committee and the institutional review board of each participating hospital (approval number B09-003). Furthermore, the study was registered in the UMIN Clinical Trial Registry as UMIN000003396 (http://www.umin.ac.jp/ctr/index.htm). The inclusion criteria of this study were as follows: (i) histologically proven rectal carcinoma; (ii) tumor located in the rectum (Ra [rectum/above the peritoneal reflection], Rb [rectum/below the peritoneal reflection], and P [anal canal]); (iii) cancer classified as T3-4 N0-3 M0 according to the Japanese classification system (Japanese Classification of Colorectal Carcinoma, Second English edition)[12]; (iv) no bowel obstruction; (v) age > 20 and < 80 years; (vi) sufficient organ function; (vii) no history of gastrointestinal surgery; (viii) no history of chemotherapy or radiotherapy; and (ix) provision of written informed consent. Eligible cases were evaluated with multidisciplinary assessment. The adjuvant chemotherapy was not specified. Lymph nodes sized >10 mm on the computed tomography (CT) scan were considered clinically metastatic lymph nodes.

We analyzed late adverse events, disease-free survival (DFS), and overall survival (OS). Adverse events, including those of preoperative CRT and surgical complications, were evaluated according to the Common Terminology Criteria for Adverse Events version 4.0.

Chemoradiotherapy

S-1 was administered orally twice daily on days 1-5, 8-12, 22-26, and 29-33 and was dosed according to the body surface area (BSA): patients with a BSA of less than 1.25 m^2 received 80 mg/day, those with a BSA between 1.25 and 1.5 m^2 received 100 mg/day, and those with a BSA of 1.5 m^2 or greater received 120 mg/day. Radiotherapy was performed on days 1-5, 8-12, 15-19, 22-26, and 29-33 with 1.8 Gy/day (the total dose was 45 Gy in 25 fractions). The whole small pelvic cavity was irradiated, including the lateral lymph nodes, using four gate irradiations.

Surgery

Resection of the rectum with D3 lymphadenectomy was performed according to the Japanese Classification of Colorectal Carcinoma (Japanese Society for Cancer of the Colon and Rectum) and the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus, 6th edition[13]. Surgery was performed during the fourth and eighth weeks following the completion of neoadjuvant CRT. The proposed surgical routes were anterior resection with or without covering ileostomy and abdominoperineal resection. If the preoperative and intraoperative findings indicated no lateral lymph node metastasis, these nodes were not dissected.

Follow-up

Patients were examined every 3 months for 1 year after surgery, and every 6 months afterwards at their respective hospitals. Blood tests including those for the tumor markers, carcinoembryonic antigen (CEA) and CA19-9, abdominal CT, and plain chest radiography were performed during each visit.

Statistical methods

According to our protocol[10,11], the planned sample size was 35 patients. The DFS and OS curves were estimated using the Kaplan-Meier method, and the local recurrence-related factors were examined using short variable analysis, the Mann-Whitney U-test, multivariate analysis, and logistic regression analysis. Multivariate logistic regression analysis was performed to compare the independent factors associated with the local recurrence of rectal cancer following surgery after adjusting for other variables. All demographic variables with P values less than 0.05 on univariate analyses were subjected to a multivariate logistic regression model. All statistical analyses were performed using SPSS software

Table 1. Patient Characteristics.

Characteristics	Number of patients (N = 37)
Sex (male/female)	23/14
Median age, years (range)	59 (32-79) [a]
Tumor location (Ra/Rb/P)	9/27/1
cT stage[b] (T3/T4)	32/5
cN stage[b] (N0/N1-3)	10/27
cStage[b] (II/III)	10/27
Operation (LAR/ISR/APR/Hartmann) [c]	13/3/18/2
Adjuvant chemotherapy (performed /not performed)	24/13

Ra, rectum-above the peritoneal reflection; Rb, rectum-below the peritoneal reflection; P, anal canal; APR, abdominoperineal resection; ISR, intersphincteric resection; LAR, low anterior resection

[a]These values represent ages, not number of patients.

