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Efficacy of drug-eluting bead transarterial chemoembolization (DEB-TACE) combined with radiofrequency ablation versus DEB-TACE alone in Chinese hepatocellular carcinoma patients

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Abstract

To compare the efficacy of drug-eluting bead transarterial chemoembolization combined with radiofrequency ablation (DEB-TACE +RFA) versus DEB-TACE alone in Chinese hepatocellular carcinoma (HCC) patients.

The 28 patients receiving DEB-TACE+RFA and 74 HCC patients receiving DEB-TACE were recruited in this study. Treatment responses, progression-free survival (PFS), and overall survival (OS) were evaluated.

One to 3 months after treatments, the proportion of patients achieving complete response (CR) (78.6% vs 33.8%, $P<.001$) and objective response rate (ORR) (92.9% vs 78.4%, $P=.010$) were elevated in DEB-TACE+RFA group compared with DEB-TACE group. Multivariate logistic regression displayed that DEB-TACE+RFA was an independently predicting factor for better CR ($P=.006$). Subgroup analysis of CR achievement illuminated that DEB-TACE+RFA disclosed better CR achievement in patients with history of cirrhosis ($P<.001$), tumor located in right liver ($P=.003$), bilobar disease ($P=.013$), tumor size <3.3 cm ($P=.001$), no portal vein invasion ($P=.001$), no hepatic vein invasion ($P<.001$), Child-pugh stage A ($P<.001$), Barcelona Clinic Liver Cancer (BCLC) stage 0, A-B ($P<.001$), abnormal alpha-fetoprotein (AFP) ($P=.001$) and normal AFP ($P=.016$). The PFSs were similar between 2 groups ($P=.112$), however, the OS was more prolonged in DEB-TACE+RFA group ($P=.025$) compared with DEB-TACE group. And subgroup analysis displayed that PFS of patients with largest nodule size >3.3 cm ($P=.025$) was longer and patients with unilobar disease ($P=.009$), and patients with no hepatic invasion ($P=.019$) and Child-pugh stage A ($P=.037$) had more favorable OS in DEB-TACE+RFA group compared with DEB-TACE group.

DEB-TACE+RFA achieved better treatment responses and OS compared with DEB-TACE alone in Chinese HCC patients.

Abbreviations: AFP = alpha fetoprotein, ALP = alkaline phosphatase, BCLC = Barcelona Clinic Liver Cancer, CBs = CalliSpheres Beads, CR = complete response, CT = computerized tomography, DCR = disease control rate, DEB-TACE = TACE using drug eluting bead, DEB-TACE+RFA = DEB-TACE combined with RFA, ECOG = Eastern Cooperative Oncology Group, HCC = hepatocellular carcinoma, MRI = magnetic resonance image, ORR = objective response rate, OS = overall survival, PD = progressive disease, PFS = progression free survival, RFA = radiofrequency ablation, RFS = recurrence-free survival, RT = room temperature, TACE = transarterial chemoembolization.

Keywords: combination, drug-eluting bead transarterial chemoembolization (DEB-TACE), hepatocellular carcinoma, radiofrequency ablation, survival, treatment response

1. Introduction

Hepatocellular carcinoma (HCC), displaying declining incidence among younger adults (0–49) in the developed countries, is still the most frequent primary liver cancer also in younger population (below 60) in China.[1,2] As one of the top cancers with worst prognosis due to lacking symptoms at early stage, most patients are at intermediate and advanced stages at diagnosis, who can only be treated with non-potential curative therapies.[3] The management of HCC patients in addition to early stage in clinical practice now includes chemotherapy, radiotherapy, chemoradiation, local regional therapy and sorafenib, among which transarterial chemoembolization (TACE) is recommended as a standard therapy for HCC patients in Barcelona Clinic Liver Cancer (BCLC) B stage.[4]

For the purpose of eliminating systemic toxicity, better standardizing the operation procedure and improving treatment responses, TACE using drug-eluting bead (DEB-TACE) is developed and applied in HCC patients since 2006, presenting better efficacy and less chemotherapy-related systemic toxicity compared with conventional TACE (cTACE).[5,6] Radiofrequency ablation (RFA) is a potential curative therapy with minimal invasion for HCC patients in early stage who are not able to receive liver transplantation or hepatectomy due to poor liver function or diffuse tumors, disclosing good tumor ablation rate, mild adverse events (AEs) and good cost-effectiveness in clinical practice.[7–10] Previous studies elucidate that RFA combined with TACE is efficacious in HCC patients,

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nonetheless, effort and evidence of whether DEB-TACE combined with RFA (DEB-TACE+RFA) is more effective than the single use of DEB-TACE is still scarce.[11–13] Therefore, our study aimed to compare the efficacy of DEB-TACE+RFA versus DEB-TACE alone in Chinese HCC patients.

