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ORIGINAL ARTICLE

Preoperative FOLFOX in resectable locally advanced rectal cancer can be a safe and promising strategy: the R-NAC-01 study

Nobuki Ichikawa[1] · Shigenori Homma[1] · Tohru Funakoshi[2] · Masahiro Hattori[3] · Masanori Sato[3] · You Kamiizumi[4] · Kazuyoshi Omori[5] · Masaru Nomura[5] · Ryoichi Yokota[6] · Masahiko Koike[7] · Hirofumi Kon[7] · Keisa Takeda[7] · Hiroyuki Ishizu[8] · Kunihiro Hirose[9] · Daisuke Kuraya[9] · Takahisa Ishikawa[10] · Ryohei Murata[11] · Hiroaki Iijima[12] · Futoshi Kawamata[1] · Tadashi Yoshida[1] · Yosuke Ohno[1] · Nozomi Minagawa[1] · Norihiko Takahashi[1] · Akinobu Taketomi[1]

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Abstract

Purpose The aim of this study was to assess the safety of rectal surgery after 5-fluorouracil–leucovorin–oxaliplatin chemotherapy (FOLFOX6).

Methods This was a prospective, multicenter study in 11 Japanese hospitals. We included patients with rectal cancer who received 4 courses of modified FOLFOX6 (mFOLFOX6) before rectal surgery and examined the postoperative complication rate, the clinicopathological response, and the rate of chemotherapy-related adverse events (UMIN 000012559).

Results The study population included 36 men and 5 women. The average age of the patients was 60.8 years and the average body mass index was 23.1 kg/m^2. After 4 courses of chemotherapy, grade 2 peripheral nerve disorder and other grade 3 adverse events were seen in 3 patients each (7.3%). Twenty-eight (73.7%) and 8 (21.1%) patients underwent low anterior resection and abdominoperineal resection, respectively. The pelvic nerves were preserved in 35 patients. Surgical morbidity (grade ≥ 3) occurred in 4 patients (10.5%). Anastomotic leakage occurred after surgery in 2 patients (7.1%). No patients achieved pathologically complete remission. However, downstaging of the clinical stage and N stage was seen in 17 (41.5%) and 22 (53.7%) patients, respectively.

Conclusions Surgery after four courses of mFOLFOX6 chemotherapy can be a safe and promising strategy for patients with locally advanced rectal cancer.

Keywords FOLFOX · Neoadjuvant therapy · Rectal cancer · Resection · Downstaging

✉ Shigenori Homma
homma.s@nifty.com

[1] Department of Gastroenterological Surgery I, Graduate School of Medicine, Hokkaido University, N-15, W-7, Kita-ku, Sapporo 060-8638, Japan

[2] Department of Surgery, Asahikawa-Kosei General Hospital, Asahikawa 078-8211, Japan

[3] Department of Surgery, Sapporo Hokuyu Hospital, Sapporo 003-0006, Japan

[4] Department of Surgery, Iwamizawa Municipal Hospital, Iwamizawa 068-8555, Japan

[5] Department of Surgery, Keiwakai Ebetsu Hospital, Ebetsu 069-0817, Japan

[6] Department of Surgery, Sunagawa City Medical Center, Sunagawa 073-0196, Japan

[7] Department of Surgery, KKR Sapporo Medical Center, Toyohira-ku, Sapporo 062-0931, Japan

[8] Department of Surgery, Sapporo-Kosei, General Hospital, Sapporo 060-0033, Japan

[9] Department of Surgery, Tomakomai City Hospital, Tomakomai 053-8567, Japan

[10] Department of Surgery, Abashiri-Kosei General Hospital, Abashiri 093-0076, Japan

[11] Department of Surgery, Otaru General Hospital, Otaru 047-8550, Japan

[12] Clinical Research and Medical Innovation Center, Hokkaido University Hospital, Sapporo 060-8638, Japan