[b]Japanese classification system.

[c]One patient in whom radical excision could not be performed was excluded.

Table 2. Adverse Events Occurring in Locally Advanced Rectal Cancer Patients Treated with Neoadjuvant S-1.

Late adverse events	Grade	Event/patients (%)
Gastrointestinal	Grade 1	1 (2.7)
	Grade 2	2 (5.4)
	Grade 3	5 (13.5)
	Grade 4	0 (0)
Sexual	Grade 1	0 (0)
	Grade 2	1 (2.7)
	Grade 3	0 (0)
	Grade 4	0 (0)
Urologic	Grade 1	1 (2.7)
	Grade 2	0 (0)
	Grade 3	1 (2.7)
	Grade 4	0 (0)
Vascular	Grade 1	0 (0)
	Grade 2	1 (2.7)
	Grade 3	0 (0)
	Grade 4	0 (0)

Adverse events were assessed using the Common Terminology Criteria for Adverse Events version 4.0.

(version 23.0; SPSS, Chicago, IL, USA).

Results

CONSORT

Thirty-seven patients were enrolled at the 17 participating hospitals in Oita; all were evaluated according to the intention-to-treat principle. One patient who developed an unresectable distant metastasis preoperatively was unable to undergo surgery. One patient received lateral lymph node dissection because lateral lymph node metastasis was indicated in the preoperative findings. R0 resection with Cur A was performed in 35 cases; one case was diagnosed as R1, Cur B due to a positive circumferential resection margin. The patients' demographics and tumor characteristics are shown in Table 1. Postoperative adjuvant chemotherapy was administered to 24 of the 37 patients; 11 patients did not undergo chemotherapy because of Stage 0, I, or II disease, and 2 did not because of postoperative recovery delay in their general or local conditions. Of the patients who received postoperative adjuvant chemotherapy, 15 received S-1, 1 received capecitabine, 5 received uracil-tegafur/leucovorin, 2 received UFT, and 1 received capecitabine plus oxaliplatin.

Safety

Twelve patients (32.4%) had late adverse events, which were defined as adverse events during follow-up more than 3 months after surgery. Seven of these patients (18.9%) had grade 3 events (hydronephrosis associated with cystitis, 1; bowel obstruction, 1; anastomotic stenosis, 3; pelvic abscess, 1; and late anastomotic leakage, 1). One case of anastomotic stenosis occurred following pelvic abscess (Table 2). These events were deemed to be related to the treatment protocols according to the attending physician's judgment. No patient experienced any grade 4 adverse events, and there was no mortality.

Recurrences and prognoses

The 5-year DFS rate was 66.7%, and the 5-year OS rate was 74.7% (Figure 1a, b). The median follow-up duration was 57 months. Eleven patients (29.7%) developed recurrence after surgery. Local recurrences developed in 5 patients (13.5%), and distant metastases developed in 8 (21.6%) (Table 3). Two patients had anastomotic recurrence, and 3 had intrapelvic recurrence. One patient who had in-