2. Methods

2.1. Patients

The 28 patients receiving DEB-TACE+RFA and 74 HCC patients receiving DEB-TACE were recruited in this study from July, 2016 to May, 2017 at the Department of Liver Cancer in Ningbo No.2 Hospital. The inclusion criteria were:

(1) patients diagnosed as primary HCC following the American Association for the Study of the Liver Diseases (AASLD) guidelines;
(2) age above 18 years old;
(3) about to receive DEB-TACE or DEB-TACE+RFA on demand. Meanwhile, the exclusion criteria were:
(4) contraindications to magnetic resonance image (MRI), computerized tomography (CT), ultrasonic technique, hepatic artery puncture or the use of Epirubicin;
(5) invisible tumor;
(6) ascites;
(7) cardiac disease, including congestive heart failure, recent myocardial infarction, or uncontrolled arrhythmias;
(8) severe liver or renal failure;
(9) coagulopathy;
(10) severe infection or sepsis;
(11) women who were pregnant or nursing.

This study was approved by the Ethical Committee of Ningbo No.2 Hospital and conducted strictly following the Declaration of Helsinki. Written informed consents were obtained from all participants.

2.2. DEB-TACE Procedure

The 100 to 300 μm CalliSpheres Beads (CBs) (Jiangsu Hengrui Medicine Co. Ltd., Jiangsu, China) were loaded with Epirubicin (80 mg) for each DEB-TACE procedure. To start with, Epirubicin was dissolved by water for injection into solution of concentration at 20 mg/mL and stored in a 10 mL syringe afterward. Subsequently, 1 bottle of CBs was shaken and the beads suspension was extracted by a 20 mL syringe, which stood at room temperature (RT) for 5 minutes. Discarding the supernatant in the syringe and mixed the remaining CBs with drug solution by a tee joint. Lastly, non-ionic contrast agent was added in the mixture at the ratio of 1:1, which stood for another 30 mins at RT for further application.

Each DEB-TACE procedure was performed on demand according to the evaluation of the multidisciplinary team in our hospital. The detection of tumor supplying vascular was performed by digital subtraction angiography (DSA). After the tumor supplying vascular was located, a microcatheter with diameter of 2.4F (Merit Maestro, Merit Medical System, Inc., UT) was super selectively catheterized leading by a microware, using Seldinger's technique. Then CBs loaded with Epirubicin mixed with non-ionic contrast agent was injected through microcatheter by the pulse injection method at the speed of 1 mL/min. The indication of the injection end was the stasis flow of contrast agent, and another time of angiography was performed to detect the blushed tumor post 5 minutes of the delivery, and the embolization was stopped if no more blushed tumor existed.

2.3. RFA procedure

RFA was performed if HCC patients who tolerated to RFA and still had residual tumor after 1 to 3 months post-DEB-TACE, which was confirmed by image examination. The RFA was conducted under the guidance of ultrasound, which was used to detect the size and location of residual tumor. Subsequently, under general anesthesia, monopole ablation electrode was punctured at intercostal area or costal margin post local disinfection, and overlay ablation was performed on each residual tumor for 10 to 20 minutes until complete ablation of the tumor existed, and the ablation area should reach over 5 cm from the edge of the tumor.

2.4. Evaluations of treatment responses and survival

Treatment responses were evaluated by MRI or CT post 1 to 3 months after DEB-TACE or DEB-TACE+RFA according to the criteria of modified Response Evaluation Criteria in Solid Tumors (mRECIST).[14]

(1) complete response (CR): the loss of any intratumoral arterial enhancement in the target nodules;
(2) partial response (PR): at least a 30% decline 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;
(3) stable disease (SD): any cases that do not measure up either PR or progressive disease (PD);
(4) PD: an elevation 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 initiation of treatment.

Objective response rate (ORR) was the proportion of patients achieving CR and PR, and disease control rate (DCR) was the proportion of HCC patients were CR, PR, and SD.

The median follow up time was 220 (range: 2–465) days and the last follow up date was November 20, 2017. Progression free survival (PFS) was the duration from treatment time to the date of disease progression or death from any cause, and overall survival (OS) is the duration from treatment time to the date of death from any cause.

2.5. Statistical analysis

Statistical analysis of our study was performed by SPSS 22.0 software (IBM Co., NY) and Graphpad Prism 6.0 software (GraphPad Software Inc). Comparison between 2 groups was determined by t test, Chi-square test or Wilcoxon rank sum test. Kaplan–Meier curves were performed to evaluate the PFS and OS. Univariate and multivariate logistic regressions were conducted to assess independent predictive value of DEB-TACE+RFA for treatment responses, and univariate as well as multivariate Cox's regression analyses were carried out for evaluating the independent predicting value of DEB-TACE+RFA for survival. $P < .05$ was considered significant.

