A Retrospective Analysis of Locally Advanced Rectal Cancer Treated by Neoadjuvant Chemoradiotherapy Combined With Surgery

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Research

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Abstract

Purpose

Neoadjuvant chemoradiotherapy (nCRT) has been recommended as a standard treatment for locally advanced rectal cancer. In our study, we retrospectively analyzed the oncological outcomes of patients with stage II-III rectal cancer who were treated in our department.

Patients and Methods

During March 2014 to June 2020, total 139 patients were retrospectively reviewed, of whom 121 were analyzable. All of our enrolled patients with stage II to III rectal cancer were treated with nCRT with a capecitabine-based regimen, total mesorectal excision surgery, and an adjuvant capecitabine-based chemotherapy regimen. We examined the pathologic complete response (pCR) rate after neoadjuvant chemoradiotherapy, 3-year overall survival (OS), and disease-free survival (DFS) and investigated adverse factors related to the survival of this group of patients. We used the Kaplane-Meier method and Cox modeling to estimate and compare survival in our populations.

Results

With a median follow-up of 36 months, overall survival at 3 years was 83.2%, and disease-free survival at 3 years was 74.4% in this arm. After multivariate adjustment, ypTNM stage(TNM stage after neoadjuvant therapy) was significantly associated with disease-free survival (DFS). A positive circumferential resection margin (CRM) status on MRI and ypTNM stage were significantly related to a worse overall survival (OS). Among the 121 patients, 24 achieved a pCR (19.8%); two patients did not complete radiation therapy. Eighteen patients died due to a cancer-related cause.

Conclusion

The oncological outcomes of nCRT at our institution are comparable with those of other clinical studies on rectal cancer in which patients were treated with neoadjuvant therapy. Among the 121 patients, 24 had a pCR (19.8%). ypTNM stage was significantly associated with DFS; CRM status and ypTNM stage were were significantly related to overall survival (OS) after multivariate analysis.

Introduction

Neoadjuvant or preoperative chemoradiotherapy (nCRT) followed by total mesorectal excision (TME) have become the standard treatment strategies for locally advanced (T3-4 or N+) rectal cancer (LARC) in the United States, Germany, and Europe after several clinical trials[1–5]. Numerous clinical studies have confirmed that the efficacy of neoadjuvant chemoradiotherapy is superior to that of neoadjuvant radiotherapy or neoadjuvant chemotherapy alone[6]. NCRT has led to a better quality of life by increasing anal preservation operations, a decreased risk of local recurrence result from consistent tumor and lymph node downstaging and a remarkably higher rate of pathologic complete response (pCR) [6,7]. Radiation

therapy concurrent with capecitabine chemotherapy is the standard nCRT treatment based on clinical studies[8,9]. Some study reported adding oxaliplatin to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy significantly improved the DFS of patients with stage II/III rectal cancer[10,11]. Other studies[9,12,13] demonstrated that the addition of oxaliplatin to single drug capecitabine as neoadjuvant chemoradiotherapy for locally advanced rectal cancer did not improve pCR or DFS. PCR rates after neoadjuvant therapy ranged from 10.9-32%[10,14–17]. The disease-free survival rate at 5 years was 68%, and the overall survival rate at 10 years was 59.6% for the neoadjuvant chemoradiotherapy group of the German CAO/ARO/AIO-94 Randomized Phase III Trial[1]. This rate was higher than that in the EORTC 22921[2] trial, in which the 10-year overall survival and 10-year disease-free survival rates were 50·7% and 46·4%, respectively, in the long-term results from the preoperative chemoradiotherapy arm.

Recently, more attention has been given to the overall neoadjuvant treatment[14,18,19] of LARC and the management of patients with clinical complete response by the watch-and-wait method after neoadjuvant chemoradiotherapy for rectal cancer[20], but long-term outcomes need to be followed.

In the study, we describe the oncological outcomes of LARC patients who were treated at our department with neoadjuvant chemoradiotherapy (nCRT) followed by total mesorectal excision (TME) and adjuvant chemotherapy. The main study endpoints included the pCR rate, OS and DFS. The secondary study endpoints were prognostic factors associated with survival.

