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ORIGINAL ARTICLE

Comparison of treatment response, survival and safety between drug-eluting bead transarterial chemoembolization with CalliSpheres® microspheres versus conventional transarterial chemoembolization in treating hepatocellular carcinoma

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Summary

Purpose: *To compare the efficacy and safety between drug-eluting bead (DEB) transarterial chemoembolization (TACE) with CalliSpheres® microspheres (CSM) and conventional TACE (cTACE) in hepatocellular carcinoma (HCC) patients, and to explore the predictive factors for treatment response and survival.*

Methods: *89 HCC patients receiving DEB-TACE with CSM or cTACE were consecutively recruited in this cohort study. Treatment response was assessed at month 1 (M1)/M3/M6. Progression free survival (PFS) and overall survival (OS) were calculated. Liver function indexes were measured at M1 and adverse events occurred during operation and hospitalization were recorded.*

Results: *Higher complete response (CR) rate and objective response rate (ORR) at M1/M3 in DEB-TACE group were found compared to cTACE group, and no difference of PFS and OS was noted between the two groups. Multivariate analysis of ORR, DFS and OS disclosed that multifocal disease, ALT≥1upper limit of normal (ULN) and ALP≥1ULN independently predicted lower ORR, while bilobar tumor location and abnormal CA19.9 level were independent predictive factors for unfavorable PFS. As for liver function, there was no difference of all liver function indexes changes (M1-M0) between the two groups. Moreover, DEB-TACE group displayed more frequent pain during treatment, and more frequent pain and fever during hospitalization compared to cTACE group.*

Conclusions: *The short-term CR and ORR of DEB-TACE treatment with CSM are better, while OS, DFS and safety were equivalent compared to cTACE in treating HCC patients.*

Key words: *CalliSpheres® microspheres, drug-eluting bead, efficacy, hepatocellular carcinoma, safety, transarterial chemoembolization*

Introduction

As the most frequent primary liver cancer, hepatocellular carcinoma (HCC) ranks as sixth most common cancer and the third leading cause of cancer-related death worldwide [1]. For the treatment of early-stage HCC, 3 types of treatments, including resection, liver transplantation and percutaneous ablation are potentially curative therapies [2-4]. Although cancer surveillance program increases the detection rate of early-stage HCC, the majority of HCC patients (exceeding 80%) are still diagnosed in intermediate or advanced stage, which excludes them from receiving curative treatments [2-5]. According to Barcelona Clinic Liver Cancer (BCLC) staging system guideline, transarterial chemoem-

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bolization (TACE) is the first-line treatment for HCC patients in intermediate stage, and TACE has recently been applied as bridge therapy to liver resection or transplantation in early-stage HCC as well [6-13].

TACE is a locoregional treatment that is utilized most commonly in unresectable HCC patients. The principle for conventional TACE (cTACE) is that carriers, such as lipiodol and ethiodized poppyseed oil (EPO), transport chemotherapeutic agents to targeted tumor and then the tumor supplying vessels are blocked by injecting vascular embolic agents, which would result in cytotoxic effect and ischemia [14,15]. To date, a large number of studies illuminate that cTACE treatment has relatively high systemic release of chemotherapeutic agents, contributing to systemic side effects in HCC patients [16-18]. To avoid the shortcomings of cTACE, drug-eluting bead transarterial chemoembolization (DEB-TACE) has been developed, which uses microspheres loaded with chemotherapeutic agents instead as drug carriers, meanwhile, microspheres also serve as embolic agents. As a result, DEB-TACE is considered to minimize systemic exposure of chemotherapeutic agents and maximize the chemotherapeutic agent concentration in the tumor region in comparison to cTACE [17,19-23]. So far, several drug-eluting bead (DEB) products are available for clinical use, including CalliSpheres® microspheres (CSM), DC Beads®, HepaSphere Microspheres® and superadsorbent microspheres (SAP) [24]. As the first DEB product in China, CSM possesses many good features like other DEBs, such as qualified biocompatibility, adequate physicochemical stability and advantages in drug loading and release [25,26]. However, there are limited studies evaluating the clinical efficacy and safety of DEB-TACE with CSM in treating HCC patients. Therefore, the aim of this study was to compare the efficacy and safety between DEB-TACE with CSM and cTACE in HCC patients, and to explore their predictive factors for treatment response and survival profiles.

Methods

Patients

From 2016/2/1 to 2017/8/28, 89 HCC patients about to receive DEB-TACE or cTACE therapy in the Affiliated Tumor Hospital of Guangxi Medical University were consecutively recruited in this retrospective cohort study. The inclusion criteria were as follows: (1) primary HCC confirmed by clinical and pathological examinations according to the European Association for the Study of the Liver (EASL) criteria; (2) age above 18 years; (3) about to receive DEB-TACE or cTACE treatment; (4) life expectancy was more than 12 months; (5) able to be followed up regularly. Patients were excluded if they had the following conditions: (1) contraindications to TACE or anthracyclines; (2) undergoing thrombolysis or anticoagulant therapy; (3) history of hematological malignancies; (4) renal failure, congestive heart failure, recent myocardial infarction or uncontrolled arrhythmias; (5) active infection (hepatitis infection could be accepted); (6) during gestation or lactation period or planned to be pregnant. All patients receiving DEB-TACE or cTACE treatment were assigned to DEB-TACE group (n=42) or cTACE group (n=47). This study protocol was approved by Ethics Committee of the Affiliated Tumor Hospital of Guangxi Medical University, and the study was performed according to the Declaration of Helsinki. All patients provided written informed consents before enrollment.

Characteristics of patients at baseline (M0)

Comprehensive baseline characteristics of patients were collected after clinicopathological examinations and biochemical tests, which included demographic features, medical history and clinical characteristics, biochemical indexes and previous treatments, and the details were as follows: (1) demographic features: age, gender; (2) medical history and clinical characteristics: history of hepatitis B (HB), history of hepatitis C (HC), history of drink, history of cirrhosis, tumor location, tumor distribution, largest nodule size, portal vein invasion, hepatic vein invasion, Eastern Cooperative Oncology Group (ECOG) performance status, Child-Pugh stage and Barcelona Clinic Liver Cancer (BCLC) stage; (3) blood routine indexes: white blood cell (WBC), red blood cell (RBC), absolute neutrophil count (ANC), haemoglobin (Hb) and platelet (PLT); (4) liver function indexes: albumin (ALB), total protein (TP), total bilirubin (TBIL), total bile acid (TBA), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP); (5) renal function indexes: blood creatinine (BCr) and blood urea nitrogen (BUN); (6) tumor markers: alpha fetoprotein (AFP), carcinoembryonic antigen (CEA) and carbohydrate antigen19.9 (CA19.9); (7) previous treatments: cTACE, surgery, systemic chemotherapy, radiofrequency ablation and targeted therapy.

Procedures

1. Pretreatments: before DEB-TACE or cTACE treatment, antiemetic treatment using tropisetron (Chia Tai Tianqing Pharmaceutical Group Co., Ltd., Shandong Province, China), analgesic treatment using dezocine (Yangtze River Pharmaceutical Group, Jiangsu Province, China) and anti-infection treatments were given to patients.
2. Drug loading process of DEB-TACE: the CSM (Jiangsu Hengrui Medicine Co., Ltd., Jiangsu Province, China) with diameters of 100-300 μm was used as carrier for chemotherapeutics and embolization agents in the DEB-TACE procedures. The CSM was loaded with pirarubicin (60-80 mg) (Shenzhen Main Luck Pharmaceuticals Inc., Guangdong Province, China) using the following methods: the CSM and normal saline were extracted by a 20 mL syringe and were erectly placed at room temperature (RT) for 1-2 min until the CSM was totally precipitated, then the chemoembolization

reagent which was dissolved into a 20 mg/mL solution was mixed with the CSM, and the mixture was shaken gently every 5 min within 15 min until the CSM was totally loaded with the chemoembolization reagent. Subsequently, the high concentration contrast agent was added into the mixture as 1:1, 1:1.1 or 1:1.2 ratio, and then the mixture was kept still for 5 min for further use.

