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ORIGINAL RESEARCH

Toxicity, Disease Control, and Survival Outcomes of Intensified Preoperative Chemoradiotherapy in Patients with Locally Advanced Rectal Cancer: A Single-Institution Study

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Purpose: The standard treatment regimen of preoperative chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC) is still controversial. The purpose of this study was to analyze the efficacy and safety of preoperative intensive CRT in our institution.

Methods: A retrospective data collection and analysis of 181 LARC patients receiving oxaliplatin (85%) of standard doses in capecitabine-based preoperative CRT and two additional cycle of neoadjuvant chemotherapy between the end of concurrent CRT and surgery.

Results: The compliance of the preoperative CRT was satisfactory with 99.4%patients completed radiotherapy and 97.19%patients completed all 2 cycles of concurrent chemotherapy. Except for 20 patients diagnosed clinical complete remission (cCR) managed according to watch and wait strategy, 160 patients received R0 radical surgery. The pathological complete response (pCR) rate was 23.75% (38/160) and tumor regression grade (TRG) 0/1 was 40% (72/180). In terms of tumor downstaging, 89 (55.63%) had T downstaging while 115 (71.88%) had N downstaging. The 1-overall survival (OS),2-OS,3-OS and 5-OS were 98.7%, 96.5%, 91.4% and 81.5%, respectively. The total rate of sphincter preservation was 86.25% (138/160) and the rate of patients with low rectal cancer was 73.0% (54/74) without affecting local control rates and survival rates. Both acute adverse reactions to preoperative CRT and postoperative complications were tolerable and controllable.

Conclusion: In this retrospective study, preoperative intensive CRT of patients with LARC achieved satisfied disease control and survival outcomes and well acquired the sphincter retention rate in recent years in our institution. On the basis of these findings, a Phase III study to definitively test the intensified preoperative CRT strategy is warranted.

Keywords: rectal cancer, preoperative chemoradiotherapy, overall survival, disease control

Introduction

For patients with locally advanced rectal cancer (LARC), preoperative concurrent chemoradiotherapy (CRT) combined with total mesorectal excision (TME) is the standard treatment approach.[1] However, the standard treatment regimen of preoperative CRT for locally advanced rectal cancer is now changing. To improve the efficacy of preoperative CRT for locally advanced rectal cancer, researchers have explored some enhanced concurrent chemotherapy regimens in recent years. In Chinese patients, oncologists found that adding irinotecan guided by UGT1A1 genotype to capecitabine-based neoadjuvant CRT significantly increased complete tumor response.[2] Whereas, the more studied was the addition of oxaliplatin in capecitabine-based preoperative CRT and there have been some large phase III studies that got extensive attention in the world.[3–9] However, the results of these studies were inconsistent, suggesting that it may be necessary to select a more appropriate population and explore a better method of administration to achieve a greater value of concurrent chemotherapy with two drugs. In our institution, patients with LARC received an intensified preoperative treatment that capecitabine-based preoperative CRT by adding standard doses of oxaliplatin and two additional cycle of

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neoadjuvant chemotherapy between the end of concurrent CRT and TME surgery. This article summarized and reported the toxicity, disease control and survival outcomes of this intensified preoperative treatment for patients with LARC in our institution.

Methods

Patient Eligibility

A retrospective analysis was performed on 181 patients with LARC who underwent preoperative CRT at Jinling Hospital in China from December 2015 to November 2020. Inclusion criteria: (1) Age range 18–75 years; (2) Primary rectal adenocarcinoma confirmed by biopsy and pathology; (3) The lower margin of the tumor was 12 cm from the anal margin; (4) According to the staging criteria of the 8th edition of the American JointCommittee on Cancer (AJCC),[10] the clinical stage is stage II (T3 to 4N0) or stage III (T1 to 4N1 to 2); (5) Newly treated patients who have not previously received radiotherapy, chemotherapy, surgery or other anti-tumor therapy; (6) The physical status score of Eastern Collaborative Oncology Group (ECOG) was 0~1;(7) No relevant contraindications of CRT and surgery. Exclusion criteria: (1) History of malignancy at other sites or concurrent occurrence of a second tumor; (2) Newly diagnosed patients with distant metastasis (clinical stage) or local recurrence of rectal cancer; (3) Accompanied by acute obstruction symptoms; (4) Contraindications of CRT in liver and kidney function and bone marrow function; (5) With severe cardiovascular and cerebrovascular diseases. This study was approved by the ethics committee of Jinling Hospital. All patients who received the treatment signed the informed consent for radiotherapy, chemotherapy and surgery before treatment. All experiments were conducted in accordance with the Declaration of Helsinki.

