

# Prognostic factors for transarterial chemoembolization combined with sustained oxaliplatin-based hepatic arterial infusion chemotherapy of colorectal cancer liver metastasis

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## Abstract

**Objective:** To investigate the prognostic factors in chemorefractory colorectal cancer liver metastasis (CRCLM) patients treated by transarterial chemoembolization (TACE) and sustained hepatic arterial infusion chemotherapy (HAIC).

**Methods:** Between 2006 and 2015, 162 patients who underwent 763 TACE and HAIC in total were enrolled in this retrospective study, including 110 males and 52 females, with a median age of 60 (range, 26–83) years. Prognostic factors were assessed with Log-rank test, Cox univariate and multivariate analyses.

**Results:** The median survival time (MST) and median progression-free survival (PFS) of the 162 patients from first TACE/HAIC were 15.6 months and 5.5 months respectively. Normal serum carbohydrate antigen 19-9 (CA19-9, <37 U/mL) ( $P < 0.001$ ) and carbohydrate antigen 72-4 (CA72-4, <6.7 U/mL) ( $P = 0.026$ ), combination with other local treatment (liver radiotherapy or liver radiofrequency ablation) ( $P = 0.034$ ) and response to TACE/HAIC ( $P < 0.001$ ) were significant factors related to survival after TACE/HAIC in univariate analysis. A multivariate analysis revealed that normal serum CA19-9 ( $P < 0.001$ ), response to TACE/HAIC ( $P < 0.001$ ) and combination with other local treatment ( $P = 0.001$ ) were independent factors among them.

**Conclusions:** Our findings indicate that serum CA19-9 <37 U/mL and response to TACE/HAIC are significant prognostic indicators for this combined treatment, and treated with other local treatment could reach a considerable survival benefit for CRCLM. This could be useful for making decisions regarding the treatment of CRCLM.

**Keywords:** Colorectal cancer; transarterial chemoembolization; hepatic artery infusion chemotherapy

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## Introduction

Liver metastasis occurs frequently in colorectal cancer and develops in about 50% of patients (1). Hepatic resection is still the only potentially therapeutic treatment for

colorectal cancer liver metastasis (CRCLM), which can be available for no more than 20% of patients (2,3). Patients who were involved in inoperable liver metastases or contraindications to surgical resection are routinely treated with systemic chemotherapy. Standard first-line

chemotherapy can achieve 7.0–12.3 months of median progression-free survival (PFS) and 15.0–29.8 months of median overall survival (OS) (4–6), but the median PFS and OS would be only 4.8–6.8 months and 11–15 months even with molecular target drugs in second and subsequent treatment (7,8).

Without other treatment, the median OS of patients who failed from primary chemotherapy could be only 3.5 months (9). Alternative treatment is in great need. Compared with systemic chemotherapy and surgery, minimally invasive interventional therapy such as radiofrequency ablation (RFA), transarterial chemoembolization (TACE) and hepatic artery infusion chemotherapy (HAIC) has the advantages of repeatability and minimal invasion. Minimally invasive interventional therapy in the multi-disciplinary treatment (MDT) has gained more acceptance.

TACE and HAIC are the most typical treatments of interventional therapies via the vessels. TACE has been proved to have a higher response rate than systemic chemotherapy (10–14), and HAIC with oxaliplatin (OXA), calcium folinate (CF) and 5-fluorouracil (5-Fu) in pre-treated patients with CRCLM had also proved to be a feasible and low-toxicity treatment (15,16). Liver metastasis of colorectal cancer is considered lack of blood supply, so the clinical outcome of TACE for patients with CRCLM is expected to be improved by HAIC; however, there has so far been no evidence for this expectation. Previous studies have described prognostic indicators for CRCLM, including the primary colorectal cancer stage, tumor differentiation, the size and number of metastases, carcinoembryonic antigen (CEA) level, time to liver metastasis, and extrahepatic disease (17,18). However, no consensus exists regarding the indications for combined TACE and HAIC. A new strategy to improve the prognoses of patients undergoing TACE/HAIC is needed. The aim of the present study was to investigate the prognostic factors in chemorefractory CRCLM patients treated by TACE/HAIC.

