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Efficacy and Safety of Drug-Eluting Beads Transarterial Chemoembolization by CalliSpheres® in 275 Hepatocellular Carcinoma Patients: Results From the Chinese CalliSpheres® Transarterial Chemoembolization in Liver Cancer (CTILC) Study

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The purpose of this study was to investigate the efficacy and safety of drug-eluting beads transarterial chemoembolization (DEB-TACE) treatment in Chinese hepatocellular carcinoma (HCC) patients and the prognostic factors for treatment response as well as survival. A total of 275 HCC patients were included in this prospective study. Treatment response was assessed by modified Response Evaluation Criteria in Solid Tumors (mRECIST), and progression-free survival (PFS) as well as overall survival (OS) were determined. Liver

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function and adverse events (AEs) were assessed before and after DEB-TACE operation. Complete response (CR), partial response (PR), and objective response rate (ORR) were 22.9%, 60.7%, and 83.6%, respectively. The mean PFS was 362 (95% CI: 34.9–375) days, the 6-month PFS rate was 89.4 ± 2.1%, while the mean OS was 380 (95% CI: 370–389) days, and the 6-month OS rate was 94.4 ± 1.7%. Multivariate logistic regression revealed that portal vein invasion ($p = 0.011$) was an independent predictor of worse clinical response. Portal vein invasion ($p = 0.040$), previous cTACE treatment ($p = 0.030$), as well as abnormal serum creatinine level (BCr) ($p = 0.017$) were independent factors that predicted worse ORR. In terms of survival, higher Barcelona Clinic Liver Cancer (BCLC) stage ($p = 0.029$) predicted for worse PFS, and abnormal albumin (ALB) ($p = 0.011$) and total serum bilirubin (TBIL) ($p = 0.009$) predicted for worse OS. The number of patients with abnormal albumin, total protein (TP), TBIL, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were augmented at 1 week posttreatment and were similar at 1–3 months compared with baseline. The most common AEs were pain, fever, nausea, and vomiting, and no severe AEs were observed in this study. DEB-TACE was effective and tolerable in treating Chinese HCC patients, and portal vein invasion, previous cTACE treatment, abnormal BCr, ALB, and TBIL appear to be important factors that predict worse clinical outcome.

Key words: Drug-eluting beads transarterial chemoembolization (DEB-TACE); Hepatocellular carcinoma (HCC); Clinical efficacy; Safety; Prognostic factors; Liver function

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer deaths worldwide and the most frequently diagnosed cancer in males in China[1,2]. HCC often develops in the presence of underlying liver disease, such as hepatitis B, hepatitis C, alcoholic liver disease, or nonalcoholic fatty liver diseases, and in general, when diagnosed, it is associated with an extremely poor prognosis[3,4]. The treatment of HCC is stratified according to disease severity. Patients with early stage HCC are eligible to undergo surgical resection or liver transplantation, whereas moderate to advanced HCC, which results from delayed diagnosis, constitutes the majority of patients. In this setting, patients are usually treated with noncurative approaches, with chemoembolization being one of those therapies[4–6].

Drug-eluting beads transarterial chemoembolization (DEB-TACE) was first adopted in 2006 and is a relatively new type of TACE using microspheres as the core technique. It is considered as a modified version of conventional TACE (cTACE)[7]. The advantages of DEB-TACE are the ability to target multiple tumors at a time, reduce systemic toxicity, and can be repeated on patients. When compared to cTACE, DEB-TACE has the advantage of providing more sustained drug concentrations and is associated with reduced adverse events, including liver toxicity[8]. DEB-TACE is predominantly used for patients with intermediate stage HCC and also for patients with advanced HCC. In addition, this approach can be used as a form of bridge therapy for patients who are being considered for liver surgery and/or transplantation[8–10]. The clinical efficacy and safety of DEB has been well-established in the European and US patient populations[11–13]. Although a considerable number of studies have been conducted to date in East Asia, including Japan and Korea, the clinical experience of DEB-TACE in China remains limited[14,15]. For this reason, multicenter, cross-regional, and large-sample size studies evaluating the efficacy and safety of DEB-TACE treatment in Chinese HCC patients are urgently needed.

Therefore, this multicenter, cross-regional study of 275 HCC patients was conducted to investigate the efficacy and safety of DEB-TACE treatment in Chinese HCC patients. In addition, we investigated the potential prognostic factors for treatment response as well as overall survival.

MATERIALS AND METHODS

Study Design

This study was a part of the CTILC study (Chinese CalliSpheres® Transarterial Chemoembolization In Liver Cancer), which is a multicenter, prospective cohort study that aimed to investigate the efficacy and safety of DEB-TACE treatment by CalliSpheres® in Chinese patients and to improve the prognosis and patients' satisfaction. The CTILC study included 24 medical centers in China, and it was registered on clinicaltrials.gov with No. NCT03317483. This study was approved by the ethics committee of Zhejiang Provincial Cancer Hospital. All the patients and/or their legal guardians signed written informed consent forms. This study was conducted according to the Declaration of Helsinki.

Patients

A total of 275 HCC patients were prospectively included in this study during the period of November 12, 2015 to November 4, 2016. The inclusion criteria were as follows: (1) diagnosed as primary HCC confirmed by pathological findings, clinical features, or radiographic

examinations according to the American Association for the Study of the Liver Diseases (AASLD) guidelines; (2) age >18 years; (3) plans to receive DEB-TACE treatment with CalliSpheres® according to clinical needs and patients' acceptance; (4) able to be followed-up regularly; and (5) life expectancy >12 months. The exclusion criteria were as follows: (1) prior history of liver transplantation; (2) history of hematological malignances; (3) severe hepatic failure or renal failure; (4) contraindication for angiography, embolization procedure, or artery puncture; (5) patients with cognitive impairment or unable to give informed consent; and (6) women in gestation or lactation period. The inclusion and exclusion criteria are available at clinicaltrials.gov with registry No. NCT03317483.

Treatment Procedure

All DEB-TACE procedures were performed using the superselective method and under the supervision of several interventional radiologists. In our study, the CalliSpheres® Beads (CB; Jiangsu Hengrui Medicine Co, Ltd., Jiangsu, P.R. China) with a diameter of 100 to 300 μm were used as carriers. Before the initiation of the procedure, beads were loaded with epirubicin, pirubicin, or doxorubicin (60–80 mg). The chemoembolization reagent was dissolved to solution (20 mg/ml) and extracted into a 10-ml injector. The CB was then loaded as follows: one bottle of CB was shaken up, and the bead suspension was subsequently extracted into a 20-ml injector, which was allowed to stand at room temperature (RT) for 5 min, and the liquid supernatant was pushed out, leaving the beads in the injector. The chemotherapy reagent solution was then mixed with the beads by a tee joint, after which the nonionic contrast agent was administered at a ratio of 1:1, and the mixture was placed for 30 min at RT for further application. Ordinary embolization agents were used if the embolization point was not reached after a bottle of CalliSpheres® Beads was emptied.

Digital subtraction angiography (DSA) was performed to detect the arteries supplying the tumors. Once the artery was selected, a 2.4 F microcatheter (Merit Maestro, Merit Medical System, Inc., Jordan, UT, USA) was inserted, which was led by a microwire. The chemotherapy drug-loaded beads with nonionic contrast agent were delivered at a rate of 1 ml/min through a microcatheter to the tumor-supplying artery and stopped until the existence of stasis. After 5 min of delivery, another angiography was performed to detect the blushed/tinted tumor. The embolization procedure was repeated if the blushed/tinted tumor was still present and then terminated when no more blushed/tinted tumor was visualized.

Treatment Response, Survival, and Safety Evaluations

Treatment responses were assessed by computerized tomography (CT), enhancement CT, or magnetic resonance image (MRI) within 1–3 months after DEB-TACE procedure. It should be noted that the imaging assessment modality for each patient was not the same and varied from one center to another. Treatment responses were assessed according to the imaging findings as per the modified Response Evaluation Criteria in Solid Tumors (mRECIST). The response evaluation was as follows[16]: complete response (CR) was defined as the disappearance of any intratumoral arterial enhancement in all target nodules; partial response (PR) was defined as at least a 30% reduction in the sum of diameters of viable (enhancement in the arterial phase) target nodules, taking as reference the baseline sum of the diameters of target nodules; stable disease (SD) was defined as any situation that did not qualify for either PR or progressive disease; progressive disease (PD) was an increase of at least 20% in the sum of the diameters of viable (enhancing) target nodules, taking as reference the smallest sum of the diameters of viable (enhancing) target nodules recorded since treatment started; objective response rate (ORR) was defined as the proportion of patients who achieved CR and PR.

Progression-free survival (PFS) and overall survival (OS) were recorded for each patient. The median follow-up time was 161 (30–398) days, and the last follow-up date was December 28, 2016. Safety evaluation included an assessment of liver function, which was assessed according to the laboratory indices related to liver function at 1 week and 1–3 months posttreatment, and adverse events (AEs) during operation and 1 month after operation.

