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Original Article

Long-term results of a multicenter phase II study of preoperative chemoradiotherapy with S-1 plus oxaliplatin for locally advanced rectal cancer (JACCRO CC-04: SHOGUN Trial)

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ABSTRACT

Purpose: The study was designed to evaluate the safety and efficacy of adding oxaliplatin to py (CRT) with S-1 in patients with locally advanced rectal carcinoma (LARC). We report here the final results of the study.

Patients and methods: Patients with histopathologically confirmed LARC (cT3-T4, any N) were eligible. They received oral S-1 (80 mg/m^2/day on days 1–5, 8–12, 22–26, and 29–33) and infusional oxaliplatin (60 mg/m^2/day on days 1, 8, 22, 29) plus radiotherapy (1.8 Gy/day, total dose of 50.4 Gy in 28 fractions), with a chemotherapy gap in the third week of radiotherapy. Primary endpoint of the study was pathological complete response (pCR) rate. Secondary endpoints were rates of R0 resection, down-staging, cumulative 3-year local recurrence, 3-year disease-free survival (DFS), and toxicity.

Results: Forty-five patients were enrolled at six centers in Japan. All patients received CRT, and 44 underwent operation. The pCR rate was 27.3% (12/44). The R0 resection rate was 95.5% (42/44). T-down-staging rate was 59.1% (26/44), and N-down staging rate was 65.9% (29/44); the combined pathological down-staging rate was 79.5% (35/44). There were no grade 4 adverse events, but 11.1% of the patients had grade 3 adverse events. Cumulative 3-year local recurrence rate was 0%. However, 13 (30.0%) patients suffered from distant metastasis, and one patient suffered from secondary esophageal cancer that was unrelated to rectal cancer. Eight patients had lung metastasis, 4 had liver metastasis, and 3 patients died of the metastatic disease. The 3-year DFS rate of the 44 patients was 67.5% (median follow-up 36.3 months), and the 3-year overall survival (OS) rate was 93.0% (median follow-up 39.6 months). The patients were then divided into the pCR (12 patients) group and non pCR (32 patients) group. The 3-year rate of DFS for each group was 91.7% and 58.1% and that of OS was 100% and 90.3%, respectively.

Conclusions: The study showed a high pCR rate with no severe toxicity, good follow-up results, and good loco-regional control. Therefore, addition of oxaliplatin to preoperative CRT with S-1 in patients with LARC might be feasible and lead to better local control than standard treatment.

Several clinical trials in western countries have revealed that preoperative chemoradiotherapy (CRT) reduces loco-reginal recurrence in patients with locally advanced rectal carcinoma (LARC) [1,2], and current standard treatment comprises preoperative CRT in these countries. However preoperative CRT is not performed as standard treatment in Japan [3], and preoperative CRT is now gradually emerging as an option for the treatment of LARC. Recently, some literature has reported the same good local control in Japan [4–6]. Oral fluoropyrimidines such as capecitabine and S-1 have been combined with radiotherapy in patients with LARC owing to the convenience of oral preparations over infusional 5-fluorouracil (5-FU). S-1 is an oral anticancer drug that combines

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tegafur (a prodrug of 5-FU) with 5-chloro-2, 4-dihydropyridine (CDHP: gimeracil) and potassium oxonate (Oxo). S-1 has shown high anticancer activity and good compliance in patients with gastric cancer and other solid cancers [7]. In addition, CDHP has also been shown to enhance the antitumor activity of irradiation in human colonic carcinoma xenograft models [8]. Some studies have reported that CRT with S-1 was an effective and well-tolerated regimen for LARC [9]. These findings have provided a rationale for the evaluation of S-1 based CRT regimens.

The FORWARC trial reported that the addition of oxaliplatin to 5-FU-based CRT as a neoadjuvant therapy for LARC caused significant improvement in the pCR rate and an increase in adverse events [10]. Currently, several other phase III trials have reported oxaliplatin in combination with 5-fluorouracil (5-FU)-based CRT as a neoadjuvant therapy for LARC (Table 1). In the STAR-01 [11], ACCORD 12/0405 [12], NSABP R-04 [13], and PETACC-6 [14] trials, adverse influences occurred at high rates, and fluoropyrimidine plus oxaliplatin was not significantly superior to fluoropyrimidine alone. However, the CAO/ARO/AIO-04 [15,16] trial reported that the addition of oxaliplatin to fluorouracil contributed to improve pCR and disease-free survival (DFS) at 3 years as compared with fluorouracil alone, with no significant difference in grade 3–4 toxicities or postoperative complications. The good response in the fluoropyrimidine plus oxaliplatin group was ascribed to the excellent compliance rates. Rödel et al. claimed that the incorporation of a "chemotherapy gap" in the third week of radiotherapy apparently promoted compliance with all components of preoperative CRT. The CRT regimen used in the SHOGUN trial similarly included a chemotherapy gap in the third week of radiotherapy. The benefit of including a chemotherapy gap requires further study.

