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ORIGINAL ARTICLE

Retrospective Study

Prediction of pathological complete response and prognosis in locally advanced rectal cancer

Yi-Jun Xu, Dan Tao, Song-Bing Qin, Xiao-Yan Xu, Kai-Wen Yang, Zhong-Xu Xing, Ju-Ying Zhou, Yang Jiao, Li-Li Wang

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Abstract

BACKGROUND

Colorectal cancer is currently the third most common malignant tumor and the second leading cause of cancer-related death worldwide. Neoadjuvant chemoradiotherapy (nCRT) is standard for locally advanced rectal cancer (LARC). Except for pathological examination after resection, it is not known exactly whether LARC patients have achieved pathological complete response (pCR) before surgery. To date, there are no clear clinical indicators that can predict the efficacy of nCRT and patient outcomes.

AIM

To investigate the indicators that can predict pCR and long-term outcomes following nCRT in patients with LARC.

METHODS

Clinical data of 128 LARC patients admitted to our hospital between September 2013 and November 2022 were retrospectively analyzed. Patients were categorized into pCR and non-pCR groups. Univariate analysis (using the χ^2 test or Fisher's exact test) and logistic multivariate regression analysis were used to

study clinical predictors affecting pCR. The 5-year disease-free survival (DFS) and overall survival (OS) rates were calculated using Kaplan-Meier analysis, and differences in survival curves were assessed with the log-rank test.

RESULTS

Univariate analysis showed that pretreatment carcinoembryonic antigen (CEA) level, lymphocyte-monocyte ratio (LMR), time interval between neoadjuvant therapy completion and total mesorectal excision, and tumor size were correlated with pCR. Multivariate results showed that CEA ≤ 5 ng/mL (P = 0.039), LMR > 2.73 (P = 0.023), and time interval > 10 wk (P = 0.039) were independent predictors for pCR. Survival analysis demonstrated that patients in the pCR group had significantly higher 5-year DFS rates (94.7% *vs* 59.7%, P = 0.002) and 5-year OS rates (95.8% *vs* 80.1%, P = 0.019) compared to the non-pCR group. Tumor deposits (TDs) were significantly correlated with shorter DFS (P = 0.002) and OS (P < 0.001).

CONCLUSION

Pretreatment CEA, LMR, and time interval contribute to predicting nCRT efficacy in LARC patients. Achieving pCR demonstrates longer DFS and OS. TDs correlate with poor prognosis.

Key Words: Locally advanced rectal cancer; Neoadjuvant chemoradiotherapy; Pathological complete response; Carcinoembryonic antigen; Inflammation-related markers; Tumor deposit; Prognosis

Core Tip: At present, there are no clinical indicators clearly related to the efficacy and long-term outcomes of neoadjuvant chemoradiotherapy (nCRT) for locally advanced rectal cancer (LARC). In this study, inflammation-related markers and tumor deposits (TDs) were added. The final results showed that pretreatment carcinoembryonic antigen ≤ 5 ng/mL, lymphocyte-monocyte ratio > 2.73, and time interval between neoadjuvant therapy completion and total mesorectal excision > 10 wk are independent predictors of nCRT efficacy in LARC patients. Patients achieving pCR have longer disease-free survival and overall survival. Among patients without pCR, TDs are positively correlated with poor prognosis.

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INTRODUCTION

Rectal cancer is one of the most common malignant tumors worldwide. According to a recent survey, there has been a significant increase in the incidence of colorectal cancer, especially among younger individuals[1]. Approximately 70% of patients are diagnosed with locally advanced rectal cancer (LARC) at their first visit[2]. LARC is characterized by tumor invasion of the muscularis propria or regional lymph nodes. The standard care for LARC is a sandwich regimen, consisting of neoadjuvant chemoradiotherapy (nCRT), total mesorectal excision (TME) and adjuvant chemotherapy. This comprehensive approach not only decreases tumor stage, but also significantly improves the rate of surgical resection and anal retention[3]. Pathological complete response (pCR) rates in LARC patients with nCRT ranged from 14.9% to 38.5% [4].

