


CalliSpheres Drug-Eluting Bead Transcatheter Arterial Chemoembolization Presents With Better Efficacy and Equal Safety Compared to Conventional TACE in Treating Patients With Hepatocellular Carcinoma

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Hua Xiang, MB¹, Lin Long, MM¹, Yuanhui Yao, MM¹,
Zhiyong Fang, MM¹, Zhiming Zhang, MB¹, and Yongjin Zhang, MM¹ 

Abstract

The aim of this study was to compare the treatment response, survival, liver function, and adverse event incidence of drug-eluting bead transcatheter arterial chemoembolization using CalliSpheres microspheres with conventional transcatheter arterial chemoembolization in patients with hepatocellular carcinoma. Seventy-three patients with hepatocellular carcinoma who received drug-eluting bead transcatheter arterial chemoembolization (using CalliSpheres microspheres) or conventional transcatheter arterial chemoembolization treatment were consecutively enrolled. Treatment response was assessed by modified Response Evaluation Criteria in Solid Tumors at month 1/month 3/month 6; posttreatment, liver function indexes, and adverse events were recorded. Progression-free survival and overall survival were also calculated. Objective response rate of patients at months 1, 3, and 6, disease control rate of patients and objective response rate of nodules at month 3 were increased in drug-eluting bead transcatheter arterial chemoembolization group compared with conventional transcatheter arterial chemoembolization group. In addition, drug-eluting bead transcatheter arterial chemoembolization using CalliSpheres microspheres was an independent factor for predicting better objective response rate at month 1. Patients in drug-eluting bead transcatheter arterial chemoembolization group achieved longer progression-free survival and similar overall survival compared to those in conventional transcatheter arterial chemoembolization group; Cox proportional hazards regression model analyses revealed that drug-eluting bead transcatheter arterial chemoembolization using CalliSpheres microspheres was associated with better progression-free survival while it did not affect overall survival. Meanwhile, most of the occurrences of abnormal liver function indexes were similar between 2 groups, whereas drug-eluting bead transcatheter arterial chemoembolization group had a higher percentage of patients with total bile acid ≥ 2 upper limit of normal compared to conventional transcatheter arterial chemoembolization group at month 1. Moreover, the adverse event incidences between 2 groups were similar. In conclusion, drug-eluting bead transcatheter arterial chemoembolization using CalliSpheres microspheres achieves better treatment response and progression-free survival while equal safety compared to conventional transcatheter arterial chemoembolization in patients with hepatocellular carcinoma.

Keywords

CalliSpheres beads, transcatheter arterial chemoembolization, hepatocellular carcinoma, overall survival, progression-free survival

¹ Department of Interventional Radiology & Vascular Surgery, Hunan Provincial People's Hospital, Changsha, Hunan, China

Corresponding Authors:

Yongjin Zhang, MM, Department of Interventional Radiology & Vascular Surgery, Hunan Provincial People's Hospital, 61 Jiefang West Road, Changsha, China.
Email: zhangyongjin_zyj@163.com

Zhiming Zhang, MB, Department of Interventional Radiology & Vascular Surgery, Hunan Provincial People's Hospital, 61 Jiefang West Road, Changsha, China.
Email: shi31779553@163.com



Abbreviations

ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CA199, carbohydrate antigen 199; CEA, carcinoembryonic antigen; CSM, CalliSpheres microspheres; CR, complete response; CT, computed tomography; cTACE, conventional TACE; DCR, disease control rate; DEB-TACE, drug-eluting bead TACE; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PVA, polyvinyl alcohol; RBC, red blood cell; SD, stable disease; TACE, transcatheter arterial chemoembolization; TBA, total bile acid; TBIL, total bilirubin; TP, total protein; ULN, upper limit of normal

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Introduction

Hepatocellular carcinoma (HCC), the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide, is among the most dangerous cancers.¹ Approximately 1% of deaths all around the world is related to HCC each year, of which about 50% are Chinese.^{2,3} Current curative therapies including surgical resection, radiofrequency ablation, and liver transplantation contribute to great survival improvements for patients with early-stage HCC, while for patients with intermediate- and advanced-stage HCC who account for the majority of newly diagnosed patients, the survival remains unsatisfactory.^{4,5}

Transcatheter arterial chemoembolization (TACE) is a minimally invasive procedure that directly releases chemotherapy drug to tumor tissues with drug carriers and embolizes blood supply of tumor tissues with embolization agents.^{6,7} The TACE is widely used as first-line therapy in patients with intermediate-stage HCC, which provides favorable treatment response and prolongs progression-free survival (PFS) as well as overall survival (OS) in patients with HCC.^{8,9} As a novel TACE technique, drug-eluting bead TACE (DEB-TACE) contributes to better treatment response while less systemic drug toxicity compared to conventional TACE (cTACE).¹⁰ CalliSpheres microspheres (CSM), the first microsphere product that is independently researched and developed in China, was launched in 2015.^{11,12} The CSM not only loads several kinds of chemotherapeutic drugs such as doxorubicin, epirubicin, pirarubicin, gemcitabine, oxaliplatin, and irinotecan but also presents with a lot of outstanding features including high drug-loading efficiency and stable releasing profiles; besides, there are various sized CSM available (ranging from 100 to 1200 μm) in clinical practices to fully meet the needs.^{11,12} These great properties of CSM make DEB-TACE using CSM a promising therapeutic option in treating patients with HCC. Although a few studies find that patients with HCC treated by DEB-TACE using other microspheres illuminate better efficacy and safety compared with cTACE, the difference of efficacy and safety between DEB-TACE using CSM and cTACE is still unclear, in particular, no study compares the survival benefit of DEB-TACE using CSM with cTACE in patients with HCC.¹³⁻¹⁵ Therefore, the aim of the current study was to compare treatment response, survival, liver function, and incidence

of adverse events in patients with HCC treated by DEB-TACE using CSM with patients treated by cTACE.