In our preliminary study, patients with rectal cancer received escalating doses of oxaliplatin combined with fixed doses of S-1 and pelvic radiotherapy [17]. The recommended dose of oxaliplatin was established to be 60 mg/m^2. In the present multicenter trial, CRT with S-1 plus oxaliplatin with a chemoradiotherapy gap was effective and safe for the management of LARC. We have reported the results of short-term outcomes, which showed that preoperative CRT with S-1 plus oxaliplatin had a high pCR rate and favorable toxicity [18]. The aim of the current report was to evaluate the following endpoints: long-term survival, incidence of loco-regional recurrence, and distant metastasis.

Patients and method

Patient eligibility

The JACCRO CC-04: SHOGUN trial was a multicenter phase II study approved by the central ethics committee of the Japan Clinical Cancer Research Organization (JACCRO) and the institutional review boards of all participating centers. Each patient provided written informed consent before participating in the study. This study is registered with Clinical Trials.gov under number NCT01227239.

Patients 20–80 years of age who had a histologically confirmed diagnosis of non-metastatic, primary adenocarcinoma (well differentiated adenocarcinoma/moderately differentiated adenocarcinoma) diagnosis of the middle or lower rectum (cT3-cT4, any N, M0) were eligible for enrollment. Additional eligibility criteria included a T stage of T3 or T4 on computed tomography (CT) plus magnetic resonance imaging (MRI); a resectable tumor as prospectively define by the surgeon in charge; good general condition enabling major surgery (Eastern Cooperative Oncology Group performance status 0 or 1); and normal liver, renal, and bone marrow functions. Exclusion criteria were prior chemotherapy for rectal cancer or any prior pelvic irradiation; a history of malignant disease; severe heart disease, uncontrolled infection or metabolic disorders; or severe neurologic impairment or inflammatory bowel disease.

Study design and treatment

Concurrent chemotherapy consisted of an infusion of oxaliplatin (60 mg/m^2) on days 1, 8, 22, and 29 plus oral S-1 (80 mg/m^2) on days 1–5, 8–12, 22–27, and 29–33. Preoperative 3-dimensional conformal radiotherapy was started at the same time as chemotherapy. A total dose of 50.4 Gy was delivered photons (≧10 MV) in 28 fractions over the course of 6 weeks (1.8 Gy/day), using a 3- or 4-field technique. A chemotherapy gap was thus incorporated in the third week of radiotherapy (Fig. 1). The clinical target volume of radiotherapy included the following volumes: (1) the primary gross tumor volume plus 5 mm in all directions except for the craniocaudal margin, which had to be least 2 cm; (2) lymph nodes 1 cm or more in diameter; (3) the mesorectum; (4) regional lymph nodes (internal iliac, obturator, and presacral lymph nodes up to L5/S1); and (5) invaded surrounding organs (in T4 disease). The radiotherapy protocol of the JACCRO CC-04 trial did not allow any volume reduction in the planned target volume. All radiotherapy protocols, verification films, and radiotherapy charts were reviewed by the Radiotherapy Quality Assurance Committee of the JACCRO CC-04 trial. Before we initiated the JACCRO CC-04 trial, participating radiation oncologists had a start-up meeting to reach a consensus concerning the clinical target volume. The radiation therapy investigator reviewed anonymous data on radiotherapy planning via the Internet before each course of radiotherapy.

Surgery, including total mesorectal excision or tumor-specific mesorectal excision technique, was performed between 6 and 10 weeks after the completion of CRT. Oral S-1 based-adjuvant chemotherapy was recommended for postoperative treatment.

Table 1
Evaluation of additional L-OHP–cross-trial comparison.