pCR is defined as no viable tumor cells found on pathological examination after treatment. A comprehensive meta-analysis has shown that pCR plays a significant role in predicting the prognosis of patients treated with nCRT. The results indicate that patients who achieve pCR after nCRT have a significantly better prognosis than those who do not achieve pCR[5]. Patients with pCR can choose a watch and wait approach, a nonoperative management approach that can avoid surgery-related complications such as sexual dysfunction and urinary dysfunction. In addition, it can improve the quality of life of patients. However, accurately predicting which patients will achieve pCR remains a significant clinical challenge. At present, we confirm that whether patients achieve pCR mainly depends on pathological examination, which is an invasive and costly procedure. It is necessary to explore accessible, inexpensive, reliable indicators for clinical prediction of pCR. Appropriate indicators are conducive to individualized treatment and prognostic evaluation of LARC patients. Thus, this study investigated potential predictors associated with efficacy after nCRT in LARC patients. The subsequent exploration will delve into the correlation between pCR and prognosis.

MATERIALS AND METHODS

Patient characteristics

From September 2013 to November 2022, 181 patients with pathologically confirmed rectal cancer underwent nCRT at the First Affiliated Hospital of Soochow University. According to the inclusion and exclusion criteria, 128 LARC patients were assigned to the pCR group (42 patients) or the non-pCR group (86 patients).

Inclusion criteria were as follows: (1) Age 18-75 years; (2) Rectal cancer diagnosed by histology and pathology; (3) cT3/4 or cN+, M0; (4) Good general condition, Eastern Cooperative Oncology Group performance score 0-2; and (5) Long-term radiotherapy and TME. Exclusion criteria were as follows: (1) Incomplete clinical or pathological data; (2) Preoperative short-course radiotherapy; (3) Multiple primary cancers or other malignant tumors in the past 5 years; and (4) Palliative treatment.

Treatment

Patients in both groups received nCRT. The irradiated sites included the primary tumor, positive pelvic lymph nodes, and lymph drainage areas. The delineation of clinical target volume was completed with reference to the radiation therapy oncology group[6]. The dose of radiotherapy was 45-50.4 Gy, 1.8-2.0 Gy each time, which was completed in 25-28 fractions. All patients received 0-2 cycles of induction chemotherapy and 1-4 cycles of concurrent chemotherapy. The chemotherapy regimen was XELOX (oxaliplatin 130 mg/m^2 on day 1, capecitabine 1 g/m^2 twice daily for 14 d; 21 d as one cycle) or capecitabine monotherapy (825 mg/m^2 twice daily, taken on the day of radiotherapy). Surgery and adjuvant chemotherapy were performed after neoadjuvant therapy. All operations followed the principle of TME.

Data collection

The following data were collected using the Electronic Medical Record System: (1) General data: Gender, age, weight, height, body mass index (BMI); (2) Diagnostic information: Tumor size, distance from the anal verge to rectal cancer, tumor circumference proportion, cT/N stage, and tumor-node-metastasis stage; (3) Treatment information: Preoperative radiotherapy plan and concurrent chemotherapy regimen, and time interval between neoadjuvant therapy completion and TME; (4) Tumor makers: Carcinoembryonic antigen (CEA), carbohydrate antigen (CA)19-9, CA125, and CA724 before nCRT; and (5) Blood routine and inflammation-related markers: White blood cell (W) count, neutrophil (N) count, platelet (P) count, lymphocyte (L) count, monocyte (M) count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), systemic immune-inflammation index (SII), panimmune inflammation value (PIV), SII = P × N/L, PIV = N × P × M/L.

pCR is defined as ypT0N0M0 by the American Joint Committee on Cancer (AJCC) staging system (9th edition); overall survival (OS) as the time from the beginning of neoadjuvant therapy to the last follow-up or death; and disease-free survival (DFS), as the time between the beginning of neoadjuvant therapy and disease metastasis or recurrence or death as a result of any cause.

