JBUON 2021; 26(3): 1002-1008
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Efficacy of transcatheter arterial chemoembolization combined with capecitabine and cetuximab in the treatment of colorectal cancer with liver metastasis

Xiong Yun[1]*, Hua Meng[2]*, Anfu Zhou[3], Jingchao Jia[2], Weiling Qian[4]

[1]Department of Pharmacy, Hainan General Hospital (Hainan Affiliated Hospital of Hainan Medical University), Haikou, China. [2]Department of Pharmacy, People's Hospital of Ningxia Hui Autonomous Region, Yinchuan, China. [3]Department of Gastroenterology, The First Affiliated Hospital of Hainan Medical University, Haikou, China. [4]Quality Control Office, Hainan Cancer Hospital, Haikou, China.

*Xiong Yun and Hua Meng contributed equally to this work

Summary

Purpose: *The purpose of this study was to investigate the efficacy and safety of transcatheter arterial chemoembolization (TACE) combined with capecitabine and cetuximab in the treatment of colorectal cancer with liver metastasis.*

Methods: *The colorectal cancer patients with liver metastasis were divided into two groups, namely, Capecitabine group (receiving TACE combined with capecitabine and cetuximab, n=70) and Control group (undergoing TACE combined with cetuximab, n=70). The short-term clinical efficacy, serum tumor markers and liver function indexes were compared. Besides, the survival of patients was analyzed.*

Results: *At 3 months after treatment, the serum levels of carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and vascular endothelial growth factor (VEGF) were significantly lower than those before treatment in both group, and they were lower in Capecitabine group than those in Control group after treatment. The liver function indexes, alanine aminotransferase and aspartate aminotransferase, were significantly increased, while the level of albumin was significantly decreased in both groups at 3 d after treatment, and they were improved significantly at 7 d after treatment in contrast with those at 3 d after treatment. After treatment, there were no statistically significant differences in the Karnofsky performance status score and Quality of Life score between Capecitabine group and Control group. The median survival time of patients in Capecitabine group and Control group was 18.1 months and 14.7 months, respectively. There was a statistically significant difference in the 1-year overall survival rate between Capecitabine group and Control group. Moreover, the cumulative survival rate was significantly higher in Capecitabine group than that in Control group.*

Conclusion: *The short-term efficacy of TACE combined with capecitabine and cetuximab in treating colorectal cancer with liver metastasis is superior to that of TACE combined with cetuximab.*

Key words: *colorectal cancer, liver metastasis, transcatheter arterial chemoembolization, capecitabine, cetuximab*

Introduction

The liver is the major target organ of colorectal cancer with hematogenous metastasis. Studies have demonstrated that about 15-25% of colorectal cancer patients are complicated with liver metastasis upon diagnosis, and another 15-25% of colorectal cancer patients will have liver metastasis after radical resection of primary colorectal cancer, most of which (80-90%) cannot be resected radically [1,2]. Currently, systemic therapy based on chemotherapy and local therapy based on transcatheter

Corresponding author: Weiling Qian, BM. Quality Control Office, Hainan Cancer Hospital, 6 Changbin West Fourth Street, Xiuying District, Haikou, Hainan 570100, China.
Tel: +86015595738721, Email: 21282997@qq.com
Received: 05/03/2021; Accepted: 18/04/2021

arterial chemoembolization (TACE) are widely applied in patients with inoperable liver metastasis of colorectal cancer [3,4]. In systemic therapy, the application of targeted drugs represented by monoclonal antibodies, including cetuximab, can also dramatically prolong the survival time of colorectal cancer patients [5,6].

Capecitabine, a new type of oral fluoropyrimidine nucleoside analogue, is more effective in the treatment of digestive tract tumors [7]. It has been reported that arterial infusion of oxaliplatin combined with oral capecitabine in treating digestive tract cancer with liver metastasis has a relatively high clinical benefit rate and can increase the chance of surgical resection [8,9]. In this retrospective study, the clinical data of colorectal cancer patients with liver metastasis were analyzed so as to investigate the efficacy and safety of TACE combined with capecitabine and cetuximab in treating colorectal cancer with liver metastasis.

