Original Study

Neoadjuvant Chemotherapy With mFOLFOXIRI Without Routine Use of Radiotherapy for Locally Advanced Rectal Cancer

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Abstract

The efficacy of preoperative chemotherapy with mFOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan) in 106 enrolled patients with locally advanced rectal cancer in a phase II trial was explored. The endpoints included tumor downstaging to $ypT_{0\text{-}2}N_0M_0$, pathologic complete response rate, disease-free survival rate, and safety. The pathologic complete response and tumor downstaging rates were 20.4% and 42.7%, respectively. Neoadjuvant chemotherapy with mFOLFOXIRI and selective radiation did not compromise outcomes in locally advanced rectal cancer.

Introduction: Although neoadjuvant chemo-radiotherapy (CRT) achieves low local recurrence rates in locally advanced rectal cancer (LARC), it raises a lot of concerns about long-term anal and sexual functions. We explored the efficacy of preoperative chemotherapy with mFOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan) in patients with LARC. **Patients and Methods:** Patients with LARC evaluated by pelvic magnetic resonance imaging (MRI) were enrolled in this trial. All received 4 to 6 cycles of mFOLFOXIRI. MRI was performed to assess clinical response after chemotherapy. Patients with mesorectal fascia-positive or ycT4a/b after re-evaluation would receive radiation before surgery, whereas responders would have immediate total mesorectal excision (TME). Adjuvant chemotherapy with mFOLFOX6 (folinic acid, 5-fluorouracil, and oxaliplatin) was recommended. The primary endpoint was the proportion of tumor downstaging to $ypT_{0\text{-}2}N_0M_0$. The secondary endpoints were pathologic complete response rate (pCR), 3-year disease-free survival rate, and safety. **Results:** Overall, 106 patients were enrolled and received neoadjuvant mFOLFOXIRI chemotherapy. A total of 103 participants underwent TME surgery. Among 103 patients who completed at least 4 cycles of preoperative chemotherapy, 2 received short-term radiation before TME, and 12 underwent long-term CRT after MRI evaluation. The pCR rate was 20.4%, and the tumor downstaging rate was 42.7%. Among patients without preoperative long-term radiotherapy, the pCR rate and tumor downstaging rate were 17.4% and 41.3%, respectively. Among the per-protocol population, the tumor downstaging rate was 48.1%, and the pCR rate was 20.3%. The chemotherapy-related toxicity was well-tolerated. **Conclusion:** Neoadjuvant chemotherapy

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with mFOLFOXIRI and selective radiation does not seem to compromise outcomes in LARC. It could be a reasonable alternative to CRT in previously untreated patients with LARC.

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Introduction

Neoadjuvant therapy that is comprised of preoperative fluoropyrimidine with concurrent radiotherapy followed by total mesorectal excision (TME) surgery is the standard treatment for patients with stage II/III rectal cancer.[1-3] Evidence suggests that preoperative chemo-radiotherapy (CRT) significantly reduces the risk of local recurrence compared with postoperative CRT.[4] However, the toxicities caused by radiation are still one of the main concerns. Moreover, about 30% of patients still develop distant metastasis, which remains the main obstacle for improving survival.[5,6]

Studies have reported a high response rate and favorable outcomes with FOLFOX (folinic acid, 5-fluorouracil, and oxaliplatin) before CRT.[7,8] Neoadjuvant chemotherapy alone also showed promising results in previous studies.[9,10] The Neoadjuvant FOLFOX6 Chemotherapy With or Without Radiation in Rectal Cancer (FOWARC) study demonstrated that preoperative mFOLFOX6 chemotherapy alone could achieve a similar downstaging (ypT0-2N0M0) proportion of 35% compared with fluorouracil radiotherapy in patients with rectal cancer.[11]

In the era of TME, it is evident that the long-term (10 years) cumulative incidence of local recurrence is about 11% with surgery alone.[12,13] In this scenario, the addition of radiotherapy does not exhibit an obvious survival benefit, but rather it is associated with safety concerns such as higher rates of incontinence, anal mucous loss, sexual dysfunction, and bowel dysfunction.[14,15] To omit radiotherapy and avoid the toxicities of radiation without compromising local control, intensifying preoperative chemotherapy would be an option. It is also evident that FOLFOXIRI, a triplet regimen composed of folinic acid, 5-fluouracil, oxaliplatin, and irinotecan, has a higher response rate in metastatic colorectal cancer than that of a doublet regimen.[16-18] Based on these results, as well as our own experience in treating metastatic colorectal cancer with FOLFOXIRI,[19] we hypothesized that neoadjuvant mFOLFOXIRI would further improve the efficacy of the tumor downstaging rate to avoid more radiation. Moreover, it is possible that earlier introduction of full-dose chemotherapy might improve distant control.