3. Results

3.1. Patients

As listed in Table 1, the mean age of DEB-TACE group and DEB-TACE+RFA group were 59.93 ± 12.98 years and 58.72 ± 10.91 years ($P = .636$), respectively. In addition, the female/male ratio were 12/62 and 6/22 in DEB-TACE group and DEB-TACE+RFA group ($P = .538$). The number of patients with cirrhosis history in DEB-TACE group (60 (81.1%)) was predominantly larger compared

Table 1

Baseline characteristics of HCC patients.

Parameters	DEB-TACE group (N = 74)	DEB-TACE+RFA group (N = 28)	*P* value
Age, yr	59.93 ± 12.98	58.72 ± 10.91	.636
Gender (Female/Male)	12/62	6/22	.538
History of HB (n/%)	59 (79.7)	20 (71.4)	.371
History of HC (n/%)	1 (1.4)	2 (7.1)	.182
History of drink (n/%)	12 (16.2)	3 (10.7)	.699
History of cirrhosis (n/%)	60 (81.1)	17 (60.7)	**.033**
Tumor distribution			.145
Multifocal (n/%)	30 (40.5)	7 (25.0)	
Unifocal (n/%)	44 (59.5)	21 (75.0)	
Tumor location			
Left liver (n/%)	9 (12.2)	6 (21.4)	.238
Right liver (n/%)	45 (60.8)	19 (67.9)	.511
Bilobar (n/%)	20 (27.0)	3 (10.7)	.079
Largest nodule size, cm	3.85 (2.23–8.35)	2.70 (2.13–4.85)	.071
Portal vein invasion (n/%)	21 (28.4)	4 (14.3)	.140
Hepatic vein invasion (n/%)	3 (4.1)	2 (7.1)	.896
ECOG performance status			.186
0 (n/%)	43 (58.1)	22 (78.6)	
1 (n/%)	3 (4.1)	1 (3.6)	
2 (n/%)	26 (35.1)	4 (14.2)	
3 (n/%)	2 (2.7)	1 (3.6)	
Child-pugh Stage			.290
A (n/%)	58 (78.4)	25 (89.3)	
B (n/%)	14 (18.9)	3 (10.7)	
C (n/%)	2 (2.7)	0 (0.0)	
BCLC Stage			.444
0 (n/%)	1 (1.3)	1 (3.6)	
A (n/%)	19 (25.7)	10 (35.7)	
B (n/%)	22 (29.7)	10 (35.7)	
C (n/%)	25 (33.8)	6 (8.1)	
D (n/%)	2 (2.7)	0 (0.0)	
unknown	5 (6.8)	1 (3.6)	
Blood routine			
WBC (x 10^9 cell/L)	4.90 (3.88–6.33)	4.80 (3.10–5.85)	.239
RBC (x 10^{12} cell/L)	4.26 (3.75–4.68)	4.23 (3.70–4.70)	1.000
ANC%	65.4 (57.5–71.8)	64.9 (59.2–73.9)	.505
Hb (g/L)	131 (111–145)	133 (116–144)	.863
PLT (x 10^9 cell/L)	126 (80–164)	96 (70–152)	.213
Liver function			
ALB (g/L)	37.8 (34.7–41.5)	40.8 (36.7–46.7)	.069
TP (g/L)	70.0 (64.9–74.8)	73.1 (65.9–76.3)	.109
TBIL (umol/L)	13.1 (9.5–20.4)	13.5 (10.4–21.9)	.652
TBA (l/L)	13.9 (8.4–33.8)	12.7 (7.1–35.8)	.633
ALT (u/L)	27.0 (17.0–37.5)	22 (16–43.8)	.991
AST (u/L)	37.0 (25.5–49.5)	35.5 (24.0–53.5)	.912
ALP (u/L)	123.0 (82.5–162.0)	91 (70–135.5)	**.036**
Kidney function			
BCr (umol/L)	65.5 (54.2–75.2)	64.5 (56.6–72.6)	.898
BUN (mmol/L)	4.74 (4.03–5.42)	5.00 (4.16–6.02)	.584
Tumor markers			
AFP (ug/L)	26.8 (3.7–253.3)	17.8 (3.3–411.9)	.672
CEA (ug/L)	1.9 (1.1–3.2)	1.6 (0.9–3.6)	.461
CA199 (ku/L)	18.7 (10.3–31.3)	15.8 (8.4–25.9)	.407
Previous treatments			
cTACE (n/%)	45 (60.8)	12 (42.9)	.103
Surgery (n/%)	13 (17.6)	4 (17.3)	.921
Systematic chemotherapy (n/%)	1 (1.4)	1 (3.6)	.476
Radiofrequency ablation (n/%)	34 (45.9)	13 (46.4)	.965
Targeted therapy (n/%)	3 (4.1)	1 (3.6)	1.000
No previous treatments (n/%)	21 (28.4)	11 (39.3)	.289
Chemoembolization reagents			
Epirubicin (n/%)	74 (100.0)	28 (100.0)	1.000
Combination of ordinary embolization agent (n/%)	8 (10.8)	2 (7.1)	.855

