Pretreatment high cholesterol and low neutrophils predict complete pathological response after neoadjuvant short-course radiotherapy followed by chemotherapy and immunotherapy in locally advanced rectal cancer

FANGYUAN ZHANG[1,2], DANDAN YU[1,2], JINRU YANG[1,2], MENGLAN ZHAI[1,2], LISHA LI[1,2], LEI ZHAO[1,2], JING WANG[1,2], TAO ZHANG[1,2] and ZHENYU LIN[1,2]

[1]Cancer Center; [2]Institute of Radiation Oncology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430022, P.R. China

Received January 12, 2023; Accepted March 28, 2023

DOI: 10.3892/ol.2023.13905

Abstract. The present study was aimed at looking for hematological indicators that could predict pathological complete response (pCR) in patients with locally advanced rectal cancer (LARC) treated with short-course radiotherapy (SCRT) followed by chemotherapy and immunotherapy. A total of 171 patients were enrolled in this observational retrospective study. Pretreatment values of albumin, total cholesterol, lactate dehydrogenase, neutrophil, platelet and lymphocytes were available. Univariate and multivariate logistics analyses were used to determine the prognostic factor for pCR. SCRT followed by chemotherapy and immunotherapy was demonstrated to double the pCR rate (50.5%) compared with long-course chemoradiotherapy. For the former group, baseline high platelet to lymphocyte ratio (P=0.047), high cholesterol (P=0.026) and low neutrophils (P=0.012) level were associated with high pCR rate and baseline high cholesterol (P=0.016) and low neutrophils (P=0.020) level were the independent prognostic factors for pCR. In conclusion, pretreatment high cholesterol and low neutrophils were the independent prognostic predictors of pCR in patients with LARC treated with SCRT followed by chemotherapy and immunotherapy. Clinical trial no. NCT04928807, June 16, 2021.

Correspondence to: Dr Zhenyu Lin or Dr Tao Zhang, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 109 Machang Road, Wuhan, Hubei 430022, P.R. China
E-mail: whxhlzy@hust.edu.cn
E-mail: taozhangxh@hust.edu.cn

Key words: locally advanced rectal cancer, short-course radiotherapy, immunotherapy, pathological complete response

Introduction

Preoperative neoadjuvant long-course chemoradiotherapy (LC-CRT) is the current standard of therapy for locally advanced rectal cancer (LARC) with the lower edge of the tumor <10-cm from the anal verge (1). Since neoadjuvant short-course radiotherapy (SCRT) can achieve similar survival outcomes without significantly increasing toxicities compared with LC-CRT it can be used as an alternative option (2,3). Numerous studies have confirmed the synergistic effects between radiotherapy and immune checkpoint inhibitors (ICIs) (4,5). Radiotherapy can increase exposure to tumor antigens, alter the tumor microenvironment and promote the recruitment of inflammatory factors (6-8), and ICIs can simultaneously strengthen the ablility of the immune response of the patient against tumors. Based on these theories and studies, the present study conducted a phase 2 clinical trial of preoperative SCR followed by chemotherapy and camrelizumab as a treatment regimen for LARC, which showed a measurable increase in the pathological complete response (pCR) rate (48.1%; 13/27) (9). A phase 3 randomized controlled clinical trial is underway and the current results are concordant with the phase 2 results, showing a significant increase in pCR rate compared with preoperative neoadjuvant LC-CRT.

In rectal cancer, a number of patients may opt for watchful waiting treatment due to the presence of special situation of complete clinical remission (CCR). However, the dilemma is that there is no uniform definition of CCR. Moreover, there is controversy on watchful waiting as a treatment method (10). A prospective study has demonstrated that imaging is not a sensitive predictor of pCR in patients with rectal cancer. The accuracy of fluorodeoxyglucose positron emission tomography and computed tomography (CT) in predicting pCR is only 54 and 19%, respectively (11). This is also a hindrance when choosing treatment options (surgery or observation) in clinical practice. Therefore, early and correct identification of patients with pCR and avoiding them to have the operation is one of the urgent clinical issues to be addressed.

Numerous studies have demonstrated that economical and widely available hematological indicators are often

used to predict the prognosis of patients with cancer (12-14). For example, in patients with rectal cancer treated with neoadjuvant CRT, Huang *et al* (15) suggested that a higher neutrophil to lymphocyte ratio (NLR) pretreatment is associated with poorer prognosis, and that these patients not only have a higher risk of recurrence, but also have worse overall survival (OS) and disease-free survival (DFS). Even in patients with LARC treated with SCRT, high levels of NLR are independently associated with poor OS (16). Similarly, the platelet to lymphocyte ratio (PLR) is negatively associated with prognosis in patients with rectal cancer (17). In addition to these inflammatory indicators, there are a number of peripheral blood indicators that also reflect the prognosis of patients with cancer. For example, elevated lactate dehydrogenase (LDH) at baseline serves as a poor prognostic biomarker in advanced non-small cell lung cancer (18). A meta-analysis of 76 studies indicated that LDH is a predictive biomarker of prognosis in a variety of solid tumors (19). In metastatic colorectal cancer, patients with high LDH also have a poor prognosis (20). Notably, to the best of our knowledge, studies of LDH in the neoadjuvant treatment of LARC are rare.

The above findings suggest that baseline peripheral blood indicators, including NLR, PLR and LDH, can be used as predictors of prognosis in patients with cancer. Therefore, the aim of the present study was to investigate whether these indicators could predict the pathological response of patients with LARC treated with SCR followed by chemotherapy and camrelizumab, while also searching for hematological markers at baseline that may potentially play a predictive role.