Radiotherapy

The gross tumor volume (GTV) was the rectal tumor and pelvic metastatic lymph nodes visible on CT scout image. The clinical target volume (CTV) included 2cm above and below the tumor, the mesorectal region, presacral areas, internal iliac lymphatic drainage area, and obturator lymphatic drainage area. The upper boundary of CTV is the bifurcation of the common iliac artery, internal iliac artery and external iliac artery, and the lower boundary of CTV is determined according to the location of the tumor, generally reaching the lower edge of the obturator. The posterior and lateral boundaries of CTV extend outward to the inner margins of the pelvic muscles and bones, and the inclusion of bone and pelvic muscles should be avoided. The anterior boundary of CTV extended 1cm to the posterior wall of the bladder to accommodate the change of bladder filling. The presacral area comprises the area 1cm in front of the sacrum. GTV is expanded by 0.5cm to planning gross tumor volume (PGTV) and CTV is expanded by 0.5cm to the planning target volume (PTV). Prescription dose: 95%PGTV 50 Gy/95%PTV 45 Gy (25f, Monday to Friday, once a day).

Chemotherapy

Concurrent chemotherapy was performed using oxaliplatin intravenous infusion combined with oral capecitabine regimen: oxaliplatin 85mg/m^2 intravenously every 3 weeks + oral capecitabine 825mg /m^2 twice a day on the day of radiotherapy. Oxaliplatin was administered on day 1 and 21 of radiotherapy, respectively. Neoadjuvant chemotherapy began 2 weeks after the end of concurrent CRT, and postoperative chemotherapy began 4 weeks after the operation. The specific regimen was: intravenous infusion of oxaliplatin 85mg/m^2(d1)+ capecitabine 825 mg/m^2 (d1-14) oral twice a day, one course every three weeks.

Surgery

Excluding surgical contraindications, radical rectal surgery was performed in accordance with the principle of total mesorectal excision (TME). Clinical complete response (cCR) was diagnosed according to diagnostic criteria ofDr. Habr-Gama and her group.[11] For cCR patients, radical surgery or watch-and-wait was selected according to the wishes of the patients. The tumor specimens were pathologically evaluated after surgical resection.

Evaluation and Management of Adverse Reactions

According to the acute radiation injury classification standard of North American Radiation Oncology Cooperative and evaluation criteria of common adverse reactions 4.0,[12] short-term adverse reactions associated with CRT were evaluated. The evaluation time window was from the beginning of CRT to adjuvant chemotherapy, once a week. If persistent grade 3 hematologic or non-hematologic adverse reactions occur, oxaliplatin should be suspended and capecitabine monotherapy should be used instead. In case of grade 4 hematological adverse reactions, oral capecitabine should be suspended and radiotherapy alone should be used until the adverse reactions are reduced to grade 1 or return to normal. If grade 4 or persistent grade 3 non-hematological adverse reactions occur, radiotherapy should be suspended until the adverse reactions are reduced to grade 1 or non-persistent grade 2.

Observational Index

The primary endpoint and outcome indicators were tumor complete response rate, including cCR rate and complete pathological response (pCR) rate. cCR was defined as: no residual lesions were found by various clinical and imaging examinations (digital rectal examination, rectoscope, MRI).[13] Tumor regression grade (TRG) according to Ryan R's improved grading system for evaluating tumor treatment response recommended by NCCN guidelines: TRG Grade 0: complete regression, TRG Grade 1: nearly complete regression, TRG Grade 2: partial regression, TRG Grade 3: poor or no regression. Restaging of postoperative pathology for all surgery patients. pCR was defined as a complete response of the primary rectal tumor (ypT0 stage) confirmed by postoperative pathology and no tumor cell residue, regardless of whether regional lymph nodes were involved.[14] Secondary outcome indicators included: incidence of adverse reactions to CRT, especially grade 3 and above toxic reactions, the incidence of postoperative complications, R0 resection rate, anal preservation rate, tumor regression rate, downstage rate, recurrence and metastasis rate. Two blinded radiologists measured MRI-detected circumferential resection margin (mrCRM) and extramural vascular invasion (EMVI) on MRI T2-weighted image. EMVI was evaluated and defined as mrEMVI-positive or mrEMVI-negative depending on the radiologic features using the EMVI scoring system.[15] The CRM was defined as histopathologically positive if the tumor was less than or equal to 1 mm from the inked non-peritonealized surface, and negative if greater than 1 mm.[16]