Statistical analysis

Continuous variables, such as tumor size and inflammation-related factors, were converted into categorical variables based on the optimal cut-off value determined by receiver operating characteristic curve and Youden Index. The association between categorical variables and pCR was compared using either the χ^2 test or Fisher's exact test. Variables that showed a significant association with pCR on univariate analysis ($P < 0.05$) were included in the multivariate logistic regression analysis. Kaplan-Meier analysis calculated 5-year DFS and OS rates, and the log-rank test compared the difference in survival curves. $P < 0.05$ was considered statistically significant. All data were statistically analyzed using SPSS version 26.0 (IBM Corporation, Armonk, NY, United States). Figures were drawn by R software (R Development Core Team 2014, www.r-project.org).

RESULTS

This study collects relevant data on 128 patients, aged 28-75 years, with an average age of 58 years. Postoperative pathology showed pCR in 42 cases (32.8%) and non-pCR in 86 cases (67.2%); two cases (1.56%) of vascular tumor thrombus, 14 cases of tumor deposits (TDs) (10.94%), and six cases of nerve invasion (4.69%). The optimal cut-off values of NLR, PLR, LMR, SII, and PIV were 3.05, 117.08, 2.73, 284.51, and 102.41, respectively. We divided them into high groups (> optimal cut-off value) and low groups (≤ optimal cut-off value). The clinical indicators, tumor marker levels, and inflammation-related markers of the 128 patients are shown in Table 1.

Univariate and multivariate analysis of pCR after nCRT for LARC

The χ^2 test or Fisher's exact test was used for comparisons. Post-nCRT pCR of LARC was not related to gender, age, BMI, cT stage, cN stage, distance from the anal verge to rectal cancer, tumor circumference proportion, chemotherapy, CA19-9, CA125, CA153, CA724, NLR, PLR, SII, and PIV, but was associated with CEA ($P = 0.021$) and LMR levels ($P = 0.019$), time interval ($P = 0.028$), and tumor size ($P = 0.038$) (Table 2). Logistic regression multivariate analysis showed that CEA ≤ 5 ng/mL ($P = 0.039$) and LMR > 2.73 ($P = 0.023$), time interval > 10 wk ($P = 0.039$) were independent predictors of pCR after nCRT in LARC (Table 3).

Table 1 Characteristics of patients with or without pathologic complete response

Factors	*n* (%)
Gender	
Male	97 (75.8)
Female	31 (24.2)
Age group (yr)	
≤ 60	65 (50.8)
> 60	63 (49.2)
BMI (kg/m^2)	
< 18.5	9 (7.0)
18.5-23.9	64 (50.0)
≥ 24	55 (43.0)
cT stage	
cT3	105 (82.0)
cT4	23 (18.0)
cN stage	
cN0	11 (8.6)
cN+	117 (91.4)
Distance from the anal verge to rectal cancer (cm)	
≤ 5	65 (51.6)
> 5	62 (48.4)
Tumor size (cm)	
≤ 5.75	95 (74.2)
> 5.75	33 (25.8)
Tumor circumference proportion	
≤ 1/2	18 (14.1)
> 1/2	110 (85.9)
Chemotherapy	
XELOX	88 (68.8)
Capecitabine monotherapy	7 (5.5)
Others	33 (25.8)
Time interval (wk)	
≤ 6	15 (11.7)
6-10	85 (66.4)
> 10	28 (21.9)
CEA (ng/mL)	
≤ 5	73 (57.0)
> 5	55 (43.0)
CA199 (U/mL)	
≤ 37	105 (82.0)
> 37	23 (18.0)
CA125 (U/mL)	
≤ 35	124 (96.9)

> 35	4 (3.1)
CA153 (U/mL)	
≤ 25	126 (98.4)
> 25	2 (1.6)
CA724 (U/mL)	
≤ 8	118 (92.2)
> 8	10 (7.8)
NLR	
≤ 3.05	92 (71.9)
> 3.05	36 (28.1)
PLR	
≤ 117.08	46 (35.9)
> 117.08	82 (64.1)
LMR	
≤ 2.73	24 (18.8)
> 2.73	104 (81.2)
SII	
≤ 284.51	16 (12.5)
> 284.51	112 (87.5)
PIV	
≤ 102.41	17 (13.3)
> 102.41	111 (86.7)
pCR	
Yes	42 (32.8)
No	86 (67.2)

BMI: Body mass index; CEA: Carcinoembryonic antigen; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio; SII: Systemic immune-inflammation index; PIV: Pan immune inflammation value; pCR: Pathologic complete response.

