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Phase II Study of Preoperative Chemoradiotherapy With S-1 Plus Oxaliplatin for Locally Advanced Rectal Cancer (PerSeUS-RC01)

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Abstract. *Background/Aim: We report the end results of a study evaluating the safety and efficacy of preoperative chemoradiotherapy with S-1 plus oxaliplatin. Patients and Methods: Eligible patients had histopathologically confirmed locally advanced rectal carcinoma (LARC; cT3-T4, any N). They received oral S-1 (80 mg/m^2/day on days 1-5, 8-12, 22-26, and 29-33) and oxaliplatin by infusion (50 mg/m^2/day on days 1, 8, 22, and 29) along with radiotherapy (1.8 Gy/day, total dose: 45 Gy/25 fractions). A chemotherapy gap was included in the third week of radiotherapy. The study endpoint was pathological response rate (Grade 2, 3). Secondary endpoints included rates of pathologic complete response (pCR), R0 resection, disease-free survival (DFS), overall survival (OS), local and distant recurrence, and safety and relative dose intensity. Results: The study enrolled 23 patients at three Centres in Gifu, Japan. All patients received chemoradiotherapy, and 22 underwent surgery. Rates of pathological response, R0 resection, and pathological down-staging were 56.5% (13/23), 95.7% (22/23), and 63.6% (14/22), respectively. There were no grade 4 adverse events, but grade 3 events occurred in 21.7% of patients. The cumulative 3-year local recurrence rate was 8.7%. Distant metastasis occurred in 10 (43.5%) patients, 2 (8.7%) from local recurrence and 2 from secondary pancreatic cancer and lung cancer. There were 8 patients with lung metastasis, 2 with liver metastasis, one with ovarian metastasis, and one with bone metastasis. Three-year rates of DFS and OS were 51.1% (median follow-up 34.3 months) and 91.1% (45.2 months), respectively. Conclusion: The study showed high pathological response rate without severe toxicity and good follow-up results. Unexpectedly, however, this regimen could not control local recurrence and distant metastasis. Nevertheless, adding oxaliplatin to preoperative chemoradiotherapy with S-1 in patients with LARC appears feasible and may safely result in better local control than standard treatment. The study suggests adding treatment with induction chemotherapy in consideration of CEA level and N factor.*

When treating locally resectable rectal cancer with preoperative chemoradiation therapy, a regimen with 5-fluorouracil (5-FU) with radiosensitising effects is recommended as concomitant chemotherapy. Results of various clinical trials in rectal cancer have confirmed that bolus infusion of 5-FU is non-inferior to bolus infusion of 5-FU plus levamisole when given concurrently with radiation therapy (1), and 5-FU administered *via* continuous intravenous infusion is equivalent to bolus infusion of 5-FU plus levamisole (2). Further, the NSABP R-04 study showed that capecitabine, an oral 5-FU drug, is also non-inferior to the intravenous 5-FU regimen. In other words (3), there are no standardized doses, schedules, or routes of administration for 5-FU regimens when combined with radiation therapy. Therefore, in this study, we decided to use oral 5-FU, which is easier to administer than intravenous 5-FU, does not require port placement, and is thought to better maintain patient quality of life (4-8). In Japan, three oral 5-FU drugs, TS-1 (tegafur, gimeracil,

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Key Words: Preoperative chemoradiotherapy, S-1 plus oxaliplatin, locally advanced rectal cancer.

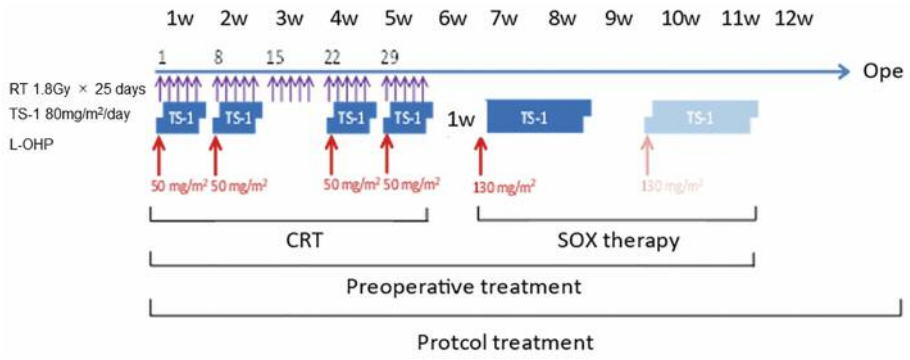

Figure 1. *Treatment schedule*.