3. DEB-TACE operation: all DEB-TACE procedures were performed in the digital subtraction angiography (DSA) room and before DEB-TACE, the targeted tumor was assessed by triphasic computerized tomography (CT) or magnetic resonance imaging (MRI) according to the Milan criteria [27,28]. DEB-TACE procedures were performed as follows: the hepatic angiography was performed to detect the tumor supplying vessels using segment or subsegment super selective catheterization; right after the tumor supplying vessels were selected, the femoral artery was punctured using the Seldinger technique, and the microcatheter with a diameter of 2.7F (Merit Maestro, Merit Medical System, Inc., Utah, USA) was used for catheterization. Afterwards, the CSMs were injected through the microcatheter by pulse injection, and the embolization ended as soon as the flow of contrast agent stagnated. After the embolization, the microcatheter was pulled out, and the wound was pressed for hemostasis and bandaged. In addition, for the patients with massive HCC, DEB-TACE was performed multiple times.
4. cTACE operation: cTACE procedures were also performed in the DSA room. Firstly, the hepatic angiography was performed to detect the tumor supplying vessel using the same methods as the ones used in DEB-TACE procedures. Secondly, once the tumor supplying vessel was identified, the percutaneous femoral artery was punctured using the Seldinger technique. Thirdly, a 2.7F microcatheter was subsequently used for catheterization, and the chemotherapy drug solution (pirarubicin 60-80 mg, 20 mg/mL), normal lipiodol or ethiodized poppyseed oil (EPO) (Jiangsu Hengrui Medicine Co., Ltd., Jiangsu Province, China) as drug carriers and blank CSMs (Jiangsu Hengrui Medicine Co., Ltd., Jiangsu Province, China) with diameters of 100-300μm, 300-500μm or 500-700μm as embolization agents were injected into the tumor supplying vessel. Finally, the embolization was stopped when the flow of infusion became stagnated. In addition, the angiography was performed for another time to ensure the normal lipiodol, EPO or blank CSMs were deposited and to detect if there was incomplete embolization.
5. Posttreatments: all patients were told to lie on one side and extend the punctured leg for 6-12 h after embolization. Patients with postoperative nausea and vomiting were treated by tropisetron (IV), and analgesic treatment was given to patients using pethidine, dexamethasone or lidocaine. In addition, the liver protection treatments using Magnesium isoglycyrrhizinate, glutathione and polyene phosphatidyl choline were also given to patients.

Assessments after treatment

Clinical examinations such as enhanced CT or MRI scanning were performed at month 1 (M1), M3 or M6 after treatment to assess the treatment response, and liver function indexes including ALT, AST, ALP, TBIL, ALB, TP and TBA were measured at M1 after treatment to evaluate the biochemical toxicity. In addition, adverse events which occurred during the operation and hospitalization were recorded. Pain grade was evaluated using Numeric rating scale (NRS), which was a 10-point numeric scale, with 0 representing "no pain", 1-3 "mild pain", 4-6 "moderate pain", 7-9 "severe pain" and 10 "unbearable pain".

Definitions

According to the modified Response Evaluation Criteria in Solid Tumors (mRECIST), the response criteria included complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD), and the detailed definitions were as follows: (1) CR: no existence of arterial enhancement of target tumors; (2) PR: at least a 30% decrease in the sum of the diameters of target tumors (contrast enhancing); (3) SD: any cases that did not qualify for either PR or PD; (4) PD: the increase in the sum of diameters of target tumors (with arterial enhancement) ≥20% or occurrence of new tumors. In addition, objective response rate (ORR) was defined as the percentage of patients who achieved CR or PR, and disease control rate (DCR) was defined as the percentage of patients who achieved CR, PR or SD.

Survival assessment

Progression free survival (PFS) and overall survival (OS) were calculated for survival assessment, which were defined as follows: (1) PFS: the duration from the time of treatment to the time of disease progression; (2) OS: the duration from the time of treatment to the time of patient's death from any cause.

Follow up

Patients were followed up by phone calls or hospitalization, the median follow-up duration was 9.9 months (range 1.8-24.5), and the last follow-up date was 2018/4/21. Finally, patients with at least one response assessment after DEB-TACE or cTACE treatment were included in the final analysis, while patients were excluded from final analysis if they (1) switched to cTACE treatment due to lack of efficacy within the duration of treatment response assessment of DEB-TACE therapy, (2) received DEB-TACE treatment because of lacking efficacy within the duration of treatment response assessment of cTACE therapy, (3) lost to follow-up without any response assessment, (4) withdrew the informed consents.

Statistics

SPSS 21.0 statistical software (SPSS Inc., Chicago, USA) and Graphpad Prism 6.01 software (GraphPad Software Inc., San Diego, USA) were used for statistical analyses and chart making. Categorical variables were expressed as count (percentage), and the comparison

Table 1. Patient baseline characteristics

Characteristics	*DEB-TACE group (n=42)*	*cTACE group (n=47)*	*p value*
Age (years), mean±SD	52.9 ± 11.8	51.9 ± 13.1	0.703
Gender (male/female)	37/5	44/3	0.363
History of drinking, n (%)	16 (38.1)	13 (27.7)	0.294
History of HBV, n (%)	36 (85.7)	38 (80.9)	0.541
History of HCV, n (%)	1 (2.4)	0 (0.0)	0.287
History of cirrhosis, n (%)	21 (50.0)	31 (60.0)	0.127
Tumor location, n (%)			0.183
Unilobar	29 (69.0)	26 (55.3)	
Bilobar	13 (31.0)	21 (44.7)	
Tumor distribution, n (%)			**0.034**
Unifocal	29 (69.0)	22 (46.8)	
Multifocal	13 (31.0)	25 (53.2)	
Largest nodule size (cm), median (range)	12.2 (7.9-15.3)	8.1 (4.1-12.2)	**0.005**
Portal vein invasion, n (%)	22 (52.4)	17 (36.2)	0.124
Hepatic vein invasion, n (%)	17 (40.5)	17 (36.2)	0.676
ECOG performance status, n (%)			0.168
0	9 (21.4)	4 (8.5)	
1	32 (76.2)	43 (91.5)	
2	1 (2.4)	0 (0.0)	
Child-Pugh stage, n (%)			**0.032**
A	25 (59.5)	38 (80.9)	
B	16 (38.1)	8 (17.0)	
C	1 (2.4)	1 (2.1)	
BCLC stage, n (%)			0.696
A	5 (19.1)	9 (11.9)	
B	9 (23.4)	11 (21.4)	
C	22 (36.2)	17 (52.4)	
D	6 (21.3)	10 (14.3)	
Blood routine tests, median (range)			
WBC ($\times 10^9$ cell/L)	6.0 (4.5-7.8)	6.2 (5.0-7.6)	0.694
RBC ($\times 10^{12}$ cell/L)	4.3 (3.6-4.9)	4.6 (4.2-5.0)	0.068
ANC (%)	62.1 (51.4-72.9)	60.7 (54.6-65.5)	0.444
Hb (g/L), median (range)	130.0 (110.0-140.0)	135.0 (120.0-145.3)	0.360
PLT ($\times 10^9$ cell/L), median (range)	198.0 (119.0-298.0)	183.0 (131.0-26.28)	0.319
Liver function			
ALB (g/L)	34.2 (31.2-38.0)	36.5 (32.5-39.5)	0.051
ALB ≥1ULN, n (%)	0 (0.0)	1 (2.1)	0.342
TP (g/L)	65.9 (63.2-71.5)	67.0 (61.7-71.7)	0.535
TP ≥1ULN, n (%)	3 (7.1)	3 (6.4)	0.887
TBIL (μmol/L)	21.4 (15.5-27.8)	14.8 (10.4-20.2)	**0.003**
TBIL ≥1ULN, n (%)	23 (54.8)	15 (31.9)	**0.002**
TBA (I/L)	14.8 (5.0-25.4)	8.2 (5.1-29.7)	0.602
TBA ≥1ULN, n (%)	25 (59.5)	23 (48.9)	0.317
ALT (μ/L)	43.5 (27.0-72.0)	38.0 (21.0-56.0)	0.218
ALT ≥1ULN, n (%)	22 (52.4)	20 (42.6)	0.354
AST (μ/L)	65.5 (41.0-92.3)	47.0 (37.0-91.0)	0.105
AST ≥1ULN, n (%)	33 (78.6)	30 (63.8)	0.127
ALP (μ/L)	145.5 (106.0-178.0)	125.0 (86.0-163.0)	0.072
ALP ≥1ULN, n (%)	25 (59.5)	21 (44.7)	0.162
Targeted therapy, n (%)	1 (2.4)	1 (2.1)	0.936