Data was presented as mean ± standard deviation, median (25th–75th) or count (%). Comparison between 2 groups was determined by *t* test, Chi-square test or Wilcoxon rank sum test. $P < .05$ was considered significant. AFP = alpha fetoprotein, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, ANC = absolute neutrophil count, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, BCr = blood creatinine, BUN = blood urea nitrogen, CA199 = carbohydrate antigen199, CEA = carcino-embryonic antigen, cTACE = conventional transarterial chemo-embolization, DEB-TACE = drug-eluting bead transarterial chemoembolization, ECOG = Eastern Cooperative Oncology Group, Hb = hemoglobin, HB = hepatitis b, HC = hepatic c, HCC = hepatocellular carcinoma, PLT = platelet, RBC = red blood cell, RFA = radiofrequency ablation, TBA = total bile acid, TBIL = total bilirubin, TP = total protein, WBC = white blood cell.

Table 2

Treatment response.

Treatment response	DEB-TACEgroup (N = 74)	DEB-TACE+RFA group (N = 28)	*P* value
CR (n/%)	25 (33.8)	22 (78.6)	**<.001**
PR (n/%)	33 (44.6)	4 (14.3)	**.008**
SD (n/%)	12 (16.2)	0 (0)	**.033**
PD (n/%)	4 (5.4)	0 (0)	.570
Not assessed (n/%)	0 (0)	2 (7.1)	.073
ORR (n/%)	58 (78.4)	26 (92.9)	**.010**
DCR (n/%)	70 (94.6)	26 (92.9)	.570

Data was presented as count (percentage). Comparison between 2 groups was determined by Chi-square test. CR = complete response, DCR = disease control rate, DEB-TACE = drug-eluting bead transarterial chemoembolization, ORR = objective response rate, PD = progressive disease, PR = partial response, RFA = radiofrequency ablation, SD = stable disease.

with DEB-TACE+RFA group (17 (60.7%)) ($P = .033$). 30 (40.5%) patients had multifocal disease and 44 (59.5%) patients had unifocal disease in DEB-TACE group, while, 7 (25.0%) patients had multifocal disease and 21 (75.0%) patients had unifocal disease in DEB-TACE+RFA group ($P = .145$). Median largest nodule size were 3.85 (2.23–8.35) cm and 2.70 (2.13–4.85) cm in 2 groups ($P = .071$), respectively. The numbers of patients had portal vein invasion ($P = .140$) and hepatic vein invasion ($P = .896$) were 21 (28.4%) and 3 (4.1%) in DEB-TACE group, and 4 (14.3%) as well as 2 (7.1%) in DEB-TACE+RFA group. In addition, the alkaline phosphatase (ALP) level was elevated in DEB-TACE group than DEB-TACE +RFA group ($P = .036$). Other history, clinical characteristics, and laboratory indices were similar between 2 groups (Table 1).

3.2. Treatment responses

At 1–3 months after treatments, the percentage of patients achieved CR (78.6% vs 33.8%, $P < .001$) and ORR (92.9% vs 78.4%, $P = .010$) was increased in DEB-TACE+RFA group compared with DEB-TACE group (Table 2). However, the DCR in DEB-TACE+RFA group was of no difference compared with DEB-TACE group (92.9% vs 94.6%, $P = .570$).

3.3. Factors affecting treatment responses

As listed in Table 3, univariate logistic regression revealed that DEB-TACE+RFA correlated with elevated CR ($P < .001$). And

Table 3

Factors affecting CR achievement by logistic regression model analysis.