Patients and materials

Patients. Eligible patients at Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (Wuhan, China) were enrolled in the present retrospective study between June, 2021 and October, 2022. The percentages of females were 35.2, 31.0 and 31.4% and the mean age were 56.91, 53.69 and 56.98 years in Arm A, Arm b and Arm C, respectively. The study was approved by the Institutional Ethics Committee of the Tongji Medical College, Huazhong University of Science and Technology (approval no. 0271-21). The inclusion criteria were as follows: i) Patients or their family members agree to participate in the study and sign the informed consent form; ii) aged 18-75 years, male or female; iii) histologically confirmed T3-44 and/or N+ rectal adenocarcinoma (AJCC/UICC TNM staging (8th Edition, 2017) (21); iv) inferior margin ≤10 cm from the anal verge; v) it is expected to reach R0; vi) Eastern Cooperative Oncology Group performance status score is 0-1; vii) can swallow pills normally; viii) untreated with antitumor therapy for rectal cancer, including radiotherapy, chemotherapy, surgery and traditional Chinese medicine; ix) surgical treatment is planned after neoadjuvant treatment; x) there was no operative contraindication; xi) laboratory tests were required to meet the following requirements: White blood cells $\geq 4x10^9/l$; absolute neutrophil count $\geq 1.5x10^9/l$; platelet count $\geq 100x10^9/l$; hemoglobin ≥90 g/l; serum total bilirubin ≤1.5x upper limit of normal (ULN); serum alanine aminotransferase and aspartate aminotransferase ≤2.5x ULN; serum creatinine ≤1.5x ULN value or creatinine clearance rate ≥50 ml/min; international normalized ratio ≤1.5x ULN; activated partial thromboplastin time ≤1.5x ULN; and xii) males or females with reproductive ability who are willing to use contraception in the trial. The exclusion criteria were as follows: i) Documented history of allergy to study drugs, including any component of Camrelizumab, capecitabine, irinotecan, oxaliplatin and other platinum drugs; ii) have received or are receiving any of the following treatments: Any radiotherapy, chemotherapy or other anti-tumor drugs for tumors; patients who need to be treated with corticosteroid (dose equivalent to prednisone of >10 mg/day) or other immunosuppressive agents within 2 weeks prior to study drug administration; received live attenuated vaccine within 4 weeks before the first use of the study drug; underwent major surgery or severe trauma within 4 weeks before the first use of the study drug; iii) any active autoimmune disease or history of autoimmune disease; iv) have a history of immunodeficiency, including HIV positive, or other acquired or congenital immunodeficiency diseases, or have a history of organ transplantation or allogeneic bone marrow transplantation; v) there are clinical symptoms or diseases of heart that are not well controlled; vi) severe infection (CTCAE >2) occurred within 4 weeks before the first use of the study drug; baseline chest imaging revealed active pulmonary inflammation, signs and symptoms of infection within 14 days prior to the first use of the study drug or oral or patient is taking intravenous antibiotic therapy, except for prophylactic use of antibiotics; vii) patients with active pulmonary tuberculosis infection found by medical history or CT examination, or with a history of active pulmonary tuberculosis infection within one year before enrollment, or with a history of active pulmonary tuberculosis infection >1 year ago but without regular treatment; viii) the presence of active hepatitis B (HBV DNA >2,000 IU/ml or 10^4 copies/ml) was positive for hepatitis C (hepatitis C antibody) and HCV RNA was higher compared with the lower limit of analytical method; ix) female subject who is pregnant or breastfeeding; x) patients who are not suitable for participation in clinical trials in the opinion of the investigator. View inclusion criteria and exclusion criteria using the following link: https://clinicaltrials.gov/ct2/show/NCT04928807?term=NCT04928807&draw=2&rank=1.

Eligible patients were divided into 3 cohorts depending on the neoadjuvant treatment regimen: Arm A (SCRT plus 2 cycles of chemotherapy and camrelizumab); Arm B (SCRT plus 2 cycles of chemotherapy); and Arm C (LC-CRT plus 2 cycles of chemotherapy). The more detailed treatment regimen was presented in Fig. 1. Albumin, total cholesterol, LDH, neutrophil, platelet and lymphocyte values in the peripheral blood were collected before treatment. pCR was defined as postoperative pathologic confirmation of no active cancer cells remaining in either the primary site or the resected regional lymph nodes with a ypT0N0M0 stage.

Statistical analysis. Continuous variables are described by mean ± standard deviation (SD) or median and range (determined by whether the data are normally distributed according to Shapiro-wilk test), and categorical variables are presented as frequencies and percentages. The non-parametric test, χ^2 and Fisher's exact tests were performed to compare the three groups. The receiver operating characteristic (ROC) curve was used to determine the optimal cut-off value to define the level of hematological indicators and univariate and multivariate logistics regressions were used to determine independent

Table I. Baseline patient and tumor characteristics in three cohorts.