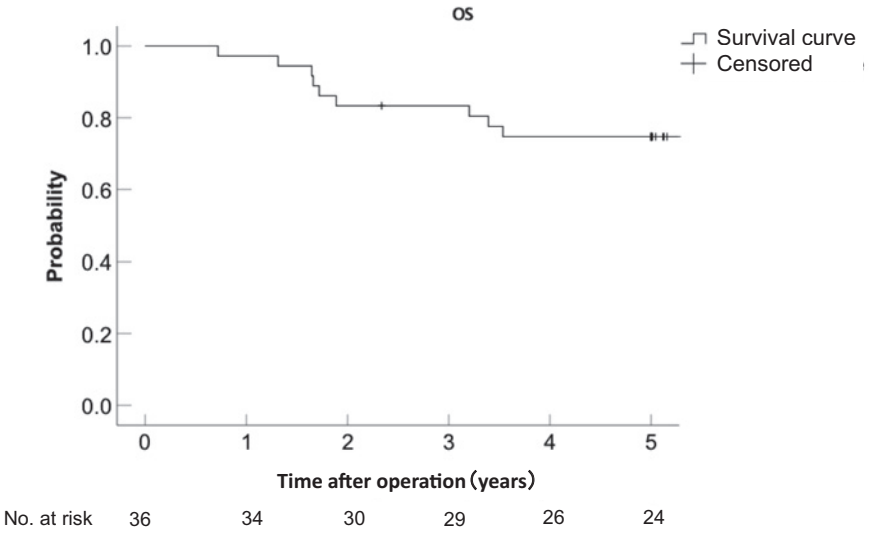

Figure 1a. Five-year disease-free survival (DFS) of rectal cancer patients receiving neoadjuvant S-1 plus radiotherapy.

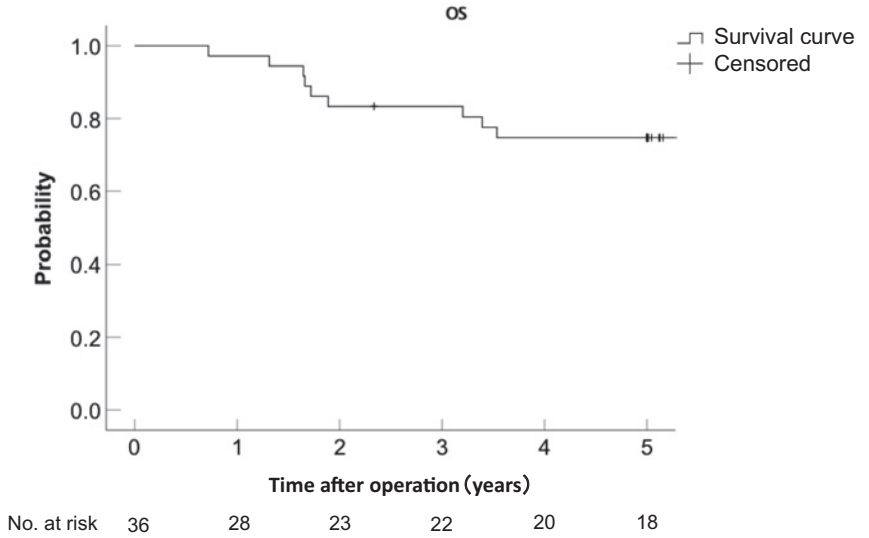

Figure 1b. Five-year overall survival (OS) of rectal cancer patients receiving neoadjuvant S-1 plus radiotherapy.

Table 3. Recurrences Occurring in Locally Advanced Rectal Cancer Patients Treated with Neoadjuvant S-1.

Type of recurrence	Number of patients (%)
Local recurrence	5 (13.5)
Distant metastasis	8 (21.6)
Lung	6 (16.2)
Liver	1 (2.7)
Paraaortic lymph node	1 (2.7)

trapelvic recurrence also had a lateral lymph node metastasis. Lung resection was performed for two cases of pulmonary metastasis. Abdominoperineal resection, lateral lymph node dissection, and inguinal lymph node dissection were performed for cases of inguinal lymph node metastasis and recurrence of anastomosis.

Risk factors for local recurrence

Univariate analysis revealed that the following factors were associated with a significantly high incidence of local recurrence: pretreatment serum CEA level, pretreatment tumor size ≥ 60 mm, lymph node metastasis (clinical), clinical stage, operative time ≥ 540 min, postoperative tumor size, depth of invasion (pathological), and histological effect (all $P < 0.05$). Multivariate analysis revealed no significant risk

factor for local recurrence (Table 4).

