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Original Article

Comparison of treatment efficacy and safety between drug-eluting bead transarterial chemoembolization with CalliSpheres® microspheres and conventional transarterial chemoembolization as first-line treatment in hepatocellular carcinoma patients

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Abstract: We aimed to compare the treatment response, survivals and safety of drug-eluting bead (DEB) transarterial chemoembolization (TACE) with CalliSpheres® microspheres (CSM) and conventional TACE (cTACE) as first-line treatment in Chinese HCC patients. 192 HCC patients from multiple centers received DEB-TACE with CSM or cTACE treatment as first-line treatment were included and assigned to DEB-TACE group (N=94) or cTACE group (N=98) accordingly. Treatment response was assessed at 1 month (M1), M3 and M6 after treatment. Progression-free survival (PFS) and overall survival (OS) was evaluated. Liver function indexes and adverse events were recorded. Complete response (CR) and objective response rate (ORR) were higher, while disease control rate (DCR) rate was similar in DEB-TACE group compared with cTACE group, and further multivariate logistic regression analysis validated that DEB-TACE vs cTACE independently predicted higher ORR. For survivals, no difference in PFS or OS was observed between DEB-TACE and cTACE groups, and multivariate Cox's proportional hazards regression revealed that DEB-TACE vs cTACE was not correlated with PFS or OS either. Additionally, no difference in liver function indexes at M1 or changes of liver function indexes from M0 to M1 between DEB-TACE and cTACE groups after treatment was observed, whereas DEB-TACE resulted in higher incidence of pain and fever during treatment or hospitalization. DEB-TACE with CSM discloses better treatment response, similar survival profiles and equal liver function injury but increased incidence of short-term adverse events than cTACE as the first-line therapy in treating HCC patients.

Keywords: DEB-TACE, HCC, tumor response, survival profiles, safety

Introduction

Hepatocellular carcinoma (HCC) is the primary epithelial tumor of the liver mainly resulted from chronic liver diseases of viral infection or alcohol abuse, which is ranked as the second cause of cancer death globally [1-4]. In China, it presents with the highest incidence rate due to the top occurrence of hepatitis B virus infection and death rate around 24.6 per 100,000, which is a serious problem threatening people's health and taking up a huge amount of medical resources annually [3, 5, 6]. As common therapies, surgical resection as well as liver transplantation are effective in managing disease and improving survivals in HCC patients, whereas these therapeutic approaches are just applicable in a small proportion of HCC patients on

account of late diagnosis, lack of liver sources or severe distant metastasis [7]. Therefore, locoregional therapies that are suitable for unresectable HCC is necessary to be investigated to improve survivals and achieve patients' well-being.

In clinical practice, transarterial chemoembolization (TACE) has become the first-line therapeutic selection for intermediate stage HCC according to the Barcelona Clinic Liver Cancer (BCLC) staging system, benefiting from the highly local drug release, low peripheral concentration as well as the blocking effect on tumor blood supply [8]. Conventional TACE (cTACE) is one of common drug delivery system and involves injection of anti-cancer drugs (e.g. pirarubicin and doxorubicin) with drug carriers (e.g. lipiodol) and the embolization agents (e.g. gelatin) into the tumor feeding artery. Considering relatively high systemic toxicity from cTACE, another drug delivery system drug-eluting bead TACE (DEB-TACE) uses microspheres to load drugs and more precisely and slowly release drugs, which could not only embolize the targeted arteries to block nutrition supply for tumor, but also result in better localization of the drugs as well as less systemic toxicity in HCC patients [9]. The differences in treatment response and safety between DEB-TACE and cTACE in treatment of HCC have already been investigated, whereas due to that majority of HCC patients enrolled in previous studies are with HCC treatment history, there is still a lack of knowledge comparing the efficacy of DEB-TACE and cTACE as first-line treatment for HCC patients [10, 11]. Moreover, considering that CalliSpheres® microspheres (CSM) is the first DEB developed in China with good loading and releasing profiles as well as satisfied biocompatibility, and its influence on treatment outcomes in HCC patients is less investigated [12]. Thus, this multi-center, retrospective registry cohort study aimed to compare the treatment response, survival profiles and safety between DEB-TACE with CSM and cTACE as the first-line treatment in Chinese HCC patients.

Methods

Patients

This study included 192 HCC patients who received DEB-TACE or cTACE treatment as first-line treatment for HCC, and all patients came from the DECTH study (Drug-Eluting beads transarterial chemoembolization versus Conventional Transarterial chemoembolization for Hepatocellular carcinoma), which was a multi-center, retrospective cohort study with the purpose of comparing the efficacy and safety between DEB-TACE treatment and cTACE treatment in Chinese HCC patients and was approved by Institutional Review Board at each participating center. Patients in the present study were from eight medical centers (Table S1), and the inclusion criteria were as follows: (1) diagnosed as primary HCC confirmed by clinical and pathological findings; (2) aged at least 18 years old; (3) treatment-naïve patients for HCC; (4) underwent DEB-TACE or cTACE treatment; (5) with complete data of demography, history, diagnosis, clinic, pathology, treatment, measurement and assessment. The exclusion criteria were: (1) patients who were diagnosed as diffuse HCC, hepatobiliary cell carcinoma, mixed cell carcinoma or lamellar cell carcinoma; (2) patients with history of liver transplantation or other malignancies; (3) patients who lost follow up without any follow-up data; (4) patients who switched treatment between DEB-TACE and cTACE within 6 months.

Data collection

After the written informed consents were obtained from the eligible patients or their statutory guardians, patients' data were extracted from electronic medical records and Medical Records Department, which included the demographic characteristics, medical history, clinical features, laboratory indexes of blood routine, liver function and kidney function, tumor marker indexes, previous treatments, the records of equipment and drugs used in DEB-TACE and cTACE procedures, assessment of treatment response, documentation of adverse events and follow ups of patients' survivals. Patients' baseline information were collected including: (1) demographic characteristics: age and gender; (2) medical history: drink, hepatitis B (HB), hepatitis C (HC) and cirrhosis; (3) clinical features: tumor location (unilobar or bilobar), tumor distribution (multifocal disease or unifocal disease), 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; (4) laboratory indexes of blood routine, liver function and kidney function: white blood cell (WBC), red blood cell (RBC), absolute neutrophil count (ANC), haemo-

globin (Hb), platelet (PLT), albumin (ALB), total protein (TP), total bilirubin (TBIL), total bile acid (TBA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood creatinine (BCr) and blood urea nitrogen (BUN); (5) tumor marker indexes: alpha fetoprotein (AFP), carcino-embryonic antigen (CEA) and carbohydrate antigen199 (CA199).

Grouping

Patients who received DEB-TACE treatment were assigned to DEB-TACE group (N=94), and the others who received cTACE treatment were assigned to cTACE group (N=98).

DEB-TACE procedures

In the DEB-TACE procedures, the CSM (Jiangsu Hengrui Medicine Co., Ltd., Jiangsu Province, China) with diameters of 100-300 μm or 300-500 μm were used as chemoembolization reagent carriers and embolization agents. Before the initiation of the operation, the CSM were loaded with pirarubicin (60 mg or 80 mg) using the following methods: firstly, one bottle of CSM was shaken gently to make the CSM equally distributed in the bottle. After that, the CSM and normal saline were extracted by a 20 mL syringe, which was erectly placed at room temperature (RT) for 1-2 min until the CSM were totally precipitated. Meanwhile, the chemoembolization reagent was dissolved into a 20 mg/mL solution, which was mixed with the CSM using a tea joint and then stored by a syringe. Then the syringe containing the mixture of CSM and chemoembolization reagent solution was placed at RT and shaken gently every 5 min within 15 min until the CSM were loaded with chemoembolization reagent. Subsequently, contrast agent with high concentration was added into the mixture as 1:1, 1:1.1 or 1:1.2 ratio, after which the mixture was kept still for 5 min for further application. For massive HCC, if the embolization point was not reached after a bottle of CSM was emptied, another bottle of CSM was used.