Statistical Analysis

Local recurrence-free survival (LRFS), distant metastases-free survival (DMFS), cancer-specific survival (CSS), disease free survival (DFS) and OS were calculated using the Kaplan–Meier method. Analyses for DFS and OS were carried out by fitting the Cox proportional hazards regression model stratified by the randomization stratification factors to obtain an estimate and a two-sided 95% CI for the stratified hazard ratio (HR) between the two arms. A two-sided P value of <0.05 was considered statistically significant. Post hoc subgroup analyses were performed within well known prognostic factors for the better understanding of treatment effects. Univariate and multivariate Cox regression were used to determine whether covariates were significantly associated with OS.

Result

Clinical Data

From December 2015 to November 2020, a total of 181 patients with LARC were assessed and instituted therapeutic method by the multi-disciplinary team in our institution, and all patients received preoperative CRT (Figure 1), the clinical features are shown in Table 1. There were 86 patients with a tumour <5 cm from the anal verge and 67 patients with a tumour 5–10 cm from the anal verge. Thirty-two (17.68%) patients had elevated CEA levels before treatment.180 (99.4%) patients completed the whole course of radiotherapy except 1 patient who underwent emergency surgery after the 14th time of radiotherapy for acute ileus. One hundred and seventy-five patients (97.22%) completed all 2 cycles of concurrent chemotherapy, and 5 patients (2.78%) changed to single drug capecitabine in the second cycle of concurrent chemotherapy for grade 3 hematologic or non-hematologic adverse reactions. Among the 160 patients undergoing surgery, 145 patients received median 2 cycles of preoperative chemotherapy, while 15 did not. Moreover, 140 patients

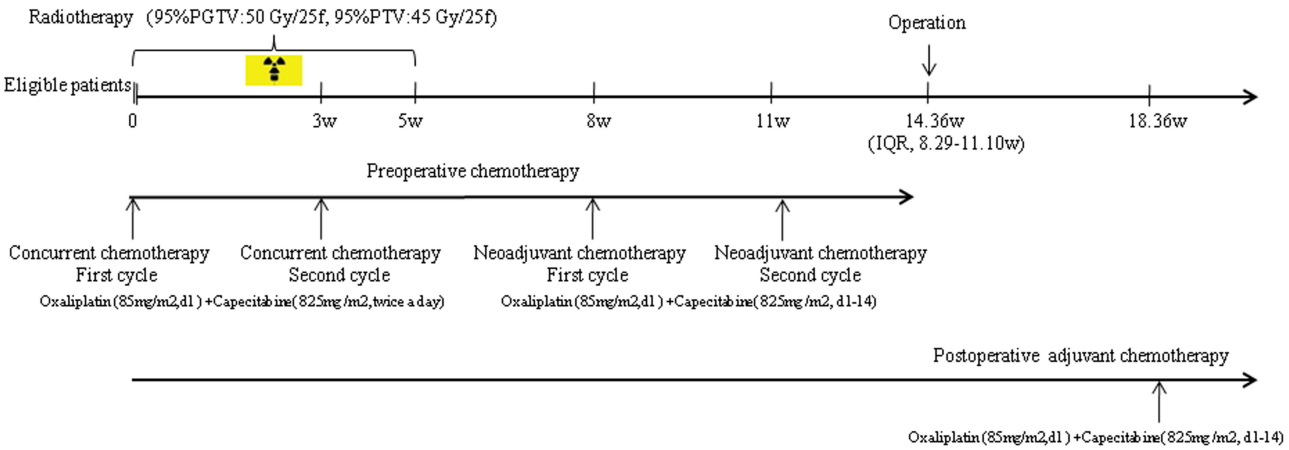

Figure 1 Flow chart of preoperative chemoradiotherapy in patients with rectal cancer.

(87.5%,140/160) received adjuvant chemotherapy after surgery. The median course of adjuvant chemotherapy was 4 cycles (IQR, 2–4.75), as shown in Table 2 for treatment compliance.

