Effectiveness and safety of neoadjuvant apatinib in combination with capecitabine and oxaliplatin for the therapy of locally advanced colorectal cancer: A retrospective study

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Received September 22, 2023; Accepted November 30, 2023

DOI: 10.3892/ol.2024.14335

Abstract. The goal of the present study was to appraise the efficacy and safety of neoadjuvant apatinib in combination with capecitabine and oxaliplatin (XELOX) in patients with locally advanced colorectal cancer (CRC), as relevant data on its usage in this setting are lacking. A retrospective analysis was implemented on 100 patients with locally advanced CRC who received either neoadjuvant apatinib in combination with XELOX (N=50) or neoadjuvant XELOX alone (N=50). Radiological response and pathological complete response rates were evaluated. Furthermore, the researchers obtained data pertaining to disease-free survival (DFS), overall survival, as well as adverse events. The consequences of the present study indicated that the neoadjuvant apatinib in combination with XELOX treatment approach yielded higher rates of radiological objective response (86.0 vs. 68.0%, P=0.032) and major pathological response (46.0 vs. 22.0%, P=0.011) compared with XELOX alone. These findings were further confirmed through multivariate logistic regression analyses (P=0.037 and P=0.008, respectively). Interestingly, the neoadjuvant apatinib in combination with XELOX treatment approach significantly prolonged DFS when compared with XELOX alone (P=0.033). In summary, the administration of neoadjuvant apatinib in combination with XELOX demonstrates superiority over the use of XELOX alone in terms of achieving a more favorable pathological response and a longer duration of DFS in patients diagnosed with locally advanced CRC.

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Key words: locally advanced colorectal cancer, apatinib, neoadjuvant therapy, efficacy, safety

Introduction

Colorectal cancer (CRC) is a prevalent malignant tumor worldwide, with significant mortality rates (1,2). Unfortunately, multiple patients are diagnosed with locally advanced CRC at the time of initial diagnosis (3,4). In such cases, neoadjuvant therapy plays a crucial role in providing patients with more opportunities for subsequent surgical resection and improving their long-term survival outcomes (5-7). Currently, the primary neoadjuvant regimen for patients with locally advanced CRC involves platinum-based chemotherapy, such as capecitabine plus oxaliplatin (XELOX) and fluorouracil (8,9). Nonetheless, the effectiveness of these treatment protocols is deemed unsatisfactory (10). Consequently, it is imperative to devise alternative neoadjuvant regimens to manage patients with locally advanced CRC.

As an oral inhibitor of vascular endothelial growth factor receptor-2 (VEGFR2), apatinib possesses anti-angiogenic properties that are considered to regulate angiogenesis and β-catenin signaling, thereby inhibiting CRC cell proliferation, migration and invasion (11). Previous studies have established the efficacy and safety of combining apatinib with chemotherapy for the therapy of patients with advanced CRC (12,13). For instance, a meta-analysis has demonstrated that the combination of apatinib and chemotherapy yields a favorable objective response rate (ORR), disease control rate (DCR), and survival rate with manageable adverse reactions among patients with advanced CRC (12). Furthermore, another study has indicated that the combination of apatinib and chemotherapy enhances progression-free survival and exhibits an acceptable tolerance in patients with refractory metastatic CRC (13). Nevertheless, there is a dearth of pertinent evidence concerning neoadjuvant apatinib in combination with XELOX in patients with locally advanced CRC.

The purpose of the present study was to investigate radiological response, pathological response, survival outcomes and adverse events in patients diagnosed with locally advanced CRC who underwent neoadjuvant treatment with apatinib and XELOX.