Methods

General data

The clinical data of 140 colorectal cancer patients with liver metastasis were collected. The subjects included 88 males and 52 females, aged 37.39-75.84 years old, with a mean of (58.57±9.78) years old. The inclusion criteria involved: (1) patients diagnosed with unresectable colorectal cancer with liver metastasis by histology and cytology or imaging, with measurable lesions, (2) those pathologically confirmed to have wild-type KRAS gene, (3) those with Karnofsky performance status (KPS) score ≥70 points, and (4) those with expected survival time ≥3 months. The exclusion criteria were as follows: (1) patients undergoing previous systemic treatment with cetuximab or other monoclonal antibodies, (2) those with liver function of Child-Pugh grade C, (3) those with severe dysfunction of heart, lung, kidney or other organs, (4) those with platelet count $<50\times10^9$/L in blood routine test, (5) those who were pregnant or breastfeeding, or (6) those with mental abnormality or unable to cooperate during the treatment due to other reasons. The subjects were divided into two groups, namely, Capecitabine group (receiving TACE combined with capecitabine and cetuximab, n=70) and Control group (undergoing TACE combined with cetuximab, n=70) There were no statistically significant differences in the general clinical baseline data between the two groups ($p>0.05$), which were comparable (Table 1). All subjects were informed of the study and signed the informed consent in accordance with the Declaration of Helsinki.

Treatment methods

In Capecitabine group, puncture catheterization was performed *via* femoral artery to celiac trunk and superior mesenteric artery by using the Seldinger technique, followed by angiography. Next, superselective catheterization was conducted on the tumor feeding artery after its location was confirmed. Later, 130 mg/m^2 oxaliplatin +

Table 1. Demographics and general clinical data of all studied patients

Indicators	*Capecitabine group (n=70)* n (%)	*Control group (n=70)* n (%)	*p*
Gender (Male/Female)	47/23	41/29	0.382
Age (years)	59.19±9.47	57.78±9.84	0.389
BMI (kg/m^2)	24.88±3.10	25.15±3.24	0.515
Primary Tumor			0.479
Colon	43 (61.4)	48 (68.6)	
Rectum	27 (38.6)	22 (31.4)	
Pathological type			0.496
Highly differentiated adenocarcinoma	36 (51.4)	39 (55.7)	
Moderately differentiated adenocarcinoma	21 (30.0)	23 (32.9)	
Poorly differentiated adenocarcinoma	13 (18.6)	8 (11.4)	
Number of tumors			0.486
Single	24 (34.3)	29 (41.4)	
Multiple	46 (65.7)	41 (58.6)	
Largest tumor diameter (cm)	2.28±0.56	2.36±0.61	
Child-Pugh grade			0.288
A	42 (60.0)	49 (70.0)	
B	28 (40.0)	21 (30.0)	
KPS score (points)			0.283
80-90	27 (38.6)	20 (28.6)	
70-80	43 (61.4)	50 (71.4)	

BMI: body mass index; KPS: Karnofsky Performance Status.

0.75-1.00 g of 5-fluorouracil (5-FU) was infused. Then, 30 mg of epirubicin + 3-15 mL of ultra-fluid lipiodol emulsion was used for embolization. In addition, cetuximab was intravenously infused at 400 mg/m^2 for 120 min for the first time, and then at 250 mg/m^2 for 60 min once a week in the following weeks. Capecitabine was orally taken at 1250 mg/m^2 twice a day for 14 d and 2-4 cycles (1 cycle =4 weeks).

In Control group, the patients were treated with TACE combined with cetuximab, and the specific usage and dosage were the same as those in Capecitabine group. Before treatment, the patients in both groups were given peripheral intravenous injection of palonosetron hydrochloride (0.25 mg) for antiemesis, and leukopenia was treated with recombinant human granulocyte colony stimulating factor. Besides, the patients received psychological and relevant nursing before, during and after treatment, and timely symptomatic treatment was given in case of adverse reactions of chemotherapy.

Observation indexes

At 4-6 weeks after treatment, contrast-enhanced computed tomography (CT) was performed to determine the lesion activity, and the treatment efficacy was evaluated based on the modified Response Evaluation Criteria in Solid Tumors, which was divided into complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD). CR: All the target lesions disappeared, which lasted for >4 weeks. PR: The sum of the longest diameters of the target lesions was decreased by ≥30% compared with the baseline data. PD: The sum of the longest diameters of the target lesions was increased by 20% in contrast with the minimum sum of the longest diameters of the target lesions recorded after the start of treatment, or the presence of ≥1 new lesions. SD was between PR and PD. The overall response rate (ORR) was calculated as CR+PR, and the disease control rate (DCR) was calculated as CR+PR+SD.