Operation

The median interval between the end of concurrent CRT and surgery was 9.36 weeks (IQR, 8.29–11.10). Among 180 patients, about 1 month after concurrent CRT, 20 patients were determined to be cCR after rigorous examination, and the

Table 1 Baseline Characteristics

Characteristic	No.	%
Age, years		
Mean (IQR)	60	
Range	51–66.25	
Sex		
Male	109	60.22%
Female	72	39.78%
Distance from anal verge		
≤5cm	81	44.75%
>5–10cm	72	39.78%
>10cm	19	10.50%
Uncertain	9	4.97%
Clinical T category		
cT1	1	0.55%
cT2	15	8.29%
cT3	150	82.87%
cT4a	8	4.42%
cT4b	7	3.87%

(*Continued*)

Table 1 (Continued).

Characteristic	No.	%
Clinical N category		
cN0	14	7.9%
cN1	90	49.72%
cN2	77	42.54%
Pathologic T category		
ypT0	38	23.75%
ypT1–2	52	32.5%
ypT3–4	70	43.75%
ypN0	113	70.63%
ypN1-2	47	29.37%
Perineural invasion		
Absent	10	6.25%
Present	150	93.75%
Lymphovascular invasion		
Absent	7	4.38%
Present	153	95.62%
EMVI		
Absent	35	19.34%
Present	146	80.66%
mrCRM		
Absent	99	54.70%
Present	82	45.30%
CEA		
Normal	149	82.32%
Abnormal	32	17.68%

patients chose not to undergo surgery and waited for observation. Most of these patients are elderly and complicated with other diseases.160 patients underwent radical surgery, R0 resection rate was 100%, median lymph node dissection was 8 (range: 0–34). The metastatic abdominal para-aortic lymph node was found in one patient after concurrent CRT, and CyberKnife radiotherapy as local treatment was performed and followed TME surgery. All the 160 patients who received radical surgery were R0 resections, and in that 138 (86.25%, 138/160) patients received sphincter preservation operation. Among these patients with sphincter preservation, 133 patients (96.38%, 133/138) undergone preventive stoma and 5 patients (3.62%, 5/138) experienced anastomosis directly. Up to the last follow-up time, the total stoma closure rate was 83.5% (111/133). Among the 86 patients with low rectal cancer, 12 (14.0%, 12/86) patients diagnosed with cCR chose

Table 2 Treatment Compliance with Preoperative Chemoradiotherapy and Consolidation Chemotherapy

Treatment Compliance	N(%)
Radiotherapy (45Gy) complete rates	180 (99.45)
Concurrent chemotherapy	
Full dose	175 (96.69)
Monotherapy in second cycle	5 (3.31)
No. of chemotherapycyclesduring intermission between the end of chemoradiatherapy and surgery	
1	142 (88.75)
2–4	18 (11.25)
No. of consolidation chemotherapy cycles	
0	20 (12.5)
1–2	39 (24.37)
3–4	66 (41.25)
>5	35 (21.88)

a watchful waiting strategy after comprehensive evaluation, and 74 patients received radical surgery including 54 (73.0%, 54/74) patients received sphincter preservation operation and the stoma closure rate was 81.5% (44/54).

Short-Term Effects

Among 160 patients who received surgery, the rectal tumors were reduced to varying degrees after concurrent CRT and preoperative chemotherapy. Thirty-eight patients achieved pathologically proven pCR and the tumor complete remission rate was 23.75% (38/160). In general, there were 58 cases (32.22%, 58/180),14 cases (7.78%,14/180),39 cases (21.67%,39/180),69 cases (38.33%, 69/180) in TRG 0, 1, 2, 3, respectively. TRG grade 0/1 (complete response and significant response) was 72 cases (40%, 70/180). In terms of tumor downstaging, 89 (55.63%) had T downstaging while 115 (71.88%) had N downstaging in the 160 patients who underwent surgery.

