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CAPECITABINE, OXALIPLATIN, AND IRINOTECAN (XELOXIRI) AS NEOADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED RECTAL CANCER

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ABSTRACT

Purpose: *This study describes the efficacy and safety of irinotecan and oxaliplatin in combination with capecitabine (XELOXIRI) as a neoadjuvant chemotherapy (NAC) regimen for patients with locally advanced rectal cancer (LARC).*

Methods: *From January 2019 through December 2022, 68 LARC patients treated with XELOXIRI were enrolled in the study. XELOXIRI is administered in a three-week cycle consisting of oxaliplatin 70-110 mg/m2 IV for >120 min on day 1; irinotecan 120-160 mg/m2 IV for 90 min on day 1; and capecitabine 700-1100 mg/m2 orally twice daily for 14 days followed by 7 days off. Sixteen cases were treated with combined radiotherapy, including 8 with long-course radiotherapy and 8 with short-course radiotherapy. The efficacy was evaluated based on pelvic MRI (including TNM stage, CRM, and EMVI status), tumor downstaging rate (to ypT0-2N0M0), pCR rate, R0 resection rate, DFS, and OS, and the safety was assessed according to the incidence of adverse events.*

Results: *Sixty-six people had surgery; the R0 resection rate was 100%, and the rate of anal preservation was 97%. The tumor downstaging rate (to ypT0-2N0M0) in the entire group was 53.0%, and the pCR rate was 12.1%. In the XELOXIRI alone group (N = 47), the tumor downstaging rate was 55.3%, and the pCR rate was 12.8%. In the group receiving radiotherapy (N = 16), the tumor downstaging rate was 56.3%, and the pCR rate was 12.5%. In the whole group, the 3-year DFS was 89.0%, and the 3-year survival rate was 98.5%. The 3-year DFS of the XELOXIRI and XELOXIRI + RT groups was 89.9% and 87.2%, respectively. The most frequent grade 3–4 preoperative toxic reactions were neutropenia (8.8%), diarrhea (4.4%), and anemia (2.9%). All adverse events were tolerable.*

Conclusions: *Neoadjuvant chemotherapy with XELOXIRI appears to be feasible and efficacious for patients with LARC. Although neoadjuvant XELOXIRI alone did not yield our expected pCR rate as NAC for LARC, tumor downstaging, R0 resection, sphincter preservation, local recurrence rate, 3-year DFS, OS, and safety were all satisfactory.*

INTRODUCTION

The Global Cancer Statistics 2020 ranked colorectal cancer as the third most commonly diagnosed cancer after female breast and lung cancer (approximately 1.9 million cases, 10 %) and the second leading cause of cancer-related death after lung cancer (approximately

930,000 cases, 9.4%).[1] A study based on the National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results, SEER) database revealed that the majority of rectal cancer patients presented in locally advanced stages, with $T_{3-4}N_0$ and T_xN+ patients representing 72.2% of rectal malignancies evaluable at TN stage.[2]

The standard treatment strategy for locally advanced rectal cancer (LARC) is preoperative neoadjuvant chemoradiotherapy (nCRT) + total rectal mesenteric excision (TME).[3–5] Neoadjuvant radiotherapy regimens based on fluorouracil (5-FU) have achieved significant tumor downstaging, increased surgical R0 resection, and decreased local recurrence rates.[6,7] However, nCRT does not improve disease-free (DFS) or overall survival (OS).[8,9] Moreover, nCRT may increase the risk of postoperative anastomotic fistula and have long-term effects on anal function, sexual function, and urinary function.[10–13] Therefore, neoadjuvant chemotherapy (NAC) alone is emerging as a viable alternative.

Several studies have shown that NAC initially achieves comparable tumor downstaging rates, R0 resection rates, 3-year DFS, and OS to nCRT. However, nCRT still has advantages regarding pCR rates and reduced recurrence rates.[14,15] New chemotherapeutic drug combinations, as well as the use of targeted drugs and immunotherapeutic agents, appear to circumvent or compensate for NAC's deficiencies. Preoperative use of molecularly targeted agents promises to shrink tumors and improve prognosis.[16] However, there is an increased risk of postoperative complications such as anastomotic fistula.[17,18] Multiple phase III randomized controlled clinical trials demonstrate that the FOLFOXIRI triplet regimen, as compared to the conventional FOLFOX or FOLFIRI two-drug regimens, achieved better ORR, PFS, and OS in advanced colorectal cancer (mCRC).[19–21] The FORTUNE trial is the first study to evaluate the FOLFOXIRI triplet regimen without routine radiotherapy as a neo-adjuvant treatment option for LARC. The results showed a pCR of 20.4% for triple-agent nCT (selective radiotherapy) and an improved tumor downstaging rate of 42.7%.[22] In addition, the PRODIGE23 study's preliminary results showed that, compared to the nCRT group, the mFOLFIRINOX±RT group had significantly higher pCR rates, 3-year disease-free survival, and 3-year metastasis-free survival.[23] Therefore, FOLFOXIRI three-drug neoadjuvant chemotherapy + selective concurrent radiotherapy is an effective and safe treatment strategy for patients with locally advanced rectal cancer.