Materials And Methods

Eligibility of patients

Patients aged 18-75 years old with histopathologically confirmed, newly diagnosed primary rectal adenocarcinoma lied ≤12 cm above the anal verge and considered suitable for curative resection were eligible. All patients who were analyzed had image-confirmed (pelvic magnetic resonance images) advanced rectal cancer (T3/4 or N+) without distant metastasis (M0) after conventional chest and abdominal computed tomography (CT) scans prior to visiting our MDT clinic, which includes colorectal surgeons, oncologists, radiologists, radiologists, and pathologists. According to the protocol, patients with one or more the following potentially high-risk factors were recommended to receive nCRT: a positive circumferential resection margin (CRM) status on MRI; cT3 within 5 cm from the anal verge tumor; a cT4 stage tumor that has adjacent organ involvement; or cN2 disease (≥four lymph nodes). All patients' physical condition and organ function were assessed to confirm that they were eligible for treatment. Patients were also required to have a Karnofsky performance status score ≥ 70 and adequate marrow, liver, and renal function. The main exclusion criteria were confirmed metastatic disease, clinically significant cardio-cerebrovascular disease, and diagnosed peripheral neuropathy. The study was approved by the central ethics committee and informed consent was obtained from all participants before the initial treatment.

Treatment

Patients were placed in the treatment position, and simulated CT scans were performed with a full bladder. The clinical target volume (CTV) includes the primary rectum tumor, and any significant surrounding lymphadenopathy and high-risk nodal area, including the mesorectal, presacral, internal iliac and obturator lymph nodes. The planning target volume (PTV) was defined as the CTV plus a 0.7-cm margin to make up system error and organ motion. Radiotherapy was delivered with 6-MV photons via intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) to include the PTV. Patients were assigned to a total dose of 45-50.4 Gy in 25-28 fractions over 5-6 weeks and the dose was required to include the 95% isodose line.

Patients received concurrent chemotherapy, either with capecitabine (825 mg/m2 twice daily 5 d/week) or CapeOX (oxaliplatin 50 mg/m2 IV weekly and capecitabine 625 mg/m2 twice daily 5d/week) during radiation therapy followed by capecitabine (capecitabine 1250 mg/m2 twice daily on days 1-14) or capecitabine combined with oxaliplatin (CapeOX) 2 weeks after the end of CRT (oxaliplatin 130 mg/m2 on day 1 and capecitabine 1,000 mg/m2 twice daily on days 1-14) before surgery. Irinotecan in combination with capecitabine was used selectively in some patients based on the UGT1A1 status according to a Chinese clinical trial[17]. Capecitabine was administrated at 625 mg/m2 twice daily for 5d/week, and weekly irinotecan (irinotecan was given weekly at a dose of 80 mg/m2 or 65 mg/m2 to patients with the UGT1A1*1*1 genotype or the UGT1A1*1*28 genotype, respectively), followed by one cycle of capecitabine plus irinotecan (XELIRI) two weeks after the completion of nCRT (irinotecan 200 mg/m2 on day 1 and capecitabine 1,000 mg/m2 twice daily on days 1-14).

Several studies have shown that adding additional chemotherapy between the end of nCRT and TME surgery improved survival outcomes[14]. We performed MRI examinations approximately 6-7 weeks after the completion of chemoradiation to evaluate the status of tumor regression. Then, 0-4 cycles of chemotherapy were arranged preoperatively after nCRT according to the patient's condition and MRI assessment. Generally, radical surgery was arranged 8-12 weeks after the completion of nCRT. Patients with poor tumor regression on MRI considered for additional more chemotherapy courses.

We took patient age, comorbidities, the Karnofsky performance status score, surgical complications, and pathological stage into consideration before selecting adjuvant chemotherapy regimens. Adjuvant chemotherapy started 4 weeks after surgery, or when patients recovered from surgery. Treatment options included capecitabine (1250 mg/m2 twice daily on days 1-14) or CapeOX (oxaliplatin 130 mg/m2 on day 1 and capecitabine 1000 mg/m2 twice daily on days 1-14), both scheduled every 3 weeks until 6 months of perioperative chemotherapy was completed.

