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Efficacy of hepatic arterial infusion chemotherapy in patients with primary liver cancer with portal vein tumor thrombosis: a comparative analysis of different perfusion chemotherapeutic regimens

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Abstract

Background Portal vein tumor thrombosis (PVTT) commonly occurs in patients with primary liver cancer (PLC). Transarterial chemoembolization (TACE) is a treatment for patients with PLC and PVTT. Some studies have shown that combining TACE therapy with hepatic arterial infusion chemotherapy (HAIC) might improve the survival rate of PLC patients with PVTT. However, few studies have compared the different regimens of PLC with PVTT. We aimed to compare the differences between the oxaliplatin + raltetrexed regimen and FOLFOX regimen.

Methods We divided the 248 patients into two groups. There were 60 patients in the oxaliplatin + ratitetrexed group and 74 patients in the FOLFOX group. The primary endpoints were OS and PFS. The secondary endpoints were ORR and adverse events. We used SPSS software, the Kaplan–Meier method, the *t* test, and the rank sum test to compare the differences between the two groups.

Results The median OS was 10.82 months in the oxaliplatin + raltitrexed group and 8.67 months in the FOLFOX group. The median PFS time was greater in the oxaliplatin + raltitrexed group (10.0 months) than that in the FOLFOX group (7.1 months). The ORR was greater in the oxaliplatin + raltitrexed group than that in the FOLFOX group (18.3% vs. 13.5%; $P = 0.445$). The DCR in the oxaliplatin + raltitrexed group was higher than that in the FOLFOX group (70.0% vs. 64.8%; $P = 0.529$). However, in the subgroup analysis, the difference between them was more significant in the type II PVTT subgroup. The OS was 12.08 months in the oxaliplatin + raltitrexed group and 7.26 months in the FOLFOX group ($P = 0.008$). The PFS was 11.68 months in the oxaliplatin + raltitrexed group and 6.26 months in the FOLFOX group ($P = 0.014$). In the right branch of type II PVTT, the OS was 13.54 months in the oxaliplatin + raltitrexed group and 6.89 months in the FOLFOX group ($P = 0.015$), and the PFS was 13.35 months in the oxaliplatin + raltitrexed group and 6.27 months in the FOLFOX group ($P = 0.030$). The incidence of adverse reactions was similar between the two groups.

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Conclusions Compared with the FOLFOX regimen, the oxaliplatin + raltitrexed chemoembolization regimen had longer OS, PFS time and ORR and DCR and it was safe and tolerable.

Keywords Transarterial chemoembolization, Hepatic arterial infusion chemotherapy, portal vein tumor thrombosis, Primary liver cancer

Background

Primary liver cancer (PLC) is a common malignancy and the fourth leading cause of cancer-related death worldwide [1]. There are two types of hepatic vascular invasion: macroscopic and microscopic. Portal vein tumor thrombosis (PVTT) is the most common form of macrovascular invasion of the PLC [2]. Patients with PVTT usually lose the opportunity for surgery and have an aggressive disease course, decreased liver function reserve, limited treatment options, higher recurrence rates after treatment, and, therefore, worse overall survival [3–5]. Clinically, PVTT is related to tumor size, tumor number, tumor stage, Child–Pugh score, and serum alpha-fetoprotein (AFP) levels [6]. Some studies have shown that combining transarterial chemoembolization (TACE) therapy with hepatic arterial infusion chemotherapy (HAIC) might improve the survival rate of patients with PLC with PVTT [7].

TACE is a treatment in which embolic agents and chemotherapy drugs are mixed together and injected from the hepatic artery to the tumor site, serving to embolize the tumor-feeding arteries and induce ischemic necrosis in the tumor tissue and it is one of the most commonly recommended first-line treatments for PLC, especially combined with PVTT [8–10]. Many studies have shown that TACE combined with HAIC is superior to TACE alone in terms of overall survival (OS) and progression-free survival (PFS), and the treatment-associated toxicities are generally well tolerated [7, 11, 12]. Other studies have shown that in the unresectable and advanced PLC, compared with those in patients treated with two chemoembolization regimens [oxaliplatin + raltetrexed and oxaliplatin + fluorouracil + leucovorin calcium regimen (FOLFOX)], the disease control rates (DCRs) of patients treated with oxaliplatin and realtitrexed were greater than those in patients in the FOLFOX group, and the incidence of adverse reactions was similar [13, 14]. However, the clinical data on the use of raltitrexed in TACE for treating PLC are compared with those on specific chemotherapeutic drug regimens and related effectiveness comparisons [15]. To date, there are still arguments about the effectiveness of different drug regimens for HAIC combined with TACE in patients with PLC with PVTT.

Methods

Aim

Therefore, we designed this retrospective study to compare the effectiveness and safety of different drug regimens for patients with PLC with PVTT treated with HAIC combined with TACE.

Section of patients

Patients were recruited from the Second Affiliated Hospital of Chongqing Medical University. The inclusion criteria were as follows: (1) patients aged > 18 years with PLC who were unsuitable for resection or percutaneous ablation, (2) the Barcelona Clinic Liver Cancer (BCLC) stage is the B–C, or Chinese liver cancer (CNLC) stage is Ib, IIa and llb, (3) Eastern Cooperative Oncology Group (ECOG) performance status is less than or equal to 2, (4) preserved liver function (Child–Pugh) class A or B, (5) a life expectancy greater 12 weeks, (6) a leukocyte count of $> 3.0 \times 10^9$/L, platelet count $\geq 80 \times 10^9$/L, hemoglobin (Hb) ≥ 80 g/L; creatinine (Cr) ≤ 2.0 × UNL (upper normal limits), bilirubin (BIL) ≤ 2.0 × UNL, alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 7.0 × UNL and (7) treatment with programmed cell death protein 1 (PD1) or programmed cell death-ligand 1 (PD-L1) before.

All patients were excluded if they had any other primary tumors, severe liver dysfunction, Child–Pugh class C disease, including severe jaundice, hepatic encephalopathy, refractory intraperitoneal effusion, or hepatorenal syndrome. Patients were also excluded if they had coagulation dysfunction that could not be corrected, if the main portal vein was completely embolized by cancer thrombolysis, if the portal vein collateral compensation was insufficient, if the portal vein could not flow back through the portal vein, if it was combined with severe infection and could not be effectively controlled, or if other serious illnesses or medical conditions occurred. In addition to TACE and HAIC, patients receiving other invasive therapies [radiofrequency, liver resection, high-intensity focused ultrasound (HIFU), etc.] were also excluded.