Introduction

Colorectal cancer is the third most common cancer in men and the second most common cancer in women worldwide [1], and is a frequent cause of cancer-related death [2, 3]. Rectal cancer has a poorer prognosis than colon cancer, and it typically manifests as locally advanced disease. The 5-year survival rates of patients with stages II, IIIa, and IIIb rectal cancer are 2.3%, 6.6%, and 10.3% lower than those of patients with stage-matched colon cancer, respectively [4]. To improve the treatment outcomes of rectal cancer, neoadjuvant chemoradiotherapy and adjuvant chemotherapy are often accompanied by total mesorectal excision (TME) [5, 6]. Preoperative radiotherapy with concomitant radiation sensitization using fluoropyrimidine chemotherapy has been reported to prevent local recurrence in patients with locally advanced rectal cancer [7, 8]. However, this regimen does not control distant metastasis and does not prolong survival [7, 8]. Furthermore, radiation therapy may cause sexual or defecation dysfunction [9–11]. In contrast, oxaliplatin has been shown to be of great value in systemically treating colorectal cancer, although its merit as a radiation sensitizer is controversial [12]. The FOLFOX [leucovorin, 5-fluorouracil (FU), and oxaliplatin] regimen, including oxaliplatin in combination with a fluorinated pyrimidine, is beneficial in the treatment of advanced metastatic cancer of both the colon and rectum [13, 14], and its efficacy as a postoperative adjuvant therapy for colon cancer has been proven [15]. Thus, postoperative FOLFOX therapy is often considered as an adjuvant therapy option. We hypothesized that preoperative FOLFOX therapy (in contrast to postoperative FOLFOX therapy) may not only control local recurrence without functional damage from radiotherapy, but also prevent distant recurrence. Preoperative FOLFOX therapy may downstage the cancer and facilitate the surgical handling of the tumor, as well as help to secure the surgical margin. Additionally, effective systemic chemotherapy could suppress preoperative micrometastasis and confer a long-term survival benefit. However, the safety and efficacy of FOLFOX therapy before surgery remain unclear. We, therefore, aimed to assess the safety of surgery after modified FOLFOX (mFOLFOX6) chemotherapy in patients with locally advanced rectal cancer.

Methods

This was an open-label, single-arm, multi-institutional, prospective, phase 2 study with 44 patients who were registered from September 2013 to August 2017. The study protocol received ethical approval from the institutional review boards of Hokkaido University Hospital (no. 013-0187) and each participating hospital. Written informed consent was obtained from all patients.

Patient eligibility

The inclusion criteria for this study were as follows: age 20–75 years; histologically confirmed adenocarcinoma of the rectum; Stage II (cT3-4N0M0) or Stage III (anyTN1-3M0) tumor, as preoperatively assessed by transrectal ultrasound, computed tomography, or magnetic resonance imaging; tumor located at Ra (defined as the rectal segment between the second sacral joint and the peritoneal reflection) [16, 17] or Rb (defined as the rectal segment below the peritoneal reflection) [16, 17]; an Eastern Cooperative Oncology Group performance score of 0–1 [18]; and provided written informed consent. The diagnosis of the node status was confirmed by the attending radiologist based on computed tomography. In addition, evidence of preserved organ functions within 14 days before registration was needed, and was defined as follows: white blood cell, neutrophil, and platelet counts in the peripheral blood of ≥ 3000, ≥ 1500, and $\geq 100{,}000/m^2$, respectively; and serum total bilirubin, aspartate transaminase, alanine transaminase, and creatinine levels of ≤ 2.0 mg/dL, ≤ 100 IU/L, ≤ 100 IU/L, and ≤ 1.5 mg/dL, respectively. Previous surgery, chemotherapy, or pelvic irradiation for the primary rectal lesion were not needed for inclusion. Patients who had a history of colorectal cancer or any other cancer within the past 5 years (except intramucosal carcinoma) were excluded. Patients who were pregnant, breastfeeding, or presented with peripheral neuropathy, infectious disease, mental disorder, or uncontrollable cardiovascular disease (ischemic heart disease, high blood pressure, or arrhythmia) were also excluded. This study was registered in the UMIN Clinical Trials Registry System on 16th December 2013 (UMIN 000012559).