Discussion

There are a few reports of S-1 used alone as an anticancer drug in preoperative CRT for locally advanced rectal cancer[14-16], but the long-term results of this treatment have not been clearly determined. To our knowledge, ours is the first study to show the long-term results of preoperative CRT using S-1 as a single agent. In a phase III clinical trial of preoperative CRT using 5-FU for locally advanced rectal cancer, the OS rates were 77.6%[17], which were similar to our rates. Furthermore, S-1-based chemotherapy was reported to have similar efficacy to, and a comparable safety profile with, capecitabine[18]. The 5-year DFS rates for preoperative CRT for Stage II or Stage III rectal cancer using continuous infusion 5-FU or capecitabine were respectively 66.4% and 67.7%, and the 5-year OS rates were respectively 67-79.9% and 61.4-80.8%. The 5-year local-regional recurrence rate was 3.1-7.4% for neoadjuvant CRT using capecitabine for locally advanced rectal cancer[6,19,20].

The 13.5% rate of local recurrence in our study was higher than that of previous phase III trials of preoperative CRT for locally advanced rectal cancer (3-6%)[7,20,21]. This may be because the proportion of Rb tumors in our study (75.8%) was higher than that in previous studies (35-66.8%)[7,21]. Moreover, all patients (100%) in our study had stage cT3/4 disease, whereas such patients comprised 93-97% of cohorts in other studies[7,21]. Data from several large clinical trials indicated that the most significant pathological risk factors for the recurrence of locally advanced rectal cancer were advanced T stage, a positive circumferential resection margin, lymphovascular invasion, extramural venous invasion, poor tumor differentiation, and a low tumor location[22,23]. In our study, although there were no factors significantly related to local recurrence in multivariate analysis, univariate analysis revealed preoperative CEA, preoperative stage, preoperative and postoperative tumor size, preoperative lymph node metastasis, operation time, pathological T factor, and histological effect as significant related factors. This suggests that even if there is radiosensitivity, patients with a large tumor diameter and lymph node metastasis may have a high risk of local recurrence. Considering the definition of locally advanced rectal cancer, including the recent addition of mesorectal fascia-involved cancer, our study included both intermediate-risk rectal cancer (T3b or T4 with peritoneal or vaginal involvement, N1/N2, and CRM clear) and locally advanced risk rectal cancer (T4 with overgrowth to the prostate, seminal vesicles, base of urinary bladder, pelvic side walls or floor, sacrum, positive lateral lymph nodes, and CRM positive)[24,25]. It is also possible that the local recurrence rate was relatively high in our study because our study cases may include the large number of cases of locally advanced rectal cancer, which has the higher risk of failing locally compared with intermediate-risk rectal cancer.

A recent study indicates that a longer interval (more than the classical 6-8 weeks) between the end of preoperative CRT and surgery increases the rate of pCR by 6% in rectal cancer, with similar outcomes and complication rates[26]. This longer interval between neoadjuvant CRT and surgery should be considered in the future.

We previously reported that the acute adverse event rate was 10.8% in a feasibility study[10], whereas the ≥grade 3 late adverse event rate in the current study was 18.9%. The rate of ≥grade 3 late adverse events in a phase III study using 5-FU was 24%[7], which was higher than the rate in our study. Meanwhile, the rate of late toxicity in a phase III study using capecitabine without any adjuvant chemotherapy was 6.5%[21]. However, Velenik et al. reported that late long-term toxicity after preoperative CRT using 45 Gy radiation and capecitabine for rectal cancer was severe (Subjective, Objective, Management, and Analytic grades 3 and 4), with rates of rectal, bladder, and sexual toxicity of 40%, 19.2%, and 51.7%, respectively[19]. In our study, the rates of grade 3 rectal, bladder, and sexual toxicity were 2.7% (data not shown), 2.7%, and 0%, respectively. Preoperative CRT with capecitabine was associated with higher incidences of diarrhea (62%) and hand-foot syndrome (53%)[20,27], whereas CRT with S-1 was associated with mild adverse events, but not hand-foot syndrome[15]. Although late adverse events may still occur among our patients in the future, the rate of late adverse events to date is considered reasonable. According to reports, including recent meta-analyses, there is little evidence that adjuvant chemotherapy after RT or CRT contributes to an increase in the survival rate of rectal cancer; therefore, guidelines from Western countries do not recommend adjuvant chemotherapy for rectal cancer following CRT, except in poor-response patients in the USA. We relied on the judgment of physicians in each facility for the adaptation of adjuvant chemotherapy after CRT, although this may require confirmation about the adaptation in the future[28,29].