oteracil potassium), UFT (tegafur plus uracil), and capecitabine, are available, but TS-1 was selected in this study because not only FU but also gimeracil, a compound of TS-1, is expected to have radiosensitising effects. Oxaliplatin is one of the main drugs used in chemotherapy for colorectal cancer along with 5-FU and CPT-11 (irinotecan), and as oxaliplatin was also reported to have radiosensitising effects, a phase II study was undertaken using a regimen of 5-FU chemoradiotherapy (CRT) combined with oxaliplatin. In a different phase II study of 5-FU chemoradiation combined with oxaliplatin, the pathologic complete response (pCR) rate was reported to be 10-28% (9, 10). In addition, several large, randomised, phase III trials are now underway to evaluate the value of combining oxaliplatin with 5-FU CRT. An interim report on tumour shrinkage in the STAR-01 trial showed the incidence of grade 3/4 adverse events to be higher with 5-FU+oxaliplatin chemoradiation than with 5-FU chemoradiation (24% *vs*. 8%, $p<0.001$), but the pathologic response was not different between the two groups (16% *vs*. 16%) (11). Similar results were obtained in the ACCORD12 trial. Therefore, presently, the National Comprehensive Cancer Network (NCCN) guidelines do not recommend the use of oxaliplatin. However, in the ACCORD12 trial, a higher number of patients treated with oxaliplatin had minimal residual disease at the time of surgery (39.4% *vs*. 28.9%, $p=0.008$), which may lead to an improvement in the long-term local recurrence rate. The distant recurrence rate in each study was as follows (12): STAR-01: 5-FU 2.9% *vs*. 5-FU+oxaliplatin 0.5%, $p=0.014$; ACCORD12: Cape 4.2% *vs*. CapeOX 2.8% and CAO/ARO/AIO-0425: 5-FU 6% *vs*. 5-FU+oxaliplatin 4% (13). In all cases, favorable results were suggested in the oxaliplatin combination group. Therefore, in the present study, we investigated the efficacy of chemoradiation with oxaliplatin combined with a 5-FU-based regimen.

Patients and Methods

Patient eligibility. The multicenter, phase II PerSeUS-RC01 trial was approved by the central ethics committee of Gifu University Hospital, Gifu Prefectural General Medical Center, Gifu Municipal Hospital, and the institutional review boards of all of the participating hospitals (Approval number: 27-323). Written informed consent was obtained from each patient before they participated in the study. The patients eligible for enrolment included those aged 20-80 years with a histologically confirmed diagnosis of non-metastatic primary adenocarcinoma (well/mod) of the middle or lower rectum (cT3–T4, any N, M0). Other eligibility criteria included a T stage of T3/T4 on computed tomography (CT) and magnetic resonance imaging (MRI); a tumour prospectively defined as resectable by the surgeon in charge; overall good general condition that would allow major surgery (Eastern Cooperative Oncology Group performance status 0 or 1); and normal function of the liver, kidney, and bone marrow. The criteria for exclusion were prior chemotherapy for rectal cancer or prior pelvic irradiation, previous malignant disease, uncontrollable infection or metabolic disorders, severe heart disease or neurologic impairment, or inflammatory bowel disease.

Study design and treatment. As concurrent chemotherapy, infusions of oxaliplatin (50 mg/m^2) on days 1, 8, 22, and 29 along with oral S-1 (80 mg/m^2/day) on days 1-5, 8-12, 22-26, and 29-33 were administered. Three-dimensional conformal radiotherapy was begun preoperatively at the time of chemotherapy administration. In total, a dose of 45 Gy was delivered with photons (P10 MV) in 25 fractions over the 5-week treatment course (1.8 Gy/day) *via* a 3- or 4-field technique. The third week of radiotherapy included a chemotherapy gap (Figure 1).

The following clinical target volumes of radiotherapy were included:

1) primary gross tumour volume+5 mm in every direction except at the craniocaudal margin, for which a minimum of 1.5-2 cm was required;
2) lymph nodes of ≥1 cm in diameter;
3) the mesorectum;
4) regional lymph nodes such as the internal iliac, obturator, and presacral nodes up to L5/S1); and
5) any invasion surrounding the organs (in T4 disease).

Table I. *Patient characteristics*.

N	23
Age	63.2±9.2 (49-80)
Gender	
Male	19 (82.6%)
Female	4 (17.4%)
BMI	22.3±4.6 (14.3-38.1)
PS	
0	17 (73.9%)
1	6 (26.1%)
Tumor location	
Ra	1 (4.3%)
Rab	5 (21.7%)
Rba	3 (13.0%)
Rb	10 (43.5%)
RbP	3 (13.0%)
RabS	1 (4.3%)

The radiotherapy protocol of PerSeUS-RC01 permitted no reduction of the planned target volume. The Radiotherapy Quality Assurance Committee of the PerSeUS-RC01 trial reviewed all radiotherapy protocols, verification films, and radiotherapy charts. Before the PerSeUS-RC01 trial was started, a start-up meeting was with the participating radiation oncologists to reach consensus on the clinical target volume. Before each course of radiotherapy, the radiation therapy investigator reviewed anonymous data on radiotherapy planning for each patient *via* the Internet. Surgery that included mesorectal excision or tumour-specific mesorectal excision techniques was performed 6 to 10 weeks after the CRT was completed, but this protocol allowed oral intake of S-1 before surgery. As postoperative treatment, adjuvant chemotherapy WITH oral S-1 was recommended for 6 months.

Study assessments. The primary endpoint of this study was the pathological response rate (Grade 2, 3) defined by Grade evaluation of the anus of the Japanese Society for Cancer of the Colon and Rectum (JSCCR 7th edition).