Statistics

The SPSS 21.0 Software (IBM, San Jose, CA, USA) was used for statistical analysis. Data are presented as count (%), mean ± standard deviation or median (25th–75th). Comparison between two groups was determined by chi-square test. The McNemar test was performed to compare the difference in liver function indexes at each visit. Kaplan–Meier (K–M) curves were performed to assess the OS of patients and the comparison between two groups was determined by log-rank test. Univariate logistic regression analysis was performed to determine the factors affecting CR or ORR, while all factors with a value of $p < 0.1$ were further detected by multivariate logistic regression analysis. Factors affecting OS were determined by univariate Cox's proportional hazards regression model analysis, after which all factors with a value of $p < 0.1$ were further analyzed by multivariate Cox's proportional hazards regression analysis. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

Study Flow

The study flow is presented in Figure 1. At the start of this study, 824 HCC patients were invited. However, 286 patients were subsequently excluded due to missed

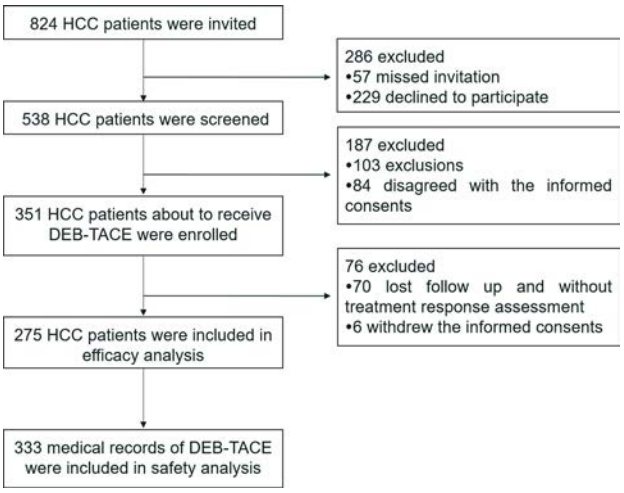

Figure 1. Study flow.

invitations, and another 229 patients did not wish to be included in this study. As a result, 538 HCC patients were left to be screened for study enrollment. Subsequently, 187 patients were excluded postscreening (103 exclusions and 84 did not agree to sign the informed consent), and the remaining 351 HCC patients about to receive DEB-TACE were enrolled in our study. After enrollment of 351 HCC patients, 70 patients were lost to follow-up and another 6 patients decided to withdraw their consent. As a result, 275 HCC patients were included in the final efficacy analysis of this study, and 333 patients were used for safety analysis.

Baseline Characteristics of 275 HCC Patients

The mean age of the patients enrolled in this study was 58.7 ± 11.5 years, with the large majority being male (228 male, 47 female) (Table 1). Most of the patients had history of hepatitis B (HB) [228 (82.9%)], and the number of patients with history of alcohol use and liver cirrhosis were 130 (47.3%) and 165 (60.0%), respectively. In addition, 180 (65.5%) patients were found to have multifocal disease, and 95 (34.5%) had unifocal disease. The median value of the largest tumor size was 4.8 (2.8–8.6) cm. The number of patients with portal vein invasion and hepatic vein invasion were 82 (29.8%) and 37 (13.5%), respectively. Nearly all of the patients had Child–Pugh stage A [228 (82.9%)] disease, while the number of patients based on the Barcelona Clinic Liver Cancer (BCLC) stage 0, A, B, C, and D were 1 (0.4%), 67 (24.4%), 108 (39.3%), 98 (35.6%), and 1 (0.4%), respectively. In addition, 227 (82.5%) patients received one cycle of DEB-TACE, and 48 (17.5%) patients received two or more cycles of DEB-TACE. A large majority of patients had been previously treated with other approaches including cTACE (42.9%), surgery (24.7%), systemic chemotherapy (2.9%), radiofrequency ablation (13.1%), and targeted therapy (2.9%), respectively. One hundred (36.4%) patients received a combination of ordinary embolization agent during the DEB-TACE procedure. With respect to the various treatments that patients received after DEB-TACE, this included no further treatment (74.9%), radiofrequency ablation (0.4%), sorafenbi (1.4%), apatinib (0.4%), antiviral therapy (7.7%), traditional Chinese medicine (8.7%), sorafenib combined with antiviral therapy (0.4%), antiviral therapy combined with traditional Chinese medicine (2.9%), chemotherapeutics combined with traditional Chinese medicine (0.4%), and other treatments (2.9%), respectively. Other detailed information on clinicopathological features, laboratory indexes, previous treatments, and combination of other embolization agents are presented in Table 1.

Treatment Response in HCC Patients

As shown in Figure 2A, at 1–3 months posttreatment, the CR, PR, and ORR rates were 22.9%, 60.7%, and 83.6%, respectively. In patients who achieved PR, the proportion of patients with necrosis rates >80%, between 50% and 80%, and <50% were 28.7%, 40.8%, and 30.5%, respectively (Fig. 2B). Additionally, in the total of 508 treated nodules, the rates of CR, PR, and ORR were 33.1%, 49.2%, and 82.3% (Fig. 2C), respectively, and 26.2%, 53.8%, and 20.0% patients who achieved PR reached the necrosis rates of >80%, 50% to 80%, and <50%, respectively (Fig. 2D).

PFS and OS in HCC Patients

PFS (Fig. 3) and OS (Fig. 4) in HCC patients were assessed by the K–M curve. The mean PFS was 362 (95% CI: 34.9–375) days, and the 6-month PFS rate was 89.4 ± 2.1%. The mean OS was 380 (95% CI: 370–389) days, and the 6-month OS rate was 94.4 ± 1.7%.

Analysis of Factors Affecting CR

As presented in Table 2, subgroup analysis was performed to evaluate the difference of CR between/among

Table 1. Characteristics of 275 Hepatocellular Carcinoma (HCC) Patients Who Underwent Drug-Eluting Beads Transarterial Chemoembolization (DEB-TACE) Treatment

Parameters	Patients ($N = 275$)
Age (years)	58.7 ± 11.5
Gender (male/female)	228/47
History of HB (*n*/%)	228 (82.9)
History of drink (*n*/%)	130 (47.3)
History of cirrhosis (*n*/%)	165 (60.0)
Tumor distribution	
Multifocal disease (*n*/%)	180 (65.5)
Unifocal disease (*n*/%)	95 (34.5)
Tumor location	
Left liver (*n*/%)	42 (15.3)
Right liver (*n*/%)	144 (52.4)
Bilobar (*n*/%)	89 (32.4)
Largest nodule size (cm)	4.8 (2.8–8.6)
Portal vein invasion (*n*/%)	82 (29.8)
Hepatic vein invasion (*n*/%)	37 (13.5)
ECOG performance status	
0 (*n*/%)	172 (62.5)
1 (*n*/%)	83 (30.2)
2 (*n*/%)	14 (5.1)
3 (*n*/%)	6 (2.2)
Child–Pugh stage	
A (*n*/%)	228 (82.9)
B (*n*/%)	45 (16.4)
C (*n*/%)	2 (0.7)
BCLC stage	
0 (*n*/%)	1 (0.4)
A (*n*/%)	67 (24.4)
B (*n*/%)	108 (39.3)
C (*n*/%)	98 (35.6)
D (*n*/%)	1 (0.4)
Cycles of DEB-TACE treatment	
One cycle (*n*/%)	227 (82.5)
Two or more cycles (*n*/%)	48 (17.5)
CBC	
WBC ($\times 10^9$ cell/L)	5.0 (3.6–6.3)
RBC ($\times 10^{12}$ cell/L)	4.3 (3.9–4.8)
ANC%	61.0 (52.1–68.9)
Hb (g/L)	129.0 (107.0–146.5)
PLT ($\times 10^9$ cell/L)	112.0 (70.5–164.5)
Liver function	
ALB (g/L)	39.1 (35.2–42.9)
TP (g/L)	68.6 (64.3–73.3)
TBIL (μmol/L)	16.0 (11.5–23.0)
TBA (I/L)	12.0 (6.7–26.9)
ALT (μ/L)	28.0 (20.0–42.0)
AST (μ/L)	37.0 (27.0–56.0)
ALP (μ/L)	117.0 (85.0–162.0)
Kidney function	
BCr (μmol/L)	72.0 (62.0–81.0)
BUN (mmol/L)	4.9 (4.0–6.2)
Tumor markers	
AFP (μg/L)	59.2 (7.4–1280.9)
CEA (μg/L)	2.7 (1.8–4.3)
CA19-9 (kU/L)	13.7 (6.5–28.8)
Previous treatments	
cTACE (*n*/%)	118 (42.9)
Surgery (*n*/%)	68 (24.7)
Systematic chemotherapy (*n*/%)	8 (2.9)
Radiofrequency ablation (*n*/%)	36 (13.1)
Targeted therapy (*n*/%)	8 (2.9)
Combination of ordinary embolization agent	100 (36.4)
Treatments post-DEB-TACE	
No treatment (*n*/%)	206 (74.9)
Radiofrequency ablation (*n*/%)	1 (0.4)
Sorafenib (*n*/%)	4 (1.4)
Apatinib (*n*/%)	1 (0.4)
Antiviral therapy (*n*/%)	21 (7.7)
Traditional Chinese medicine (*n*/%)	24 (8.7)
Sorafenib combined with antiviral therapy (*n*/%)	1 (0.4)
Antiviral therapy combined with traditional Chinese medicine (*n*/%)	8 (2.9)
Chemotherapeutics combined with traditional Chinese medicine (*n*/%)	1 (0.4)
Other (*n*/%)	8 (2.9)

Data are presented as mean ± standard deviation, median (25th–75th), or count (%). HCC, hepatocellular carcinoma; HB, hepatitis B; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; DEB-TACE, drug-eluting bead transarterial chemoembolization; WBC, white blood cell; RBC, red blood cell; ANC, absolute neutrophil count; Hb, hemoglobin; PLT, platelet; ALB, albumin; TP, total protein; TBIL, total bilirubin; TBA, total bile acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BCr, blood creatinine; BUN, blood urea nitrogen; AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen19-9; cTACE, conventional transarterial chemoembolization.

subgroups divided by demographic and clinical characteristics, which showed that patients with largest nodule size 5 cm ($p = 0.004$), portal vein invasion ($p < 0.001$), and higher BCLC stages ($p = 0.019$) presented with less CR achievement. As to subgroup analysis divided by laboratory indexes, the CR rates were decreased in patients with abnormal ALB ($p = 0.035$), AST ($p = 0.036$), and BUN ($p = 0.047$) at baseline (Table 3).

Furthermore, univariate logistic regression revealed that largest nodule size 5 cm ($p = 0.005$), portal vein invasion ($p = <0.001$), higher BCLC stage ($p = 0.018$), ALB abnormal ($p = 0.037$), AST abnormal ($p = 0.038$), and BUN abnormal ($p = 0.050$) were associated with worse CR achievement (Table 4). All factors with a value of $p < 0.1$ from univariate logistic regression were further analyzed in the multivariate logistic regression, which showed that only portal vein invasion ($p = 0.011$) was an independent predictor for worse CR in HCC patients (Table 4).

Analysis of Factors Influencing ORR in HCC Patients

Subgroup analysis of ORR divided by demographic and clinical characteristics revealed that ORR was decreased in patients with portal vein invasion ($p = 0.019$) (Table 5). A subgroup analysis of ORR divided by laboratory indexes revealed that patients with abnormal BCr achieved lower ORR ($p = 0.008$) (Table 6).