The body surface area and comprehensive physical status, electrocardiogram, blood routine, liver function, renal function, blood coagulation function and tumor markers, such as carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA), were detected before and after treatment. Besides, the levels of liver function indexes [alanine aminotransferase (ALT), aspartate aminotransferase (AST) and albumin (Alb)] and tumor markers [CA19-9, CEA and vascular endothelial growth factor (VEGF)] were compared between the two groups before and after treatment.

The quality of life of the patients was evaluated by KPS score and Quality of Life (QOL) score. The total score of KPS is 100 points. The higher the score was, the better the patient's health status would be. The total QOL score is 60 points, and a higher QOL score indicated higher quality of life of patients. During the treatment, the adverse reactions of patients, such as gastrointestinal reactions, myelosuppression, liver function damage, peripheral neuritis and hand-foot syndrome, were closely observed, recorded and compared between the two groups.

The survival of the patients was followed up and recorded until September 2020. The overall survival (OS) was from the beginning of the treatment to the death of the patient or the end of follow-up.

Statistics

Statistical Product and Service Solutions (SPSS) 22.0 software (IBM, Armonk, NY, USA) was utilized for statistical analysis. The measurement data were expressed as mean ± standard deviation (x±s) and t-test was conducted for intergroup comparison. The enumeration data were expressed as percentage (%), and x^2 test was performed for intergroup comparison. Kaplan-Meier method was adopted to plot the survival curve, and the log-rank test was employed to compare the difference in survival rate between the two groups. P<0.05 suggested that the difference was statistically significant.

Results

Comparison of clinical efficacy between the two groups

At 4-6 weeks after treatment, the treatment efficacy was evaluated by CT in all the patients. Among the 70 patients in Capecitabine group, there were 7 cases of CR, 29 cases of PR, 37 cases of SD and 4 cases of PD, and the ORR and DCR were 51.4% (36/70) and 94.3% (66/70), respectively. In Control group, there were 2 cases of CR, 24 cases of PR, 35 cases of SD and 9 cases of PD, and the ORR and DCR were 37.0% (26/70) and 87.4% (61/70), respectively. No statistically significant differences were found in the ORR (p=0.125) and DCR (p=0.244) between the two groups (Table 2).

Table 2. Clinical effective rates of the two studied groups

	Capecitabine group (n=70) *n (%)*	*Control group (n=70)* *n (%)*	*p*
CR	7 (10.0)	2 (2.9)	
PR	29 (41.4)	24 (34.3)	
SD	37 (52.9)	35 (50.0)	
PD	4 (5.7)	9 (12.9)	
ORR	36 (51.4)	26 (37.1)	0.125
DCR	66 (94.3)	61 (87.4)	0.244

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate; DCR: disease control rate.

Comparison of serum tumor markers and liver function indexes between the two groups before and after treatment

Before treatment, there were no statistically significant differences in the serum levels of CEA, CA19-9 and VEGF between the two groups (p>0.05). At 3 months after treatment, the serum CEA level in Capecitabine group and Control group was decreased from (63.85±20.79) μg/L and (61.39±19.18) μg/L to (22.48±5.45) μg/L and (28.67±6.72) μg/L, respectively. Meanwhile, the serum CA19-9 level was decreased from (105.75±31.51) kU/L and (100.68±29.77) kU/L to (29.49±8.78) kU/L and (33.34±9.32) kU/L, respectively. In addition, the serum VEGF level was decreased from (321.6±56.94) ng/mL and (316.16±59.45) ng/mL to (159.54±22.38) ng/mL and (168.86±31.24) ng/mL, respectively. These indexes were reduced significantly after treatment in contrast with those before treatment in both groups (p<0.05). After treatment, the serum levels of CEA, CA19-9 and VEGF in Capecitabine group were lower than those in Control group, and there were statistically significant differences in the levels of CEA (p<0.001) and CA19-9 (p=0.013), but no statistically significant difference in the VEGF level (p=0.113) between the two groups (Figure 1).