Survival analysis

The deadline for the last follow-up was February 1, 2024. The follow-up time of all patients ranged from 15 to 101 months, with a median follow-up time of 36 months. There were two cases of local recurrence by the end of follow-up; a total of 27 cases of distant metastasis, including eight simple liver metastasis, nine simple lung metastasis, one simple bone metastasis, and nine multiple metastases. Sixteen patients died and six were lost to follow-up. The 5-year DFS rate of 128 LARC patients was 69.8% and the 5-year OS rate was 85.0%.

The pCR group demonstrated significantly better 5-year DFS than the non-pCR group (94.7% *vs* 59.7%, $P = 0.002$) (Figure 1A). The 5-year OS rates were 95.8% and 80.1% for the pCR group and non-pCR group, respectively, with a significant difference between the two groups of patients ($P = 0.019$) (Figure 1B). TDs were found in 14 of 86 non-pCR patients (16.2%) after surgery. The TDs- group exhibited a higher DFS rate at 5 years compared to the TDs+ group (94.7% *vs* 38.6%, $P = 0.002$) (Figure 1C). Similarly, the TDs- group had a higher 5-year OS rate of 85.9% compared to the TDs+ group rate of only 52.9% ($P < 0.001$) (Figure 1D). These findings suggest that patients in the TDs+ group experienced lower DFS and OS rates when compared to those in the TDs- group.

DISCUSSION

In recent years, there has been a consensus on two critical points regarding the treatment of patients with LARC: (1) nCRT followed by TME and adjuvant chemotherapy is the standard for patients with LARC[7]; and (2) pCR following nCRT is a predictive indicator for a more favorable outcome in patients[5]. However, we do not know whether a patient achieves pCR until after surgery, so it cannot provide guidance for neoadjuvant therapy. Previous studies have explored various methods, including magnetic resonance imaging[8], endorectal ultrasonography[9], and molecular markers[10] to

Table 2 Univariate analysis of pathologic complete response after neoadjuvant chemoradiotherapy for locally advanced rectal cancer

Factor	Non-pCR (*n* = 86)	pCR (*n* = 42)	χ^2	*P* value
Gender			0.64	0.422
Male	67	30		
Female	19	12		
Age group (yr)			0.015	0.902
≤ 60	44	21		
> 60	42	21		
BMI (kg/m^2)			0.162	0.922
< 18.5	6	3		
18.5-23.9	42	22		
≥ 24	38	17		
cT stage			0.575	0.448
cT3	69	36		
cT4	17	6		
cN stage			-	0.750
cN0	7	4		
cN+	79	38		
Distance from the anal verge to rectal cancer (cm)			0.061	0.805
≤ 5	45	21		
> 5	41	21		
Tumor size (cm)			4.317	0.038
≤ 5.75	59	36		
> 5.75	27	6		
Tumor circumference proportion			0.351	0.554
≤ 1/2	11	7		
> 1/2	75	35		
Chemotherapy			2.313	0.323
XELOX	59	29		
Capecitabine monotherapy	3	4		
Others	24	9		
Time interval (wk)			-	0.028
≤ 6	12	3		
6-10	61	24		
> 10	13	15		
CEA (ng/mL)			5.288	0.021
≤ 5	43	30		
> 5	43	12		
CA199 (U/mL)			1.559	0.212
≤ 37	68	37		
> 37	18	5		
CA125 (U/mL)			-	0.597

≤ 35	84	40		
> 35	2	2		
CA153 (U/mL)			-	0.550
≤ 25	85	41		
> 25	1	1		
CA724 (U/mL)			-	0.295
≤ 8	81	37		
> 8	5	5		
NLR			1.781	0.182
≤ 3.05	65	27		
> 3.05	21	15		
PLR			0.675	0.411
≤ 117.08	33	13		
> 117.08	53	29		
LMR			5.528	0.019
≤ 2.73	21	3		
> 2.73	65	39		
SII			1.640	0.200
≤ 284.51	13	3		
> 284.51	73	39		
PIV			0.766	0.381
≤ 102.41	13	4		
> 102.41	73	38		

BMI: Body mass index; CEA: Carcinoembryonic antigen; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio; SII: Systemic immune-inflammation index; PIV: Pan immune inflammation value; pCR: Pathologic complete response.