Follow-up

The patients were required to consult with the physician weekly or at the time of discomfort and the physician should record the patient's symptoms, make physical examination, monitor peripheral blood

cell counts, biochemistry and evaluate therapeutic toxicity during treatment.

Posttreatment follow-up was carried out every 3 months for the first 2 years from the completion of treatment and at 6-month intervals thereafter. Evaluations consisted of a physical examination, KPS assessment and peripheral blood cell counts, biochemistry and carcinoembryonic antigen (CEA) tests were performed during every follow-up, and any significant findings were documented. Rectoscopy and imaging examination were performed according to clinical indications.

End point and statistical methods

We aimed to report the PCR rate after neoadjuvant chemoradiotherapy and 3-year oncological outcomes for overall survival and disease-free survival. In addition, we investigated the adverse factors related to the survival of this group of patients. We conducted all statistical analyses by SPSS version 26.0 software (IBM Corporation). Survival data and differences were calculated with the Kaplan-Meier method. Overall survival (OS) was defined as the time of initial treatment to death from any reason. Disease-free survival (DFS) was defined as the time of initial treatment to the date of disease locoregional recurrence or distant metastasis or death. Patients who did not experience the interest events were analyzed as censored observations at the time of last follow-up. A Cox proportional hazards regression model was used to perform multivariate analysis of prognostic factors. A two-sided P value ≤.05 was considered significant. Categorical variables between the arms were compared by the chi-square test. Analyses of the main end points were performed as time- to-event data.

Results

Patient details

Between March 2014 and June 2020, a total of 139 consecutive advanced rectal cancer patients were diagnosed and treated at our institution with neoadjuvant chemoradiotherapy (nCRT) and total mesorectal excision (TME) with/without postoperative chemotherapy. A total of 121 of 139 patients were eligible for this analysis, while the other 18 patients were excluded owing to ineligibility, among whom 10 were found to have distant metastases preoperatively or intraoperatively, 2 were complicated with other diseases and 6 were older than 75 years. Almost all the patients were in good condition with the KPS score over 70 when they visited the doctor. Table 1 presents the patients' baseline characteristics. Our study population consisted of 76 males and 45 females, with a median age of 56 years old (range 22–75 years). Among the 121 patients, 24 achieved a pCR (19.8%). Potentially high-risk factors defined by imaging were as follows: 59 patients (48.8%) had a positive circumferential resection margin (CRM) status (by MRI); 42 patients (34.7%) were staged as having cT4 disease with the invasion of adjacent organ(s); 48 patients (39.7%) had low-lying tumors; and 73 patients (60.3%) had cN2 disease (≥4 lymph nodes). Based on postoperative pathology, 15 patients had N1C disease (tumor deposits in the pelvic tissues); 20 patients had perineural invasion; PCR was obtained in 24 cases and 20, 39, and 38 patients had pathological stages □, □, and □, respectively. In this study, patients were staged on the basis of the

eighth edition American Joint Committee on Cancer/International Union for Cancer Control staging criteria.

Table 1
Baseline clinical characteristics of patient.

Clinical Characteristics	Patients (n =121)
Age,years	
Median (range)	56 (22-75)
Sex, n (%)	
Male	76 (62.8)
Female	45(37.2)
Distance from the anal verge (cm), n (%)	
0 to ≤10 (lower-mid)	48 (39.7)
>5 to 12 (mid to high)	73 (60.3)
Clinical T stage, n (%)	
T3	79 (65.3)
T4	42 (34.7)
Clinical N stage, n (%)	
N0	12 (9.9)
N1	36 (29.8)
N2	73 (60.3)
MRI CRM, n (%)	
Negative	62 (51.2)
Positive	59 (48.8)
PCR, n (%)	24 (19.8)
Pathological T stage	
T0	27(22.3)
T1	2(1.7)
T2	20(16.5)
T3	65(53.7)
T4	7(5.8)
Pathological N stage	
N0	84(69.4)

