Original Article

Locally advanced rectal mucinous adenocarcinoma: is preoperative radiation necessary?

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Background: Neoadjuvant chemoradiotherapy is recommended for locally advanced rectal cancer, allowing preoperative down-staging of the primary tumor to facilitate complete surgical removal. However, further investigation is warranted for identifying whether radiotherapy is necessary for rectal mucinous adenocarcinoma (RMAC). Thus, this study was designed to explore the relationship between mFOLFOX6 with or without preoperative radiotherapy and therapeutic efficacy in locally advanced RMAC.

Methods: A total of 81 patients were retrospectively enrolled, with MRI-defined clinical stage II/III RMAC received neoadjuvant treatment with mFOLFOX6 alone (group A) or mFOLFOX6 plus radiation (group B), followed by total mesorectal excision. Tumor down-staging and tumor response were assessed based on post-treatment MRI-defined radiographical and pathological findings. Follow-up data were retrieved, and the Kaplan-Meier curve was used to determine the relationship between the 3-year disease-free survival (DFS) and overall survival (OS) in the two groups.

Results: There were no significant differences in the clinical baseline characteristics of patients between group A and group B. The sphincter preservation rate in group B was 60.9%, higher than in group A (20.0%) (P=0.031). The rate of pathological complete response (pCR) was 14.0% in group B, while no patients had pCR in group A (P=0.029), and the tumor response rate in group B was higher than in group A (52.0% *vs.* 16.1%, P=0.001). The 3-year probability of OS in group A and B was 77.4% and 72.0% (P=0.509), and 3-year DFS was 58.1% and 56.0% (P=0.592), respectively.

Conclusions: Neoadjuvant mFOLFOX6-based chemoradiotherapy could be a promising therapeutic option for patients with RMAC, which was associated with a high rate of pCR and sphincter preservation in comparison to treated with mFOLFOX6 alone.

Keywords: Rectal cancer; mucinous adenocarcinoma; magnetic resonance imaging (MRI); neoadjuvant chemoradiotherapy (NCRT)

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Introduction

Neoadjuvant chemoradiotherapy (NCRT) followed by total mesorectal excision (TME) is the standard treatment for locally advanced rectal cancer. The aim of this protocol is to allow preoperative down-staging of the primary tumor to facilitate complete surgical removal (1-3). However, the response to NCRT is variable, with pathological complete response (pCR) rates ranging from 4% to 30%, whereas tumor downstaging occurs in up to 45% (4). It is crucial to stratify patients into those who will benefit from NCRT and those who will not, to optimize strategies for patient-tailored treatment.

Rectal mucinous adenocarcinoma (RMAC) is a histologic subtype, characterized by abundant extracellular mucin that constitutes more than 50% of the tumor volume, and presents approximately 6.2–12.3% of rectal cancers (5,6). Compared with non-RMAC, RMAC is considered a discrete subclass showing aggressive features both biologically and clinically, with a tendency to present with more advanced T and N stages, poorer response to NCRT, and higher rates of metastases (5-8). Some studies suggest patients with RMAC are unlikely to be down-staged after NCRT due to unobvious tumor shrinkage, and with a higher rate of positive circumferential resection margin (9-12), and there is ongoing debate on the exact therapy efficacy of NCRT for RMACs. Modified infusional fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) is a common chemotherapy regimen used as neoadjuvant treatment for locally advanced rectal cancer. Recently, Deng *et al.* alerted that neoadjuvant mFOLFOX6 alone had a lower pCR rate than mFOLFOX6 plus radiation, but there was no significant difference in three-year disease-free survival (DFS) for locally rectal cancers (13,14). However, the value of adding radiotherapy to neoadjuvant chemotherapy in the treatment of patients with RMAC remains under-investigated.