Materials and Methods

Patients

This study was a retrospective cohort study approved by Ethics Committee of Hunan Provincial People's Hospital with approval no. 2017-09, and the written informed consents were obtained from all patients or their statutory guardians. A total of 73 patients with HCC who received DEB-TACE using CSM or cTACE treatment at Hunan Provincial People's Hospital between March 6, 2015, and September 1, 2017, were consecutively analyzed in the present study. The inclusion criteria include (1) diagnosed as primary HCC confirmed by clinical and pathological findings according to American Association for the Study of the Liver Diseases guidelines; (2) age ≥ 18 years old; (3) underwent DEB-TACE using CSM or cTACE treatment; and (4) medical records were complete and available. The patients were excluded if (1) they had a history of malignancies other than HCC; (2) they had severe complications; (3) they converted treatment between cTACE and DEB-TACE within 6 months; and (4) they lost follow-up without any follow-up records. In total, there were 36 patients who received DEB-TACE treatment being assigned to DEB-TACE group, and another 37 patients who received cTACE treatment were assigned to cTACE group, respectively.

Collection of Baseline Features

Baseline features of all patients were collected from medical records, which included age, gender, history of hepatitis B, 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, Barcelona Clinic Liver Cancer (BCLC) stage, blood routine indexes (white blood cell, red blood cell [RBC], absolute neutrophil count [ANC], hemoglobin [Hb], and platelet), 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]), renal function indexes (blood creatinine and blood urea nitrogen), tumor

markers (α -fetoprotein, carcinoembryonic antigen [CEA], and carbohydrate antigen199 [CA199]), and previous treatments (cTACE, surgery, systematic chemotherapy, radiofrequency ablation, and targeted therapy).

Preoperative Treatments and Preparations

Routine treatments were performed before DEB-TACE or cTACE operation, which included analgesic treatment using pethidine and anti-infection treatments. For DEB-TACE, the CSM (Jiangsu Hengrui Medicine Co, Ltd, Jiangsu Province, China) with diameters of 100 to 300 μ m or 300 to 500 μ m were used as carriers and embolization agents. And the CSM were loaded with pirarubicin (60 or 80 mg, 20 mg/mL; Shenzhen Main Luck Pharmaceuticals Inc, Guangdong Province, China) and mixed with high concentration contrast agent as 1:1, 1:1.1, or 1:1.2 ratio. As for the cTACE, the chemotherapy drug solution contained pirarubicin of 60 mg or 80 mg with a concentration of 20 mg/mL, lipiodol was used as drug carriers, and polyvinyl alcohol (PVA) particles (Cook Medical LLC, Bloomington) were used as embolization agents. In addition, the 3F, 4F, and 5F microcatheters (Merit Maestro, Merit Medical System, Inc, Utah) were used in both DEB-TACE and cTACE operations.

Treatments

All the DEB-TACE or cTACE procedures were conducted in the digital subtraction angiography room in our hospital. Each patient with HCC received assessment of the targeted tumor by triphasic computed tomography (CT) or magnetic resonance imaging (MRI) according to the Milan criteria.^{16,17} The tumor supplying vessel was identified by hepatic angiography, then the femoral artery was punctured using Seldinger technique, and 3F, 4F, and 5F microcatheters were catheterized for embolization. Subsequently, the mixture of CSM for DEB-TACE or the mixture of chemotherapy drug solution, lipiodol, and PVA particles for cTACE was infused into the tumor supplying vessel through the microcatheter by pulse injection. Right after the flow of contrast agent stagnated, the embolization was stopped. After procedure, the microcatheter was pulled out, and the wound was pressed for hemostasis and then bandaged. In addition, the angiography was performed for another time to detect if there was incomplete embolization.

Postoperative Treatments

Postprocedural treatments were as follows: All patients were told to lie on one side and extend the punctured leg for 6 to 12 hours; and patients with postoperative pain were treated by pethidine.

Evaluation of Efficacy and Safety

Evaluation of treatment response was performed at month 1 (M1), M3, or M6 after DEB-TACE or cTACE treatment by enhanced CT or MRI examination. The evaluation criteria of

treatment response were in conformity with the modified Response Evaluation Criteria in Solid Tumors, which were defined as follows: (1) complete response (CR): the disappearance of any intratumoral arterial enhancement in all target lesions; (2) partial response (PR): at least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions; (3) stable disease (SD): the cases that did not qualify as either PR or progressive disease (PD); (4) PD: the increase in diameter of targeted tumor (with arterial enhancement) \geq 20% or existence of new tumor. Moreover, objective response rate (ORR) was defined as the percent of patients who achieved CR or PR, and disease control rate (DCR) was defined as the percent of patients who achieved CR, PR, or SD. Liver function indexes (ALT, AST, ALP, TBIL, ALB, TP, and TBA) which were measured at baseline (M0) and M1 after treatment and adverse events that occurred during DEB-TACE or cTACE operation and hospitalization were used to assess the safety profiles.

Patients were followed up by hospitalization or phone calls, the median follow-up duration was 12.7 months (range: 1.0-33.0 months), and the last follow-up date was March 12, 2018. Both PFS and OS were used to evaluate the survival profiles. The PFS was calculated from the time of treatment to the time of disease progression or death, and OS was calculated from the time of treatment to the time of patient's death.

Statistical Analysis

Statistical analysis was performed using SPSS 19.0 software (SPSS Inc, Chicago) and GraphPad Prism 6.01 software (GraphPad Software Inc, San Diego). Data were expressed as count (percentage), mean (standard deviation) or median (25th-75th quantiles). Comparison between 2 groups was performed by χ^2 test, *t* test, or Wilcoxon rank-sum test. Factors affecting ORR (M1) were determined by univariate and multivariate logistic regression analysis, and the multivariate logistic regression analysis was performed using forward stepwise (conditional) method, while the univariate and multivariate logistic regression analyses for ORR of M3 and M6 were unable to carry out due to fewer patients with treatment response assessments. Survival analysis was performed using Kaplan-Meier method and log-rank test. Factors affecting PFS and OS were determined by univariate and multivariate Cox proportional hazards regression analyses, and the multivariate Cox proportional hazards regression analysis was performed using forward stepwise (conditional LR) method. *P* value $<.05$ was considered significant, and the significant results are shown in boldface.