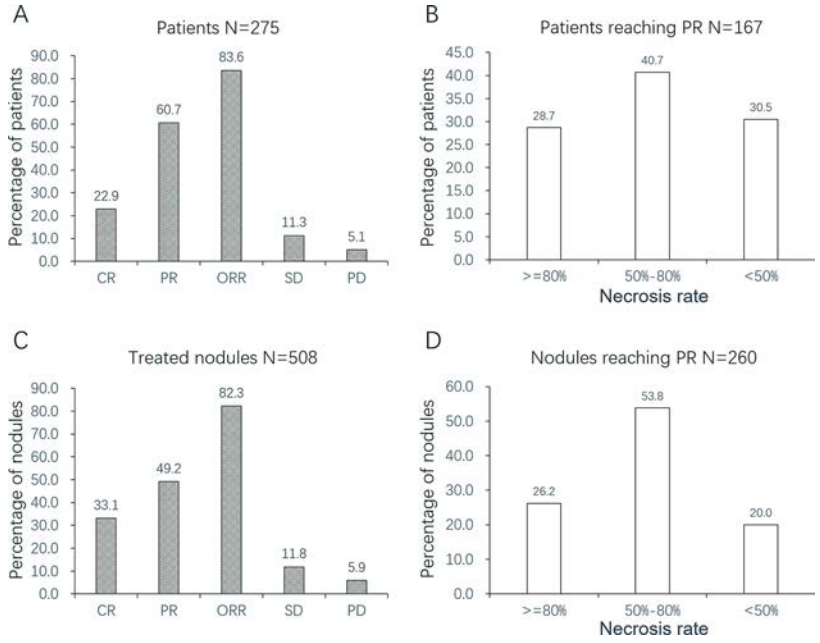

Figure 2. Treatment responses. The percentage of patients with complete response (CR), partial response (PR), objective response rate (ORR), stable disease (SD), and progressive disease (PD) were 22.9%, 60.7%, 83.6%, 11.3%, and 5.1%, respectively (A), and among 167 patients who achieved PR, the proportion of patients who achieved necrosis rates of >80%, 50%–80%, and <50% were 28.7%, 40.8%, and 30.5%, respectively (B). Among 508 treated nodules, 33.1% achieved CR, 49.2% achieved PR, and 82.3% achieved ORR, and 11.8% was SD as well as 5.9% was PD (C). The percentages of nodules that achieved PR with necrosis rates of >80%, 50%–80%, and <50% were 26.2%, 53.8% and 20.0%, respectively (D).

Univariate logistic regression analysis demonstrated that portal vein invasion ($p = 0.021$) and BCr abnormal ($p = 0.010$) were associated with decreased ORR in HCC patients. In contrast, the multivariate logistic regression, which included all factors with a value of $p < 0.1$ from the univariate logistic regression analysis, showed that portal vein invasion ($p = 0.040$), previous cTACE treatment ($p = 0.030$), and abnormal BCr ($p = 0.017$) were independent predictive factors for worse ORR (Table 7).

Analysis of Factors Affecting PFS

PFS was much shorter in patients with tumor size 5 cm ($p = 0.046$) (Fig. 5A), portal vein invasion ($p = 0.001$) (Fig. 5B), higher BCLC stage ($p = 0.009$) (Fig. 5F), and

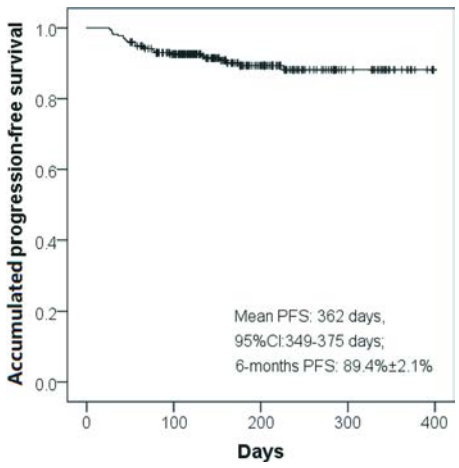

Figure 3. Progression-free survival (PFS) in hepatocellular carcinoma (HCC) patients with post-drug-eluting beads transarterial chemoembolization (DEB-TACE) procedures. The mean PFS was 362 (95% CI: 349–375) days, and the 6-month PFS rate was 89.4% ± 2.1%. Kaplan–Meier (K–M) analysis was performed to evaluate the PFS in HCC patient post-DEB-TACE procedures.

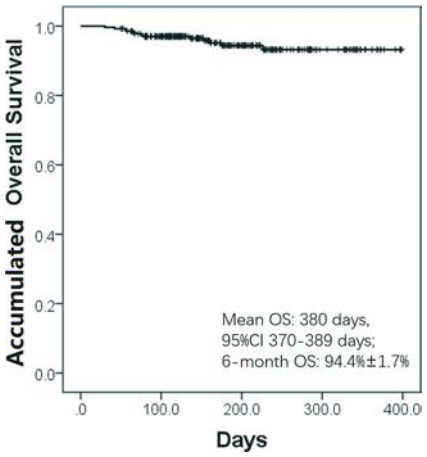

Figure 4. OS in HCC patients after DEB-TACE procedures. The mean OS was 380 (95% CI: 370–389) days, and the 6-month OS rate was 94.4% ± 1.7%. K–M analysis was performed to evaluate the OS in HCC patients after DEB-TACE procedures.

Table 2. Comparison of Complete Response (CR) Among/Between Subgroups Divided by Demographic and Clinical Characteristics

Parameters	*N*	Not CR	CR	*p* Value
Age				0.086
>60 years (*n*/%)	122	100 (82.0)	22 (18.0)	
<60 years (*n*/%)	153	112 (73.2)	41 (26.8)	
Gender				0.501
Male (*n*/%)	228	174 (76.3)	54 (23.7)	
Female (*n*/%)	47	38 (80.9)	9 (19.1)	
History of HB				0.069
Yes (*n*/%)	228	171(75.0)	57 (25.0)	
No (*n*/%)	47	41 (87.2)	6 (12.8)	
History of alcohol use				0.726
Yes (*n*/%)	130	99 (76.2)	31 (23.8)	
No (*n*/%)	145	113 (77.9)	32 (22.1)	
History of cirrhosis				0.128
Yes (*n*/%)	165	122 (73.9)	43 (26.1)	
No (*n*/%)	110	90 (81.8)	20 (18.2)	
Tumor distribution				0.114
Multifocal disease (*n*/%)	180	144 (80.0)	36 (20.0)	
Unifocal disease (*n*/%)	95	68 (71.6)	27 (28.4)	
Tumor location				0.246
Left liver (*n*/%)	42	29 (69.0)	13 (31.0)	
Right liver (*n*/%)	144	110 (76.4)	34 (23.6)	
Bilobar (*n*/%)	89	73 (82.0)	16 (18.0)	
Largest nodule size				0.004
≥5 cm (*n*/%)	135	114 (84.4)	21 (15.6)	
<5 cm (*n*/%)	140	98 (70.0)	42 (30.0)	
Portal vein invasion				<0.001
Yes (*n*/%)	82	76 (92.7)	6 (7.3)	
No (*n*/%)	193	136 (70.5)	57 (29.5)	
Hepatic vein invasion				0.060
Yes (*n*/%)	37	33 (89.2)	4 (10.8)	
No (*n*/%)	238	179 (75.2)	59 (24.8)	
ECOG performance status				0.125
0 (*n*/%)	172	128 (74.4)	44 (25.6)	
1 (*n*/%)	83	66 (79.5)	17 (20.5)	
2 (*n*/%)	14	12 (85.7)	2 (14.3)	
3 (*n*/%)	6	6 (100.0)	0 (0.0)	
Child–Pugh stage				0.147
A (*n*/%)	228	172 (75.4)	56 (24.6)	
B (*n*/%)	45	38 (84.4)	7 (15.6)	
C (*n*/%)	2	2 (100.0)	0 (0.0)	
BCLC stage				0.019
0 (*n*/%)	1	1 (100)	0 (0)	
A (*n*/%)	67	43 (64.2)	24 (35.8)	
B (*n*/%)	108	87 (80.6)	21 (19.4)	
C (*n*/%)	98	80 (81.6)	18 (18.4)	
D (*n*/%)	1	1 (100)	0 (0)	
Cycles of DEB-TACE treatment				0.999
One cycle (*n*/%)	227	175 (77.1)	52 (22.9)	
Two or more cycles (*n*/%)	48	37 (77.1)	11 (22.9)	
Previous cTACE treatment				0.390
Yes (*n*/%)	118	124 (79.0)	33 (21.0)	
No (*n*/%)	157	88 (74.6)	30 (25.4)	
Previous surgery				0.636
Yes (*n*/%)	68	51 (75.0)	17 (25.0)	
No (*n*/%)	207	161 (77.8)	46 (22.2)	
Previous systematic chemotherapy				0.389
Yes (*n*/%)	8	5 (62.5)	3 (37.5)	
No (*n*/%)	267	207 (77.5)	60 (22.5)	

(*continued*)

Table 2. (Continued)

Parameters	*N*	Not CR	CR	*p* Value
Previous radiofrequency ablation				0.167
Yes (*n*/%)	36	31 (86.1)	5 (13.9)	
No (*n*/%)	239	181 (75.7)	58 (24.3)	
Previous targeted therapy				1.000
Yes (*n*/%)	8	6 (75.0)	2 (25.0)	
No (*n*/%)	267	206 (77.2)	61 (22.8)	
Combination of ordinary embolization agent				0.078
Yes (*n*/%)	100	83 (83.0)	17 (17.0)	
No (*n*/%)	175	129 (73.7)	46 (26.3)	

Data are presented as count (%). Comparison between two groups was determined by chi-square test. A value of $p < 0.05$ was considered significant.