## Materials and methods

### Patients

Between 2006 and 2015, 214 CRCLM patients underwent TACE and sustained HAIC in Peking University Cancer Hospital & Institute (Figure 1). The indications for performing the TACE were defined as follows: 1)

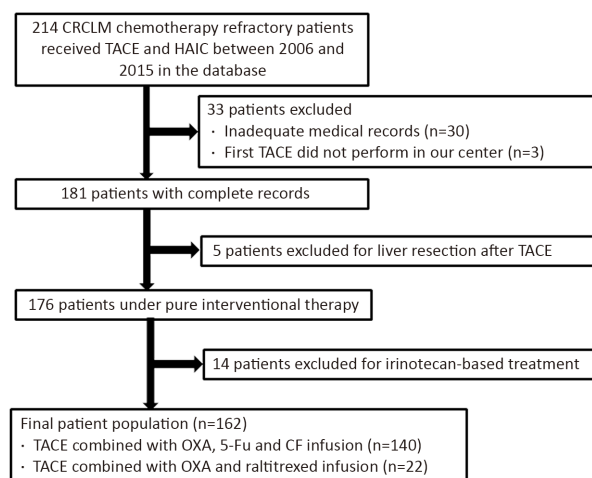


Figure 1 Flowchart detailing patient selection.

pathologically diagnosed as adenocarcinoma of the colon or rectum; 2) inoperable liver metastases or contraindications to liver resection; 3) failed from previous systemic chemotherapy (experience at least one line of chemotherapy) or could not suffer its side effects; and 4) the Eastern Cooperative Oncology Group (ECOG) performance status score was less than 2. Patients (56%, n=91) who had extrahepatic metastases were included, considering their main lesion still remained in the liver. Excluded criteria of this retrospective study were conditions as followed: 1) inadequate medical records (n=30); 2) previously received TACE or other interventional treatment (n=3); 3) acquired further resection of liver metastasis after TACE (n=5); or 4) infused chemotherapy agents were not based on OXA (n=14). Patients with poor performance status (ECOG  $\geq 2$ ), tumor involvement of more than 70% of liver volume and liver or renal dysfunction (total bilirubin serum levels  $>3$  mg/dL, serum albumin level  $<20$  g/L, serum creatinine level  $>2$  mg/dL) would not consider a TACE/HAIC. Finally, 162 CRCLM patients who underwent 763 TACE/HAIC in total were enrolled in this retrospective study, including 110 males and 52 females, with a median age of 60 (range, 26–83) years.

The retrospective study was in accordance with the ethical standards of the Ethic Committee of Peking University Cancer Hospital and received Institutional Review Board approval. The informed consent was waived.

### TACE

The Seldinger technique was used to access the femoral

artery after rejection of local anesthesia. Then arteriography was performed routinely before the chemoembolization to gather information about abdominal aortic, celiac trunk and portal venous system was evaluated indirectly. Then a coaxial catheter (Renegade Hi Flo, Boston Scientific, USA; Stride ASAHI INTECC, Japan) was inserted into the hepatic artery and subsegmental arteries. Another arteriography was performed to find the feeding arteries to the tumor. According to tumor stain, Spongostan particles (Jinling, Nanjing, China), and iodized oil (Lipiodol; Laboratoire Andre Guerbet, Aulnay-sous-Bois, France), which was mixed with 20–40 mg epirubicin hydrochloride (Main Luck Pharmaceutical, Shenzhen, China) were injected. Tumor stain under arteriography was artificially classified as “poor” when tumor feeding vessels could not be found, there is no stain or only light stain in the tumor area, and the boundary of normal liver tissue is not clear; “moderate” when tumor vessels were rare and slender, tumor stain was stronger than normal liver tissue, and the boundary of normal liver tissue could be found; and “well” when tumor vessels were clear and definite, contrast stain was significantly, and the boundary between tumor and normal liver tissue is clear. Lipiodol deposit after TACE was artificially classified as “poor” when the lesion outline was incomplete and the internal iodine oil deposits were not obvious; “moderate” when the lesion outline was relatively complete and the internal iodine oil deposits were weak; and “well” when the shape of the lesion was complete and the internal iodine oil deposits were compact. Two experienced professional doctors made the judgement together.