ALL DEB-TACE procedures were conducted in the digital subtraction angiography (DSA) room. Before the initiation of DEB-TACE, the targeted tumor was assessed by triphasic computerized tomography (CT) or magnetic resonance imaging (MRI) according to the Milan criteria: if the diameter of targeted tumor was less than 5 cm or the multiple targeted tumors were all with diameters less than 3 cm, the CSM were loaded with 60 mg of pirarubicin per procedure, otherwise the CSM were loaded with 80 mg of pirarubicin [13, 14]. At the initiation of DEB-TACE procedure, the hepatic angiography was performed to detect the tumor supplying vessels using segment or subsegment super selective catheterization, which was conducted as follows: (1) if an area was found with no or scarce vessel, the potential tumor supplying vessel would be identified in this area; (2) then the femoral artery was punctured using Seldinger technique, and microcatheters with diameters ranging from 2.4 F to 5 F (Merit Maestro, Merit Medical System, Inc., Utah, USA) were used for the puncture; (3) subsequently, the CSM were injected through the microcatheter by pulse injection, during which the syringe was rotated or a tea joint was used to avoid the deposition of the CSM. The embolization was stopped when the flow of contrast agent stagnated. After the embolization, the microcatheter was pulled out, and the wound was pressed for hemostasis and then bandaged. In addition, for the patients with massive HCC, DEB-TACE was performed for multiple times.

cTACE procedures

All the cTACE procedures were performed in the DSA room as well. Same as the DEB-TACE procedures, firstly, the hepatic angiography was performed to detect the tumor supplying vessel using the same methods as described above. Secondly, once the tumor supplying vessel was selected, the percutaneous femoral artery was punctured using Seldinger technique. Thirdly, 2.4 F to 5 F microcatheters (Merit Maestro, Merit Medical System, Inc., Utah, USA) were subsequently used for catheterization, and the chemotherapy drug solution (pirarubicin 60 mg or 80 mg, 20 mg/mL), ethiodized poppyseed oil (EPO) (Jiangsu Hengrui Medicine Co., Ltd., Jiangsu Province, China) as drug carriers and Polyvinyl Alcohol (PVA) particles (Cook Medical LLC, Bloomington, USA) as embolization agents were injected into the tumor supplying vessel. Finally, the embolization was stopped when the stenosis of the flow occurred. In addition, the angiography was performed for another time to ensure the EPO/PVA particles were deposited and to detect if there was incomplete embolization.

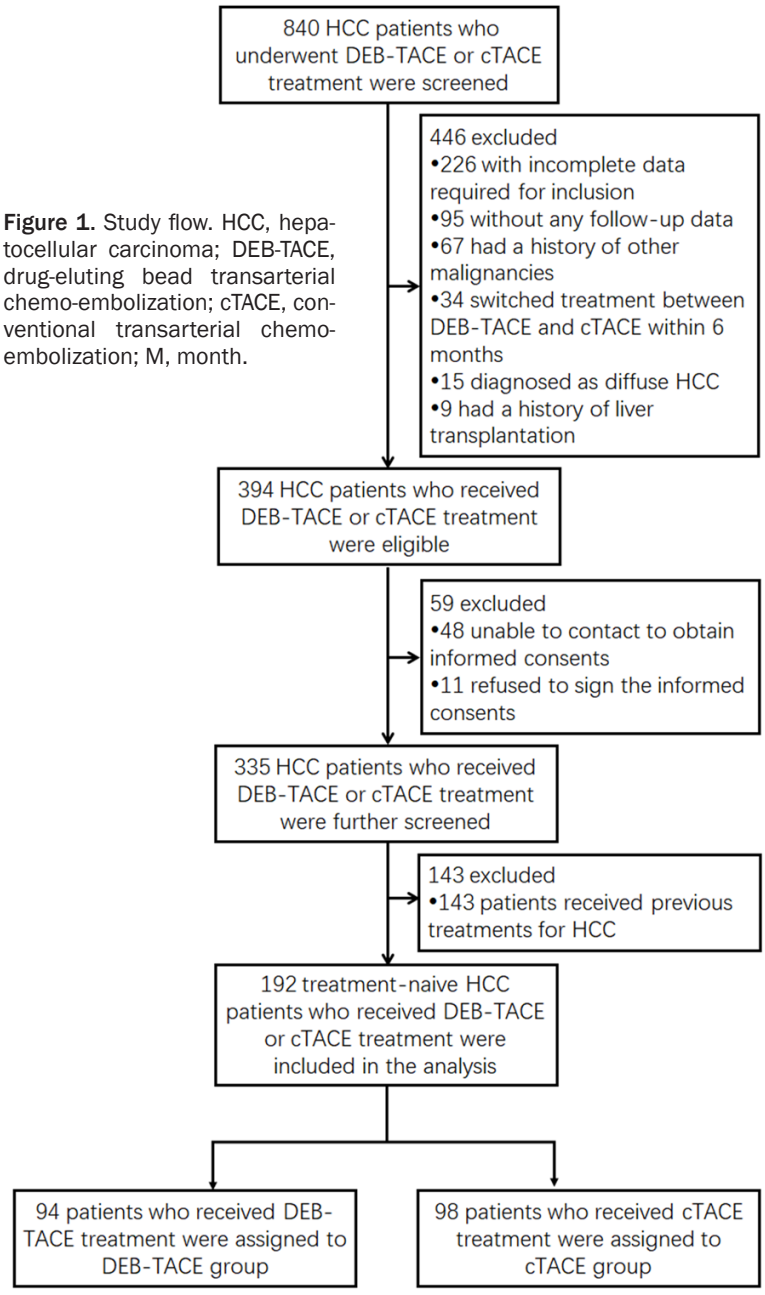

Figure 1. Study flow. HCC, hepatocellular carcinoma; DEB-TACE, drug-eluting bead transarterial chemo-embolization; cTACE, conventional transarterial chemo-embolization; M, month.

Pre-procedure and post-procedure treatments

Pre-procedure and post-procedure treatments were performed in all patients treated by DEB-TACE or cTACE. Pre-procedure treatments were as follows: 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. Post-procedure treatments were as follows: all patients were told to lie on one side and extend the punctured leg for 6-12 h post-embolization. Patients with postoperative nausea and vomiting were treated by tropisetron (IV), and analgesic treatment was given to patients using pethidine, dexamethasone or lidocaine.

Assessment of treatment response

Treatment response of DEB-TACE and cTACE was evaluated at month 1 (M1), M3 or M6 after treatment according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). The response criteria were defined as follows: (1) complete response (CR): 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): any cases that did not qualify either PR or progressive disease (PD); (4) PD: an increase of at least 20% in the sum of the diameters of the viable (enhancing) target lesions. In addition, objective response rate (ORR) was defined as CR+PR, and disease control rate (DCR) was defined as CR+PR+SD.

Assessment of safety

The influence of DEB-TACE or cTACE treatment on liver function was assessed by liver function indexes, which ALT, AST, ALP, TBIL, ALB, TP and TBA, and the liver function indexes were measured at baseline (M0) and 1 month (M1) after treatment. adverse events that occurred during operation and hospitalization were used to