The oral formulation of fluorouracil, capecitabine, exerts antitumor effects on both 5-FU-sensitive and resistant cells and is more synergistic when combined with oxaliplatin or irinotecan.[24,25] Multiple phase III clinical trials have demonstrated the efficacy and safety of capecitabine in the first-line treatment of mCRC.[26–28] Given that capecitabine is not inferior to 5-FU, the XELOXIRI regimen with oral capecitabine instead of intravenous pumped 5-FU may provide the same or even more significant benefit.[29] Several phase I and II clinical studies have been conducted to investigate the optimal dose and safety of the XELOXIRI regimen and its preliminary efficacy in neoadjuvant therapy.

METHODOLOGY

Patients and eligibility criteria

This research systematically gathered patients with locally advanced rectal cancer (LARC) who had neoadjuvant therapy with the XELOXIRI regimen at The First Hospital of Chongqing Medical University's Department of Gastroenterology between January 2019 and December 2022.

Eligibility criteria: (1) Pathologically proven adenocarcinoma of the rectum; (2) Clinically confirmed stage II (T3-4N0) or stage III (T1-4N1-2) tumor with the lower tumor margin 12

cm from the anal verge; (3) Age 18-75, ECOG: 0-1; (4) Adequate hematological, cardiac, hepatic, and renal function.

Exclusion criteria: (1) existence of distant metastases; (2) presence of intestinal obstruction or perforation; (3) previous radiotherapy or chemotherapy; (4) combination of malignancies other than intestinal cancer; (5) hypersensitivity to oxaliplatin, irinotecan, or any investigational drug component, presence of persistent grade 3–4 oxaliplatin-related neurotoxicity; (6) involvement of clinically significant cardiac disease, recurrent infections, or known peripheral neuropathy; (7) lack of clinical information and unrecoverable.

This study's protocol was approved by the central ethics committee of the First Affiliated Hospital of Chongqing Medical University. Ethics Review Grant Number: 2022 Research Ethics (2022-K429). All study participants provided written informed consent.

1.2 Treatment:

In this trial, the XELOXIRI regimen was administered as a 3-week cycle consisting of oxaliplatin 70-110 mg/m2 IV for >120 min on day 1, irinotecan 120-160 mg/m2 IV for 90 min on day 1, and capecitabine 700-1100 mg/m2 orally twice daily for 14 days followed by 7 days off.

Targeted agents: bevacizumab 5 mg/kg, first IV drip >90 min, followed by 30-60 min IV drip, day 1, repeated every 3 weeks.

Combined radiotherapy: long course radiotherapy dose of 1.8-2.0 Gy per day for 5 days per week for 23-28 sessions over 5-6 weeks for a total dose of 46.0-50.4 Gy. The XELOX regimen was administered concurrently with long-term radiotherapy. The short-term radiation dose was 5 Gy per day for 5 days.

Adverse events were evaluated according to the National Cancer Institute's Common Toxicity Criteria (version 4.0). Treatment with a 5-HT3 antagonist is used as standard therapy to prevent vomiting. Loperamide is used as standard treatment for diarrhea, and montelukast may also be used. Administer colony-stimulating factors for grade 3 or higher leukopenia or neutropenia. Give recombinant human interleukin-11, recombinant human thrombopoietin, or platelet transfusion for thrombocytopenia. Simultaneous supportive therapy such as gastroprotection, hepatoprotection, and nutrition.

1.3 Re-staging After Neoadjuvant Chemotherapy

After 2-4 cycles of neoadjuvant chemotherapy, a pelvic MRI was reviewed to assess clinical response. Restaging after *neoadjuvant chemotherapy* was defined as ycTNM staging. Any degree of primary tumor regression without distant metastasis was defined as the clinical response. Clinical T4 stage, CRM positivity, and EMVI positivity were high-risk factors. Rectal cancer mrTRG was evaluated according to pathological Mandard diagnostic criteria: defined as follows: 1: no residual tumor; 2: sizeable fibrous component with a small amount of residual tumor; 3: approximately 50% each of fibrous/mucinous component and residual tumor; 4: small fibrous/mucinous component with mostly residual tumor; 5: no definite change in tumor.