Histological response criteria were as follows:

Grade 0 (Invalid): There is no degeneration or necrosis of cancer cells due to treatment.

Grade 1 (Mild effect) a): Very mild effect: Less than 1/3 of the cancer cells show degeneration or necrosis.

Grade 1 (Mild effect) b): Mild effect: There is degeneration, necrosis, or shrinking of cancer cells in more than 1/3 but less than 2/3 of the cancer.

Grade 2 (Considerable effect): There is degeneration, necrosis, shrinking or disappearance of cancer cells in more than 2/3 of the cancer.

Grade 3 (Markedly effective): The whole cancer has become necrotic or has shrunk or disappeared. The cancer has been replaced by granulomatous tissue or fibrotic nests (14).

The secondary endpoints included the rates of pCR, R0 resection, disease-free survival (DFS), overall survival (OS), local recurrence, and distant recurrence, and safety and relative dose intensity. Tumour response in all specimens from the three participating hospitals was confirmed by pathological review. pCR was defined as the absence of viable tumour cells in the primary tumour in the resected specimen as evaluated pathologically by Grade classification, which was assessed in accordance with the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus of the JSCCR. Downstaging was defined as any postoperative reduction in pathological T or N stage as compared with that before starting treatment. Patients were observed for the presence of complications for up to 30 days postoperatively. Adverse events were graded in accordance with the Common Terminology Criteria for Adverse Events, version 4.0 of the National Cancer Institute.

On the basis of the pathological responses in the STAR-012, ACCORD12, and CAO/ARO/AIO-04 trials (62.5%, 39.4%, and 44%, respectively), and assuming a pathological response of 45% in the present study's treatment, 37 patients were needed to detect a statistically significant difference at a one-sided significance level of 0.1 and power of 90% compared to a threshold of 25%. On 1 February 2016, the steering committee revised the sample size to 20 patients with a one-sided significance level of 0.1 and power of 75% because of the slow accrual rate. Hence, the number of patients enrolled was changed to 23 considering the possibility of enrolment and withdrawal of patient consent.

Statistical analysis. Values of patient characteristics are presented as the mean±SD and range for the continuous variables and as frequencies and percentages for the categorical variables. The primary analysis involved comparing the frequencies of pathological responses with a threshold of 25% using one sample binomial test. A one-sided p-value <0.1 was considered to indicate statistical significance. For the binary variables of the primary and secondary endpoints, 80% and 95% confidence intervals (CIs) of the proportion were calculated. Kaplan-Meier estimation was conducted to estimate the rates of DFS, recurrence-free survival (RFS), and OS. The patients were split into four subgroups according to different combinations of carcinoembryonic antigen (CEA) and N factor, and the survival curves of each group were compared. Differences in survival curves among the four groups were confirmed with hazard ratios (HRs) estimated by a Cox proportional hazards model. The frequencies of adverse events are summarized by grade. R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses.

Results

In total, 23 patients were enrolled in this phase II study at the 3 Centres in Gifu from September 2013 through August 2016. Among them, 11 patients had a clinical tumour stage of cT3, 12 were at stage cT4, and clinical evidence of lymph node metastasis (cN+) was present in 22 patients. The patient and tumour characteristics at baseline are summarized in Table I and Table II). All 23 patients underwent CRT. The median interval between radiotherapy and surgery was 99 days [interquartile range (IQR)=86.3-105.5]. Relative dose intensities of oxaliplatin and S-1 were received by 19 patients (82.7%), and full-dose radiotherapy was received by 21 patients (91.3%).

Of the 23 patients, 22 received surgery of low anterior resection in 6 patients, super low anterior resection in 4 patients, intersphincteric resection in 6 patients, and Miles' operation in 6 patients. The remaining patient refused surgery after CRT because anal pain had been resolved (Table III).

Table II. *Tumour characteristics*.

Tumor size (mm)	50 (35-120)
T factor	
T3	11 (47.8%)
T4a	6 (26.1%)
T4b	6 (26.1%)
N factor	
N0	1 (4.3%)
N1	9 (39.1%)
N2	10 (43.5%)
N3	3 (13.0%)
Pathology	
tub1	15 (65.2%)
tub2	8 (34.8%)

Table III. *Primary and secondary outcomes*.

	N=22
Operative procedure	
Open	12 (54.5%)
Lap	10 (45.5%)
Anal preserve	
Yes	16 (72.7%)
No	6 (27.3%)
Method	
Open:Lap	
LAR	5:1 (27.3%)
sLAR	2:2 (18.2%)
ISR	1:5 (27.3%)
APR	4:2 (27.3%)
Diverting stoma	
Yes	14 (87.5%)
No	2 (12.5%)
LLD	
Yes	7 (31.8%)
No	15 (68.2%)
Another resection	
Yes	1 (4.5%)
No	21 (95.5%)
D3 dissection	
Yes	22 (100%)
No	0
Operative time	360 (204-683)
Bleeding	299 (1-1,145)
ypStage	
pCR	1 (4.5%)
I	3 (13.6%)
II	8 (36.4%)
IIIa	6 (27.3%)
IIIb	4 (18.2%)
Down stage	
Yes	14 (63.6%)
No	8 (36.4%)