Magnetic resonance imaging (MRI) is widely used to evaluate the preoperative stage (15), and accumulating evidence indicates some radiographical characteristics are associated with the tumor response to neoadjuvant therapy and prognosis (9,16-19). In RMAC, the mucinous component has high signal intensity on T2-weighted images, which is easily identifiable for radiologists, and MRI has been reported to be diagnostically superior to biopsy in the preoperative detection of the mucinous component of rectal cancers (20). The individualized treatment of RMAC patients requires MRI evidence to predict the outcome in advance, and to evaluate the efficacy evaluation of the two neoadjuvant treatment strategies (mFOLFOX6 alone or mFOLFOX6 plus radiation), which could play a key role in assessing tumor characteristics at baseline.

To explore differences between these two neoadjuvant regimens (mFOLFOX6 with or without radiation) in the prognosis of patients with RMAC, we used MRI to evaluate the characteristics of tumors at baseline combined with pathology to determine tumor regression and collected patient information to determine the difference in prognosis brought by these two options. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-817/rc).

Methods

Patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University (No. 2021ZSLYEC-457), and the informed consent requirement was waived due to the retrospective nature of the study.

Patient data were obtained consecutively from the Sixth Affiliated Hospital of Sun Yat-sen University, and those diagnosed with biopsy-proven primary rectal adenocarcinoma between January 2015 and January 2021 were involved. The inclusion criteria were locally advanced disease as determined with baseline MRI (T3-4N_{any}, or T2N1-2); no distal metastasis [M0]; tumors with several high-signal mucus components (greater than 50%) determined by T2WI at baseline (10); completion of neoadjuvant therapy with mFOLFOX6 without radiation (group A) or mFOLFOX6 plus radiation (group B); TME with or without intersphincter resection (ISR) or Miles operation after neoadjuvant therapy; numerous postoperative pathological mucus lakes (greater than 50%); and patients with a total follow-up time exceeding 48 weeks. Patients were excluded from the study if they had a history of other malignant tumors, did not complete neoadjuvant treatment or had other chemotherapy regimens (non mFOLFOX6), had poor quality MRI, were lost to follow-up, or were diagnosed with signet-ring cell carcinoma diagnosis after surgery. The flowchart is showed in *Figure 1*.

MRI acquisition

MRI was conducted using a 1.5-T MR system (Optimal 360, GE Healthcare, Waukesha, Wis) with a phased-array

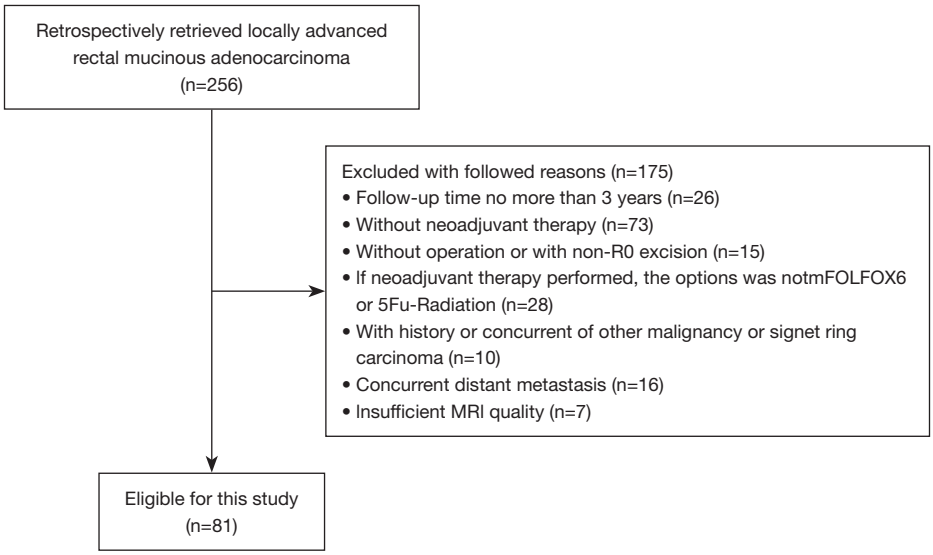

Figure 1 The study flowchart.

body coil (eight-channel phased-array body coil). The standard procedure included coronal, axial oblique, and sagittal T2-weighted sequences, transverse T1-weighted sequence, gadolinium-enhanced T1-weighted sequences, and diffusion-weighted sequence, the details of imaging protocol were previously reported (21).