Clinical Characteristics	Patients (n =121)
N1	27 (22.3)
N2	10 (8.3)
Lymphatic vascular invasion	
Yes	2 (1.6)
No	119 (98.3)
Perineural invasion (PNI)	
Yes	15 (12.4)
No	106 (87.6)
TRG	
0	24 (19.8)
1	38 (31.4)
2	51 (42.1)
3	8 (6.6)
Pathological stage	
0	24 (19.8)
I	20 (16.5)
II	39 (32.2)
III	38 (31.4)

Only two patients failed to complete the planned course of nCRT. Both of them refused nCRT at 18 Gy and 20 Gy because they could not tolerate the treatment toxicity. A total of 119 patients completed neoadjuvant radiotherapy, all of whom received pelvic radiation. All these patients received concurrent chemotherapy, 75 with concurrent capecitabine (CapRT), 12 with concurrent capecitabine and irinotecan (CapIriRT) and 34 with concurrent capecitabine and oxaliplatin (CapeOXRT). According to our institutional protocol, 24 patients with the UGT1A1 genotype *1*1 or *1*28 were enrolled in the CinClare study[17] and randomized to the experimental group (radiation with capecitabine combined with irinotecan followed by irinotecan and capecitabine) or the control group (radiation with concurrent capecitabine (12), followed by CapeOX). The median time from the end of chemoradiotherapy to surgery was 8 weeks (interquartile range: 1-20 weeks). During the interval between nCRT and surgery, 100 patients received chemotherapy, and 21 patients did not receive any consolidation therapy. In total, 121 patients underwent TME surgery.

Seventy-six (62.8%) patients received adjuvant chemotherapy after TME. A total of 37 (30.6%) patients did not undergo systemic adjuvant treatment: 11 due to a pCR, 10 without high-risk pathological factors, 2 due to patient refusal, 8 due to poor postoperative recovery or complications, 2 because of medical contraindications, and 4 due to rapid disease progression. In addition, 8 (6.6%) patients did not complete a full chemotherapy course due to therapeutic toxicity.

Two patients had a positive circumferential resection margin (CRM) status on pathological specimens. Lymphatic vascular invasion occurred in 3 patients. Twenty-four (19.8%) patients achieved a pathological complete response (pCR) after TME. Thirty-eight (31.4%) had only microscopic foci; 51 (42.1%) had partial regression; and 8 (6.6%) reported no tumor regression. The distribution of pathological downstaging is shown in Table 3. A total of 94(77.7%) patients had N downstaging,71(58.7%) had T downstaging and 60(49.6%) had both N downstaging and T-downstaging; 42(34.7%) of these patients had downstaging to pathological stage I disease (ypT0-2N0) after nCRT, on whom radical surgery can be performed completely.

Twenty-seven of 121 patients who received TME have developed recurrent or metastatic cancer. Distant failure was the most common mode of failure and occurred in 25 patients. The most common organ of distant metastasis was the lung (n=9). Other types of distant failure included liver disease (n=3), bone metastasis (n=3), peritoneal disease (n=2), para-aortic lymph node metastasis (n=1), inguinal lymph node metastasis (n=1), and breast metastasis (n=1). Simultaneous multiple sites metastases were detected in 5 individuals. Three patients were observed pelvic recurrence, and one patient presented with synchronous local and distant diseases. Most of the failures were asymptomatic and were detected by an increase in CEA levels followed by subsequent imaging. A total of 18 patients have died from tumor-related causes.

Survival outcomes

Survival curves were generated to evaluate OS and DFS by Kaplan-Meier methoed. A Cox regression model were used to performed univariate and multivariate analyses in order to find out different prognostic factors associated with survival (univariate analysis is shown in Table 2). Related factors for 3-year OS and DFS were investigated in univariate and multivariable analyses that included age, sex, circumferential resection margin (CRM) by MRI, tumor regression grade, perineural invasion, pathological T stage, pathological N stage, ypTNM stage, pathological N1c stage (tumor deposits), completion of adjuvant chemotherapy at a full course, pathological complete response, synchronous chemotherapy regimen, and chemotherapy during the interval before surgery.