Table 1. Baseline characteristics of HCC patients

Parameters	DEB-TACE group (N=94)	cTACE group (N=98)	*P* value
Age (years)	55.0 ± 12.9	54.7 ± 13.4	0.900
Gender (male/female)	78/16	87/11	0.248
History of drink (n/%)	29 (30.9)	19 (19.4)	0.067
History of HB (n/%)	61 (64.9)	67 (68.4)	0.610
History of HC (n/%)	2 (2.1)	2 (2.0)	0.966
History of cirrhosis (n/%)	39 (41.5)	51 (52.0)	0.143
Tumor location (n/%)			0.415
Unilobar	72 (76.6)	70 (71.4)	
Bilobar	22 (23.4)	28 (28.6)	
Tumor distribution (n/%)			**0.047**
Unifocal	71 (75.5)	61 (62.2)	
Multifocal	23 (24.5)	37 (37.8)	
Largest nodule size (cm)	9.6 (4.8-13.0)	7.5 (3.9-11.1)	0.071
Portal vein invasion (n/%)	35 (37.2)	29 (29.6)	0.261
Hepatic vein invasion (n/%)	22 (23.4)	19 (19.4)	0.497
ECOG performance status (n/%)			**0.017**
0	32 (34.0)	47 (48.0)	
1	47 (50.0)	45 (45.9)	
2	15 (16.0)	5 (5.1)	
3	0 (0.0)	1 (1.0)	
Child-pugh Stage (n/%)			0.621
A	69 (73.4)	75 (76.5)	
B	24 (25.5)	22 (22.5)	
C	1 (1.1)	1 (1.0)	
BCLC Stage (n/%)			0.532
A	22 (23.4)	23 (23.5)	
B	32 (34.0)	40 (40.8)	
C	34 (36.2)	29 (29.6)	
D	6 (6.4)	6 (6.1)	
Blood routine			
WBC (× 10^9 cell/L)	5.1 (3.7-7.3)	5.2 (3.7-7.5)	0.887
RBC (× 10^{12} cell/L)	4.3 (3.6-4.8)	4.4 (3.9-4.8)	0.491
ANC (%)	57.0 (3.5-69.1)	60.6 (4.0-67.3)	0.738
Hb (g/L)	129.0 (110.0-145.0)	132.0 (118.3-142.8)	0.695
PLT (× 10^9 cell/L)	154.0 (78.0-220.0)	157.0 (97.0-240.0)	0.455
Liver function			
ALT (u/L)	43.0 (21.0-72.5)	38.0 (24.7-56.5)	0.720
ALT ≥1 ULN (n/%)	50/93 (53.8)	45/96 (46.9)	0.344
AST (u/L)	53.3 (35.2-86.5)	54.0 (38.0-85.0)	0.528
AST ≥1 ULN (n/%)	65/93 (69.9)	67/96 (69.8)	0.988
ALP (u/L)	127.0 (86.0-174.5)	121.0 (89.0-173.6)	0.886
ALP ≥1 ULN (n/%)	39/83 (47.0)	39/86 (45.3)	0.831
TBIL (umol/L)	18.2 (14.6-24.6)	15.1 (12.3-19.9)	**0.003**
TBIL ≥1 ULN (n/%)	45/93 (48.4)	28/95 (29.5)	**0.008**
ALB (g/L)	36.0 (31.3-40.1)	35.9 (32.6-39.1)	0.967
ALB ≥1 ULN (n/%)	0/93 (0.0)	1/95 (1.1)	0.321
TP (g/L)	66.7 (61.8-71.1)	65.1 (60.8-69.1)	0.090
TP ≥1 ULN (n/%)	6/93 (6.5)	2/93 (2.2)	0.148

TBA (I/L)	11.0 (46.0-23.4)	8.4 (4.5-19.5)	0.547
TBA ≥1 ULN (n/%)	47/91 (51.6)	40/87 (46.0)	0.449
Kidney function			
BCr (umol/L)	71.0 (61.5-80.0)	73.0 (61.0-81.9)	0.671
BUN (mmol/L)	4.8 (3.9-5.8)	4.8 (3.7-6.0)	0.625
Tumor markers			
AFP (μg/L)	255.6 (8.1-1274.8)	127.4 (6.5-1000.0)	0.413
CEA (μg/L)	1.6 (1.1-2.8)	1.9 (1.2-3.3)	0.240
CA199 (ku/L)	21.7 (9.1-32.0)	22.5 (12.0-42.7)	0.403

Data were presented as mean ± standard deviation, median (25^{th}-75^{th} quantiles) or count (%). 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 were shown in boldface. HCC, hepatocellular carcinoma; DEB-TACE, drug-eluting bead transarterial chemoembolization; cTACE, conventional transarterial chemo-embolization; HB, hepatitis b; HC, hepatitis c; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; WBC, white blood cell; RBC, red blood cell; ANC, absolute neutrophil count; Hb, hemoglobin; PLT, platelet; ULN, upper limit of normal; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TBIL, total bilirubin; ALB, albumin; TP, total protein; TBA, total bile acid; BCr, blood creatinine; BUN, blood urea nitrogen; AFP, alpha fetoprotein; CEA, carcino-embryonic antigen; CA199, carbohydrate antigen199.

Table 2. Comparison of treatment response assessed at M1, M3 and M6 after treatment between DEB-TACE group and cTACE group

Items	M1			M3			M6		
	DEB-TACE group	cTACE group	*P* value	DEB-TACE group	cTACE group	*P* value	DEB-TACE group	cTACE group	*P* value
Number of assessed patients	57	82		44	40		27	31	
CR	7 (12.3)	5 (6.1)	0.202	9 (20.5)	0 (0.0)	**0.002**	5 (18.5)	2 (6.5)	0.159
PR	33 (57.9)	31 (37.8)	**0.019**	23 (52.3)	17 (42.5)	0.370	15 (55.6)	11 (35.5)	0.125
SD	12 (21.1)	37 (45.1)	**0.003**	2 (4.5)	17 (42.5)	**<0.001**	4 (14.8)	12 (38.7)	**0.042**
PD	5 (8.7)	9 (11.0)	0.671	10 (22.7)	6 (15.0)	0.368	3 (11.1)	6 (19.3)	0.387
ORR	40 (70.2)	36 (43.9)	**0.002**	32 (72.7)	17 (42.5)	**0.005**	20 (74.1)	13 (41.9)	**0.014**
DCR	52 (91.2)	73 (89.0)	0.671	34 (77.3)	34 (85.0)	0.368	24 (88.9)	25 (80.6)	0.387
Number of assessed nodules	91	134		70	65		42	36	
CR	14 (15.4)	14 (10.4)	0.271	17 (24.3)	7 (10.8)	**0.040**	12 (28.6)	10 (27.8)	0.782
PR	46 (50.5)	47 (35.2)	**0.021**	35 (50.0)	23 (35.4)	0.087	13 (31.0)	0 (0.0)	**<0.001**
SD	31 (30.1)	72 (53.7)	**0.004**	18 (25.7)	33 (50.8)	**0.003**	17 (40.5)	26 (72.2)	**0.050**
PD	0 (0.0)	1 (0.7)	0.409	0 (0.0)	2 (3.1)	0.139	0 (0.0)	0 (0.0)	-
ORR	60 (65.9)	61 (45.5)	**0.003**	52 (74.3)	30 (46.2)	**<0.001**	25 (59.5)	10 (27.8)	**0.007**
DCR	91 (100.0)	133 (99.3)	0.409	70 (100.0)	63 (96.9)	0.139	42 (100.0)	36 (100.0)	-

Data were presented as count (%). Comparison between 2 groups was determined by 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 chemo-embolization; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ORR, objective response rate; DCR, disease control rate.

evaluate the safety profiles including pain, nausea/vomiting, rise in blood pressure and fever. Pain grade was evaluated with the use of numeric rating scale (NRS), and the NRS for pain 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".