Trial (Phase)	N	Chemotherapy regimen	Chemo gap	pCR rate (%)	Toxicity (%) Grade 3 or 4	3-yr-DFS (%)	3-yr-local recurrence (%)
STAR-01 (III)	747	5-FU vs 5-FU + Oxa	No	16 vs 16 n.s.	8 vs 24 P < 0.001	–	–
ACCORD 12/0405 (III)	598	Cape vs Cape + Oxa	No	13.9 vs 19.2 n.s.	10.9 vs 25.4 P < 0.001	67.9 vs 72.3 n.s.	6.1 vs 4.4 n.s.
NSABP R-04 (III)	1608	5-FU or Cape vs 5-FU or Cape + Oxa	No	19.1 vs 20.9 n.s.	NR	64.2 (5 yrs) 69.2 (5 yrs) n.s.	11.2 vs 12.1 n.s.
PETACC-6 (III)	1094	Cape vs Cape + Oxa	No	11.5 vs 13 n.s.	15.4 vs 38.2 P < 0.001	74.5 vs 73.9 n.s.	7.6 vs 4.6 n.s.
CAO/ARO/AIO-04 (III)	1265	5-FU vs 5-FU + Oxa	Yes	13 vs 17 P = 0.038	20 vs 23 n.s.	71.2 vs 75.9 P = 0.03	4.6 vs 2.9
JACCROCC-04 (II)	44	SOX	Yes	27.3	11.1	67.5	0

5-FU = 5-fluorouracil; Cape = capecitabine; DFS = disease-free survival; L-OHP = oxaliplatin; Oxa = oxaliplatin; pCR = preoperative chemoradiotherapy; SOX = S1+oxaliplatin.

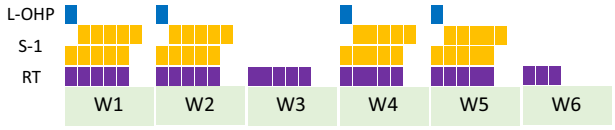

Fig. 1. Treatment schedule (Phase II). L-OHP: The prescribed dose (60 mg/m^2) was given as an intravenous infusion on days 1, 8, 22, and 29. S-1: The prescribed dose (80 mg/m^2 [80, 100, 120 mg/body), in 2 divided doses) was given orally twice daily after breakfast and dinner from the evening of day 1 to the morning of day 6, the evening of day 8 to the morning of day 13, the evening of day 22 to the evening of day 27, and the evening of day 19 to the morning of day 34. Irradiation: 1.8 Gy/day × 5 days/week + 3 days. Total 50.4 Gy. Dose & Fraction: The total dose of 50.4 Gy was delivered with photons (≧10 MV) in 28 fractions over 5.6 weeks (1.8 Gy/day) using a 3- or 4-field technique. W = week.

Patients were followed for 3 years. Evaluation consisted of physical examination and blood test including tumor markers (carcinoembryonic antigen, carbohydrate antigen 19-9), and chest, abdominal, and pelvic CT. Other examinations were performed on symptomatic patients. Loco-regional recurrence was defined as any reappearance of a pelvic tumor mass located within the irradiated volume or the peritoneum. Detection of local recurrence was performed by physical examination and/or pelvic CT or MRI.

The primary endpoint of this study was the pathological complete response (pCR) rate. The secondary endpoints were the rates of R0 resection, down-staging, cumulative 3-year local recurrence, 3-year disease-free survival (DFS), and toxicity.

Study assessments

The tumor response was confirmed by a central pathological review with all specimens from the six participating centers evaluated at one institution, and pCR was defined as the absence of viable tumor cells in the primary tumor of the resected specimen, pathologically evaluated according to the tumor regression grade (TRG). The TRG was assessed according to General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus of the Japanese Society for Cancer of the Colon and the Rectum [19]. Downstaging was defined as any reduction in pathological T or N stage after operation as compared with the clinical T or N stage before starting treatment. Patients were observed for complications up to 28 days after surgery. Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

Statistical analysis

Fleming's one-stage design was used to estimate the required sample size for this phase II study. We estimate that 45 patients were required to test the hypothesis that the pCR rate would be greater than 30% with 80% power and to reject the hypothesis that the pCR rate would be less than or equal to 15% at a significance level of 5% (one-sided).