Materials and Methods

Study Design

The FORTUNE study was a prospective single-arm phase II study, and its protocol was approved by the central ethics committee of The Sixth Affiliated Hospital of Sun Yat-sen University (Guangzhou, China). The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. All study participants provided written informed consent.

Eligibility

Eligible patients were 18 to 70 years old with pathologically confirmed rectal adenocarcinoma and no previous treatment. All patients had baseline staging that include contrast-enhanced computed tomography scan of the chest, abdomen, and pelvis to rule out metastatic disease, and contrast-enhanced pelvic magnetic resonance imaging (MRI) to define local clinical stage, including location, tumor size, the involvement of lymph nodes, and extra mucosa venous infiltration. Endorectal ultrasonography was used if MRI was not allowed. Participants with tumors that were clinically confirmed to be stage II (T3-4N0) or stage III (T1-4N1-2), and a distal edge located < 12 cm from the anal verge were enrolled in the study. A positive lymph node was defined as ≥ 0.8 cm in short diameter or irregular shape on imaging. Patients needed to have an Eastern Cooperative Oncology Group performance status ≤ 1 and adequate hematologic, liver, and renal function. Patients with metastatic disease, intestinal obstruction or perforation, prior radiotherapy or chemotherapy, presence of other cancers, clinically significant cardiac disease, and known peripheral neuropathy were excluded.

Treatment

Neoadjuvant Chemotherapy. All enrolled patients received mFOLFOXIRI (irinotecan 150-165 mg/m^2 on day 1, oxaliplatin 85 mg/m^2, and leucovorin 400 mg/m^2 followed by 48-hour continuous intravenous infusion of 5-fluorouracil 2800 mg/m^2) as initial treatment every 2 weeks for 4 to 6 cycles, solely dependent on the patient's tolerance and the doctor's decision. Toxicity was assessed after each 2-week cycle according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Granulocyte colony stimulating factor was administered prophylactically when grade 3 or grade 4 neutropenia occurred for one time.

Re-staging After Neoadjuvant Chemotherapy. Pelvic MRI was performed to access clinical response after 4 and/or 6 cycles of neoadjuvant chemotherapy, and the re-staging after neoadjuvant chemotherapy was defined as the ycTNM stage. Any degree of primary tumor shrinkage without distant metastases was defined as clinical response. For patients who showed tumor shrinkage with ycT0-3 without mesorectal fascia (MRF) involved after 4 to 6 cycles of chemotherapy, surgery would be recommended. Clinical T4 stage or MRF-positive were defined as high risk factors. Any evidence of primary tumor progression, high-risk factors after neoadjuvant chemotherapy with positive MRF, or ycT4a/b was an indication for radiotherapy. Long-term radiotherapy was delivered at 1.8 to 2.0 Gy daily for 5 days per week for a total of 23 to 28 fractions over 5 to 6 weeks, and a total dose of 46.0 to 50.4 Gy. During long-term radiotherapy, mFOLFOX6 was given as concurrent treatment. Short-term radiation was delivered at 5 Gy daily continuously for 5 days.

Surgery. For patients with tumor shrinkage without high-risk factors, TME was performed 3 weeks after the final cycles of mFOLFOXIRI. If the patients received long-term chemoradiation, surgery was scheduled for 6 to 8 weeks after completion of chemoradiation. If short-term radiation was added, TME should be performed within 1 week after radiation. Creation of a temporary diverting ostomy was at the discretion of the surgeon.