Continued on the next page

Characteristics	*DEB-TACE group (n=42)*	*cTACE group (n=47)*	*p value*
Kidney function			
BCr (μmol/L)	72.5 (62.0-85.3)	75.5 (64.8-84.5)	0.472
BUN (mmol/L)	4.3 (3.7-5.3)	4.7 (3.9-5.7)	0.347
Tumor markers			
AFP (μg/L)	420.3 (20.6-1000.0)	164.1 (10.4-1000.0)	0.130
CEA (μg/L)	1.3 (0.6-1.9)	1.9 (1.0-2.7)	**0.022**
CA19.9 (ku/L)	25.1 (14.3-32.4)	21.0 (13.2-33.6)	0.738
Previous treatments			
cTACE, n (%)	11 (26.2)	9 (19.1)	0.427
Surgery, n (%)	4 (9.5)	13 (27.7)	**0.030**
Systemic chemotherapy, n (%)	1 (2.4)	0 (0.0)	0.287
Radiofrequency ablation, n (%)	4 (9.5)	3 (6.4)	0.583
Targeted therapy, n (%)	1 (2.4)	1 (2.1)	0.936

Data are presented as mean ± standard deviation, median (25^{th}-75^{th} quantiles) or percents (%). Comparison between 2 groups was determined by t-test, Wilcoxon rank sum test or Chi-square test. P value <0.05 was considered significant, and the significant results are shown in boldface. HCC: hepatocellular carcinoma, DEB-TACE: drug-eluting bead transarterial chemoembolization, cTACE: conventional transarterial chemoembolization, HBV: hepatitis B virus, HCV: hepatitis C virus, ECOG: Eastern Cooperative Oncology Group, BCLC: Barcelona Clinic Liver Cancer, WBC: white blood cells, RBC: red blood cells, ANC: absolute neutrophil count, Hb: hemoglobin, PLT: platelets, ULN: upper limit of normal, ALB: albumin, TP: total protein, TBIL: total bilirubin, TBA: total bile acid, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, BCr: blood creatinine, BUN: blood urea nitrogen, AFP: alpha fetoprotein, CEA: carcinoembryonic antigen, CA19.9: carbohydrate antigen19.9.

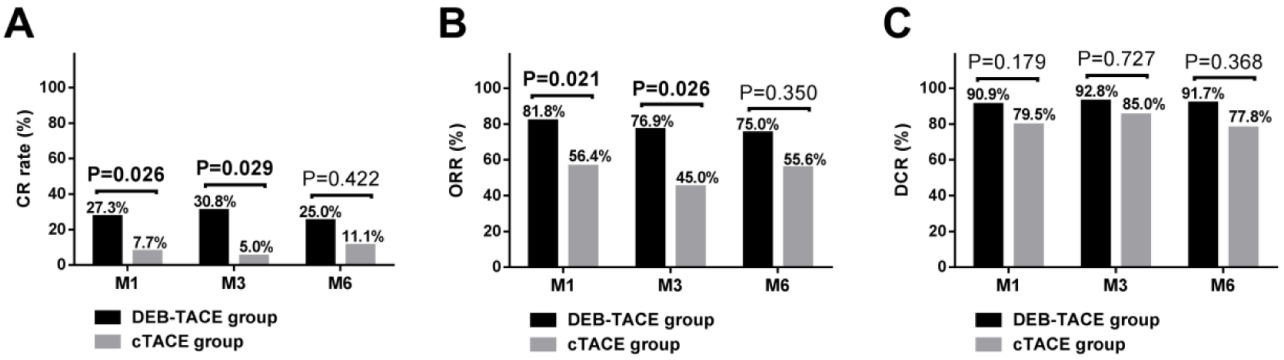

Figure 1. Difference of CR rate, ORR and DCR between DEB-TACE group and cTACE group at M1, M3 and M6. Higher CR rate **(A)** and ORR **(B)** at M1/M3 were present in DEB-TACE group compared to cTACE group and no difference was discovered at M6, while there was no difference of DCR **(C)** at M1/M3/M6 between the two groups. Chi-square test was used to compare the difference of CR rate, ORR and DCR between the two groups. P value <0.05 was considered significant. CR: complete response; ORR: objective response rate; DCR: disease control rate; DEB-TACE: drug-eluting bead transarterial chemoembolization; cTACE: transarterial chemoembolization; M: month.

between two groups was determined by Chi-square test; normally distributed continuous variables were presented as mean value ± standard deviation, and the comparison between two groups was determined by t-test; skewed distributed continuous variables were described as median (25^{th}-75^{th} quantiles), and the comparison between two groups was determined by Wilcoxon rank sum test. Factors affecting ORR were determined by univariate and multivariate logistic regression analysis, and the multivariate logistic regression analysis was performed using the Forward Stepwise (Conditional) method. PFS and OS were analyzed using the Kaplan–Meier method and Log-rank test. Univariate Cox's proportional hazards regression analyses were performed to determine the prognostic factors of PFS and OS, and multivariate Cox's proportional hazards regression analyses were further performed to determine the independent prognostic factors of PFS and OS with the use of Forward Stepwise (Conditional LR) method. P value <0.05 was considered statistically significant.

Results

Baseline characteristics

The mean age was 52.9 ± 11.8 years in the DEB-TACE group (n=42) and 51.9 ± 13.1 years in the cTACE group (n=47) (p=0.703), and there were 37 males and 5 females in the DEB-TACE group, and 44 males as well as 3 females in the cTACE group (p=0.363). As for tumor features, DEB-TACE group exhibited more patients with unifocal tumor distribution (p=0.034), larger mean largest nodule size (p=0.005), more patients in B/C stage (p=0.032) compared to cTACE group, while no difference of

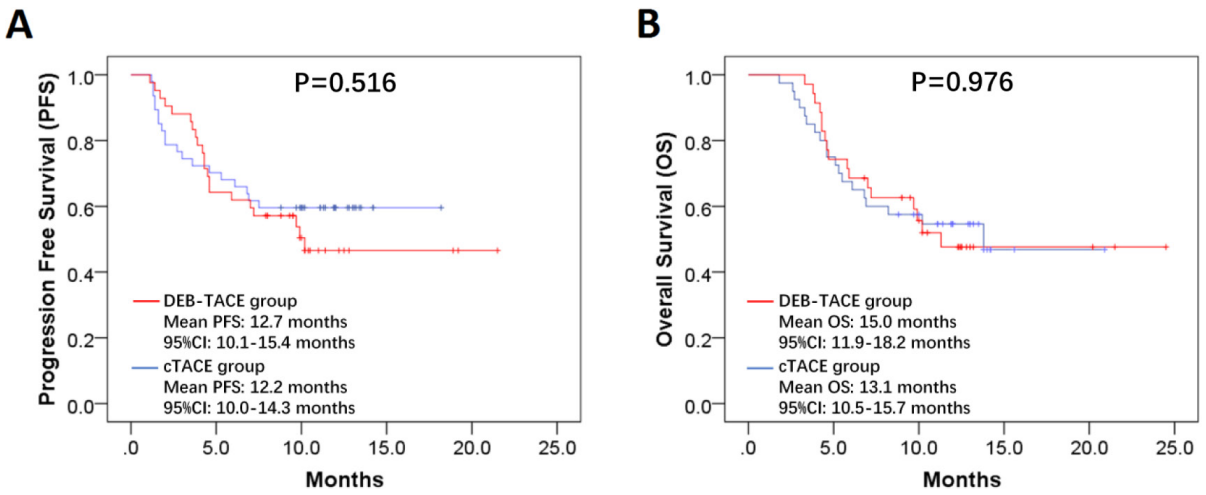

Figure 2. Disease-free survival (DFS)/overall survival (OS) in DEB-TACE group and cTACE group. No difference of DFS **(A)** and OS **(B)** was noted between DEB-TACE group and cTACE group. Kaplan-Meier curves and log-rank test were used to compare DFS and OS between DEB-TACE group and cTACE group. P value <0.05 was considered significant. DEB-TACE: drug-eluting bead transarterial chemoembolization; cTACE: transarterial chemoembolization.

ECOG PS (p=0.168) and BCLC stage (p=0.696) was noted between the two groups. As for liver function, higher TBIL level (p=0.003) and more patient with TBIL ≥1ULN (p=0.002) were present in DEB-TACE group compared to cTACE group. Concerning tumor markers, the CEA level was decreased in DEB-TACE group compared to cTACE group (p=0.022). Additionally, less patients were operated in the DEB-TACE group compared to cTACE group (p=0.030). Other detailed baseline characteristics were shown in Table 1.