The case report forms were collected at the central trial office. Time intervals were calculated from the date of starting treatment. In this study, secondary cancer was included as a DFS event. For the calculation of actuarial DFS, the events were death from any cause, local recurrence, or distant metastases, whichever was observed first. For the calculation of the actuarial cumulative incidence of local recurrence, the data from patients who were alive and free from local control or who died without local recurrence were censored. The DFS rate between the pCR-group and non pCR-group was compared. Yothers et al. proposed the neoadjuvant rectal cancer (NAR) score based on the pathological N-stage (pN) and downstaging of T-stage as a potential surrogate endpoint for early-phase clinical trials of neoadjuvant-therapy [20]. The NAR score was categorized as low (<8), intermediate (8–16), and high (>16) based on tertiles of the observed scores. The DFS rate and overall survival (OS) rate were compared between NAR score grades. The x^2 test was used to compare continuous variables. Actuarial curves were calculated by the Kaplan–Meier method and were compared by the log-rank test. A p value < 0.05 was considered to indicate a statistically significant difference. Statistical analysis was performed using JMP for Windows (SAS Institute, Inc., Cary, NC, USA).

Results

Patient demographics and clinical characteristics

From August 2011 through October 2012, 45 patients were enrolled in this Phase II trial at six centers in Japan. The clinical tumor stage was cT3 in 42 patients and cT4 in 3 patients; 35 patients had clinical evidence of lymph node metastasis (cN+). The patient and tumor characteristics at baseline are summarized in Table 2.

Efficacy

The Radiotherapy Quality Assurance Committee of JACCRO CC-04 confirmed that all patients completed radiotherapy without any protocol violations in terms of dose, target volumes, or treatment period. All 45 patients completed CRT. We have reported their short-term outcomes previously [18].

Of the 45 patients who received CRT, 44 underwent surgery. A low anterior resection was performed in 31 patients, abdominoperineal resection in 11 patients, the Hartmann procedure in one patient, and total pelvic exenteration in one patient. One patient rejected surgery after CRT because anal pain had disappeared. As for the primary endpoint, a pCR was achieved in 12 (27.3%, 90% CI: 16.6–40.4%, null hypothesis 15%) of 44 patients who underwent surgery, and 21 (47.7%) of the 44 patients had nearly total tumor regression (tiny cancer foci observed in the resected specimen). R0 resection was performed in 42 of the 44 patients. Twenty-six (59.1%) of the 44 patients had T downstaging, and 29 (65.9%) had N downstaging; the combined pathological downstaging rate was 79.5%.

Safety

There were no grade 4 adverse events in the 45 patients, but the rate of grade 3 adverse events was 11.1%, which included leucopenia (2.2%), neutropenia (2.2%), and diarrhea (8.9%). Intraoperative or postoperative complications occurred in 12 patients (27.3%): 4 patients had infection, 4 required drainage, and 1 patient each had ileus, urinary impairment, and anal pain. No other serious postoperative complications occurred. There was no mortality.

Table 2
Patient characteristics.

	Number
Sex: male/female	32/13
Age: median (range)	59 (31-75)
PS: 0/1	43/2
Histology: tub1/tub2	21/24
Tumor site: Ra/Rb	13/32
Clinical Lateral lymph-node metastasis: -/•	40/5
Clinical T stage: cT3/cT4	42/3
Clinical N stage cN0/cN+	10/35
TNM stage: II/IIIa/IIIb	10/18/17

PS = performance status.

Local recurrence, DFS, OS

The median follow-up of living patients for DFS and local recurrence was 36.3 (range 2.7–49.0) months and for OS was 39.6 (range 5.2–50.4) months. No patients were lost to follow-up. In total, 29 (65.9%) of the 44 patients received adjuvant chemotherapy. The most frequent regimen was S-1 (22 patients); the others were FOLFOX (5 patients) and tegafur-uracil plus leucovorin (2 patients).

The rate of local recurrence was calculated in the 44 patients who underwent operation. However, local recurrence did not occur in any of these patients during the follow-up period.