	Univariate logistic regression				Multivariate logistic regression			
	P value	OR	95% CI		*P* value	OR	95% CI	
Parameters			Lower	Higher			Lower	Higher
DEB-TACE+RFA (vs DEB-TACE)	**<.001**	10.780	3.348	34.705	**.006**	27.318	2.558	291.715
Age>60 years	.715	1.158	0.527	2.544	–	–	–	–
Male	.591	0.751	0.264	2.136	–	–	–	–
History of HB	.390	1.516	0.587	3.916	–	–	–	–
History of HC	.500	2.311	0.203	26.341	–	–	–	–
History of drink	.978	0.984	0.328	2.958	–	–	–	–
History of cirrhosis	.908	0.948	0.383	2.346	–	–	–	–
Multifocal disease	**.001**	0.228	0.092	0.563	.123	0.201	0.026	1.540
Tumor location-left liver	.415	1.607	0.514	5.027	–	–	–	–
Tumor location-right liver	**.015**	2.922	1.231	6.934	.537	0.556	0.086	3.583
Tumor location-Bilobar	**.001**	0.122	0.033	0.446	.248	0.208	0.014	2.986
Largest nodule size>3.3 cm	**<.001**	0.218	0.094	0.508	.861	1.207	0.146	9.951
Portal vein invasion	**<.001**	0.063	0.014	0.286	**.010**	0.010	0.000	0.327
Hepatic vein invasion	.244	0.266	0.029	2.472	–	–	–	–
Higher ECOG performance status	**.001**	0.447	0.280	0.713	.263	2.569	0.492	13.419
Higher Child-pugh Stage	.954	1.026	0.432	2.436	–	–	–	–
Higher BCLC Stage	**<.001**	0.299	0.168	0.533	.334	0.349	0.041	2.945
Previous cTACE treatment	.897	0.949	0.430	2.094	–	–	–	–
Previous Surgery	.996	1.003	0.353	2.853	–	–	–	–
Previous systematic chemotherapy	.999	-	0.000	-	–	–	–	–
Previous radiofrequency ablation	.118	1.887	0.851	4.182	–	–	–	–
Previous targeted therapy	.280	3.545	0.356	35.310	–	–	–	–
History of treatments	.267	1.630	0.688	3.864	–	–	–	–
Combination of ordinary embolization agent	.999	0.000	0.000	-	–	–	–	–
WBC abnormal	**.028**	3.080	1.128	8.409	.573	1.672	0.279	10.008
RBC abnormal	.564	1.261	0.574	2.770	–	–	–	–
ANC abnormal	.409	0.629	0.210	1.888	–	–	–	–
Hb abnormal	.715	1.158	0.527	2.544	–	–	–	–
PLT abnormal	.216	1.651	0.746	3.651	–	–	–	–
ALB abnormal	.147	0.552	0.247	1.232	–	–	–	–
TP abnormal	.264	0.584	0.228	1.499	–	–	–	–
TBIL abnormal	.712	0.846	0.348	2.057	—	–	–	–
TBA abnormal	.253	0.628	0.283	1.394	–	–	–	–
ALT abnormal	.296	1.816	0.593	5.558	–	–	–	–
AST abnormal	.849	0.925	0.415	2.062	–	–	–	–
ALP abnormal	**.008**	0.317	0.135	0.744	.795	1.240	0.246	6.251
BCr abnormal	**.039**	0.341	0.123	0.948	.562	0.558	0.077	4.022
BUN abnormal	.231	0.260	0.029	2.355	–	–	-	–
AFP abnormal	**.003**	0.272	0.115	0.643	.713	0.765	0.184	3.177
CEA abnormal	.661	0.578	0.050	6.677	–	–	–	–
CA199 abnormal	.259	0.438	0.104	1.837	–	–	–	–

Data was presented as *P* value, OR (odds ratio), and 95% CI (confidence interval). Factors affecting CR (complete response) achievement were determined by univariate logistic regression analysis, while all factors with *P* value no more than .1 were further detected by multivariate logistic regression analysis. *P* value <.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. AFP = alpha fetoprotein, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, ANC = absolute neutrophil count, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, BCr = blood creatinine, BUN = blood urea nitrogen, CA199 = carbohydrate antigen199, CEA = carcino-embryonic antigen, cTACE = conventional transarterial chemo-embolization, DEB-TACE = drug-eluting bead transarterial chemoembolization, ECOG = Eastern Cooperative Oncology Group, Hb = hemoglobin, HB = hepatitis b, HC = hepatic c, PLT = platelet, RBC = red blood cell, RFA = radiofrequency ablation, TBA = total bile acid, TBIL = total bilirubin, TP = total protein, WBC = white blood cell.

Table 4

CR achievement in subgroups analysis.

	DEB-TACE group (N = 74)	DEB-TACE+RFA group (N = 28)	*P* value
History of cirrhosis			
Yes (n/%)	20 (33.3)	15 (100.0)	**<.001**
No (n/%)	5 (35.7)	7 (63.6)	.238
Tumor location			
Left liver (n/%)	4 (44.4)	4 (80.0)	.301
Right liver (n/%)	20 (44.4)	16 (84.2)	**.003**
Bilobar (n/%)	1 (5.0)	2 (100.0)	**.013**
Largest nodule size			
>3.3 cm (n/%)	9 (22.0)	5 (62.5)	.058
≤3.3 cm (n/%)	16 (48.5)	17 (94.4)	**.001**
Portal vein invasion			
Yes (n/%)	1 (4.8)	1 (33.3)	.239
No (n/%)	24 (45.3)	21 (91.3)	**.001**
Hepatic vein invasion			
Yes (n/%)	0 (0.0)	1 (50.0)	.400
No (n/%)	25 (35.2)	21 (87.5)	**<.001**
Child-pugh Stage			
A	20 (34.5)	19 (82.6)	**<.001**
B-C	5 (31.3)	3 (100.0)	.058
BCLC Stage			
0,A-B	20 (47.6)	19 (95.0)	**<.001**
C-D	4 (14.8)	2 (40.0)	.228
AFP abnormal			
Yes (n/%)	9 (20.9)	8 (80.0)	**.001**
No (n/%)	15 (51.7)	11 (91.7)	**.016**