Results

Baseline Characteristics of HCC Patient log

As depicted in Table 1, mean ages in DEB-TACE group and cTACE group were 57.6 (11.3) and 54.9 (10.7) years, respectively (*P* = .300); the number of males and females were 31

Table 1. Baseline Characteristics of Patients With HCC.^a

Parameters	DEB-TACE Group, N = 36	cTACE Group, N = 37	P Value
Age (years)	57.6 (11.3)	54.9 (10.7)	.300
Gender (male/female)	31/5	33/4	.689
History of drink (n/%)	5 (13.9)	1 (2.7)	.082
History of HB (n/%)	18 (50.0)	26 (70.3)	.077
History of cirrhosis (n/%)	14 (38.9)	21 (56.8)	.127
Tumor location (n/%)			.287
Unilobar	21 (58.3)	26 (70.3)	
Bilobar	15 (41.7)	11 (29.7)	
Tumor distribution (n/%)			.705
Unifocal	22 (61.1)	21 (56.8)	
Multifocal	14 (38.9)	16 (43.2)	
Largest nodule size (cm)	5.5 (4.3-9.7)	5.6 (2.4-8.2)	.168
Portal vein invasion (n/%)	9 (25.0)	5 (13.5)	.213
Hepatic vein invasion (n/%)	1 (2.8)	1 (2.7)	.984
ECOG performance status (n/%)			.044
0	10 (27.8)	17 (45.9)	
1	17 (47.2)	17 (45.9)	
2	9 (25.0)	2 (5.4)	
3	0 (0.0)	1 (2.8)	
Child-Pugh stage (n/%)			.803
A	30 (83.3)	30 (81.1)	
B	6 (16.7)	7 (18.9)	
BCLC stage (n/%)			.203
A	9 (25.0)	13 (35.1)	
B	17 (47.2)	18 (48.6)	
C	10 (27.8)	6 (16.3)	
Blood routine			
WBC ($\times 10^9$ cell/L)	5.6 (4.2-6.7)	3.9 (3.3-6.9)	.290
RBC ($\times 10^{12}$ cell/L)	3.8 (3.5-4.4)	4.6 (3.8-5.1)	.020
ANC (%)	5.6 (2.7-58.1)	2.3 (1.8-4.3)	.002
Hb (g/L)	122.0 (107.5-132.0)	134.5 (119.8-147.8)	.011
PLT ($\times 10^9$ cell/L)	131.0 (100.5-215.5)	110.0 (66.5-213.3)	.298
Liver function			
ALB (g/L)	35.6 (31.5-39.3)	35.9 (31.7-38.7)	.787
ALB ≥ 1 ULN (n/%)	0/35 (0.0)	0/36 (0.0)	–
TP (g/L)	63.6 (58.8-67.2)	62.0 (58.7-64.3)	.462
TP ≥ 1 ULN (n/%)	0/35 (0.0)	0/36 (0.0)	–
TBIL ($\mu\text{mol/L}$)	16.6 (11.2-22.8)	16.3 (11.4-29.6)	.982
TBIL ≥ 1 ULN (n/%)	13/35 (36.1)	13/36 (37.1)	.928
TBA (I/L)	8.8 (3.1-30.8)	7.1 (3.4-14.3)	.483
TBA ≥ 1 ULN (n/%)	14/36 (38.9)	12/35 (34.3)	.687
ALT (U/L)	36.0 (23.2-46.8)	35.0 (25.2-52.5)	.756
ALT ≥ 1 ULN (n/%)	15/36 (41.7)	15/35 (42.9)	.919
AST (U/L)	45.4 (33.0-75.0)	48.7 (28.6-89.3)	.954
AST ≥ 1 ULN (n/%)	21/36 (58.3)	20/35 (57.1)	.919
ALP (U/L)	101.0 (81.8-173.0)	97.5 (79.5-131.8)	.488
ALP ≥ 1 ULN (n/%)	12/34 (35.3)	9/34 (26.5)	.431
Kidney function			
BCr ($\mu\text{mol/L}$)	62.6 (52.9-74.4)	64.8 (52.8-77.0)	.585
BUN (mmol/L)	4.7 (3.9-5.5)	4.5 (3.6-5.5)	.377
Tumor markers			
AFP ($\mu\text{g/L}$)	46.5 (4.1-227.6)	35.0 (4.9-228.8)	.392
CEA ($\mu\text{g/L}$)	2.0 (1.1-3.6)	2.0 (1.2-3.5)	.935
CA199 (kU/L)	11.4 (6.4-36.0)	33.0 (6.5-57.5)	.230

(continued)

Table 1. (continued)

Parameters	DEB-TACE Group, N = 36	cTACE Group, N = 37	P Value
Previous treatments			
cTACE (n/%)	16 (44.4)	3 (8.1)	<.001
Surgery (n/%)	3 (8.3)	7 (18.9)	.188
Radiofrequency ablation (n/%)	2 (5.6)	1 (2.7)	.539

Abbreviations: AFP, α -fetoprotein; ALB, albumin; ANC, absolute neutrophil count; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; BCr, blood creatinine; BUN, blood urea nitrogen; CA199, carbohydrate antigen199; CEA, carcinoembryonic antigen; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; HB, hepatitis B; HCC, hepatocellular carcinoma; PLT, platelet; RBC, red blood cell; TBA, total bile acid; TBIL, total bilirubin; TP, total protein; ULN, upper limit of normal; WBC, white blood cell.

^a Data were presented as mean (standard deviation), median (25th-75th quantiles), or count (%). Comparison between 2 groups was determined by *t* test, Wilcoxon rank-sum test or χ^2 test. *P* value <.05 was considered significant, and the significant results are shown in boldface.

Table 2. Comparison of Treatment Response Between DEB-TACE Group and cTACE Group.^a

Items	M1			M3			M6		
	DEB-TACE Group	cTACE Group	<i>P</i> Value	DEB-TACE Group	cTACE Group	<i>P</i> Value	DEB-TACE Group	cTACE Group	<i>P</i> Value
Number of assessed patients	25	28		15	8		9	7	
CR	4 (16.0)	3 (10.7)	.570	3 (20.0)	0 (0.0)	.175	3 (33.3)	1 (14.3)	.383
PR	13 (52.0)	8 (28.6)	.082	12 (80.0)	5 (62.5)	.363	6 (66.7)	3 (42.9)	.341
SD	7 (28.0)	14 (50.0)	.102	0 (0.0)	1 (12.5)	.169	0 (0.0)	1 (14.3)	.242
PD	1 (4.0)	3 (10.7)	.356	0 (0.0)	2 (25.0)	.037	0 (0.0)	2 (28.5)	.086
ORR	17 (68.0)	11 (39.3)	.037	15 (100.0)	5 (62.5)	.011	9 (100.0)	4 (57.1)	.029
DCR	24 (96.0)	25 (89.3)	.356	15 (100.0)	6 (75.0)	.037	9 (100.0)	5 (71.4)	.086
Number of assessed nodules	46	51		26	16		13	9	
CR	8 (17.4)	4 (7.8)	.154	7 (26.9)	3 (18.8)	.131	6 (46.2)	1 (11.1)	.083
PR	21 (45.6)	20 (39.3)	.522	19 (73.1)	7 (43.7)	.546	6 (46.2)	6 (66.7)	.342
SD	17 (37.0)	27 (52.9)	.114	0 (0.0)	5 (31.3)	.002	1 (7.6)	2 (22.2)	.329
PD	0 (0.0)	0 (0.0)	–	0 (0.0)	1 (6.2)	.197	0 (0.0)	0 (0.0)	–
ORR	29 (63.0)	24 (47.1)	.114	26 (100.0)	10 (62.5)	<.001	12 (92.3)	7 (77.8)	.329
DCR	46 (100.0)	51 (100.0)	–	26 (100.0)	15 (93.7)	.197	13 (100.0)	9 (100.0)	–