Patients and methods

Patients. A retrospective analysis was conducted on a total of 100 patients with locally advanced CRC who received treatment at The Affiliated Hospital of Hebei University (Baoding,

China) between January 2017 and January 2019. The inclusion criteria contained: i) Patients who were histologically or cytologically confirmed to have CRC; ii) had a clinical stage of cT3-4b/N + /M0 for patients with rectal cancer or cT4b/N + /M0 for patients with colon cancer, which was appraised by computed tomography (CT) or magnetic resonance imaging; iii) >18 years old; iv) the eastern cooperative oncology group performance status (ECOG PS) score of 0-1; v) received surgical resection; vi) had accessible and available clinical data for study analysis. The exclusion criteria contained: i) Had severe infections; ii) had severe dysfunctions of the liver or kidney; iii) had coagulation disorders; iv) had severe heart failures; v) had uncontrollable hypertensive diseases. Clinical characteristics of patients (including sex and age distribution) are included in Table I. The present study was approved by (approval no. ChiECRCT20210395) by the Ethics Committee of The Affiliated Hospital of Hebei University (Baoding, China). Written informed consent was provided by each patient or their guardian (if the patient died).

Data collection and treatment. Patient clinical characteristics, biochemical indices and treatment data were collected, along with poorly differentiated clusters (PDC) and tumor budding (TB) measurements. PDC was categorized as low (0-4) or high (≥5), while TB was classified as low (0-4 buds) or high (≥5 buds) based on the International Consortium on TB Recommendations (14,15). Patients were stratified into two groups based on their neoadjuvant regimens: The XELOX group and the apatinib plus XELOX group. Neoadjuvant therapy was administered for three cycles, with each cycle lasting 21 days. The standard regimens for the XELOX group were as follows: For the XELOX group, 130 mg/m^2 XELOX was administered intravenously on day 1, 1.0 g/m^2 capecitabine was given orally 2 times/day for 14 days with a 7-day-off; for the apatinib plus XELOX group, apatinib was given orally at 0.25 g/day on the basis of XELOX. The dose of apatinib was determined referring to the instruction, and the dose of neoadjuvant XELOX was determined referring to the clinical guidelines (16). Moreover, surgical information (laparoscopic radical resection or radical resection) was collected based on an assessment at 4-5 weeks after discontinuing neoadjuvant therapy.

Assessment. The imaging data obtained from patients after neoadjuvant treatment were utilized to assess clinical response based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v.1.1) and evaluated post-neoadjuvant pathologic tumor-node-metastasis (ypTNM) (17). Furthermore, the Becker's grading system was employed to evaluate tumor regression grade (TRG) based on surgery information, which was graded as 0, 1, 2, and 3 (18). Major pathological response was defined as grade 0-1 of TRG. Additionally, follow-up information was collected to appraise disease-free survival (DFS) and overall survival (OS) of patients. Additionally, adverse events were detected. The primary outcome of the present study was DFS.

Statistical analysis. SPSS v20.0 (IBM Corp.) was utilized for analyses. GraphPad Prism v7.02 (Dotmatics) was utilized for plotting. Comparison analyses were conducted using the Chi-square test and Wilcoxon rank sum test. Factors related to ORR and major pathological response were screened using forward-stepwise multivariate logistic regression models. Survival information was shown using Kaplan-Meier curves with a log-rank test. Factors linked with DFS and OS were determined using forward-stepwise and enter method multivariate Cox's proportional hazard regression models. P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline characteristics. The baseline traits of the present study population were analyzed. The apatinib plus XELOX group comprised 18 (36.0%) female and 32 (64.0%) male patients, with 29 (58.0%) patients <65 and 21 (42.0%) patients aged ≥65 years. The XELOX group consisted of 22 (44.0%) female and 28 (56.0%) male patients, with 21 (42.0%) patients <65 and 29 (58.0%) patients ≥65 years. In the apatinib plus XELOX group, there were 45 (90.0%) patients with left lesions and 5 (10.0%) patients with right lesions. In the XELOX group, there were 49 (98.0%) patients with left lesions and 1 (2.0%) patient with right lesions. The majority of clinical characteristics were similar between groups (all P>0.05), except that the proportion of patients with high TB in the apatinib plus XELOX group was lower than the proportion of patients with high TB in the XELOX group (42.0 vs. 64.0%) (P=0.028). A more detailed description of the two groups is presented in Table I.