As the primary endpoint, pathological grade was attained in 12 patients (52.7%; 80% CI=37.0%-67.0%), and the rate of downstaging was 63.6% (14 of 22 patients). Among the secondary endpoints, the high rate of R0 surgery of 95.7% (80% CI=84.1%-99.5%) might be attributable to the high rates of downstaging. pCR was confirmed in only one patient (4.4%; 80% CI=0.5%-15.9%). The median (range) follow-up period was 45.3 (23.4-63.2) months. The cumulative 3-year rate of local recurrence was 8.7%. In addition, 10 (43.5%) patients experienced distant metastasis, and local recurrence happened in 2 (8.7%) patients (Table IV).

The 3-year rate of DFS of the 23 patients was 51.1% (95% CI=34.0%-76.9%; median follow-up 34.3 months), and that of OS was 91.1% (median follow-up 45.3 months) (Figure 2, Figure 3, Figure 4). The 3-year rates of RFS were 80% (95% CI=51.61-100), 60% (95% CI=29.33-100), 80% (95% CI=51.61-100), and 25% (95% CI=7.53-83.02) in the N0-1&CEA– group, N0-1&CEA+ group, N2-3&CEA– group, and N2-3&CEA+ group, respectively. The rates of 3-year RFS, DFS, and OS are shown in Figure 5 and Table V.

Safety. Table VI summarizes the most common clinical adverse events and laboratory abnormalities. Overall, leucopenia was the most frequently occurring adverse event and was manageable in all 17 patients (65.2%). Although no grade 4 adverse events occurred, grade 3 adverse events occurred at a rate of 21.7%, with leucopenia at 4.3% and diarrhoea at 17.4%. As an intraoperative or postoperative complication of ≥Grade 3b, anastomotic leakage occurred in one patient (4.3%). There were no other serious postoperative complications or treatment-related deaths (Table VII).

Discussion

Compared to that of colon cancer, the risk of local recurrence of rectal cancer is relatively high due to its proximity to pelvic structures and organs, the lack of serosa around the rectum, and technical difficulties in achieving a wide resection margin. In fact, the recurrence rates by site of first recurrence for colon cancer/rectal cancer were 14.1%/24.3% overall, 0.3%/0.8% at the anastomosis, 1.8%/8.8% locally, 3.5%/7.5% in the lung, 7.0%/7.3% in the liver, and 3.6%/4.2% in other locations. Therefore, to improve the prognosis of rectal cancer, both local and distant recurrences need to be suppressed (14). Different approaches have been taken in Japan and Europe to reduce this risk, and as a result, the standard treatments now differ.

In Europe and the United States, clinical trials on perioperative (preoperative and postoperative) radiation therapy to reduce local recurrence have been conducted since the 1980s. The results show that in regard to OS and local control rate, the preoperative radiation group was significantly superior. The Dutch Trial compared a group with total mesorectal excision (TME), which is standard surgery for rectal cancer, with a preoperative radiation group and

Table IV. *Operative procedures*.

	N	Counts (%)	80%CI (%)	95%CI (%)
Primary endpoint:Pathological response rate (Grade2,3)	23	13 (56.52%)	[41.1, 71.0]	[34.5, 76.8]
Secondary:pCR	23	1 (4.35%)	[0.5, 15.9]	[0.1, 21.9]
Secondary:R0	23	22 (95.65%)	[84.1, 99.5]	[78.1, 99.9]
Secondary:Local recurrence	23	2 (8.70%)	[2.3, 21.5]	[1.1, 28]
Secondary:Distant metastasis	23	10 (43.48%)	[29, 58.9]	[23.2, 65.5]

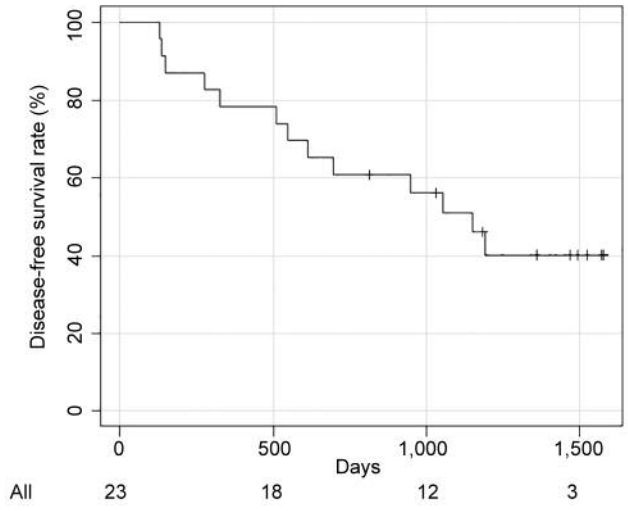

Figure 2. *Three-year rates of disease-free survival*.