Treatment protocol

Patients received four cycles of mFOLFOX6 and followed by surgery within 4–6 weeks. The clinical responses were regularly assessed after courses of FOLFOX and before the surgery. The protocol-prescribed therapy was terminated in the case of disease progression, non-permissive chemotherapy-related adverse events (as described below), or patient refusal. Surgery after the termination of the protocol was allowed at the discretion of the attending surgeons.

Chemotherapy

Four courses of FOLFOX were planned in this study considering that the onset of tumor response reaches a plateau by 8 weeks, whereas the time of the onset of grade 3 neurotoxicity is greater than 8 weeks [19]. The mFOLFOX6 regimen was administered every 2 weeks. In each cycle, the patients received oxaliplatin (85 mg/m^2) followed by 5-FU (400 mg/m^2) and L-leucovorin (200 mg/m^2) on the first day, and continuous venous infusion of 5-FU (2400 mg/m^2) for the next 2 days. Routine supportive therapy was administered as per the Japanese health insurance rules. The combination of chemotherapy with any other anti-cancer therapy was not allowed. Toxicity was assessed according to the National Cancer Institute Common Terminology for Adverse Events, version 4.0 [20]. Dose reduction of any drug was allowed in the event of grade 4 hematological toxicity. Dose reduction of 5-FU was recommended after grade 3 skin/mucosal disorder. Dose reduction of oxaliplatin was recommended after grade 2 peripheral neural disorder. Discontinuation of oxaliplatin was recommended after grade 3 peripheral neural disorder or after grade ≥ 2 anaphylaxis. The treatment protocol was terminated in the event of grade 4 non-hematological toxicity, a 2-week delay of the chemotherapy due to any toxicity, grade 4 hematological toxicity after a 2-rank dose decrease of all drugs, and any adverse event that was judged as too harmful to allow further therapy.

Surgery

TME or tumor-specific mesorectal excision was prescribed as the surgical procedure. D3 surgery was performed by high ligation of the inferior mesenteric artery with lateral lymph node dissection. In Japan, lateral lymph node dissection is often performed for low rectal cancer instead of neoadjuvant chemoradiotherapy [1]. It is indicated when the lower border of the tumor is located distal to the peritoneal reflection and has invaded beyond the muscularis propria because of the 20.1% incidence rate of lateral lymph node metastasis [4]. However, lateral lymph node dissection was performed according to the decision by the attending surgeon. Though not established as a standard procedure, if informed consent was provided, laparoscopic surgery was also permitted. Postoperative complications were evaluated according to the Clavien–Dindo classification [21].

Endpoints

The primary endpoint of the study was the postoperative complication rate (within 30 days after surgery) in patients who completed the protocol. The secondary endpoints were the clinicopathological response and the rate of neoadjuvant chemotherapy-related adverse events, which were assessed in patients who received more than 1 cycle of neoadjuvant chemotherapy.

Adjuvant therapy

The application and regimen of postoperative chemotherapy were decided by the attending surgeon in each case. The initiation of chemotherapy was allowed from 30 days after surgery; it was recommended that chemotherapy be initiated within 8 weeks after surgery.

Statistical methods

All continuous data are presented as the mean and 95% confidence interval (CI). The rate of grade ≥ 3 postoperative complications, which was the primary endpoint of this study, was compared with the expected complication rate. We further evaluated whether the expected complication rate was within the 95% CI of the actual complication rate. In this study, based on the JCOG0212 study [22], the incidence of grade ≥ 3 postoperative complications was estimated to be 18.8%. Accordingly, 41 patients were necessary to ensure that the incidence of complications would be between 6.8% and 30.8% [within 12% (the 95% CI of the expected 18.8%)]. Thus, we aimed to enroll 45 cases (over 2 years) in anticipation that approximately 10% of cases would be inappropriate.