Comparison of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and carcinoembryonic antigen (CEA) levels between cohorts. Prior to neoadjuvant therapy, no significant difference was illustrated between groups regarding abnormal NLR (14.0 vs. 6.0%) (P=0.182) or abnormal PLR (60.0 vs. 46.0%) (P=0.161), but the proportion of patients with abnormal CEA was found to be higher in the apatinib plus XELOX group vs. the XELOX group (58.0 vs. 36.0%) (P=0.028). Following neoadjuvant therapy, no significant discrepancy was observed between groups in abnormal NLR (16.0 vs. 30.0%) (P=0.096), abnormal PLR (48.0 vs. 44.0%) (P=0.688), and abnormal CEA (38.0 vs. 24.0%) (P=0.130) between cohorts (Table II).

Radiological and pathological comparisons between cohorts. The findings of the present study indicated a significant discrepancy in radiological response between the apatinib plus XELOX group and the XELOX group (P=0.012), with the former exhibiting a more favorable outcome. The proportion of patients achieving ORR was also revealed to be higher in the apatinib plus XELOX group vs. the XELOX group (86.0 vs. 68.0%) (P=0.032). However, the DCR was not different between groups (98.0 vs. 86.0%) (P=0.059).

As a whole, based on Dworak's scale, tumor regression was staged as follows: TRG 0 received 5.0% of the cases, TRG 1 received 29.0%, TRG 2 received 29.0%, and TRG 3 received 37.0%. The TRG demonstrated superiority in the apatinib plus XELOX group as compared with the XELOX group (P<0.001). The apatinib plus XELOX group exhibited an increased rate of major pathological response compared with the XELOX group

Table I. Clinical characteristics.

Clinical characteristics	XELOX group (n=50)	Apatinib plus XELOX group (n=50)	P-value
Age, years (%)			0.110
<65	21 (42.0)	29 (58.0)	
≥65	29 (58.0)	21 (42.0)	
Sex, n (%)			0.414
Female	22 (44.0)	18 (36.0)	
Male	28 (56.0)	32 (64.0)	
BMI, n (%)			0.841
<24 kg/m^2	25 (50.0)	24 (48.0)	
≥24 kg/m^2	25 (50.0)	26 (52.0)	
ECOG PS score, n (%)			0.841
0	22 (44.0)	23 (46.0)	
1	28 (56.0)	27 (54.0)	
Diagnosis, n (%)			0.275
Colon cancer	6 (12.0)	10 (20.0)	
Rectal cancer	44 (88.0)	40 (80.0)	
Lesion site, n (%)			0.204
Left	49 (98.0)	45 (90.0)	
Right	1 (2.0)	5 (10.0)	
Differentiation, n (%)			0.086
Well	6 (12.0)	10 (20.0)	
Moderate	36 (72.0)	37 (74.0)	
Poor	8 (16.0)	3 (6.0)	
Distance of tumor from anus, n (%)			0.509
≤5 cm	16 (32.0)	13 (26.0)	
>5 cm	34 (68.0)	37 (74.0)	
Vascular invasion, n (%)			0.298
No	39 (78.0)	43 (86.0)	
Yes	11 (22.0)	7 (14.0)	
Perineural invasion, n (%)			1.000
No	44 (88.0)	44 (88.0)	
Yes	6 (12.0)	6 (12.0)	
cTNM stage, n (%)			0.812
IIIB	39 (78.0)	38 (76.0)	
IIIC	11 (22.0)	12 (24.0)	
PDC, n (%)			0.221
Low (0-4)	17 (34.0)	23 (46.0)	
High (≥5)	33 (66.0)	27 (54.0)	
TB, n (%)			0.028
Low (0-4)	18 (36.0)	29 (58.0)	
High (≥5)	32 (64.0)	21 (42.0)	

XELOX, capecitabine plus oxaliplatin; BMI, body mass index; ECOG PS, the eastern cooperative oncology group performance status; cTNM, clinical tumor-node-metastasis; PDC, poorly differentiated clusters; TB, tumor budding.

(46.0 vs. 22.0%) (P=0.011). With regards to the TNM stage following neoadjuvant therapy, no discernible difference was illustrated in ypTNM stage (P=0.200) or TNM stage decline (60.0 vs. 46.0%) (P=0.161) between groups (Table III).

Associated factors with ORR and major pathological responses. A forward-stepwise multivariate logistic regression model was applied to recognize factors associated with ORR and major pathological response. The results indicated that

Table II. Levels of NLR, PLR and CEA.