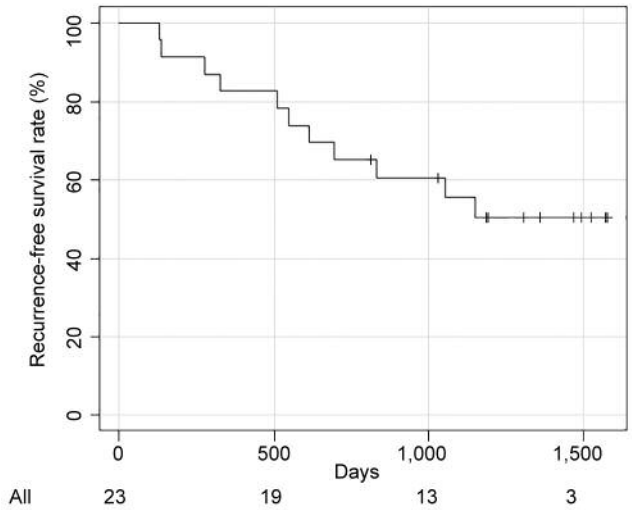

Figure 3. *Three-year rates of recurrence-free survival*.

showed that the results in the preoperative radiation group were significantly better in terms of local recurrence rates, although the difference in OS was not significant (15). Subsequently, studies comparing preoperative chemoradiation with preoperative short-term radiation therapy, chemoradiation with radiation therapy alone, and preoperative chemoradiation with postoperative chemoradiation were conducted. As a result of these phase III studies, preoperative chemoradiation followed by TME is now the current standard of care (16). However, a meta-analysis of many trials that compared preoperative radiation therapy with surgery alone showed a significant reduction in the local recurrence rate and significant prolongation of both survival and cancer-specific survival with preoperative radiation therapy (17-19).

Although there is a risk of overtreatment with preoperative treatment, it offers many benefits, including 1) improved local control, 2) improved sphincter and anorectal preservation due to decreased tumour volume, 3) less toxicity and sensitivity compared to postoperative irradiation, and 4) avoidance of the possibility of radiation-induced injury. The NCCN Clinical Practice Guideline recommends preoperative chemoradiation including 5-FU for resectable T3N0 or any T and N1-2 and T4 rectal cancer.

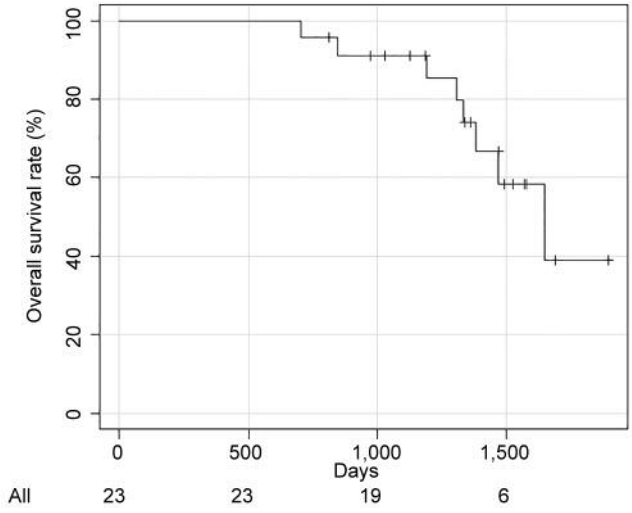

Figure 4. *Three-year rates of overall survival*.

Contrastingly, the current standard procedure in Japan is TME or tumour-specific mesorectal excision plus lateral lymph node dissection with the aim of reducing the local

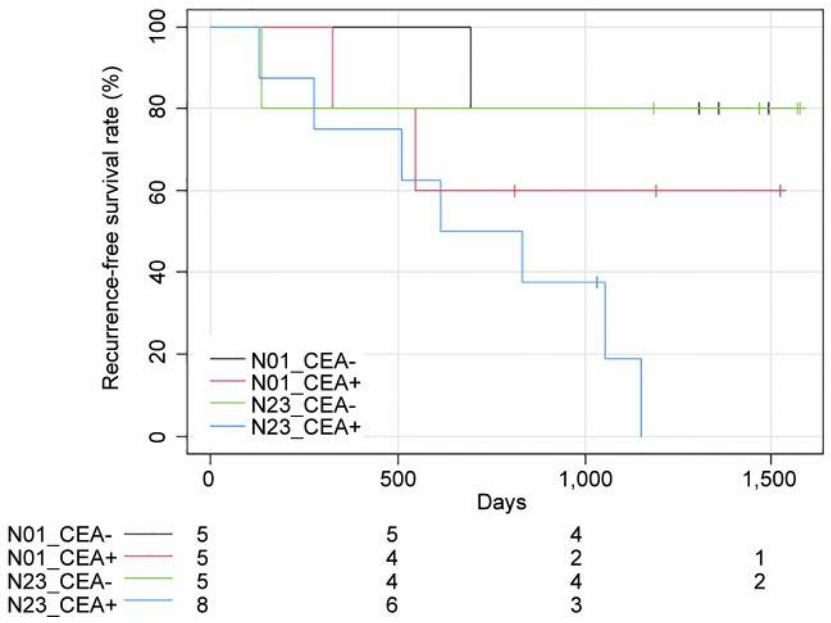

Figure 5. *Three-year rates of recurrence-free survival. The predictive factors have a relationship with carcinoembryonic antigen (CEA) and the N factor.*

recurrence rate through lymph node dissection. However, although the local recurrence rate was reduced following extended dissection, postoperative complications such as dysuria and sexual dysfunction were observed that decreased patient quality of life. Therefore, the JCOG0212 trial is currently investigating the significance of performing lateral lymph node dissection while protecting the autonomic nervous system at the same time (20).