Comparison of treatment response rate between DEB-TACE group and cTACE group

Compared to cTACE group, CR (M1, p=0.026; M3, p=0.029) and ORR (M1, p=0.021; M3, p=0.026) were increased in the DEB-TACE group at M1/M3, whereas no difference in CR (p=0.422) or ORR at M6 (p=0.350) was seen between the two groups (Figure 1A-1B). In addition, there was no difference of DCR at M1 (p=0.179), M3 (p=0.727) or M6 (p=0.368) between the two groups (Figure 1C).

Factors affecting ORR at M1, M3 and M6

Univariate logistic regression analysis revealed that at M1, DEB-TACE was associated with higher ORR with OR 3.477, 95% CI 1.172-10.319 (p=0.025), while bilobar tumor location (p=0.017, OR 0.284, 95% CI 0.101-0.798) and multifocal disease (p=0.026, OR 0.312, 95% CI 0.111-0.872) were correlated with lower ORR (Table 2). Further multivariate logistic regression analysis indicated that only multifocal disease (p=0.025, OR 0.224, 95% CI 0.060-0.830) and ALT ≥1ULN (p=0.009, OR 0.158, 95% CI 0.040-0.628) were independent predictive factors for decreased ORR. In addition, univariate logistic regression analysis revealed that at M3, DEB-TACE was also correlated with elevated ORR with OR 4.074, 95% CI 1.146-14.481 (p=0.030), whereas ALP ≥1ULN (p=0.042, OR 0.250, 95% CI 0.066-0.953) was associated with decreased ORR. Further multivariate logistic regression analysis indicated that ALP ≥1ULN could predict reduced ORR independently (p=0.035, OR 0.200, 95% CI 0.045-0.892) (Table 3). However, there was no significant finding in factors affecting ORR at M6 by univariate and multivariate logistic regression analysis (Table 4).

Comparison of PFS/OS between DEB-TACE group and cTACE group

The mean PFS was 12.7 months (95% CI, 10.1-15.4) in DEB-TACE group and 12.2 months (95% CI, 10.0-14.3) in cTACE group, and no difference of PFS was discovered between the two groups (p=0.516) (Figure 2A). As for OS, the mean OS was 15.0 months (95% CI, 11.9-18.2) in the DEB-TACE group and 13.1 months (95% CI, 10.5-15.7) in the cTACE group (p=0.976) (Figure 2B).

Factors affecting survival

Univariate Cox's proportional hazards regression model analysis displayed that bilobar tumor location (p=0.006, HR 2.412, 95% CI 1.294-4.495), portal vein invasion (p=0.034, HR 1.973, 95% CI 1.053-3.696) and abnormal CA19.9 (p=0.020, HR 4.080, 95% CI 1.252-13.293) were associated with worse PFS, while DEB-TACE or cTACE did not affect DFS (p=0.518, HR 1.227, 95% CI 0.659-2.286) (Table 5). Multivariate Cox's proportional hazards regression

Table 2. Factors affecting ORR (M1) by univariate and multivariate logistic regression model analysis

Parameters	*Logistic regression*			
	P value	*OR*	*95% CI*	
			Lower	*Higher*
Univariate logistic regression				
DEB-TACE vs cTACE	**0.025**	3.477	1.172	10.319
Age≥60 years	0.229	1.954	0.656	5.819
Male	0.416	0.400	0.044	3.636
History of drinking	0.282	0.562	0.196	1.606
History of HBV	0.432	1.667	0.466	5.956
History of HCV	1.000	-	0.000	-
History of cirrhosis	0.516	0.711	0.254	1.988
Tumor location-Bilobar	**0.017**	0.284	0.101	0.798
Multifocal disease	**0.026**	0.312	0.111	0.872
Largest nodule size ≥7 cm	0.872	0.919	0.326	2.589
Portal vein invasion	0.784	1.150	0.424	3.117
Hepatic vein invasion	0.591	0.754	0.270	2.109
ECOG performance status (≥1 vs 0)	0.395	1.853	0.448	7.669
Child-Pugh stage (B/C vs A)	0.662	1.300	0.401	4.215
BCLC stage (C/D vs A/B)	0.744	0.842	0.300	2.365
Previous cTACE treatment	0.312	1.900	0.548	6.590
Previous surgery	0.085	0.366	0.116	1.149
Previous systemic chemotherapy	1.000	-	0.000	-
Previous radiofrequency ablation	0.939	0.933	0.158	5.505
Previous targeted therapy	0.999	0.000	0.000	-
WBC abnormal	0.608	1.360	0.420	4.400
RBC abnormal	0.538	1.417	0.468	4.288
ANC abnormal	0.289	2.111	0.530	8.407
Hb abnormal	0.916	0.946	0.339	2.646
PLT abnormal	0.351	1.689	0.562	5.075
ALB ≥1ULN	1.000	0.000	0.000	-
TP ≥1ULN	0.999	-	0.000	-
TBIL ≥1ULN	0.071	2.720	0.918	8.060
TBA ≥1ULN	0.910	0.944	0.348	2.562
ALT ≥1ULN	0.111	0.435	0.156	1.213
AST ≥1ULN	0.104	0.363	0.107	1.234
ALP ≥1ULN	0.927	1.047	0.389	2.823
BCr abnormal	0.313	3.070	0.348	27.114
BUN abnormal	0.721	0.758	0.165	3.484
AFP abnormal	0.703	0.779	0.216	2.815
CEA abnormal	1.000	0.000	0.000	-
CA19.9 abnormal	0.876	1.100	0.332	3.649
Multivariate logistic regression				
Multifocal disease	**0.025**	0.224	0.060	0.830
ALT ≥1ULN	**0.009**	0.158	0.040	0.628

For abbreviations see footnote of Table 1. Significant results are shown in boldface.

Table 3. Factors affecting ORR (M3) by univariate and multivariate logistic regression model analysis

Parameters	*Logistic regression*			
	P value	*OR*	*95% CI*	
			Lower	*Higher*
Univariate logistic regression				
DEB-TACE vs cTACE	**0.030**	4.074	1.146	14.481
Age≥60 years	0.304	1.950	0.545	6.974
Male	0.844	0.833	0.136	5.113
History of drinking	0.723	1.263	0.346	4.608
History of HBV	0.999	0.000	0.000	-
History of HCV	1.000	-	0.000	-
History of cirrhosis	0.214	0.446	0.125	1.593
Tumor location-Bilobar	0.185	0.429	0.122	1.500
Multifocal disease	0.545	0.688	0.205	2.311
Largest nodule size≥7 cm	0.158	0.351	0.082	1.503
Portal vein invasion	0.936	1.050	0.317	3.482
Hepatic vein invasion	0.956	0.965	0.275	3.386
ECOG performance status (≥1 vs 0)	0.292	0.300	0.032	2.813
Child-Pugh stage (B/C vs A)	0.584	0.698	0.193	2.526
BCLC stage (C/D vs A/B)	0.858	0.893	0.257	3.102
Previous cTACE treatment	0.229	2.456	0.569	10.611
Previous surgery	0.972	0.972	0.201	4.700
Previous systemic chemotherapy	1.000	-	0.000	-
Previous radiofrequency ablation	0.609	1.846	0.177	19.306
Previous targeted therapy	0.699	0.571	0.033	9.771
WBC abnormal	0.660	0.750	0.208	2.703
RBC abnormal	0.703	0.786	0.227	2.716
ANC abnormal	0.795	0.838	0.221	3.183
Hb abnormal	0.577	0.698	0.198	2.466
PLT abnormal	0.504	1.553	0.428	5.640
ALB ≥1ULN	1.000	0.000	0.000	-
TP ≥1ULN	0.609	1.846	0.177	19.306
TBIL ≥1ULN	0.174	2.338	0.688	7.941
TBA ≥1ULN	0.393	0.584	0.170	2.005
ALT ≥1ULN	0.304	1.950	0.545	6.974
AST ≥1ULN	0.723	0.792	0.217	2.888
ALP ≥1ULN	**0.042**	0.250	0.066	0.953
BCr abnormal	0.999	-	0.000	-
BUN abnormal	0.647	1.731	0.165	18.161
AFP abnormal	0.554	0.587	0.100	3.431
CEA abnormal	1.000	0.000	0.000	-
CA19.9 abnormal	0.484	1.719	0.377	7.849
Multivariate logistic regression				
ALP ≥1ULN	**0.035**	0.200	0.045	0.892

For abbreviations see footnote of Table 1. Significant results are shown in boldface.