### HAIC

The temporary indwelling catheter would be kept into the hepatic artery after TACE until the end of HAIC. HAIC was carried out via the catheter with OXA (Jiangsu Hengrui Medicine Co, Ltd., China) 85 mg/m<sup>2</sup> in 4 h, 5-Fu (Jinyao Aminoacid Co, Ltd., Tianjing, China) 2,000 mg/m<sup>2</sup> in about 44 h and CF (Jiangsu Hengrui Medicine Co, Ltd., China) 200 mg/m<sup>2</sup> in 2–4 h versus peripheral vein. A small part of patients (n=22) received raltitrexed instead of 5-Fu, which was given 4 mg per patient in 1 h.

Treatment was repeated every 3–4 weeks by experienced physicians, until patient died, complete response (CR) was obtained, liver function turned out to Child-pugh C, disease progressed, or adverse effects became intolerable to the patients.

### Follow-up care

All the patients were regularly followed up. The laboratory examinations were obtained every week, and enhanced computed tomography (CT) or magnetic resonance imaging (MRI) was periodically performed to evaluate therapeutic efficiency every 6–8 weeks after first TACE/HAIC. Objective response rate (ORR) and disease control rate (DCR) were evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 (before 2009) and RECIST version 1.1, and adverse reaction was recorded. The decision of another TACE was depending on the results of the examinations and patients' general state.

### Survival analysis

To identify the prognostic factors for the long-term outcome, we analyzed factors related to the primary lesion and liver metastases and factors related to the treatment. The endpoint evaluated was patient survival from the date of first TACE. PFS is defined as the time from first TACE to the date of “progresses” judged by RECIST or the date on which the patient died. Data of patients lost to follow-up were censored at the date of the last observation. The survival durations after first TACE and HAIC were calculated using the Kaplan-Meier method and were analyzed by the Log-rank test to compare the cumulative survival durations. The Cox proportional hazards model was used to determine the univariate and multivariate hazards ratios for the study parameters. Pearson product-moment correlation analysis was used to measure the relationship between the two variables. For all tests, P<0.05 was defined as statistically significant. The IBM SPSS Statistics (Version 19.0; IBM Corp., New York, USA) was used for the analyses. The GraphPad Prism 6 (GraphPad Software, Inc., La Jolla, CA, USA) was used for chart making.

## Results

### Characteristics of patients

All the patients were heavily pre-treated by systemic chemotherapy. The characteristics of patients (*Table 1*) showed that the primary tumor was located in the right hemicolon in 33 (20.4%) patients and in the left hemicolon in 129 (79.6%) patients. Most of the patients (81.5%, n=132) had primary tumor resected. As the time of liver metastases, 125 (77.2%) patients had synchronous liver