1.4 Pathologic Analysis

The pathology report should contain tumor staging and grading, infiltration depth, lymph node status, proximal and distal resection margins, circumferential margins, and tumor regression grading (American Joint Committee on Cancer [AJCC]). Pathologic complete remission (pCR) was defined as the absence of tumor cells at the primary site and lymph

nodes. Following neoadjuvant therapy, tumor regression grading (TRG) was evaluated using AJCC criteria and was defined as follows: 0 (complete regression): no residual cancer cells; 1 (almost complete regression): single or small focal cancer cells; 2 (low response): residual tumor cells; 3 (poor response): very few or no tumor cells are eliminated.

1.5 Postoperative Adjuvant Therapy

Adjuvant treatment strategy was evaluated according to response after NAC treatment and postoperative pathological staging: 1) pCR and ypT1-2N0 with close observation and follow-up; 2) ypT3-4/T0-4N1-2 with 6-8 cycles of adjuvant chemotherapy with XELOX regimen; 3) If surgery was not R0 resection, postoperative radiotherapy was given.

1.6 Study Endpoints

This was a single-arm study with the primary endpoint being the proportion of pCR and tumor downstaging (to ypT0-2N0M0). All resected specimens were examined according to a standardized protocol, which included TNM staging according to the AJCC-International Union Against Cancer (7th edition). Secondary endpoints included R0 resection, sphincter preservation, safety, local recurrence, disease-free survival (DFS), distant metastasis, and overall survival.

1.7 Statistical Analysis

For statistical analysis, SPSS 26.0 software was utilized. Data on demographic and baseline characteristics, efficacy, and safety were assessed using descriptive statistical values. Tables were supplied that summarized pCR, tumor regression, and adverse events, including the number and percentage of instances. Using the Kaplan-Meire technique to estimate event rates across time, medians and 95% confidence intervals were calculated for a survival study (CIs). Log-rank analysis was used for subgroup analysis. DFS was defined as death from R0 surgery to imaging-confirmed disease progression or death from any cause before no evidence of disease recurrence or the emergence of a second primary malignancy. The definition of overall survival (OS) was death from the beginning of chemotherapy to death from any cause.

RESULTS AND DISCUSSION

2.1 Baseline Characteristics

This retrospective study included 68 patients with locally advanced rectal cancer (LARC) treated with XELOXIRI at our institution between January 2019 and December 2022, with patient baseline characteristics listed in Table 1. The median age was 58, and the group included 17.6% of stage II patients, 45.6% of stage IIIA/B patients, and 36.8% of stage IIIC Patients. The demographic and disease characteristics of patients with tumors located >5 cm and within 5 cm of the anal verge, depending on the tumor's location, are listed in Table 2.

2.2 Treatment Management and imaging evaluation

All 68 patients received at least 2 cycles of XELOXIRI treatment, and 1 patient was lost to follow-up after 3 courses. After neoadjuvant therapy, all 67 patients underwent MRI evaluation and restaging (Figure 1). Of the patients with high-risk factors at baseline, the following were evaluated after neoadjuvant therapy: 1) 2 of 3 patients with cT4 remained ycT4, including 1 with combined CRM+ and EMVI+; 2) 1 of 9 patients with CRM+ remained CRM+; 3) 4 of 15 patients with EMVI+ remained EMVI+; 4) 1 of 6 patients with cT4 combined with CRM+ remained both cT4 and CRM+; 1 case was CRM+ only; 5) among 4 cT4 combined EMVI+ patients, 1 case was still concurrent ycT4, EMVI+; 6) among 5 CRM+ combined EMVI+ patients, 1 case was still concurrent CRM+, EMVI+, 1 case was CRM+ only; 7) among 10 concurrent cT4, CRM+, EMVI+ patients, 2 cases were still present with three high-level factors; 1 case was still the presence of ycT4, CRM+; in addition, one patient with cT3d, progressed to ycT4, CRM+, EMVI+ after treatment; (Figure 2).