Table 2
Univariate analysis of OS and DFS.

Factors	OS		DFS	
	Univariate X^2	p-Values	Univariate X^2	p-values
Age	0.266	0.606	1.829	0.176
Sex (female VS male)	0.16	0.693	0.407	0.524
Positive circumferential resection margin (CRM) status (yes vs no)	9.968	0.002	1.379	0.240
Tumor regression grade (per 1 grade increase)	30.710	0.000	14.280	0.003
Perineural invasion (PNI)	9.191	0.002	2.246	0.134
Pathological T stage	4.606	0.330	7.475	0.113
Pathological N stage	23.621	0.000	19.557	0.000
Pathological stage (PCR, I, II, III, IV)	18.079	0.000	21.206	0.000
Pathological N1c stage (yes vs. no)	13.684	0.000	15.358	0.000
Completion of adjuvant chemotherapy (yes vs. no)	0.015	0.902	1.697	0.193
Pathological complete response (yes vs. no)	2.978	0.084	6.386	0.012
Synchronous chemotherapy regimen	2.659	0.265	0.915	0.633
Chemotherapy during the interval before surgery (yes VS no)	0.121	0.728	0.037	0.847

Table 3
Pathological downstaging after nCRT.

Pathological downstaging	n	Proportion (%)
T downstaging	71	58.7%
N downstaging	94	77.7%
Both T and N downstaging	60	49.6%

The 3-year OS was 83.2% (Fig. 1A). The 3-year DFS was 74.4% (Fig. 1B). Univariate analysis of OS showed that MRI CRM status, tumor regression grade, pathological N stage, ypTNM stage, pathological N1c stage, and perineural invasion (PNI) had p-values ≤ 0.05. After multivariate adjustment, MRI CRM

status (X^2=7.431, p=.006), and ypTNM stage (X^2=8.192, p=.042) remained significant (Fig. 2A1-2). Univariate analysis revealed that tumor regression grade, pathological N stage, ypTNM stage, PCR and pathological N1c stage (tumor deposits) potentially influenced DFS, but only ypTNM stage (X^2=14.101, p=.003) remained related to DFS after multivariate analysis (Fig. 2B).

Discussion

The pCR rate in our study was 19.8%, which is comparable to local and international clinical trial data. In the German CAO/ARO/AIO-04 trial[10], a pCR rate was 17% in the fluorouracil and oxaliplatin arm and 13% in the fluorouracil arm after surgery. The CAO/ARO/AIO-12 trial[14] reported that a pCR of the intention-to-treat individuals was achieved in 17% of group A patients who were received three cycles induction chemotherapy of fluorouracil, leucovorin, and oxaliplatin before fluorouracil/oxaliplatin CRT (50.4 Gy) and in 25% of group B patients with consolidation chemotherapy after CRT. Other TNT-related studies[19] had similar pCR rates. A Chinese study[17] in which we included 24 patients had a pCR rate of up to 30% in the experimental group. It is worth mentioning that 5 (41.7%) out of 12 patients who received CapIriRT, 8 (23.5%) out of 34 in the CapeOXRT arm and 11 (14.7%) out of 75 in the CapRT arm achieved a pCR, respectively, at our institution. According to the UGT1A1 genotype, choosing radiotherapy in combination with irinotecan and capecitabine as neoadjuvant therapy may be an innovative, promising treatment option[17]. It is worth putting forward that the addition of irinotecan was also associated with increase in the occurrence of grade 3-4 toxicities. Long-term follow-up will determine if the improvement in the pCR is translated into improved survival.