Evaluation of MRI features

The mesorectal fascia (MRF) tumor involvement status at baseline MRI was assessed based on the shortest distance from the outermost margin of any tumor (the primary mucin pool and/or solid tumor tissue, and/or separate tumor deposit, positive regional lymph node) to the adjacent MRF, and was classified as positive (<1 mm) or negative (≥1 mm) (15-19,22). In addition, the tumor maximal length (TML) and the distance from the inferior part of the tumor to the anal verge (DTA) at baseline MRI were evaluated and were then divided into various groups respectively (TML, <5 or ≥5 cm, and DTA, <5, 5–10, or ≥10 cm).

The MRI-defined T stage at baseline was assessed based on the depth of tumor penetration (soft tissue or mucin) relative to the muscularis propria as follows: T2 (tumor invades muscularis propria but not through), T3 (penetration beyond the muscularis propria), and T4 (involvement of other organs). Signal heterogeneity/high signal intensity on T2WI, irregular contour, and the smallest diameter of regional lymph node ≥6 mm were considered as reliable signs of nodal involvement on MRI. The N stage was classified as follows: N1 (metastasis in one-three regional lymph nodes) or N2 (metastasis in four or more regional lymph nodes). If the smallest diameter of the largest lymph node was <6 mm and no irregular border or mixed signal intensity was observed, the N status at baseline was graded as negative (16-19,22,23).

The above baseline radiographical features were independently analyzed by two gastrointestinal radiologists (reader1# and reader2#, with 6 and 10 years of rectal MRI interpretation experience, respectively). To assess the interobserver reproducibility of the image features, the κ coefficient was calculated, and generally, κ coefficient >0.60 was considered as good agreement in reproducibility.

Neoadjuvant regimen and surgery

Two treatment regimens were enrolled in this study, following the FOWARC clinical trial (13,14). In group A, patients received preoperative treatment with four to six cycles of mFOLFOX6 (85 mg/m^2 of oxaliplatin over 120 minutes and 400 mg/m^2 of leucovorin over 2 hours followed by a 400 mg/m^2 bolus of fluorouracil then a 2,400 mg/m^2 bolus of fluorouracil by a 46- to 48-hour infusion, repeated every 2 weeks). Patients in group B were administered a similar mFOLFOX6 regimen, with concurrent radiotherapy during cycles two to four. Radiotherapy was administered at 1.8–2.0 Gy for 23–

28 fractions over 5–6 weeks and a total dose of 46.0–50.4 Gy. To assess whether the anal sphincter could be preserved, surgical approaches were divided into two categories [preservation approach (TME), or non-preservation approach (Miles or TME + ISR)]. The surgical specimens were subjected to pathological analysis by following the methods described in the American Joint Committee on Cancer (AJCC) TNM staging system (the 7th edition) and Ryan *et al.* (24,25). Pathologically assessed tumor staging (pT0–T4), regional lymph node staging (pN0–N2), and tumor regression grade (pTRG) were collected. All patients were categorized by therapy response based on the TRG into a responsive group (TRG 0 with no viable cancer cells, or TRG 1 with single cells) and a nonresponsive group (TRG 2 with residual cancer outgrown by fibrosis, or TRG 3 with fibrosis outgrown by residual cancer or only with extensive residual cancer) (10).

The pCR was defined as the complete absence of residual tumor cells within the specimen. The MRI-defined tumor and lymph node staging based on pretherapeutic images and the postoperative pathologic staging after neoadjuvant therapy were compared, and the down-staging was evaluated as the therapeutic efficacy. Primary TN down-staging was defined as reductions in T and N stages by at least one level, and the over tumor down-staging was defined as tumor or lymph node down-staging.