Table 4. Factors affecting ORR (M6) by univariate and multivariate logistic regression model analysis

Parameters	*Logistic regression*			
	P value	*OR*	*95% CI*	
			Lower	*Higher*
Univariate logistic regression				
DEB-TACE vs cTACE	0.355	2.400	0.376	15.319
Age≥60 years	0.604	1.018	0.950	1.091
Male	0.606	2.167	0.115	40.811
History of drinking	0.477	2.400	0.215	26.822
History of HBV	0.216	5.200	0.381	70.903
History of HCV	1.000	-	0.000	-
History of cirrhosis	0.356	0.400	0.057	2.800
Tumor location-Bilobar	1.000	1.000	0.160	6.255
Multifocal disease	0.528	0.533	0.076	3.755
Largest nodule size≥7 cm	1.000	1.000	0.160	6.255
Portal vein invasion	0.718	0.682	0.085	5.448
Hepatic vein invasion	0.999	-	0.000	-
ECOG performance status (≥1 vs 0)	0.440	2.400	0.261	22.105
Child-Pugh stage (B/C vs A)	0.696	1.636	0.138	19.387
BCLC stage (C/D vs A/B)	0.744	1.389	0.194	9.967
Previous cTACE treatment	0.538	0.563	0.090	3.518
Previous surgery	0.718	0.682	0.085	5.448
Previous systemic chemotherapy	1.000	-	0.000	-
Previous radiofrequency ablation	0.696	1.636	0.138	19.387
Previous targeted therapy	1.000	-	0.000	-
WBC abnormal	0.744	1.389	0.194	9.967
RBC abnormal	0.213	0.300	0.045	1.993
ANC abnormal	0.696	1.636	0.138	19.387
Hb abnormal	0.214	0.278	0.037	2.092
PLT abnormal	1.000	1.000	0.160	6.255
ALB ≥1ULN	1.000	0.000	0.000	-
TP ≥1ULN	1.000	-	0.000	-
TBIL ≥1ULN	1.000	1.000	0.160	6.255
TBA ≥1ULN	0.758	0.750	0.121	4.662
ALT ≥1ULN	0.718	0.682	0.085	5.448
AST ≥1ULN	0.538	1.778	0.284	11.120
ALP ≥1ULN	0.528	1.875	0.266	13.202
BCr abnormal	0.999	-	0.000	-
BUN abnormal	1.000	-	0.000	-
AFP abnormal	0.919	0.900	0.120	6.777
CEA abnormal	1.000	0.000	0.000	-
CA19.9 abnormal	0.440	0.308	0.015	6.117
Multivariate logistic regression				
No independent factor	-	-	-	-

For abbreviations see footnote of Table 1

Table 5. Factors affecting progression-free survival by univariate and multivariate Cox's proportional hazards regression model analysis

Parameters	*Cox's regression*			
	P value	*OR*	*95% CI*	
			Lower	*Higher*
Univariate Cox's regression				
DEB-TACE vs cTACE	0.518	1.227	0.659	2.286
Age≥60 years	0.293	0.695	0.353	1.368
Male	0.879	0.923	0.328	2.595
History of drinking	0.399	0.742	0.370	1.485
History of HBV	0.657	1.218	0.511	2.902
History of HCV	0.552	1.828	0.251	13.337
History of cirrhosis	0.906	0.963	0.514	1.803
Tumor location-Bilobar	**0.006**	2.412	1.294	4.495
Multifocal disease	0.143	1.589	0.855	2.954
Largest nodule size≥7 cm	0.246	1.528	0.747	3.128
Portal vein invasion	**0.034**	1.973	1.053	3.696
Hepatic vein invasion	0.684	1.140	0.606	2.147
ECOG performance status (≥1 vs 0)	0.720	0.853	0.358	2.035
Child-Pugh stage (B/C vs A)	0.926	1.033	0.525	2.031
BCLC stage (C/D vs A/B)	0.064	1.925	0.961	3.856
Previous cTACE treatment	0.976	1.011	0.481	2.124
Previous surgery	0.189	1.645	0.782	3.460
Previous systemic chemotherapy	0.580	1.752	0.240	12.770
Previous radiofrequency ablation	0.646	1.274	0.453	3.580
Previous targeted therapy	0.306	2.104	0.507	8.737
WBC abnormal	0.694	0.866	0.422	1.777
RBC abnormal	0.859	0.943	0.495	1.798
ANC abnormal	0.171	1.629	0.810	3.274
Hb abnormal	0.814	0.927	0.494	1.740
PLT abnormal	0.326	0.711	0.360	1.404
ALB ≥1ULN	0.971	0.989	0.532	1.838
TP ≥1ULN	0.676	1.286	0.396	4.177
TBIL ≥1ULN	0.431	0.775	0.412	1.461
TBA ≥1ULN	0.780	1.093	0.586	2.039
ALT ≥1ULN	0.321	1.370	0.736	2.550
AST ≥1ULN	0.391	1.368	0.669	2.799
ALP ≥1ULN	0.441	1.280	0.684	2.396
BCr abnormal	0.416	0.554	0.134	2.299
BUN abnormal	0.100	0.303	0.073	1.255
AFP abnormal	0.693	1.000	1.000	1.000
CEA abnormal	0.621	0.606	0.083	4.420
CA19.9 abnormal	**0.020**	4.080	1.252	13.293
Multivariate Cox's regression				
Tumor location-Bilobar	**0.003**	2.678	1.398	5.130
CA19.9 abnormal	**0.015**	4.374	1.339	14.286

For abbreviations see footnote of Table 1. Significant results are shown in boldface.

Table 6. Factors affecting overall survival by univariate and multivariate Cox's proportional hazards regression model analysis

Parameters	*Cox's regression*			
	P value	*OR*	*95% CI*	
			Lower	*Higher*
Univariate Cox's regression				
DEB-TACE vs cTACE	0.976	1.010	0.524	1.947
Age≥60 years	0.113	0.552	0.265	1.151
Male	0.355	0.612	0.216	1.732
History of drinking	0.441	0.751	0.362	1.558
History of HBV	0.878	0.933	0.385	2.261
History of HCV	0.524	1.912	0.260	14.033
History of cirrhosis	0.267	0.689	0.357	1.330
Tumor location-Bilobar	0.101	1.731	0.899	3.333
Multifocal disease	0.086	1.776	0.922	3.421
Largest nodule size≥7 cm	0.224	1.573	0.757	3.266
Portal vein invasion	0.052	1.925	0.995	3.726
Hepatic vein invasion	0.094	1.762	0.907	3.423
ECOG performance status (≥1 vs 0)	0.782	0.875	0.340	2.254
Child-Pugh stage (B/C vs A)	0.724	1.140	0.550	2.366
BCLC stage (C/D vs A/B)	**0.049**	2.080	1.002	4.319
Previous cTACE treatment	0.426	0.726	0.331	1.597
Previous surgery	0.469	1.338	0.608	2.949
Previous systemic chemotherapy	0.556	1.819	0.248	13.342
Previous radiofrequency ablation	0.342	1.661	0.584	4.727
Previous targeted therapy	0.097	3.397	0.800	14.417
WBC abnormal	0.653	0.840	0.393	1.797
RBC abnormal	0.277	1.456	0.740	2.866
ANC abnormal	0.493	1.295	0.619	2.709
Hb abnormal	0.107	1.726	0.888	3.353
PLT abnormal	0.337	0.704	0.344	1.441
ALB ≥1ULN	1.000	1.000	0.000	-
TP ≥1ULN	0.483	1.528	0.467	4.998
TBIL ≥1ULN	0.852	0.939	0.483	1.824
TBA ≥1ULN	0.588	0.834	0.433	1.607
ALT ≥1ULN	0.418	1.311	0.681	2.526
AST ≥1ULN	0.132	1.788	0.839	3.811
ALP ≥1ULN	0.140	1.652	0.848	3.218
BCr abnormal	0.369	0.519	0.125	2.166
BUN abnormal	0.256	0.437	0.105	1.823
AFP abnormal	**0.040**	3.482	1.058	11.462
CEA abnormal	0.356	2.566	0.346	19.010
CA19.9 abnormal	0.435	0.703	0.291	1.700
Multivariate Cox's regression				
No independent factor	-	-	-	-

For abbreviations see footnote of Table 1. Significant results are shown in boldface.

model analysis further disclosed that bilobar tumor location (p=0.003, HR 2.678, 95% CI 1.398-5.130) and abnormal CA19.9 (p=0.015, HR 4.374, 95% CI 1.339-14.286) were independent factors for predicting poorer PFS. Concerning OS, univariate Cox's proportional hazards regression model analysis displayed that BCLC Stage (C/D) (p=0.049, HR 2.080, 95% CI 1.002-4.319) and abnormal AFP (p=0.040, HR 3.482, 95% CI 1.058-11.462) were correlated with unfavorable OS, whereas DEB-TACE or cTACE did not affect OS (p=0.976, HR 1.010, 95% CI 0.524-1.947) (Table 6). Further multivariate Cox's proportional hazards regression model analysis did not reveal any independent factors for OS.

