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ORIGINAL ARTICLE – COLORECTAL CANCER

Phase II Trial of Neoadjuvant Chemotherapy, Chemoradiotherapy, and Laparoscopic Surgery with Selective Lateral Node Dissection for Poor-Risk Low Rectal Cancer

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ABSTRACT

Purpose. The aim of this study is to evaluate the safety and efficacy of induction modified 5-fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) plus bevacizumab followed by S− 1-based chemoradiotherapy in magnetic resonance imaging (MRI)-defined poor-risk locally advanced low rectal cancer.

Patients and Methods. This was a prospective phase II trial at a single comprehensive cancer center. The primary endpoint was the pathological complete response (pCR) rate. Eligible patients had clinical stage II–III low rectal adenocarcinoma with any of the following MRI-defined poor-risk features: circumferential resection margin (CRM) $\leq$ 1 mm, cT4, positive lateral nodes, mesorectal N2 disease, and/or requiring abdominoperineal resection. Patients received six cycles of mFOLFOX6 with 5 mg/kg bevacizumab followed by oral S-1 (80 mg/m^2/day on days 1–14 and 22–35) plus radiotherapy (50.4 Gy). Surgery was conducted through a laparoscopic approach. Lateral node dissection was selectively added when the patient had enlarged lateral nodes.

Results. A total of 43 patients were enrolled. Grade 3–4 adverse events occurred in nine patients during induction chemotherapy and in five patients during chemoradiotherapy. One patient declined surgery with a clinical complete response. Forty-two patients underwent surgery, and 16 had pCR [37.2%, 95% confidence interval (CI) 24.4–52.1%]. All underwent R0 resection without conversion, including combined resection of adjacent structures (n = 14) and lateral node dissection (n = 30). Clavien–Dindo grade 3–4 complications occurred in six patients (14.3%). With median follow-up of 52 months, six developed recurrences (lung n = 5, local n = 1; 3-year relapse-free survival 86.0%).

Conclusions. This study achieved a high pCR rate with favorable toxicity and postoperative complications in poor-risk locally advanced low rectal cancer. Multicenter study is warranted to evaluate this regimen.

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Neoadjuvant chemoradiotherapy reduces local recurrence but does not improve survival in stage II–III rectal cancer.[1] Although guidelines recommend postoperative adjuvant chemotherapy,[2,3] previous studies have shown controversial results regarding the oncological benefit of adjuvant chemotherapy after neoadjuvant chemoradiotherapy.[4–8] Toxicity during chemoradiotherapy and postoperative complications often prevent patients from completing postoperative chemotherapy.[4] Instead, preoperative systemic chemotherapy before chemoradiotherapy has been explored as a novel option to improve treatment compliance and outcomes. Several phase 2 trials have shown slight improvements in tumor response and pathological complete response (pCR) rate.[9–15]

Recent advances in radiologic staging using magnetic resonance imaging (MRI) have established poor-risk features in rectal cancer, including cT4 disease, tumors with threatened or involved circumferential resection margin (CRM), mesorectal N2 disease, and lateral nodal disease.[2,16] Particularly in low rectal cancer with such poor-risk features, the risk for developing surgical complications is high due to low anastomosis, abdominoperineal resection, and extended resection beyond total mesorectal excision (TME). A novel and intensive neoadjuvant regimen is warranted to improve outcomes.

The aim of the present study is to evaluate the safety and efficacy of induction mFOLFOX6 with bevacizumab followed by S-1-based chemoradiotherapy in MRI-defined poor-risk locally advanced low rectal cancer.