**Table 1** Clinical characteristics of 162 patients

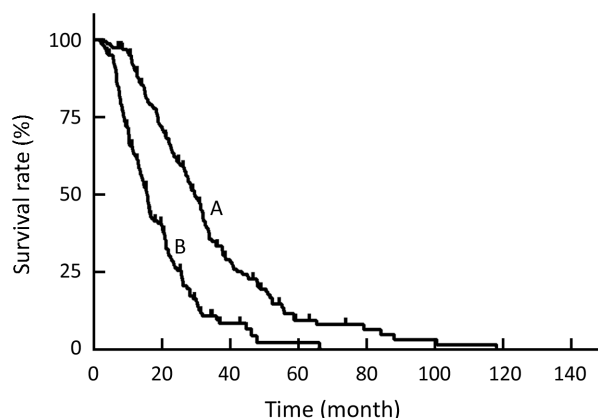
Characteristics	Case No. (%)
Gender	
Male	110 (67.9)
Female	52 (32.1)
Age at first TACE (year)	
Median	60
Range	26–83
Primary location	
Right side	33 (20.4)
Left side	129 (79.6)
Primary tumor grade	
Poor	22 (13.6)
Well to moderate	124 (76.5)
Unknown	16 (9.9)
Time of liver metastases	
Synchronous	125 (77.2)
Metachronous	37 (22.8)
Genetic condition	
KRAS mutation	24 (14.8)
KRAS wild type	51 (31.5)
Unknown	87 (53.7)
Extrahepatic metastasis	
Present	91 (56.2)
Absent	71 (43.8)
Combination with other local treatment	
Yes	34 (21.0)
No	128 (79.0)
Resection of primary cancer	
No	30 (18.5)
Palliative	74 (45.7)
Radical	58 (35.8)
Infusion agents	
OXA+5-Fu+CF	140 (86.4)
OXA+raltitrexed	22 (13.6)

TACE, transarterial chemoembolization; OXA, oxaliplatin; 5-Fu, 5-fluorouracil; CF, calcium folinate.

metastasis and 37 (22.8%) were metachronous. In all patients, only 9 patients had single liver metastasis. A small part of (n=28) patients received epirubicin only combined sustained HAIC during the procedure in accordance with the poor blood supply. OXA, CF and 5-Fu infusion were administered in 140 patients, and OXA and raltitrexed infusion was carried out in 22 patients.

**Survival data and response rate**

During the follow-up time, 134 out of 162 patients died, 11 patients lost follow-up and 17 patients remained alive. The median survival time (MST) was 29.5 months from diagnosis of colorectal cancer and was 15.6 months from the start of TACE/HAIC treatment (Figure 2). The median PFS was 5.5 months after first TACE and HAIC. The actuarial survival rate after TACE and HAIC was 63% [95% confidence interval (95% CI), 56%–70%], 26% (95% CI, 19%–33%), and 10% (95% CI, 5%–15%) after 1, 2 and 3 years.



**Figure 2** Survival data of patients received transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) (n=162). The median survival time (MST) after diagnosis of colorectal cancer was 29.5 months (curve A). The MST after first TACE was 15.6 months (curve B).

There were 2–20 (mean 4.7) repeated TACE performed per patient. There was only one patient identified as CR. Forty-seven (29.0%) patients achieved partial response (PR), 74 (45.7%) achieved stable disease (SD) and 40 (24.7%) achieved progressive disease (PD). The DCR was 75%. Patients achieving CR benefited the most while those with PD benefited little in survival. During the treatment, 35 patients progressed due to extrahepatic disease, but analysis showed no significance (P=0.474) between these two groups in OS after first TACE and HAIC. Most patients (86.4%, n=140) were infused OXA, CF and 5-Fu after embolization and other patients (13.6%, n=22) received raltitrexed plus OXA. There was no significant (P=0.994) difference in survival between these two different chemotherapy regimens. Analysis showed that poorer blood supply and lower lipiodol deposit may result in better prognostic, but there was no significant difference (P=0.079).

for tumor stain,  $P=0.162$  for lipiodol deposit).

The hospital mortality rate and 30 d treatment-related mortality were 0% for all 162 patients analyzed. The most common complications were anorexia, nausea, transient fever, abdominal pain, neuropathy, and increased alanine aminotransferase levels, which were controlled with symptomatic treatments. Grade 3–4 bone marrow toxicity occurred in 13 patients and there were two patients died of grade 4 bone marrow suppression. One patient developed liver abscess after treatment and recovered by effective drainage.