Pathologic Analysis

Pathologic reports should contain the tumor type and extension, proximal and distal resection margins, circumferential resection margin, tumor regression grade (American Joint Committee on Cancer [AJCC]), and lymph node status. Pathologic complete response (pCR) was defined as no evidence of residual tumor cells in the primary site and resected lymph nodes of the operative specimens. Tumor regression grade (TRG) after neoadjuvant treatment was evaluated using the criteria developed by the AJCC and the College of American Pathologists, defined as follows: 0 (complete response), no viable cancer cells; 1 (moderated response), single or small groups of cancer cells; 2 (minimal response), residual cancer outgrown by fibrosis; and 3 (poor response), minimal or no tumor response, extensive residual cancer.

Postoperative Adjuvant Treatment

For patients who received mFOLFOXIRI alone preoperatively, 6 to 8 cycles of mFOLFOX6 would be recommended postoperatively. However, if the surgery was not an R0 resection, postoperative chemoradiation would be indicated. For patients who had received long-term CRT before surgery, 6 months of perioperative treatment would be given.

Surveillance

After completion of all treatments, patients without disease recurrence had symptom assessment and physical examination every 3 months in the first 2 years and at least every 6 months thereafter. Contrast-enhanced computed tomography scan of the chest/abdomen and pelvis and pelvic-enhanced MRI were performed every 6 months in the first 2 years and annually thereafter. Colonoscopy was performed annually.

Primary and Secondary Study Endpoints

The primary endpoint is the proportion of tumor downstaging, which is defined as ypT0-2N0M0. A pCR was defined as absence of viable tumor cells in both the primary tumor and in the lymph nodes (ypT0N0). All resection specimens were examined on the basis of a standardized protocol that included TNM classification according to the AJCC-International Union Against Cancer (7th edition). Secondary endpoints included pCR, R0 resection, sphincter preservation, safety, locoregional recurrence, disease-free survival (DFS), distant metastases, and overall survival.

Statistical Analysis

This is a single-arm study, and the primary endpoint was tumor downstaging (ypT0-2N0M0) proportion. According to our previous study, neoadjuvant treatment with CRT led to about 35% of tumor downstaging.[5] We hypothesized that mFOLFOXIRI would further improve the proportion of tumor downstaging to 50%. With a 2-sided type I error of 0.05 and a power of 80%, and with 18% of dropout rate taken into account, the intended number of patients was 100. All statistical analyses were conducted with SPSS 23.0 software.

All patients enrolled in the study (the intention-to-treat population) were included in the clinical response analysis and overall survival analysis. The pathologic response was evaluated among patients who had received surgery. The per-protocol population was defined as all patients who received preplanned treatment and surgery. Only the patients who achieved R0 resection were included in the DFS assessment. All patients who received at least 1 cycle of chemotherapy were included in the safety analysis.

Results

Baseline Characteristics

Between August 2014 and September 2016, 106 patients were recruited. Patient baseline characteristics are listed in Table 1. The median age was 48 years, and the group included 15.1% of patients in stage II, 51.9% in stage IIIB, and 33.0% in stage IIIC. According to the tumor location, the demographic and disease characteristics of patients with tumor located > 5 cm and within 5 cm from the anal verge are listed in Table 2.

Treatment Administration and Imaging Evaluation

All 106 patients received at least 4 cycles of mFOLFOXIRI. After re-evaluation, no disease progression was observed during treatment among the patients. All patients showed varying degrees of tumor shrinkage with imaging evaluation. The clinical response rate achieved was 100%.

After neoadjuvant treatment, all patients received MRI imaging evaluation and re-staging (Figure 1). Among the 13 patients with cT4 disease only, 5 patients remained with ycT4 disease after neoadjuvant treatment, and in the 14 patients who were MRF-positive, 5 were still MRF-involved after MRI re-assessment. In the 17 patients with 2 risk factors, 8 patients were still in the ycT4 stage and MRF-positive, whereas another 6 patients had tumor downstaging to ycT3 but remained MRF-involved (Figure 2). Overall, there were 24 patients with high-risk factors after neoadjuvant treatment through imaging evaluation. Theoretically, these 24 patients were assigned to receive radiotherapy before surgery according to the protocol. However, 2 patients withdrew informed consent and refused surgery and further treatment. Only 6 patients received long-term CRT before surgery among the 24 patients with high-risk factors. Five of the 6 patients had tumors located < 5 cm from the anal verge, and 1 had a tumor located 5.4 cm from the anal verge. Among these 6 patients, 5 patients had anal preservation, and 1 patient with a tumor located 1 cm from the anal verge received Miles' surgery. Sixteen patients underwent TME after assessment. Among the 16 patients, 11 had middle or upper rectal cancer, including 6 with tumor located > 10 cm from the anal verge, 5 patients with tumor located > 5 cm from the anal verge, and another 5 patients with low-lying (< 5 cm) rectal cancer; 3 of them had Miles' surgery.