Assessment of survivals

According to the follow-up records, the median follow-up duration was 11.4 months (range: 1.0-37.0 months), and the last follow-up date was 2018/3/20. Progression free survival (PFS) was calculated from the time of operation to the time of disease progression or death. Overall survival (OS) was calculated from the time of operation to the time of patient's death.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 statistical software (SPSS Inc., Chicago, USA), and figures were made by GraphPad Prism 6.01 software (GraphPad Software Inc.,

Table 3. Comparison of ORR in subgroup analysis

Items	M1			M3			M6		
	DEB-TACE group	cTACE group	*P* value	DEB-TACE group	cTACE group	*P* value	DEB-TACE group	cTACE group	*P* value
Number of assessed patients	57	82		44	40		27	31	
Age (n/%)									
≥60 years	14 (70.0)	14 (43.8)	0.065	10 (71.4)	11 (64.7)	0.690	9 (100.0)	6 (46.2)	**0.008**
<60 years	26 (70.3)	22 (44.0)	**0.015**	22 (73.3)	6 (26.1)	**0.001**	11 (61.1)	7 (38.9)	0.182
Gender (n/%)									
Male	33 (67.3)	33 (44.6)	**0.013**	21 (67.7)	14 (38.9)	**0.018**	16 (80.0)	11 (39.3)	**0.005**
Female	7 (87.5)	3 (37.5)	**0.039**	11 (84.6)	3 (75.0)	0.659	4 (57.1)	2 (66.7)	0.778
Largest nodule size ≥7 cm (n/%)									
Yes	24 (68.6)	20 (44.4)	**0.031**	14 (58.3)	9 (40.9)	0.238	10 (62.5)	4 (30.8)	0.089
No	16 (72.7)	16 (43.2)	**0.028**	18 (90.0)	8 (44.4)	**0.003**	10 (90.9)	9 (50.0)	**0.025**
Portal vein invasion (n/%)									
Yes	18 (78.3)	12 (52.2)	0.063	9 (69.2)	6 (42.9)	0.168	4 (50.0)	1 (14.3)	0.143
No	22 (64.7)	24 (40.7)	**0.026**	23 (74.2)	11 (42.3)	**0.015**	16 (84.2)	12 (50.0)	**0.019**
Hepatic vein invasion (n/%)									
Yes	10 (66.7)	6 (46.2)	0.274	6 (66.7)	4 (57.1)	0.696	3 (50.0)	2 (66.7)	0.635
No	30 (71.4)	30 (43.5)	**0.004**	26 (74.3)	13 (39.4)	**0.004**	17 (81.0)	11 (39.3)	**0.004**
Child-pugh Stage (n/%)									
A	31 (72.1)	28 (42.4)	**0.002**	24 (75.0)	14 (42.4)	**0.008**	17 (77.3)	10 (40.0)	**0.010**
B/C	9 (64.3)	8 (50.0)	0.431	8 (66.7)	3 (42.9)	0.311	3 (60.0)	3 (50.0)	0.740
BCLC Stage (n/%)									
A/B	20 (64.5)	22 (60.0)	**0.029**	21 (75.0)	10 (40.0)	**0.010**	14 (82.4)	11 (47.8)	**0.026**
C/D	20 (76.9)	14 (51.9)	0.057	11 (68.8)	7 (46.7)	0.213	6 (6.0)	2 (25.0)	0.138
AFP (n/%)#									
≥196.9 μg/L	26 (74.3)	15 (50.0)	**0.043**	17 (73.9)	3 (20.0)	**0.001**	10 (66.7)	2 (18.2)	**0.014**
<196.9 μg/L	11 (57.9)	18 (42.9)	0.276	14 (73.7)	11 (55.0)	0.224	9 (90.0)	10 (52.6)	**0.044**

Data were presented as count (%). Comparison between 2 groups was determined by Chi-square test. *P* value <0.05 was considered significant, and the significant results were shown in boldface. #: AFP was divided by median value (196.9 μg/L). ORR, objective response rate; DEB-TACE, drug-eluting bead transarterial chemoembolization; cTACE, conventional transarterial chemo-embolization; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha fetoprotein.

San Diego, USA). Normally distributed continuous variable was presented as mean value ± standard deviation, skewed distributed continuous variable was presented as median (25^{th}-75^{th} quantiles), and categorized variable was presented as count (percentage). Comparison between two groups was determined by t test, Wilcoxon rank sum test or Chi-square test. Multivariate logistic regression analysis was performed to determine the factors affecting ORR with the use of Forward Stepwise (Conditional) method. Kaplan-Meier method and Log-rank test were applied to determine the difference of survivals between two groups. Factors affecting PFS and OS were determined by multivariate Cox's proportional hazards regression analyses with the Forward Stepwise (Conditional LR) method. All statistical tests were two-sided. *P* value <0.05 was considered significant, and the significant results were shown in boldface.

Results

Study flow

840 HCC patients who underwent DEB-TACE or cTACE treatment were initially screened, whereas 446 patients were excluded (including 226 patients were with incomplete data for inclusion, 95 patients were without any follow-up data, 67 patients had history of other malignancies, 34 patients switched treatment between DEB-TACE and cTACE within 6 months, 15 patients were diagnosed as diffuse HCC, 9 patients had history of liver transplantation) (**Figure 1**). The remaining 394 HCC patients who received DEB-TACE or cTACE treatment were eligible, while 59 of them were excluded (including 48 patients were unable to contact to obtain informed consents and 11 patients refused to sign the informed consents). Following that, 335 HCC patients who received DEB-

Table 4. Factors affecting ORR by multivariate logistic regression model analysis with Forward Stepwise (Conditional) method

Items	Multivariate logistic regression			
	P value	OR	95% CI	
			Lower	Higher
M1				
DEB-TACE vs cTACE	**0.023**	3.180	1.170	8.643
ECOG performance status (≥1 vs 0)	**0.030**	0.334	0.124	0.901
M3				
No independent factors#	-	-	-	-
M6				
No independent factors#	-	-	-	-

Data were presented as *P* value, OR (odds ratio) and 95% CI (confidence interval). Factors affecting ORR were determined by multivariate logistic regression analysis with Forward Stepwise (Conditional) method. *P* value <0.05 was considered significant, and the significant results were shown in boldface. #: There was no independent factor being discovered to affect ORR (M3 and M6) due to lack of the original assessment. ORR, objective response rate; DEB-TACE, drug-eluting bead transarterial chemoembolization; cTACE, conventional transarterial chemo-embolization; ECOG, Eastern Cooperative Oncology Group.

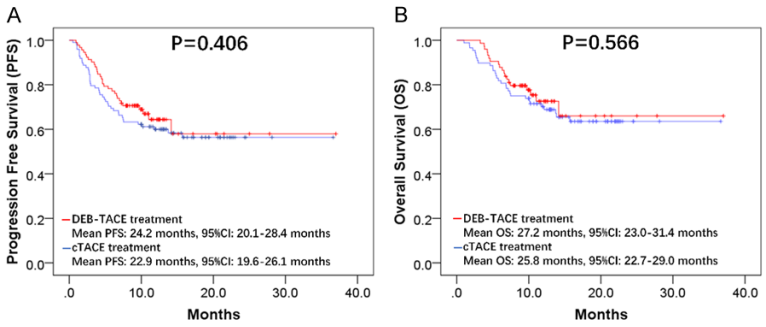

Figure 2. Comparing PFS and OS between DEB-TACE and cTACE groups. No difference in PFS (A) or OS (B) was observed between DEB-TACE and cTACE groups. Kaplan-Meier method was used to evaluate PFS and OS of patients and Log-rank test was applied to determine the difference of PFS and OS between the two groups. *P* value <0.05 was considered significant. PFS, progression free survival; OS, overall survival; DEB-TACE, drug-eluting bead transarterial chemo-embolization; cTACE, conventional transarterial chemo-embolization.

TACE or cTACE treatment were further screened, and 143 patients who received previous treatment for HCC were excluded. Eventually, 192 treatment-naïve HCC patients received DEB-TACE or cTACE treatment as first-line treatment were included in the analysis. 94 patients who received DEB-TACE treatment were assigned to DEB-TACE group, and 98 patients who received cTACE treatment were assigned to cTACE group.

Patients characteristics

The mean age for HCC patients in DEB-TACE group and cTACE group were 55.0 ± 12.9 and 54.7 ± 13.4 years (P=0.900). 78 males and 16 females were included in DEB-TACE group, while 87 males and 11 females were included in cTACE group (P=0.248). The ratio of unifocal tumors (P=0.047) was larger, and ECOG performance score was worse (P=0.017) in DEB-TACE group compared with cTACE group. Additionally, the median concentration of TBIL (P=0.003) and proportion of patients with TBIL ≥1 ULN (P=0.008) was higher in DEB-TACE group compared to cTACE group. Other detailed baseline characteristics of patients were listed in **Table 1**, and no difference was observed between the two groups (all P>0.05).