Table 3 Multivariate analysis of pathologic complete response after neoadjuvant chemoradiotherapy for locally advanced rectal cancer

Factor	OR	95%CI	*P* value
Tumor size > 5.75 cm	0.440	0.156-1.235	0.119
Time interval			0.039
≤ 6 wk	reference		-
6-10 wk	1.602	0.391-6.562	-
> 10 wk	4.854	1.045-22.540	-
CEA > 5 ng/mL	0.405	0.172-0.954	0.039
LMR > 2.73	4.761	1.236-18.338	0.023

CEA: Carcinoembryonic antigen; LMR: Lymphocyte to monocyte ratio; OR: Odds ratio; CI: Confidence interval.

predict the short-term efficacy of nCRT. Despite these efforts, an accurate evaluation method remains unclear. Therefore, there is a crucial need to identify simple and reliable indicators for evaluating the sensitivity of nCRT. Our study investigated the role of clinical indicators in assessing the efficacy and prognosis of nCRT, which is important for the development of nCRT for rectal cancer.

CEA is a tumor-related antigen that was first derived from colon cancer and embryonic tissue. It serves as a prognostic marker in colorectal cancer for diagnosis and monitoring response to therapy[11]. A rapid increase in CEA levels indicates the potential presence of tumor. In this study, univariate analysis showed that patients with CEA ≤ 5 ng/mL were more likely to achieve pCR than those with CEA > 5 ng/mL (41.10% *vs* 21.82%, χ^2 = 5.288, *P* = 0.021). A retrospective