Items	Before neoadjuvant therapy			After neoadjuvant therapy		
	XELOX group (n=50)	Apatinib plus XELOX group (n=50)	P-value	XELOX group (n=50)	Apatinib plus XELOX group (n=50)	P-value
NLR, n (%)			0.182			0.096
Normal	47 (94.0)	43 (86.0)		35 (70.0)	42 (84.0)	
Abnormal	3 (6.0)	7 (14.0)		15 (30.0)	8 (16.0)	
PLR, n (%)			0.161			0.688
Normal	27 (54.0)	20 (40.0)		28 (56.0)	26 (52.0)	
Abnormal	23 (46.0)	30 (60.0)		22 (44.0)	24 (48.0)	
CEA, n (%)			0.028			0.130
Normal	32 (64.0)	21 (42.0)		38 (76.0)	31 (62.0)	
Abnormal	18 (36.0)	29 (58.0)		12 (24.0)	19 (38.0)	

XELOX, capecitabine plus oxaliplatin; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CEA, carcinoembryonic antigen.

treatment with apatinib plus XELOX, as opposed to XELOX alone, was independently associated with higher ORR rates in patients with locally advanced CRC [odds ratio (OR)=2.891, P=0.037], as depicted in Fig. 1A. Furthermore, treatment with apatinib plus XELOX was independently linked with higher rates of major pathological response (OR=3.431, P=0.008), while the distance of the tumor from the anus (>5 cm vs. ≤5 cm) was independently related to lower rates of major pathological response (OR=0.354, P=0.032) in patients with locally advanced CRC, as demonstrated in Fig. 1B.

DFS and OS between cohorts. The DFS was found to be significantly higher in the apatinib plus XELOX group compared with the XELOX group (P=0.033; Fig. 2A). Nevertheless, no significant difference was revealed in OS between the two groups (P=0.107; Fig. 2B). The forward-stepwise multivariate Cox's regression model revealed that treatment (apatinib plus XELOX vs. XELOX) was independently linked with prolonged DFS [hazard ratio (HR)=0.368, P=0.037]. Additionally, cTNM stage (IIIC vs. IIIB) was found to be independently associated with shorter DFS (HR=3.061, P=0.009) in patients with locally advanced CRC, as illustrated in Fig. 3A. Furthermore, cTNM stage (IIIC vs. IIIB) was independently related to shorter OS in patients with locally advanced CRC (HR=3.010, P=0.015), as revealed in Fig. 3B. Meanwhile, independent factors linked with DFS and OS in patients with locally advanced CRC by multivariate Cox's regression model with the enter method are presented in Table SI.

Comparison of adverse events between cohorts. The present study revealed that the apatinib plus XELOX group exhibited a higher incidence of leukopenia (72.0 vs. 52.0%; P=0.039), neutropenia (48.0 vs. 12.0%; P<0.001) and anorexia (46.0 vs. 26.0%; P=0.037) compared with the XELOX group. No difference was disclosed in the incidences of other adverse events, including nausea and vomiting, thrombocytopenia, hypertension, proteinuria and hemoglobinopenia (all P>0.05). Notably, all adverse events were grade 1-2, and there was no grade 3-4 adverse event in both groups (Table IV).

Discussion

The VEGF pathway-mediated angiogenesis plays a crucial role in providing nutrients for tumor growth, thereby contributing to the progression of CRC (19). Apatinib, an oral antiangiogenic agent, has been shown to inhibit tumor angiogenesis by restraining VEGFR-2, which presents a promising treatment strategy for CRC (11,20). The present study demonstrated that neoadjuvant apatinib in combination with XELOX significantly increased the ORR and major pathological response compared with XELOX alone. In addition, the results of the present study revealed that apatinib in combination with XELOX improved radiological response compared with XELOX alone. This was attributed to apatinib's enhancement of conventional chemotherapy. This effect could be attributed to the ability of apatinib to restrain angiogenesis and the VEGFR2-β-catenin pathway, leading to tumor regression in patients with locally advanced CRC (11). Furthermore, apatinib promoted ferroptosis by targeting the elongation of very long chain fatty acids protein 6/acyl-CoA synthetase long-chain family member 4 signaling in CRC cells, which eliminated CRC cells and inhibited CRC growth (21). Therefore, neoadjuvant apatinib in combination with XELOX improved ORR and major pathological response in patients with locally advanced CRC.