Comparison of treatment response between DEB-TACE group and cTACE group at M1, M3 and M6 after treatment

At M1 after treatment, 57 patients in DEB-TACE group and 82 patients in cTACE group were assessed for treatment response (**Table 2**), and higher ORR (P=0.002) but no difference of CR (P=0.202) or DCR (P=0.671) was observed in DEB-TACE group compared with cTACE group. At M3, 44 patients in DEB-TACE group and 40 patients in cTACE group were included, and CR rate (P=0.002) as well as ORR (P=0.005) were higher, whereas DCR was similar (P=0.368) in DEB-TACE group compared to cTACE group. At M6, 27 patients in DEB-TACE group and 31 patients in cTACE group were assessed, and ORR (P=0.014) was elevated, while no difference of CR (P=0.159) or DCR (P=0.387) was presented in DEB-TACE group compared with cTACE group.

As for the assessment based on nodules, 91 nodules in DEB-TACE group and 134 nodules in cTACE group were assessed at M1 after treatment, and ORR (P=0.003) was improved, while CR (P=0.271) and DCR (P=0.409) were similar

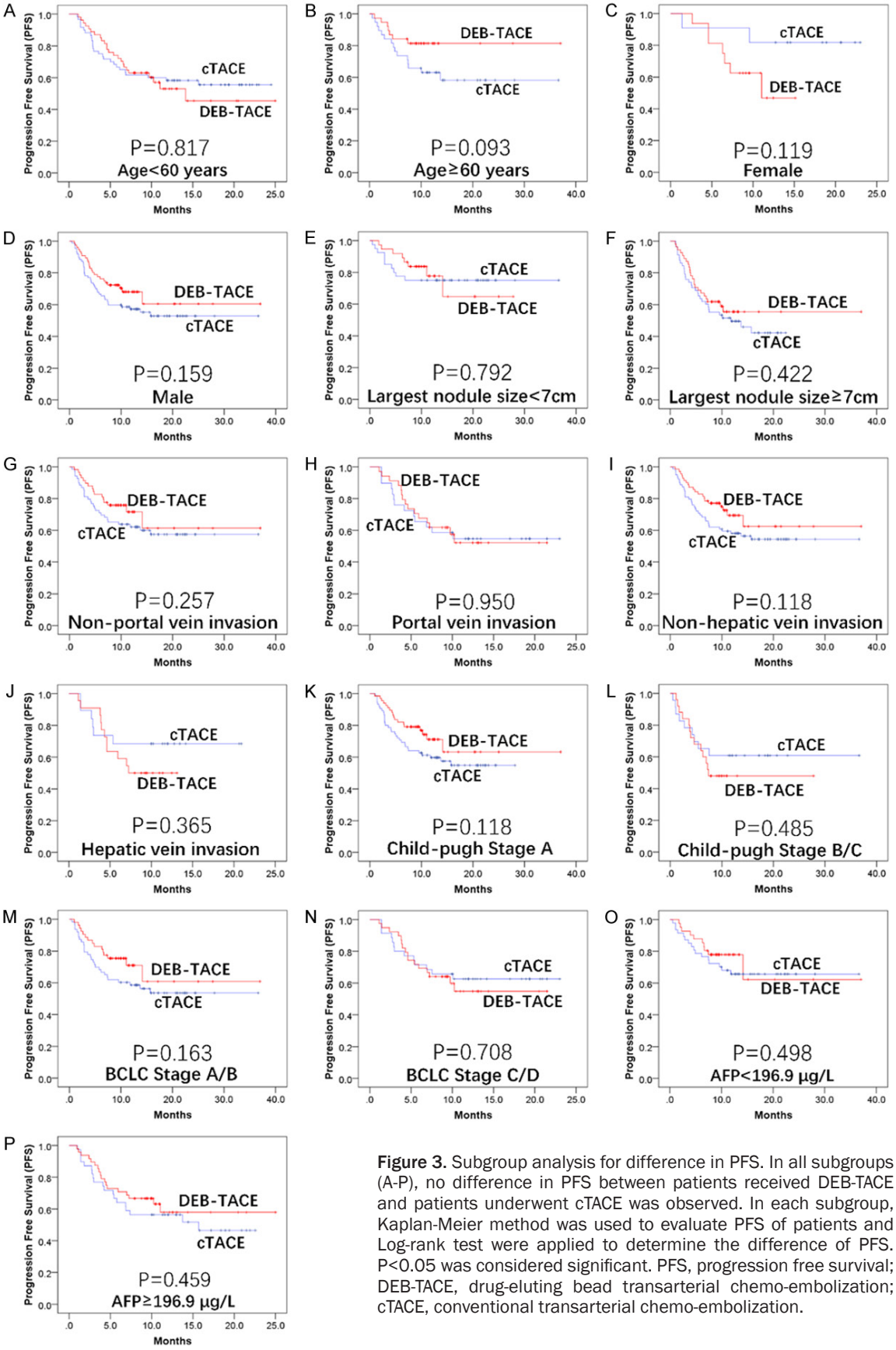

Figure 3. Subgroup analysis for difference in PFS. In all subgroups (A-P), no difference in PFS between patients received DEB-TACE and patients underwent cTACE was observed. In each subgroup, Kaplan-Meier method was used to evaluate PFS of patients and Log-rank test were applied to determine the difference of PFS. P<0.05 was considered significant. PFS, progression free survival; DEB-TACE, drug-eluting bead transarterial chemo-embolization; cTACE, conventional transarterial chemo-embolization.