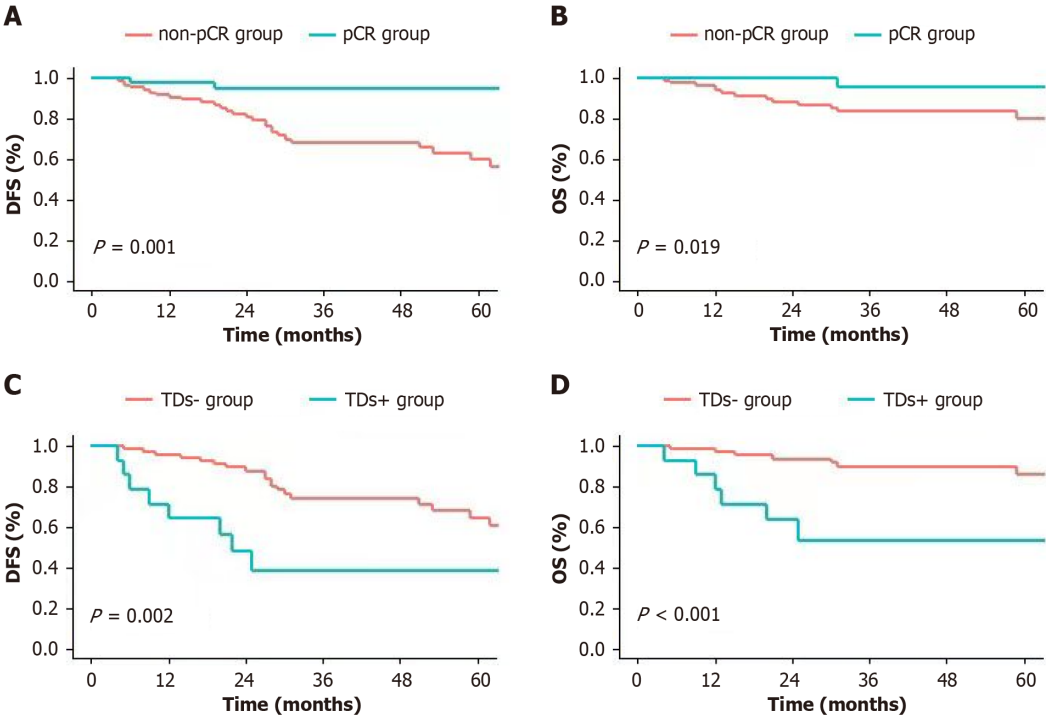

Figure 1 The Kaplan-Meier survival curves of overall survival and disease-free survival in different groups. A: Disease-free survival of pathological complete response (pCR) group and non-pCR group; B: Overall survival of pCR group and non-pCR group; C: Disease-free survival of tumor deposits (TDs)+ group and TDs- group; D: Overall survival of TDs+ group and TDs- group. pCR: Pathologic complete response; TDs: Tumor deposits; DFS: Disease-free survival; OS: Overall survival.

study analyzed 432 LARC patients who underwent nCRT and found a significant difference in pretreatment serum CEA levels between the pCR and non-pCR groups (2.6 *vs* 5.8 ng/mL, $P = 0.001$)[12]. Engel *et al*[13] found a correlation between CEA levels and nCRT efficacy. The high CEA level group (≥ 2.5 μg/L) exhibited a lower proportion of pCR than the low CEA level group (13.50% *vs* 30.10%, $P = 0.003$). This is in line with our results, which suggested that pretreatment CEA ≤ 5 ng/mL could be an independent predictor for pCR in LARC ($P = 0.039$). Patients with low levels of CEA exhibited a higher likelihood of achieving pCR.

As previously described, there is a clear link between inflammatory status and tumor progression. Therefore, inflammation-related markers are receiving increased attention in the assessment of nCRT efficacy for rectal cancer. The number and ratio of lymphocytes, monocytes, neutrophils, and platelets in peripheral blood before treatment are related to the clinical prognosis of colorectal cancer[14-16]. LMR indirectly reflects the variations in immune cells within the tumor microenvironment, and is related to the function of lymphocytes and monocytes. The elevation of LMR results from an increase in lymphocytes and/or a decrease in monocytes. Lymphocytes act as protective factors against tumor formation, and their increase serves as a positive prognostic indicator. In contrast, monocytes can promote tumor progression and suppress the anti-tumor immunity[17]. We revealed a correlation between LMR and pCR, with pCR being more common in the high LMR group (≥ 2.73) than in the low LMR group (< 2.73) (12.5% *vs* 31.45%, $\chi^2 = 5.528$, $P = 0.019$). Logistic regression analysis further identified LMR ≥ 2.73 as an independent predictor for pCR in LARC after nCRT [$P = 0.023$, odds ratio (OR) = 4.761, 95% confidence interval (CI): 1.236-18.338]. These findings align with the research of Li *et al*[18] that lower CEA can predict better pathological response to nCRT.

We evaluated the potential value of the time interval between neoadjuvant therapy completion and TME in LARC patients undergoing nCRT. An appropriate time interval can improve the rate of anal retention without increasing surgical complications. A too-short time interval is detrimental to tumor regression and complete resection, while an excessively long time interval may cause fibrosis in the radiation area, increase the difficulty of surgery, and delay optimal surgery timing[19,20]. In this study, the average time interval between neoadjuvant therapy completion and TME was 10 wk. Patients were categorized into three groups: ≤ 6 wk, 6-10 wk, and > 10 wk. The pCR rates for these groups were 46.4%, 28.2%, and 20.0%, respectively, with a significant difference ($P = 0.028$). Multivariate analysis confirmed that the time interval > 10 wk was an independent predictor of pCR for patients with LARC ($P = 0.039$, OR = 4.854, 95%CI: 1.045-22.540). A meta-analysis indicated that pCR was increased significantly in the long waiting interval group compared to the short waiting interval group[21]. This is consistent with another meta-analysis in 2022, which included 18 studies, and emphasized that time intervals > 8 wk after neoadjuvant treatment before surgery can significantly increase the pCR rate ($P < 0.00001$)[22]. In conclusion, prolonging the interval between nCRT completion and surgery is associated with better nCRT efficacy.