After neoadjuvant therapy, imaging analysis revealed that 18 patients possessed high-risk factors. One patient withdrew consent and refused surgery and further treatment. 5 patients were administered long-term radiotherapy, 2 patients were administered short-term radiotherapy, and 2 patients were administered bevacizumab-targeted therapy. 5 of the 7 patients who received radiotherapy had tumors located less than 5 cm from the anal verge, and 2 of the 7 patients had tumors located at the anal verge. On the seven patients who received radiotherapy, five tumors were located at the anal margin of fewer than 5 cm. Two tumors were located at the anal margin of 5.4 and 5.6 cm, respectively. Following evaluation, the remaining nine patients underwent TME immediately. 6 of them had upper middle rectal cancer, with 2 having tumors located >10 cm from the anal verge, 4 having tumors located >5 cm from the anal verge, and 3 having low-grade (5 cm) rectal cancer; the anus was preserved in all cases.

Among the 49 patients without high-risk factors, 4 received long-course radiotherapy, 6 received short-course radiotherapy, and 1 received bevacizumab targeted therapy. 8 of the 10 patients who received radiotherapy had tumors located ≤5 cm from the anal verge, and 2 had tumors located 5.4 and 5.6 cm from the anal verge, respectively; 9 of these patients preserved the anus, including 3 with tumors located 1.3 cm, 1.9 cm, and 2.1 cm from the anal verge, respectively. In three cases, the tumor was located at 1.3 cm, 1.9 cm, and 2.1 cm from the anal verge, and the tumor was preserved by TaTME surgery. In the remaining 38 patients without high-risk factors, 16 tumors were located >5 cm from the anal verge, and 22 tumors were located ≤5 cm from the anal verge; 37 of them preserved the anus, and 1 tumor was located 0.6 cm from the anal verge and was treated by MILES surgery.

2.3 pCR rate and postoperative pathological response

Of the 68 patients, 2 patients with stage IIIC tumors located within 5 cm from the anal verge withdrew informed consent and refused further treatment, and 66 patients underwent surgery with an R0 resection rate of 100.0% (66/66). The tumor down-staging reduction rate (to ypT0-2N0M0) was 53.0%, and the pCR rate was 12.1% in the whole group, and in the neoadjuvant chemotherapy alone group (N=47), the tumor stage reduction rate (to ypT0-2N0M0) was 55.3%, and the pCR rate was 12.8%. In the group receiving radiotherapy (N=16), the tumor stage reduction rate (to ypT0-2N0M0) was 56.3%, and the pCR rate was 12.5%. In the group receiving bevacizumab-targeted therapy (N=3), all three cases had stage III at baseline, one was downgraded to stage IIA after surgery, and two cases had stage IIB (Table 3). According to the definition of TRG, 15 patients achieved TRG 0-1, 22 patients achieved TRG 2-3, 1 patient achieved TRG 4, and 28 patients had pathology reports that did not provide TRG scores, including 8 cases of ypT2N0, 2 cases of ypT1N0, and 1 case of pCR (Table 4). pCR rate was 10.5% in 38 patients with tumors located ≤5 cm from the anal verge and tumor.

Among the 38 patients with low rectal cancer, 12 patients received radiotherapy due to high-risk factors or the desire to preserve the anus, including 6 long-course radiotherapy cases and 6 short-course radiotherapy cases. 28 patients with tumors >5 cm had a pCR rate of 14.3% and a tumor regression rate (to ypT0-2N0M0) of 42.9%, and 4 patients received radiotherapy, including 2 long-course radiotherapy cases and 1 pCR case. Including 2 cases of long-course radiotherapy and 2 cases of short-course radiotherapy. (Table 5). The relationship between pathologic staging and baseline T and N staging in patients on the XELOXIRI regimen alone is shown in Table 6. 59.6% (28/47) of patients with T staging were stage-reduced, and 66.7% (8/12) of cT4 patients were stage-reduced after neoadjuvant chemotherapy. 70.2% (33/47) of patients with N staging were stage-reduced.

2.4 Adverse effects

89.7% of 68 patients experienced AEs of all grades during treatment, including 16.2% (11/68) severe grade III to IV adverse reactions. Preoperatively, neutropenia 8.8 (6/68), diarrhea 4.4% (3/68), and anemia 2.9% (2/68) were the most frequent adverse reactions of grade 3 to 4 severity. Each adverse event was manageable (Table 8). There were no mortalities during the perioperative period.