Follow-up

A standard follow-up via evaluating the medical imaging or telephone interviews was performed at 3-month intervals for 2 years, then 6-month intervals for 3 years, and 12-month intervals until death. Overall survival (OS) was defined as the interval from surgery to death, and DFS was calculated as the time between surgery and the date of any recurrent disease detection.

Statistical analysis

First, the κ-coefficient was used to evaluate the inter-reader agreement for MRI-defined tumor features (T and N stage, MRF status, classification of DTA, and TML). Pearson's chi-square or Fisher's exact test was used to assess the association between the neoadjuvant therapy regimen (group A and B) and therapeutic efficacy (TN down-staging, responsiveness, and sphincter preservation), or baseline MRI-defined and clinical characteristics. Kaplan-Meier method with univariate log-rank test was used to conduct survival analysis. Analyses were performed using SPSS (version 22.0; SPSS, Chicago, IL, USA). Statistical significance was considered when the two-sided P value less than 0.05.

Results

A total of 81 patients with locally advanced RMAC were enrolled (*Figure 1*) in the analysis of treatment efficacy and 3-year outcomes, including 57 (70.4%) men and 24 (29.6%) women, with a mean age of 51.0±13.7 years (range, 22–78 years). The median follow-up time was 185 weeks (range, 45–318 weeks).

Baseline MRI-defined and postoperative pathological characteristics

Among all participants, there were 29 (35.8%) patients with positive MRF status, 33 (40.7%) with DTA less than 5 cm, and 44.4% of patients were evaluated as TML greater than 5 cm. Of the 22 of all patients who had tumors staged as T4, nodal involvement was observed in 66.7% of patients. Of note, there were no significant differences in T and N staging, MRF status, classification of DTA and TML, sex, baseline CEA level, and BMI (P>0.05) between group A and group B (*Table 1*).

Tumor response and down-staging

Table 2 shows the pathological stage after neoadjuvant therapy and surgery. Univariate analysis showed the tumor response rate in group B was higher than in group A (*Table 3*). Nine patients underwent Miles operation and eight underwent ISR with TME surgery, and the rate of sphincter preservation in the group B was 60.9%, higher than that in group A (20.0%) (P=0.031). While there were no significant differences in T and N down-staging between the two groups (P>0.05), the overall down-staging rate of group B was higher than group A (52.0% *vs.* 16.1%, P=0.001).

3-year survival outcomes

At the 3-year follow-up interval, locoregional recurrence, metastasis, or death as a result of any cause were observed in 35 patients (43.2%), and the total probability of 3-year

Table 1 Patients characteristics

Variable	No. of patients	Group A (n=31)	Group B (n=50)	P value
Age (y)				0.550
<51	41	17 (54.8)	24 (48.0)	
≥51	40	14 (45.2)	26 (52.0)	
Sex				0.926
Men	57	22 (71.0)	35 (70.0)	
Women	24	9 (29.0)	15 (30.0)	
Baseline CEA (ng/mL)				0.476
<5	61	22 (71.0)	39 (78.0)	
≥5	20	9 (29.0)	11 (22.0)	
Baseline MRF status				0.962
Positive	29	11 (35.5)	18 (36.0)	
Negative	52	20 (64.5)	32 (64.0)	
Baseline DTA (cm)				0.341
<5	33	10 (32.3)	23 (46.0)	
5–10	39	16 (51.6)	23 (46.0)	
≥10	9	5 (16.1)	4 (8.0)	
TML (cm)				0.138
<5.0	45	14 (45.2)	31 (62.0)	
≥5.0	36	17 (54.8)	19 (38.0)	
BMI (kg/m^2)				0.201
<22	45	20 (64.5)	25 (50.0)	
≥22	36	11 (35.5)	25 (50.0)	
Baseline T stage				0.332
2	5	1 (3.2)	4 (6.2)	
3	54	19 (61.3)	35 (66.7)	
4	22	11 (35.5)	11 (27.2)	
Baseline N stage				0.626
0	27	11 (35.5)	16 (32.0)	
1	26	8 (25.8)	18 (36.0)	
2	28	12 (38.7)	16 (32.0)	

Data are number of patients, with percentages in parentheses. MRF, mesorectal fascia; DTA, distance from inferior part of tumor to the anal verge; TML, tumor maximal length; BMI, body mass index; group A, mFOLFOX6; group B, mFOLFOX6 plus radiation; CEA, Carcinoma Embryonic Antigen.