The actual 3-year DFS rate was 67.5% (Fig. 2). A secondary cancer unrelated to the rectal cancer occurred in one patient. Recurrence occurred in 13 patients. Of these, right common iliac lymph node metastasis occurred in one and distant metastasis occurred in the other 12 patients. The distant metastases included 8 lung metastases, 4 liver metastases, and 4 lymph node metastases. The rate of 3-year DFS was 91.7% in the pCR group ($n = 12$) and 58.1% in the non-pCR group ($n = 32$) ($p < 0.05$) (Fig. 3). The rate of 3-year DFS was 88.2% in low NAR score group ($n = 17$), 70.6% in the intermediate NAR score group ($n = 18$), and 22.2% in the high NAR score group ($n = 9$) ($p < 0.05$) (Fig. 4a)

The actual 3-year OS was 93.0% (Fig. 2). Three patients died of metastatic disease. The rate of 3-year OS was 94.71% in the low

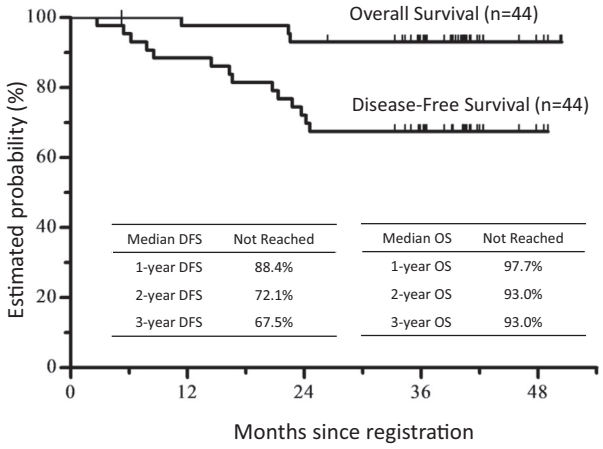

Fig. 2. Three-year rates of disease-free survival (DFS) and overall survival (OS).

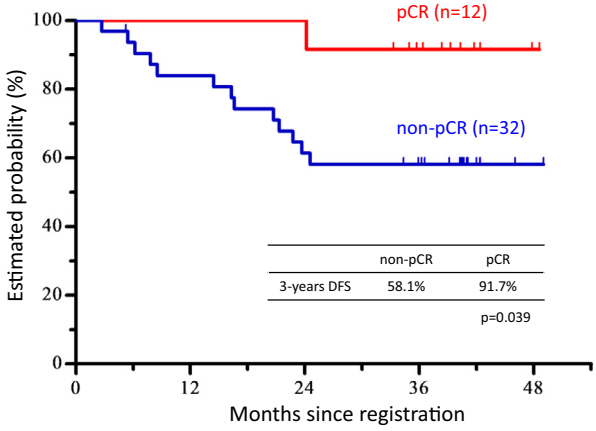

Fig. 3. Three-year disease-free survival rates in the two groups (pCR versus Non-pCR). The rate in the pCR group was better than that in the Non-pCR group. pCR = pathological complete response.

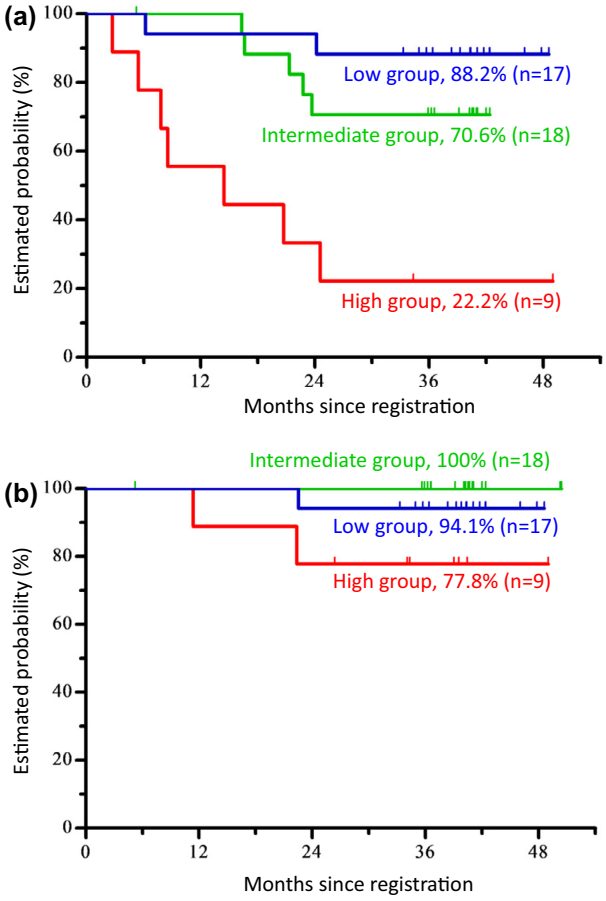

Fig. 4. a: Three-year disease-free survival rates in the three groups (High versus Intermediate versus Low NAR score). Rates in the Low and the Intermediate groups were better than that that in the High group. b: Three-year overall survival rates in the three groups (High versus Intermediate versus Low NAR score). Rates in the Low and the Intermediate groups were better than that in the High group. NAR = neoadjuvant rectal cancer.