Characteristic	Arm A (n=91)	Arm B (n=29)	Arm C (n=51)	P-value
Sex (%)				0.863
Male	59 (64.8)	20 (69.0)	35 (68.6)	
Female	32 (35.2)	9 (31.0)	16 (31.4)	
Age (mean ± SD)	56.91±0.962	53.69±11.720	56.98±8.620	0.243
Clinical T stage (%)				0.440
2-3	69 (75.8)	25 (76.2)	38 (74.5)	
4	22 (24.1)	4 (13.8)	13 (25.5)	
Clinical N stage (%)				0.161
0-1	48 (52.7)	20 (69.0)	24 (47.1)	
2	43 (47.3)	9 (31.0)	27 (52.9)	
Tumor node metastasis (%)				0.102
II	9 (9.9)	7 (24.1)	5 (9.8)	
III	82 (90.1)	22 (75.9)	46 (90.2)	
MMR status (%)				0.056
dMMR/unknown	27 (29.7)	10 (34.5)	7 (13.7)	
pMMR	64 (70.3)	19 (65.5)	44 (86.3)	
Circumferential resection margin (%)				<0.001
Positive	48 (52.7)	7 (24.1)	30 (58.8)	
Negative	27 (29.7)	6 (20.7)	17 (33.3)	
Unknown	16 (17.6)	16 (55.2)	4 (7.8)	
Extramural vascular invasion (%)				<0.001
Positive	40 (43.9)	5 (17.2)	24 (47.1)	
Negative	29 (31.9)	4 (13.8)	19 (37.3)	
Unknown	22 (24.2)	20 (69.0)	8 (15.7)	
Distance from primary tumor to anal verge (median + range, cm)	5.0 (0.5-10.0)	5.0 (2.0-10.0)	6.0 (1.5-9.8)	0.830

MMR, microsatellite stable; dMMR, deficient mismatch repair; pMMR, proficient mismatch repair.

prognostic factors of pCR among these indicators. P<0.05 was considered to indicate a statistically significant difference. All data analysis was performed in IBM SPSS 27.0 (IBM Corp.).

Results

Patient clinical features. The basic clinical characteristics of the three cohorts of patients are presented in Table I. The mean ages of Arm A, Arm B and Arm C were 56.91, 53.69 and 56.98 years old, respectively. The percentages of males in Arm A, Arm B and Arm C were 64.8, 69.0 and 68.6%, respectively. The proportion of phase III in any cohort is higher compared with the proportion of phase II (Arm A: 90.1% vs. 9.9%; Arm B: 75.9% vs. 24.1%; Arm C: 90.2% vs. 9.8%). Sex, age, T stage, N stage, TNM stage and distance from primary tumor to anal verge were generally well balanced among each group.

Efficacy. The pCR rates for Arm A, Arm B and Arm C were 50.5, 24.1 and 23.5%, respectively (Table II). The pCR rate was different between Arm A and Arm B, and between Arm A and Arm C, while there was no significant difference between Arm B and Arm C (Fig. 2A). The percentages of pT0 were 50.5 (Arm A), 24.1 (Arm B) and 23.5% (Arm C) and pN0 were 80.2 (Arm A), 79.3 (Arm B) and 74.5% (Arm C) in different groups, respectively (Table II). The percentage of TRG (the criterion of TRG refers to the American Joint Committee on Cancer 8th edition) (21) of grade 0-1 was higher in Arm A compared with that in the remaining two Arms (Arm A: 76.9%, Arm B: 44.8%, Arm C:52.9%) (Table II and Fig. 2B). The proportions of Arm A, Arm B and Arm C with a decrease of at least one level in T stage were 81.3, 58.6 and 66.7% and with a N downstaging at least one level were 76.9, F65.5 and 78.4%, respectively (Table II). There was no difference in T and N downstaging between either group, except that Arm A has a significant T-downstaging vs. Arm B (Fig. 2C and D). Fig. 3 presents the T stage and N stage of Arm A patients at baseline and postoperative.

Table II. Postoperative pathological results in Arm A, Arm B and Arm C.

Pathological results	Arm A (n=91) (%)	Arm B (n=29) (%)	Arm C (n=51) (%)
ypT			
tis	2 (2.2)	0 (0)	0 (0)
0	46 (50.5)	7 (24.1)	12 (23.5)
1	2 (2.2)	2 (6.9)	2 (3.9)
2	14 (15.4)	5 (17.2)	13 (25.5)
3	27 (29.7)	15 (51.7)	23 (45.1)
4	0 (0)	0 (0)	1 (2.0)
ypN			
0	73 (80.2)	23 (79.3)	38 (74.5)
1	15 (16.5)	5 (17.2)	9 (17.6)
2	3 (3.3)	1 (3.4)	4 (7.8)
ypTNM			
pCR	46 (50.5)	7 (24.1)	12 (23.5)
0	2 (2.2)	0 (0)	0 (0)
I	9 (9.9)	6 (20.7)	10 (19.6)
II	16 (17.6)	10 (34.5)	16 (31.4)
III	18 (19.8)	6 (20.7)	13 (25.5)
TRG			
0	46 (50.5)	7 (24.1)	12 (23.5)
1	22 (24.2)	6 (20.7)	15 (29.4)
2	19 (20.9)	14 (48.3)	22 (43.1)
3	4 (4.4)	2 (6.9)	2 (3.9)

pT, pathologic T-stage; pN, pathologic N-stage; pTNM, pathologic TNM-stage; pCR, pathological complete response; TRG, tumor regression grade.

Prognostic factors associated with pCR in Arm A. In the ROC analysis for the albumin, total cholesterol, LDH, neutrophil, platelet, lymphocyte, NLR and PLR cutoff values, the areas under the curve were 0.525 (P=0.688), 0.594 (P=0.156), 0.502 (P=0.982), 0.581 (P=0.179), 0.541 (P=0.505), 0.507 (P=0.916), 0.549 (P=0.425) and 0.549 (P=0.422) for pCR, respectively (data not shown). Finally, albumin >37.9 g/l, total cholesterol >4.45 mmol/l, LDH >141 U/l, neutrophil >2.62x10^9/l, platelet >244x10^9/l, lymphocyte >1.44x10^9/l, NLR >3 and PLR >128 were classified into the high-level group. Binary logistic regression analysis was performed for the following 10 criteria: i) Sex; ii) age; iii) albumin; iv) total cholesterol; v) LDH; vi) neutrophil; vii) platelet; viii) lymphocyte; ix) NLR; x) PLR. Univariate logistic regression analysis was performed showing that baseline total cholesterol >4.45 mmol/l, neutrophil ≤2.62x10^9/l and PLR >128 were significant prognostic factors of pCR, and multivariate regression analysis showed that baseline total cholesterol >4.45 mmol/l, neutrophil ≤2.62x10^9/l were selected as the independent factors for pCR (Table III).