After re-assessment, the other 82 patients should undergo surgery immediately according to the protocol (Figure 1). However, 8 patients received radiation before surgery, including long-course CRT in 6 patients and short-course radiation in 2 patients. Seven

Table 1 Patient Demographic and Disease Characteristics (N = 106)

Characteristics	N (%)
Age, y	
Median (range)	48 (19-70)
Gender	
Male	74 (69.8)
Clinical T category	
T2	1 (1.0)
T3	75 (70.8)
T4a	8 (7.5)
T4b	22 (20.7)
Clinical N category	
N0	16 (15.1)
N1	39 (36.8)
N2a	33 (31.1)
N2b	18 (17.0)
cTNM staging	
IIA	15 (14.2)
IIB	1 (0.9)
IIIB	55 (51.9)
IIIC	35 (33.0)
MRF-positive	
Yes	31 (29.2)
Mean tumor length, cm (SD)	5.04 (1.9)
Distance from anal verge, cm	
10-12 cm	11 (10.4)
5-10 cm	36 (34.0)
≤5 cm	59 (55.6)
Median distance, cm	5.5

Abbreviations: MRF = mesorectal fascia; SD = standard deviation.

Table 2 Patient Demographic and Disease Characteristics With Tumors Located > 5 cm and Within 5 cm From the Anal Verge (N = 106)

Variable	Tumor Location	
	> 5 cm From Anal Verge (N = 47), N (%)	≤ 5 cm From Anal Verge (N = 59), N (%)
Age, y		
Median (range)	49 (19-70)	47 (23-70)
Gender		
Male	35 (74.5)	39 (66.1)
Clinical T category		
T2	0 (0)	1 (1.7)
T3	28 (48.9)	47 (79.7)
T4a	7 (14.9)	1 (1.7)
T4b	12 (25.5)	10 (16.9)
Clinical N category		
N0	5 (10.6)	11 (18.6)
N1	10 (21.3)	29 (49.2)
N2a	21 (44.7)	12 (20.3)
N2b	11 (23.4)	7 (11.9)
cTNM staging		
IIA	4 (8.5)	11 (18.6)
IIB	1 (2.1)	0 (0)
IIIB	23 (48.9)	32 (54.2)
IIIC	19 (40.4)	16 (27.1)
Mean tumor length, cm (SD)	5.2 (1.8)	4.8 (1.9)
MRF-positive		
Yes	16 (34.0)	15 (25.4)

Abbreviations: MRF = mesorectal fascia; SD = standard deviation.

of the 8 patients with tumor located < 5 cm from the anal verge and 1 patient with tumor located 5.6 cm from the anal verge achieved anal preservation.

Postoperative Pathologic Response

Among the 106 patients, 103 underwent surgery. Three patients with tumor located within 5 cm from the anal verge withdrew informed consent and refused further treatment. The R0 resection rate was 98.8% (102/103). One patient with initial clinical stage T3N2 showed positive CRM after surgery and received postoperative radiotherapy. The tumor downstaging (to $ypT_{0\text{-}2}N_0M_0$) proportion was 42.7%, and the pCR rate was 20.4% in the whole group (Table 3). According to the definition of TRG, 39 patients achieved TRG 0 to 1, and 64 patients were TRG 2 to 3.

Among patients with neoadjuvant chemotherapy alone (92 patients, including 2 patients with short-course radiotherapy), the pCR rate and the tumor downstaging rate were 17.4% and 41.3%, respectively. Among the 79 patients in the per-protocol population, the tumor downstaging rate was 48.1%, and the pCR rate was 20.3%. Moreover, in the 56 patients with tumors located within 5 cm from the anal verge who underwent surgery, the pCR rate was 21.4% and the tumor downstaging rate was 50.0%. It is worth noting that 11 patients had long-term chemoradiation and 1 received short-course radiotherapy in the group of patients with low-lying rectal cancer, mainly because of the high-risk factors or desire for anal preservation. Another 47 patients with tumor located above 5 cm had a pCR rate of 19.1% and tumor downstaging rate of 34.0%, respectively. Only 2 patients received radiotherapy in this group (Table 4).