Results

Patient characteristics

Forty-one patients (male, $n = 36$; female, $n = 5$) were eligible for inclusion in the analysis; three ineligible patients were excluded. The patient characteristics are shown in Table 1. The mean age and body mass index were 60.8 years and 23.1 kg/m^2, respectively. The main locations of the tumors were the Ra in 20 patients and Rb in 21 patients. Thirty-eight cases involved well- or moderately differentiated carcinoma. The clinical stage was II in 9 patients and III in 32 patients. Local invasion was suspected before treatment in five patients. Thirty-eight patients completed the protocol therapy and three patients discontinued treatment (non-permissive adverse event due to chemotherapy, $n = 1$; disease progression, $n = 1$; and patient refusal, $n = 1$) (Fig. 1).

Table 1 Patient characteristics

	Eligible ($n=41$)	Protocol completion ($n=38$)
Age, years	60.8 (58.3–63.3)	60.8 (58.5–63.1)
Sex		
Male	36 (87.8%)	33 (86.8%)
Female	5 (12.1%)	5 (13.1%)
Body mass index, kg/m^2	23.1 (22.0–24.2)	23.2 (22.1–24.3)
Body surface area, m^2	1.76 (1.65–1.76)	1.71 (1.66–1.76)
Performance status		
0	41 (100%)	38 (100%)
Comorbidity		
Diabetes	6 (14.6%)	6 (15.7%)
Hypertension	8 (19.5%)	8 (21.1%)
Hyperlipidemia	3 (7.3%)	3 (7.8%)
Asthma	1 (2.4%)	1 (2.6%)
Cardiomyopathy	1 (2.4%)	1 (2.6%)
Helicobacter gastritis	1 (2.4%)	1 (2.6%)
Ischemic colitis	1 (2.4%)	1 (2.6%)
History of previous abdominal surgery	5 (12.1%)	5 (13.1%)
Allergic history	1 (2.4%)	1 (2.6%)
Clinical stage		
II	9 (22.0%)	8 (21.1%)
III	32 (78.0%)	30 (78.9%)
T stage		
2	3 (7.3%)	3 (7.8%)
3	28 (68.3%)	27 (71.1%)
4a	5 (12.1%)	4 (10.5%)
4b	5 (12.1%)	4 (10.5%)
N stage		
0	9 (22.0%)	8 (21.1%)
1	10 (24.4%)	10 (26.3%)
2	17 (41.5%)	16 (42.1%)
3[a]	5 (12.1%)	4 (10.5%)
Tumor location		
Ra[b]	20 (48.8%)	18 (47.4%)
Rb[c]	21 (51.2%)	20 (52.6%)
Histology		
tub1, tub2	38 (92.7%)	36 (94.7%)
por1	2 (4.9%)	1 (2.6%)
Unknown (group 5)	1 (2.4%)	1 (2.6%)

[a]N stage 3 indicates lymph node metastasis in lateral lesions or at the root of the inferior mesenteric artery

[b]Ra indicates the rectum between the second sacral joint and the peritoneal reflection

[c]Rb indicates the rectum below the peritoneal reflection

Adverse events from preoperative chemotherapy

Grade 2 peripheral nerve disorders were seen in three patients (7.3%). Grade 3 nausea after chemotherapy was seen in one patient (2.4%). Grade 4 infusion port infection (catheter-related infection) occurred in one patient, after which septic shock and acute renal failure were observed. With the exception of one patient with febrile neutropenia, there were no grade ≥ 3 hematotoxicity (Table 2). There were no complications related to the primary tumor that resulted in the need for emergency surgery during the preoperative chemotherapy period.

Surgery

For the assessment of the primary endpoint, 38 patients who completed the protocol therapy were included. Twenty-eight (73.7%), 1 (2.6%), 8 (21.1%), and 1 (2.6%) patients underwent low anterior resection, Hartmann's procedure, abdominoperineal excision, and total pelvic exenteration, respectively. D3 lymph node dissection was performed for all proximal lesions (high-ligation of the inferior mesenteric artery) and in 10 lateral lesions (26.3%). Extended excision of the surrounding organs and total pelvic nerve preservation were performed in 2 (4.9%) and 35 (92.1%) patients, respectively. Laparoscopic surgery was performed in 35 patients (92.1%) (Table 3).