Long-Term Effects

Among the 181 patients, 8 patients were lost to follow-up after postoperative adjuvant chemotherapy, and 173 patients were regularly followed up. As of December 2021, the median follow-up time was 37.37 months (range, 6.33–131.17 months), and the median survival time was not reached. Median survival was not reached. The 1-OS,2-OS,3-OS and 5-OS were 98.7%, 96.5%,91.4% and 81.5%, respectively (Figure 2A). The survival rate of patients who obtained pCR and cCR after concurrent CRT was significantly higher than patients who did not achieve pCR and cCR. (P = 0.013) (Figure 2B). The 1-DFS, 2-DFS and 3-DFS were 91.3%, 85.0%, 78.5%, respectively. During the follow-up, 15 patients died, and local recurrence rate was 5.78% (10/173), distant metastasis rate was 10.40% (18/173), and lung was the most common site of distant metastasis (7.51%, 13/173). Of the 86 patients with low rectal cancer, 3 patients had local recurrence and 4 patients had distant metastasis. The 3-LRFS, 3-DMFS and 3-CSS were 83.4%, 80.1%, 92.6%, respectively. There was no statistical significance in OS between anus preservation and non-anus preservation in patients with low rectal cancer (P = 0.740) (Figure 2C). During the observation and waiting period, no local tumor regeneration occurred in cCR patients. In a univariate analysis, age, ypN stage, ypTNM stage, tumor regression grade were prognostic factors for OS. In a multivariate analysis, only age, ypTNM stage and tumor regression grade were significantly associated with OS (Table 3).

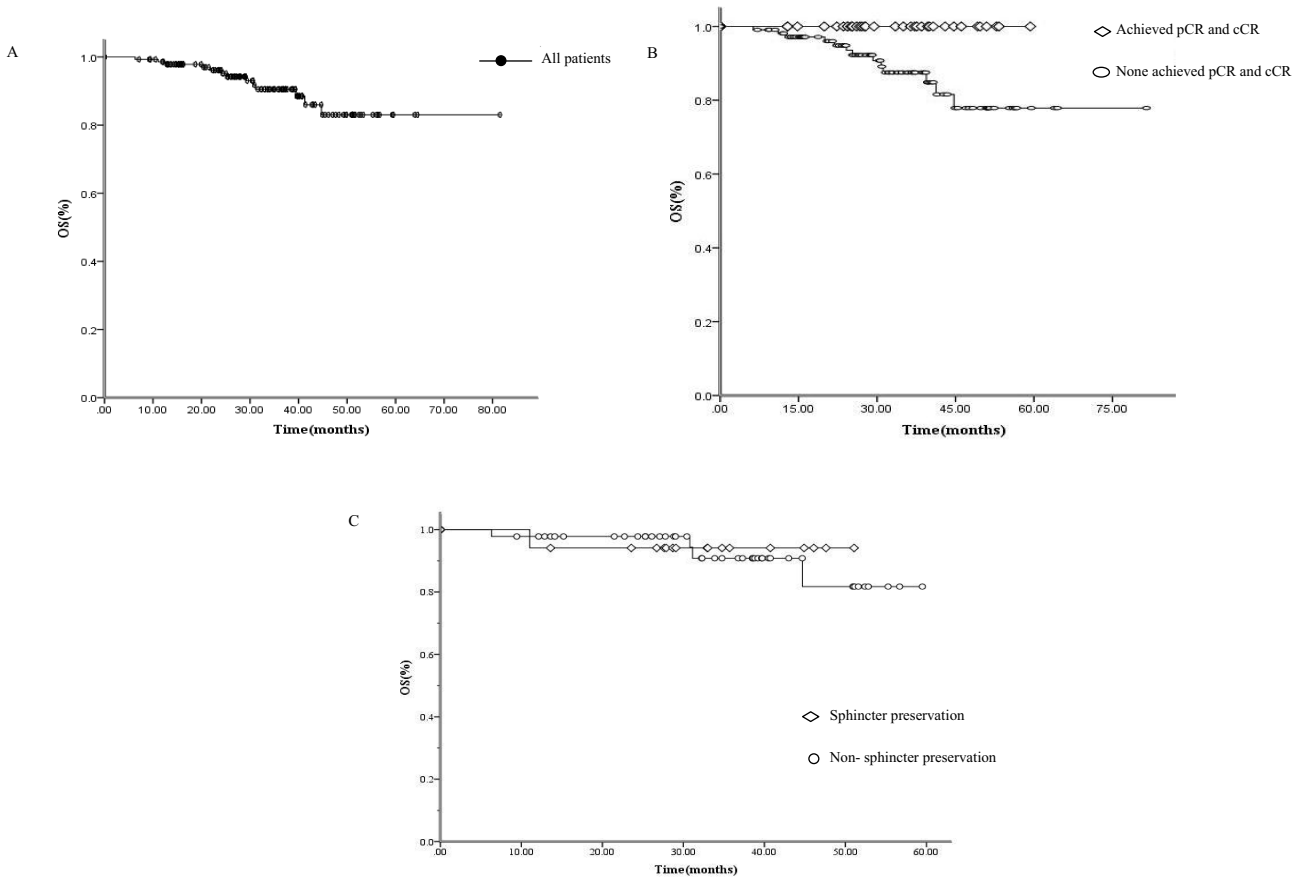

Figure 2 Overall survival (OS). (**A**) All patients in the study. (**B**) Achieved pCR vs None achieved pCR, *P* = 0.013. (**C**) Sphincter preservation vs Non- sphincter preservation in patients with low rectal cancer, *P* = 0.740.