Before treatment, no statistically significant differences were observed in liver function indexes ALT, AST and Alb between the two groups (p>0.05). At 3 d after treatment, the liver function indexes ALT and AST rose significantly (p<0.05), while the Alb level declined significantly (p<0.05) in both groups, but no statistically significant differences were found between the two groups (p<0.05). At 7 d after treatment, the liver function indexes ALT and AST in both groups were significantly lower than those at 3 d after treatment (p<0.05), but they were still higher than those before treatment. Meanwhile, at 7 d after treatment, the Alb level was still slightly lower than that at 3 d after treatment, showing no statistically significant difference between the two groups (p>0.05) (Figure 2).

Comparison of quality-of-life scores between the two groups

After treatment, there were no statistically significant differences in the KPS score [(80.82±7.54) *vs.* (78.69±7.07), p=0.087] and QOL score [(46.74±5.63)

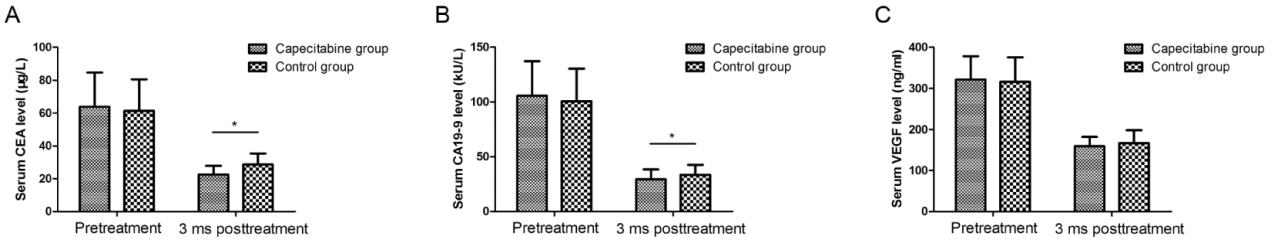

Figure 1. Comparison of serum CEA, CA19-9, VEGF levels between the two groups of patients. Pretreatment CEA **(A)**, CA19-9 **(B)** and VEGF **(C)** levels of patients had no significant difference between Capecitabine group and Control group (p=0.468, p=0.330, p=0.579). Posttreatment serum CEA **(A)**, CA19-9 **(B)** and VEGF **(C)** levels of patients in both groups were significantly decreased after treatment (*p<0.05). Posttreatment serum CEA **(A)** and CA19-9 **(B)** levels of patients in Capecitabine group were significantly lower than those in Control group (*p<0.05). The difference in the posttreatment serum VEGF **(C)** level of patients between Capecitabine group and Control group had no statistical significance (p=0.113).

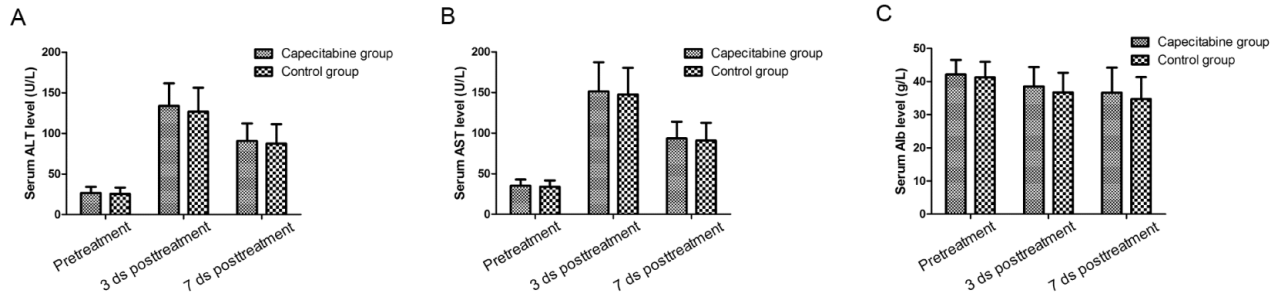

Figure 2. Comparison of serum ALT, AST and Alb levels between the two groups of patients. Pretreatment ALT **(A)**, AST **(B)** and Alb **(C)** levels of patients had no significant difference between Capecitabine group and Control group (p=0.444, p=0.314, p=0.253). 3 days posttreatment serum ALT **(A)** and AST **(B)** levels of patients in both groups were significantly increased, butt the level of Alb **(C)** was significantly decreased after treatment (p<0.05). 7 days posttreatment serum ALT **(A)** and AST **(B)** levels of patients declined, while 3 days posttreatment Alb **(C)** level rose up. The difference in the posttreatment serum ALT **(A)**, AST **(B)** and Alb **(C)** levels of patients between Capecitabine group and Control group had no statistical significance (p>0.05).