Discussion

The present study validated that the regimen of SCRT plus 2 cycles of chemotherapy and camrelizumab could significantly increase the pCR rate in patients with LARC by two-fold (Arm A vs. Arm C, 50.5% vs. 23.5%). Unfortunately, the mechanism of such a high pCR rate with this regimen is not clarified. At the same time, studies using hematological indicators to predict pCR in this specific cohort have not been conducted. Therefore, the present study performed this study on 91 patients who were enrolled in the Arm A.

As aforementioned, NLR, LDH and PLR can be used as predictors of prognosis in rectal cancer and are negatively correlated with OS and PFS (15,22,23). However, the results of a study that included 1,237 patients showed that NLR and PLR not only did not predict the prognosis of patients with locally advanced rectal cancer, but also did not predict the pCR rate after neoadjuvant chemoradiotherapy (24). Instead, this is consistent with the present findings, which showed that although PLR was associated with pCR, it was not an independent predictor of pCR. These studies with contradictory results indicates that the role of these indicators in predicting prognosis needs to be explored in depth.

However, notably, the present study revealed that high total cholesterol and low neutrophils at baseline were associated with higher pCR rates. As early as 1997, it has been suggested that total serum cholesterol levels are positively correlated with the development of colorectal cancer (25). Cholesterol can promote tumorigenesis and progression by participating in the regulation of different signaling pathways (26,27). Cholesterol plays an

Table III. Univariate and multivariate logistics regressions for predicting pCR.

	Univariate		Multivariate	
Variable	P-value	HR (95% CI)	P-value	HR (95% CI)
Albumin (g/l)				
>37.9	0.208	1.857 (0.708-4.868)		
≤37.9		1		
Total cholesterol (mmol/l)				
>4.45	0.026	2.856 (1.134-7.190)	0.016	3.456 (1.255-9.517)
≤4.45		1		1
LDH (U/l)				
≤141	0.217	0.465 (0.138-1.568)		
>141		1		
Neutrophil (x10^9/l)				
≤2.62	0.012	3.810 (1.337-10.861)	0.020	4.370 (1.258-15.180)
>2.62		1		1
Platelet (x10^9/l)				
>244	0.090	2.175 (0.886-5.340)		
≤244		1		
Lymphocyte (x10^9/l)				
>1.44	0.347	1.500 (0.644-3.492)		
≤1.44		1		
NLR				
≤3	0.999	-		
>3		-		
PLR				
>128	0.047	2.390 (1.013-5.635)	0.075	2.481 (0.913-6.744)
≤128		1		1

LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

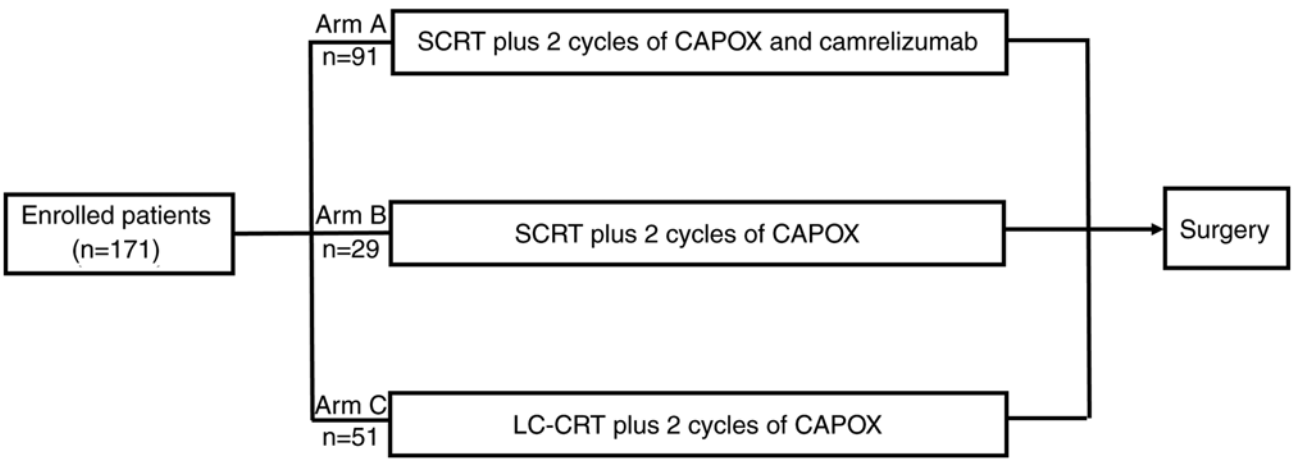


Figure 1. Treatment regimen. CAPOX course, oxaliplatin 130 mg/m^2 intravenously, day 1; capecitabine 1,000 mg/m^2 oral twice daily, days 1-14. Camrelizumab, 200 mg intravenous drip, day 1. LC-CRT course, 28x1.8 Gy on 5 days per week, oral capecitabine (825 mg/m^2, bid, days 1-5) during radiotherapy. Surgery was performed according to total mesorectal excision principles. CAPOX, capecitabine plus oxaliplatin; SCRT, short-course radiotherapy; LC-CRT, long-course chemoradiotherapy; SCRT, 5x5 Gy over 5 days.