PATIENTS AND METHODS

Study Design and Participants

This was a prospective phase II trial at a single comprehensive cancer center in Japan (UMIN000011457). Patients with clinical stage II–III rectal adenocarcinoma with distal tumor border at or below peritoneal reflection and at least one of the following poor-risk features on MRI were eligible for inclusion: cT4 disease, threatened ($\leq$ 1 mm) or involved CRM, mesorectal N2 disease, lateral nodal disease, and/or tumors requiring abdominoperineal resection due to involvement of the levator muscle or anal canal. Node positivity was defined as adenopathy of 7 mm or larger measured on axial view on MRI.[17,18] Morphology and texture of the nodes were not used in the diagnosis. Initial staging was done by MRI of the pelvis, contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis, and full colonoscopy. Patients were required to have Eastern Collaborative Oncology Group performance status score of 0 or 1. Patients with history of pelvic radiation, any malignant tumors within the previous 5 years, metastatic disease, substantial cardiac disease, lung disease, diabetes, neurological disease, or renal, hepatic, or bone marrow dysfunction were ineligible. The study protocol was approved by the institutional review board and met the guidelines of the responsible governmental agency. Patients provided written informed consent before enrolment in the study.

Study Treatment

Induction chemotherapy was six cycles of mFOLFOX6 plus bevacizumab. Each cycle consisted of leucovorin 200 mg/m^2, oxaliplatin 85 mg/m^2, bolus fluorouracil 400 mg/m^2, bevacizumab 5 mg/kg on day 1, and 46-h infusion of fluorouracil 2400 mg/m^2. Chemoradiotherapy was started 4–6 weeks after the last dose of oxaliplatin. Concurrent chemotherapy consisted of oral S-1 (80 mg/m^2/day) on days 1–14 and 22–35. Preoperative three-dimensional conformal radiotherapy was started at the same time as chemotherapy. A total dose of 50.4 Gy was delivered in 28 fractions (1.8 Gy/day), using a three- or four-field technique. Surgery was performed 6–10 weeks after completion of chemoradiotherapy. In patients who had 7 mm or larger lateral nodes on pretreatment MRI, lateral node dissection on the positive side was selectively added, regardless of shrinkage or persistence of the nodes after neoadjuvant therapy.[18,19] All procedures were conducted through a laparoscopic approach by board-certified colorectal surgeons. Adjuvant chemotherapy was given at physician discretion; six cycles of mFOLFOX6 was the recommended regimen.

Outcomes and Statistics

The primary endpoint of the study was the proportion of patients achieving pCR, defined as absence of tumor cells in the surgical specimen, at both the primary tumor and regional lymph nodes. The surgical specimens were assessed using the Rödel scale.[20] Other endpoints included percentage of R0 resections, toxicity, compliance, surgical complications, and recurrences. Adverse events during neoadjuvant treatment were measured using the Common Terminology Criteria for Adverse Events version 4.0. Surgical complications were graded according to the Clavien–Dindo classification.[21] Surgical complications were monitored through the 90-day postoperative period.

Sample size was calculated using the method of Fleming.[22] The required sample size was estimated based on a threshold pCR rate of 15% and an expected pCR rate of 35%, power of 90%, and an alpha value of 0.05 (one-sided). Assuming 10% ineligible patients, the target sample size was determined to be 43 patients. Analyses were

performed using JMP version 10.1.2 software (SAS Institute Inc., Cary, NC).

RESULTS

Patient Demographics and Tumor Characteristics

Between November 2012 and September 2014, a total of 43 patients were enrolled in the study. Patient demographics and tumor characteristics are summarized in Table 1. The study included 30 patients with suspected lateral nodes, 14 with mesorectal N2 disease, 13 with cT4 disease, 21 with CRM $\leq$ 1 mm, and 16 requiring abdominoperineal resection.

Compliance and Toxicity during Neoadjuvant Treatment

The flow of participants is shown in Supplementary Fig. 1. Eleven patients had ostomy created before commencing neoadjuvant therapy due to stenosis of the primary tumor. Among 43 patients commencing induction chemotherapy, 42 completed the planned six cycles. One patient had asymptomatic radiologic aortic dissection after completing four cycles and commenced chemoradiotherapy without receiving further induction chemotherapy.