Abbreviations: CR, complete response; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; DCR, disease control rate; ORR, objective response rate; PD, progression disease; PR, partial response; SD, stable disease.

^a Data were presented as count (%). Comparison between 2 groups was determined by χ^2 test. *P* value <.05 was considered significant, and the significant results are shown in boldface. “–” indicated that the data were unable to be compared due to lack of events.

and 5 in DEB group and 33 and 4 in cTACE group, respectively ($P = .689$). Thirty (83.3%) patients and 6 (16.7%) in DEB-TACE group as well as 30 (81.1%) patients and 7 (18.9%) in cTACE group were at Child-Pugh stages A and B, respectively ($P = .803$). As regard to BCLC stage, 9 patients (25.0%), 17 (47.2%), and 10 (27.8%) were at stages A, B, and C in DEB-TACE group, and 13 patients (35.1%), 18 (48.6%), and 6 (16.3%) were at stages A, B, and C in cTACE group, respectively ($P = .203$). Most importantly, ECOG performance score was higher in DEB-TACE group compared to cTACE group ($P = .044$); and median RBC ($P = .020$) as well as Hb ($P = .011$) were decreased while median ANC ($P = .002$) was increased in DEB-TACE group compared with cTACE group. In addition, the percent of patients with cTACE treatment history in

DEB-TACE group were larger than that in cTACE group ($P < .001$). Other baseline characteristics between 2 groups were displayed in Table 1.

Treatment Response in DEB-TACE Group and cTACE Group

The ORR of patients was elevated in DEB-TACE group compared to cTACE group at M1 (68.0% vs 39.3%, $P = .037$), M3 (100.0% vs 62.5%, $P = .011$) as well as M6 (100.0% vs 57.1%, $P = .029$), and DCR of patients was also increased in DEB-TACE group compared with cTACE group at M3 (100.0% vs 75.0%, $P = .037$; Table 2). As for treatment responses of nodules, there was no difference between 2 groups at M1 or

M6, while at M3, ORR was elevated in DEB-TACE group compared to cTACE group (100.0% vs 62.5%, $P < .001$; Table 2).

Univariate and Multivariate Logistic Regression Model Analyses of Factors Affecting ORR (M1)

Univariate logistic regression model analysis was applied for analyzing factors affecting ORR (M1), which indicated that DEB-TACE was associated with higher possibility of achieving ORR (M1; $P = .040$, Table 3). All factors were further analyzed via multivariate logistic regression model with forward stepwise (conditional) method, illustrating that DEB-TACE was an independent factor for predicting higher possibility of ORR (M1) achievement ($P = .045$, Table 3). As to analyses for factors affecting ORR at M3 and M6, the univariate and multivariate logistic regression were not carried out due to fewer events with treatment response assessments.

Comparison of PFS and OS Between DEB-TACE Group and cTACE Group

K-M curves and log-rank tests disclosed that PFS was more prolonged in DEB-TACE group (25.1 months, 95% CI, 22.0-28.3 months) compared to cTACE group (21.8 months, 95% CI, 17.3-26.2 months; $P = .023$, Figure 1A), while OS between DEB-TACE group (26.3 months, 95% CI, 23.0-29.6 months) and cTACE group (23.9 months, 95% CI, 19.2-28.6 months) was similar ($P = .106$, Figure 1B).

Univariate and Multivariate Cox Proportional Hazards Regression Model Analyses of Factors Affecting PFS

Univariate Cox proportional hazards regression model was applied for analyzing factors affecting PFS, which revealed that DEB-TACE was correlated with better PFS ($P = .030$), while higher Child-Pugh stage ($P = .045$), CEA abnormal ($P = .021$), and CA199 abnormal ($P = .002$) were associated with worse PFS (Table 4). Multivariate Cox proportional hazards regression model analysis using forward stepwise (conditional LR) method was further conducted with all factors included, which suggested that DEB-TACE did not affect PFS, while CA199 abnormal ($P = .008$) was an independent factor for predicting poorer PFS (Table 4).

Univariate and Multivariate Cox Proportional Hazards Regression Model Analyses of Factors Affecting OS

Analysis of factors affecting OS was performed by univariate Cox proportional hazards regression model, which disclosed that DEB-TACE was not associated with OS, and CEA abnormal ($P = .042$) and CA199 abnormal ($P = .022$) were correlated with worse OS (Table 5). All factors were further analyzed in multivariate Cox proportional hazards regression model using forward stepwise (conditional LR) method, and it showed that DEB-TACE did not affect OS, while CA199