Perioperative chemotherapy and radiotherapy have not been sufficiently investigated in Japan, and no standard treatment incorporating preoperative CRT has been established to date. However, the effectiveness of CRT continues to be reported primarily in Europe and the United States, new anticancer agents such as oxaliplatin and CPT-11 have been introduced, and improvements in radiation equipment and techniques have been remarkable. As a result, preoperative CRT is now being investigated together with the question of the efficacy of the preservation of anal function and autonomic nerves and lateral lymph node dissection (21, 22).

Although excellent control of local disease can be attained by standard management of locally advanced rectal cancer, namely with CRT followed by surgery and adjuvant chemotherapy, the risk of distant metastases has not been reduced. In this study, we determined a treatment schedule based on the regimen in the SHOGUN preoperative CRT phase II trial in which the same oral 5-FU drugs were used: TS-1+oxaliplatin (23-25).

In the SHOGUN trial, an infusion of oxaliplatin (60 mg/m^2) was scheduled on days 1, 8, 22, and 29 along with oral S-1 (80 mg/m^2/day) on days 1-5, 8-12, 22-27, and 29-33. Preoperative 3-dimensional conformal radiotherapy was started simultaneously with chemotherapy. A 50.4-Gy total dose was delivered with photons (P10 MV) in 28 fractions over a 5.6-week treatment course (1.8 Gy/day) with a 3- or 4-field technique. The third week of radiotherapy also incorporated a chemotherapy gap. The present PerSeUS-RC01 study planned concurrent chemotherapy consisting of

Table V. *Three-year survival rates.*

Outcome	Group	3-year survival rate (%) (95%CI)
Disease free survival	All	51.08 [33.95, 76.86]
	N01_CEA-	60 [29.33, 100]
	N01_CEA+	60 [29.33, 100]
	N23_CEA-	80 [51.61, 100]
	N23_CEA+	18.75 [3.6, 97.59]
Recurrence free survival	All	55.51 [38.22, 80.63]
	N01_CEA-	80 [51.61, 100]
	N01_CEA+	60 [29.33, 100]
	N23_CEA-	80 [51.61, 100]
	N23_CEA+	18.75 [3.6, 97.59]
Overall survival	All	91.1 [80.04, 100]
	N01_CEA-	80 [51.61, 100]
	N01_CEA+	100 [100, 100]
	N23_CEA-	100 [100, 100]
	N23_CEA+	87.5 [67.34, 100]

Table VI. *Adverse events*.

	Grade			
	1	2	3	4
Hematologic				
Leucopenia	0	14 (60.9%)	1 (4.3%)	0
Neutropenia	6 (26.1%)	3 (13.0%)	0	0
Anemia	1 (4.3%)	0	0	0
AST	1 (4.3%)	0	0	0
ALT	2 (8.7%)	1 (4.3%)	0	0
Total bilirubin	1 (4.3%)	0	0	0
Thrombocytopenia	1 (4.3%)	1 (4.3%)	0	0
Non hematologic				
Nausea	4 (17.4%)	7 (30.4%)	0	0
Vomiting	1 (4.3%)	1 (4.3%)	0	0
Diarrhea	4 (17.4%)	6 (26.1%)	4 (17.4%)	0
Constipation	1 (4.3%)	0	0	0
Anorexia	9 (39.1%)	1 (4.3%)	0	0
Fatigue	7 (30.4%)	2 (8.7%)	0	0
Abdominal pain	1 (4.3%)	0	0	0
Neuropathy	12 (52.2%)	0	0	0
Dysgeusia	2 (8.7%)	0	0	0
Eruption	2 (8.7%)	0	0	0
Anal pain	5 (21.7%)	0	0	0
Urinary tract pain	1 (4.3%)	1 (4.3%)	0	0
Skin hyperpigmentation	2 (8.7%)	0	0	0
Oral mucositis	2 (8.7%)	0	0	0

the same treatment schedule as the SHOGUN trial but with the dose of oxaliplatin reduced to 50 mg/m^2. Three-dimensional conformal radiotherapy was started preoperatively simultaneously with the chemotherapy. Different from the SHOGUN trial, a 45-Gy total dose was delivered with photons (P10 MV) in 25 fractions over the 5week course (1.8 Gy/day) using a 3- or 4-field technique. The same chemotherapy gap was incorporated.

Although previous phase II trials produced positive results with a combination of oxaliplatin and S-1-based CRT, the SHOGUN trial and our study with the third-week chemotherapy gap during CRT resulted in beneficial effects and less toxicity than those of similar regimens. In their phase II study, Kondo *et al*. also reported that CRT with oxaliplatin and S-1 that included the third-week chemotherapy gap resulted in a favorable toxicity profile and high pCR rate (27.3%) (25).