Acute Adverse Reactions To preoperative CRT

In the process of neoadjuvant CRT, adverse reactions of the whole group of patients are shown in Table 4. A total of 15 kinds of adverse reactions occurred, 35 (19.34%) cases of above degree III adverse reactions. The most common adverse reactions were myelosuppression, mainly leukopenia and thrombocytopenia, followed by diarrhea, proctitis, nausea, obstipation, anorexia, and regurgitation of gastric acid. Other reactions such as dyspepsia, intestinal spasm, radioactive cystitis, radioactive enteritis, and abnormal liver function are relatively rare. One patient developed low rectal ileus after 14 times of radiotherapy, and concurrent CRT was terminated and emergency surgery was performed. No death complications related to neoadjuvant radiotherapy and chemotherapy were observed. Five patients presented with grade III to IV myelosuppression, relieved after expectant treatment.

Postoperative Complications

Postoperative complications are shown in Table 5. There were no deaths among the 160 patients due to intraoperative and postoperative complications. Thirty-three patients developed postoperative complications, mostly infection and anastomotic leakage, with a complication rate of 20.62%, most of which were improved by conservative treatment.4 patients underwent secondary surgery due to postoperative complications, including 1 patient who underwent abdominal irrigation due to postoperative anastomotic leakage, 1 patient underwent mesentery hemostasis due to small-bowel mesenteric hemorrhage, 1 patient underwent neostomy due to postoperative ileus, and 1 patient underwent incisional hernia repair due to postoperative incisional hernia.

Table 3 Subgroup Analysis for Overall Survival (OS)

	Univariate HR(95% CI)	*P*	Multivariate HR(95% CI)	*P*
Age (<65 vs≥65years=	3.564 (1.177–10.789)	**0.025**	5.263 (1.607–17.233)	**0.006**
Sex (female vs male)	0.286 (0.063–1.293)	0.104	–	–
cT (cT1-2 vs T3-4)	0.91 (0.117–7.093)	0.928	–	–
cN (cN0 vs cN1-2)	23.089 (0.005–115,016.914)	0.470	–	–
ypN (ypN0 vs ypN1-2)	4.442 (1.508–13.084)	**0.007**	–	–
ypTNM (0 vs 1 vs 2 vs 3)	2.779 (1.352–5.712)	**0.005**	2.499 (1.133–5.510)	**0.023**
Distance from anal verge (≤5cm vs>5–10cm vs>10cm)	1.059 (0.567–1.978)	0.858	–	–
Postoperative chemotherapy	1.427 (0.316–6.447)	0.644	–	–
Intervals between end of preoperative chemoradiotherapy and surgery (≤8w vs>8w)	0.677 (0.227–2.018)	0.484	–	–
Perineuralinvasion (Absent vs Present)	1.984 (0.156–25.215)	0.597	–	–
Lymphovascular invasion (Absent vs Present)	1.352 (0.061–29.807)	0.849	–	–
Tumor regression grade	2.459 (1.151–5.252)	**0.02**	2.732 (1.131–6.597)	**0.025**
EMVI (Absent vs Present)	0.371 (0.046–2.973)	*0.350*	–	–
mrCRM (Absent vs Present)	1.088 (0.153–7.767)	*0.933*	–	–

Notes: *P*<0.05 display in bold font.
Abbreviation: HR, hazard ratio.

Discussion

The purpose of this study was to analyze the efficacy and safety of preoperative intensive CRT and whether it could increase the anal retention rate, especially in patients with low rectal cancer. In this retrospective study, preoperative intensive CRTcould achieve satisfied PCRrate (23.75%) and the tumor regression grade, anus preservation rate and survival rates were also considerable. Regarding patients with low rectal cancer, all patients underwent R0 resection with a low incidence of postoperative complications and, most encouragingly, sphincter preservation rate was 73.0%and the stoma closure rate was 81.5%without affecting the local control rates and survival rates.