A total of 248 patients with PLC and PVTT were selected from the Department of Hepatobiliary Surgery, Gastroenterology and Hepatic Disease Center from January 2019 to October 2022. All patients underwent contrast-enhanced ultrasound (CEUS) imaging. It represents

an important tool for the identification of PVTT, particularly for identifying differentiating neoplastic and nonneoplastic thrombosis through the analysis of the ultrasound enhancement characteristics of the thrombosis (malignant findings are characterized by intraluminal arterial hyperenhancement during the arterial phase and washout in the portal or late phase, while benign thrombosis lacks contrast enhancement in any phase) [16]. The 248 patients were divided into the oxaliplatin + raltitrexed group and FOLFOX groups. After excluding 26 patients with metastatic tumors from other sites and 88 patients who were lost to follow-up after one treatment session, there were 60 patients in the oxaliplatin + ratitetrexed regimen group and 74 patients in the FOLFOX regimen group were included (Fig. 1). The primary endpoints were OS and PFS. The secondary endpoints were ORR and adverse events.

Treatment plan

Using the Seldinger technique, we punctured the 5Fr micropuncture into the right femoral artery of patients and placed the 5F vascular sheath. The tumor nourishing arteries were hyperselectively intubated with a microcatheter and a superslip wire. Then, we injected chemicals (3 mg of realtitrexed, 50 mg of loplatin, 20 mg of pyrorubicin mixed with 5–20 ml of iodized oil or loplatin combined with pyrorubicin mixed with iodized oil) into the tumor nourishing arteries. The actual dose was determined based on the size and number of target tumors and the patients' liver function. Polyvinyl alcohol (PVA) particles were used after embolization of the iodooil emulsions, and digital subtraction angiography (DSA) was performed 5 min after embolization to confirm stagnant blood flow in the feeding artery. We placed an arterial catheter after TACE and performed perfusion chemotherapy in the general ward. We intravenously administered dexamethasone (5 mg i. v) and micropumped oxaliplatin (85 mg/m^2) through the catheter sheath artery for 3 h and raltetrexed (3 mg/m^2) for 5 h in the oxaliplatin + raltitrexed group. We intravenously administered dexamethasone (5 mg i. v) and micropumped oxaliplatin (85 mg/m^2) through the catheter sheath artery for 3 h, calcium folinate (200 mg/m^2) for 2 h and fluorouracil (2500 mg/m^2) for 46 h in the FOLFOX group. All patients were followed up every 4–6 weeks after the last TACE and then every 1–3 months if there was no significant recurrence or metastasis. If new lesions or residual tumors were identified, TACE was repeated until untreatable progression occurred.

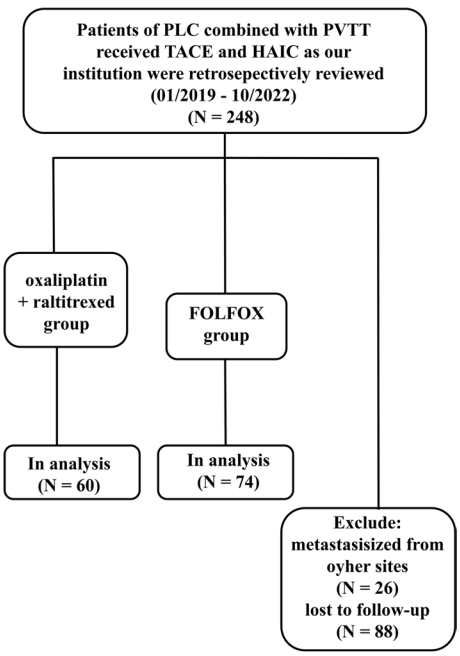


Fig. 1 Flow diagram showing patient selection. *Abbreviations* PLC, primary liver cancer; PVTT, portal vein tumor thrombosis; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy

Statement of ethics

This retrospective study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Chongqing Medical University, the Second Affiliated Hospital of Chongqing Medical University. All patients provided written informed consent form.

Statistics

The data were statistically analyzed using the SPSS 26.0 software. The measurement data were expressed as the mean ± standard deviation (x ± s), with groups compared utilizing the t test and χ^2 test for count data, OS and PFS were analyzed via Kaplan–Meier curves, with statistically significant indicated by $P < 0.05$.

Results

Study subject

Between January 2019 and October 2022, 248 patients were received HAIC combined with TACE treatment. After excluding 26 patients with metastatic tumors from other sites and 88 patients who were lost to follow-up after one treatment session, there were 60 patients in the oxaliplatin + ratitetrexed regimen group and 74 patients in the FOLFOX regimen group (Fig. 1). The median tumor size was 9.4 cm (range 3.0–18.7 cm). The baseline characteristics of the two groups are summarized in Table 1; none of these characteristics differed significantly between the two groups. Most patients were

Table 1 Baseline characteristics of all recruited patients

	Oxaliplatin + raltitrexed group ***N* = 60**	**FOLFOX group** ***N* = 74**	***P* value**
Age (years)	54.18 (51.22–57.18)	51.89 (49.64–54.29)	0.401
Sex (*N*%)			0.471
Female	5	9	
Male	55	65	
ECOG			0.444
0	35	50	
1	24	22	
2	1	2	
Child–puge stage (*N*%)			0.153
A	50	54	
B	10	20	
Vascular invasion (*N*%)			1
No	0	0	
Yes	60	74	
Extrahepatic metastasis (*N*%)			0.474
No	47	54	
Yes	13	20	
Tumor number			0.006
1	38	29	
> 1	22	45	
Tumor size			0.879
1–5 cm	6	9	
5–10 cm	29	33	
> 10 cm	25	32	
d (mm)	93.9 (84.3–103.8)	96.9 (87.2–106.7)	0.926
Classification of PVTT			0.166
I	8	9	
II	28	46	
III	24	19	
IV	0	0	
HBSAg (*N*%)			0.891
Negative	10	13	
Positive	50	61	
Liver cirrhosis (*N*%)			0.795
No	23	30	
Yes	37	44	
AFP			0.517
< 13.2	9	14	
13.2 < *N* < 200	13	9	
200 < *N* < 1210	12	16	
> 1210	26	35	
Ferroprotein	316.95 (253.98–385.47)	384.05 (331.81–443.16)	0.147
Tumor abnormal protein	17,585.11 (11,612.24–24,310.84)	22,798.09 (17,020.07–29112.98)	0.253
Metrafetoprotein heterogeneity	796.16 (514.99–1096.70)	832.30 (561.21–1106.34)	0.858
CA125	130.18 (86.54–184.44)	129.91 (92.42–177.60)	0.982
CA199	43.75 (21.69–76.60)	93.79 (48.19–148.72)	0.061
CA242	7.82 (4.36–14.11)	9.06 (4.71–15.96)	0.505
CA50	48.05 (36.15–61.28)	57.58 (44.22–72.18)	0.252