### Prognostic factors

Prognostic factors including age, gender, primary tumor characteristic, liver metastasis characteristic, extrahepatic metastasis, different treatment and serum tumor marker were examined. Among the factors related to survival time after TACE/HAIC, combination with other local treatment ( $P=0.034$ ), response to TACE ( $P<0.001$ ), and normal serum CA19-9 ( $P<0.001$ ) were significant predictors (Table 2). Factors including gender, age, primary tumor site, size of liver metastasis, number of liver metastasis, infusion agents, tumor stain and lipiodol deposit had no significant differences.

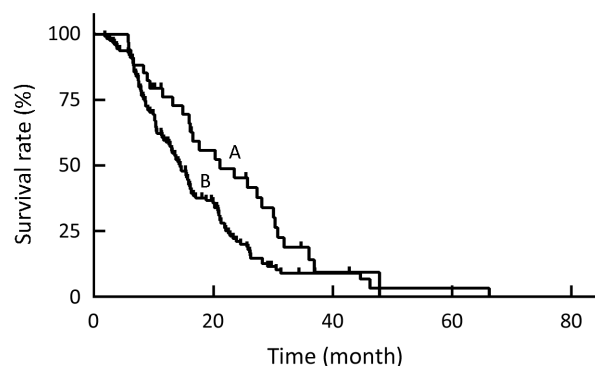
The multivariate analysis was conducted to identify the predictive indicators for a good prognosis using the parameters which were identified to have P value less than 0.15 by the univariate analysis. Among these parameters, normal serum CA19-9 ( $P<0.001$ ), response to TACE ( $P<0.001$ ) and combination with other local treatment ( $P=0.001$ ) were independent factors for OS after TACE/HAIC (Table 3, Figure 3–5). Pearson product-moment correlation analysis showed that serum CEA ( $P=0.029$ ) and CA-724 ( $P=0.024$ ) had significant correlation with survival time after first TACE/HAIC.

### Discussion

Local treatments are increasingly accepted as alternative selections for CRCLM patients. Meta-analyses (19–21) about hepatic arterial infusion (HAI) for chemotherapy refractory patients show higher local response rate but give controversial views of its advantage in OS. Since TACE could reduce the blood supply and sustained HAIC could reach high level of chemotherapeutic agent in tumor area, the combination of these two treatments is worth further exploration. Our study found some prognostic factors, and

discussed response rate and survival benefit of this treatment.

Patients received TACE/HAIC in our study achieved 75% DCR, the median PFS reached 5.5 months and OS reached 15.6 months in chemotherapy refractory patients, which were longer than results in other similar researches (9,22–25). As reported in patients treated by TACE only (14), local response turned out to be a significant prognostic factor of this combined therapy. Previous studies (26–28) revealed that elevated CEA and CA19-9 could be poor prognostic factors for CRCLM patients who underwent liver resection. But the meanings of tumor markers in TACE and HAIC were not clear. The tumor marker CA19-9 was found to be an effective prognostic factor in our study. Patients with elevated serum CA19-9 seemed to have a poorer prognosis, which was supported by several other studies (29,30). While elevated serum CEA did not achieve great significance when classified as normal group or elevated group. But Pearson product-moment correlation analysis showed significant correlation between this tumor marker and survival. That may be attributed to the large number (140/162) of elevated serum CEA patients. There is interaction between serum CA72-4 and CA19-9, so multivariate analysis found no significant difference of CA72-4. The patients received other local treatment such RFA and liver radiotherapy significantly reduce the risk in survival rate either from diagnosis of the disease or from first TACE and HAIC, demonstrating that non-vascular minimally invasive treatment could be a necessary complement to the comprehensive treatment of



**Figure 3** The Kaplan-Meier curves show the survival data after transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) combined with or without other local treatment. The median survival time (MST) after TACE, HAIC and other local treatment was 21.1 months (curve A) and that of TACE and HAIC only was 14.4 months (curve B).