2.5 3-year local recurrence rate, 3-year DFS, and OS

The follow-up period was 6-48 months (median 24.5 months). 66 patients underwent R0 resection. Local recurrence occurred in 1 case; distant metastases occurred in 4 cases: 3 lung metastases and 1 liver metastasis. The local recurrence rate was 1.5% (1/66). 5 of the 66 patients had local recurrence or metastasis, and 1 died. The Kaplan-Meier curve of DFS is shown in Figure 3. the DFS at 3 years was 89.0%. The three-year survival rate was 98.5% (data not shown). This study compared the DFS of 47 patients receiving XELOXIRI and 16 patients receiving XELOXIRI + RT. 3-year DFS was 89.9% and 87.2%, respectively, and no statistically significant differences were found. (P = .17 by log-rank test; Figure 3)

3. Discussion

This study describes the efficacy and safety of irinotecan and oxaliplatin combined with capecitabine (XELOXIRI) as a NAC regimen for patients with LARC. The regimen completion rate was 97.1% (66/68). The XELOXIRI regimen alone had a tumor down-staging rate (to ypT2N0) of 55.3% and a pCR rate of 12.8%. The reported pCR rates were 2.4%-13% in the dual NAC[30–32] trial and 10%-20% in the nCRT trial.[33–36] In the Japanese phase II kudo study, 83.3% of patients received the full-dose XELOXIRIR biweekly regimen, with a pCR rate of only 7.7%. The reasons were the limited therapeutic effect of preoperative cytotoxic chemotherapeutic agents and the non-use of molecularly targeted drugs to prevent side effects.[37] However, the mFOLFOXIRI regimen significantly increased the pCR rate by 20.4% in the FORTUNE study.[22]

One of the possible reasons for the pCR rate not meeting expectations in this study is the reduced drug dose intensity due to the 3-week regimen model. The Scheithauer study in Australia showed that two-week capecitabine combined with oxaliplatin regimen had a higher ORR and PFS than the standard three-week XELOX regimen.[38] For the 3-week mode of the XELOXIRI regimen, the recommended RP2D for the Canadian phase I Maroun study was oxaliplatin 100 mg/m2, d1, capecitabine 1900 mg/m2/d in 2 divided doses, d2-15, and irinotecan 160 mg/m2, d1. [39] Considering the essential characteristics and safe tolerability of the Asian population and the fact that most patients were not tested for the UGA1T1 gene, capecitabine, oxaliplatin, and irinotecan were moderately reduced in this study. 15 patients achieved TRG 0-1, 22 patients achieved TRG 2-3, and 28 pathological Of the TRG scores not provided in the report, 8 cases ypT2N0, 2 cases ypT1N0,1 case pCR， which may be due to the effect of triple chemotherapy. Notably, the proportion of patients involved in high-risk factors in this study was large: 36.8% of patients were stage IIIC, 45.6% CRM+, and 51.5% EMVI+. Most of them respond well and thus avoid radiotherapy.

Although triple combination regimens such as FOLFOXIRI and XELOXIRI are standard in metastatic or recurrent colorectal cancer, and their safety and tolerability have been demonstrated, these have not been established in neoadjuvant therapy.[40,41] This triple combination regimen has a high incidence of grade 3 or higher neutropenia and diarrhea. The primary grade 3 adverse reactions in this study: were neutropenia 8.8 (6/68), diarrhea 4.4% (3/68), and anemia 2.9% (2/68). The reported incidence of neutropenia (≥ grade 3): 12.5%-17% for the XELOX regimen,[30,31] 50% for the FOLFOXIRI regimen, 28% for the FOLFIRI regimen, 25.9% for the Kudo study and 42.5% for FORTUNE study.[22,32,37] As for diarrhea rates (≥ grade 3): 2.4%-3.1% for the XELOX regimen,[30,31] 17%- 30% for the FOLFOXIRI

regimen, 11%- 14% for the dual regimen, 11.1% for the Kudo study, and 1.9% for the FORTUNE study.[22,32,37] Hematologic toxicity (≥ grade 3) was higher than in the CRT trial (3.7%-6%).[42,43] However, there was no radiotherapy toxicity such as dermatitis, anal pain, and facial incontinence. Notably, despite receiving many cycles, the incidence of grade 3/4 oxaliplatin-related neurotoxicity was lower than expected, possibly due to the reduced dose intensity associated with the 3-week schedule and dose adjustments. Postoperative complications were also less common than other treatments, with three patients developing anastomotic fistulas.