All 43 patients commenced neoadjuvant chemoradiotherapy, and 42 completed the planned 50.4-Gy irradiation. The relative dose intensity of S-1 was 96.4%. One patient had perforated sigmoid colon diverticulitis after receiving 28.8 Gy and underwent surgery without receiving further radiotherapy.

Table 2 summarizes toxicity and compliance during the neoadjuvant treatment. Nine (20.9%) patients experienced grade 3 adverse events from induction chemotherapy, with the most common adverse event being neutropenia (n = 6; 14.0%). Five (11.6%) patients experienced grade 3 adverse events from chemoradiotherapy, with the most common adverse events being diarrhea (n = 2; 4.7%) and rectal stenosis requiring ostomy formation (n = 2; 4.7%). No grade 4 complications or deaths occurred during neoadjuvant treatment. No patients experienced progression of disease during neoadjuvant treatment.

TABLE 1 Patient demographics and tumor characteristics

Age, years, median (range)	54	(28–75)
Gender, no. (%)		
Male	27	(62.8)
Female	16	(37.2)
Body mass index, kg/m^2, median (range)	23.1	(17.2–30.0)
ECOG performance status, no. (%)		
0	42	(97.7)
1	1	(2.3)
Distance from anal verge, cm, median (range)	5.0	(1.0–8.0)
Clinical T stage, no. (%)		
cT3	31	(72.1)
cT4	12	(27.9)
Clinical N stage, no. (%)		
cN0	3	(7.0)
cN + (lateral node −)	10	(23.3)
cN + (lateral node +)	30	(69.8)
MRI-defined high-risk features, no. (%)		
Circumferential resection margin $\leq$ 1 mm	21	(48.8)
cT4	13	(30.2)
Mesorectal cN2	14	(32.6)
Lateral node +	30	(69.8)
Requiring APR	16	(37.2)
Hisotology grade, no. (%)		
Grade 1	8	(18.6)
Grade 2	32	(74.4)
Grade 3	3	(7.0)

ECOG Eastern Collaborative Oncology Group, *MRI* magnetic resonance imaging, *APR* abdominoperineal resection

TABLE 2 Toxicity and compliance during neoadjuvant treatment

Induction chemotherapy		
All grade 3–4, no. (%)	9	(20.9)
Grade 3–4 hematologic, no. (%)	6	(14.0)
Neutropenia	6	(14.0)
Grade 3–4 nonhematologic, no. (%)	4	(9.3)
Hypertension	2	(4.7)
Diarrhea	1	(2.3)
Stomatitis	1	(2.3)
Treatment compliance, no. (%)		
Completed six cycles	42	(97.7)
Received 100% dose without interruption	21	(48.8)
Received 100% dose with interruptions	17	(39.5)
Required dose reduction	4	(9.3)
Chemoradiotherapy		
All grade 3–4, no. (%)	5	(11.6)
Grade 3–4 hematologic, no. (%)	0	(0)
Grade 3–4 nonhematologic, no. (%)	5	(11.6)
Rectal stenosis requiring ostomy creation	2	(4.7)
Diarrhea	2	(4.7)
Nausea and vomiting	1	(2.3)
Treatment compliance, no. (%)		
Completed planned 50.4 Gy	42	(97.7)
Received 100% dose of S-1	38	(88.4)
Required dose reduction of S-1	4	(9.3)
Required interruptions	3	(7.0)

Pathological Outcomes

A total of 42 patients underwent surgery, while 1 patient declined surgery with a clinical complete response. The interval between radiotherapy and surgery was 52 ± 1.6 days (mean ± standard error, SE). Pathological outcomes are summarized in Table 3. Sixteen patients (37.2%; 95% confidence interval: 22.2–52.3%, intention-to-treat analysis) had pCR in the primary tumor and lymph nodes, which met the primary endpoint. An additional one patient had pathological complete response in the primary tumor with a few remaining cancer cells within a lymph node. Lymph node metastasis was found in eight patients (18.6%), including mesorectal lymph nodes in four, lateral lymph nodes in one, and both in three. One patient who declined surgery maintained clinical complete response without recurrence for 55 months after completion of chemoradiotherapy.