Table 3. Factors Affecting ORR (M1) by Logistic Regression Model Analysis.^a

Parameters	P Value	Logistic Regression Model		
		OR	95% CI	
			Lower	Higher
Univariate logistic regression				
DEB-TACE vs cTACE	.040	3.284	1.059	10.186
Age ≥ 60 years	.523	0.701	0.235	2.087
Male	.550	1.773	0.271	11.584
History of drink	.906	0.885	0.115	6.794
History of HB	.241	1.949	0.639	5.946
History of cirrhosis	.662	1.273	0.431	3.758
Multifocal disease	.417	1.594	0.517	4.911
Tumor location: bilobar	.523	0.701	0.235	2.087
Largest nodule size ≥ 7 cm	.564	0.711	0.224	2.262
Portal vein invasion	.367	2.000	0.443	9.023
Hepatic vein invasion	1.000	0.000	0.000	–
Higher ECOG performance status	.313	0.663	0.299	1.471
Higher Child-Pugh stage	.353	0.480	0.102	2.256
Higher BCLC stage	.484	0.763	0.358	1.628
Previous cTACE treatment	.484	0.763	0.358	1.628
Previous surgery	.883	0.880	0.161	4.816
Previous radiofrequency ablation	.999	–	0.000	–
WBC abnormal	.925	0.944	0.289	3.083
RBC abnormal	.140	0.520	0.218	1.240
ANC abnormal	.953	0.956	0.213	4.284
Hb abnormal	.071	2.844	0.913	8.861
PLT abnormal	.540	0.686	0.205	2.295
ALB ≥ 1 ULN	–	–	–	–
TP ≥ 1 ULN	–	–	–	–
TBIL ≥ 1 ULN	.168	2.182	0.720	6.613
TBA ≥ 1 ULN	.434	0.632	0.200	1.995
ALT ≥ 1 ULN	.625	0.749	0.234	2.392
AST ≥ 1 ULN	.726	0.818	0.267	2.510
ALP ≥ 1 ULN	.629	1.333	0.415	4.281
BCr abnormal	1.152	0.190	0.020	1.841
BUN abnormal	.868	1.131	0.264	4.840
AFP abnormal	.252	2.000	0.610	6.553
CEA abnormal	.274	3.579	0.364	35.233
CA199 abnormal	.716	0.778	0.201	3.008
Multivariate logistic regression with forward stepwise (conditional) method				
DEB-TACE vs cTACE	.045	12.000	1.053	136.794

Abbreviations: AFP, α -fetoprotein; ALB, albumin; ALT, alanine aminotransferase; ALP, alkaline phosphatase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; BCr, blood creatinine; BUN, blood urea nitrogen; CA199, carbohydrate antigen199; CEA, carcinoembryonic antigen; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; HB, hepatitis B; ORR, objective response rate; PLT, platelet; RBC, red blood cell; TBA, total bile acid; TBIL, total bilirubin; TP, total protein; ULN, upper limit of normal; WBC, white blood cell.

^a Data were presented as P value, odds ratio (OR), and 95% confidence interval (CI). Factors affecting ORR (M1) were determined by univariate and multivariate logistic regression analyses with forward stepwise (conditional) method. P value $< .05$ was considered significant, and the significant results are shown in boldface. Child-Pugh stage was scored as 0 for A and 1 for B; BCLC stage was scored as 1 for stage A, 2 for stage B, and 3 for stage C; and the logistic analysis was performed based on these definitions. “–” indicated that the value was unable to be calculated due to lack of events.

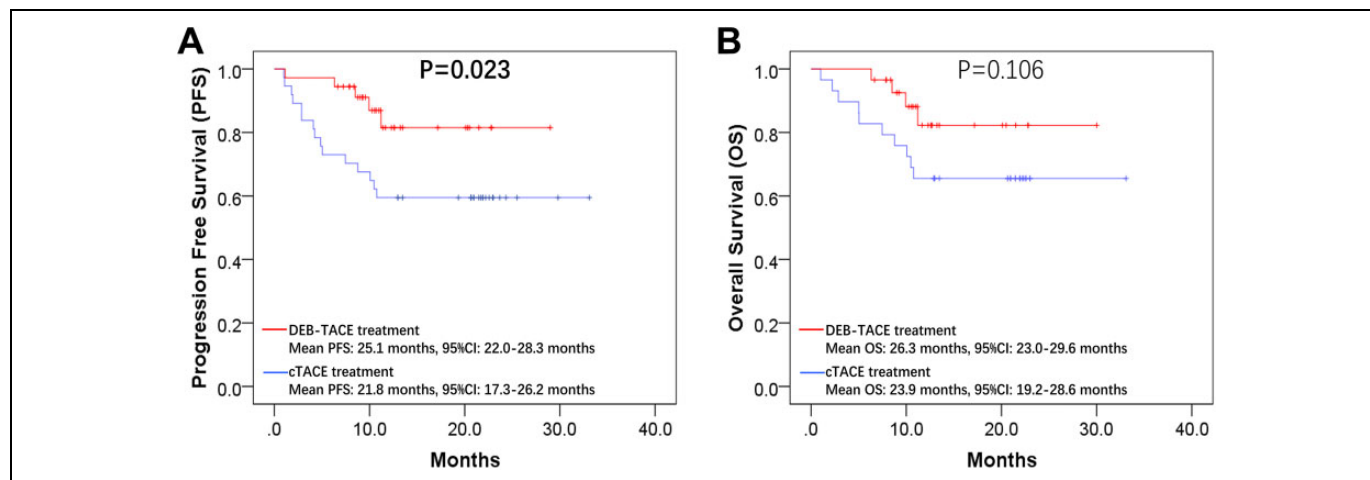


Figure 1. PFS as well as OS in DEB-TACE group and cTACE group. PFS in DEB-TACE group was longer than that in cTACE group (A), while OS between 2 groups was of no difference (B). Survival analysis was performed using Kaplan-Meier method and log-rank test. P value $< .05$ was considered significant, and the significant results are shown in boldface. PFS indicates progression-free survival; OS, overall survival; DEB-TACE, drug-eluting bead transarterial chemoembolization; cTACE, conventional transarterial chemoembolization.

abnormal was an independent factor for predicting poorer OS ($P = .006$, Table 5).

Comparison of Liver Function Indexes (M1) and Their Changes (M1-M0) Between DEB-TACE Group and cTACE Group

The percent of patients presented with TBA ≥ 2 upper limit of normal (ULN) at M1 in DEB-TACE group was increased compared to cTACE group (34.5% vs 7.1%, $P = .011$), while no difference of other liver function indexes between 2 groups was observed ($P_s > .05$, Table 6). In addition, there was no difference of liver function index changes from M1 to M0 between 2 groups either ($P_s > .05$, Figure 2).

Comparison of Adverse Events Between DEB-TACE Group and cTACE Group

No difference was discovered between DEB-TACE group and cTACE group regarding percentages of patients with pain ($P = .467$), nausea/vomiting ($P = .620$), or rise in blood pressure ($P = .307$) during treatment, as well as proportions of patients with pain ($P = .515$), fever ($P = .429$), or nausea/vomiting ($P = .978$) during hospitalization (Table 7).

Discussion

In the current study, we discovered that (1) DEB-TACE using CSM was associated with better treatment response and was an independent factor for predicting higher possibility of ORR achievement; (2) DEB-TACE using CSM was associated with longer PFS; (3) percent of patients with TBA ≥ 2 ULN in DEB-TACE group was higher than that in cTACE group; and (4) no difference of adverse event incidences was found between 2 groups.