Table 2 Tumor postoperative pathologic stage distribution

AJCC pathologic stage	Group A (n=31)	Group B (n=50)	P value
pCR (T0N0M0)	0 (0)	7 (14.0)*	0.086
I	3 (9.7)	6 (12.0)	
T1N0M0	1	1	
T2N0M0	2	5	
II	8 (25.8)	16 (32.0)	
T3N0M0	8	15	
T4N0M0	0	1	
III	20 (64.5)	21 (42.0)	
T0N1M0	0	2	
T0N2M0	1	1	
T1N2M0	0	1	
T2N2M0	2	2	
T3N1M0	8	7	
T3N2M0	8	6	
T4N1M0	1	2	
IV ($T_{any}N_{any}M1$)	0 (0)	0 (0)	

*, P value between group A and group B was 0.029. Group A, mFOLFOX6; group B, mFOLFOX6 plus radiation; AJCC, American Joint Committee on Cancer.

DFS was 56.8% (standard SD: 12.6%). Overall, 21 died during the study, resulting in a total OS of 74.1% (SD: 12.1%). The 3-year probability of OS in groups A and B was 77.4% and 72.0% (P=0.509 by the log-rank test), and 3-year DFS was 58.1% and 56.0% (P=0.592), respectively. No differences in 3-year OS or DFS were detected between the two groups (*Figure 2*).

Agreement of evaluation for MRI-defined features

An acceptable agreement rate of assessment of MRI-defined T, N stage, MRF, and classification of TML and DTA was achieved between the two readers of 87.7% (71/81), 86.4% (70/81), 91.4% (74/81), 90.1% (73/81), and 90.1% (73/81), with a κ coefficient of 0.784 (95% CI: 0.659–0.910), 0.832 (95% CI: 0.734–0.930), 0822 (95% CI: 0.698–0.946), 0.803 (95% CI: 0.675–0.931), and 0.790 (95% CI: 0.655–0.924), respectively (Tables S1-S5).

Table 3 Down-staging, responsiveness by comparing pre-therapeutic MRI-defined stage with post-treatment pathological stage and sphincter preservation

Variable	No. of patients	Group A (n=31)	Group B (n=50)	P value
T down-staging				0.560
Yes	32	11 (35.5)	21 (42.0)	
Non	49	20 (64.5)	29 (58.0)	
N down-staging				0.062
Yes	30	9 (32.1)	21 (55.3)	
Non	36	19 (67.9)	17 (44.7)	
Overall down-staging				0.042
Yes	48	14 (45.2)	34 (59.3)	
Non	33	17 (54.8)	16 (40.7)	
Responsiveness				0.001
Yes	31	5 (16.1)	26 (52.0)	
Non	50	26 (83.9)	24 (48.0)	
Sphincter preservation*				0.031
Yes	16	2 (20.0)	14 (60.9)	
Non	17	8 (80.0)	9 (39.1)	

*, tumors initially located within 5 cm of the anal verge on pretreatment digital rectal examination, and nine patients underwent Miles surgery and eight patients underwent ISR with TME surgery. Group A, mFOLFOX6; group B, mFOLFOX6 plus radiation. ISR, intersphincter resection; TME, total mesorectal resection.