There are some limitations in this study. First, it is a single-arm study; therefore, comparison with the standard treatment ought to be performed in a phase III study. Second, the quality of life was not assessed sufficiently. Third, the sample size was small, and the follow-up periods were short. Therefore, additional studies are warranted to address these shortcomings.

In conclusion, our prospective phase II study showed that neoadjuvant-synchronous S-1 plus radiotherapy for locally advanced rectal cancer is feasible in terms of pathological response and adverse events and is accompanied by favorable long-term outcomes. Further trials are required to confirm the benefits of including S-1 in a preoperative CRT regimen for rectal cancer.

Table 4. Univariate Analyses of the Risk Factors for Local Recurrence in Locally Advanced Rectal Cancer Patients Treated with Neoadjuvant S-1.

Clinical variable	Local recurrence		P value
	Present (5)	Absent (31)	
Sex			0.965
Male	2	19	
Female	3	12	
Age			0.894
Median	60	60	
Range	32-69	36-81	
CEA (ng/mL)			＜0.05
Median	11.3	4.9	
Range	1.6-84.8	10.4-51.8	
Operation method			0.563
LAR	0	7	
sLAR	2	4	
APR	1	16	
Hartmann	2	0	
Total colectomy	0	1	
ISR	0	3	
Location			0.657
Rb/P	4	29	
Rs/Ra	1	2	
Tumor size (length of major axis, mm)			0.295
Median	61	39	
Range	28-110	20-85	
≦60 mm	3	3	＜0.05
＞60 mm	2	28	
Clinical depth of invasion			0.369
T3	3	28	
T4	2	3	
Clinical lymph node metastasis			＜0.05
N0	0	10	
N1	0	18	
N2	4	3	
N3	1	0	
Clinical stage (Japanese classification)			＜0.05
Ⅱ	0	10	
Ⅲa	0	16	
Ⅲb	5	5	

sLAR, super low anterior resection; LAR, low anterior resection; APR, abdominoperineal resection; ISR, intersphincteric resection; CEA, carcinoembryonic antigen

Surgical variable	Local recurrence		P value
	Present (5)	Absent (31)	
Operative time (min)			0.053
Median	543	426	
Range	444-581	36-81	
≦540	3	3	0.031
＞540	2	28	
Blood loss (mL)			＞0.99
Median	270	425	
Range	100-1680	30-1550	

Table 4. (continued)

Intraoperative complication			0.666
Present	1	5	
Absent	4	26	
Tumor size (length of major axis)			0.039
Median	68	30	
Range	50-100	8-60	
Surgical depth of invasion			0.134
T3	3	28	
T4	2	3	
Surgical lymph node metastasis			0.262
N0	2	19	
N1	1	9	
N2	1	3	
N3	1	0	
Surgical stage (Japanese classification)			0.262
Ⅱ	3	19	
Ⅲa	2	9	
Ⅲb	0	3	

Pathological variable	Local recurrence		P value
	Present (5)	Absent (31)	
Histological type			0.656
tub1/tub2/pup	5	29	
Mucinous	0	2	
Pathological depth of invasion			＜0.05
Tx	0	5	
T2	0	3	
T3a	0	5	
T3b	3	16	
T4	2	1	
Pathological lymph node metastasis			0.827
N0	3	20	
N1	1	9	
N2	0	2	
N3	1	0	
Pathological stage (Japanese classification)			0.101
0	0	4	
Ⅰ	0	4	
Ⅱ	2	12	
Ⅲa	1	9	
Ⅲb	1	2	
Ⅳ	1	0	
Histological effect			＜0.05
0	0	1	
1a	4	3	
1b	0	10	
2	1	13	
3	0	4	

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Conflicts of Interest

There are no conflicts of interest.

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