The efficacy of current neoadjuvant chemotherapy for patients with CRC remains suboptimal, as evidenced by previous research (22-24). Specifically, studies have illustrated a 5-year OS rate of 67-76% in patients with locally advanced CRC who undergo neoadjuvant chemotherapy (23,24). By contrast, the investigation of the present study demonstrated that patients with locally advanced CRC who received neoadjuvant apatinib in combination with XELOX had a 5-year DFS rate of 86.9% and a 5-year OS rate of 81.7%, which surpassed the outcomes of neoadjuvant XELOX alone in

Table III. Radiological and pathological response.

A, Radiological response

Items	XELOX group (n=50)	Apatinib plus XELOX group (n=50)	P-value
Radiological response, n (%)			0.012
CR	1 (2.0)	4 (8.0)	
R	33 (66.0)	39 (78.0)	
SD	9 (18.0)	6 (12.0)	
D	7 (14.0)	1 (2.0)	
ORR, n (%)			0.032
Yes	34 (68.0)	43 (86.0)	
No	16 (32.0)	7 (14.0)	
DCR, n (%)			0.059
Yes	43 (86.0)	49 (98.0)	
No	7 (14.0)	1 (2.0)	

B, Pathological response

Items	XELOX group (n=50)	Apatinib plus XELOX group (n=50)	P-value
TRG, n (%)			<0.001
Grade 0	1 (2.0)	4 (8.0)	
Grade 1	10 (20.0)	19 (38.0)	
Grade 2	10 (20.0)	19 (38.0)	
Grade 3	29 (58.0)	8 (16.0)	
Major pathological response, n (%)	11 (22.0)	23 (46.0)	0.011

C, TNM stage after neoadjuvant therapy

Items	XELOX group (n=50)	Apatinib plus XELOX group (n=50)	P-value
ypTNM stage, n (%)			0.200
0	1 (2.0)	4 (8.0)	
I	11 (22.0)	10 (20.0)	
II	11 (22.0)	16 (32.0)	
III	27 (54.0)	20 (40.0)	
TNM stage decline, n (%)	23 (46.0)	30 (60.0)	0.161

XELOX, capecitabine plus oxaliplatin; CR, complete response; R, partial response; SD, stable disease; D, progressive disease; ORR, objective response rate; DCR, disease control rate; TRG, tumor regression grade; ypTNM, post-neoadjuvant pathologic tumor-node-metastasis; TNM, tumor-node-metastasis.

the present study and neoadjuvant chemotherapy in previous studies (23,24). Additionally, it was identified that cTNM stage (IIIC vs. IIIB) was independently associated with shorter DFS and OS in patients with locally advanced CRC. This superiority might be attributed to the inclusion of apatinib in the treatment regimen. The potential rationales were as follows: Firstly, apatinib was found to inhibit angiogenesis and induce ferroptosis, thereby impeding the progression and recurrence of CRC (11,21,25). Secondly, apatinib was linked to a more favorable pathological response, leading to an extension of DFS in patients with CRC (26). Consequently, the administration of neoadjuvant apatinib in combination with XELOX resulted in an improved DFS in patients with locally advanced CRC. Additionally, no significant difference was suggested in OS between the apatinib plus XELOX group and the XELOX group. This could be attributed to the relatively low mortality rate during the follow-up period, which resulted in a small effect. The impact of neoadjuvant chemotherapy on patients' OS depended on numerous factors, such as the effectiveness of surgery and the selection of postoperative treatment methods. Therefore, the OS between groups did not differ statistically significantly.