Table 3. Comparison of CR Between/Among Subgroups Divided by Biochemical Indexes

Parameters	*N*	Not CR	CR	*p* Value
CBC				
WBC				0.901
Abnormal (*n*/%)	80	62 (77.5)	18 (22.5)	
Normal (*n*/%)	194	149 (76.8)	45 (23.2)	
RBC				0.294
Abnormal (*n*/%)	93	75 (80.6)	18 (19.4)	
Normal (*n*/%)	180	135 (75.0)	45 (25.0)	
ANC				0.268
Abnormal (*n*/%)	71	58 (81.7)	13 (18.3)	
Normal (*n*/%)	202	152 (75.2)	50 (24.8)	
Hb				0.212
Abnormal (*n*/%)	105	85 (81.0)	20 (19.0)	
Normal (*n*/%)	168	125 (74.4)	43 (25.6)	
PLT				0.755
Abnormal (*n*/%)	121	92 (76.0)	29 (24.0)	
Normal (*n*/%)	152	118 (77.6)	34 (22.4)	
Liver function				
ALB				0.035
Abnormal (*n*/%)	105	88 (83.8)	17 (16.2)	
Normal (*n*/%)	169	123 (72.8)	46 (27.2)	
TP				0.583
Abnormal (*n*/%)	71	53 (74.6)	18 (25.4)	
Normal (*n*/%)	203	158 (77.8)	45 (22.2)	
TBIL				0.575
Abnormal (*n*/%)	79	59 (74.7)	20 (25.3)	
Normal (*n*/%)	194	151 (77.8)	43 (22.2)	
TBA				0.955
Abnormal (*n*/%)	110	84 (76.4)	26 (23.6)	
Normal (*n*/%)	150	115 (76.7)	35 (23.3)	
ALT				0.843
Abnormal (*n*/%)	59	46 (78.0)	13 (22.0)	
Normal (*n*/%)	215	165 (76.7)	50 (23.3)	
AST				0.036
Abnormal (*n*/%)	113	94 (83.2)	19 (16.8)	
Normal (*n*/%)	159	115 (72.3)	44 (27.7)	
ALP				0.445
Abnormal (*n*/%)	101	80 (79.2)	21 (20.8)	
Normal (*n*/%)	169	127 (75.1)	42 (24.9)	
Kidney function				
BCr				0.422
Abnormal (*n*/%)	34	28 (82.4)	6 (17.6)	

(*continued*)

Table 3. (Continued)

Parameters	*N*	Not CR	CR	*p* Value
Normal (*n*/%)	239	182 (76.2)	57 (23.8)	
BUN				0.047
Abnormal (*n*/%)	33	30 (90.9)	3 (9.1)	
Normal (*n*/%)	237	177 (74.7)	60 (25.3)	
Tumor markers				
AFP				0.066
Abnormal (*n*/%)	168	135 (80.4)	33 (19.6)	
Normal (*n*/%)	102	72 (70.6)	30 (29.4)	
CEA				0.482
Abnormal (*n*/%)	44	35 (79.5)	9 (20.5)	
Normal (*n*/%)	204	162 (74.5)	52 (25.5)	
CA199				0.724
Abnormal (*n*/%)	65	50 (76.9)	15 (23.1)	
Normal (*n*/%)	182	136 (74.7)	46 (25.3)	

Data are presented as count (%). Comparison between two groups was determined by chi-square test. A value of $p < 0.05$ was considered significant.

BCLC stage C/D ($p < 0.001$) (Fig. 5G), while ECOG score ($p = 0.322$) (Fig. 5C) or Child–Pugh stages ($p = 0.479$ and $p = 0.287$) (Fig. 5D and E) were not correlated with PFS. In addition, univariate Cox's proportional hazards regression model analysis revealed that portal vein invasion ($p = 0.002$), higher BCLC stage ($p = 0.003$), ALP abnormal ($p = 0.001$), BCr abnormal ($p = 0.002$), and abnormal CA19-9 ($p = 0.007$) were predictive for worse PFS (Table 8). When the factors with a value of $p < 0.1$ were included in the multivariate Cox's proportional hazards regression model analysis, higher BCLC stage was found to be an independent predictive factor for worse PFS ($p = 0.029$).

Analysis of Factors Influencing OS in HCC Patients

Subgroup analysis was performed to evaluate the difference of OS in patients with different clinicopathological features (Fig. 6), and the results showed that tumor size 5 cm ($p = 0.016$) (Fig. 6A), portal vein invasion ($p = 0.012$) (Fig. 6B), higher ECOG performance stage ($p = 0.032$) (Fig. 6C), and higher Child–Pugh stage ($p = 0.044$) (Fig. 6D) were correlated with worse OS, while higher BCLC stage did not associate with OS ($p = 0.189$) (Fig. 6F). When patients were divided into Child–Pugh stage A and Child–Pugh stage B/C subgroups, the latter subgroup presented with worse OS as well ($p = 0.016$) (Fig. 6E), and when patients were categorized into BCLC stage 0/A/B and BCLC stage C/D subgroups, the latter one showed unfavorable OS ($p = 0.015$) (Fig. 6G).

As highlighted in Table 9, the univariate Cox's regression analysis identified several factors that correlated with reduced OS in HCC patients, and these included the following: largest nodule size 5 cm ($p = 0.031$), portal vein invasion ($p = 0.019$), worse ECOG performance status ($p = 0.048$), higher Child–Pugh stage ($p = 0.045$), RBC abnormal ($p = 0.025$), ALB abnormal ($p = 0.003$), TBIL abnormal ($p = 0.004$), AST abnormal ($p = 0.025$), ALP abnormal ($p = 0.028$), and BCr abnormal ($p = 0.004$). All factors with a value of $p < 0.1$ were then included in the multivariate Cox's regression, which revealed that abnormal ALB ($p = 0.011$) and abnormal TBIL ($p = 0.009$) independently predicted worse OS in patients.

The Change in Liver Function Before and After DEB-TACE Treatments

Liver function was evaluated according to the change in laboratory indexes related to liver function. As presented in Table 10, the numbers of patients with abnormal ALB, TP, TBIL, ALT, and AST were augmented at 1 week (all $p < 0.001$) posttreatment and were similar at 1–3 months (all $p > 0.05$) compared with baseline. No difference in TBA levels at 1 week or 1–3 months compared with baseline was observed ($p = 0.609$ and $p = 1.000$, respectively). However, the number of patients with abnormal ALP was similar at 1 week posttreatment to that of baseline ($p = 0.105$), while the number was notably elevated at 1–3 months ($p < 0.001$).

AEs of 333 DEB-TACE Records During and Posttreatment

As seen in Table 11, during DEB-TACE treatments, pain [183 (55.0%)] and fever [123 (36.9%)] were the most frequent AEs, and the number of patients with nausea, vomiting, and other AEs were 42 (12.6%), 35 (10.5%), and 21 (6.3%), respectively. At 1 month after the surgical procedure, 95 (28.5%) patients had pain, 78 (23.4%) patients presented with fever, and 37 (11.1%) and 32 (9.6%) patients were with vomiting and nausea, respectively. In addition, only a few patients presented with discoloration [4 (1.2%)], bone marrow toxicity [4 (1.2%)], and other AEs [3 (0.9%)].

Table 4. Factors Influencing CR Achievement by Logistic Regression Model Analysis

	Univariate Logistic Regression				Multivariate Logistic Regression			
			95% CI				95% CI	
Parameters	*p* Value	OR	Lower	Higher	*p* Value	OR	Lower	Higher
Age >60 years	0.087	0.601	0.335	1.078	0.243	0.682	0.359	1.297
Male	0.501	1.310	0.596	2.882	–	–	–	–
History of HB	0.075	2.278	0.919	5.645	0.299	1.684	0.630	4.496
History of alcohol use	0.726	1.106	0.630	1.941	–	–	–	–
History of cirrhosis	0.129	1.586	0.874	2.879	–	–	–	–
Multifocal disease	0.116	0.630	0.354	1.120	–	–	–	–
Tumor location: left liver	0.181	1.641	0.795	3.388	–	–	–	–
Tumor location: right liver	0.772	1.087	0.619	1.911	–	–	–	–
Tumor location: bilobar	0.180	0.648	0.344	1.222	–	–	–	–
Largest nodule size ≥5 cm	**0.005**	0.430	0.238	0.775	0.666	0.854	0.418	1.746
Portal vein invasion	**<0.001**	0.188	0.078	0.457	**0.011**	0.242	0.081	0.719
Hepatic vein invasion	0.069	0.368	0.125	1.081	0.898	1.088	0.300	3.941
Higher ECOG performance status	0.081	0.657	0.410	1.052	0.816	0.937	0.543	1.617
Higher Child–Pugh stage	0.134	0.536	0.237	1.210	–	–	–	–
Higher BCLC stage	**0.018**	0.645	0.449	0.927	0.830	0.953	0.615	1.476
Two or more cycles of DEB-TACE treatment	0.999	1.001	0.477	2.099	–	–	–	–
Previous cTACE treatment	0.390	1.281	0.728	2.254	–	–	–	–
Previous surgery	0.636	1.167	0.616	2.211	–	–	–	–
Previous systematic chemotherapy	0.329	2.070	0.481	8.913	–	–	–	–
Previous radiofrequency ablation	0.174	0.503	0.187	1.354	–	–	–	–
Previous targeted therapy	0.886	1.126	0.222	5.720	–	–	–	–
Combination of ordinary embolization agent	0.080	0.574	0.309	1.069	0.731	0.880	0.425	1.824
WBC abnormal	0.901	0.961	0.516	1.790	–	–	–	–
RBC abnormal	0.295	0.720	0.389	1.332	–	–	–	–
ANC abnormal	0.270	0.681	0.345	1.346	–	–	–	–
Hb abnormal	0.213	0.684	0.376	1.244	–	–	–	–
PLT abnormal	0.756	1.094	0.621	1.926	–	–	–	–
ALB abnormal	**0.037**	0.517	0.278	0.960	0.582	0.821	0.406	1.659
TP abnormal	0.583	1.192	0.636	2.237	–	–	–	–
TBIL abnormal	0.575	1.190	0.647	2.191	–	–	–	–
TBA abnormal	0.955	1.017	0.569	1.817	–	–	–	–
ALT abnormal	0.843	0.933	0.467	1.863	–	–	–	–
AST abnormal	**0.038**	0.528	0.289	0.966	0.978	1.010	0.491	2.078
ALP abnormal	0.446	0.794	0.438	1.437	–	–	–	–
BCr abnormal	0.424	0.684	0.270	1.735	–	–	–	–
BUN abnormal	**0.050**	0.295	0.087	1.002	0.101	0.346	0.098	1.229
AFP abnormal	0.067	0.587	0.331	1.039	0.363	0.740	0.388	1.414
CEA abnormal	0.483	0.752	0.339	1.668	–	–	–	–
CA199 abnormal	0.724	0.887	0.455	1.728	–	–	–	–

Data are presented as *p* value, OR (odds ratio), and 95% CI (confidence interval). Factors affecting CR achievement were determined by univariate logistic regression analysis, while all factors with a value of $p \leq 0.1$ were further detected by multivariate logistic regression analysis. A value of $p < 0.05$ was considered significant. Child–Pugh stage was scored as 0—A, 1—B, 2—C; BCLC stage was scored as 0—stage 0, 1—stage A, 2—stage B, 3—stage C, 4—stage D. The logistic analysis was performed based on these definitions. HB, hepatitis B.