Table 3. Comparison of adverse reactions between the two groups of patients

Indicators	*Capecitabine group (n=70)*		*Control group (n=70)*		*p*
	Grade I-II *n (%)*	*GradeIII-IV* *n (%)*	*Grade I-II* *n (%)*	*Grade III-IV* *n (%)*	
Myelosuppression	27 (38.6)	2 (2.9)	21 (30.0)	1 (1.4)	0.292
Fever	31 (44.3)	0 (0)	29 (41.4)	0 (0)	0.665
Alopecia	16 (22.9)	0 (0)	13 (18.6)	0 (0)	0.577
Gastrointestinal reaction	38 (54.3)	0 (0)	33 (47.1)	1 (1.4)	0.412
Liver function damage	22 (31.4)	0 (0)	18 (25.7)	0 (0)	0.475
Abdominal pain	24 (34.3)	0 (0)	19 (27.1)	0 (0)	0.386
Peripheral neuritis	33 (47.1)	0 (0)	26 (37.1)	0 (0)	0.204
Hand-foot syndrome	23 (32.9)	1 (1.4)	20 (28.6)	0 (0)	0.485

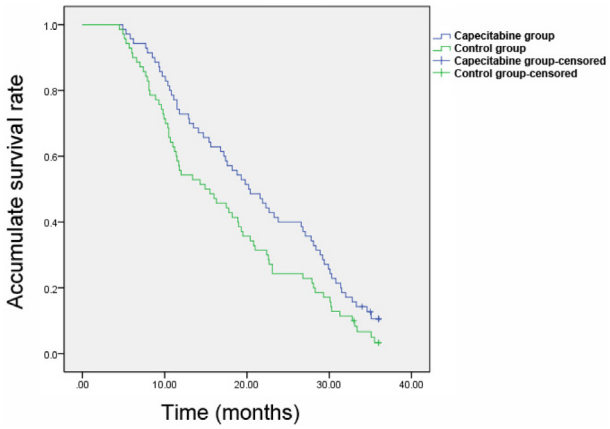

Figure 3. Kaplan-Meier survival curves of patients in Capecitabine group and Control group. The overall survival rate of patients in Capecitabine group was significantly higher than that in Control group (p=0.031).

vs. (45.35±4.94), p=0.123] between Capecitabine group and Control group.

Comparison of adverse reactions between the two groups

The treatment-related adverse reactions in both groups mainly included myelosuppression, fever, alopecia, gastrointestinal reaction, liver function damage, abdominal pain, peripheral neuritis and hand-foot syndrome (mainly in grade I-II), all of which were improved after symptomatic treatment. No patients dropped out because of toxic reaction in both groups. The incidence rate of adverse reactions was higher in Capecitabine group than that in Control group, but there was no statistically significant difference between the two groups (p>0.05, Table 3).

Postoperative follow-up of patients in both groups

By September 2020, all patients were followed up for 4-36 months, and the median survival time of patients in Capecitabine group and Control group was 18.1 months and 14.7 months, respectively. There was a statistically significant difference in the 1-year OS rate between Capecitabine group and Control group [72.9% (51/70) *vs.* 54.3% (38/70), p=0.035]. However, there were no statistically significant differences in the 2-year survival rate [40.0% (28/70) *vs.* 24.3% (17/70), p=0.070] and 3-year survival rate [11.4% (8/70) *vs.* 4.3% (3/70), p=0.208] between the two groups. The survival curve of both groups of patients was plotted by using the Kaplan-Meier method (Figure 3). The results of log-rank test suggested that the cumulative survival rate in Capecitabine group was significantly higher than that in Control group (p=0.031).

Discussion

The liver, rich in blood supply, is the most common organ for metastasis of cancer cells. Currently, surgery is the only effective cure for liver metastasis. However, only less than 20% of the patients meet the indications of surgical excision. The comprehensive treatment for patients with unresectable colorectal cancer and liver metastasis mainly includes systemic chemotherapy, local interventional chemoembolization, molecular targeted drug therapy, local radiotherapy, radio frequency ablation and anhydrous alcohol injection, among which, systemic and interventional chemotherapy and molecular targeted drug therapy are dominant [10,11].