Thirty-four patients were treated with oxaliplatin combined with capecitabine chemotherapy during radiotherapy. Adding oxaliplatin to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy significantly improved the disease-free survival of patients with staged stage II/III rectal cancer compared with a former fluorouracil-based combined regimen (based on CAO/ARO/AIO-94)[1]. Seventy-five patients in our study received combinations with concurrent capecitabine chemotherapy during radiotherapy based on clinical studies[8,9]. Twelve patients received concurrent capecitabine and irinotecan (CapIriRT)[17], and the efficacy and safety were demonstrated in previous clinical studies[21,22]. There were no obviously differences were found in OS and DFS among different concurrent chemotherapy regimens in our study. Some studies have shown that adding additional chemotherapy between the end of nCRT and surgery improved survival outcomes[14]. After neoadjuvant therapy, there was little tumor regression based on MRI, and we gave the patient more interval consolidation therapy. Three to four cycles of chemotherapy were arranged for 7 patients. Generally, TME surgery was scheduled for 8-12 weeks after the completion of nCRT. We found that 45patients failed to complete all of the chemotherapy cycles. There were also no significant differences in OS and DFS among patients who did and did not complete postoperative chemotherapy at the full dose (yes vs. no) in our study. It is consistent with another study that showed the value of adjuvant chemotherapy might be controversial[23]. However, Sandra-Petrescu F et al pointed that the complete administration of chemotherapy cycles after

surgery were associated with improved the overall and disease-free survival at 5 years in patients with locally advanced rectal cancer[24].

Pelvic MRI were required to performed for all our patients to help their staging evaluation before radiation and surgery, similar to other studies[15]. This allows a better assessment of the efficacy of neoadjuvant therapy and patient staging. In this study, the MRI CRM status was an independent prognostic factor for OS. Preoperative MRI examination can confirm the status of CRM, which can help to make more individualized treatment plans. During follow-up, regular MRI can detect local recurrence and metastasis earlier and help to provide timely intervention treatment.

The 3-year OS was 83.2%, and the 3-year DFS was 74.7% (Fig. 1). After multivariate adjustment, MRI CRM status (X^2=7.431, p=.006), and ypTNM stage (X^2=8.192, p=.042) remained significant for OS (Fig. 2A1-2). The 3-year OS with PCR, yp stage I, II, III was 94.4%, 81.3%, 92.9%, and 67.6%, respectively. The 3-year OS with or without CRM positivity was 72.1% and 93.8%, respectively. ypTNM stage (X2=14.101, p=.003) was the only independent risk factor for DFS after multivariate Cox regression analysis (Fig. 2B). The 3-year DFS rates with PCR, yp stage I, II, III were 95.7%, 72.7%, 85.1% and 50%, respectively.

One study from Hong Kong[15] reported that the 3-year and 5-year OS rates were 77.2% and 63.9%, respectively. The 3-year and 5-year DFS rates were 69.4% and 68.3%, respectively. The survival of patients with positive CRM was significantly reduced compared with those with negative CRM and the 3-year OS for CRM-negative patients was 88.3%. After multivariate adjustment, only suspected CRM and histological grade remained significant for OS. Only suspected CRM and pathological N stage remained significant after multivariate adjustment for DFS. A phase III Germany study[8] showed that the 5-year overall survival in the capecitabine arm was not inferior to that in the fluorouracil arm (76% vs 67%; p=0.0004); 3-year disease-free survival was 75% and 67% in the capecitabine group and the fluorouracil group (p=0·07), respectively. The results of FFCD 9203[3] show that there was no difference for neoadjuvant radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers in the 5-year OS and 5-year PFS in both arms (67.9% *v* 67.4%; and 55.5% *v* 59.4%). The total 5-year overall survival rate for all groups was 65.2% in the EORTC Radiotherapy Group Trial 22921[5]. The German CAO/ARO/AIO-04 study published its final results in 2015: the 3-year disease-free survival was 75·9% in the investigational group (infusion fluorouracil and oxaliplatin) and 71.2% in the control group in which patients were underwent chemotherapy with fluorouracil-based combined modality regimen.

Several large trials of TNT[14,18,25,26] have reported that TNT had the following therapeutic advantages: it significantly increased the completion of systemic treatment, improved tumor regression, reduced the incidence of tumor-related treatment metastasis and recurrence and increased the CCR ratio and W&W probability. Choosing the watch-and-wait strategy for carefully selected patients who have achieved a clinical complete response with neoadjuvant therapy may be feasible[20]. As research progresses, individualized treatment plans need to be developed for specific patients.