Comparison of liver function between DEB-TACE group and cTACE group

At M1 after treatment, decreased ALB level (p=0.007), increased ALP level (p=0.001) and larger proportion of patients with ALP≥1ULN (p=0.004) were observed in DEB-TACE group compared to cTACE group (Table 7). However, these differences were associated with numerically lower ALB level, higher ALP level and more patients with ALP≥1ULN in DEB-TACE group at M0. According to these findings, it is difficult to evaluate liver injury between the two groups. In order to further assess the effect of DEB-TACE and cTACE on liver injury, we further compared the changes (M1-M0) of liver function indexes, which disclosed that there was no difference of all liver function indexes changes between two groups (Figure 3).

Comparison of adverse events between DEB-TACE group and cTACE group during treatment and hospitalization

During treatment, pain was higher in the DEB-TACE group compared to cTACE group (p<0.001).

Table 7. Liver function testing at 1 month (M1) post-treatment

Parameters	*DEB-TACE group n (%)*	*cTACE group n (%)*	*p value*
ALB (g/L)	32.5 (28.8-35.2)	36.1 (30.3-40.4)	**0.007**
ALB ≥1ULN	0/34 (0.0)	0/46 (0.0)	-
ALB ≥2ULN	0/34 (0.0)	0/46 (0.0)	-
ALB ≥3ULN	0/34 (0.0)	0/46 (0.0)	-
TP (g/L)	70.7 (65.0-73.7)	69.5 (65.2-75.8)	0.546
TP ≥1ULN	0/34 (0.0)	5/46 (10.9)	0.129
TP ≥2ULN	0/34 (0.0)	1/46 (2.2)	0.387
TP ≥3ULN	0/34 (0.0)	1/46 (2.2)	0.387
TBIL (μmol/L)	19.0 (13.6-28.6)	18.0 (12.2-25.9)	0.730
TBIL ≥1ULN	17/34 (50.0)	18/46 (39.1)	0.333
TBIL ≥2ULN	2/34 (59.0)	3/46 (65.0)	0.907
TBIL ≥3ULN	1/34 (2.9)	3/46 (6.5)	0.468
TBA (I/L)	11.6 (7.9-28.1)	9.4 (5.8-37.7)	0.544
TBA ≥1ULN	18/33 (54.5)	22/46 (47.8)	0.556
TBA ≥2ULN	14/33 (42.4)	17/46 (37.0)	0.624
TBA ≥3ULN	7/33 (21.1)	13/46 (28.3)	0.477
ALT (μ/L)	47.0 (29.5-67.0)	31.0 (24.1-51.0)	0.055
ALT ≥1ULN	18/34 (52.9)	16/46 (34.8)	0.104
ALT ≥2ULN	7/34 (20.6)	5/46 (10.9)	0.229
ALT ≥3ULN	4/34 (11.8)	3/46 (6.5)	0.412
AST (μ/L)	62.0 (44.3-110.5)	49.5 (35.0-85.0)	0.184
AST ≥1ULN	27/34 (79.4)	29/46 (63.0)	0.114
AST ≥2ULN	12/34 (35.3)	13/46 (28.3)	0.502
AST ≥3ULN	7/34 (20.6)	7/46 (15.2)	0.532
ALP (μ/L)	165.0 (143.0-218.5)	125.0 (84.0-165.0)	**0.001**
ALP ≥1ULN	27/34 (79.4)	22/46 (47.8)	**0.004**
ALP ≥2ULN	6/34 (17.6)	4/46 (8.7)	0.231
ALP ≥3ULN	2/34 (5.9)	1/46 (2.2)	0.388

Data were presented as median (25^{th}-75^{th} quantiles) or percents. Comparison between 2 groups was determined by Wilcoxon rank sum test or Chi-square test. P value <0.05 was considered significant, and the significant results were shown in boldface. "-" indicated that the data were unable to compare due to lack of events. DEB-TACE: drug-eluting bead transarterial chemoembolization; cTACE: conventional transarterial chemoembolization; ULN: upper limit of normal; ALB: albumin; TP: total protein; TBIL: total bilirubin; TBA: total bile acid; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase. Significant results are shown in boldface.

Table 8. Adverse events occurring during treatment and hospitalization

Parameters	*DEB-TACE group (N=42) n (%)*	*cTACE group (N=47) n (%)*	*p value*
During treatment			
Pain	22 (52.4)	8 (17.0)	**<0.001**
Pain grade (NRS)			0.730
Mild pain	20 (90.9)	8 (100.0)	
Moderate pain	0 (0.0)	0 (0.0)	
Severe pain	2 (9.1)	0 (0.0)	
Nausea/ Vomiting	6 (14.3)	9 (19.1)	0.541
Rise in blood pressure	2 (4.8)	0 (0.0)	0.130
During hospitalization			
Pain	24 (57.1)	15 (31.9)	**0.017**
Pain grade (NRS)			0.743
Mild pain	24 (100.0)	14 (93.3)	
Moderate pain	0 (0.0)	1 (6.7)	
Severe pain	0 (0.0)	0 (0.0)	
Fever	16 (38.1)	7 (14.9)	**0.013**
Nausea/ Vomiting	5 (11.9)	2 (4.3)	0.181

Data are presented as numbers and percents. Comparison between 2 groups was determined by Chi-square test or Wilcoxon rank sum test. P value <0.05 was considered significant, and the significant results are shown in boldface. DEB-TACE: drug-eluting bead transarterial chemoembolization; cTACE: conventional transarterial chemoembolization; NRS: numeric rating scale.

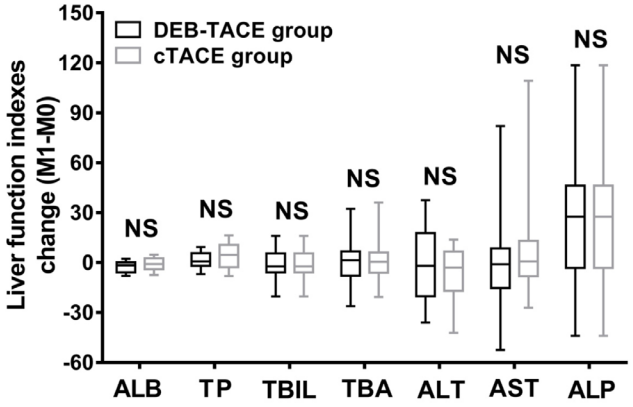

Figure 3. Liver function indexes changes in DEB-TACE group and cTACE group. No difference of liver function indexes changes (M1-M0) was noted between DEB-TACE group and cTACE group. Wilcoxon rank sum test was used to compare liver function indexes changes between DEB-TACE group and cTACE group during M0-M1. NS: not significant; ALB: albumin; TP: total protein; TBIL: total bilirubin; TBA: total bile acid; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; DEB-TACE: drug-eluting bead transarterial chemoembolization; cTACE: transarterial chemoembolization.

During hospitalization, pain (p=0.017) and fever (p=0.013) were also more intense in the DEB-TACE group compared to cTACE group (Table 8).

Discussion

In the present study, we observed the following: 1) higher CR/ORR and similar DFS/OS were observed in DEB-TACE group compared with cTACE group; 2) multifocal disease, ALT ≥1ULN and ALP ≥1ULN predicted lower ORR independently, and bilobar tumor location as well as abnormal CA19.9 level were independent predictive factors for unfavorable PFS; 3) liver function damage of patients did not differ between DEB-TACE group and cTACE group; 4) DEB-TACE group exhibited more frequent pain during treatment, and more frequent pain/ fever during hospitalization compared to cTACE group.