Postoperative complications

Surgical morbidity occurred in 11 patients (28.9%), and grade ≥ 3 morbidities (Clavien–Dindo classification [21]) occurred in 4 patients (10.5%). Complications following surgery included anastomotic leakage in 2 patients (7.1%) and ileus in 5 patients (13.1%) (Table 4). The enrollment target to ensure that the complication rate would fall between 6.8% and 30.8% (the expected complication rate was 18.8% [22]; thus its 95% CI was within 12%) was 41 patients. The actual number of patients who were eligible for this primary endpoint was 38. However, the rate of grade ≥ 3 postoperative complications (the primary endpoint of this study) was 10.5% (95% CI 4.1–24.1%), and the expected complication rate was within the 95% CI. This implies that the postoperative complication rate in the current study was not inferior to the expected rate.

Clinicopathological response

Seventeen patients (41.5%) were downstaged by neoadjuvant chemotherapy. The T grade was downstaged in 14 patients (34.1%). Surrounding organ invasion was suspected in 5 patients prior to chemotherapy, and 4 patients with differentiated carcinoma completed the protocol; extended excision of the surrounding organs was prevented in 2 of these patients and R0 resection was achieved in T3, while 1 patient received extended excision of the surrounding organs and was proved to be downstaged to T3 based on pathological findings and 1

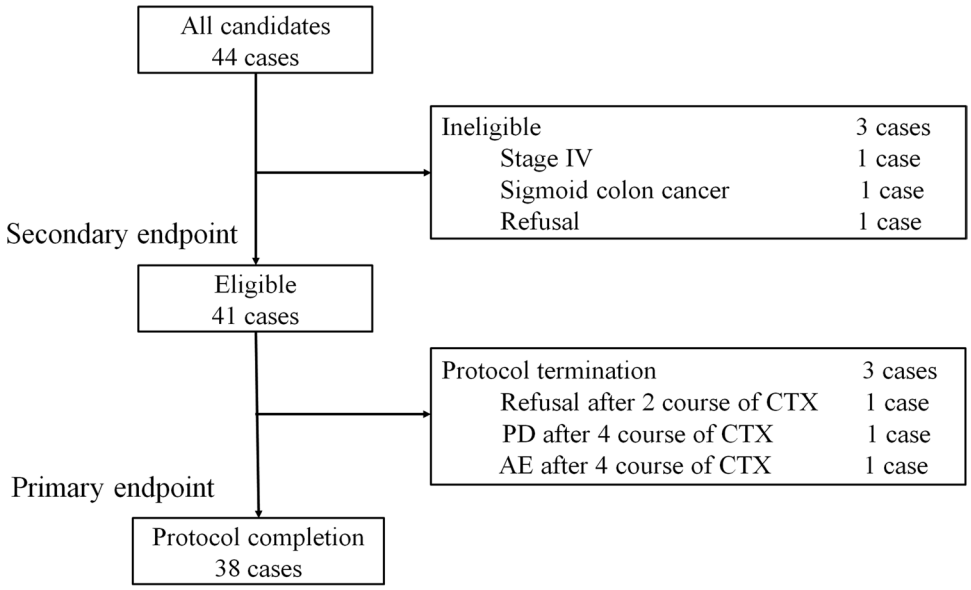

Fig. 1 Flowchart of patient participation. *CTX* preoperative chemotherapy, *PD* progressive disease, *AE* adverse event