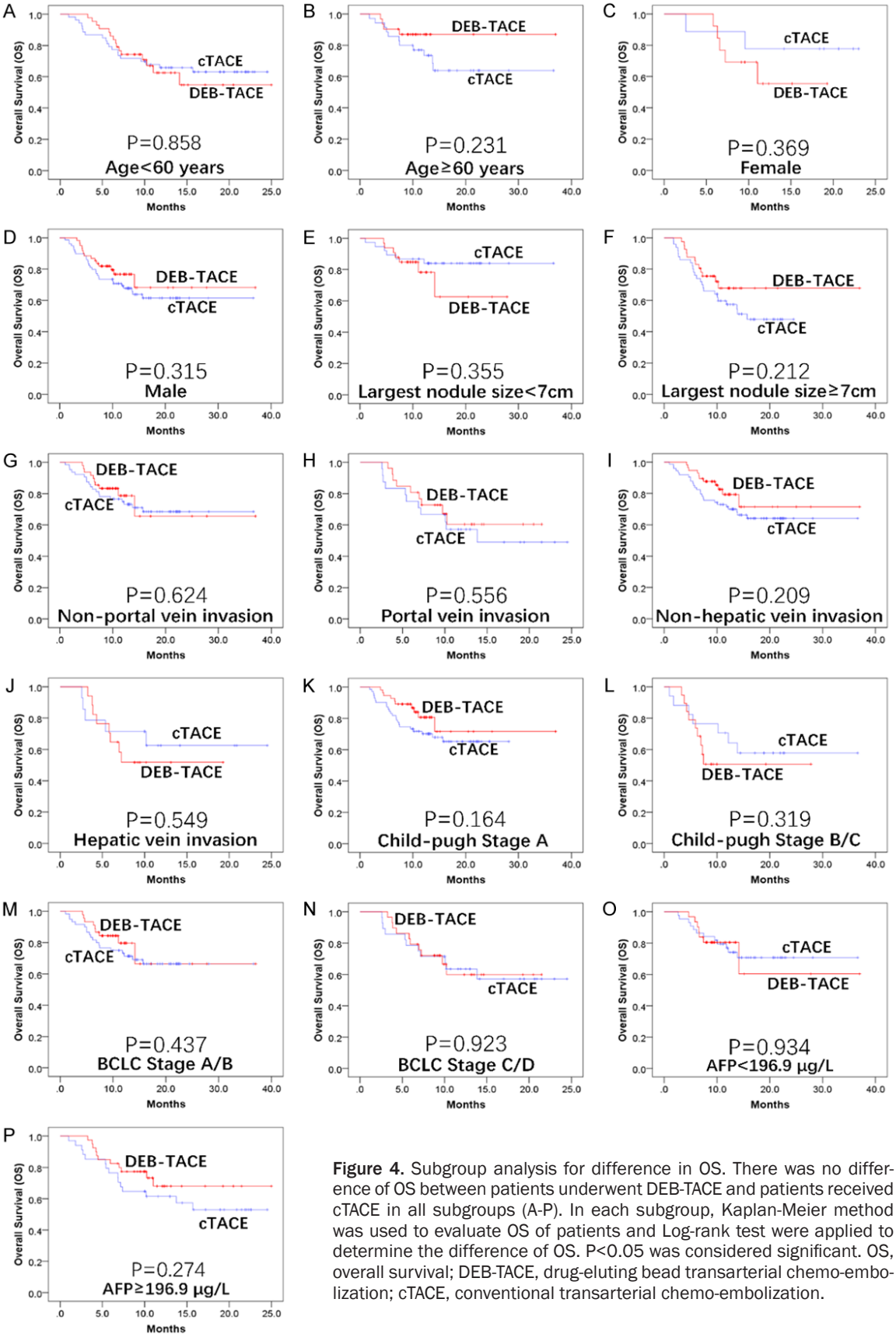

Figure 4. Subgroup analysis for difference in OS. There was no difference of OS between patients underwent DEB-TACE and patients received cTACE in all subgroups (A-P). In each subgroup, Kaplan-Meier method was used to evaluate OS of patients and Log-rank test were applied to determine the difference of OS. P<0.05 was considered significant. OS, overall survival; DEB-TACE, drug-eluting bead transarterial chemo-embolization; cTACE, conventional transarterial chemo-embolization.

Table 5. Multivariate Cox's proportional hazards regression model analysis of factors affecting PFS and OS with Forward Stepwise (Conditional LR) method

Parameters	Multivariate Cox's regression			
	P value	HR	95% CI	
			Lower	Higher
PFS				
Largest nodule size ≥7 cm	**0.004**	3.668	1.532	8.783
OS				
Largest nodule size ≥7 cm	**0.004**	4.884	1.669	14.293
Child-pugh Stage (B/C vs A)	**0.006**	3.045	1.381	6.712
AFP abnormal	**0.038**	3.121	1.065	9.142

Data were presented as *P* value, HR (hazards ratio) and 95% CI (confidence interval). Factors affecting PFS and OS were determined by multivariate Cox's proportional hazards regression analysis with Forward Stepwise (Conditional LR) method. *P* value <0.05 was considered significant, and the significant results were shown in boldface. PFS, progression free survival; OS, overall survival; AFP, alpha fetoprotein.

in DEB-TACE group compared with cTACE group. At M3, 70 nodules from DEB-TACE group and 65 nodules from cTACE group were analyzed, and higher CR rate (P=0.040) as well as ORR (P<0.001) but no difference in DCR (P=0.139) was observed in DEB-TACE group compared with cTACE group. At M6, 42 nodules from DEB-TACE group and 36 nodules from cTACE group were assessed, and ORR (P=0.007) was higher, whereas CR (P=0.782) and DCR were similar in DEB-TACE group compared with cTACE group.

Subgroup analysis for comparison of ORR

According to previous studies and clinical experiences, several characteristics of HCC patients that were important predictive factors for treatment response to TACE were chosen, and patients were divided into subgroups accordingly (**Table 3**). Subgroup analysis displayed that DEB-TACE achieved higher ORR than cTACE in HCC patients characterized as age <60 years, male, no largest nodule size ≥7 cm, no portal invasion, no hepatic vein invasion, child-pugh stage A, BCLC stage A/B and APF ≥196.9 μg/L.

Factors affecting ORR after treatment in HCC patients

Multivariate logistic regression with Forward Stepwise method disclosed that DEB-TACE independently predicted high ORR (OR=3.180, P=0.023) in HCC patients at M1 after treatment, while ECOG performance score ≥1 was an independent factor predicting lower ORR (OR=0.334, P=0.030) (**Table 4**). No factor independently affecting ORR at M3 or M6 after treatment in HCC patients was discovered due to lack of the original assessment.

Comparison of PFS and OS between DEB-TACE and cTACE groups

There was no difference of PFS between DEB-TACE group (mean PFS: 24.2 months, 95% CI: 20.1-28.4 months) and cTACE group (mean PFS: 22.9 months, 95% CI: 19.6-26.1 months) (P=0.406) (**Figure 2A**). Regarding OS, no difference was observed between DEB-TACE group (mean OS: 27.2 months, 95% CI: 23.0-31.4 months) and cTACE group (mean OS: 25.8, 95% CI: 22.7-29.0 months) (P=0.566) either (**Figure 2B**).

Subgroup analysis for comparison of PFS and OS between DEB-TACE and cTACE groups

As described above, HCC patients were divided into subgroups according to characteristics that were critical predictors for treatment response to TACE, and analyses comparing PFS as well as OS between patients underwent DEB-TACE and patients received cTACE were further performed in each subgroup. In subgroup analysis, there was no difference in PFS (All P>0.05) (**Figure 3A-P**) or OS (All P>0.05) (**Figure 4A-P**) between patients received DEB-TACE and patients underwent cTACE treatments in all subgroups.

Factors affecting PFS and OS by multivariate Cox's proportional hazards regression model analysis with Forward Stepwise (Conditional LR) method

Multivariate Cox's proportional hazards regression analysis revealed that DEB-TACE versus cTACE did not affect PFS or OS, whereas largest nodule size ≥7 cm (HR=3.668, P=0.004) was an independent risk factor for worse PFS in HCC patients; and largest nodule size ≥7 cm (HR=4.884, P=0.004), child-pugh Stage B/C (HR=3.045, P=0.006) and AFP abnormal (HR=3.121, P=0.038) independently predicted poor OS in HCC patients (**Table 5**).

Table 6. Liver function testing at 1 month (M1) post-treatment

Parameters	DEB-TACE group (N=94)	cTACE group (N=98)	*P* value
ALT (u/L)	37.8 (21.0-64.8)	35.0 (21.8-51.7)	0.454
ALT ≥1 ULN (n/%)	33/71 (46.5)	34/90 (37.8)	0.266
ALT ≥2 ULN (n/%)	13/71 (18.3)	8/90 (8.9)	0.078
ALT ≥3 ULN (n/%)	5/71 (7.0)	3/90 (3.3)	0.282
AST (u/L)	55.4 (31.8-85.5)	47.0 (34.8-72.2)	0.583
AST ≥1 ULN (n/%)	47/70 (67.1)	60/90 (66.7)	0.949
AST ≥2 ULN (n/%)	19/70 (27.1)	18/90 (20.0)	0.288
AST ≥3 ULN (n/%)	9/70 (12.9)	10/90 (11.1)	0.735
ALP (u/L)	146.0 (109.0-197.4)	133.0 (101.3-189.0)	0.356
ALP ≥1 ULN (n/%)	40/63 (63.5)	47/85 (55.3)	0.316
ALP ≥2 ULN (n/%)	7/63 (11.1)	11/85 (12.9)	0.736
ALP ≥3 ULN (n/%)	3/63 (4.8)	1/85 (1.2)	0.184
TBIL (umol/L)	17.0 (13.7-24.0)	14.5 (11.0-23.4)	0.053
TBIL ≥1 ULN (n/%)	29/71 (40.8)	34/91 (37.4)	0.652
TBIL ≥2 ULN (n/%)	7/71 (9.9)	6/91 (6.6)	0.448
TBIL ≥3 ULN (n/%)	2/71 (2.8)	5/91 (5.5)	0.406
ALB (g/L)	35.5 (29.6-38.4)	34.9 (30.9-37.9)	0.875
ALB ≥1 ULN (n/%)	1/71 (1.4)	0/91 (0.0)	0.256
ALB ≥2 ULN (n/%)	0/71 (0.0)	0/91 (0.0)	-
ALB ≥3 ULN (n/%)	0/71 (0.0)	0/91 (0.0)	-
TP (g/L)	69.7 (63.1-75.2)	66.4 (62.2-72.5)	0.237
TP ≥1 ULN (n/%)	4/71 (5.6)	7/90 (7.8)	0.592
TP ≥2 ULN (n/%)	0/71 (0.0)	2/90 (2.2)	0.206
TP ≥3 ULN (n/%)	0/71 (0.0)	1/90 (1.1)	0.373
TBA (I/L)	9.7 (5.9-28.4)	11.6 (5.5-22.6)	0.757
TBA ≥1 ULN (n/%)	34/69 (49.3)	45/86 (52.3)	0.706
TBA ≥2 ULN (n/%)	26/69 (37.7)	26/86 (30.2)	0.329
TBA ≥3 ULN (n/%)	16/69 (23.2)	18/86 (20.9)	0.736

Data were presented as median (25^{th}-75^{th} quantiles) or count (%). 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 chemo-embolization; ULN, upper limit of normal; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TBIL, total bilirubin; ALB, albumin; TP, total protein; TBA, total bile acid.