Table 1 (continued)

	Oxaliplatin + raltitrexed group *N* = 60	FOLFOX group *N* = 74	*P* value
CA724	4.99 (2.48–9.62)	3.82 (1.84–6.94)	0.633
INR	1.06 (1.04–1.08)	1.08 (1.05–1.10)	0.283
Hb	130.15 (124.81–134.87)	132.56 (127.55–137.77)	0.604
WBC	5.38 (4.90–5.91)	6.30 (5.67–6.94)	0.290
PLT	159.15 (137.44–181.99)	187.79 (162.29–214.86)	0.096
ALT	56.22 (47.53–65.43)	66.48 (56.81–77.33)	0.146
AST	99.29 (77.23–126.39)	98.76 (85.59–113.89)	0.970
ALP	174.62 (151.18–199.69)	210.13 (179.58–245.12)	0.097
GGT	233.80 (185.33–287.55)	336.94 (283.90–396.41)	0.11
Total bilirubin levels (umol/L)	17.54 (14.95–20.53)	24.84 (19.38–33.13)	0.065
Albumin levels	36.59 (35.45–37.75)	37.38 (36.33–38.40)	0.231
Number of TACE (*N*)	2.42	2.23	0.467

Among the 134 patients in our study, the mean number of TACE sessions per person was 2.31 (range 1–7 sessions, total: 311 sessions). The maximum numbers of TACE sessions per person in the raltitrexed and control groups were seven and six, respectively. There was no significant difference in the other indices except for the number of tumors

HBsAg, hepatitis B surface antigen; AFP, alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; PVTT, portal vein tumor thrombosis; CA125, carbohydrate antigen 125; CA199, carbohydrate antigen 199; CA242, carbohydrate antigen 242; CA50, carbohydrate antigen 50; CA724, carbohydrate antigen 724; INR, international normalized ratio; HB, hemoglobin; WBC, white blood cell; PLT, platelet; ALT, aminotransferase; AST, aspartate; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase

diagnosed with hepatitis B virus (HBV) related PLC, and most of them were male (Table 1).

Safety and toxicity

Toxic and adverse reactions were evaluated according to the standards for toxicity and side reactions of World Health Organization (WHO) anticancer drugs [17]. There were no cases of procedure-related mortality or 30-day mortality. The complications are listed in Table 2. The most common complications were postembolization syndrome and liver dysfunction. Six of the 60 patients in the oxaliplatin + raltitrexed group and ten of the 74 patients in the FOLFOX group experienced grade 3–4 adverse events. Pain adverse effects occurred in 24 (40.0%) patients in the oxaliplatin + raltitrexed group and 42 (56.7%) patients in the FOLFOX group ($P = 0.034$). The other adverse reactions were similar between the two groups (Table 2).

Tumor response

We evaluated the therapeutic efficacy of PLC according to the WHO modified Response Evaluation Criteria in Solid Tumors (mRECEIST) [18] divided into complete remission (CR) (no enhancement of the intratumoral artery), partial remission (PR) (the tumor was reduced by 30%), stable disease (SD), and progressive disease (PD) (tumor diameter increase of 20% or new tumors). CR + PR was the objective response rate (ORR) and CR + PR + SD was the disease control rate (DCR). Efficacy was evaluated by review after 2 cycles of chemotherapy. A physical examination was performed before the start of each cycle of chemotherapy and routine blood routine, liver and kidney function, AFP, electrocardiogram, computed tomography (CT) or magnetic resonance imaging (MRI), and color ultrasound examinations were performed. Follow-up visits were used to assessed the median survival time. Tumor response was assessed at 4–6 weeks. The results for the two groups are shown in Table 3. The ORR and DCR were higher in the oxaliplatin + raltitrexed group than that in the FOLFOX group (ORR: 18.3% vs. 13.5%; $P = 0.445$; DCR: 70.0% vs. 64.8%; $P = 0.529$).

Survival analysis

At the end of the study period, 12 (20.0%) patients in the oxaliplatin + raltitrexed group and 6 (8.1%) patients in the FOLFOX group were still alive. The median follow-up time was 6 months, and the total follow-up time was 20 months. The median OS was 10.82 months in the oxaliplatin + raltitrexed group [95% confidence interval (CI) 8.80, 12.85] and 8.67 months in the FOLFOX group (95% CI 7.11, 10.22; $P = 0.066$) (Fig. 2a). The median PFS time was slightly longer in the oxaliplatin + raltitrexed group (10.02 months, 95% CI 7.69, 12.36) than in the FOLFOX group (7.07 months, 95% CI 5.28, 8.85; $P = 0.102$) (Fig. 2b). The ORR was greater in the oxaliplatin + raltitrexed group than that in the FOLFOX group (18.3% vs. 13.5%; $P = 0.445$). The DCR of the oxaliplatin + raltitrexed group was also greater thanthat of the FOLFOX group (70.0% vs. 64.8%; $P = 0.529$).

Table 2 Number of complications in the two groups

Total	Oxaliplatin + raltitrexed group	FOLFOX group	*P* value
Postembolization syndrome			
Fever	10	22	0.078
Pain	24	42	0.034
Vomiting	9	5	0.121
Nausea	11	19	0.311
Liver dysfunction			
Elevated ALT/AST levels	7	18	0.061
Hypoalbuminemia	9	15	0.429
Jaundice	10	12	0.944
Systemic disease			
Anemia	6	13	0.212
Leukopenia	9	17	0.246
Neutropenia	8	20	0.053
Thrombocytopenia	10	17	0.365
Anorexia	2	8	0.101
Myelosuppression	7	10	0.749
Ascites	11	11	1
Diarrhea	1	3	0.419
Hepatic failure	6	10	0.533
Renal failure	6	8	0.879
Hepatic encephalopathy	2	1	0.441
Gastrointestinal bleeding	2	2	1
Elevated blood ammonia	10	7	0.213

Number of complications in 134 patients in our study, in oxaliplatin + raltitrexed group and FOLFOX group. There was no significant difference in any of the other indices except for the pain associated with postembolization syndrome. The *P* value was calculated by a two-sided χ^2 test

Table 3 Tumor response in the two groups

	Oxaliplatin + raltitrexed group	FOLFOX group	*P* value
	N = 60	*N* = 74	
Tumor response			0.685
PR	11	10	
SD	31	38	
PD	18	26	
ORR (%)	18.3 (11/60)	13.5 (10/74)	0.445
DCR (%)	70.0 (42/60)	64.8 (48/74)	0.529

Among the 134 patients in our study, the number of complications in the oxaliplatin + raltitrexed group and FOLFOX group. There was no significant difference in any of the other indices except for the pain associated with postembolization syndrome. The *P* value was calculated by a two-sided χ^2 test

PR, partial remission; SD, stable disease; PD, progressive disease; ORR, objective remission rate; DCR, disease control rate

Univariate and multivariate logistic regression analyses

We used univariate and multivariate logistic regression analyses to assess risk factors for each variable (Table 4). We found that age, the type of PVTT, tumor size and extrahepatic metastasis were independent risk factors affecting the prognosis of patients with PLC.