The treatment efficacy of DEB-TACE with various DEBs versus cTACE in HCC patients has been investigated in numerous studies, whereas no consensus has been achieved [29-36]. A cohort study disclosed that at M3 post operation, the CR rate (55 *vs.* 23.1%) and ORR (81.6 *vs.* 49.4%) were higher in patients treated with DEB-TACE using DC beads® compared to cTACE [29]. Another clinical study of DEB-TACE with SAP versus cTACE revealed no difference of ORR (50 *vs.* 62%) between two groups [37]. For CSM as drug carrier, one published study compared the efficacy between DEB-TACE with CSM and cTACE, which disclosed that CR (M3: 25.0 *vs.* 3.3%; M6: 20.8 *vs.* 0%) and ORR (M3: 83.3 *vs.* 43.3%; M6: 62.5 *vs.* 30.0%) at M3/M6 were increased compared to cTACE group [38]. With respect to survival, multiple studies illuminate that the DFS and OS in HCC patients receiving DEB-TACE were not inferior to that in patients receiving cTACE [31-34]. For instance, a retrospective study

reported that patients treated with DEB-TACE using DC beads® had higher PFS compared to cTACE, while similar OS between DEB-TACE with DC beads® and cTACE was also noted in other previous studies [30-34]. With regard to CSM, there was no study comparing survival between DEB-TACE with CSM and cTACE. In the present study, we observed that HCC patients treated with DEB-TACE using CSM displayed increased CR (M1: 27.3 *vs.* 7.7%; M3: 30.8 *vs.* 5.0%) and ORR (M1: 81.8 *vs.* 56.4%; M3: 76.9 *vs.* 45.0%) at M1/M3 compared to cTACE group, whereas there was no difference of PFS and OS between the two groups. The higher short-term CR and ORR in patients receiving DEB-TACE treatment with CSM may be due to the fact that CSM could achieve continuously high concentration of chemotherapeutic agents at least 1 month and over 200μm diffusing distance, which led to higher tumor tissue concentration of pirarubicin compared to cTACE, thereby DEB-TACE group showed better treatment response [38,39]. In addition, DEB-TACE group exhibited comparable PFS and OS, which might be attributed to relatively short follow-up time and survival profiles affected by various factors, such as comorbidities and patients receiving other therapies.

With regard to the predictive factors for treatment response and survival, a growing number of studies have disclosed 3 major factors including tumor features, tumor markers and liver function index levels [32,33,40-42]. Concerning treatment response, one study in HCC patients receiving DEB-TACE with DC beads® displayed that tumor location in the segments 1 and 4 were independent factors for predicting decreased CR, whereas tumor size <5 cm independently predicted increased CR [41]. Another study conducted in HCC patients treated with DEB-TACE using CSM revealed that number of nodules > 3, elevated BCLC stage and previous cTACE were associated with worse ORR, while none of these three factors independently predicted ORR [42]. With respect to survival, a retrospective, single-center study revealed that increased Child-Pugh stage and more severe portal invasion independently predicted poorer OS in HCC patients receiving cTACE or DEB-TACE with DC beads® [33]. A randomized controlled trial discovered that advanced Eastern Cooperative Oncology Group performance status (ECOG PS), elevated ALB and multiple tumors were independent factors for predicting shorter OS in HCC patients receiving cTACE or DEB-TACE with DC beads® [32]. In addition, hepatitis B, presence of ascites, advanced ECOG PS, higher Okuda stage and AFP level (>400) were independent predictors of worse OS in advanced HCC patients receiving DEB-TACE with DC beads® [40]. In this study, we disclosed that multifocal disease, ALT ≥1ULN and ALP ≥1ULN were independent predicting factors for poorer treatment response, and bilobar tumor location as well as abnormal CA19.9 level independently predicted shorter PFS in HCC patients treated with DEB-TACE using CSM or cTACE. These findings in our study could result from that: 1) multifocal disease and tumor location-bilobar were associated with more severe disease condition of HCC patients, suggesting increasing chances of blood vessels invasion and metastasis, which limited treatment efficacy of DEB-TACE or TACE in these patients, thereby leading to unfavorable treatment response or survival; 2) abnormal ALT and ALP levels indicated worse liver function, contributing to less tolerability to DEB-TACE or cTACE procedure and greater procedure-related damage to liver, thus these patients presented with poorer prognosis; 3) as an important tumor marker, increased CA19.9 level was associated with elevated grade of liver tumor malignancy, resulting in less response to DEB-TACE or cTACE treatment, hence treatment efficacy might shrink [43,44].

Damaged liver function is one of the major safety concerns in HCC patients treated by TACE, and a large number of studies uncover that DEB-TACE is similar to cTACE regarding liver damage [29-33,35,36,45-47]. For example, no difference of liver function indexes changes (including ALP, ALT, TBIL, AST, ALB) in HCC patients was observed between DEB-TACE with DC beads® and cTACE [48]. Another study compared liver function indexes (including ALB, TP, ALT, AST and TBIL) before and after treatment between DEB-TACE with CSM and cTACE, which revealed that no differences in liver function indexes between the two groups before treatment, while at M1 after treatment, there were lower levels of AST, ALT and TBIL in patients receiving DEB-TACE with CSM compared to cTACE [38]. Partially in accordance with these previous studies, we also discovered no difference of liver function indexes changes (M1-M0) (including ALB, TP, TBIL, TBA, ALT, AST, ALP) between DEB-TACE with CSM and cTACE. Liver damage of HCC patients receiving TACE treatments is a result of heterogeneous causes, including chemotherapeutic agent toxicity and procedure-related damage to liver, as well as tumor ischemic necrosis. Whatever the reason may be, we found that in our study DEB-TACE with CSM and cTACE had parallel effects on liver function.

A majority of studies disclose no difference of procedure-related adverse events (including abdominal pain, transient fever, nausea and vomiting) between DEB-TACE and cTACE in HCC patients

[29,31,32,35,36,40,46-48]. For example, a short-term study concluded that HCC patients treated by DEB-TACE with DC beads® showed similar adverse events rates compared to patients treated with cTACE [48]. And a randomized controlled trial (RCT) revealed that the incidence and severity of adverse events (including post-procedural fever, fatigue, nausea/vomiting, haematoma, cholecystitis, spleen infarction, infection, liver abscess) did not differ between DEB-TACE with DC beads® and cTACE, while post-procedural pain was less frequent and severe in HCC patients receiving DEB-TACE with DC beads® [32]. In this study, compared to cTACE group, patients treated with DEB-TACE using CSM exhibited higher rates of pain during treatment and increased rates of pain/fever during hospitalization. Worse baseline tumor features in DEB-TACE group might require larger dose of pirarubicin, and the high chemotherapeutic dose along with the better treatment response in DEB-TACE group that caused more necrosis of the tumor together increased the incidence of pain and fever occurring during treatment and hospitalization in DEB-TACE group [49].

Limitations existed in this study. Firstly, the number of enrolled patients was relatively small, leading to less statistical power. Secondly, as a retrospective study, there might be some confounding factors, however, we conducted multivariate regression analyses to diminish the confounding effect. Thirdly, the follow-up duration for assessing treatment response and survival was relatively short, thus the long-term efficacy of DEB-TACE with CSM compared to cTACE in HCC were not evaluated.

In summary, the short-term CR and ORR of DEB-TACE treatment with CSM are better, while OS, DFS and safety were equivalent compared to cTACE in treating HCC patients.

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Conflict of interests

The authors declare no conflict of interests.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
2. Bruix J, Sherman M, Llovet JM et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35:421-30.
3. Kudo M. Local ablation therapy for hepatocellular carcinoma: current status and future perspectives. J Gastroenterol 2004;39:205-14.
4. Llovet JM, Bruix J, Fuster J et al. Liver transplantation for small hepatocellular carcinoma: the tumor-node-metastasis classification does not have prognostic power. Hepatology 1998;27:1572-7.
5. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. Hepatology 2002;35:519-24.
6. Lencioni R, Petruzzi P, Crocetti L. Chemoembolization of hepatocellular carcinoma. Semin Intervent Radiol 2013;30:3-11.
7. Llovet JM. Updated treatment approach to hepatocellular carcinoma. J Gastroenterol 2005;40:225-35.
8. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329-38.
9. Yu CY, Ou HY, Weng CC et al. Drug-Eluting Bead Transarterial Chemoembolization as Bridge Therapy for Hepatocellular Carcinoma Before Living-Donor Liver Transplantation. TransPlant Proc 2016;48:1045-8.
10. Vasnani R, Ginsburg M, Ahmed O et al. Radiofrequency and microwave ablation in combination with transarterial chemoembolization induce equivalent histopathologic coagulation necrosis in hepatocellular carcinoma patients bridged to liver transplantation. Hepatobiliary Surg Nutr 2016;5:225-33.
11. Bruix J, Sherman M and Practice Guidelines Committee of American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005;42:1208-36.
12. European Association for the Study of Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-43.
13. Bruix J, Sherman M and American Association for the Study of Liver D. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020-2.
14. Lencioni R. Loco-regional treatment of hepatocellular carcinoma. Hepatology 2010;52:762-73.
15. Brown DB, Cardella JF, Sacks D et al. Quality improvement guidelines for transhepatic arterial chemoembolization, embolization, and chemotherapeutic infusion for hepatic malignancy. J Vasc Interv Radiol 2009;20:S219-26.
16. Johnson PJ, Kalayci C, Dobbs N et al. Pharmacokinetics and toxicity of intraarterial adriamycin for hepatocel-

lular carcinoma: effect of coadministration of lipiodol. J Hepatol 1991;13:120-7.