Table 2 Univariate analysis of survival after first TACE and HAIC

Variables	MST (month)	Univariate analysis		P
		HR	95% CI	
Age (year) (>60 vs. ≤60)	15.8 vs. 15.4	0.937	0.664–1.323	0.712
Gender (male vs. female)	16.3 vs. 13.0	0.788	0.549–1.131	0.196
Histology (poorly vs. well and moderate)	16.7 vs. 22.0	1.656	0.973–2.821	0.063
Primary tumor site (left side vs. right side)	16.9 vs. 11.4	0.767	0.499–1.181	0.229
Serum CA19-9 (U/mL) (≥37 vs. <37)	12.5 vs. 21.1	2.120	1.445–3.110	<0.001
Serum CA72-4 (U/mL) (≥6.7 vs. <6.7)	13.5 vs. 20.3	1.525	1.052–2.209	0.026
Serum CEA (U/mL) (≥5 vs. <5)	14.4 vs. 21.1	1.460	0.885–2.408	0.139
Extrahepatic metastasis (present vs. absent)	19.2 vs. 23.3	1.172	0.825–1.667	0.376
Time to liver metastasis (synchronous vs. metachronous)	14.8 vs. 16.5	1.293	0.850–1.966	0.230
Largest size of metastases (cm) (≥5 vs. <5)	13.1 vs. 16.6	1.281	0.857–1.913	0.228
No. of metastases (single vs. multiple)	27.4 vs. 20.8	0.662	0.308–1.420	0.289
Treatment times of TACE and HAIC				0.183
≤2	11.6	1.447	0.974–2.149	0.068
2–4	12.7	1.233	0.793–2.149	1.233
≥5	19.9	1	1	NA
Other local treatment (combined vs. uncombined)	21.1 vs. 14.4	0.630	0.411–0.966	0.034
Response to TACE				<0.001
PR (29.0%)	21.1	0.242	0.150–0.390	<0.001
SD (45.7%)	16.6	0.305	0.197–0.472	<0.001
PD (24.7%)	7.8	1	1	NA
Embolization (yes vs. no)	21.7 vs. 24.3	1.032	0.664–1.605	0.887
Tumor stain				0.157
Poor	16.5	0.941	0.712–1.245	0.672
Moderate	14.2	1.292	0.971–1.720	0.079
Well	13.0	1	1	NA
Infusion agents (OXA+5-Fu+CF vs. OXA+raltitrexed)	15.5 vs. 16.5	1.002	0.592–1.696	0.994
Lipiodol deposit				0.162
Poor	21.1	0.831	0.387–1.785	0.635
Moderate	14.2	1.280	0.640–2.561	0.485
Well	17.6	1	1	NA

TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; PR, partial response; SD, stable disease; PD, progressive disease; OXA, oxaliplatin; 5-Fu, 5-fluorouracil; CF, calcium folinate; MST, median survival time; HR, hazard ratio; 95% CI, 95% confidence interval; NA, not available.

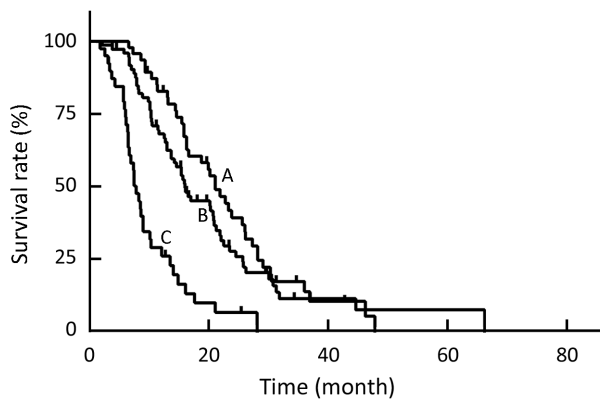
colorectal liver metastases. Wieners *et al.* (31) had also reported that combination of two regional treatment approaches may prolong OS. That means CRCLM patients could get more chance to be treated. RAS mutation was proved to be a prognostic biomarker for CRCLM patients (32). The test rate of gene expression analysis (75/162) is relatively low in our study and we did not get significant difference in these groups. There were no significant difference observed in size and number of

liver metastasis, which was also controversial in previous reports (28,33). This could mainly attribute to that all the patients were heavily treated before, and there was only 9 patients had single liver metastases. Patients received embolization had a tendency of longer survival than that of counterpart, but there was no significant difference either. Survival benefit tendency was also discovered in the patients who had poorer tumor straining under arteriography or lower Lipiodol deposit after TACE. This