Subgroup analysis

Subgroup analysis by age

Previous studies have indicated a better protective effect of ralterexed on myocardial function [19], so our study divided patients into four subgroups by age (< 36 years, 36–50 years, 51–65 years and > 65 years). In the 1st subgroup, the OS was 4.00 months in the oxaliplatin + raltitrexed group (95% CI 2.04, 5.96) and 4.50 months in the FOLFOX group (95% CI 3.90, 5.10; $P = 0.695$); the PFS was 1.50 months in the oxaliplatin + raltitrexed group (95% CI 0.00, 4.44) and 3.75 months in the FOLFOX group (95% CI 1.78, 5.72; $P = 0.107$). In the 2nd subgroup, the OS was 13.80 months in the oxaliplatin + raltitrexed group (95% CI 10.01, 17.58) and 8.44 months in the FOLFOX group (95% CI 6.65, 10.43; $P = 0.080$); the PFS was 13.23 months in the oxaliplatin + raltitrexed group (95% CI 8.98, 17.48) and 6.47 months in the FOLFOX group (95% CI 4.52, 8.41; $P = 0.072$). In the 3rd subgroup, the OS was 12.95 months in the oxaliplatin + raltitrexed

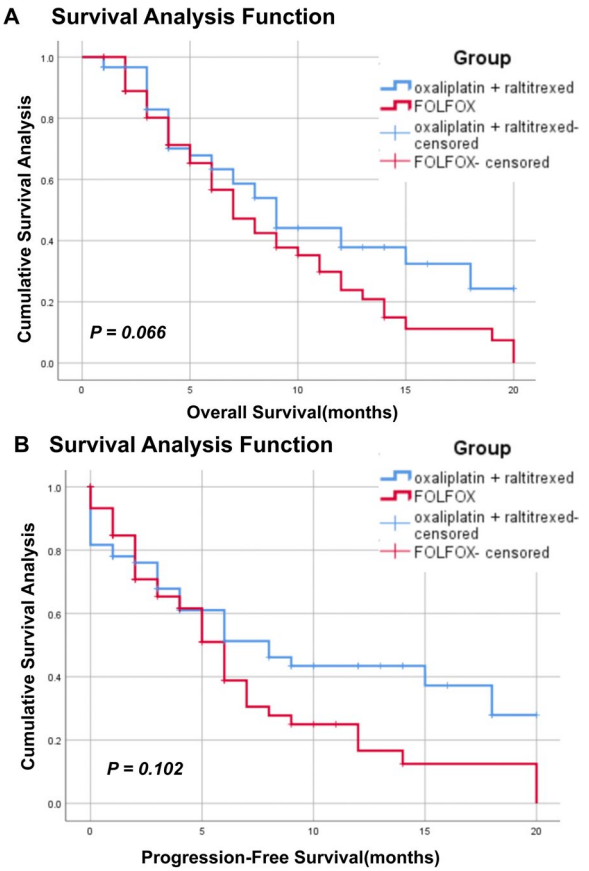


Fig. 2 Survival analysis function of the two groups. The median follow-up time was 6 months, and the total follow-up time was 20 months. **A** Kaplan–Meier curves of OS in patients with unresectable primary liver cancer who underwent TACE in the two groups. **B** Kaplan–Meier curves of PFS in patients with unresectable primary liver cancer who underwent TACE in the two groups

Table 4 Univariable and multivariable logistic regression analysis

Variables	Univariate analysis		Multivariate analysis	
	OR (95%CI)	*P*value	OR (95%CI)	*P* value
Age	0.774 (0.547, 1.096)	0.148		
Sex	0.606 (0.220, 1.671)	0.297		
HBSAg	0.751 (0.381, 1.478)	0.407		
Child-Puge Stage	1.247 (0.688, 2.263)	0.467		
Liver Cirrhosis	0.988 (0.603, 1.618)	0.960		
AFP	1.155 (0.940, 1.418)	0.073		
Extrahepatic Metastasis	3.110 (1.774, 5.449)	0.005	2.826 (1.576, 5.069)	0.006
Tumor Size	0.651 (0.305, 1.392)	0.009	0.651 (0.303, 1.402)	0.024
Tumor Number	0.898 (0.554, 1.457)	0.035	1.080 (0.635, 1.838)	0.777
Classification of PVTT	1.496 (0.654, 3.424)	0.085	1.493 (0.628, 3.550)	0.032
Total Bilirubin Levels	0.583 (0.436, 0.754)	0.040	0.564 (0.445, 0.819)	0.158
Number of TACE	0.636 (0.502, 0.807)	0.664		

group (95% CI 10.06, 15.83) and 9.17 months in the FOLFOX group (95% CI 6.12, 12.21; $P=0.128$); the PFS was 12.32 months in the oxaliplatin + raltitrexed group (95% CI 8.93, 15.72) and 7.71 months in the FOLFOX group (95% CI 4.35, 11.07; $P=0.095$). In the 4th subgroup, the OS was 10.03 months in the oxaliplatin + raltitrexed group (95% CI 6.42, 13.64) and 8.27 months in the FOLFOX group (95% CI 5.36, 11.19; $P=0.951$); the PFS was 9.68 months in the oxaliplatin + raltitrexed group (95% CI 5.66, 13.70) and 8.28 months in the FOLFOX group (95% CI 5.36, 11.19; $P=0.728$) (Table 5). Overall, the OS and PFS of the oxaliplatin + raltitrexed group were longer than those of the FOLFOX group, but there were no significant differences between the two groups, and the examination indices of myocardial enzyme levels, cardiac color ultrasound results and other indicators did not appear significantly differ among the age groups. Therefore, the cardioprotective effect of raltetrexed needs to be further verified.