The follow-up time of this study was 6-48 months (median 24.5 months). Local recurrence rate: 1.5% (1/66). Distant metastases: 3 lung metastases and 1 liver metastasis. Kudo's study local recurrence rate was 3.9%.[37] The local recurrence rate was 7%-10% in the Doublet NAC trial[30–32] and 4%-7.6% in the CRT trial.[42,43] In contrast, the local recurrence rate in the present study was meager. The local control achieved by XELOXIRI NAC can be comparable to that achieved by CRT. In this study, the T-decrease rate:59.6% (28/47), and N-decrease rate:70.2% (33/47). in the Kudo study, the T-decrease rate:63.5% (33/52).[37]

Three-year DFS in this study: 89.0%. Three-year OS: 98.5%. Subgroup analysis showed that 3-year DFS: XELOXIRI (N=47): 89.9%, XELOXIRI+RT (N=16): 87.2%. Doublet NAC trial resulted in 3-year DFS rates of 71%-73%. The CRT trial resulted in 3-year DFS rates of 71%-75%.[42] In the FOWARC study, the FU+RT group, the mFOLFOX+RT group, and the mFOLFOX group were 72.9%, 77.2%, and 73.5% (P=0.709), respectively, and the 3-year OS rates were 91.3%, 89.1%, and 90.7% (P=0.971), respectively.[15] The 3-year DFS and 3-year OS rates in this study were higher than those in the FOWARC and kudo studies. This difference may be due to the effectiveness of triple therapy and high adjuvant chemotherapy completion rate.

Compared to the FOLFOXIRI regimen, the XELOXIRI regimen eliminates the need for intravenous access and continuous 5-FU infusion, which may be preferable for many eligible patients, and reduces dosing costs. In addition, XELOXIRI given every 3 weeks appears to be associated with a lower frequency of oxaliplatin-related neurotoxicity compared to regimens given once every 2 weeks.

The trial was a single-arm study without a control group; due to the limited sample size, we could not investigate which type of LARC was most susceptible to being affected as NAC. Most patients were not tested for the UGA1T1 gene, and patients may have been overtreated due to exposure to irinotecan. However, pCR did not meet expectations, tumor stage reduction rates improved, and R0 resection rates, local recurrence rates, 3-year DFS, and safety were acceptable. Our results suggest that for some LARC patients, the damage caused by radiotherapy can be avoided.

CONCLUSION

Although neoadjuvant XELOXIRI alone did not yield our expected pCR rate as NAC for LARC, tumor downstaging, R0 resection, sphincter preservation, local recurrence rate, 3-year DFS, OS, and safety met current standards. Therefore, neoadjuvant chemotherapy with XELOXIRI appears to be feasible and efficacious for patients with LARC.

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CONFLICT OF INTEREST: None declared

ETHICAL APPROVAL: The study was approved by the Institutional Ethics Committee

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Table 1：Patient Demographic and Disease Characteristics(N=68)

Characteristics	N (%)
Age, y	
Median (range)	58（33-75）
Gender	
Male	44（64.7）
ECOG performance status	
0-1	68（100）
Clinical T category	
T2	6（8.8）
T3	38（55.9）
T4a	11（16.2）
T4b	13（19.1）
Clinical N category	
N0	12（17.6）
N1	31（45.6）
N2a	9（13.2）
N2b	16（23.5）
cTNM staging	
IIA	9（13.2）
IIB	2（2.9）
IIC	1（1.5）
IIIA	6（8.8）
IIIB	25（36.8）
IIIC	25（36.8）
CRM-positive	
Yes	31（45.6）
EMVI-positive	
Yes	35（51.5）
Mean tumor length, cm (SD)	5.1（1.6）
Distance from anal verge, cm	
10-12 cm	3（4.4）
5-10 cm	25（36.8）
⩽5 cm	40（58.8）
Median distance, cm	4.5

Table 2：Patient Demographic and Disease Characteristics With Tumors Located > 5 cm and Within 5 cm From the Anal Verge (N=68)

Variable	Tumor Location	
	> 5 cm From Anal Verge (N=28),N (%)	⩽5 cm From Anal Verge (N=40),N (%)
Age, y		
Median (range)	61.5（41-75）	56（33-71）
Gender		
Male	17（60.7）	27（67.5）
Clinical T category		
T2	0（0）	6（15.0）
T3	16（57.1）	22（55.0）
T4a	7（25.0）	4（10.0）
T4b	5（17.9）	8（20.0）
Clinical N category		
N0	6（21.4）	6（15.0）
N1	12（42.9）	19（47.5）
N2a	5（17.9）	4（10.0）
N2b	5（17.9）	11（27.5）
cTNM staging		
IIA	5（17.9）	4（10.0）
IIB	0（0）	2（5.0）
IIC	1（3.6）	0（0）
IIIA	0（0）	6（15.0）
IIIB	14（50.0）	11（27.5）
IIIC	8（28.6）	17（42.5）
CRM-positive		
Yes	13（46.4）	18（45.0）
EMVI-positive		
Yes	15（53.6）	20（50.0）
Mean tumor length, cm (SD)	4.7（1.4）	5.3（1.8）