Data was presented as count (percentage). Comparison between 2 groups was determined by Chi-square test. *P* value <.05 was considered significant. AFP = alpha fetoprotein, BCLC = Barcelona Clinic Liver Cancer, CR = complete response, DEB-TACE = drug-eluting bead transarterial chemoembolization, RFA = radiofrequency ablation.

tumor location-right liver ($P = .015$), as well as white blood cell (WBC) abnormal ($P = .028$), were also associated with better CR. However, multifocal disease ($P = .001$), tumor location-bilobar ($P = .001$), largest nodule size >3.3 cm ($P < .001$), portal vein invasion ($P < .001$), higher Eastern Cooperative Oncology Group (ECOG) performance status ($P = .001$), higher BCLC stage ($P < .001$), ALP abnormal ($P = .008$), blood creatinine (BCr) abnormal ($P = .039$) and alpha fetoprotein (AFP) abnormal ($P = .003$) were correlated with worse CR. All factors with *P* value <.1 were include in the multivariate logistic regression, which displayed that DEB-TACE+RFA ($P = .006$) was an independently predicting factor for increased CR, while portal vein invasion ($P = .010$) independently associated with worse CR.

3.4. Subgroup analysis of CR achievement

As presented in Table 4, DEB-TACE+RFA attained better CR in patients with history of cirrhosis ($P < .001$), tumor located in right liver ($P = .003$), bilobar disease ($P = .013$), largest nodule size ≤3.3 cm ($P = .001$), no portal vein invasion ($P = .001$), no hepatic vein invasion ($P < .001$), Child-pugh stage A ($P < .001$), BCLC stage 0, A-B ($P < .001$), abnormal AFP ($P = .001$) and normal AFP ($P = .016$) compared with DEB-TACE.

3.5. PFS and OS in DEB-TACE group and DEB-TACE +RFA group

As shown in Figure 1, the mean PFS was 268 days (95% CI: 217–319 days) in DEB-TACE +RFA group and 213 days (95% CI: 181–245 days) in DEB-TACE group, and there was no difference between 2 groups ($P = .112$). However, the mean OS in DEB-TACE+RFA group (380 days, 95% CI: 338–423 days) was notably better than that in DEB-TACE group (320 days, 95% CI: 278–360 days) ($P = .025$).

3.6. Factors affecting PFS and OS

Univariate Cox's regression modal analysis displayed that DEB-TACE+RFA was not a predictive factor for PFS ($P = .116$). And multifocal disease ($P < .001$), tumor location-bilobar ($P = .001$), largest nodule size>3.3 cm ($P = .002$), portal vein invasion ($P < .001$), hepatic vein invasion ($P < .001$), higher ECOG

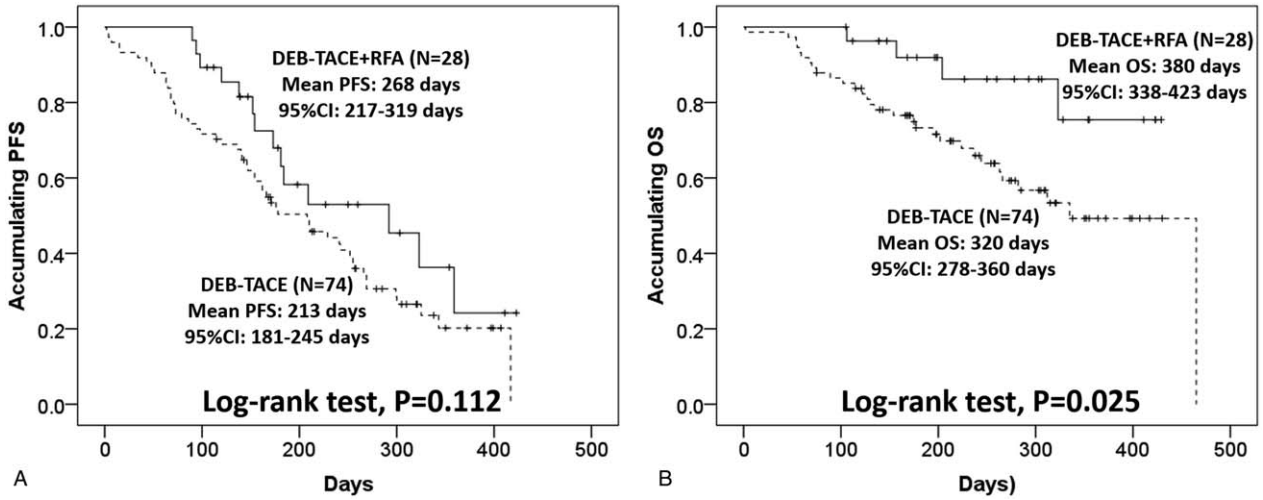

Figure 1. PFS and OS in DEB-TACE+RFA group and DEB-TACE group. The PFS (A) was of no difference while the OS (B) was markedly more prolonged in the DEB-TACE+RFA group compared with DEB-TACE group. K-M curve and log-rank test were conducted to evaluate the PFS and OS between 2 groups. $P < 0.05$ was considered significant. DEB-TACE = drug-eluting bead transarterial chemoembolization, HCC = hepatocellular carcinoma, K–M = Kaplan–Meier, OS = overall survival, PFS = progression free survival, RFA = radiofrequency ablation.