Subgroup analysis by PVTT classification

The more conventional and better-known classification of PVTT was proposed by the Liver Cancer Study Group of Japan (LCSGJ) [20, 21]. Chen et al. proposed Cheng's classification type: Type I0: microscopic tumor thrombosis formation; Type I: tumor thrombosis involving secondary level and above portal vein branch (type Ia: tumor thrombosis involving portal vein grade i and j level and above branch; type Ib: tumor thrombosis involving portal vein secondary branch); Type II: tumor thrombosis involving primary portal branch [type IIa: primary portal branch (such as left or right portal stem); type IIb: secondary primary portal branch (involving left and right portal stem)]; Type III: tumor thrombolysis involving the main portal vein (type IIIa: tumor thrombolysis involving the main portal vein, portal vein trunk confluence below no more than 2 cm; type IIIb: tumor thrombolysis involving the main portal vein, portal vein trunk trunk confluence below more than 2 cm); Type IV: tumor thrombolysis involving superior mesenteric vein or inferior vena cava (type IVa: tumor thrombolysis involving

superior mesenteric vein; type IVb: cancer thrombolysis involving inferior vena cava) [22].

We subjected all patients to PVTT subgroup analysis by Cheng's classification type. In the type II PVTT subgroup, the OS was 12.08 months in the oxaliplatin + raltitrexed group (95% CI 9.18, 14.98) and 7.26 months in the FOLFOX group (95% CI 5.79, 8.72; $P=0.008$) (Fig. 3a); the PFS was 11.68 months in the oxaliplatin + raltitrexed group (95% CI 8.46, 14.90) and 6.26 months in the FOLFOX group (95% CI 4.80, 7.73; $P=0.014$) (Fig. 3b). The ORR and DCR were greater in the oxaliplatin + raltitrexed group than in the FOLFOX group (ORR: 24.1% vs. 15.2%; $P=0.357$; DCR: 75.8% vs. 60.9%; $P=0.221$) (Table 6).

Subgroup analysis by tumor number

In the baseline comparison, there were significant differences between the number of tumors in the two groups, so we performed Cox multivariate regression analysis. All patients were divided into two subgroups: a single-tumor subgroup and a multiple-tumor subgroup. In the single-tumor subgroup, the OS was 11.25 months in the oxaliplatin + raltitrexed group (95% CI 8.58, 13.91) and 7.81 months in the FOLFOX group (95% CI 5.27, 10.35; $P=0.044$) (Fig. 4a); the PFS was 10.66 months in the oxaliplatin + raltitrexed group (95% CI 7.53, 13.80) and 5.95 months in the FOLFOX group (95% CI 3.34, 8.56; $P=0.041$) (Fig. 4b). In the multiple-tumor subgroup, the OS was 12.96 months in the oxaliplatin + raltitrexed group (95% CI 9.83, 16.08) and 9.10 months in the FOLFOX group (95% CI 7.10, 11.09; $P=0.046$) (Fig. 4c); the PFS was 12.54 months in the oxaliplatin + raltitrexed group (95% CI 9.10, 15.87) and 8.24 months in the FOLFOX group (95% CI 5.90, 10.57; $P=0.047$) (Fig. 4d) (Table 7).

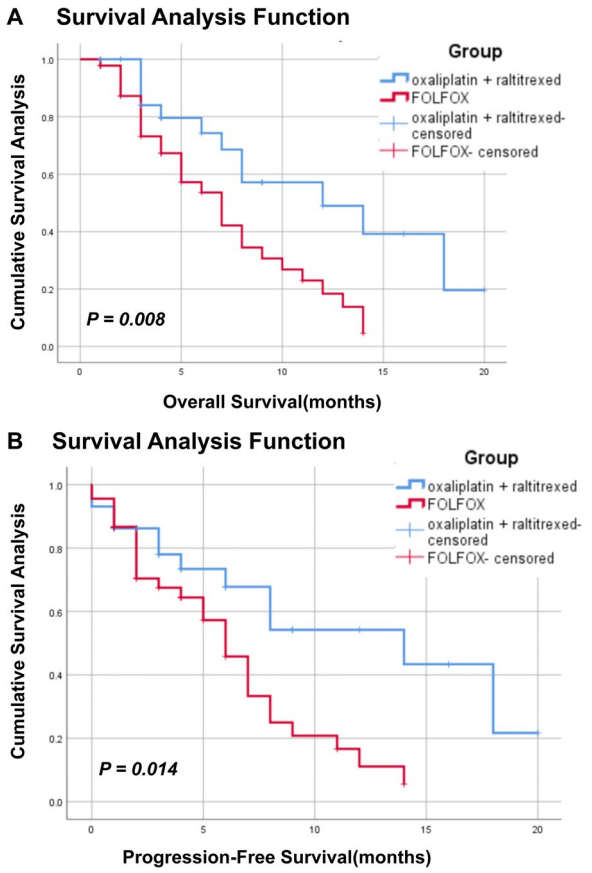


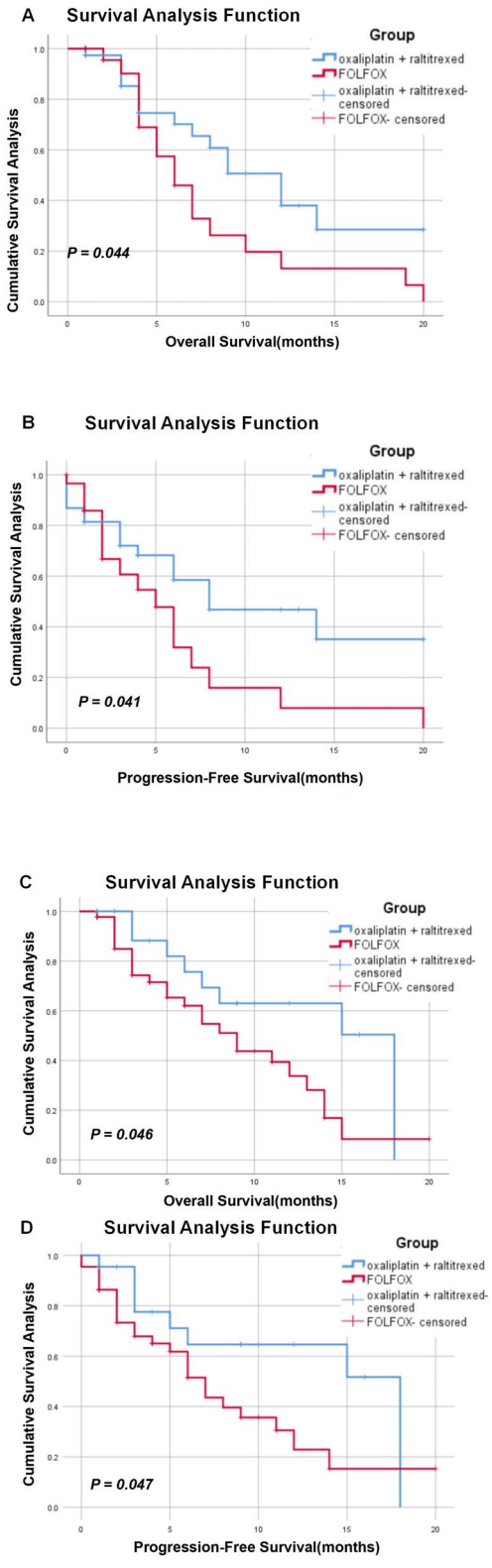
Fig. 3 Survival analysis function of patients in the type II PVTT subgroup. **A** Kaplan–Meier curves of OS in patients with type II PVTT who underwent TACE in the two groups. **B** Kaplan–Meier curves of PFS in patients with type II PVTT who underwent TACE in the two groups