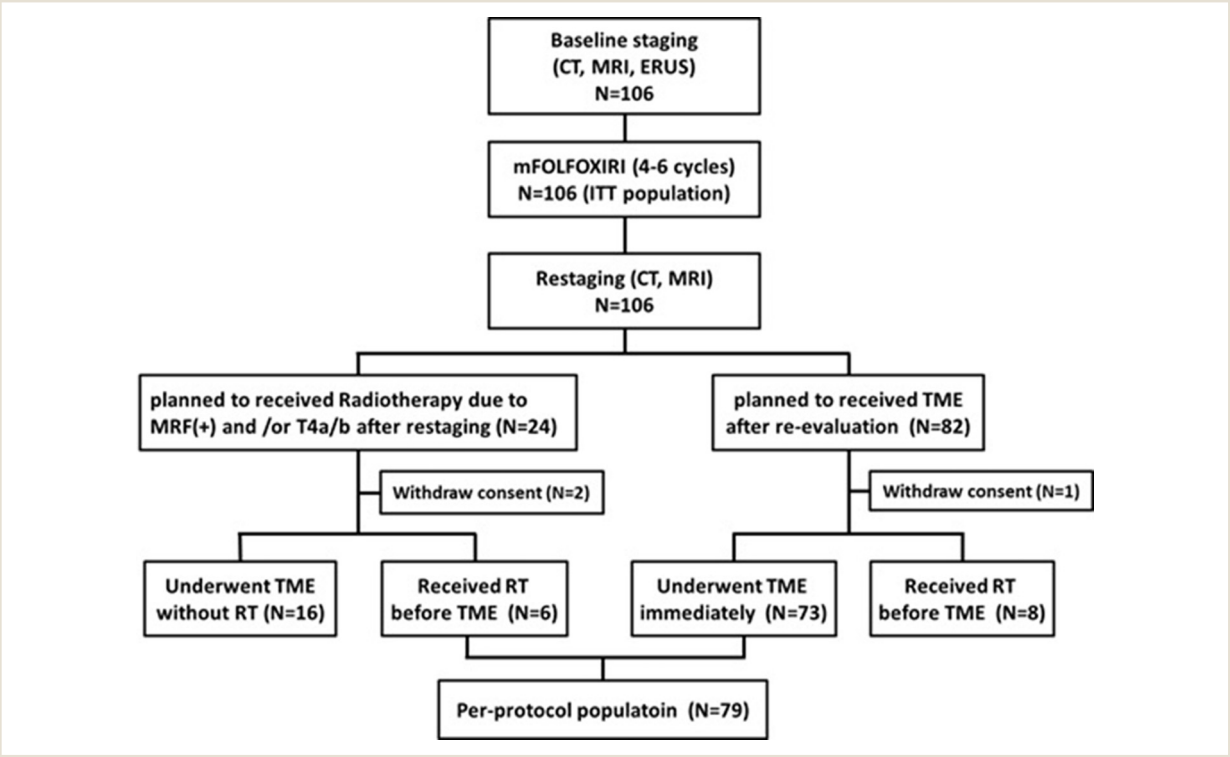
Safety and Postoperative Treatment

There was no mortality during perioperative treatment. The most common grade 3 to 4 toxicities preoperatively were neutropenia (42.5%), nausea (8.5%), and fatigue (3.8%). All the adverse events were tolerable (Table 5).

Discussion

The results of the FORTUNE study showed that neoadjuvant mFOLFOXIRI alone resulted in a pCR rate of 20.4% and a tumor downstaging rate of 42.7% in patients with LARC. To our knowledge, this is the first study to evaluate the efficacy and safety of triplet regimen FOLFOXIRI without routine radiotherapy as neoadjuvant treatment in LARC. Compared with the historic data of CRT, the study showed a tendency toward a higher tumor

Figure 1 Patient Flow Diagram



Abbreviations: CT = computed tomography; ERUS = endorectal ultrasound; FOLFOXIRI = folinic acid, 5-fluorouracil, oxaliplatin, and irinotecan; ITT = intent-to-treat; MRF = mesorectal fascia; MRI = magnetic resonance imaging; RT = radiotherapy; TME = total mesorectal excision.

downstaging rate. It provides data suggestive of the strategy for full-dose enhancive neoadjuvant chemotherapy without routine radiation for LARC.