Comparison of liver function between DEB-TACE and cTACE groups

Laboratory indexes for liver function was recorded at M1 after treatment, and there was no difference in levels of liver function indexes including ALT, AST, ALP, TIBL, ALB, TP or TBA (All P>0.05) between DEB-TACE and cTACE groups (**Table 6**). The changes of liver function parameters from M0 to M1 post treatment were also calculated, and no difference was observed between DEB-TACE group and cTACE group either (All P>0.05) (**Table 7**).

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

Compared with cTACE group, higher incidence of pain (P=0.037) was discovered in DEB-TACE group during treatment. And patients from DEB-TACE group occurred with increased incidence of pain (P=0.035) and fever (P=0.023) compared with cTACE group during hospitalization (**Table 8**).

Discussion

In this study comparing the efficacy and safety of DEB-TACE with CSM and cTACE as first-line treatment in HCC patients, we observed that: (1) DEB-TACE group presented with better treatment response compared to cTACE group. (2) No difference was discovered in patients' survival profiles between DEB-TACE and cTACE groups. (3) The effect of DEB-TACE and cTACE on liver function injury was similar, while DEB-TACE was associated with increased occurrence of pain and fever in HCC patients during treatment and hospitalization.

CSM, the first drug-loading microspheres developed in China, are polyvinyl alcohol hydrogel microspheres with different diameters, which are capable of loading drugs by ion-changing, and the advantages of CSM in drug loading and releasing as well as pharmacokinetics have been demonstrated in rabbit liver tissues [12, 15]. Although clinical studies have revealed that DEB-TACE using other beads (such as DC® Beads and LC® Beads) presents better treatment response compared with cTACE in HCC patients, very few but only two available studies compare the treatment response between DEB-TACE with CSM and cTACE and discover that ORR is higher in DEB-TACE group with CSM compared with

Table 7. Change of liver function indexes from baseline (M0) to 1 month (M1) post-treatment (M1-M0)

Parameters	DEB-TACE group (N=94)	cTACE group (N=98)	*P* value
ALT (u/L)	-2.10 (-21.75~11.25)	-3.00 (-23.00~5.75)	0.874
AST (u/L)	-5.18 (-20.00~10.00)	-2.00 (-24.50~11.18)	0.968
ALP (u/L)	14.65 (-7.05~43.00)	5.00 (-10.0~30.25)	0.553
TBIL (umol/L)	-1.86 (-7.30~3.48)	0.95 (-3.65~7.43)	0.226
ALB (g/L)	-1.40 (-4.3~1.83)	-1.50 (-4.55~2.08)	0.874
TP (g/L)	2.04 (-2.20~6.05)	1.35 (-2.80~6.38)	0.824
TBA (l/L)	-0.19 (-7.35~4.73)	1.20 (-3.63~6.53)	0.391

Data were presented as median (25^{th}~75^{th} quantiles). Comparison between 2 groups was determined by Wilcoxon rank sum test. *P* value <0.05 was considered significant, and the significant results were shown in boldface. DEB-TACE, drug-eluting bead transarterial chemoembolization; cTACE, conventional transarterial chemo-embolization; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; TBIL, total bilirubin; ALB, albumin; TP, total protein; TBA, total bile acid.

Table 8. Adverse events occurred during treatment and hospitalization

Parameters	DEB-TACE group (N=94)	cTACE group (N=98)	*P* value
During treatment			
Pain (n/%)	26 (27.7)	15 (15.3)	**0.037**
Pain grade (NRS) (n/%)			0.201
Mild pain	18 (69.2)	14 (93.3)	
Moderate pain	7 (26.9)	1 (6.7)	
Severe pain	1 (3.8)	0 (0.0)	
Nausea/Vomiting (n/%)	11 (11.7)	8 (8.2)	0.412
Rise in blood pressure (n/%)	4 (4.3)	1 (1.0)	0.159
During hospitalization			
Pain (n/%)	34 (36.2)	22 (22.4)	**0.035**
Pain grade (NRS) (n/%)			0.570
Mild pain	27 (79.4)	19 (86.4)	
Moderate pain	7 (20.6)	2 (9.1)	
Severe pain	0 (0.0)	1 (4.5)	
Fever (n/%)	26 (27.7)	14 (14.3)	**0.023**
Nausea/Vomiting (n/%)	10 (10.6)	11 (11.2)	0.896

Data were presented as count (%). 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 were shown in boldface. DEB-TACE, drug-eluting bead transarterial chemoembolization; cTACE, conventional transarterial chemo-embolization; NRS, numeric rating scale.

cTACE group at M3 and M6 after treatment [15-18]. Moreover, in these previous studies, most of the patients are with HCC treatment history and their sample sizes were very small, thus, information on efficacy of DEB-TACE as first-line treatment compared with cTACE is still sparse. Therefore, we compared the treatment response to DEB-TACE with CSM and cTACE as first-line treatment in HCC patients at M1, M3 and M6 after treatment, and discovered that the treatment response was better in DEB-TACE group with CSM compared with cTACE group. These might result from that: DEB-TACE with CSM was designed to not only locally and precisely release chemotherapy drugs, but also effectively occlude the blood supply to tumor tissues, and these above features to some extent overcame several limitations of cTACE (including high systemic toxicity and escape of drugs), which made DEB-TACE with CSM more selective to tumors and provided higher drug concentration at target lesion to more effectively kill tumor cells, thereby presenting with higher ORR in HCC patients [19, 20]. Also, in multivariate logistic regression model analysis, DEB-TACE vs cTACE independently predicted better ORR in HCC patients, which further supported our result that DEB-TACE with CSM lead to better treatment response than cTACE.

As for the influence of DEB-TACE with CSM on survival profiles of HCC patients compared with cTACE, especially when it is applied as first-line treatment, no study is available till now. Therefore, we recorded survival information of HCC patients in our study and discovered that both PFS and OS were similar in DEB-TACE with CSM and cTACE groups, and Cox's proportional hazards regression model analysis revealed that DEB-TACE or cTACE was not correlated with survivals. This might be due to that, the follow-up duration in our study was relatively short, which might be insufficient for evaluation of PFS and OS to see any clear differences. Moreover, various factors such as

change in treatment methods and other complications might affect the survivals of HCC patients after 6 months, therefore the difference in survival profile between DEB-TACE with CSM and cTACE needed longer observation time.