**Table 3** Multiple Cox regression analysis of survival after first TACE and HAIC

Variables	Multivariate analysis		P
	HR	95% CI	
Serum CA19-9 (U/mL) ( $\geq 37$ vs. $< 37$ )	2.093	1.392–3.147	<0.001
Serum CEA (U/mL) ( $\geq 5$ vs. $< 5$ )	0.935	0.530–1.650	0.818
Serum CA72-4 (U/mL) ( $\geq 6.7$ vs. $< 6.7$ )	1.062	0.667–1.691	0.799
Histology (poorly vs. well and moderate)	0.704	0.408–1.216	0.208
Response to TACE			<0.001
PR	0.207	0.122–0.353	<0.001
SD	0.256	0.154–0.427	<0.001
PD	1	1	NA
Other local treatment (combined vs. uncombined)	0.439	0.268–0.721	0.001

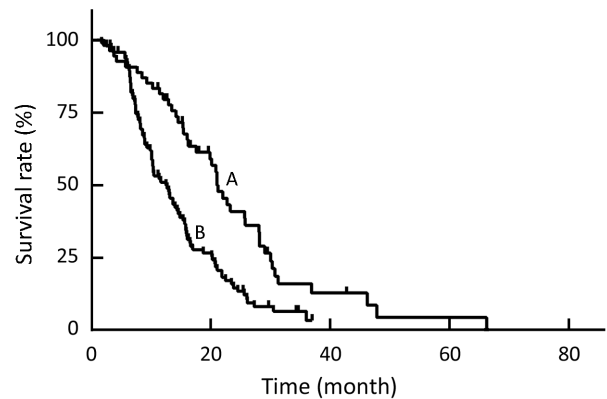
TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; PR, partial response; SD, stable disease; PD, progressive disease; HR, hazard ratio; 95% CI, 95% confidence interval; NA, not available.



**Figure 4** The Kaplan-Meier curves show the survival data after transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) according to the results of tumor response. The median survival time (MST) of patients achieved partial response (PR) was 21.1 months (curve A), for patients achieved stable disease (SD) was 16.6 months (curve B), and for patients achieved progressive disease (PD) was 7.8 months (curve C).

reveals that sufficient blood supply of CRCLM may result in poor prognosis and this trend remains even under efficient treatment.

As our study is a single-center retrospective research, we could not avoid some biases for the evaluation of clinical outcome and the incomplete patient data. The number of patient was unbalanced in different groups, which result in no significant difference of serum elevated CEA and size and number of liver metastases. A larger study may have demonstrated a statistical difference. Another limitation of our study is the subjectivity in image interpretation of



**Figure 5** The Kaplan-Meier curves show the survival data after transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) according to serum carbohydrate antigen 19-9 (CA19-9). Patients with normal serum CA19-9 had a median survival time (MST) of 21.1 months (curve A), and patients with elevated CA19-9 was 12.5 months (curve B).

tumor stain and lipidol deposit, but all the doctors joined in this study were experienced and professional doctors and worked in the same department and obeyed the same criteria. But our results provide some new directions for clinical practice and ideas. The relationship of serum tumor markers and survival was analyzed and we found that CA19-9 was a significant prognostic factor. Response to TACE/HAIC was proved to be an excellent predictive factor for OS. We also tried to explore the relation between tumor blood supply and survival, and pointed out that poorer blood supply may lead to better prognosis. But further randomized control clinical trials are needed to confirm it.

## Conclusions

TACE combined with OXA based HAIC could be a safe, feasible and effective choice for liver-dominant refractory disease for whom there are limited treatment options. Normal serum CA19-9 and different response to TACE are independent risk factors for prognosis.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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