NAR score group ($n = 17$), 100% in the intermediate NAR score group ($n = 18$), and 77.8% in the high NAR score group ($n = 9$) ($p < 0.05$) (Fig. 4b).

Discussion

This study suggests that the addition of oxaliplatin to preoperative CRT with S-1 in patients with LARC is feasible to improve the pCR rate and loco-regional control. The present study had a pCR rate (the primary endpoint) of 27.3%, a downstaging rate of 79.5%, and a 3-year cumulative local recurrence rate (the secondary endpoint) of 0%.

This trial regimen was designed to decrease adverse events, and we adopted a regimen that included a chemotherapy gap in the third week of CRT. A combination of oxaliplatin and fluoropyrimidine-based CRT without a chemotherapy gap in the third week generated negative results in previous phase III trials [11–14], but beneficial effects with similar regimens were obtained in the CAO/ARO/AIO-04 trial [15,16] and the present study, both with a chemotherapy gap. The difference in our study may be attributed to a favorable toxicity profile (11.1%) and the high rates of relative performance in the latter three studies, which resulted in excellent compliance with all components of preoperative CRT, including radiotherapy. In the CAO/ARO/AIO-04 trial, the pCR rate

was 17%, the 3-year local recurrence rate was 2.9%, and the toxicity rate (Grade 3) was 23% for the 5-FU+oxaliplatin arm. In terms of our trial, pCR and the 3-year local recurrence and toxicity rates (pCR: 27.3%, 3-year local recurrence: 0%) were superior to those of the CAO/ARO/AIO-04 trial. As a result, we consider that gimeracil, one of the constituents of S-1, may increase the concentration of 5-FU, improving sensitivity to radiation, whereas oteracil potassium, another ingredient in S-1, may act to reduce adverse effects. In this trial, 31.8% (14/44) of patients underwent lateral pelvic lymphadenectomy, which may be a reason for the improvement in loco-regional control. This trial did not specify adjuvant chemotherapy after surgery, and this also may have affected the results.

We verified the reliability of the NAR score prospectively in this trial. Our results revealed that a high NAR score prospectively indicated worse prognosis compared with intermediate and low NAR scores not only for DFS but also for OS, suggesting that the NAR score may be a possible surrogate of DFS and OS in the future. In this trial, OS was not included in the evaluation of secondary endpoints, but we followed up registered patients strictly. The 3-year OS rate was 93% in this study, indicating an excellent result. Currently, among the several trials reporting oxaliplatin in combination with 5-FU-based CRT as a neoadjuvant therapy for LARC, the present study showed the best results. We adopted a chemotherapy gap and S-1 in the regimen in this trial, and these may have been factors in the excellent results. A number of trials of regimens containing irinotecan have also reported good outcomes [21,22]; however, Phase III trial results comparing 5-FU monotherapy with a regimen including irinotecan have not been reported.

Molecular targeted drugs are another alternative for addition to the regimens. Although some trials of regimens including molecular targeted drugs have been performed, the results showed no improvement of the pCR rate and survival rate [23]. Willett et al. reported that regimens including molecular targeted drugs improved the pCR rate [24]. However, their trial included few control subjects, and it cannot be said that the additional effect of molecular targeted drugs has been demonstrated clearly.

Limitations of this study include the small number of cases and that it is a Phase II trial with a single arm. Also, there was no statistical validation of the NAR score.

In conclusion, although the present data size was small, the SHOGUN trial showed that CRT with S-1 plus oxaliplatin and the incorporation of a chemotherapy gap in the third week of radiotherapy was feasible and resulted in a high pCR rate without severe toxicity and excellent loco-regional control. As expected, pCR could provide a favorable outcome. A high NAR score might be a useful predictor of poor prognosis. However, a future prospective phase III trial will be required to clarify the benefits of our regimen.

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Conflict of interest statement

All authors declare no conflicts of interest.

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