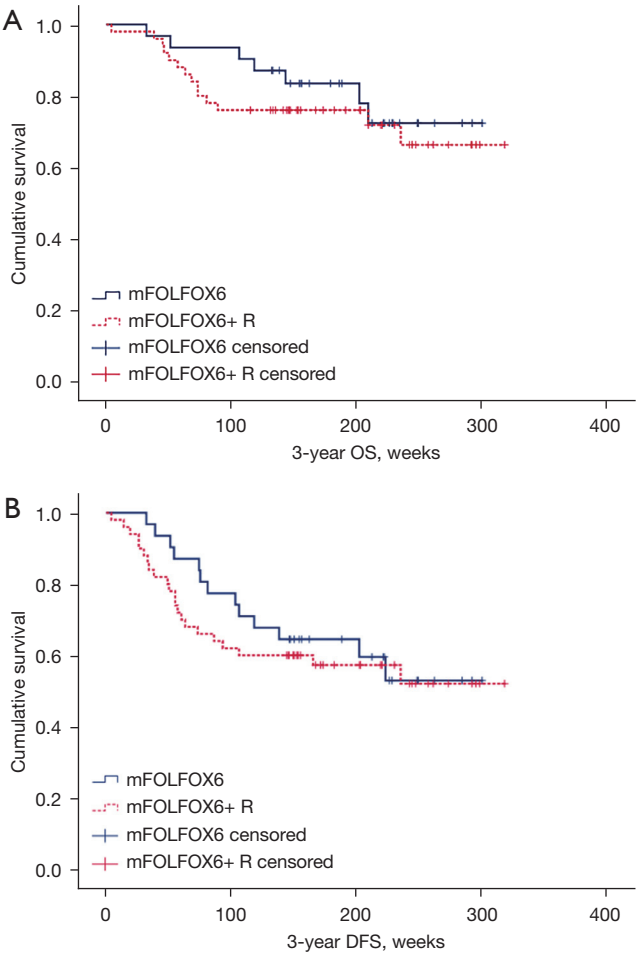

Figure 2 Kaplan-Meier analyses of OS and DFS in group A (mFOLFOX6 without radiation) and group B (mFOLFOX6 plus radiation). (A) OS curve, (B) DFS curve. R, radiation; OS, overall survival; DFS, disease-free survival.

Discussion

Findings from this study suggest the efficacy of mFOLFOX6-based chemoradiotherapy is superior to mFOLFOX6 alone in overall down-staging, tumor response rate, pCR, and sphincter preservation. However, there was no difference in 3-year OS and DFS between the two groups.

The tumor response rate of RMAC patients in the chemoradiotherapy (mFOLFOX6 plus radiation) group was higher than that in the chemotherapy group. Radiation can induce changes in the mucin pool (MP), and the reduction of tumor components in MP could be behind the tumor response (9,17). The phenomenon of MPs devoid of neoplastic cells in surgical rectal carcinomas pre-treated with neoadjuvant therapy was frequently observed, which is not considered part of the pathological tumor regression grade (18,26).

After neoadjuvant treatment, pCR occurred in patients with mFOLFOX6-based chemoradiotherapy, while none of the 31 patients in the chemotherapy group (mFOLFOX6 alone) developed pCR, indicating radiation may play a key role in the neoadjuvant regimen. Our view is similar to that of Deng *et al.* (14), who reported on a rectal non-mucinous adenocarcinoma study. They observed the pCR rate of non-mucinous adenocarcinoma after mFOLFOX6-based chemoradiotherapy was 27.5%, while that of locally advanced RMAC in this study was only 14%. Therefore, in view of the fact that the ratio of RMAC patients achieving pCR was relatively low, whether to recommend the protocol of mFOLFOX6-based radiation to RMAC requires further

discussion.