TABLE 3 Pathological outcomes

ypCR (ypT0N0),[a] no. (%, 95% CI)	16	(37.2, 24.4–52.1)
Downstaging,[b] no. (%)		
T downstaging	29	(67.4)
N downstaging	32	(74.4)
Circumferential resection margin ≤ 1 mm,[b] no. (%)	0	(0)
Tumor regression grade (primary tumor),[b] no. (%)		
4: complete regression	17	(40.5)
3: > 50% regression	18	(42.9)
2: 25–50% regression	7	(16.7)
1: < 25% regression	0	(0)
ypT stage,[b] no. (%)		
ypT0	17	(40.5)
ypTis	1	(2.4)
ypT1	0	(0)
ypT2	9	(21.4)
ypT3	12	(28.6)
ypT4b	3	(7.1)
ypN stage,[b,c] no. (%)		
ypN0	34	(81.0)
ypN1	7	(16.7)
ypN2	1	(2.4)
Mesorectal node +	7	(16.7)
Lateral node +	4	(9.5)

ypCR pathological complete response, *CI* confidence interval

[a]ypCR rate calculated among intention-to-treat population (n = 43)

[b]Other proportions calculated among patients who underwent surgery (n = 42)

[c]Lateral nodes counted as regional lymph nodes for ypN staging

Surgical and Postoperative Outcomes

Table 4 summarizes surgical outcomes of the 42 patients. All patients underwent R0 resection by laparoscopic approach without conversion, including combined resection of adjacent structures (n = 14; 33.3%) and lateral node dissection (n = 30; 71.4%). Sphincter-preserving surgery was performed in 29 patients (69.0%). Postoperative complications by Clavien–Dindo grading are summarized in Table 5. Grade 3–4 complications occurred in six patients (14.3%). Overall, only two patients (4.8%) required repeat surgical intervention, one for leakage and the other for postoperative bleeding. There were no deaths during or after surgery. Of all complications reported, the most common was grade 2 transient urinary retention (n = 10; 23.8%), which were all associated with lateral node dissection.

Thirty-four patients (79.1%) received postoperative adjuvant chemotherapy. Although not defined in the protocol, 30 patients received mFOLFOX6, with 26 completing six cycles after surgery.

After median follow-up of 52 months (range 27–68 months), 37 patients continued to be free from recurrence. The estimated 3-year relapse-free survival was

TABLE 4 Surgical outcomes

Surgical procedures, no. (%)		
Laparoscopic low anterior resection	20	(47.6)
Laparoscopic intersphincteric resection	9	(21.4)
Laparoscopic abdominoperineal resection	13	(31.0)
Additional surgical procedures, no. (%)		
Lateral node dissection	30	(71.4)
With complete autonomic nerve preservation	21	(50.0)
With partial resection of autonomic nerve	9	(21.4)
Resection of adjacent structures beyond TME[a]	14	(33.3)
R0 resection, no. (%)	42	(100)
Postoperative complications,[b] no. (%)	25	(59.5)
Clavien–Dindo grade 1	3	(7.1)
Clavien–Dindo grade 2	21	(50.0)
Clavien–Dindo grade 3a	3	(7.1)
Clavien–Dindo grade 3b	2	(4.8)
Clavien–Dindo grade 4a	1	(2.4)
Mortality, no. (%)	0	(0)

TME total mesorectal excision

Proportion calculated among patients who underwent surgery (n = 42)

[a]Autonomic nerve (n = 9), vagina (n = 5), seminal vesicle (n = 3), prostate (n = 1), uterus and adnexa (n = 1), and coccyx (n = 1). Some patients had more than one resection