indispensable role in maintaining the stability of cell membranes and in the growth and differentiation of cells, which include but are not specific to lymphocytes (28,29). Therefore, we hypothesize that the explanation for the effective and aggressive killing of tumor cells in the Arm A may also be that cholesterol provided the material source needed for the lymphocytes to

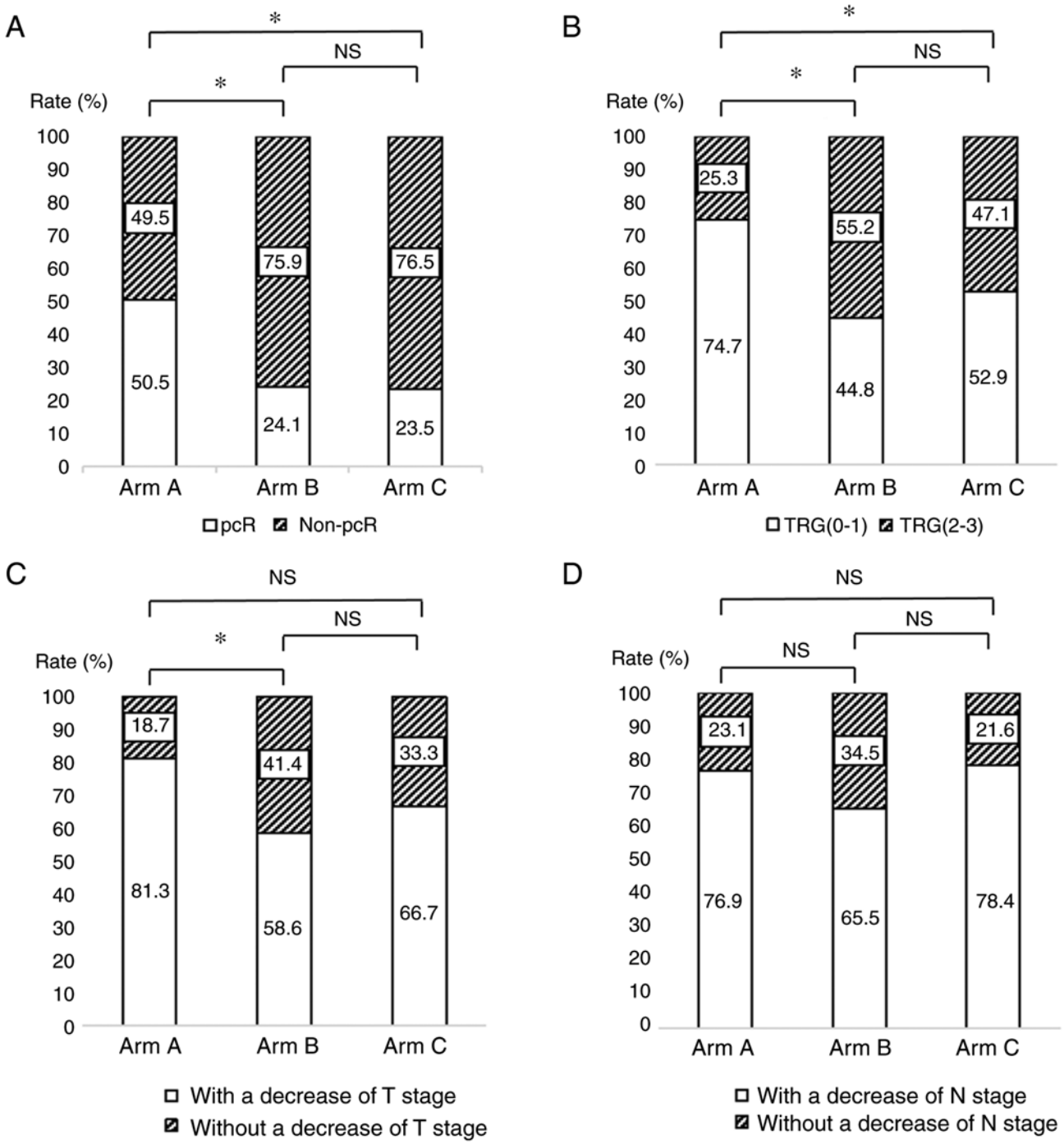
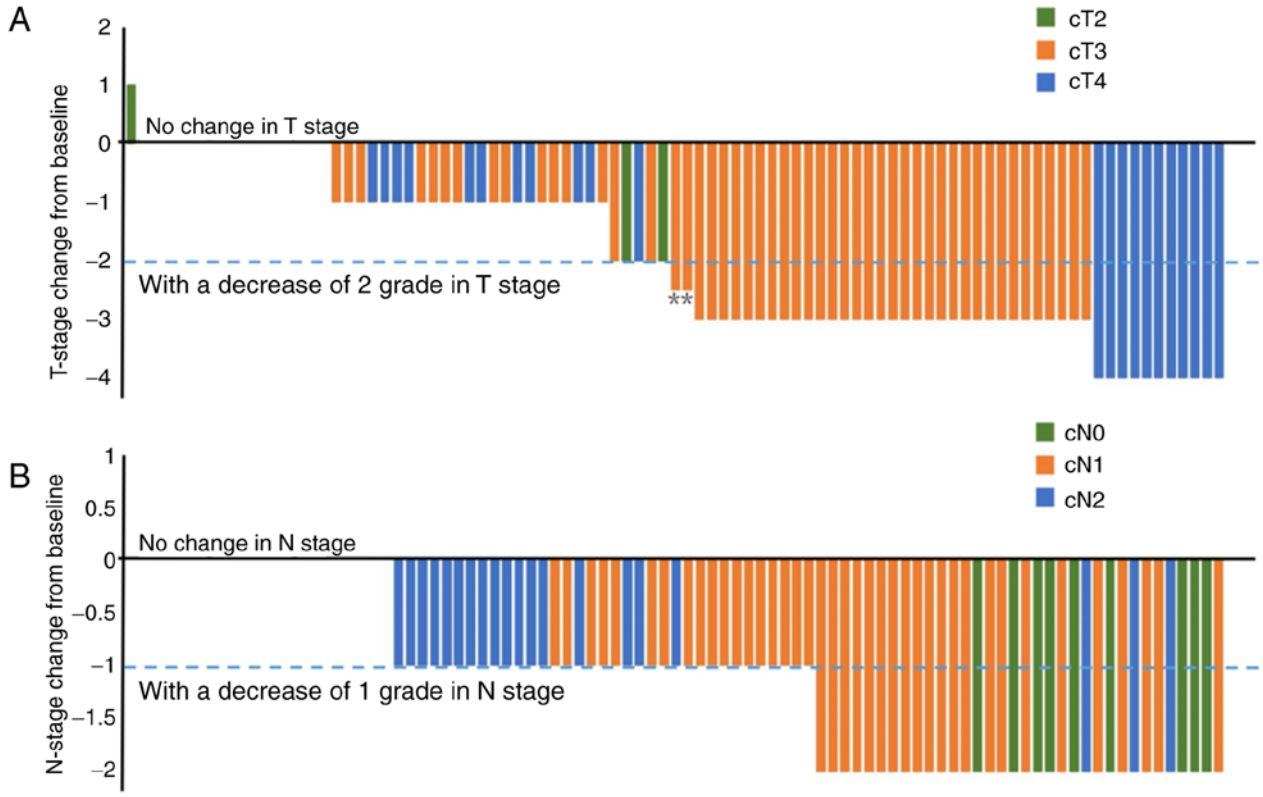