Figure1：Patient Flow Diagram

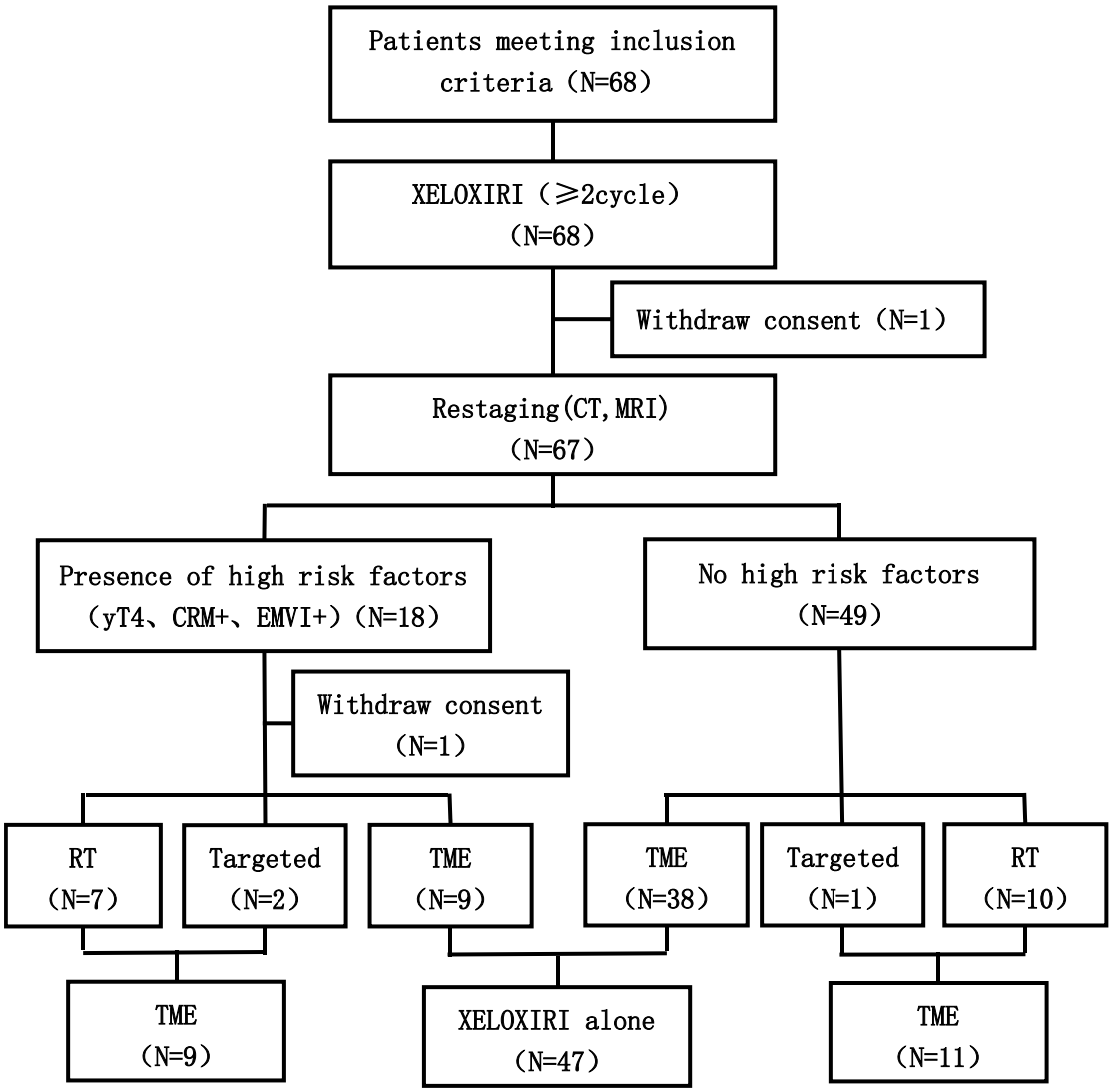

Figure 2：Assessment With Magnetic Resonance Imaging in Patients With High-risk Factors after neoadjuvant Chemotherapy（N=67）