To date, a substantial portion large phase III studies involved the addition of oxaliplatin to preoperative CRT have been reported worldwide.[6,17–20] From PCR perspective, the addition of oxaliplatin increased the degree of rectal tumor regression and, in particular, the PCR rate of FOWARC study in China reached a new high (29%). The degree of tumor regression after CRT depends on the tumor's inherent sensitivity to radiation and chemotherapy drugs, the dose of radiotherapy, the intensity of chemotherapy and the time from the end of treatment to the review. In most studies, oxaliplatin was used in the common treatment mode of "radiotherapy sensitizer", generally 50~60 mg/(m^2·w), which was used synchronously with radiotherapy for 5 weeks, and the dose intensity was completely different from systemic chemotherapy. In the present and FOWARC studies, oxaliplatin was synchronized with radiotherapy in standard systemic chemotherapy mode and drug dose. Meanwhile, in this study, researchers adopted the strategy of adding preoperative neoadjuvant chemotherapy with oxaliplatin to make good use of the waiting period of 8–10 weeks during the waiting period between long-term concurrent CRT and surgery, which was in line with the treatment wishes of patients and increased the preoperative treatment intensity. However, up till now, it is not clear how many cycles of preoperative neoadjuvant chemotherapy are optimal, most patients received one cycle of oxaliplatin-added neoadjuvant chemotherapy with a modest extension of the time between the end of concurrent CRT and surgery in the present study. This strategy has been proved to be effective and safe in previous trials,[2,21] which augment the therapeutic reactivity of the tumor in

Table 4 Acute Adverse Effects in Patients After Received Preoperative Chemoradiotherapy

Toxicity	Grade 1–2	Grade 3–4	Total
Leukocytes	131	20	151
Platelets	68	6	74
Hemoglobin	51	7	58
Diarrhea	64	1	65
Proctitis	42	1	43
Nausea	28	0	28
Obstipation	21	0	21
Anorexia	20	0	20
Regurgitation of gastric acid	15	0	15
Indigestion	5	0	5
Intestinal spasm	2	0	2
Radiocystitis	2	0	2
Radiation enteritis	1	0	1
Hepatic dysfunction	1	0	1
Ileus	0	1	1

Table 5 Postoperative Complications in Patients After Received Preoperative Chemoradiotherapy

Complications	n
Infection	7
Anastomotic leakage	6
Wound-healing problems	4
Pelvic cavity effusion	3
Ileus	3
Anastomotic stenosis	2
Fistula (small bowel)	2
Voiding dysfunction	1
Small-bowel mesenteric Hemorrhage	1
Voiding dysfunction	1
Intestinal adhesion	1
Incisional hernia	1
Hydronephrosis	1

this study and tumor descent rate without increasing the surgical difficulty, risk and surgical complications. Compared with single-agent fluorouracil standard preoperative CRT, this retrospective analysis contained oxaliplatin in standard drug doses in capecitabine-based preoperative concurrent CRT and two additional cycle of neoadjuvant chemotherapy between the end of concurrent CRT and surgery, as a consequence, our treatment might be called as "intensified".

Combined with the above analysis, enhancive intensity of preoperative CRT may be attributed to a relatively high PCR rate (23.75%) in patients with locally advanced rectal cancer, which was higher than the results of the five phases III clinical trials (CAO/ARO/AIO-04:17%, ACCORD-12:19%, STAR-01:16%, NSABP R-04:20%, PETACC-6:14%).[5–9] The 3-OS of the present retrospective study was 91.4%, slightly higher than that of CAO/ARO/AIO-04 (88.7%) which showed positive results only. This may be related to the addition of oxaliplatin into concurrent CRT, preoperative neoadjuvant chemotherapy and postoperative adjuvant chemotherapy. Furthermore, our multivariate analysis suggested that the OS of the patients receiving pCR was significantly longer than patients without pCR. Although the preoperative pCR rate achieved was not the ultimate goal of treatment, with the increase of pCR rate, the improvement of R0 excision rate and overall survival rate will increase accordingly.