Figure 2. Rates (%) of pCR, TRG, T-downstaging and N-downstaging and the differences between different groups. (A) pCR rate and (B) TRG rate were significantly different between Arm A and Arm B and between Arm A and Arm C (A, P=0.002; B, P=0.003). There was no difference between Arm B and Arm C. (C) Rate of T-downstaging was significantly different between Arm A and Arm B. There was no difference between Arm A and Arm C and between Arm B and Arm C (P=0.026). (D) Rate of N-downstaging showed no difference between the three groups (P=0.388). *P<0.05; NS, no significance; pCR, pathological complete response; TRG, tumor regression grade.

function effectively. However, the specific mechanism needs to be further explored before it can be clarified.

Neutrophils are often involved in the inflammatory response in the body and can contribute to tumorigenesis, progression and metastasis by secreting different factors (30,31). Meng *et al* (32) have demonstrated that high neutrophils indicate a worse DFS. Higher neutrophil levels in tumor tissue are a risk factor for reduced 5-DFS in patients with colorectal cancer (33). Similarly, in squamous carcinoma of the anal canal, the cohort of high neutrophils at baseline exhibit poor local control rates (34). Overall, high neutrophils are a detrimental presence for patients with rectal cancer. The present results show that low neutrophils at baseline are an independent influence in predicting high pCR, corroborating that high neutrophil status may enhance tumor resistance to therapy. To some extent, it can be considered that the relationship between NLR and neutrophil levels is positively correlated. Since immune checkpoint inhibitors eliminate tumor cells by enhancing the cytotoxic effect of T cells, the number



C

cT	n (%)	ypT	n (%)
T4	22 (24.1%)	T4	0 (0%)
T3	66 (72.5%)	T3	27 (29.7%)
T2	3 (3.3%)	T2	14 (15.4%)
-		T1	2 (2.2%)
-		T0	46 (50.5%)
-		tis	2 (2.2%)

D

cN	n (%)	ypN	n (%)
2	42 (46.2%)	2	3 (3.3%)
1	40 (44.0%)	1	15 (16.5%)
0	9 (9.9%)	0	73 (80.2%)

Figure 3. Change of (A) T-stage and (B) N-stage from baseline in Arm A. The percentage of patients in Arm A with different preoperative (cT or cN) and postoperative (ypT or ypN) (C) T-stage and (D) N-stage. *Patient with a postoperative T-stage of tis. cT, clinical-stage; cN, clinical T-stage; pT, pathologic T-stage; pN, pathologic N-stage; tis, tumor *in situ*.

of lymphocytes may not visually reflect the killing ability of lymphocytes (35). It may explain why lymphocytes and NLR are not associated with the pathological response.

For patients with rectal cancer who receive neoadjuvant therapy, if they achieve CCR, a treatment strategy of observation can be adopted (10). This can reduce the damage caused by the surgery itself including psychological and physical damage to the patient (36,37). However, the concordance between CCR rates and pCR rates varies and is highly influenced by human consciousness. The result of a study of 488 patients showed that only 25% of patients who achieved CCR were pCR (38). This means that 75% of these patients would be in a situation of delayed treatment if they did not receive surgical treatment (38). By contrast, the rate of CCR (14.3%; 13/91) in the present study was lower compared with the pCR rate, which would have led to patients receiving overtreatment. If pCR can be accurately predicted through easy and cost-effective blood indicators, then these indicators can provide some reference when making treatment decisions for patients.