Table 5 Subgroup analysis by age

Age		Oxaliplatin + raltitrexed group	FOLFOX group	*P* value
		N = 2	*N* = 4	
	PR	0	0	
< 36 years	SD	2	2	0.221
	PD	0	2	
	PFS	4.00 (2.00–5.44)	3.75 (1.78–5.72)	0.107
	OS	4.550 (3.98–5.96)	4.50 (3.90–5.10)	0.695
		N = 22	*N* = 31	
	PR	5	6	
36–50 years	SD	9	16	0.741
	PD	8	9	
	PFS	13.23 (8.98–17.48)	6.47 (4.52–8.41)	0.072
	OS	13.80 (10.01–17.58)	8.44 (6.65–10.43)	0.080
		N = 25	*N* = 33	
	PR	2	4	
51–65 years	SD	16	16	0.499
	PD	7	13	
	PFS	12.32 (8.93–15.72)	7.71 (4.35–11.07)	0.095
	OS	12.95 (10.06–15.83)	9.17 (6.12–12.21)	0.128
		N = 11	*N* = 6	
	PR	4	0	
> 65 years	SD	4	3	0.232
	PD	3	3	
	PFS	9.68 (5.66–13.70)	8.28 (5.36–11.19)	0.728
	OS	10.03 (6.42–13.64)	8.27 (5.36–11.19)	0.951

We divided the 134 patients into four subgroups by age. There was no significant difference in OS or PFS among these four subgroups. The *P* value was calculated by a two-sided χ^2 test

PR, partial remission; SD, stable disease; PD, progressive disease; ORR, objective remission rate; DCR, disease control rate



◀ **Fig. 4** Survival analysis function of subgroups by tumor numbers. **A** Kaplan–Meier curves of OS in patients with a single tumor who underwent TACE in the two groups. **B** Kaplan–Meier curves of PFS in patients with a single tumor who underwent TACE in the two groups. **C** Kaplan–Meier curves of OS in patients with a multiple tumor who underwent TACE in the two groups. **D** Kaplan–Meier curves of OS in patients with a multiple tumor who underwent TACE in the two groups

Subgroup analysis by the position of type II PVTT

In the type II PVTT subgroup, the oxaliplatin + raltitrexed regimen showed better efficacy than FOLFOX, and we again divided all patients into left, right and bilateral type II PVTT groups according to the location of the PVTT.In the right group, the OS was 13.54 months in the oxaliplatin + raltitrexed group (95% CI 9.52, 17.56) and 6.89 months in the FOLFOX group (95% CI 5.17, 8.60; $P = 0.015$) (Fig. 5a); the PFS was 13.35 months in the oxaliplatin + raltitrexed group (95% CI 9.08, 17.63) and 6.27 months in the FOLFOX group (95% CI 4.48, 8.07; $P = 0.030$) (Fig. 5b). These two drug treatment modalities were significant different (Table 8).

Discussion

In our study, after a 20-month follow-up time, the OS and PFS in the oxaliplatin + raltitrexed group were slightly longer than those in the FOLFOX group. However, neither of the two groups exhibited statistically significant differences. The ORR was 18.3% in the oxaliplatin + raltitrexed group and 13.5% in the FOLFOX group ($P = 0.445$). The DCR was 70.0% in the oxaliplatin + raltitrexed group and 64.8% in the FOLFOX group ($P = 0.529$). Pain adverse effects occurred in 24 (40.0%) patients in the oxaliplatin + raltitrexed group and 42 (56.7%) patients in the FOLFOX group ($P = 0.034$). However, the other adverse reactions were almost the same between the two groups.

The FOLFOX treatment modality was previously used to treat gastrointestinal tumors (including primary and metastatic liver cancer, biliary tract system tumors, pancreatic tumors, and colorectal tumors.) [23, 24]. According to previous reports, FOLFOX-HAIC significantly improved OS compared with TACE in patients with unresectable large hepatocellular carcinoma [25, 26]. However, fluorouracil should be administered intra-arterially for approximately 44 h, and a higher incidence of pain, catheter thrombosis and catheter-associated infection has been reported [27]. The oxaliplatin + raltitrexed regimen had been gradually used for HAIC treatment after TACE due to its advantages of less cardiotoxicity

Table 6 Subgroup analysis by PVTT classification

Classification of PVTT		Oxaliplatin + raltitrexed group	FOLFOX group	*P* value
		N = 8	*N* = 9	
	PR	0	1	
I	SD	5	2	0.198
	PD	3	6	
	PFS	13.47 (8.29–18.66)	9.02 (2.95–15.09)	0.457
	OS	13.20 (8.19–18.20)	13.13 (8.49–17.76)	0.912
		N = 29	*N* = 46	
	PR	7	7	
II	SD	15	21	0.351
	PD	7	18	
	PFS	11.68 (8.46–14.90)	6.26 (4.80–7.73)	0.014
	OS	12.08 (9.18–14.98)	7.26 (5.79–8.72)	0.008
		N = 24	*N* = 19	
	PR	5	2	
III	SD	11	14	0.184
	PD	8	3	
	PFS	8.85 (6.17–11.53)	7.71 (4.35–11.07)	0.891
	OS	12.95 (10.06–15.83)	9.17 (6.12–12.21)	0.819

We divided the 134 patients into three subgroups by PVTT classification. Except for the type II PVTT subgroup, there was no significant difference in the PR, SD, PD, OS or PFS among the other subgroups. The *P* value was calculated by a two-sided χ^2 test