Table 2 Details of chemotherapy-related adverse events

Performance status after chemotherapy	0	1	2	3
	37 (90.2%)	4 (9.8%)	0	0
Adverse event	Grade 1	Grade 2	Grade 3	Grade 4
White blood cell count decreased	5 (12.1%)	3 (7.3%)	0	0
Neutrophil count decreased	7 (17.0%)	7 (17.0%)	0	0
Anemia	7 (17.0%)	0	0	0
Platelet count decreased	0	0	0	0
Blood bilirubin increased	1 (2.4%)	0	0	0
Aspartate aminotransferase increased	16 (39.0%)	0	0	0
Alanine aminotransferase increased	19 (46.3%)	1 (2.4%)	0	0
Alkaline phosphatase increased	9 (22.0%)	0	0	0
Creatinine increased	5 (12.1%)	0	0	0
Febrile neutropenia	0	0	1 (2.4%)	0
Malaise	5 (12.1%)	1 (2.4%)	0	0
Diarrhea	5 (12.1%)	0	0	0
Constipation	5 (12.1%)	3 (7.3%)	0	0
Nausea	9 (22.0%)	2 (4.9%)	1 (2.4%)	0
Vomiting	2 (4.9%)	2 (4.9%)	0	0
Anorexia	10 (24.4%)	2 (4.9%)	1 (2.4%)	1 (2.4%)
Alopecia	2 (4.9%)	0	0	0
Palmar-plantar erythrodysesthesia syndrome	5 (12.1%)	0	0	0
Dysgeusia	4 (9.8%)	2 (4.9%)	0	0
Anaphylaxis	1 (2.4%)	0	0	0
Peripheral sensory neuropathy	19 (46.3%)	3 (7.3%)	0	0
Mucositis oral	6 (14.6%)	0	0	0
Lower gastrointestinal hemorrhage	2 (4.9%)	0	0	0
Chest pain—cardiac	1 (2.4%)	0	0	0
Epistaxis	1 (2.4%)	0	0	0
Catheter-related infection	0	0	0	1 (2.4%)

Table 3 Surgical procedures

Procedures	
Anterior resection	28 (73.7%)
With diverting ileostomy	12 (34.2%)
Without ileostomy	16 (42.1%)
Hartmann's operation	1 (2.6%)
Abdominoperineal resection	8 (21.1%)
Total pelvic exenteration	1 (2.6%)
D3 lymph node dissection	
High ligation	38 (100%)
Lateral lymph-node dissection[a]	10 (26.3%)
Anastomosis	
Double-stapling technique	25 (89.3%)
Colon anal anastomosis	3 (10.7%)
Combined resection[b]	2 (4.9%)
Pelvic nerve	
Combined resection	2 (4.9%)
Preservation	35 (92.1%)
Laparoscopic surgery	35 (92.1%)
R0 resection	38 (100%)
Operative time, min	322 (281–362)
Blood loss, mL	158 (51–264)
Transfusion	2 (4.9%)

[a]Two patients underwent lateral lymph node dissection on both sides

[b]Including 1 patient who underwent total pelvic exenteration

Table 4 Postoperative complications

Morbidity	All	Grade 3 or higher
All morbidity (cases)	11 (28.9%)[a]	4 (10.5%)
Acute circulatory failure	0	0
Wound infection	0	0
Ileus	5 (13.1%)	1 (2.6%)
Anastomotic leakage	2 (7.1%)	2 (7.1%)
Sepsis	2 (4.6%)	0
Hemoglobin decline	0	0
Others	6 (15.7%)	1 (2.6%)
Acute renal failure	1 (2.6%)	0
Neurogenic bladder	1 (2.6%)	0
Ileal duct ischemia	1 (2.6%)	0
Epididymitis	1 (2.6%)	0
Peristomal abscess	1 (2.6%)	1 (2.6%)
Chylous ascites	1 (2.6%)	0

[a]Plural morbidities occurred in three patients

patient received extended excision of the surrounding organs with R0 resection in T4b. Another patient who had been diagnosed with poorly differentiated adenocarcinoma with invasion to the seminal vesicle in pre-chemotherapy assessment experienced disease progression with the protocol termination. The N grade was downstaged in 22 patients (53.7%). The pathological responses were Grade 0, 1a, 1b, and 2 in 3 (7.3%), 21 (51.2%), 10 (24.4%), and 6 (14.6%) patients, respectively. No patients showed a pathological complete response (pCR) (Table 5).