In conclusion, short-course radiotherapy followed by chemotherapy and camrelizumab as a neoadjuvant treatment for locally advanced rectal cancer could significantly improve the pCR rate, and PLR, high cholesterol and low neutrophils at baseline were favorable prognostic factors. Furthermore, high cholesterol and low neutrophils at baseline were independently associated with high pCR rates.

Acknowledgements

Not applicable.

Funding

Shanghai Cancer Prevention and Anti-Cancer Development Foundation 2020 Discovery research funding (grant no. 2020HX025). CSCO Tongshu Oncology Research Fund (grant no. Y-tongshu2021/qn-0205). CSCO Xinda Oncology Immunotherapy Research Fund (grant no. Y-XD202002-0168).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

FZ, DY, TZ and ZL conceived and designed this study. JY, MZ, LL participated in the data curation. FZ, DY, LZ and JW analyzed the data. ZL provided the administrative support. FZ and DY drafted the manuscript and all authors reviewed it. TZ and ZL confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee of the Tongji Medical College, Huazhong University of Science and Technology (approval no. 0271-21).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Benson AB, Venook AP, Al-Hawary MM, Azad N, Chen YJ, Ciombor KK, Cohen S, Cooper HS, Deming D, Garrido-Laguna I, *et al*: Rectal cancer, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 20: 1139-1167, 2022.
2. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EM, Roodvoets AGH, Nagtegaal ID, Beets-Tan RGH, Blomqvist LK, *et al*: Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): A randomised, open-label, phase 3 trial. Lancet Oncol 22: 29-42, 2021.
3. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M and Kryj M: Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 93: 1215-1223, 2006.
4. Nagasaka M, Zaki M, Kim H, Raza SN, Yoo G, Lin HS and Sukari A: PD1/PD-L1 inhibition as a potential radiosensitizer in head and neck squamous cell carcinoma: A case report. J Immunother Cancer 4: 83, 2016.
5. Schoenhals JE, Seyedin SN, Tang C, Cortez MA, Niknam S, Tsouko E, Chang JY, Hahn SM and Welsh JW: Preclinical rationale and clinical considerations for radiotherapy plus immunotherapy: Going beyond local control. Cancer J 22: 130-137, 2016.
6. Meng X, Feng R, Yang L, Xing L and Yu J: The role of radiation oncology in immuno-oncology. Oncologist 24 (Suppl 1): S42-S52, 2019.
7. Wang Y, Deng W, Li N, Neri S, Sharma A, Jiang W and Lin SH: Combining immunotherapy and radiotherapy for cancer treatment: Current challenges and future directions. Front Pharmacol 9: 185, 2018.
8. Rodriguez-Ruiz ME, Vitale I, Harrington KJ, Melero I and Galluzzi L: Immunological impact of cell death signaling driven by radiation on the tumor microenvironment. Nat Immunol 21: 120-134, 2020.
9. Lin Z, Cai M, Zhang P, Li G, Liu T, Li X, Cai K, Nie X, Wang J, Liu J, *et al*: Phase II, single-arm trial of preoperative short-course radiotherapy followed by chemotherapy and camrelizumab in locally advanced rectal cancer. J Immunother Cancer 9: e003554, 2021.
10. López-Campos F, Martín-Martín M, Fornell-Pérez R, García-Pérez JC, Die-Trill J, Fuentes-Mateos R, López-Durán S, Domínguez-Rullán J, Ferreiro R, Riquelme-Oliveira A, *et al*: Watch and wait approach in rectal cancer: Current controversies and future directions. World J Gastroenterol 26: 4218-4239, 2020.
11. Guillem JG, Ruby JA, Leibold T, Akhurst TJ, Yeung HW, Gollub MJ, Ginsberg MS, Shia J, Suriawinata AA, Riedel ER, *et al*: Neither FDG-PET Nor CT can distinguish between a pathological complete response and an incomplete response after neoadjuvant chemoradiation in locally advanced rectal cancer: A prospective study. Ann Surg 258: 289-295, 2013.
12. Dayde D, Tanaka I, Jain R, Tai MC and Taguchi A: Predictive and prognostic molecular biomarkers for response to neoadjuvant chemoradiation in rectal cancer. Int J Mol Sci 18: 573, 2017.
13. Yamamoto T, Kawada K, Hida K, Matsusue R, Itatani Y, Mizuno R, Yamaguchi T, Ikai I and Sakai Y: Combination of lymphocyte count and albumin concentration as a new prognostic biomarker for rectal cancer. Sci Rep 11: 5027, 2021.
14. Cheong C, Shin JS and Suh KW: Prognostic value of changes in serum carcinoembryonic antigen levels for preoperative chemoradiotherapy response in locally advanced rectal cancer. World J Gastroenterol 26: 7022-7035, 2020.
15. Huang CM, Huang MY, Tsai HL, Huang CW, Su WC, Chang TK, Chen YC, Li CC and Wang JY: Pretreatment neutrophil-to-lymphocyte ratio associated with tumor recurrence and survival in patients achieving a pathological complete response following neoadjuvant chemoradiotherapy for rectal cancer. Cancers (Basel) 13: 4589, 2021.
16. Doi H, Yokoyama H, Beppu N, Fujiwara M, Harui S, Kakuno A, Yanagi H, Hishikawa Y, Yamanaka N and Kamikonya N: Neoadjuvant modified short-course radiotherapy followed by delayed surgery for locally advanced rectal cancer. Cancers (Basel) 13: 4112, 2021.
17. Ergen ŞA, Barlas C, Yıldırım C and Öksüz D: Prognostic role of peripheral neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in patients with rectal cancer undergoing neoadjuvant chemoradiotherapy. J Gastrointest Cancer 53: 151-160, 2022.
18. Tjokrowidjaja A, Lord SJ, John T, Lewis CR, Kok PS, Marschner IC and Lee CK: Pre- and on-treatment lactate dehydrogenase as a prognostic and predictive biomarker in advanced non-small cell lung cancer. Cancer 128: 1574-1583, 2022.
19. Petrelli F, Cabiddu M, Coinu A, Borgonovo K, Ghilardi M, Lonati V and Barni S: Prognostic role of lactate dehydrogenase in solid tumors: A systematic review and meta-analysis of 76 studies. Acta Oncol 54: 961-970, 2015.
20. Scartozzi M, Giampieri R, Maccaroni E, Del Prete M, Faloppi L, Bianconi M, Galizia E, Loretelli C, Belvederesi L, Bittoni A and Cascinu S: Pre-treatment lactate dehydrogenase levels as predictor of efficacy of first-line bevacizumab-based therapy in metastatic colorectal cancer patients. Br J Cancer 106: 799-804, 2012.

21. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, *et al* (eds): AJCC cancer staging manual (8th edition). Springer International Publishing: American Joint Commission on Cancer, 2017.
22. Basile D, Garattini SK, Corvaja C, Montico M, Cortiula F, Pelizzari G, Gerratana L, Audisio M, Lisanti C, Fanotto V, *et al*: The MIMIC study: Prognostic role and cutoff definition of monocyte-to-lymphocyte ratio and lactate dehydrogenase levels in metastatic colorectal cancer. Oncologist 25: 661-668, 2020.
23. Partl R, Paal K, Stranz B, Hassler E, Magyar M, Brunner TB and Langsenlehner T: The pre-treatment platelet-to-lymphocyte ratio as a prognostic factor for loco-regional control in locally advanced rectal cancer. Diagnostics (Basel) 13: 679, 2023.
24. Dudani S, Marginean H, Tang PA, Monzon JG, Raissouni S, Asmis TR, Goodwin RA, Gotfrit J, Cheung WY and Vickers MM: Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios as predictive and prognostic markers in patients with locally advanced rectal cancer treated with neoadjuvant chemoradiation. BMC Cancer 19: 664, 2019.
25. Yamada K, Araki S, Tamura M, Sakai I, Takahashi Y, Kashihara H and Kono S: Relation of serum total cholesterol, serum triglycerides and fasting plasma glucose to colorectal carcinoma in situ. Int J Epidemiol 27: 794-798, 1998.
26. Oneyama C, Iino T, Saito K, Suzuki K, Ogawa A and Okada M: Transforming potential of Src family kinases is limited by the cholesterol-enriched membrane microdomain. Mol Cell Biol 29: 6462-6472, 2009.
27. Sheng R, Kim H, Lee H, Xin Y, Chen Y, Tian W, Cui Y, Choi JC, Doh J, Han JK and Cho W: Cholesterol selectively activates canonical Wnt signalling over non-canonical Wnt signalling. Nat Commun 5: 4393, 2014.
28. Blank N, Schiller M, Gabler C, Kalden JR and Lorenz HM: Inhibition of sphingolipid synthesis impairs cellular activation, cytokine production and proliferation in human lymphocytes. Biochem Pharmacol 71: 126-135, 2005.
29. Yamaguchi T and Ishimatu T: Effects of cholesterol on membrane stability of human erythrocytes. Biol Pharm Bull 43: 1604-1608, 2020.
30. Xiong S, Dong L and Cheng L: Neutrophils in cancer carcinogenesis and metastasis. J Hematol Oncol 14: 173, 2021.
31. Khan U, Chowdhury S, Billah MM, Islam KMD, Thorlacius H and Rahman M: Neutrophil extracellular traps in colorectal cancer progression and metastasis. Int J Mol Sci 22: 7260, 2021.
32. Meng X, Shi D, Zheng H, Xu Y, Li Q, Cai S and Cai G: High preoperative peripheral blood neutrophil predicts poor outcome in rectal cancer treated with neoadjunctive chemoradiation therapy. Int J Clin Exp Pathol 10: 7718-7725, 2017.
33. Rottmann BG, Patel N, Ahmed M, Deng Y, Ciarleglio M, Vyas M, Jain D and Zhang X: Clinicopathological significance of neutrophil-rich colorectal carcinoma. J Clin Pathol 76: 34-39, 2023.
34. Schernberg A, Huguet F, Moureau-Zabotto L, Chargari C, Rivin Del Campo E, Schlienger M, Escande A, Touboul E and Deutsch E: External validation of leukocytosis and neutrophilia as a prognostic marker in anal carcinoma treated with definitive chemoradiation. Radiother Oncol 124: 110-117, 2017.
35. Alsaab HO, Sau S, Alzhrani R, Tatiparti K, Bhise K, Bhise K, Kashaw SK and Iyer AK: PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: mechanism, combinations, and clinical outcome. Front Pharmacol 8: 561, 2017.
36. Paun BC, Cassie S, MacLean AR, Dixon E and Buie WD: Postoperative complications following surgery for rectal cancer. Ann Surg 251: 807-818, 2010.
37. Mei F, Yang X, Na L and Yang L: Anal preservation on the psychology and quality of life of low rectal cancer. J Surg Oncol 125: 484-492, 2022.
38. Hiotis SP, Weber SM, Cohen AM, Minsky BD, Paty PB, Guillem JG, Wagman R, Saltz LB and Wong WD: Assessing the predictive value of clinical complete response to neoadjuvant therapy for rectal cancer: An analysis of 488 patients. J Am Coll Surg 194: 131-136, 2002.