Many previous studies analyzed the relationship between tumor size and nCRT efficacy in patients with LARC. Shin *et al*[23] found that pretreatment tumor size < 4 cm was a significant independent clinical predictor for achieving pCR ($P < 0.001$, OR = 0.028, 95%CI: 0.136-0.383). Zhou *et al*[24] studied 124 patients, suggesting that patients with longitudinal

tumor length < 5 cm were more likely to achieve pCR (24.0% *vs* 9.46%, $P = 0.027$) but the multivariate analysis did not show significance. The results of our study showed that the optimal cut-off value was 5.75 cm, and a larger tumor size was associated with a worse outcome in univariate analysis ($\chi^2 = 4.317$, $P = 0.038$). However, tumor size before nCRT was not an independent predictor of pCR in LARC. This may be due to the limited number of cases, and further research is needed to validate its prognostic value. The findings from various studies diverge, and it is still uncertain whether tumor size is the influencing factor of pCR in LARC patients. We should pay more attention to the cut-off value of tumor size, as it may significantly affect the study outcomes.

In a phase 2 clinical trial, Hu *et al*[25] suggested that there was a relationship between the high pCR rate of nCRT in LARC and better long-term survival benefit. In our study, patients in the pCR group had a higher 5-year DFS rate (94.7% *vs* 59.7%, $P = 0.002$) and 5-year OS rate (95.8% *vs* 80.1%, $P = 0.019$) than those in the non-pCR group. Consistently, a meta-analysis of 21 studies revealed that pCR was related to better OS ($P < 0.001$) and DFS ($P < 0.001$) for digestive cancer patients who achieved pCR compared to those who did not. In the non-pCR group, TDs were found in 16.2% of patients after surgery. According to the AJCC staging (9th edition), patients with positive TDs but negative lymph nodes are classified as N1c. However, it should be noted that TDs are not considered in the N category for patients with positive lymph nodes. The formation mechanism of TDs remains unclear. Some researchers have suggested that TDs arise from lymph node metastasis, while others have considered that TDs are a destructive type of venous invasion[26,27]. In 2019, Wang *et al*[28] confirmed that TDs were an independent risk factor for LARC patients following nCRT. In 2021, Zheng *et al*[29] reported that patients with TDs had worse OS and relapse-free survival, using propensity score matching. A population-based study in 2022 was performed by Long *et al*[30], who found that the prognostic value of the number of TDs and lymph node metastasis was similar. Survival analysis showed that patients without TDs had higher 5-year OS rates (85.9%% *vs* 52.9%, $P < 0.001$) and 5-year DFS rates (94.7% *vs* 38.6%, $P = 0.002$). TDs were significantly associated with poor prognosis. Our results contribute to the staging approach based on TDs and suggest that radiologists should pay more attention to TDs in the initial diagnosis. In addition to the presence of TDs, is the number of TDs also associated with prognosis? This requires further study.

There were some limitations to our study. The main limitations were its retrospective design and small sample size. Further multi-institutional, prospective studies with larger sample sizes are needed to confirm our findings. Another limitation was that we only focused on the indicators before treatment; however, inflammation-related markers and tumor markers are dynamic. The correlation between nCRT and the dynamic changes of indicators needs further study. It is believed that with the continuous development of clinical medicine, the combination of composite inflammatory indicators, biomarkers, clinical factors, and pathology may have more potential in the clinical diagnosis, prediction, and treatment of rectal cancer.

CONCLUSION

Achievement of pCR in LARC patients after nCRT may depend on a pretreatment low level of CEA, high level of LMR, and longer interval between nCRT completion and surgery. Patients achieving pCR have longer DFS and OS, while those with TDs after surgery have worse prognosis.

FOOTNOTES

Author contributions: Xu YJ and Tao D contributed equally to this work as co-first authors. Xu YJ and Tao D designed and performed the research and wrote the paper; Xu XY, Yang KW, and Xing ZX designed the research and contributed to the analysis; Qin SB and Zhou JY provided clinical advice; Jiao Y and Wang LL contributed equally to this work as co-corresponding authors. They supervised the study project, contributed to the conception and design of the study, and played an important role in supervising the manuscript. We believe that designating Jiao Y and Wang LL as co-corresponding authors is fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity. and all the authors reviewed the various drafts of the manuscript and have approved the final version of the manuscript.

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