[b]Some patients had more than one complication

TABLE 5 Postoperative complications by Clavien–Dindo grading

	Grade 1	Grade 2	Grade 3a	Grade 3b	Grade 4a	Overall
Urinary retention		10 (23.8)				10 (23.8)
Wound infection	3 (7.1)	4 (9.5)				7 (16.7)
Pelvic abscess		1 (2.4)	2 (4.8)			3 (7.1)
Urinary infection		3 (7.1)				3 (7.1)
Anastomotic leakage		1 (2.4)		1 (2.4)		2 (4.8)
Delirium					1 (2.4)	1 (2.4)
Bleeding				1 (2.4)		1 (2.4)
Urethral fistula			1 (2.4)			1 (2.4)
Obturator nerve palsy		1 (2.4)				1 (2.4)
Pulmonary embolism		1 (2.4)				1 (2.4)
Ileus		1 (2.4)				1 (2.4)

Proportion calculated among patients who underwent surgery (n = 42). Some patients had more than one complication

86.0% (Supplementary Fig. 2). The most common site of first recurrence was lung (five patients). Local recurrence occurred in one patient.

DISCUSSION

The results of this single-institutional phase II trial show that adding six cycles of mFOLFOX6 with bevacizumab before S-1-based chemoradiotherapy achieved a high pCR rate of 37.2% in patients with poor-risk locally advanced low rectal cancer. This is one of the highest proportions reported so far for stage II–III rectal cancer. Further, combining a laparoscopic approach with this regimen seemed to be safe from both an oncological and surgical standpoint; it achieved 100% R0 resection without conversion, and the incidence of grade 3–4 postoperative complications seemed acceptable, even though the majority of patients underwent extended resection beyond TME. If these findings can be reliably reproduced, the present regimen will provide a greater chance for curative resection and organ preservation in patients with locally advanced low rectal cancer.

Use of bevacizumab without evident distant metastasis may be controversial, as previous studies did not support survival benefit in the adjuvant setting.[23,24] However, we speculate that bevacizumab might have contributed to the high pCR rate in this study. In previous phase II trials, adding induction chemotherapy with a fluoropyrimidine and oxaliplatin before chemoradiotherapy showed only a slight improvement in pCR rates compared with conventional chemoradiotherapy.[9–15] Only the AVACROSS study.[25] reported a high pCR rate of 36%, equivalent to that in this study. Interestingly, this study and the AVACROSS study are the only trials that added bevacizumab during oxaliplatin-based induction chemotherapy. In the AVACROSS study, bevacizumab was added during induction capecitabine and oxaliplatin (CAPOX, 7.5 mg/kg), and further during capecitabine-based chemoradiotherapy (5 mg/kg). Bevacizumab may sensitize tumors to radiation by normalizing the tumor vasculature,[26] leading to greater tumor oxygenation and thereby increasing the cytotoxicity of radiation to cancer cells.[27] Particularly in locally advanced low rectal cancer, acceleration of radiation-induced tumor shrinkage by bevacizumab would provide benefits in organ preservation.

Another concern about using bevacizumab before surgery is increased surgical complications. In the AVACROSS study,[25] 11 patients (24%) needed repeat surgical intervention, mostly due to anastomotic failure. In contrast, in this study, only two patients (4.8%) required repeat surgical intervention and only two patients (4.8%) developed grade 2–3 anastomotic leakage. The proportion of overall grade 3–4 complications in our study (14.3%) was not higher than reported in a recent randomized trial without neoadjuvant therapy which compared TME alone (16%) versus TME plus lateral node dissection (22%).[28] An important difference between this study and the AVACROSS study is that bevacizumab was used only during induction chemotherapy and not during chemoradiotherapy, which ensured an interval of 14–18 weeks from the last dose of bevacizumab to surgery. The National Comprehensive Cancer Network (NCCN) guideline recommends an interval from bevacizumab to surgery at of least 6 weeks.[3] The relatively long interval in our study might have contributed to better surgical outcomes.