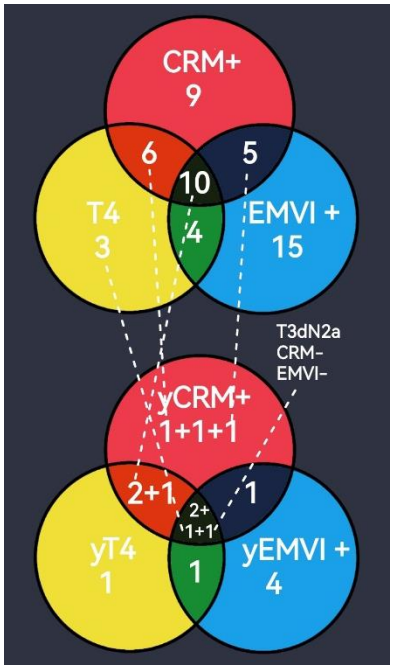

Table 3：Tumor Downstaging Rate (to ypT0-2N0M0) and pCR Rate：

All regime	Tumor downstaging (to ypT0-2N0M0), (%)	pCR rate, (%)
XELOXIRI，N=47	26（55.3）	6（12.8）
XELOXIRI+bev，N=3	0（0）	0（0）
XELOXIRI+LCRT，N=8	4（50.0）	1（12.5）
XELOXIRI+SCRT，N=8	5（62.5）	1（12.5）
TOTAL，（N=66）	35（53.0%）	8（12.1）

Table 4：Summary of Study Outcomes (N=66)

Variables	N (%)
Tumor downstaging (to ypT0-2N0M0), %	35（53.0）
pCR rate	8（12.1）
yp stage	
0-I	35（53.0）
II-III	31（47.0）
TRG	
NA	28（42.4）
0-1	15（22.7）
2-3	22（33.3）
4	1（1.5）
R0 resection	66（100.0）
R1 resection	0（0）
Anal preservation	64（97.0）
Ileostomy	38（57.6）
Laparoscopy surgery	66（100.0）
Preoperative radiotherapy	
Long-term CRT	8（12.1）
Short-course radiotherapy	8（12.1）
Anastomotic fistula	3（4.5）

Table 5：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=28),N (%)	≤5 cm From Anal Verge (N=38),N (%)
pCR rate	4（14.3）	4（10.5）
yp stage		
0-I	12（42.9）	23（60.5）
II-III	16（57.1）	15（39.5）
TRG		
NA	9（32.1）	19（50.0）
0-1	9（32.1）	6（15.8）
2-3	9（32.1）	13（34.2）
4	1（3.6）	0（0）
R0 resection	28（100.0）	38（100.0）
R1 resection	0（0）	0（0）
Anal preservation	28（100.0）	36（94.7）
Preoperative radiotherapy		
Long-term CRT	2（7.1）	6（15.8）
Short-course radiotherapy	2（7.1）	6（15.8）
Anastomotic fistula	0（0）	3（7.9）

Table 6：The relationship between baseline and pathological staging of the XELOXIRI alone group

Clinical stage	**Pathological stage**							
(baseline)	**pT0**	**pT1**	**pT2**	**pT3**	**pT4a**	**pN0**	**pN1**	**pN2**
cT2 (n=3)			3					
cT3 (n=32)	5	3	12	8	4			
cT4a (n=9)	1		2	2	4			
cT4b (n=3)		2		1				
cN0 (n=10)						6	4	
cN1 (n=22)						20	2	
cN2 (n=15)						10	3	2
Total(n=47)	6	5	17	11	8	36	9	2

Table 7：Summary of Adverse Events

	Number of patients N=68(%)				
Events	**All grades**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hematological					
Neutropenia	33(48.5)	18(26.5)	9(13.2)	6(8.8)	0
Anemia	31(45.6)	13(19.1)	16(23.5)	2(2.9)	0
Thrombocytopenia	17(25)	10(14.7)	7(10.3)	1(1.5)	0
Febrile neutropenia	1(1.5)	0	0	1(1.5)	0
Non-hematological					
Fatigue	46(67.6)	38(58.8)	7(10.3)	1(1.5)	0
Nausea	46(67.6)	33(48.5)	13(19.1)	0	0
Vomiting	26(38.2)	15(22.1)	9(13.2)	2(2.9)	0
Diarrhea	17(25.0)	8(11.8)	6(8.8)	3(4.4)	0
Oral mucositis	3(4.4)	2(2.9)	1(1.5)	0	0
Neurotoxicity	19(27.9)	12(17.6)	7(10.3)	0	0
Hand-foot syndrome	8(11.8)	8(11.8)	0	0	0

Figure 3：Kaplan-Meier curves of 3-year disease-free survival (DFS)