Difference in Treatment Response and Survival Between Child–Pugh Stage B Patients and Child–Pugh Stage C Patients

As shown in Figure 7, no differences in CR, PR, ORR, SD, or PD incidences were observed between Child–Pugh Stage B patients and Child–Pugh Stage C patients ($p = 0.806$) (Fig. 7A). With respect to PFS and OS, no differences in PFS ($p = 0.661$) (Fig. 7B) and OS ($p = 0.704$) (Fig. 7C) were noted between Child–Pugh Stage B patients and Child–Pugh Stage C patients.

DISCUSSION

TACE has been used in the treatment of HCC since the 1980s, and there are now several distinct strategies, such as cTACE, balloon-occluded TACE, and DEB-TACE[17]. The development of DEB-TACE was initially aimed to advance the efficacy and safety of cTACE, which was associated with relatively high relapse rate and significant systemic toxicities[18,19]. The DEB-TACE procedure requires microbeads with a diameter being hundreds of micrometers to load drugs through carrying negative ion

Table 5. Comparison of Objective Response Rate (ORR) Between/Among Subgroups Divided by Demographic and Clinical Characteristics

Parameters	*N*	Not ORR	ORR	*p* Value
Age				0.185
>60 years (*n*/%)	122	24 (19.7)	98 (80.3)	
<60 years (*n*/%)	153	21 (13.7)	132 (86.3)	
Gender				0.765
Male (*n*/%)	228	38 (16.7)	190 (83.3)	
Female (*n*/%)	47	7 (14.9)	40 (85.1)	
History of HB				0.062
Yes (*n*/%)	228	33 (14.5)	195 (85.5)	
No (*n*/%)	47	12 (25.5)	35 (74.5)	
History of alcohol use				0.573
Yes (*n*/%)	130	23 (17.7)	107 (82.3)	
No (*n*/%)	145	22 (15.2)	123 (84.8)	
History of cirrhosis				0.318
Yes (*n*/%)	165	24 (14.5)	141 (85.5)	
No (*n*/%)	110	21 (19.1)	89 (80.9)	
Tumor distribution				0.057
Multifocal disease (*n*/%)	180	35 (19.4)	145 (80.6)	
Unifocal disease (*n*/%)	95	10 (10.5)	85 (89.5)	
Tumor location				0.835
Left liver (*n*/%)	42	8 (19.0)	34 (81.0)	
Right liver (*n*/%)	144	22 (15.3)	122 (84.7)	
Bilobar (*n*/%)	89	15 (16.9)	74 (83.1)	
Largest nodule size				0.722
≥5 cm (*n*/%)	135	21 (15.6)	114 (84.4)	
<5 cm (*n*/%)	140	24 (17.1)	116 (82.9)	
Portal vein invasion				**0.019**
Yes (*n*/%)	82	20 (24.4)	62 (75.6)	
No (*n*/%)	193	25 (13.0)	168 (87.0)	
Hepatic vein invasion				0.159
Yes (*n*/%)	37	9 (24.3)	28 (75.7)	
No (*n*/%)	238	36 (15.1)	202 (84.9)	
ECOG performance status				0.788
0 (*n*/%)	172	29 (16.9)	143 (83.1)	
1 (*n*/%)	83	13 (15.7)	70 (84.3)	
2 (*n*/%)	14	1 (7.1)	13 (92.9)	
3 (*n*/%)	6	2 (33.3)	4 (66.7)	
Child–Pugh stage				0.914
A (*n*/%)	228	37 (16.2)	191 (83.8)	
B (*n*/%)	45	8 (17.8)	37 (82.2)	
C (*n*/%)	2	0 (0)	2 (100)	
BCLC stage				0.538
0 (*n*/%)	1	0 (0)	1 (100)	
A (*n*/%)	67	10 (14.9)	57 (85.1)	
B (*n*/%)	108	17 (15.7)	91 (84.3)	
C (*n*/%)	98	18 (18.4)	80 (81.6)	
D (*n*/%)	1	0 (0)	1 (100)	
Cycles of DEB-TACE treatment				0.426
One cycle (*n*/%)	227	39 (17.2)	188 (82.8)	
Two or more cycles (*n*/%)	48	6 (12.5)	42 (87.5)	
Previous cTACE treatment				0.061
Yes (*n*/%)	118	25 (21.2)	93 (78.8)	
No (*n*/%)	157	20 (12.7)	137 (87.3)	
Previous surgery				0.278
Yes (*n*/%)	68	14 (20.6)	54 (79.4)	
No (*n*/%)	207	31 (15.0)	176 (85.0)	
Previous systematic chemotherapy				0.101

(*Continued*)

Table 5. (Continued)

Parameters	*N*	Not ORR	ORR	*p* Value
Yes (*n*/%)	8	3 (37.5)	5 (62.5)	
No (*n*/%)	267	42 (15.7)	225 (84.3)	
Previous radiofrequency ablation				0.308
Yes (*n*/%)	36	8 (22.2)	28 (77.8)	
No (*n*/%)	239	37 (15.5)	202 (84.5)	
Previous targeted therapy				0.361
Yes (*n*/%)	8	0 (0)	8 (100)	
No (*n*/%)	267	45 (16.9)	222 (83.1)	
Combination of ordinary embolization agent				0.254
Yes (*n*/%)	100	13 (13.0)	87 (87.0)	
No (*n*/%)	175	32 (18.3)	143 (81.7)	

Data are presented as count (%). Comparison between two groups was determined by chi-square test. A value of $p < 0.05$ was considered significant.

Table 6. Comparison of ORR in Subgroups Divided by Biochemical Indexes.

Parameters	*N*	Not ORR	ORR	*p* Value
CBC				
WBC				0.960
Abnormal (n/%)	80	13 (16.3)	67 (83.8)	
Normal (n/%)	194	32 (16.5)	162 (83.5)	
RBC				0.206
Abnormal (n/%)	93	19 (20.4)	74 (79.6)	
Normal (n/%)	180	26 (14.4)	154 (85.6)	
ANC				0.393
Abnormal (n/%)	71	14 (19.7)	57 (80.3)	
Normal (n/%)	202	31 (15.3)	171 (84.7)	
Hb				0.439
Abnormal (n/%)	105	15 (14.3)	90 (85.7)	
Normal (n/%)	168	30 (17.9)	138 (82.1)	
PLT				0.729
Abnormal (n/%)	121	21 (17.4)	100 (82.6)	
Normal (n/%)	152	24 (15.8)	128 (84.2)	
Liver function				
ALB				0.935
Abnormal (n/%)	105	17 (16.2)	88 (83.8)	
Normal (n/%)	169	28 (16.6)	141 (83.4)	
TP				0.806
Abnormal (n/%)	71	11 (15.5)	60 (84.5)	
Normal (n/%)	203	34 (16.7)	169 (83.3)	
TBIL				0.467
Abnormal (n/%)	79	11 (13.9)	68 (86.1)	
Normal (n/%)	194	34 (17.5)	160 (82.5)	
TBA				0.860
Abnormal (n/%)	110	17 (15.5)	93 (84.5)	
Normal (n/%)	150	22 (14.7)	128 (85.3)	
ALT				0.143
Abnormal (n/%)	59	6 (10.2)	53 (89.8)	
Normal (n/%)	215	39 (18.1)	176 (81.9)	
AST				0.575
Abnormal (n/%)	113	17 (15.0)	96 (85.0)	
Normal (n/%)	159	28 (17.6)	131 (82.4)	
ALP				0.387

(*Continued*)

Table 6. (Continued)

Parameters	*N*	Not ORR	ORR	*p* Value
Abnormal (n/%)	101	19 (18.8)	82 (81.2)	
Normal (n/%)	169	25 (14.8)	144 (85.2)	
Kidney function				
BCr				**0.008**
Abnormal (n/%)	34	11 (32.4)	23 (67.6)	
Normal (n/%)	239	34 (14.2)	205 (85.8)	
BUN				0.339
Abnormal (n/%)	33	7 (21.2)	26 (78.8)	
Normal (n/%)	237	35 (14.8)	202 (85.2)	
Tumor markers				
AFP				0.736
Abnormal (n/%)	168	27 (16.1)	141 (83.9)	
Normal (n/%)	102	18 (17.6)	84 (82.4)	
CEA				0.620
Abnormal (n/%)	44	6 (13.6)	38 (86.4)	
Normal (n/%)	204	34 (16.7)	170 (83.3)	
CA19-9				0.638
Abnormal (n/%)	65	12 (18.5)	53 (81.5)	
Normal (n/%)	182	29 (15.9)	153 (84.1)	

Data are presented as count (%). Comparison between two groups was determined by chi-square test. A value of $p < 0.05$ was considered significant.

Table 7. Factors Influencing ORR Achievement by Logistic Regression Model Analysis.