Table 5

Cox's proportional hazards regression model analysis of factors affecting PFS.

	Univariate Cox's regression				Multivariate Cox's regression			
	P value	HR	95% CI		*P* value	HR	95% CI	
Parameters			Lower	Higher			Lower	Higher
DEB-TACE+RFA (vs DEB-TACE)	.116	0.623	0.345	1.124	–	–	–	–
Age>60 years	.444	0.828	0.511	1.342	–	–	–	–
Male	.178	1.623	0.802	3.285	–	–	–	–
History of HB	.075	0.609	0.353	1.051	.851	1.105	0.391	3.121
History of HC	.761	0.795	0.181	3.492	–	–	–	–
History of drink	.329	0.703	0.346	1.427	–	–	–	–
History of cirrhosis	.699	0.892	0.499	1.595	–	–	–	–
Multifocal disease	**<.001**	3.110	1.886	5.127	**.050**	2.720	0.999	7.411
Tumor location-left liver	.326	0.702	0.346	1.423	–	–	–	–
Tumor location-right liver	.071	0.642	0.397	1.039	.612	1.379	0.398	4.771
Tumor location-Bilobar	**.001**	2.325	1.386	3.900	.200	2.382	0.631	8.989
Largest nodule size>3.3 cm	**.002**	2.131	1.307	3.475	.379	1.566	0.576	4.256
Portal vein invasion	**<.001**	3.531	2.111	5.906	.786	1.202	0.319	4.537
Hepatic vein invasion	**<.001**	3.531	2.111	5.906	.801	0.797	0.136	4.661
Higher ECOG performance status	**<.001**	1.755	1.416	2.174	.401	1.459	0.604	3.524
Higher Child-pugh Stage	.765	1.077	0.661	1.754	–	–	–	–
Higher BCLC Stage	**<.001**	1.928	1.475	2.520	.948	0.965	0.326	2.857
Previous cTACE treatment	.888	0.965	0.591	1.576	–	–	–	–
Previous Surgery	.660	1.146	0.624	2.107	–	–	–	–
Previous systematic chemotherapy	.462	0.476	0.066	3.440	–	–	–	–
Previous radiofrequency ablation	.356	0.795	0.489	1.294	–	–	–	–
Previous targeted therapy	.885	1.078	0.390	2.976	–	–	–	–
History of treatments	.399	0.794	0.465	1.356	-	–	–	–
Combination of ordinary embolization agent	**.024**	2.298	1.118	4.725	.598	1.387	0.411	4.680
WBC abnormal	.846	0.943	0.523	1.702	–	–	–	–
RBC abnormal	.258	1.322	0.815	2.145	–	–	–	–
ANC abnormal	.939	1.025	0.536	1.961	–	–	–	–
Hb abnormal	.310	1.285	0.792	2.087	–	–	–	–
PLT abnormal	.824	0.947	0.586	1.530	–	–	–	–
ALB abnormal	.309	1.300	0.784	2.155	–	–	–	–
TP abnormal	.603	1.159	0.665	2.018	–	–	–	–
TBIL abnormal	.271	1.346	0.793	2.287	–	–	–	–
TBA abnormal	.378	1.245	0.765	2.026	–	–	–	–
ALT abnormal	.398	0.737	0.363	1.496	–	–	–	–
AST abnormal	.266	1.316	0.811	2.135	–	–	–	–
ALP abnormal	.050	1.625	1.001	2.639	.104	0.449	0.171	1.180
BCr abnormal	.940	1.021	0.598	1.741	–	–	–	–
BUN abnormal	.795	0.869	0.300	2.513	–	–	–	–
AFP abnormal	**.001**	2.502	1.435	4.362	.282	1.606	0.678	3.804
CEA abnormal	.097	2.740	0.835	8.993	–	–	–	–
CA199 abnormal	.083	1.896	0.921	3.906	.322	2.009	0.505	7.987

Data was presented as *P* value, HR (hazards ratio) and 95% CI (confidence interval). Factors affecting PFS (progression free survival) were determined by univariate Cox's proportional hazards regression model analysis, while all factors with *P* value no more than .1 were further detected by multivariate Cox's proportional hazards regression analysis. *P* value <.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 Cox's proportional hazards analysis was performed based on these definitions. AFP = alpha fetoprotein, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, ANC = absolute neutrophil count, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, BCr = blood creatinine, BUN = blood urea nitrogen, CA199 = carbohydrate antigen199, CEA = carcino-embryonic antigen, cTACE = conventional transarterial chemo-embolization, DEB-TACE = drug-eluting bead transarterial chemoembolization, ECOG = Eastern Cooperative Oncology Group, Hb = hemoglobin, HB = hepatitis b, HC = hepatic c, PLT = platelet, RBC = red blood cell, RFA = radiofrequency ablation, TBA = total bile acid, TBIL = total bilirubin, TP = total protein, WBC = white blood cell.