Since a few years ago, standard treatment for rectal cancer has increasingly been challenged by the notion of total neoadjuvant therapy (TNT). However, the lack of strong and unequivocal evidence generated substantial heterogeneity in terms of recommendations from international guidelines and treatment patterns across centres.[22] Compared with randomized clinical studies related to TNT in rectal cancer, pCR results (23.75%) in our study were lower than those in the randomised phase III RAPIDO (28.4%)[23] and PRODIGE 23 (27.8%)[24] trials. But when including patients who achieved cCR, the total complete response rate in the present study was as high as 32.22%. In addition, our results show that the 3-OS and 3-DFS in our study are surprisingly similar to or even slightly higher than the results of these randomized clinical studies related to TNT.[23–26] In terms of the rate of sphincter preservation operation, our results (86.25%) showed similar to the result (86%) in UNICANCER-PRODIGE 23 study.[24]

At present, local recurrence rate of rectal cancer after preoperative CRT and TME surgery is significantly reduced by optimizing local treatment and the local recurrence rate is below 10%,[24] which was basically the same result as 6% in this study. The main cause of death in LARC patients is distant metastasis, about 30%,[27] and the role of systemic therapy is getting increasing attention. In this retrospective study, oxaliplatin was added to preoperative CRT, the distant metastasis rate was 11% during a median follow-up of about 3 years. It is suggested that enhancive intensity of preoperative CRT may reduce the risk of systemic metastasis to some extent, and neoadjuvant chemotherapy in this study during the interval between preoperative concurrent CRT and surgery may also potentially reduce the risk of distant metastasis.

With the extension of survival and the demand of quality of life, organ function preservation has also been cumulatively emphasized. In the present study, after intensified preoperative CRT, 20 patients achieved cCR in preoperative evaluation, and the watch-and-wait strategy was adopted to avoid surgery and preserve organs. Following intensified preoperative CRT local advanced rectal cancer obviously diminished and even disappeared as well as obtained considerable pCR and TRG rates. Of the 160 patients with R0 resection, the total sphincter preservation rate in this study was 86.25%, and most encouragingly, the rate was 73% in patients with a tumour <5 cm from the anal verge without affecting local control rates and survival rates.

According to studies, elevated preoperative CEA levels have been shown to be associated with poorer survival and increased recurrence in several studies; however, contradictory studies do exist.[28,29] In our study, elevated treatment CEA was not associated with decreased overall survival. In subgroup analysis, older age, ypT3-4, 2, higheryp TNM, ypN1-grade and poor tumor regression stage corresponds to the patients with poor prognosis, and this result was similar to other studies.[4,17,30,31] Therefore, for some patients who were not sensitive and had poor efficacy to preoperative treatment, postoperative adjuvant therapy may need to be strengthened, while an adjuvant chemotherapy regimen of oxaliplatin combined with capecitabine may provide additional benefits for these high-risk patients.

The most frequent toxicities after preoperative CRT were myelosuppression, diarrhea, proctitis, vomiting, obstipation and anorexia. Nearly all toxic reactions were improved after symptomatic treatment without affecting the course of radiotherapy and chemotherapy. It was reported that one of the most frequent radiation-induced rectal toxicities of any grade was diarrhea (up to 35%).[32] Consistent with that systematic review, the incidence of diarrhea in the present retrospective analysis was similar and did not increase with the intensity of the preoperative CRT.3–4 grade the incidence of adverse reactions was 19.66%, lower than that (38%) in a phase III trial carried out to evaluate the use of irinotecan

combined with capecitabine-based neoadjuvant CRT in patients with rectal cancer[27] and that (27%) in CAO/ARO/AIO-12 clinical trial.[33] No patients were inoperable or died due to synchronous neoadjuvant CRT, and the overall incidence of postoperative complications was 20.7%, which was lower than that of CAO/ARO/AIO-12 (35%).[26] None of the patients in this group had perioperative death.

Several limitations of this retrospective analysis deserve mention. First, because the study was a single-arm retrospective analysis and did not include stratification, unrecognised factors might have contributed to the differences reported. Second, a small number of patients with cCR to the intensified preoperative CRT refused surgery and were excluded from the analyses; thus, the proportion of patients who achieved a pCR may have been underestimated.

In conclusion, the results of this study indicate that preoperative intensive CRT could achieve satisfied PCR rate and the tumor regression grade, anus preservation rate and survival rates were also considerable in our institution. Most encouragingly, benefiting from a high sphincter preservation rate and the stoma closure rate, quality of life for patients with low rectal cancer was impressively improved without affecting local control rate and survival rate. On the basis of these findings, a phase III study to definitively test the intensified preoperative CRT strategy is warranted.

Disclosure

The authors report no conflicts of interest in this work.

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