TACE, a safe and minimally invasive treatment, can increase the local drug concentration through the combination of chemotherapeutic drugs with hepatic artery embolization. Meanwhile, it creates a hypoxic environment for tumor cells, weakening the resistance of tumor cells to chemotherapeutic drugs, and thus improving the treatment efficacy. Moreover, the deposition of lipiodol in the hepatic

artery can reduce the blood supply to the tumor, thereby suppressing the metastasis of lymph nodes and cancer cells in the corresponding region [12]. Currently, TACE has become the first choice for the treatment of unresectable liver cancer [13]. A 10-year follow-up study of patients with unresectable colon cancer and liver metastasis treated by TACE manifested that the short-term response rate after TACE treatment is 16.7%, and the 1- and 2-year survival rates are 62% and 28%, respectively [14]. According to another study, after TACE treatment, the cellular immune function of colorectal cancer patients with liver metastasis is improved in contrast with that before treatment, and the short-term response rate and median survival time are 30.9-31.1% and the 10-13.8 months, respectively [15]. Though TACE treatment is effective, due to the dual blood supply from hepatic artery and portal vein, hypoxia induced after TACE treatment can up-regulate angiogenic factors and stimulate residual tumor cells to proliferate continuously. Even if TACE treatment is conducted for many times, the surrounding tumor cells still cannot be completely killed. As a result, the 5-year survival rate of patients is lower than 10% [16].

Capecitabine, a new generation of oral fluorouracil carbamate antineoplastic drugs, is highly targeted and selective. Through oral administration, capecitabine is absorbed by gastrointestinal mucosa in the form of complete molecular, which is transformed into cytotoxic 5-FU under the action of thymine phosphorylase in tumor tissues, thus exerting an anti-tumor effect [17]. According to previous studies, after oral administration of capecitabine, the concentration of fluorouracil in colorectal cancer tissues is 3.2 times higher than that in the adjacent tissues and 21.4 times of that in plasma. Oral administration of 5-FU not only is more convenient than intravenous administration, but can also effectively avoid neurological symptoms triggered by continuous intravenous administration. Moreover, it can effectively increase the blood concentration of the digestive tract, and also enhance the tolerance [18,19]. In addition, 5-FU can improve the chimeric stability of platinum drugs with tumor DNA, thus suppressing the repair of platinum-damaged DNA.

Cetuximab is effective for cancer patients with wild-type KRAS gene. Cetuximab combined with chemotherapy can achieve a high response rate and a high long-term survival rate in the first- and second-line treatment of colorectal cancer with liver metastasis [20]. TACE in combination with targeted drugs such as monoclonal antibodies in treating colorectal cancer with liver metastasis can prolong the survival time and improve the quality of life of patients [21]. In this study, the systemic therapy including cetuximab was combined with capecitabine and TACE, which remarkably improved the treatment effect of advanced colorectal cancer patients with liver metastasis. It was found that the ORR [51.4% (36/70) *vs.* 37.0% (26/70), p=0.125] and DCR [94.3% (66/70) *vs.* 87.4% (61/70), p=0.244] were higher in Capecitabine group than those in Control group, but no statistically significant differences were found. The follow-up results revealed that there was a statistically significant difference in the 1-year OS rate between Capecitabine group and Control group [72.9% (51/70) *vs.* 54.3% (38/70), p=0.035]. However, there were no statistically significant differences in the 2- and 3-year OS between the two groups (p>0.05). After treatment, the serum levels of tumor markers CEA and CA19-9 were significantly lower in Capecitabine group than those in Control group, suggesting that capecitabine have a good short-term efficacy. The score of quality of life in Capecitabine group was higher than that in Control group, but the difference were not statistically significant (p>0.05). Besides, there were no statistically significant differences in the liver function indexes between the two groups after treatment (p>0.05). In addition, the combination of capecitabine did not dramatically increase the incidence of adverse reactions, indicating that oral capecitabine is highly tolerable.

In this retrospective study, the sample size was limited, and the follow-up contents were not comprehensive enough. In the future, multicenter prospective clinical studies with a large sample size are needed to confirm the conclusions of this study.

Conclusions

The short-term efficacy of TACE combined with capecitabine and cetuximab in the treatment of colorectal cancer with liver metastasis is superior to that of TACE combined with cetuximab, and the adverse reactions are tolerable, so it is worthy of clinical popularization.

Conflict of interests

The authors declare no conflict of interests.

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