In addition to efficacy, the safety of neoadjuvant apatinib in combination with XELOX in patients with locally

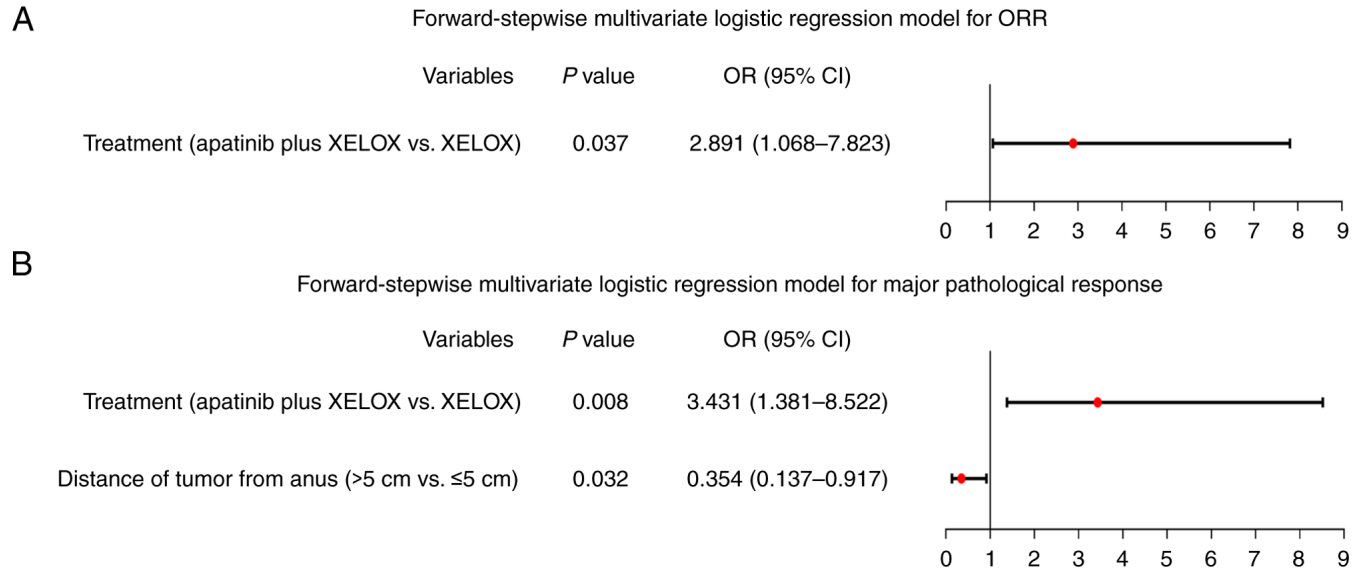
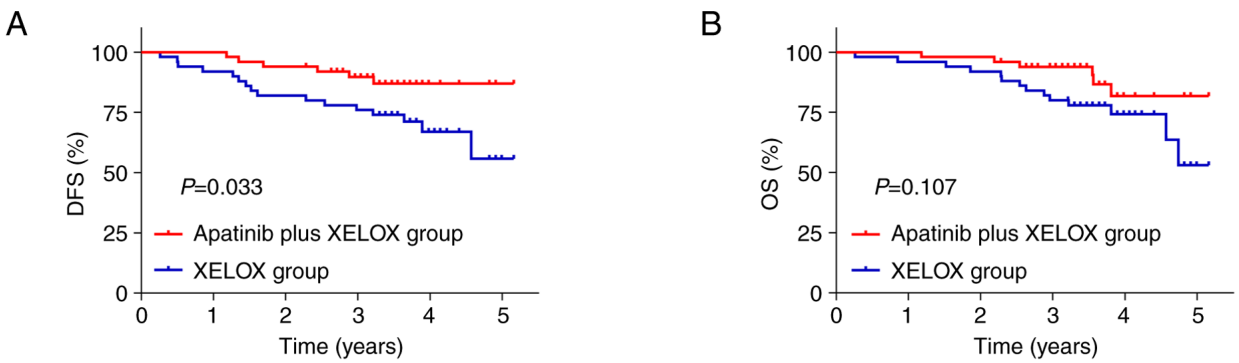


Figure 1. Independent factors related to ORR and major pathological response in patients with locally advanced CRC. Independently predictor of (A) ORR and (B) major pathological response in patients with locally advanced CRC. Statistical methods: forward-stepwise multivariate logistic regression models. ORR, objective response rate; CRC, colorectal cancer.