The main reason for treatment failure in our group was mainly distant metastasis, so ways to implement systemic treatment more effectively is are important. An increasing number of clinical studies have shown that the initial treatment of TNT is satisfactory. At present, we are conducting research on TNT or on choosing a chemotherapy regimen according to the UGT1A1 genotype, aiming to obtain better clinical results and reduce distant failures. Encouraging oncological results were obtained at the 3-year follow-up but needed to be confirmed with longer follow-up. A more detailed analysis of the toxicity and quality of life will be published separately.There are some limitations in our study, such as insufficient sample size and short follow-up time. We will extend the duration of treatment and continue follow-up to overcome the associated deficiencies.

Conclusion

Patients with stage II/III rectal cancer achieved a relatively high pCR rate after neoadjuvant therapy, and the 3-year survival showed promising oncological outcomes. Yp TNM stage was significantly associated with disease-free survival (DFS); MRI CRM status and yp TNM stage were significant factors for overall survival (OS) after multivariate analysis. Distant metastasis is the dominant mode of treatment failure, and it is crucial to optimize systemic treatment for newly diagnosed patients.

Abbreviations

nCRT: neoadjuvant or preoperative chemoradiotherapy; TME :total mesorectal excision; LARC: locally advanced rectal cancer; CRM: circumferential resection margin; DFS: disease - free survival; FU: fluorouracil; MRI: magnetic resonance imaging; OS: overall survival; pCR: pathologic complete response; Vs: versus; CEA, carcinoembryonic antigen; LN, lymph node; PNI: Perineural invasion; TRG: tumor regression grade; ypTNM stage: TNM stage after neoadjuvant therapy(patients were staged on the basis of the eighth edition American Joint Committee on Cancer/International Union for Cancer Control staging criteria).

Declarations

Ethical Approval and Consent to participate

The study was approved by the central ethics committee and informed consent was obtained from all participants before the initial treatment.

Consent for publication

The authors consent to publish the article.

Availability of supporting data

All data generated or analyzed during this study are included in this article. Individual participant data will not be available.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Fei Li, Chi Zhang and Liping Xu, collected the clinical data, analyzed the data and drafted the manuscript, Jiayan Chen and Xinchen Sun drafted and revised the manuscript; All authors read and approved the final version of the manuscript.