The significance of mFOLFOX6-based chemoradiotherapy in this study is that it allowed 60.9% of RMAC patients to retain the anal sphincter, compared with only 20% in the mFOLFOX6-alone group. This suggests the addition of radiation may have some effect on down-staging the tumor such that sphincter-preserving surgery can be performed. Compared with the mFOLFOX6 scheme, mFOLFOX6-based radiotherapy may be more suitable for patients with low RMAC within 5 cm from the anal verge. With the development of current technology, laparoscopic intersphincteric resection (ISR) has gradually been accepted as a minimally invasive technique because of its decreased blood loss, reduced incision-related complications, and faster recovery, particularly in low rectum cancers invading the internal sphincter (27,28). Therefore, our studies will need to combine this technical factor and include eligible patients undergoing ISR surgery in the future.

Radiation was not associated with 3-year survival outcomes in RMAC patients in this study, which was similar to the results of Deng *et al.* (13,14). They suggested that non-mucinous adenocarcinoma patients treated with chemotherapy (mFOLFOX6 without radiation) had a similar 3-year DFS probability compared to those with mFOLFOX6-based chemoradiotherapy. Although neoadjuvant treatment can improve outcomes for RMAC patients (29), the OS and DFS probabilities in our study were relatively low, which is in line with previous studies (7,9,11,30). The poor prognosis of RMAC patients suggests a reduced susceptibility or resistance to neoadjuvant treatment, and studies at the molecular level showed this may be attributed to a relative hypoxic state caused by a reduction in blood supply (7,31).

We acknowledge some limitations of our study. First, the design of our single-center study was retrospective. However, all eligible participants were retrieved from a prospective database in our institution. Second, our sample size was not sufficiently large due to the small proportion of mucinous adenocarcinoma. Therefore, the statistical significance of our findings may be insufficient, and further validation in a larger sample size is warranted. Third, the study population only included patients who completed mFOLFOX6 with or without radiation, and did not include other neoadjuvant schemes, which may have resulted in selection bias. Further investigation is required to determine whether other neoadjuvant schemes will affect the prognosis of patients with RMAC.

In conclusion, this study demonstrates mFOLFOX6-based chemoradiotherapy can assist in achieving pCR in RMAC patients. Importantly, it appears promising in allowing sphincter preservation in patients with low RMAC in comparison to those treated with mFOLFOX6 alone. While these findings suggest neoadjuvant mFOLFOX6 without radiation may not be suitable for RMAC patients, further high-quality prospective trials are required.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-817/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-817/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-817/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University (No. 2021ZSLYEC-457), and the informed consent requirement was waived due to the retrospective nature of the study.

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Supplementary

Table S1 MRI-defined T staging by two radiologists

Reader 1	Reader 2			Total
	T2	T3	T4	
T2	5	3	0	8
T3	0	45	1	46
T4	0	6	21	27
Total	5	54	22	81

Note. With κ coefficient, 0.784 (95% CI: 0.659-0.910).

Table S2 MRI-defined N staging by two radiologists

Reader 1	Reader 2			Total
	N0	N1	N2	
N0	23	1	1	25
N1	4	23	3	30
N2	0	2	24	26
Total	27	26	24	81

Note. With κ coefficient, 0.832 (95% CI: 0.734-0.930).

Table S3 MRI-defined DTA status by two radiologists

Reader 1	Reader 2			Total
	1*	2†	3‡	
1*	38	0	0	38
2†	6	35	0	41
3‡	1	1	0	2
Total	45	36	0	81

Note. With κ coefficient, 0.790 (95% CI: 0.655-0.924); DTA, distance from inferior part of tumor to the anal verge; 1*< 5 cm, 2†5-10 cm, 3‡≥10 cm.

Table S4 MRI-defined TML status by two radiologists

Reader 1	Reader 2		Total
	1*	2†	
1*	38	1	39
2†	7	35	42
Total	45	36	81

Note. With κ coefficient, 0.803 (95% CI: 0.675-0.931); TML, tumor maximal length; 1*< 5 cm, 2†≥5 cm.

Table S5 MRI-defined MRF status by two radiologists

Reader 1	Reader 2		Total
	+	–	
+	29	7	36
–	0	45	45
Total	29	52	81

Note. With κ coefficient, 0.822 (95% CI: 0.698-0.946); MRF, mesorectal fascia.

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