After treatment of TACE, adverse events such as liver injury, pain, nausea, fever and fatigue are commonly reported. A study comparing the safety profile of DEB-TACE with DC® Beads and cTACE illustrated that there is no difference in liver toxicity between the two groups at 1 month after treatment, while the treatment history of patients in this study is nor described [21]. Another study demonstrates that no significant difference was observed in terms of liver function indexes change, pain, fever, or nausea/vomiting between DEB-TACE with CSM and cTACE groups, while all HCC patients in their study are at BCLC stage C and received previous HCC treatment [18]. These previous studies imply that DEB-TACE and cTACE are equally tolerated in HCC patients, however, safety profile between DEB-TACE with CSM and cTACE as first-line treatment for HCC patients is still unknown. Our study first observed no difference in liver function injury between DEB-TACE with CSM and cTACE as first-line treatment for HCC patients at 1 month after treatment, whereas DEB-TACE with CSM resulted in higher incidence of pain and fever during treatment or hospitalization, which could be explained by: (1) The incidence of inflammation could be enhanced by substances released from necrotic tumor tissue, thus, HCC patients underwent DEB-TACE with CSM experienced more severe pain and fever due to more rapid tumor necrosis induced by DEB-TACE with CSM. (2) Compared to cTACE, DEB-TACE was reported to cause more damage to the hepatic artery, which might be responsible for increased pain in HCC patients after treatment of DEB-TACE with CSM [22].

The limitations of our study included: (1) The physicians from different center might possess distinct technological experiences and might influence the outcomes. (2) The CSM used in our study were in different sizes (100-300 μm or 300-500 μm in diameter) and multiple embolization were performed in patients on require, which might be confounding factors for treatment outcomes. (3) The follow-up duration for assessment of patients' survival profiles was relatively short, therefore, further study with longer follow-up is necessary. (4) In this retrospective study, various confounding factors might affect the results, therefore, prospective study (randomized control trail study is especially preferable) should be conducted in future to validate the results.

In conclusion, DEB-TACE with CSM discloses better treatment response, similar survival profiles and equal liver function injury but increased incidence of short-term adverse events than cTACE as the first-line therapy in treating HCC patients.

Disclosure of conflict of interest

None.

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References

[1] Forner A, Reig M and Bruix J. Hepatocellular carcinoma. Lancet 2018; 391: 1301-1314.

[2] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D and Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359-386.

[3] Venook AP, Papandreou C, Furuse J and de Guevara LL. The incidence and epidemiology of hepatocellular carcinoma: a global and regional perspective. Oncologist 2010; 15 Suppl 4: 5-13.

[4] Ashtari S, Pourhoseingholi MA, Sharifian A and Zali MR. Hepatocellular carcinoma in Asia: prevention strategy and planning. World J Hepatol 2015; 7: 1708-1717.

[5] Tanaka M, Katayama F, Kato H, Tanaka H, Wang J, Qiao YL and Inoue M. Hepatitis B and C virus infection and hepatocellular carcinoma in China: a review of epidemiology and control measures. J Epidemiol 2011; 21: 401-416.

[6] Zhou M, Wang H, Zhu J, Chen W, Wang L, Liu S, Li Y, Wang L, Liu Y, Yin P, Liu J, Yu S, Tan F, Barber RM, Coates MM, Dicker D, Fraser M, Gon-

zalez-Medina D, Hamavid H, Hao Y, Hu G, Jiang G, Kan H, Lopez AD, Phillips MR, She J, Vos T, Wan X, Xu G, Yan LL, Yu C, Zhao Y, Zheng Y, Zou X, Naghavi M, Wang Y, Murray CJ, Yang G and Liang X. Cause-specific mortality for 240 causes in China during 1990-2013: a systematic subnational analysis for the Global Burden of Disease Study 2013. Lancet 2016; 387: 251-272.

[7] Marelli L, Stigliano R, Triantos C, Senzolo M, Cholongitas E, Davies N, Tibballs J, Meyer T, Patch DW and Burroughs AK. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. Cardiovasc Intervent Radiol 2007; 30: 6-25.

[8] Zou JH, Zhang L, Ren ZG and Ye SL. Efficacy and safety of cTACE versus DEB-TACE in patients with hepatocellular carcinoma: a meta-analysis. J Dig Dis 2016; 17: 510-517.

[9] Imai N, Ishigami M, Ishizu Y, Kuzuya T, Honda T, Hayashi K, Hirooka Y and Goto H. Transarterial chemoembolization for hepatocellular carcinoma: a review of techniques. World J Hepatol 2014; 6: 844-850.

[10] Cucchetti A, Trevisani F, Cappelli A, Mosconi C, Renzulli M, Pinna AD and Golfieri R. Cost-effectiveness of doxorubicin-eluting beads versus conventional trans-arterial chemo-embolization for hepatocellular carcinoma. Dig Liver Dis 2016; 48: 798-805.

[11] Megias Vericat JE, Garcia Marcos R, Lopez Briz E, Gomez Munoz F, Ramos Ruiz J, Martinez Rodrigo JJ and Poveda Andres JL. Trans-arterial chemoembolization with doxorubicin-eluting particles versus conventional trans-arterial chemoembolization in unresectable hepatocellular carcinoma: a study of effectiveness, safety and costs. Radiologia 2015; 57: 496-504.

[12] Zhang S, Huang C, Li Z, Yang Y, Bao T, Chen H, Zou Y and Song L. 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: 1011-1017.

[13] Yao FY. Liver transplantation for hepatocellular carcinoma: beyond the Milan criteria. Am J Transplant 2008; 8: 1982-1989.

[14] Lencioni R, de Baere T, Burrel M, Caridi JG, Lammer J, Malagari K, Martin RC, O'Grady E, Real MI, Vogl TJ, Watkinson A and Geschwind JF. Transcatheter treatment of hepatocellular carcinoma with Doxorubicin-loaded DC Bead (DEBDOX): technical recommendations. Cardiovasc Intervent Radiol 2012; 35: 980-985.

[15] Wu B, Zhou J, Ling G, Zhu D and 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.

[16] Arabi M, BenMousa A, Bzeizi K, Garad F, Ahmed I and Al-Otaibi M. Doxorubicin-loaded drug-eluting beads versus conventional transarterial chemoembolization for nonresectable hepatocellular carcinoma. Saudi J Gastroenterol 2015; 21: 175-180.

[17] Rahman FA, Naidu J, Ngiu CS, Yaakob Y, Mohamed Z, Othman H, Jarmin R, Elias MH, Hamid NA, Mokhtar NM and Ali RR. 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: 4037-4041.

[18] Liu Y, Huang W, He M, Lian H, Guo Y, Huang J, Zhou J and Zhu K. Efficacy and safety of CalliSpheres(R) drug-eluting beads transarterial chemoembolization in Barcelona Clinic Liver Cancer stage C patients. Oncol Res 2019; 27: 565-573.

[19] Golfieri R, Giampalma E, Renzulli M, Cioni R, Bargellini I, Bartolozzi C, Breatta AD, Gandini G, Nani R, Gasparini D, Cucchetti A, Bolondi L, Trevisani F; PRECISION ITALIA STUDY GROUP. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer 2014; 111: 255-264.

[20] Facciorusso A. Drug-eluting beads transarterial chemoembolization for hepatocellular carcinoma: current state of the art. World J Gastroenterol 2018; 24: 161-169.

[21] Song MJ, Chun HJ, Song DS, Kim HY, Yoo SH, Park CH, Bae SH, Choi JY, Chang UI, Yang JM, Lee HG and Yoon SK. Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. J Hepatol 2012; 57: 1244-1250.

[22] Lee S, Kim KM, Lee SJ, Lee KH, Lee DY, Kim MD, Kim DY, Kim SU and Won JY. Hepatic arterial damage after transarterial chemoembolization for the treatment of hepatocellular carcinoma: comparison of drug-eluting bead and conventional chemoembolization in a retrospective controlled study. Acta Radiol 2017; 58: 131-139.

Table S1. Number of patients included in this study by medical center

Medical center	DEB-TACE group	cTACE group	Patients
Guangxi District Cancer Hospital (n)	31	29	60
Hunan People's Hospital (n)	18	26	44
Xiangya Affiliated Second Hospital (n)	8	24	32
Wuhan Union Hospital (n)	12	4	16
Hubei Provincial People's Hospital (n)	9	5	14
General Hospital of Hubei Army (n)	3	8	11
Xiangya Hospital (n)	10	0	10
Wuhan Zhongnan Hospital (n)	3	2	5
Total (N)	94	98	192

DEB-TACE, drug-eluting bead transarterial chemoembolization; cTACE, conventional transarterial chemo-embolization.