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Figures

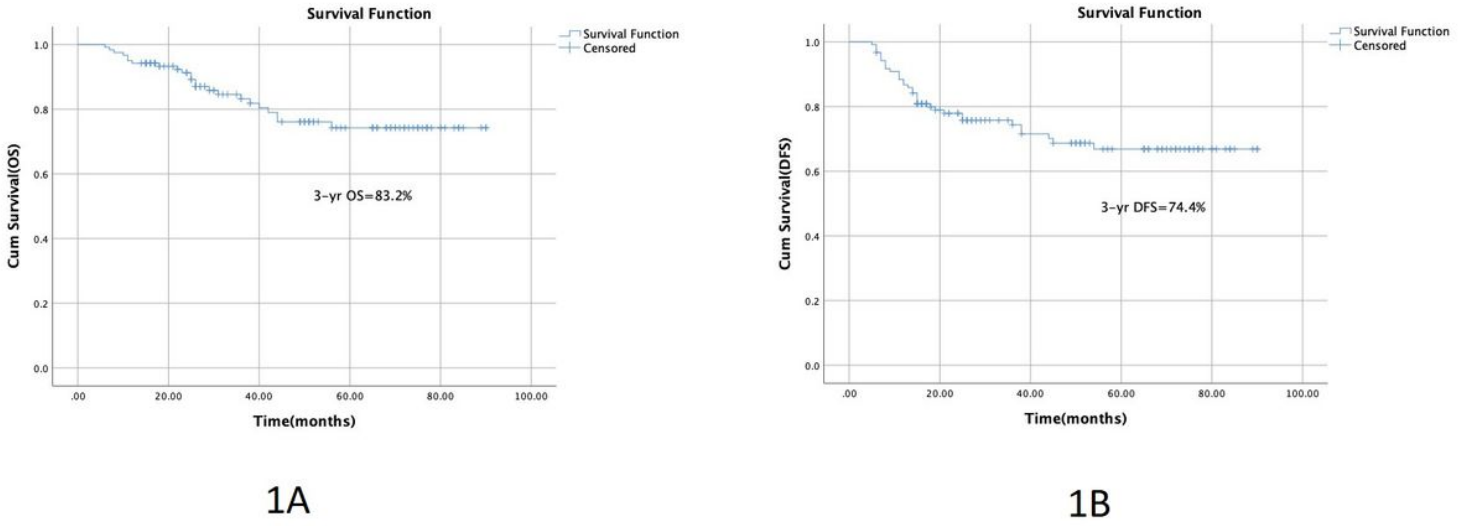
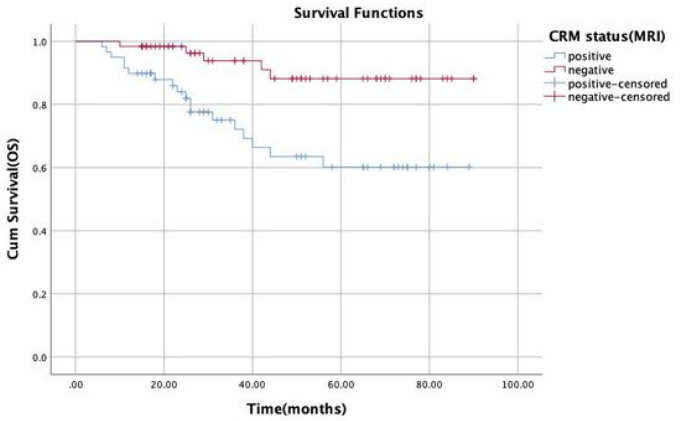
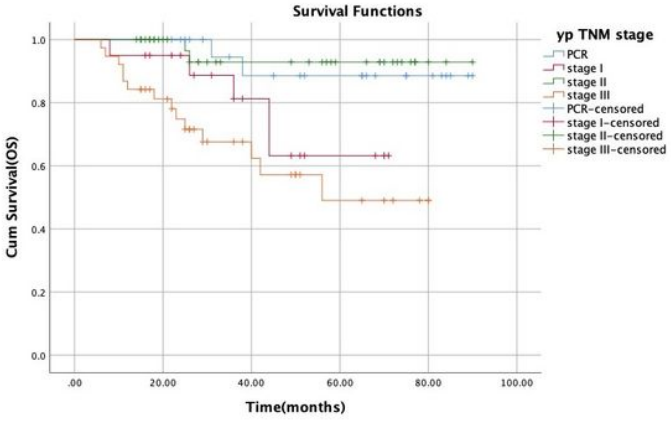


Figure 1

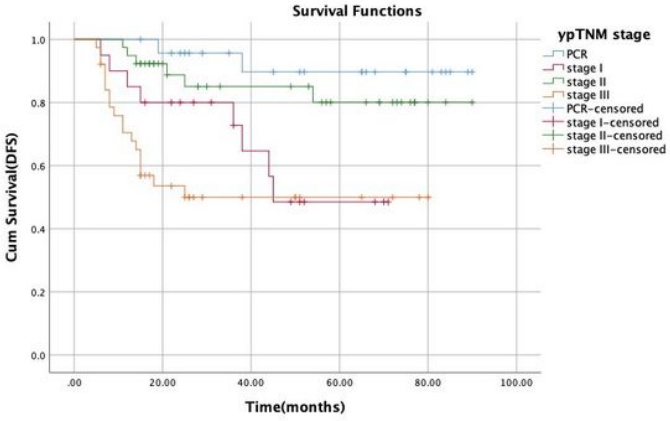
Kaplan-Meier curves. Kaplan-Meier estimates for (A) OS and (B) DFS (n =121). OS = Overall survival; DFS =Disease-free survival.



2A-1



2A-2



2B

Figure 2

Kaplan-Meier curves. Kaplan-Meier estimate for subgroups; OS = overall survival; DFS =disease-free survival; ypTNM stage: TNM stage after neoadjuvant therapy.