The DEB-TACE is a novel type of TACE that uses microspheres as both carriers and embolization agents.^{18,19} A meta-analysis reveals that DEB-TACE using other microspheres (including DC bead or HepaSphere) achieves higher ORR compared with cTACE in patients with HCC, implying the better treatment response of patients with HCC to DEB-TACE over cTACE.¹⁴ As for CSM, it is the first microsphere developed in China used for DEB-TACE; according to an animal experiment, it produces higher concentrations of doxorubicin in targeted tissues while lower concentrations of doxorubicin in plasma than that of cTACE.²⁰ Meanwhile, the treatment response between DEB-TACE using CSM and cTACE is also compared in patients with HCC in a retrospective cohort study, which reveals that compared to cTACE, DEB-TACE using CSM elevates ORR, DCR, and percent of patients with CR, while decreases percent of patients with PD at M3 and M6 posttreatment, indicating that patients with HCC who received DEB-TACE using CSM achieve better treatment response compared to those who received cTACE.¹⁵ In the current study, similar results that ORR of both patients (at M1, M3, and M6) and nodules (at M3), as well as DCR of patients (at M3) were increased in DEB-TACE group compared with cTACE group were observed; what's more, DEB-TACE using CSM was an independent factor for predicting higher possibility of ORR (M1) achievement. The possible explanation might be that DEB-TACE displays a couple of advantages over cTACE, including more constant drug release to tumor tissues, which make DEB-TACE using CSM presents with better efficacy on reducing diameters of tumor tissues than that of cTACE.^{18,21,22}

Several studies compare the long-term survival between patients with HCC who receive DEB-TACE using other microspheres and patients who receive cTACE, some of which reveal that DEB-TACE improves survival compared with cTACE, while other studies discover that DEB-TACE does not provide

Table 4. Factors Affecting PFS by Cox Proportional Hazards Regression Model Analysis.^a

Parameters	Cox Proportional Hazards Regression Model			
	<i>P</i> Value	HR	95% CI	
			Lower	Higher
Univariate Cox regression				
DEB-TACE vs cTACE	.030	0.326	0.118	0.899
Age ≥60 years	.637	0.806	0.329	1.973
Male	.290	2.964	0.397	22.148
History of drink	.694	1.341	0.311	5.791
History of HB	.217	0.575	0.238	1.385
History of cirrhosis	.658	1.220	0.505	2.946
Multifocal disease	.865	0.924	0.368	2.315
Tumor location: bilobar	.735	1.164	0.482	2.810
Largest nodule size ≥7 cm	.782	0.878	0.350	2.202
Portal vein invasion	.210	0.393	0.091	1.694
Hepatic vein invasion	.608	0.048	0.000	5337.204
Higher ECOG performance status	.733	0.903	0.502	1.623
Higher Child-Pugh stage	.045	2.681	1.022	7.034
Higher BCLC stage	.353	0.751	0.410	1.375
Previous cTACE treatment	.470	0.668	0.223	1.998
Previous surgery	.942	1.047	0.307	3.574
Previous radiofrequency ablation	.978	1.029	0.138	7.696
WBC abnormal	.864	1.088	0.413	2.864
RBC abnormal	.763	0.871	0.353	2.148
ANC abnormal	.570	1.400	0.438	4.472
Hb abnormal	.947	0.970	0.393	2.395
PLT abnormal	.407	1.514	0.568	4.034
ALB ≥1 ULN	–	–	–	–
TP ≥1 ULN	–	–	–	–
TBIL ≥1 ULN	.660	0.805	0.306	2.118
TBA ≥1 ULN	.902	1.061	0.417	2.694
ALT ≥1ULN	.408	0.665	0.253	1.749
AST ≥1 ULN	.962	0.978	0.393	2.432
ALP ≥1 ULN	.622	1.279	0.480	3.411
BCr abnormal	.725	0.696	0.092	5.253
BUN abnormal	.862	1.105	0.360	3.392
AFP abnormal	.253	0.573	0.220	1.491
CEA abnormal	.021	3.954	1.231	12.699
CA199 abnormal	.002	6.541	1.961	21.810
Multivariate Cox regression with forward stepwise (conditional LR) method				
CA199 abnormal	.008	10.058	1.820	55.598

Abbreviations: AFP, α -fetoprotein; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; BCr, blood creatinine; BUN, blood urea nitrogen; CA199, carbohydrate antigen199; CEA, carcinoembryonic antigen; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; HB, hepatitis B; PLT, platelet; TBA, total bile acid; TBIL, total bilirubin; TP, total protein; RBC, red blood cell; WBC, white blood cell; ULN, upper limit of normal.

^a Data were presented as *P* value, hazards ratio (HR), and 95% confidence interval (CI). Factors affecting progression-free survival (PFS) were determined by univariate and multivariate Cox proportional hazards regression analyses with forward stepwise (conditional LR) method. *P* value <.05 was considered significant, and the significant results are shown in boldface. “–” indicated that the value was unable to be calculated due to lack of events.

survival benefits over cTACE; as to DEB-TACE using CSM, it hasn't been compared with cTACE in patients with HCC until now.^{13,23-26} Therefore, whether DEB-TACE is more effective than cTACE in improving survival of patients with HCC remains controversial, especially for DEB-TACE using CSM. To clarify, we conducted the current study, which illustrated that PFS was more favorable in DEB-TACE group compared to cTACE group, and univariate Cox proportional hazards

regression model analysis disclosed that DEB-TACE using CSM was associated with better PFS in patients with HCC. Our results might be explained by that, as previously described, CSM presents with high drug-loading efficiency, and DEB-TACE itself provides more constant drug concentration in tumor tissues than that of cTACE, which necrotizes the tumor tissue more effectively, thereby alleviates clinical symptoms while improving treatment response and subsequently

Table 5. Factors Affecting OS by Cox Proportional Hazards Regression Model Analysis.^a