	Univariate Logistic Regression				Multivariate Logistic Regression			
			95% CI				95% CI	
Parameters	*p* Value	OR	Lower	Higher	*p* Value	OR	Lower	Higher
Age >60 years	0.187	0.650	0.342	1.234	–	–	–	–
Male	0.765	0.875	0.365	2.100	–	–	–	–
History of HB	0.066	2.026	0.955	4.299	0.150	1.727	0.821	3.633
History of alcohol use	0.573	0.832	0.439	1.577	–	–	–	–
History of cirrhosis	0.319	1.386	0.729	2.637	–	–	–	–
Multifocal disease	0.061	0.487	0.230	1.034	0.152	0.558	0.251	1.239
Tumor location: left liver	0.610	0.802	0.344	1.871	–	–	–	–
Tumor location: right liver	0.610	1.181	0.623	2.238	–	–	–	–
Tumor location: bilobar	0.879	0.949	0.481	1.870	–	–	–	–
Largest nodule size >5 cm	0.722	1.123	0.592	2.130	–	–	–	–
Portal vein invasion	**0.021**	0.461	0.239	0.889	**0.040**	0.477	0.235	0.966
Hepatic vein invasion	0.164	0.554	0.242	1.272	–	–	–	–
Higher ECOG performance status	0.980	1.006	0.634	1.596	–	–	–	–
Higher Child–Pugh stage	0.898	1.049	0.501	2.197	–	–	–	–
Higher BCLC stage	0.544	0.881	0.584	1.328	–	–	–	–
Two or more cycles of DEB-TACE treatment	0.428	1.452	0.577	3.652	–	–	–	–
Previous cTACE treatment	0.063	0.543	0.285	1.034	**0.030**	0.458	0.226	0.928
Previous surgery	0.280	0.679	0.337	1.369	–	–	–	–
Previous systematic chemotherapy	0.119	0.311	0.072	1.351	–	–	–	–
Previous radiofrequency ablation	0.311	0.641	0.271	1.516	–	–	–	–
Previous targeted therapy	–	–	–	–	–	–	–	–
Combination of ordinary embolization agent	0.256	1.498	0.746	3.008	–	–	–	–
WBC abnormal	0.960	1.018	0.503	2.060	–	–	–	–
RBC abnormal	0.208	0.658	0.342	1.264	–	–	–	–
ANC abnormal	0.394	0.738	0.367	1.484	–	–	–	–
Hb abnormal	0.440	1.304	0.665	2.560	–	–	–	–
PLT abnormal	0.729	0.893	0.470	1.696	–	–	–	–
ALB abnormal	0.935	1.028	0.532	1.987	–	–	–	–
TP abnormal	0.806	1.097	0.523	2.302	–	–	–	–
TBIL abnormal	0.468	1.314	0.629	2.744	–	–	–	–

(*Continued*)

Table 7. (Continued)

	Univariate Logistic Regression				Multivariate Logistic Regression			
			95% CI				95% CI	
Parameters	*p* Value	OR	Lower	Higher	*p* Value	OR	Lower	Higher
TBA abnormal	0.860	0.940	0.473	1.869	–	–	–	–
ALT abnormal	0.149	1.957	0.786	4.876	–	–	–	–
AST abnormal	0.575	1.207	0.625	2.330	–	–	–	–
ALP abnormal	0.388	0.749	0.389	1.443	–	–	–	–
BCr abnormal	**0.010**	0.347	0.155	0.776	**0.017**	0.353	0.149	0.833
BUN abnormal	0.342	0.644	0.259	1.596	–	–	–	–
AFP abnormal	0.736	1.119	0.581	2.154	–	–	–	–
CEA abnormal	0.621	1.267	0.497	3.231	–	–	–	–
CA199 abnormal	0.639	0.837	0.399	1.758	–	–	–	–

Data was presented as *p* value, OR, and 95% CI. Factors affecting ORR achievement were determined by univariate logistic regression analysis, while all factors with a value of $p \leq 0.1$ were further detected by multivariate logistic regression analysis. A value of $p < 0.05$ was considered significant. Child–Pugh stage was scored as 0—A, 1—B, 2—C; BCLC stage was scored as 0—Stage 0, 1—Stage A, 2—Stage B, 3—Stage C, 4—Stage D. The logistic analysis was performed based on these definitions.

groups to combine with the positive ion groups in the dilute solution of chemotherapeutics[20]. The technique of DEB-TACE using microbeads allows for higher and more sustained concentration of drugs. Moreover, the procedure prevents the flow of the chemotherapy agents to the systemic circulation, which would then reduce the potential for adverse events.

The effort in exploring the efficacy of DEB-TACE in the treatment of HCC patients has now been ongoing for more than 20 years, and the findings published to date have shown promising clinical efficacy. A prospective cohort study of 57 HCC patients revealed that the ORR at 1 month of DEB-TACE was 60%[21]. Another single-center, prospective cohort study in Germany showed a CR rate of 28.6% and an ORR of 71.4% in 28 HCC patients treated with DEB-TACE[22]. Additionally, in a study that evaluated the efficacy of DEB-TACE as a potential bridge therapy for HCC patients undergoing liver transplantation, 40% of the patients achieved CR and 33% achieved PR, giving an ORR of 73%[9]. However, most of the clinical studies have been conducted in Western countries and have had relatively small sample sizes. Our study was a multi-

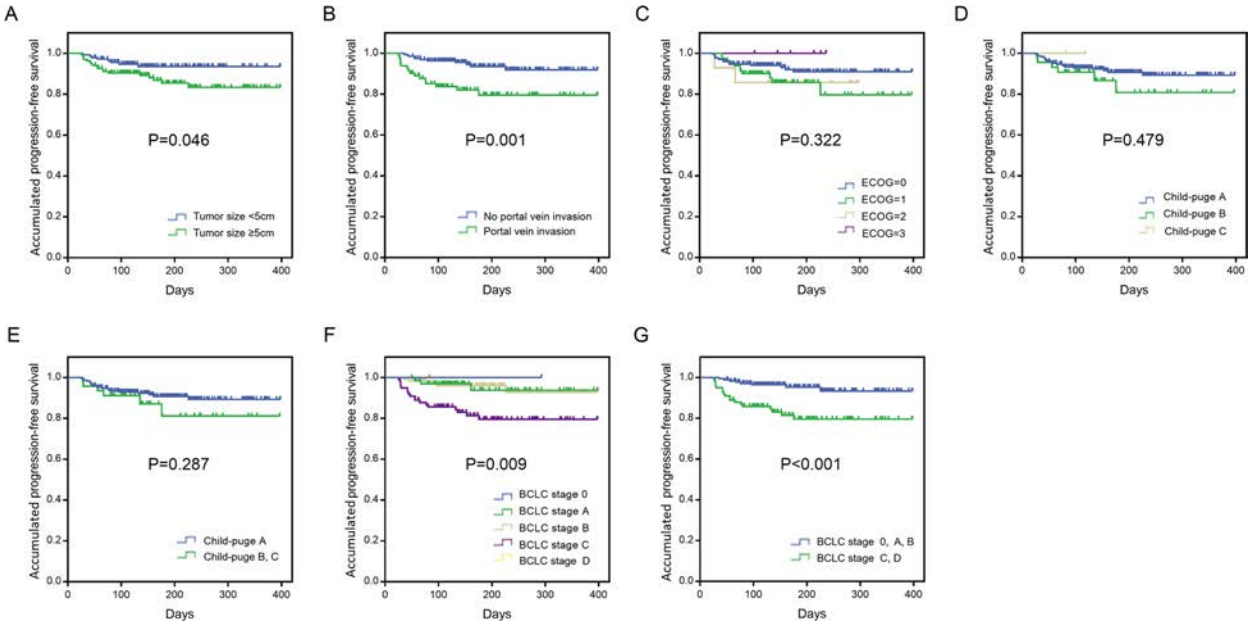

Figure 5. Comparison of PFS between/among subgroups. Tumor size >5 cm (A), portal vein invasion (B), and higher Barcelona Clinic Liver Cancer (BCLC) stage (F, G) correlated with shorter PFS, while Eastern Cooperative Oncology Group (ECOG) status (C) or Child–Pugh stage (D, E) was not associated with PFS. K–M analysis was performed to evaluate the OS between/among subgroups. Log-rank test was conducted to determine the difference between/among subgroups. A value of $p < 0.05$ was considered significant.

Table 8. Cox's Proportional Hazards Regression Model Analysis of Factors Predicting Progression-Free Survival (PFS)

	Univariate Cox's Regression				Multivariate Cox's Regression			
			95% CI				95% CI	
Parameters	*p* Value	HR	Lower	Higher	*p* Value	HR	Lower	Higher
Age >60 years	0.119	0.515	0.224	1.185	–	–	–	–
Male	0.770	0.865	0.326	2.293	–	–	–	–
HBV positive	0.759	0.858	0.324	2.276	–	–	–	–
Drink	0.746	1.136	0.526	2.450	–	–	–	–
Cirrhosis	0.376	0.706	0.327	1.525	–	–	–	–
Multifocal disease	0.112	2.204	0.831	5.848	–	–	–	–
Tumor location: left liver	0.616	0.735	0.221	2.448	–	–	–	–
Tumor location: right liver	0.544	0.787	0.364	1.703	–	–	–	–
Tumor location: bilobar	0.306	1.502	0.690	3.273	–	–	–	–
Largest nodule size ≥5 cm	0.052	2.281	0.991	5.249	0.801	1.152	0.384	3.455
Portal vein invasion	**0.002**	3.486	1.601	7.592	0.857	1.108	0.363	3.385
Hepatic vein invasion	0.696	1.237	0.426	3.589	–	–	–	–
Higher ECOG performance status	0.419	1.221	0.752	1.982	–	–	–	–
Higher Child–Pugh stage	0.434	1.354	0.634	2.893	–	–	–	–
Higher BCLC stage	**0.003**	2.467	1.362	4.469	**0.029**	2.613	1.101	6.202
Two or more cycles of DEB-TACE treatment	0.125	0.322	0.076	1.368	–	–	–	–
Previous cTACE treatment	0.751	1.133	0.524	2.450	–	–	–	–
Previous surgery	0.246	1.613	0.719	3.621	–	–	–	–
Previous systematic chemotherapy	0.822	1.258	0.170	9.293	–	–	–	–
Previous radiofrequency ablation	0.706	1.227	0.423	3.562	–	–	–	–
Previous targeted therapy	0.545	0.047	0.000	909.298	–	–	–	–
Combination of ordinary embolization agent	0.595	1.235	0.567	2.690	–	–	–	–
WBC abnormal	0.061	2.092	0.968	4.524	0.235	1.791	0.685	4.683
RBC abnormal	0.055	2.156	0.984	4.726	0.517	1.384	0.518	3.694
ANC abnormal	0.098	1.966	0.883	4.377	0.385	1.539	0.582	4.071
HB abnormal	0.352	1.452	0.662	3.182	–	–	–	–
PLT abnormal	0.491	1.311	0.607	2.830	–	–	–	–
ALB abnormal	0.174	1.706	0.790	3.682	–	–	–	–
TP abnormal	0.494	0.711	0.268	1.887	–	–	–	–
TBIL abnormal	0.129	1.828	0.840	3.981	–	–	–	–
TBA abnormal	0.116	1.917	0.852	4.316	–	–	–	–
ALT abnormal	0.193	1.740	0.756	4.006	–	–	–	–
AST abnormal	0.113	1.878	0.862	4.091	–	–	–	–
ALP abnormal	**0.001**	4.003	1.740	9.208	0.053	2.550	0.989	6.574
BCr abnormal	**0.002**	3.772	1.636	8.695	0.240	1.900	0.652	5.539
BUN abnormal	0.081	2.252	0.904	5.610	0.285	1.812	0.609	5.388
AFP abnormal	0.196	1.834	0.732	4.597	–	–	–	–
CEA abnormal	0.252	1.731	0.677	4.425	–	–	–	–
CA199 abnormal	**0.007**	3.069	1.354	6.956	0.255	1.783	0.659	4.822