DFS rate (%)	1-year	2-year	3-year	4-year	5-year
Apatinib plus XELOX group	100.0	94.0	89.7	86.9	86.9
XELOX group	92.0	82.0	66.1	55.1	55.1

OS rate (%)	1-year	2-year	3-year	4-year	5-year
Apatinib plus XELOX group	100.0	98.0	94.0	81.7	81.7
XELOX group	96.0	92.0	80.0	74.2	53.0

Figure 2. DFS and OS in apatinib plus XELOX group and XELOX group in patients with locally advanced CRC. Comparison of (A) DFS and (B) OS between apatinib plus XELOX group and XELOX group in patients with locally advanced CRC. Statistical methods: Kaplan-Meier curves with a log-rank test. DFS, disease-free survival; OS, overall survival; XELOX, capecitabine plus oxaliplatin; CRC, colorectal cancer.

advanced CRC is also a noteworthy issue. In the present study, neoadjuvant apatinib in combination with XELOX increased the incidences of leukopenia, neutropenia and anorexia compared with neoadjuvant XELOX alone. The possible reasons were as follows: i) Apatinib restrained the colony formation of bone marrow by inhibiting VEGFR-2, causing myelosuppression, thus decreasing leukocytes and neutrophils (27). ii) Apatinib inhibited VEGFR-2, which might lead to gastrointestinal mucosal injury and gastritis, thus increasing anorexia (28,29). Interestingly, hypertension and proteinuria are considered common adverse events associated with apatinib (30). A previous study reported that the incidence of hypertension and proteinuria in patients with advanced CRC who receive apatinib is 25.9 and 22.2%, respectively (31). Similar to the aforementioned study, the incidences of hypertension and proteinuria in the present study were both 28% in the apatinib plus XELOX group. Additionally, there was no new adverse event occurring in the apatinib plus XELOX group. These results supported the favorable tolerance of neoadjuvant apatinib in combination with XELOX in patients with locally advanced CRC. The findings of the present study indicated that clinicians needed to pay attention to adverse events caused by apatinib and provide timely treatment.

Notably, the present study did not intervene in the neoadjuvant treatment regimens of patients with locally advanced CRC, and all regimens were selected based on the physician's recommendations or patients' wishes. In the present study, the majority of clinical characteristics of patients in both groups were non-differential, while there was a lower proportion of patients with high TB in the apatinib plus XELOX group vs. the XELOX group. In detail, TB is a histological characteristic of tumor cells that represents the dissociation of a single cancer cell or clusters of up to

Table IV. Adverse events.

Adverse events	XELOX group, n=50 (%)	Apatinib plus XELOX group, n=50 (%)	P-value
Leukopenia, n (%)	26 (52.0)	36 (72.0)	0.039
Neutropenia, n (%)	6 (12.0)	24 (48.0)	<0.001
Nausea and vomiting, n (%)	19 (38.0)	20 (40.0)	0.838
Anorexia, n (%)	13 (26.0)	23 (46.0)	0.037
Thrombocytopenia, n (%)	7 (14.0)	15 (30.0)	0.053
Hypertension, n (%)	8 (16.0)	14 (28.0)	0.148
Proteinuria, n (%)	8 (16.0)	14 (28.0)	0.148
Hemoglobinopenia, n (%)	5 (10.0)	8 (16.0)	0.372

XELOX, capecitabine plus oxaliplatin.