PR, partial remission; SD, stable disease; PD, progressive disease; ORR, objective remission rate; DCR, disease control rate

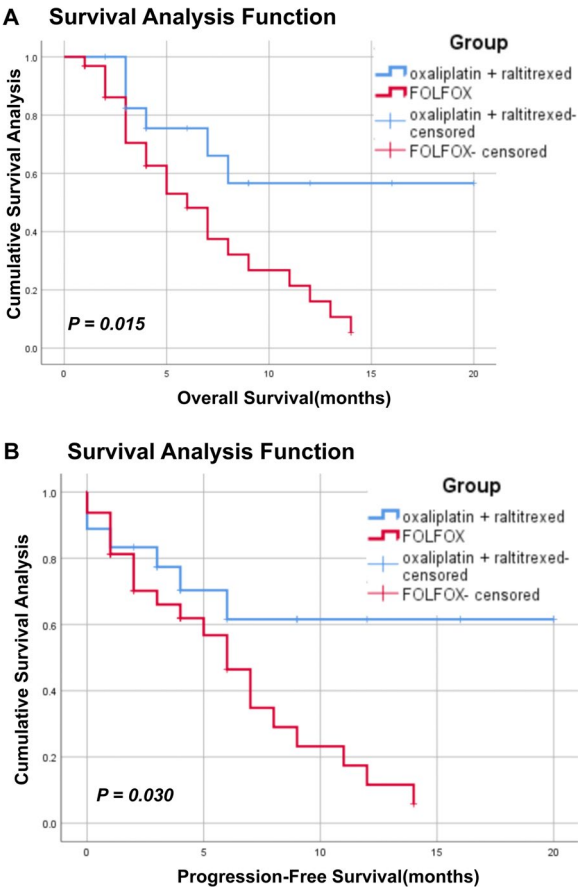


Fig. 5 Survival analysis of subgroups stratified by the location of type II PVTT. **A** Kaplan–Meier curves of OS in patients with type II PVTT in the right branch who underwent TACE in the two groups. **B** Kaplan–Meier curves of PFSS in patients with type II PVTT in the right branch who underwent TACE in the two groups

and shorter perfusion time in recent years [28]. The OS and PFS were longer than those of the FOLFOX group in previous studies not only for HCC but also for colorectal cancer (CRC) liver metastasis (CRCLM) [29, 30]. There are few studies on perfusion chemotherapy for liver cancer combined with PVTT. Cui et al. proposed that the PFS of patients treated with raltitrexed was longer in unresectable hepatocellular carcinoma complicated with PVTT, but no significant statistical difference was observed between the two groups [13]. However, this finding did not further explain the reason for the longer PFS of the oxaliplatin + raltitrexed regimen. OS and PFS were also longer in the oxaliplatin + raltitrexed group than those in the FOLFOX group, but there was no significant difference between the two groups in our study. Unlike previous studies, our drug dose was calculated by body weight in order to obtain the best results for each patient and decrease toxic side effects. In addition, we also conducted subgroup analysis through age, type of PVTT, and the number of tumors and still concluded that oxaliplatin + raltitrexed was superior to FOLFOX, and there were significant differences in the subgroups of type II PVTT and the number of tumors. Moreover, the sample size was somewhat larger than that in previous studies. It can be seen that oxaliplatin + raltitrexed regimen has beneficial advantages and safety for PLC in combination with PVTT.

According to our subgroup analysis by PVTT classification, oxaliplatin + raltitrexed showed better efficacy than FOLFOX in the type II PVTT subgroup. The OS was 12.08 months in the oxaliplatin + raltitrexed group (95% CI 9.18, 14.98) and 7.26 months in the FOLFOX group (95% CI 5.79, 8.72; $P = 0.008$); the PFS was 11.68 months in the oxaliplatin + raltitrexed group (95% CI 8.46, 14.90) and 6.26 months in the FOLFOX group (95% CI 4.80, 7.73; $P = 0.014$). Moreover, oxaliplatin + raltitrexed was more effective for type II PVTT located in the right branch in our study. Theoretically speaking, there may be two reasons for this. First, the efficacy of chemotherapy

Table 7 Subgroup analysis by tumor number

Tumor number		Oxaliplatin + raltitrexed group	FOLFOX group	*P* value
		N = 38	*N* = 29	
	PR	8	3	
Single tumor	SD	17	14	0.492
	PD	13	12	
	PFS	10.66 (7.53–13.80)	5.95 (3.34–8.56)	0.041
	OS	11.25 (8.58–13.91)	7.81 (5.27–10.35)	0.044
		N = 22	*N* = 44	
	PR	3	7	
Multiple tumor	SD	14	22	0.556
	PD	5	15	
	PFS	12.54 (9.10–15.87)	8.24 (5.90–10.57)	0.047
	OS	12.96 (9.83–16.08)	9.10 (7.10–11.09)	0.046

We divided the 134 patients into three subgroups according to tumor number. Except for the type II PVTT subgroup, there was no significant difference in the PR, SD, PD, OS or PFS among the other subgroups. The *P* value was calculated by a two-sided χ^2 test

PR, partial remission; SD, stable disease; PD, progressive disease; ORR, objective remission rate; DCR, disease control rate

Table 8 Subgroup analysis by the position of type II PVTT

Position of type II PVTT		Oxaliplatin + raltitrexed group	FOLFOX group	*P* value
		N = 18	*N* = 32	
	PR	3	3	
Right	SD	11	15	0.295
	PD	4	14	
	PFS	13.35 (9.08–17.63)	6.27 (4.48–8.07)	0.030
	OS	13.54 (9.52–17.56)	6.89 (5.17–8.60)	0.015
		N = 7	*N* = 8	
	PR	3	2	
Left	SD	2	4	0.549
	PD	2	2	
	PFS	13.00 (3.20–22.80)	6.20 (2.77–9.64)	0.233
	OS	15.00 (9.12–20.88)	7.87 (4.87–10.86)	0.083
		N = 4	*N* = 6	
	PR	1	2	
Bilateral	SD	2	2	0.870
	PD	1	2	
	PFS	6.50 (0.81–12.19)	5.60 (3.40–7.80)	0.756
	OS	7.75 (3.20–12.30)	8.20 (3.64–12.76)	0.941

We divided the 75 patients with type II PVTT into three subgroups according to the position of the tumor thrombosis. There was a significant difference in OS and PFS in the right branch PVTT subgroup. The *P* value was calculated by a two-sided χ^2 test

PR, partial remission; SD, stable disease; PD, progressive disease; ORR, objective remission rate; DCR, disease control rate

drugs may be related to the location of the PVTT. When the PVTT is located in the right branch of the portal vein and the tumor is located on the same side, the drug can be better transported to the target vessel through the right hepatic artery, while when the PVTT is located in the left or bilateral or even the main portal vein (MPV), the perfusion effect of the drug through the arteriae hepatica propria (AHP) may be slightly attenuated. On the other hand, this is due to the pharmacokinetic difference between ratitetrexed and fluorouracil. Raltitrexed can directly or specifically cause DNA chain breakage and apoptosis by inhibiting thymidylate synthase (TS), a key enzyme in the synthesis of deoxythymidine 5-triphosphate (TTP). However, fluorouracil was first converted to a 5-fluorine-deoxyuracil nucleotide at first in vivo after which TS was inhibited to inhibit DNA. Nevertheless, further prospective studies are needed to determine the possible advantages of the right-branch type II PVTT will in the oxaliplatin + raltitrexed group.