Table 5 Clinicopathological responses of the patients

Pathological stage	
I	8 (19.5%)
II	15 (36.6%)
III	18 (43.9%)
Pathological T stage	
1	1 (2.4%)
2	12 (29.2%)
3	25 (61.0%)
4a	1 (2.4%)
4b	2 (4.9%)
Pathological N stage	
0	23 (56.0%)
1	10 (24.4%)
2	4 (9.8%)
3	4 (9.8%)
Down stage	17 (41.5%)
Down T stage	14 (34.1%)
Down N stage	22 (53.7%)
Clinical response (primary lesion)	
CR	0
Non-CR-PD	41 (100%)
PD	0
Clinical response (comprehensive assessment)	
CR	0
PR	13 (31.7%)
Non-CR-PD	25 (61.0%)
SD	2 (4.9%)
PD	1 (2.4%)
New lesion	0
Pathological response	
0	3 (7.3%)
1a	21 (51.2%)
1b	10 (24.4%)
2	6 (14.6%)
3	0
4	0
Unknown	1 (2.4%)

CR complete response, *PD* progressive disease, *PR* partial response, *SD* stable disease

Discussion

In this study, we demonstrated that rectal resection after preoperative FOLFOX therapy in locally advanced rectal cancer could be performed safely. The incidence of

grade ≥ 3 postoperative complications, which was the primary endpoint of this study, was 10.5% (95% CI 4.1–24.1%). This incidence rate was acceptable as per the expected complication rate of the JCOG0212 study. The JCOG0212 study assessed the outcomes of total mesenteric excision with or without lateral lymph node dissection (without any neoadjuvant therapy) in 701 cases of rectal cancer, and the rate of grade ≥ 3 postoperative complications was 18.8% in all cases [22]. The results of the current study were in line with previous reports regarding the safety of preoperative FOLFOX-based chemotherapy, in which the rates of grade ≥ 3 postoperative complications were 9.6% [23] and 11.6% [24], respectively. Qin et al. reported that the rate of anastomotic leakage in surgery after 4–6 courses of preoperative FOLFOX was significantly lower than that after preoperative chemoradiation [25]. The damage to normal tissues caused by radiotherapy has been reported to be different from that caused by FOLFOX [26]. Moreover, chemoradiation might have a greater influence on delayed wound healing [27, 28]. Thus, preoperative FOLFOX-based chemotherapy might be a safer choice in terms of operative complications.

In the current study, R0 resection was achieved in all patients who completed the protocol. The reduction in tumor volume by neoadjuvant chemotherapy may assist in extending the surgical margins and facilitate the surgical procedures. Moreover—correlated with the findings of this report—Deng et al. reported that the rate of downstaging from T4b by chemotherapy was equivalent to that seen with chemoradiotherapy (40% in 5 cases after neoadjuvant FOLFOX and 57% in 14 cases after 5-FU-based chemoradiotherapy) [29]. Thus, the mass reduction achieved by neoadjuvant chemotherapy may facilitate surgical treatment. However, in this study, 1 patient who had been diagnosed with poorly differentiated adenocarcinoma experienced disease progression with the termination of the protocol. This patient underwent abdominoperineal resection but R0 resection could not be achieved. Poorly differentiated adenocarcinoma has been reported to have a poor prognosis in colorectal cancer patients, even after adjuvant FOLFOX therapy [15]. Thus, neoadjuvant chemotherapy should not be indicated for or administered to patients with poorly differentiated adenocarcinoma.

Protocol terminations for reasons other than disease progression were experienced in two patients (4.9%), and of in three patients experienced a total of five adverse events classified as grade 3 or 4 (7.3%). The tolerability and feasibility were acceptable in comparison to a study of 3 months of adjuvant FOLFOX, in which 9% of the patients required protocol termination and 38% developed grade 3 or 4 adverse events [30]. No patients experienced grade 3 peripheral neuropathy after 4 courses of FOLFOX, which is consistent with previous reports demonstrating that the onset of grade 3 neurotoxicity occurred after more than 8 weeks [19], although a follow-up study examining patient satisfaction is needed. Other grade ≥ 3 adverse events were observed in 3 patients (febrile neutropenia, nausea, anorexia and infusion port infection), and there was only one instance in which the protocol treatment was terminated due to an adverse event. Preoperative FOLFOX therapy may be considered a tolerable treatment, and infusion port infection may be prevented by the alternative use of CapeOX therapy, which is reported to be as effective as FOLFOX therapy [31, 32].