Data are presented as *p* value, HR (hazards ratio), and 95% CI. Factors affecting PFS were determined by univariate Cox's proportional hazards regression model analysis, while all factors with a value of $p \leq 0.1$ were further detected by multivariate Cox's proportional hazards regression analysis. A value of $p < 0.05$ was considered significant. Child–Pugh stage was scored as 0—A, 1—B, 2—C; BCLC stage was scored as 0—stage 0, 1—stage A, 2—stage B, 3—stage C, 4—stage D. The logistic analysis was performed based on these definitions.

center, cross-regional study that enrolled 275 Chinese HCC patients. Of note, we report a relatively high CR rate of 22.9% and an impressive ORR of 83.6% within 1–3 months. However, it should be noted that the treatment responses vary among studies, which might result from the fact that treatment responses in some of the previous studies were evaluated earlier in the studies[21,22]. In addition, the patients' eligibility could cause distinct treatment responses as well. In some of the previous studies, they enrolled the HCC patients undergoing liver transplant that are of better prognosis, which might partially explain the better CR rate than ours[9]. Besides, different evaluating criteria, which are that of the European Association for the Study of the Liver (EASL) criteria, and the image examination method (diffusion-weighted imaging) were utilized in the previous studies, which could also contribute to the diversified treatment responses[21].

Although a few studies elucidate that the survival of patients treated by DEB-TACE and cTACE is of no difference, accumulating evidence indicates that the survival of patients who received DEB-TACE is superior to that of those who received cTACE. In one of those

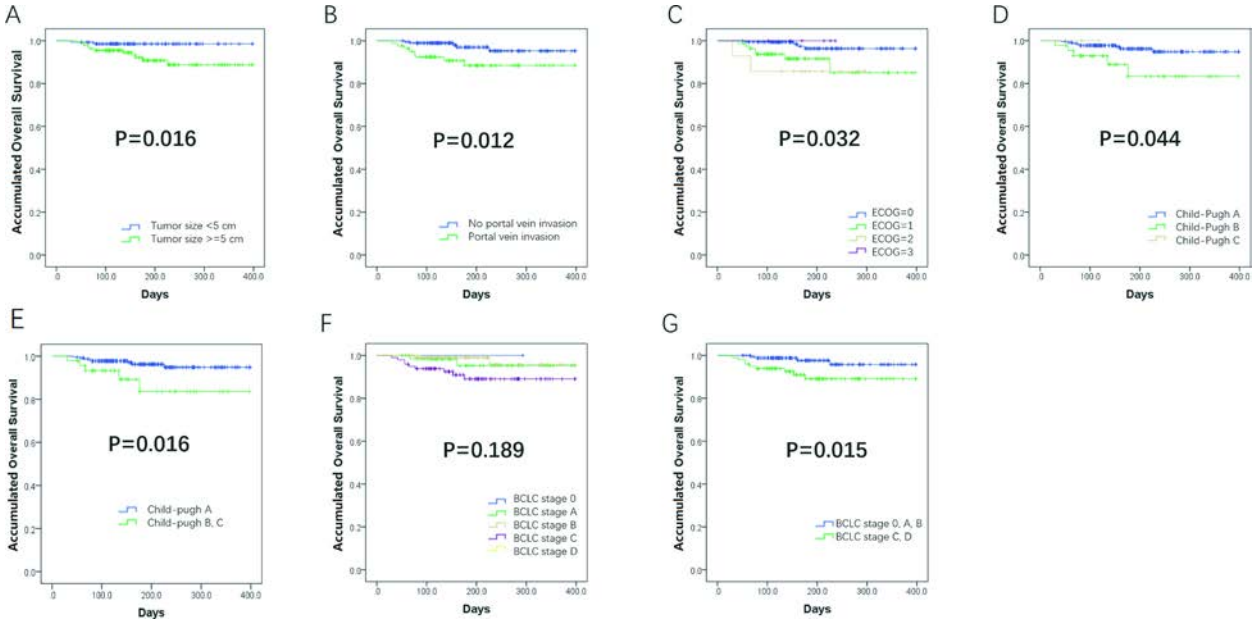

Figure 6. Comparison of OS between/among subgroups. Patients with tumor size ≥5 cm (A), portal vein invasion (B), higher ECOG performance status (C), higher Child–Pugh stage (D), Child–Pugh stage B/C (E), and BCLC stage C/D (G) had worse OS. No difference of OS in patients with tumor size ≥5 cm or <5 cm, or higher BCLC stage (F) was discovered. K–M curves were performed to evaluate the OS between/among subgroups. Log-rank test was conducted to determine the difference between/among subgroups. A value of $p < 0.05$ was considered significant.

studies that reveal the survival benefit of DEB-TACE, the mean survival of unresectable HCC patients treated with DEB-TACE is better than those treated with cTACE (651 ± 76 days vs. 414 ± 43 days)[23]. In the study by Popovic et al., the mean survival is 33.9 months, and the 1-year and 3-year OS rates were 97.1% and 65.7%, respectively, in intermediate HCC patients[24]. Moreover, in a retrospective study conducted on 313 unresectable HCC patients, the mean survival was 28.16 ± 2.75 months[25]. In this study, the mean PFS was 362 (95% CI: 34.9–375) days, the 6-month PFS rate was 89.4 ± 2.1%, and the mean OS was 380 (95% CI: 370–389) days, the 6-month OS rate was 94.4 ± 1.7%. There are several reasons that give rise to the differences on survival outcomes. First, previous survival studies mainly concern the long-term survival, the follow-up times in their studies are much longer than ours; second, the different sample sizes among studies might also contribute to the differences in survival.

Although TACE is currently recommended as the standard therapy for intermediate stage HCC patients as stated in the BCLC staging criteria, this approach has also been applied for patients with advanced as well as early stage disease. Accordingly, among all the patients treated by DEB-TACE, different HCC cohorts benefit variously from the treatment—that is to say, there might be certain factors that could predict a better treatment response or survival posttreatment. In a prospective study evaluating the predictive value of imaging parameters for efficacy of DEB-TACE, a more confined diffusion is observed in patients with an objective response (CR + PR), and patients with apparent diffusion coefficients $<0.83 \times 10$ (-3) mm^2/s have longer survival[21]. However, other factors such as AFP, performance status, advanced HCC, Child–Pugh stage, albumin level, and presence of ascites can also be used to predict survival in HCC patients receiving DEB-TACE treatment, which are partially in line with our results[17]. In the study by Vesselle et al., patients whose tumors reside in segments I and IV have been shown to have worse response rates, while tumor size <5 cm is associated with an improved treatment response[26]. In this study, we identified several independent factors for clinical efficacy: (1) portal vein invasion, previous cTACE treatment, and abnormal BCr independently were associated with worse treatment response; (2) higher BCLC stage was an independent predictive factor for worse PFS, and abnormal ALB and TBIL could independently predict poor OS. BCLC stage has been used in the prognosis of HCC patients for years, and patients with higher BCLC stages have a worse overall prognosis after treatment[27]. According to recommendations, patients with portal vein invasion are nonideal candidates for TACE treatments because of their poor overall prognosis, and in a prior study, portal vein invasion was validated to be an important factor for unfavorable survival of unresectable HCC patients

Table 9. Cox's Proportional Hazards Regression Model Analysis of Factors Predicting Overall Survival (OS)