Parameters	Cox Proportional Hazards Regression Model			
	P Value	HR	95% CI	
			Lower	Higher
Univariate Cox regression				
DEB-TACE vs cTACE	.119	0.397	0.124	1.267
Age ≥60 years	.601	1.323	0.464	3.774
Male	.616	1.684	0.220	12.890
History of drink	.256	2.395	0.530	10.816
History of HB	.115	0.426	0.147	1.231
History of cirrhosis	.904	1.067	0.374	3.043
Multifocal disease	.941	0.959	0.321	2.863
Tumor location: bilobar	.420	1.540	0.540	4.395
Largest nodule size ≥7 cm	.668	1.270	0.426	3.791
Portal vein invasion	.551	0.633	0.141	2.838
Hepatic vein invasion	.713	0.048	0.000	–
Higher ECOG performance status	.791	0.904	0.430	1.903
Higher Child-Pugh stage	.105	2.627	0.816	8.457
Higher BCLC stage	.729	0.882	0.435	1.790
Previous cTACE treatment	.514	0.654	0.182	2.347
Previous surgery	.633	1.441	0.321	6.461
Previous radiofrequency ablation	.502	2.007	0.262	15.381
WBC abnormal	.514	1.451	0.474	4.436
RBC abnormal	.886	0.923	0.309	2.760
ANC abnormal	.645	1.375	0.355	5.324
Hb abnormal	.629	1.310	0.438	3.917
PLT abnormal	.794	1.171	0.357	3.839
ALB ≥1 ULN	–	–	–	–
TP ≥1 ULN	–	–	–	–
TBIL ≥1 ULN	.510	0.673	0.207	2.186
TBA ≥1 ULN	.614	0.738	0.227	2.398
ALT ≥1 ULN	.126	0.365	0.100	1.327
AST ≥1 ULN	.425	1.616	0.498	5.249
ALP ≥1 ULN	.962	0.972	0.299	3.156
BCr abnormal	.867	0.839	0.108	6.507
BUN abnormal	.173	2.303	0.693	7.652
AFP abnormal	.108	0.390	0.123	1.232
CEA abnormal	.042	3.982	1.052	15.081
CA199 abnormal	.022	5.060	1.264	20.246
Multivariate Cox regression with forward stepwise (conditional LR) method				
CA199 abnormal	.006	13.298	2.074	85.253

Abbreviations: AFP, α -fetoprotein; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; BCr, blood creatinine; BUN, blood urea nitrogen; CA199, carbohydrate antigen199; CEA, carcinoembryonic antigen; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; HB, hepatitis B; PLT, platelet; RBC, red blood cell; TBA, total bile acid; TBIL, total bilirubin; TP, total protein; ULN, upper limit of normal; WBC, white blood cell.

^a Data were presented as *P* value, hazards ratio (HR), and 95% confidence interval (CI). Factors affecting overall survival (OS) were determined by univariate and multivariate Cox proportional hazards regression analyses with forward stepwise (conditional LR) method. *P* value <.05 was considered significant, and the significant results are shown in boldface. “–” indicated that the value was unable to be calculated due to lack of events.

prolonging PFS in patients with HCC.^{15,20,27} In the current study, we also found that the OS between 2 groups was similar, which might be due to that the relatively small sample size decreased the statistical power, and OS was affected by so many factors that decreased the influence of TACE option (DEB-TACE vs cTACE) on OS. Meanwhile, we observed that CA199 abnormal was an independent factor for predicting poorer PFS and OS, which is also reported by many other studies.²⁸⁻³⁰ As CA199 is highly expressed in tumor tissues

in various cancers, it is reasonable for CA199 being served as a biomarker for predicting worse prognosis of patients with cancer, including patients with HCC.³¹⁻³³

As to liver function indexes, they are routinely measured for monitoring liver injury in patients with HCC who receive TACE treatment.^{15,24,34} Most of the studies find that DEB-TACE by other microspheres is similar to or better than that of cTACE in terms of liver injury postoperation; moreover, an interesting study compared the liver function indexes between

Table 6. Liver Function Testing at 1-Month (M1) Post-treatment.^a

Parameters	DEB-TACE Group	cTACE Group	P Value
ALB (g/L)	35.4 (30.7-38.3)	35.7 (32.2-37.9)	.792
ALB ≥1 ULN (n/%)	1/29 (3.4)	0/28 (0.0)	.322
ALB ≥2 ULN (n/%)	0/29 (0.0)	0/28 (0.0)	–
ALB ≥3 ULN (n/%)	0/29 (0.0)	0/28 (0.0)	–
TP (g/L)	62.9 (60.6-70.0)	63.0 (59.5-68.5)	.708
TP ≥1 ULN (n/%)	0/29 (0.0)	0/28 (0.0)	–
TP ≥2 ULN (n/%)	0/29 (0.0)	0/28 (0.0)	–
TP ≥3 ULN (n/%)	0/29 (0.0)	0/28 (0.0)	–
TBIL (μmol/L)	17.0 (13.1-20.8)	15.1 (11.1-24.1)	.702
TBIL ≥1 ULN (n/%)	9/29 (31.0)	11/28 (39.3)	.514
TBIL ≥2 ULN (n/%)	3/29 (10.3)	3/28 (10.7)	.964
TBIL ≥3 ULN (n/%)	1/29 (3.4)	1/28 (3.6)	.980
TBA (I/L)	14.1 (5.4-33.5)	6.0 (2.0-18.3)	.125
TBA ≥1 ULN (n/%)	16/29 (55.2)	9/28 (32.1)	.080
TBA ≥2 ULN (n/%)	10/29 (34.5)	2/28 (7.1)	.011
TBA ≥3 ULN (n/%)	7/29 (24.1)	2/28 (7.1)	.163
ALT (U/L)	41.2 (23.8-56.9)	38.1 (24.5-52.9)	.503
ALT ≥1 ULN (n/%)	15/29 (51.7)	11/28 (39.3)	.346
ALT ≥2 ULN (n/%)	4/29 (13.8)	2/28 (7.1)	.413
ALT ≥3 ULN (n/%)	1/29 (3.4)	0/28 (0.0)	.322
AST (U/L)	50.4 (30.4-64.5)	45.3 (31.3-63.9)	.566
AST ≥1 ULN (n/%)	19/29 (65.5)	15/28 (53.6)	.358
AST ≥2 ULN (n/%)	6/29 (20.7)	3/28 (10.7)	.302
AST ≥3 ULN (n/%)	2/29 (6.9)	2/28 (7.1)	.971
ALP (U/L)	120.0 (94.0-178.0)	102.0 (80.0-140.0)	.139
ALP ≥1 ULN (n/%)	12/27 (44.4)	9/27 (33.3)	.402
ALP ≥2 ULN (n/%)	3/27 (11.1)	4/27 (14.8)	.685
ALP ≥3 ULN (n/%)	0/27 (0.0)	0/27 (0.0)	–

Abbreviations: ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; TBA, total bile acid; TBIL, total bilirubin; TP, total protein; ULN, upper limit of normal.