Presently, fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFOXIRI) are being used as the neoadjuvant regimen based on their high rates of response (66-86%) and disease control (94%) in metastatic disease (26). In the planned, randomised, open-label, phase 3 PRODIGE 23 trial, neoadjuvant chemotherapy with FOLFIRINOX and preoperative CRT were administered to patients with locally advanced rectal cancer. At data cut-off, the overall median follow-up period was 46.5 months (IQR=35.4-61.6), that for the neoadjuvant chemotherapy group was 47.7 months (IQR=35.0-60.9), and that for the standard-of-care group was 45.7 months (35.9-61.7). The rate of 3-year DFS in the neoadjuvant chemotherapy group was 76% (95% CI=69-81) and that in the standard-of-care group was 69% (95% CI=62-74) (stratified HR=0.69, 95% CI=0.49-0.97; p=0.034). The rates of 3-year OS and cancer-specific survival in the neoadjuvant chemotherapy group were 91% (95% CI=86-94) and 92% (95% CI=87-95), whereas in the standard-of-care group, they were 88% (95% CI=83-91) and 89% (95% CI=84-93), respectively (27).

The RAPIDO trial was another planned randomised, open-label, phase 3 trial that assessed treatment of locally advanced rectal cancer with short-course radiotherapy followed by chemotherapy before TME *versus* preoperative CRT, TME, and optional adjuvant chemotherapy. An overview of adverse events showed that 73 (45%) of 162 patients in the neoadjuvant chemotherapy group experienced Grade 3 or worse adverse events *versus* 120 (76%) of 158 patients in the standard-of-care group (p<0.0001). The most common grade 3-4 adverse events in the neoadjuvant chemotherapy group *versus* standard-of-care group were neutropenia [9 (6%) of 161 *vs*. 28 (18%) of 155 patients], lymphopenia [18 (11%) *vs*. 42 (27%) patients], and peripheral sensory neuropathy [19 (12%) of 162 *vs*. 32 (21%) of 155 patients]. A significant difference between groups was observed in disease-related treatment failure at 3 years: fewer failure events occurred in the experimental group *versus* the standard-of-care group [3-year cumulative probability 23.7% (95% CI=19.8-27.6) *vs*. 30.4% (95% CI=26.1-34.6); HR=0.75 (95% CI=0.60-0.95); p=0.019). The cumulative probability of distant metastases at 3 years was 20.0% (95% CI=16.4-23.7) in the experimental group *versus* 26.8% (95% CI=22.7-30.9) in the standard-of-care group [HR=0.69 (95% CI=0.54-0.90); p=0.0048] (28). Grade 3 or higher adverse events were experienced during preoperative treatment in the experimental group by 219 (48%) of 460 patients and in the standard-of-care group by 109 (25%) of 441 patients and during their adjuvant chemotherapy by 63 (34%) of 187 patients. Diarrhoea was the most common adverse event of grade 3 or higher in both treatment groups (29, 30).

In terms of safety, the rate of grade 3 diarrhoea was 17.4%, with no occurrence of grade 4 diarrhoea. Su *et al*. reported in a matched-pair analysis that S-1-based and capecitabine-based CRT are both effective and safe; however, lower incidences of diarrhoea and hand-foot syndrome occurred with preoperative CRT with S-1. Although speculations about CRT with S-1 plus oxaliplatin must be confirmed in phase III clinical trials, it expected to be a safe and effective regimen of combination chemotherapy.

In the present study, 95.7% of the patients had a pretreatment diagnosis of greater than stage III rectal cancer,

Table VII. *Operative complications*.

	Grade				
	Grade1	Grade2	Grade3a	Grade3b	Grade ≥3b (%)
Lymph fistula	1 (4.3%)	0	0	0	0
Perineal SSI	1 (4.3%)	0	0	0	0
Intraabdominal abcess	0	1 (4.3%)	0	0	0
Bowel obstruction	1 (4.3%)	0	0	0	0
Pyelonephritis	0	1 (4.3%)	0	0	0
Urinary tract infection	1 (4.3%)	1 (4.3%)	0	0	0
Urination disoder	0	3 (13.0%)	0	0	0
SSI	1 (4.3%)	2 (8.7%)	0	0	0
Anastomotic leakage	0	1 (4.3%)	0	1 (4.3%)	1 (4.3%)

which is more advanced than that of patients in previous studies. In addition, 56.5% of the patients had a pretreatment diagnosis of more than N2, which is considered to be a poor prognosis for rectal cancer. Therefore, although the primary endpoint of tumour response rate was good, the rates of PFS, RFS, and OS, including those of local recurrence and distant metastasis, were not as good as the rates in other trials.