The interval from chemoradiotherapy to surgery affects the pCR rate. A large observational study of clinical stage II–III rectal cancer showed that the pCR rate increased with longer chemoradiotherapy-to-surgery interval up to 12 weeks.[29] A phase II trial of adding mFOLFOX6 after chemoradiotherapy and lengthening the

chemoradiotherapy-to-surgery interval showed an increased pCR rate of 38% in patients who received six cycles of mFOLFOX6 after chemoradiotherapy,[30] much higher than reported in trials of alternatively sequencing oxaliplatin-based chemotherapy before chemoradiotherapy.[9–15] In this study, the mean interval from chemoradiation to surgery was less than 8 weeks. Although this study achieved a 37.2% pCR rate, the proportion might be underestimated due to the relatively short interval.

Previous studies reported 20–33% local recurrence after neoadjuvant chemoradiotherapy and TME in patients who initially had enlarged lateral nodes.[31–34] A series of selective lateral node dissection after chemoradiotherapy reported 66% pathological metastasis in the dissected lateral nodes if the patients initially had $\geq$ 7 mm lateral nodes.[18] Based on the reported high proportion of residual lateral node metastasis after neoadjuvant chemoradiotherapy, 30 patients in this study underwent lateral node dissection for initially enlarged lateral nodes. However, the results showed a lower proportion of residual lateral node metastasis than expected. Only four patients had pathological lateral node metastasis, representing 9.3% of the overall study population and 13.3% of those undergoing lateral node dissection. Interestingly, a previous study also suggested decreased lateral node metastasis after induction chemotherapy.[17] The indications for lateral node dissection could be reduced in patients receiving induction chemotherapy before chemoradiotherapy, which would avoid oversurgery and decrease postoperative complications.

Although the majority of patients received extended surgery beyond TME in this study, all had R0 resection through a laparoscopic approach without conversion. As this study was conducted at a single cancer center where all colorectal surgeons were board certified in laparoscopic surgery, these results must be interpreted with caution. Nevertheless, they indicate that a minimally invasive approach for poor-risk rectal cancer was safe and beneficial if conducted by well-experienced surgeons. Combining minimally invasive surgery with intensive neoadjuvant therapy would be a reasonable and ideal strategy that would balance the toxicity of intensive neoadjuvant treatment with lower surgical morbidity and better postoperative quality of life.

Several limitations of this study must be mentioned. Because this study was a single-arm phase II trial at a single comprehensive cancer center, the results need to be confirmed in a multicenter randomized trial. Oral S-1 was used during chemoradiotherapy instead of oral capecitabine. Although a matched analysis reported that S-1- and capecitabine-based chemoradiotherapy were similarly effective and safe,[35] the results of this study may not be extrapolatable to patients of different ethnic origins because the pharmacokinetics and pharmacodynamics of S-1 might vary.[36,37] One patient developed perforating diverticulitis during chemoradiotherapy, which might be associated with the use of bevacizumab. As this study was not powered to assess the proportion of rare complications during neoadjuvant therapy, further investigation with larger sample size is needed. An ad hoc study of the present trial with extended sample size is ongoing to assess the safety of neoadjuvant bevacizumab (UMIN000011457).

In conclusion, this trial showed that adding six cycles of mFOLFOX6 with bevacizumab before S-1-based chemoradiotherapy achieved a high pCR rate in patients with MRI-defined poor-risk low rectal cancer. Combining laparoscopic surgery after the intensified neoadjuvant therapy resulted in acceptable postoperative complications. In light of the relatively advanced disease and short chemoradiotherapy-to-surgery interval in this trial, an even higher pCR rate would be achieved when adjusting these factors. A multicenter study is warranted to further evaluate this strategy.

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