	Univariate Cox's Regression				Multivariate Cox's Regression			
			95% CI				95% CI	
Parameters	*p* Value	HR	Lower	Higher	*p* Value	HR	Lower	Higher
Age >60 years	0.066	0.243	0.054	1.098	0.248	0.332	0.051	2.158
Male	0.833	1.176	0.261	5.307	–	–	–	–
History of HB	0.576	0.692	0.190	2.515	–	–	–	–
History of alcohol use	0.953	0.967	0.325	2.879	–	–	–	–
History of cirrhosis	0.179	0.464	0.152	1.423	–	–	–	–
Multifocal disease	0.429	1.684	0.463	6.125	–	–	–	–
Tumor location: left liver	0.330	0.039	0.000	27.060	–	–	–	–
Tumor location: right liver	0.689	0.800	0.269	2.383	–	–	–	–
Tumor location: bilobar	0.120	2.376	0.798	7.076	–	–	–	–
Largest nodule size >5 cm	**0.031**	5.242	1.161	23.675	0.445	2.319	0.268	20.07
Portal vein invasion	**0.019**	3.810	1.246	11.652	0.363	2.713	0.316	23.322
Hepatic vein invasion	0.807	1.207	0.267	5.448	–	–	–	–
Higher ECOG performance status	**0.048**	1.765	1.004	3.102	0.550	0.719	0.244	2.122
Higher Child–Pugh stage	**0.045**	2.242	1.017	4.945	0.374	2.065	0.418	10.203
Higher BCLC stage	0.064	2.169	0.956	4.922	0.090	3.387	0.827	13.873
Two or more cycles of DEB-TACE treatment	0.246	0.298	0.038	2.305	–	–	–	–
Previous cTACE treatment	0.377	0.588	0.181	1.910	–	–	–	–
Previous surgery	0.423	0.540	0.120	2.439	–	–	–	–
Previous systematic chemotherapy	0.350	2.645	0.343	20.369	–	–	–	–
Previous radiofrequency ablation	0.753	1.273	0.282	5.746	–	–	–	–
Previous targeted therapy	0.670	0.047	0.000	58203	–	–	–	–
Combination of ordinary embolization agent	0.551	1.394	0.468	4.151	–	–	–	–
WBC abnormal	0.206	2.022	0.679	6.018	–	–	–	–
RBC abnormal	**0.025**	3.958	1.192	13.149	0.684	1.44	0.249	8.325
ANC abnormal	0.593	1.387	0.418	4.608	–	–	–	–
Hb abnormal	0.445	1.555	0.501	4.824	–	–	–	–
PLT abnormal	0.804	1.148	0.385	3.423	–	–	–	–
ALB abnormal	**0.003**	9.934	2.199	44.864	**0.011**	34.757	2.232	541.132
TP abnormal	0.900	0.921	0.253	3.349	–	–	–	–
TBIL abnormal	**0.004**	5.745	1.768	18.663	**0.009**	13.287	1.897	93.056
TBA abnormal	0.435	1.544	0.519	4.594	–	–	–	–
ALT abnormal	0.369	1.716	0.528	5.582	–	–	–	–
AST abnormal	**0.025**	4.400	1.210	16.005	0.798	0.776	0.111	5.435
ALP abnormal	**0.028**	3.757	1.157	12.202	0.570	0.593	0.098	3.599
BCr abnormal	**0.004**	5.219	1.705	15.982	0.107	3.614	0.758	17.231
BUN abnormal	0.057	3.144	0.968	10.214	0.887	0.88	0.15	5.158
AFP abnormal	0.192	2.750	0.602	12.570	–	–	–	–
CEA abnormal	0.408	1.751	0.464	6.605	–	–	–	–
CA199 abnormal	0.052	3.247	0.991	10.642	0.669	1.465	0.254	8.442

Data are presented as *p* value, HR, and 95% CI. Factors affecting OS were determined by univariate Cox's proportional hazards regression model analysis, while all factors with a value of $p \leq 0.1$ were further detected by multivariate Cox's proportional hazards regression analysis. A value of $p < 0.05$ was considered significant. Child–Pugh Stage was scored as 0—A, 1—B, 2—C; BCLC stage was scored as 0—stage 0, 1—stage A, 2—stage B, 3—stage C, 4—stage D. The logistic analysis was performed based on these definitions.

treated by high-intensity focused ultrasound combined with TACE[28,29]. In addition, previous treatment with cTACE was identified as a factor that predicted worse survival in our study. The concept of refractory cTACE treatment was first introduced in the clinical practice guidelines proposed by the Japan Society of Hepatology (JSH). In our study, some patients with a previous history of cTACE treatment received repeated cTACE and were refractory to cTACE, which caused damage to the normal liver tissue and led to a decreased survival time[30]. In addition, several laboratory indexes related to liver and renal function were also found to be predictive factors for clinical efficacy. BCr is a standard index for evaluating the renal function; elevated BCr level always suggests renal damage. In our study, abnormal BCr was a negative factor for survival, which might be explained by the fact that BCr level was associated with acute renal injury in HCC patients post-TACE treatment according to prior studies[31]. With respect to serum albumin, a previous study revealed that increased ALB level independently predicts shorter survival in response to DEB-TACE therapy, which is in line with the findings

Table 10. Liver Function Before and After DEB-TACE Treatment (333 HCC DEB-TACE Records)

Parameters	Baseline	1 Week Post-DEB-TACE	1-3 Months Post-DEB-TACE	*p* Value*	*p* Value†
ALB abnormal (*n*/%)	132 (39.9)	155 (54.0)	120 (40.3)	**<0.001**	0.901
TP abnormal (*n*/%)	85 (25.7)	142 (49.5)	67 (22.5)	**<0.001**	0.332
TBIL abnormal (*n*/%)	88 (26.7)	151 (52.6)	76 (25.5)	**<0.001**	0.567
TBA abnormal (*n*/%)	126 (40.4)	97 (35.7)	116 (41.0)	0.609	1.000
ALT abnormal (*n*/%)	70 (21.1)	178 (62.0)	61 (20.5)	**<0.001**	0.734
AST abnormal (*n*/%)	131 (39.8)	191 (67.5)	117 (39.4)	**<0.001**	0.494
ALP abnormal (*n*/%)	125 (38.2)	120 (42.4)	153 (51.7)	0.105	**<0.001**

Data are presented as count (%). Comparison among groups was determined by McNemar test. A value of $p < 0.05$ was considered significant. Analysis was based on 333 HCC DEB-TACE records.
*p value of liver function-related biochemical indexes of patients from baseline to 1 week posttreatment.
†p value of liver function-related biochemical indexes of patients from baseline to 1–3 months posttreatment.

from our study[17]. The results could be explained that the abnormal ALB level in HCC patients indicated a worse liver function, which was proven to be correlated with worse survival in HCC patients posttreatment[32]. Another prognostic factor related to the liver function in our study was abnormal TBIL, which has also been previously reported by other studies to be correlated with worse survival when the total serum bilirubin level is greater than 2 μmol/L[17].

In our study, the liver function based on related laboratory indexes was evaluated, and the proportions of abnormal ALB, TP, TBIL, ALT, and AST were all elevated at 1 week posttreatment and decreased at 1–3 months, while the numbers of abnormal TBA pre- and posttreatments were of no difference. Those results indicated that liver function might aggravate rapidly and recovered at 1–3 months posttreatment, suggesting that DEB-TACE treatment did not worsen the liver function of patients in the long term. A meta-analysis comparing cTACE and DEB-TACE found less liver dysfunction in the DEB-TACE groups, suggesting that the liver function might be better protected in patients receiving DEB-TACE treatment[33]. However, the number of patients with abnormal ALP at 1 week was similar to baseline, while it was strikingly elevated at 1–3 months. Like the other TACE, DEB-TACE is an invasive procedure that causes liver damage postoperation and leads to liver dysfunction, which is partially presented as the lift of liver enzymes. An elevation of ALP level might represent a bile duct obstruction, and the reason for continuous elevation of ALP level in our study might be because the median level of ALP at baseline was relatively high, indicating that the ALP level might be more difficult to recover[34].

Table 11. Safety Profiles of DEB-TACE Treatment (333 HCC DEB-TACE Records)

Parameters	*n* (%)
During DEB-TACE operation	
Pain	183 (55.0)
Fever	123 (36.9)
Nausea	42 (12.6)
Vomiting	35 (10.5)
Others	21 (6.3)
1 month after DEB-TACE operation	
Pain	95 (28.5)
Fever	78 (23.4)
Vomiting	37 (11.1)
Nausea	32 (9.6)
Discoloration	4 (1.2)
Bone marrow toxicity	4 (1.2)
Others	3 (0.9)

Data are presented as count (%). Description was based on 333 HCC DEB-TACE records. HCC, hepatocellular carcinoma; DEB-TACE, drug-eluting bead transarterial chemoembolization.

The most common adverse events in DEB-TACE observed by previous studies are chemoembolization syndrome, including abdominal pain, fever, fatigue, nausea and vomiting, and liver dysfunction[33,35]. In this study, the most common adverse events both during and postoperation were pain and fever, which are totally manageable in clinical practice. The chemotherapeutics-related adverse events, discoloration, and bone marrow toxicity were rare in our study. The results of the AEs suggested that DEB-TACE treatment is tolerable among HCC patients.

This present study had some limitations. First, the follow-up duration in our study was short, and thus the long-term efficacy was not assessed. Second, some other treatments and multiple cycles of DEB-TACE procedures might interfere with the treatment response and survival of patients. However, the multivariate regression analysis was performed to eliminate the confounding effect of those factors. Third, the assessment of treatment response was performed in a relatively large time window (1–3 months after DEB-TACE) instead of a fixed time, which might result in some bias in our study. Fourth, the imaging modality for treatment response assessment varied

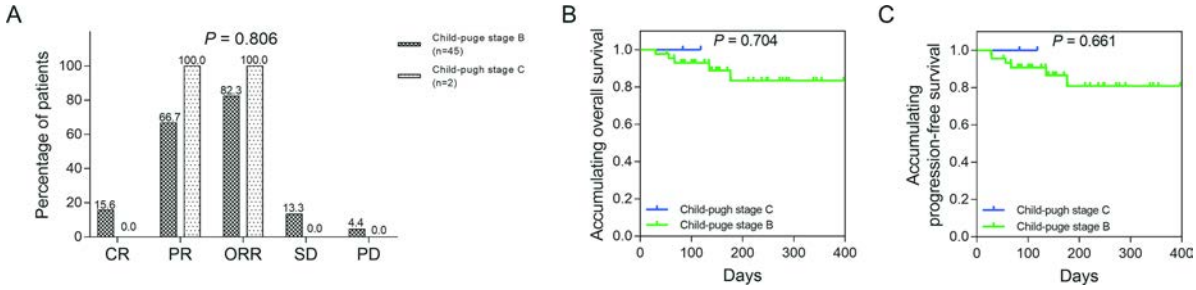

Figure 7. Comparison of efficacy between Child–Pugh stage B patients and Child–Pugh stage C patients. The treatment response rates (A), PFS (B), and OS (C) were of no difference between Child–Pugh stage B patients and Child–Pugh stage C patients. Comparison between two groups was determined by chi-square test. K–M analysis was performed to evaluate the OS between/among subgroups. Log-rank test was conducted to determine the difference between/among subgroups. A value of $p < 0.05$ was considered significant.

from one to another among the centers that were included in this study, which might cause bias.

In conclusion, we have demonstrated that DEB-TACE was a safe and effective treatment for Chinese HCC patients. We have identified several important factors that predict worse clinical outcomes, which include portal vein invasion, previous cTACE treatment, abnormal BCr, ALB, and TBIL.

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