The strength of our study lies in its multicenter nature. In addition, the most remarkable oncological finding in this study was that N stage disease was downstaged in 53.7% of the patients, and the proportion of N0 patients increased by 36.0%. Similarly, in previous studies, downstaging from a node-positive to a node-negative status was reported in 40.7% [33] and 66.6% [32, 34] of patients, and Schreg et al. reported the long-term merit of neoadjuvant chemotherapy including oxaliplatin in terms of local control, including lymph node metastasis [33]. It has been reported that neoadjuvant FOLFOX increases the proportion of node-negative patients equivalently to neoadjuvant chemoradiotherapy [29]. Thus, since neoadjuvant chemotherapy may control lymph node metastasis comparably to chemoradiotherapy, oxaliplatin-based chemotherapy may be an alternative to neoadjuvant chemoradiotherapy. If neoadjuvant chemotherapy can control potential metastasis in lateral lesions without the need for neoadjuvant chemoradiotherapy and lateral lymph node dissection, it would be a promising strategy. However, the present study was associated with a potential limitation regarding the method by which the node status was diagnosed. Although lymph node metastasis was carefully diagnosed by the attending radiologist each case, there were no uniform criteria or prescribed modalities.

No patients showed a pCR in this study, which is consistent with the reported pCR rate of only 6.7% after 6 cycles of FOLFOX [34]. In another study, a pCR rate of 11.9% was reported after 6 cycles of FOLFOX [23]. However, in that report, the proportion of clinical progressive disease increased from 2.1 to 7.3%, with 2 prolonged courses of chemotherapy (4–6 cycles) [23]. Thus, 4 courses of FOLFOX could potentially provide a suitable benefit–risk ratio. In another report, the pCR rates of neoadjuvant chemoradiotherapy and FOLFOX alone were 14.0% and 6.6%, respectively [29]. Considering this finding, it is possible that neoadjuvant FOLFOX may not be associated with a higher pCR rate than neoadjuvant chemoradiotherapy. However, there seem to be differences between neoadjuvant chemoradiotherapy and systemic chemotherapy with regard to the degree of correlation between the prognosis and the pCR rate, despite the fact that a pCR is a well-known and frequently used prognostic factor [35]. In fact, the rate of

downstaging, which is another prognostic factor [36], was similar between chemoradiotherapy and FOLFOX, despite the fact that FOLFOX was associated with a lower pCR rate [25].

The long-term oncological outcomes and issues such as quality of life factors, including the defecation, urinary, and sexual functions, have not been assessed and will be assessed in our subsequent study. However, Schreg et al. reported that the 4-year overall and disease-free survival after neoadjuvant FOLFOX and surgery were 91.6% and 92%, respectively, in patients with locally advanced rectal cancer, including 72% of stage III patients [33]. Based on this finding, neoadjuvant chemotherapy is attracting much attention. Furthermore, chemotherapy can influence immune cell profiles [37]. Since FOLFOX may enhance antitumor immunity via the suppression of Tregs [38], preoperative chemotherapy might suppress preoperative micrometastasis and confer a long-term survival benefit.

The current study was associated with some limitations including the single-arm study design and by the relatively small study population. Future randomized controlled studies are needed to confirm these preliminary results. However, since reports regarding the safety and efficacy of neoadjuvant therapy (especially with FOLFOX alone) prior to surgery are limited, the current study assumes particular importance. Additionally, the data in this study were mainly acquired from general hospitals and reflect a genuine trend in the surgical outcomes in Japanese general hospitals. Finally, we conclude that surgery after 4 courses of mFOLFOX6 chemotherapy for patients with locally advanced rectal cancer can be performed safely, and that this novel approach is a promising therapeutic strategy for rectal cancer.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in association with the present study.

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