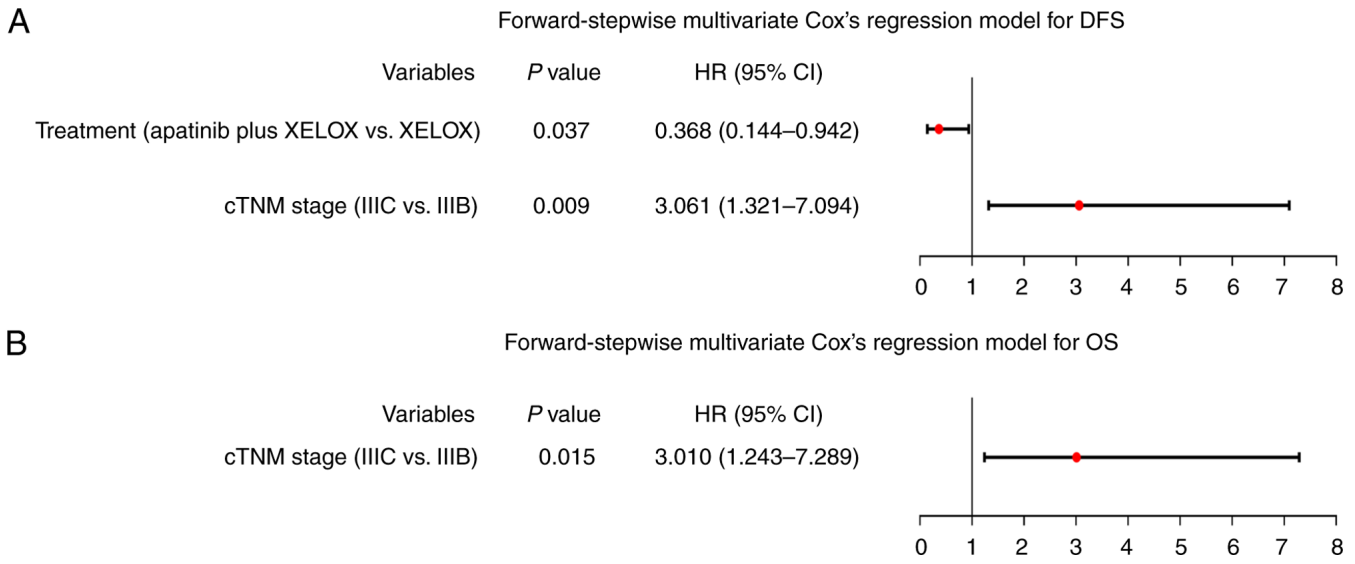


Figure 3. Independent factors related to DFS and OS in patients with locally advanced CRC. Independently predictor of (A) DFS and (B) OS in patients with locally advanced CRC. Statistical methods: forward-stepwise multivariate Cox's proportional hazard regression models. DFS, disease-free survival; OS, overall survival; CRC, colorectal cancer.

four cancer cells from the invasive tumor front (32,33). The 2016 International TB Consensus Conference (ITBCC) has indicated that TB is a well-established independent factor for predicting the prognosis of CRC patients (15). Thus, the difference in TB between the two groups in the present study represented that patients in the apatinib plus XELOX group might have improved prognosis vs. the XELOX group, which might influence the results to some extent. However, the current study used forward-stepwise multivariate Cox's proportional hazard regression models to correct confounding factors, which found that apatinib in combination with XELOX treatment was independently linked with prolonged DFS in patients with locally advanced CRC.

The present study involved several limitations worth noting: i) The present study reviewed as numerous patients as possible who met the inclusion criteria and did not meet the exclusion criteria. However, there was a small sample size, and further studies should consider including a large sample size to verify the efficacy and safety of neoadjuvant apatinib in combination with XELOX in patients with locally advanced CRC; ii) the present study was retrospective, which might lead to bias to some extent. Thus, future randomized, controlled studies are required for further verification; iii) in the present study, neither neoadjuvant apatinib in combination with XELOX nor neoadjuvant XELOX alone were evaluated for quality of life; and iv) the conventional doses of apatinib used in patients with CRC are 0.25 g/day or 0.5 g/day (34), while the present study only used 0.25 g/day doses of apatinib, and future studies should consider evaluating the clinical efficacy and safety of 0.5 g/day doses of apatinib used for neoadjuvant therapy in patients with locally advanced CRC.

In conclusion, the administration of neoadjuvant apatinib in combination with XELOX has been found to enhance radiological and pathological responses, as well as improve DFS with acceptable tolerance in patients diagnosed with locally advanced CRC. The primary outcome measured neoadjuvant apatinib in combination with XELOX is effectiveness and safety for treating locally advanced CRC.

Acknowledgements

Not applicable.

Funding

No funding was received.

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

TZ, XP, GL, LY, AZ and XJ contributed to the study conception and design. TZ, XP, GL and LY prepared material, collected data and performed analysis. TZ and XP wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. AZ and XJ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved (approval no. ChiECRCT20210395) by the Ethics Committee of the Affiliated Hospital of Hebei University (Baoding, China). Written informed consent was obtained from each patient or guardian.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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