In addition to its biological role, the canonical biomarker CEA, which is a monitor of adenocarcinoma growth and treatment efficacy, was first reported by Prager *et al*. to be possibly a predictive marker of anti-CRT therapies. Cancer cells harboured within lymph nodes surrounding the rectum may serve as the seeds for local recurrence (31-33). Recent studies have proven that tumours at stage ypT0-1 correlate with a very low incidence of positive lymph node involvement, which is present in about 20-30% of patients with stage ypT2 cancer.

We suggest that the predictive factors have a relationship with CEA level and the N factor. Unexpectedly, there were few effects of CRT in the present study. The study population included many T3-4 and N-positive cases. We predicted that many poor predictor patients were included. Furthermore, we consider patients showing a positive effect on CEA to be appropriate for induction chemotherapy. The median rate of RFS tended to be different among the four groups, as shown in Table V.

The CTCAE criteria for lymph node metastases are as follows for measurable tumour lesions. Accurate measurement in at least one direction [record the largest diameter (longest diameter) in the measured section] [record the largest diameter (longest diameter) in the measured cross-section], and the metastasis size is 10 mm or larger as measured by CT or by calliper as part of the clinical assessment. Lymph nodes that are morbidly large and measurable should have a short-axis diameter of at least 15 mm as assessed by CT (CT slice thickness should be less than 5 mm). At baseline and during the course of the study, lymph node lesions (malignant lymph nodes) judged to be pathologically enlarged and measurable should be recorded as malignant.

Recent advancements made in radiologic staging using MRI have allowed the establishment of features that indicate poor risk in rectal cancer. These include cT4 disease, tumours that threaten or involve the circumferential resection margin, and mesorectal N2 and lateral nodal disease. The risk for developing surgical complications is high especially in low rectal cancer with these poor risk features because of low anastomosis, abdominoperineal resection, and resection extended beyond the original TME. To improve outcomes, a novel and intensive neoadjuvant regimen is needed.

Previous studies reported rates of local recurrence of 20-33% after neoadjuvant CRT and TME in patients with enlarged lateral nodes initially. In a series of patients who underwent selective lateral node dissection after CRT, the rate of pathological metastasis in the dissected lateral nodes was 66% if the patients initially had a short axis of at least 7 mm lateral nodes. Another study also suggested that lateral node metastasis decreased after induction chemotherapy. In patients receiving induction chemotherapy before CRT, if the indications for lateral node dissection can be reduced, oversurgery might be avoided and the number of postoperative complications could decrease (34, 35).

In conclusion, the phase II PerSeUS-RC01 trial showed that CRT with S-1 plus oxaliplatin that incorporates a chemotherapy gap in the third week of radiotherapy was feasible. The response rate was high, and no incidences of severe acute toxicity occurred. Although this study was limited by its small sample size, the present findings suggest that substituting fluorouracil with S-1 plus oxaliplatin and incorporating a chemotherapy gap might be feasible and lead to a higher response rate than that attained with standard treatment, even though the prognosis of patients with rectal cancer of more than N2 is poor and conventional treatment is unlikely to improve it. Therefore, we need to develop more powerful preoperative treatments because CRT alone is not

powerful enough, at least in patients with preoperative positive CEA and N factors. Although genomic medicine is currently undergoing major changes in colorectal cancer and preoperative treatment using genomic tests will be developed in the future, presently, aggressive preoperative treatment may be necessary for patients who are positive for CEA and are N+.

Conflicts of Interest

K. Yoshida has received honoraria for lectures from Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Eli Lilly and Company, Yakult Honsha Co., Ltd., Merck Sharp & Dohme Co., Ltd., Daiichi Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Merck Serono Co., Ltd., Johnson & Johnson Co., Ltd., Covidien Co., Ltd., Eisai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Sanofi K.K., Nippon Kayaku Co., Ltd., Asahi Kasei Co., Ltd., Tsumura Co., Ltd., EA Pharma Co., Ltd., Bayer Yakuhin Co., Ltd., Olympus Co., Ltd., Terumo Co., Ltd., Bristol-Myers Squibb Co., Ltd., Denka Co., Ltd., Teijin Co., Ltd., SBI Pharmaceuticals Co., Ltd., Intuitive Surgical Co., Ltd., Novartis Pharma K.K., and Pfizer Inc.; and research funding from Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Eli Lilly and Company, Yakult Honsha Co., Ltd., Merck Sharp & Dohme Co., Ltd., Daiichi Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Merck Serono Co., Ltd., Johnson & Johnson Co., Ltd., Covidien Co., Ltd., Eisai Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Sanofi K.K., Nippon Kayaku Co., Ltd., Asahi Kasei Co., Ltd., Tsumura Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Astellas Pharma Co., Ltd., Toyama Chemical Co., Ltd., Kinetic Concepts Co., Ltd., Abbott Japan Co., Ltd., and Toray Industries, Co., Ltd. outside the submitted work. T. Takahashi has received honoraria for lectures from Takeda Pharmaceutical Co., Ltd. The other authors have no conflicts of interest in relation to this study.

Authors' Contributions

N.M., T.T, and C.T. drafted the initial manuscript. K.Y., M.Y., Y.I., S.K., C.M., J.Y.T., T.I. and K.Y. conducted critical revision of the manuscript. All Authors reviewed the manuscript.

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