Previous studies reported that fluorouracil has some cardiotoxic effects, such us fluoropyrimidine-induced cardiotoxicity (FIC), including coronary artery vasospasm, endothelial or cardiomyocyte damage, toxic metabolites, and dihydropyrimidine dehydrogenase deficiency and so on [31]. Compared with fluorouracil, raltitrexed is less cardiotoxic [32]. According to our subgroup analysis by age, the OS and PFS of the oxaliplatin + raltitrexed group were longer than those of the FOLFOX group in every subgroup, but neither the OS nor PFS of the two groups in the subgroups were significantly different. All patients in our study underwent accessory examinations including myocardial enzyme spectrum, type B natriuretic peptide precursor (BNP), cardiac color ultrasound and electrocardiogram before and after TACE, and none of the findings showed significant cardiac damage. Therefore, the cardioprotective effect of raltetrexed needs to be further verified. According to the subgroup analysis by tumor number, the OS and PFS in the oxaliplatin + raltitrexed group were grater than those in the FOLFOX group and there were significant differences regardless of the number of tumors. The study of Rong et al. noted that as the number of tumors increased, the OS decreased [33], while the OS of our study was slightly longer in multiple tumor groups than in a single tumor group. Therefore, further studies on the impact of tumor number on patient prognosis are needed, but these studies did not reveal an obvious prognostic benefit of raltitrexed.

Our study also evaluated the safety and tolerability of these two treatments. We found that the incidence of major complications was not significantly different between the two groups. Only a greater proportion of pain response in the FOLFOX group may be associated with a longer drug perfusion time, but all complications were reversible and adequately controlled by medical treatment. These results indicate that the combination of raltitrexed and oxaliplatin in TACE in patients with unresectable PLC is safe and tolerable.

Our study also had some limitations. First, because it was retrospective, some selection biases were unavoidable. Second, this study was conducted at a single center with a relatively small number of patients, a large number of whom carried hepatitis B (82.8%), and the proportion of males was high (89.5%). Third, the included subjects in this study had no type IV PVTT. Currently, the treatment of type IV PVTT for TACE + HAIC is still being explored currently, and further studies on this topic may be needed. Finally, the sample size of the oxaliplatin + raltitrexed group was small. If we increase the sample size, reduce the loss to follow-up and extend the follow-up time, we can obtain better results. Moreover, the number of TACE procedures differed among individuals, which may also have affected the results of our study. Larger prospective trials are needed to confirm this conclusion.

Conclusion

Despite no significant difference between the oxaliplatin + raltitrexed group and the FOLFOX group, the oxaliplatin + raltitrexed chemoembolization regimen had a longer OS, PFS, ORR and DCR than the FOLFOX regimen. This regimen was safe and tolerable, especially for PLCs with type II PVTT. Our findings suggest that the combination therapy of TACE and HAIC bvia oxaliplatin plus raltitrexed regimen confers more benefits to patients with unresectable PLC than other regimens.

Abbreviations

PVTT	Portal vein tumor thrombosis
PLC	Primary liver cancer
TACE	Transarterial chemoembolization
HAIC	Hepatic arterial infusion chemotherapy
OS	Overall survival
PFS	Progression-free survival
FOLFOX	Oxaliplatin + fluorouracil + leucovorin calcium
ORR	Objective remission rate
DCR	Disease control rate
cTACE-HAIC	Transarterial chemoembolization plus hepatic arterial infusion chemotherapy
CI	Confidence interval
AFP	Alpha-fetoprotein
BCLC	Barcelona clinic liver cancer
ECOG	Eastern Cooperative Oncology Group
Hb	Hemoglobin
Cr	Creatinine
UNL	Upper normal limits
BIL	Bilirubin
ALT	Aminotransferase
AST	Aspartate
PD1	Programmed cell death protein 1
PD-L1	Programmed cell death-ligand 1
HIFU	High intensity focused ultrasound
PVA particles	Polyvinyl alcohol particles
DSA	Digital subtraction angiography
HBsAg	Hepatitis B surface antigen
CA125	Carbohydrate antigen 125
CA199	Carbohydrate antigen 199
CA242	Carbohydrate antigen 242
CA50	Carbohydrate antigen 50
CA724	Carbohydrate antigen 724
INR	International normalized ratio
WBC	White blood cell
PLT	Platelet
ALP	Alkaline phosphatase
GGT	γ-Glutamyl transferase
WHO	World Health Organization
mRECIST	Modified response evaluation criteria in solid tumors
CR	Complete remission
PR	Partial remission
SD	Stable disease
PD	Progressive disease
ORR	Objective response rate
DCR	Disease control rate
CT	Computed tomography
MRI	Magnetic resonance imaging
LCSGJ	Liver Cancer Study Group of Japan
CI	Confidence interval
CRC	Colorectal cancer
CRCLM	Colorectal cancer liver metastasis
MPV	Main portal vein
AHP	Arteriae Hepatica Propria
TS	Thymidylate synthase
TTP	Deoxythymidine 5-triphosphate
FIC	Fluoropyrimidine-induced cardiotoxicity
BNP	B naturetic peptide precursor

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Author contributions

Study conception and experimental design, collection and analysis of data, and manuscript writing, Xinxin Tu; collection and analysis of data, Xinxin Tu, Wenfeng Zhang, Sipeng Li, Qi He; study conception, design, and supervision, Wenfeng Zhang, Yue Li; supervision, manuscript writing, and final approval of the manuscript; Yue Li. All authors read and approved the final manuscript.

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Availability of data and materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This retrospective study was conducted in accordance with the Declaration of Helsinki. This study was approved by Chongqing Medical University,

the Second Affiliated Hospital of Chongqing Medical University. All patients provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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