^a Data were presented as median (25th-75th quantiles) or count (%). Comparison between 2 groups was determined by Wilcoxon rank-sum test or χ^2 test. *P* value <.05 was considered significant, and the significant results are shown in boldface. “–” indicated that the data were unable to be compared due to lack of events.

patients with HCC who receive DEB-TACE using CSM and patients who receive cTACE, which subsequently suggests that ALT, AST, and TBIL levels are decreased in patients receiving DEB-TACE using CSM compared to those receiving cTACE.^{15,24,34} In the current study, most of liver function indexes between 2 groups were similar, indicating that DEB-TACE using CSM does not cause long-term liver injury compared with cTACE. Whereas percent of patients with TBA ≥2ULN in DEB-TACE group was higher than that in cTACE group. The possible reason might be that percent of patients with cTACE treatment history was larger in DEB-TACE group compared with cTACE group, and patients who had cTACE treatment history are more easily to have their liver injured during TACE treatment compared to those who had no cTACE treatment history; therefore, percent of patients with TBA ≥2ULN in DEB-TACE group was higher than that in cTACE group.

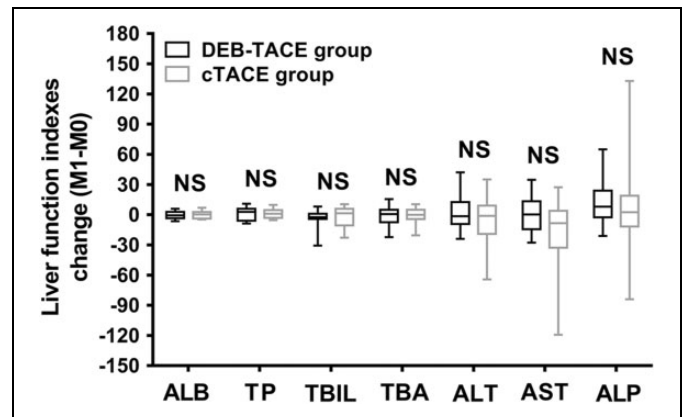


Figure 2. Liver function index change (M1-M0) in DEB-TACE group and cTACE group. All the ALB, TP, TBIL, TBA, ALT, AST, and ALP changes (M1-M0) between DEB-TACE group and cTACE group were similar. Comparison between 2 groups was performed by Wilcoxon rank-sum test. *P* value <.05 was considered significant, and the significant results are shown in boldface. DEB-TACE indicates drug-eluting bead transarterial chemoembolization; cTACE, conventional transarterial chemoembolization; ALB, albumin; TP, total protein; TBIL, total bilirubin; TBA, total bile acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

Table 7. Adverse Events Occurred During Operation and Hospitalization.^a

Parameters	DEB-TACE Group, N = 36	cTACE Group, N = 37	P Value
During treatment			
Pain (n/%)	6 (16.7)	4 (10.8)	.467
Nausea/vomiting (n/%)	3 (8.3)	2 (5.4)	.620
Rise in blood pressure (n/%)	1 (2.7)	0 (0.0)	.307
During hospitalization			
Pain (n/%)	8 (22.2)	6 (16.2)	.515
Fever (n/%)	5 (13.9)	3 (8.1)	.429
Nausea/vomiting (n/%)	2 (5.6)	2 (5.4)	.978

Abbreviations: cTACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization.

^a Data were presented as count (%). Comparison between 2 groups was determined by χ^2 test. *P* value <.05 was considered significant.

A few studies assess the safety of DEB-TACE using CSM in patients with HCC, which disclose that postembolization syndrome (including pain, fever, and vomiting) was the most common adverse events, most of which are mild and manageable postoperation, implying the good safety of DEB-TACE using CSM in patients with HCC.^{15,27} Partly in line with these studies, adverse events in the current study included pain, nausea/vomiting, rise in blood pressure as well as fever, and the incidences of these adverse events between DEB-TACE group and cTACE group were of no difference, implying that DEB-TACE using CSM was equally safe compared to cTACE in treating patients with HCC. However, the incidence of pain in our study was relatively lower than that of a previous study, which might

be due to the fact that (1) patients in the previous study are less severe than those in our study, including lower tumor distribution, smaller largest nodule size, and lower ECOG performance status, which meant that the pain threshold of patients in the previous study might be lower compared to those in our study; thus, the patients in previous study were easier to feel pain compared with those in our study; (2) percent of patients with surgery history in their study are higher than that in our study; therefore, patients in their study are more likely to be influenced by previous surgical wound, which also contributed to decreased pain incidence in our study compared to their study.

There were some limitations in the current study: (1) The sample size in our study was relatively small, which might result in a lower statistical power. However, considering that CSM is a novel microsphere that was launched recently (in 2015), the number of patients who received DEB-TACE treatment using CSM is very limited; besides, those patients who lost follow-up were excluded from the study due to the lack of follow-up records. Except for the small sample size, this study was a retrospective cohort study without randomization, which might cause selection bias; hence, future study with randomized design was needed. (2) Patients in this study were mainly from South China, which might also bring in selection bias. (3) As a cohort study, some baseline characteristics were different between DEB-TACE and cTACE group, which would cause compounding factors, while we applied multivariate analysis to reduce their influence. (4) A portion of patients who lost follow-up were excluded from this study due to the lack of follow-up records; thus, treatment response was not assessed in all patients at M1, M3, and M6, this might cause selection bias; what's more, the follow-up duration was relatively short, which disenabled us to compare the long-term efficacy between DEB-TACE and cTACE. Therefore, prospective study with stricter follow-up schedule and longer follow-up duration was needed in the future. (5) DEB-TACE with different diameters (100-300 and 300-500 μm) in this study might present with different efficacies and safeties, which might cause confounding bias. However, the use of CSM with different diameters was decided by patients' characteristics, which suggested that it was unsuitable for all patients with HCC to use CSM with the same diameter.

In conclusion, DEB-TACE using CSM presents with better treatment response and PFS while equal safety compared to cTACE in treating patients with HCC.

Authors' Note

Hua Xiang and Lin Long contributed equally to this work.


Declaration of Conflicting Interests

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ORCID iD

Yongjin Zhang, MM  <https://orcid.org/0000-0002-8979-8826>

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