17. Lewis AL, Gonzalez MV, Lloyd AW et al. DC bead: in vitro characterization of a drug-delivery device for transarterial chemoembolization. J Vasc Interv Radiol 2006;17:335-42.
18. Simonetti RG, Liberati A, Angiolini C, Pagliaro L. Treatment of hepatocellular carcinoma: a systematic review of randomized controlled trials. Ann Oncol 1997;8:117-36.
19. Lewis AL, Gonzalez MV, Leppard SW et al. Doxorubicin eluting beads - 1: effects of drug loading on bead characteristics and drug distribution. J Mater Sci Mater Med 2007;18:1691-9.
20. Lewis AL, Taylor RR, Hall B, Gonzalez MV, Willis SL, Stratford PW. Pharmacokinetic and safety study of doxorubicin-eluting beads in a porcine model of hepatic arterial embolization. J Vasc Interv Radiol 2006;17:1335-43.
21. Poon RT, Tso WK, Pang RW et al. A phase I/II trial of chemoembolization for hepatocellular carcinoma using a novel intra-arterial drug-eluting bead. Clin Gastroenterol Hepatol 2007;5:1100-8.
22. Kettenbach J, Stadler A, Katzler IV et al. Drug-loaded microspheres for the treatment of liver cancer: review of current results. Cardiovasc Intervent Radiol 2008;31:468-76.
23. Malagari K, Chatzimichael K, Alexopoulou E et al. Transarterial chemoembolization of unresectable hepatocellular carcinoma with drug eluting beads: results of an open-label study of 62 patients. Cardiovasc Intervent Radiol 2008;31:269-80.
24. Sottani C, Poggi G, Quaretti P et al. Serum pharmacokinetics in patients treated with transarterial chemoembolization (TACE) using two types of epirubicin-loaded microspheres. Anticancer Res 2012;32:1769-74.
25. Guan YS, He Q, Jin Y, Yao F. [Development of CalliSpheres(R) embolic microspheres]. Zhonghua Gan Zang Bing Za Zhi 2016;24:549-51.
26. Zhang S, Huang C, Li Z et al. Comparison of pharmacokinetics and drug release in tissues after transarterial chemoembolization with doxorubicin using diverse lipiodol emulsions and CalliSpheres Beads in rabbit livers. Drug Deliv 2017;24:1011-7.
27. Yao FY. Liver transplantation for hepatocellular carcinoma: beyond the Milan criteria. Am J Transplant 2008;8:1982-9.
28. Lencioni R, de Baere T, Burrel M et al. Transcatheter treatment of hepatocellular carcinoma with Doxorubicin-loaded DC Bead (DEBDOX): technical recommendations. Cardiovasc Intervent Radiol 2012;35:980-5.
29. Song MJ, Chun HJ, Song DS et al. Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. J Hepatol 2012;57:1244-50.
30. Liu YS, Ou MC, Tsai YS et al. Transarterial chemoembolization using gelatin sponges or microspheres plus lipiodol-doxorubicin versus doxorubicin-loaded beads for the treatment of hepatocellular carcinoma. Korean J Radiol 2015;16:125-32.
31. Sacco R, Bargellini I, Bertini M et al. Conventional versus doxorubicin-eluting bead transarterial chemoembolization for hepatocellular carcinoma. J Vasc Interv Radiol 2011;22:1545-52.
32. Golfieri R, Giampalma E, Renzulli M et al. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer 2014;111:255-64.
33. Kloeckner R, Weinmann A, Prinz F et al. Conventional transarterial chemoembolization versus drug-eluting bead transarterial chemoembolization for the treatment of hepatocellular carcinoma. BMC Cancer 2015;15:465.
34. Rahman FA, Naidu J, Ngiu CS et al. Conventional versus Doxorubicin-Eluting Beads Transarterial Chemoembolization for Unresectable Hepatocellular Carcinoma: a Tertiary Medical Centre Experience in Malaysia. Asian Pac J Cancer Prev 2016;17:4037-41.
35. Ni JY, Xu LF, Wang WD, Sun HL, Chen YT. Conventional transarterial chemoembolization vs microsphere embolization in hepatocellular carcinoma: a meta-analysis. World J Gastroenterol 2014;20:17206-17.
36. Huang K, Zhou Q, Wang R, Cheng D, Ma Y. Doxorubicin-eluting beads versus conventional transarterial chemoembolization for the treatment of hepatocellular carcinoma. J Gastroenterol Hepatol 2014;29:920-5.
37. Morimoto M, Kobayashi S, Moriya S et al. Short-term efficacy of transarterial chemoembolization with epirubicin-loaded superabsorbent polymer microspheres for hepatocellular carcinoma: comparison with conventional transarterial chemoembolization. Abdom Radiol (NY) 2017;42:612-9.
38. Wu B, Zhou J, Ling G, Zhu D, Long Q. CalliSpheres drug-eluting beads versus lipiodol transarterial chemoembolization in the treatment of hepatocellular carcinoma: a short-term efficacy and safety study. World J Surg Oncol 2018;16:69.
39. Correction to: Zhang et al. Comparison of pharmacokinetics and drug release in tissues after transarterial chemoembolization with doxorubicin using diverse lipiodol emulsions and CalliSpheres Beads in rabbit livers. Drug Deliv 2017;24:1927.
40. Prajapati HJ, Dhanasekaran R, El-Rayes BF et al. Safety and efficacy of doxorubicin drug-eluting bead transarterial chemoembolization in patients with advanced hepatocellular carcinoma. J Vasc Interv Radiol 2013;24:307-15.
41. Wu X, Chen R, Zheng W, Hu H. Comprehensive Analysis of Factors Affecting Clinical Response and Short-Term Survival to Drug-Eluting Bead Transarterial Chemoembolization for Treatment in Patients With Liver Cancer. Technol Cancer Res Treat 2018;17: https://journals.sagepub.com/doi/full/10.1177/1533033818759878 doi: 10.1177/1533033818759878.
42. Zhou GH, Han J, Sun JH et al. Efficacy and safety profile of drug-eluting beads transarterial chemoembolization by CalliSpheres(R) beads in Chinese hepatocellular carcinoma patients. BMC Cancer 2018;18:644.
43. Zhuo M, Chen H, Zhang T et al. The potential predictive value of circulating immune cell ratio and tumor marker in atezolizumab treated advanced non-small cell lung cancer patients. Cancer Biomark 2018;22:467-76.
44. Ouyang X, Dang Y, Zhang F, Huang Q. Low Serum Al-

bumin Correlates with Poor Survival in Gastric Cancer Patients. Clin Lab 2018;64:239-45.

45. Chen P, Yuan P, Chen B, Sun J, Shen H, Qian Y. Evaluation of drug-eluting beads versus conventional transcatheter arterial chemoembolization in patients with unresectable hepatocellular carcinoma: A systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2017;41:75-85.
46. Wiggermann P, Sieron D, Brosche C et al. Transarterial Chemoembolization of Child-A hepatocellular carcinoma: drug-eluting bead TACE (DEB TACE) vs. TACE with cisplatin/lipiodol (cTACE). Med Sci Monit 2011;17:189-95.
47. Song MJ, Park CH, Kim JD et al. Drug-eluting bead loaded with doxorubicin versus conventional Lipiodol-based transarterial chemoembolization in the treatment of hepatocellular carcinoma: a case-control study of Asian patients. Eur J Gastroenterol Hepatol 2011;23:521-7.
48. Duan F, Wang EQ, Lam MG et al. Superselective Chemoembolization of HCC: Comparison of Short-term Safety and Efficacy between Drug-eluting LC Beads, QuadraSpheres, and Conventional Ethiodized Oil Emulsion. Radiology 2016;278:612-21.
49. Lopez-Benitez R, Richter GM, Kauczor HU et al. Analysis of nontarget embolization mechanisms during embolization and chemoembolization procedures. Cardiovasc Intervent Radiol 2009;32:615-22.