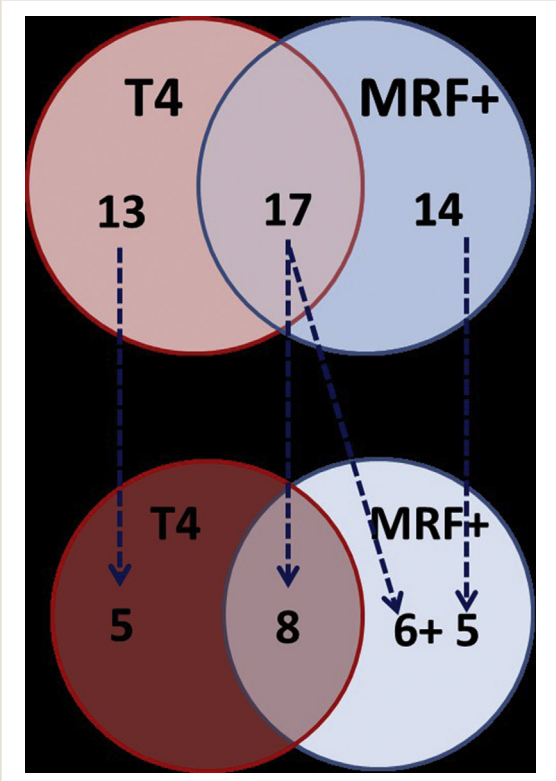
In LARC, the radiation-related toxicities are substantially significant and cannot be underestimated. These include but are not limited to fecal incontinence and sexual dysfunction.[20]

There is evidence that neoadjuvant systemic treatment with selective radiation could be delivered with a trend of improving short-term outcome in patients with rectal cancer. In our previous phase III FOWARC study[11] comparing FOLFOX with or without radiation in rectal cancer, the pCR rate and tumor downstaging rate in the group with mFOLFOX6 chemotherapy alone were 6.6% and 35.5%, respectively. Although the pCR rate was low without radiotherapy, the tumor downstaging rate was similar to that with conventional CRT, and the toxicity was significantly lower. Moreover, it has been recently reported that mFOLFOX6 without radiation did not compromise local control or 3-year DFS. In the current study, patients received a more intensive chemotherapy regimen. The pCR rate increased to 20.4%, which was similar to the pCR rate of patients receiving CRT.[21-24]

In addition to neoadjuvant FOLFOX, several studies have also explored the efficacy of biologic agents in neoadjuvant treatment in LARC. A pilot study assessing the feasibility of achieving R0 resection with neoadjuvant FOLFOX plus bevacizumab in intermediate-risk LARC (N = 32) reported that all patients achieved R0 resection and the pCR rate was 32%. After a median follow-up of 54 months, no local recurrences were observed, and only 12.5% patients experienced lung metastasis,[10] which was quite promising. However, postoperative fistulas were observed in 15% to 28% of patients with bevacizumab, much higher than that of CRT. Moreover, rectal perforation was also reported, which was considered to be related to bevacizumab.[9,25] As for cetuximab, the EXPERT-C trial[26] comparing neoadjuvant CAPOX and radiotherapy with or without cetuximab in patients with high-risk rectal cancer failed to achieve the primary endpoint of pCR (9% vs. 11%). In another phase II trial,[27] cetuximab combined with capecitabine, irinotecan, and radiotherapy led to a pCR rate of only 8%, and the most common adverse event was diarrhea. Hence, both bevacizumab and cetuximab were not recommended for further study use in the neoadjuvant setting.

In our study, we added another cytotoxic agent instead of biologic drugs in neoadjuvant therapy, avoiding the risk of surgical complication caused by bevacizumab.[9,25] With the high quality of TME surgery, downstaging is associated with a high likelihood of resection success and a low chance of local recurrence. The results were very encouraging, with a trend of improvement. Nevertheless, it is worth mentioning that more patients with advanced stage disease were enrolled in this study compared with the FOWARC[11] study. Over 20% of patients enrolled in this study were of clinical stage T4b and 30% of patients were MRF-positive, whereas in the FOWARC study, only 3% to 8% of patients were T4b. Among these patients who should have received radiation, 20 (45.5%)

Figure 2 Assessment With Magnetic Resonance Imaging in Patients With High-risk Factors after Neoadjuvant Chemotherapy



Abbreviation: MRF = mesorectal fascia.

Table 3 Summary of Study Outcomes (N = 103)

Variables	N (%)
Tumor downstaging (to ypT$_{0\text{-}2}$N$_0$M$_0$), %	42.7
pCR rate	21 (20.4)
yp stage	
0-I	44 (42.7)
II-III	59 (57.3)
TRG	
0-1	39 (37.9)
2-3	64 (62.1)
R0 resection	102 (99.0)
R1 resection	1 (1.0)
Anal preservation	89 (86.4)
Ileostomy	87 (84.5)
Laparoscopy surgery	98 (95.1)
Preoperative radiotherapy	14 (13.6)
Long-term CRT	12 (11.7)
Short-course radiotherapy	2 (1.9)
Anastomotic fistula	5 (6.1)

Abbreviations: CRT = chemoradiotherapy; pCR = pathologic complete response; TRG = tumor regression grade.

Table 4 Post-surgery Pathologic Response for Patients With Tumors Located > 5 cm and Within 5 cm From the Anal Verge

Variable	Tumor Location	
	> 5 cm From Anal Verge (N = 47), N (%)	≤ 5 cm From Anal Verge (N = 56), N (%)
pCR rate	9 (19.1)	12 (21.4)
yp stage		
0-I	16 (34.0)	28 (50.0)
II-III	31 (66.0)	28 (50.0)
TRG[a]		
0-1	19 (40.4)	20 (35.7)
2-3	28 (59.6)	36 (64.3)
R0 resection	47 (100)	55 (98.2)
R1 resection	0	1 (1.8)
Anal preservation	47 (100)	42 (75.0)
Anastomotic fistula	3 (7.9)	2 (4.5)
Preoperative radiotherapy		
Long-term CRT	1 (2.1)	11 (19.6)
Short-course RT	1 (2.1)	1 (1.8)

Abbreviations: CRT = chemoradiotherapy; pCR = pathologic complete response; TRG = tumor regression grade.
[a]TRG was evaluated semi-quantitatively on a scale of 0 to 3 (complete to poor response, respectively).

showed obvious response and avoided radiotherapy. These results strengthen the potential of neoadjuvant systemic chemotherapy without radiotherapy as an attractive therapeutic option to minimize the risk of treatment-related toxicities and potentially improve survival outcomes of patients with LARC. Nevertheless, the study requires confirmation for long-term survival outcome, and this is worthy of further investigation.

There are several limitations of this study. First, the study was a single-arm study without a control group. Second, some patients could have been overtreated owing to exposure to irinotecan. Even though the median follow-up period is 16.6 months, the results are immature in terms of recurrence/survival endpoints. Although we did not achieve the pre-specified endpoint, we obtained higher pCR, and our results demonstrate that the damage from radiotherapy could be avoided for some patients with LARC.

Table 5 Summary of Adverse Events

Events	Any Grade N = 106 (%)	Grade 3/4 N = 106 (%)
Neutropenia	85 (80.2)	45 (42.5)
Nausea/vomiting	50 (47.2)	9 (8.5)
Fatigue	90 (84.9)	4 (3.8)
Anemia	55 (51.9)	4 (3.8)
Thrombocytopenia	21 (19.8)	3 (2.8)
Mucositis	54 (50.9)	3 (2.8)
Diarrhea	28 (26.4)	2 (1.9)
Neurotoxicity	14 (13.2)	0 (0)

Conclusion

The neoadjuvant mFOLFOXIRI chemotherapy, with selective use of radiation reserved for non-responders, was a safe and effective treatment strategy for patients with LARC.

Clinical Practice Points

- Neoadjuvant CRT is not preferred in patients with LARC owing to concerns of resulting long-term anal and sexual functions.
- The pCR and tumor downstaging rates were reported to be 20.4% and 42.7%, respectively.
- Neoadjuvant treatment with mFOLFOXIRI may be an alternative option compared with CRT in patients with LARC.

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Disclosure

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