performance status ($P<.001$), higher BCLC stage ($P<.001$), combination of ordinary embolization agent ($P=.024$) and AFP abnormal ($P=.001$) were associated with shorter PFS (Table 5). All factors with *P* value <.1 were included in the multivariate Cox's regression modal analysis, which showed that multifocal disease ($P=.050$) was an independent predicting factor for worse PFS.

As presented in Table 6, DEB-TACE+RFA ($P=.033$) was associated with prolonged OS. Additionally, history of HB ($P=.046$), as well as tumor location-right liver ($P=.046$), were also correlated with better OS. While, multifocal disease ($P=.002$), tumor location-bilobar ($P=.001$), largest nodule size >3.3 cm ($P=.003$), portal vein invasion ($P<.001$), higher ECOG performance status ($P<.001$), higher BCLC Stage ($P<.001$), RBC abnormal ($P=.025$), ALB abnormal ($P=.025$), TBA abnormal ($P=.024$), ALP abnormal ($P=.009$), AFP abnormal ($P=.003$) and CEA abnormal ($P=.004$) were factors for predicting worse OS. All factors with *P* value <.1 were included in the multivariate Cox's regression analysis, which revealed that no factor was independently associated with OS.

Table 6

Cox's proportional hazards regression model analysis of factors affecting OS.

	Univariate Cox's regression				Multivariate Cox's regression			
	P value	HR	95% CI		*P* value	HR	95% CI	
Parameters			Lower	Higher			Lower	Higher
DEB-TACE+RFA (vs DEB-TACE)	**.033**	0.321	0.113	0.915	.462	0.534	0.100	2.840
Age>60 years	.933	1.030	0.520	2.039	–	–	–	–
Male	.172	2.289	0.697	7.516	–	–	–	–
History of HB	**.046**	0.485	0.239	0.987	.871	0.885	0.202	3.885
History of HC	.214	2.485	0.592	10.427	–	–	–	–
History of drink	.926	1.043	0.430	2.532	–	–	–	–
History of cirrhosis	.846	0.924	0.414	2.060	–	–	–	–
Multifocal disease	**.002**	2.963	1.481	5.930	.141	2.653	0.723	9.742
Tumor location-left liver	.323	0.549	0.168	1.801	–	–	–	–
Tumor location-right liver	**.046**	0.498	0.251	0.987	.473	0.507	0.079	3.242
Tumor location-bilobar	**.001**	3.127	1.559	6.269	.701	1.450	0.217	9.688
Largest nodule size>3.3 cm	**.003**	3.111	1.478	6.551	.405	2.006	0.390	10.308
Portal vein invasion	<**.001**	4.074	2.042	8.130	.950	1.066	0.146	7.776
Hepatic vein invasion	.825	0.850	0.203	3.570	–	–	–	–
Higher ECOG performance status	<**.001**	1.882	1.390	2.547	.824	1.198	0.245	5.843
Higher Child-pugh Stage	.114	1.621	0.890	2.953	–	–	–	–
Higher BCLC Stage	<**.001**	2.516	1.658	3.819	.958	1.054	0.150	7.384
Previous cTACE treatment	.118	0.829	0.656	1.049	–	–	–	–
Previous Surgery	.654	0.804	0.310	2.083	–	–	–	–
Previous systematic chemotherapy	.943	1.075	0.146	7.890	–	–	–	–
Previous radiofrequency ablation	.145	0.590	0.290	1.200	–	–	–	–
Previous targeted therapy	.789	1.217	0.289	5.130	–	–	–	–
History of treatments	.165	0.600	0.292	1.233	–	–	–	–
Combination of ordinary embolization agent	.902	0.928	0.282	3.050	–	–	–	–
WBC abnormal	.952	1.026	0.444	2.370	–	–	–	–
RBC abnormal	**.025**	2.264	1.110	4.617	.537	1.500	0.414	5.428
ANC abnormal	.885	1.068	0.440	2.593	–	–	–	–
Hb abnormal	.128	1.712	0.857	3.422	–	–	–	–
PLT abnormal	.644	1.176	0.592	2.336	–	–	–	–
ALB abnormal	**.025**	2.499	1.122	5.566	.804	1.270	0.193	8.356
TP abnormal	.773	0.884	0.382	2.045	–	–	–	–
TBIL abnormal	.152	1.689	0.825	3.460	–	–	–	–
TBA abnormal	**.024**	2.322	1.119	4.820	.954	1.032	0.347	3.073
ALT abnormal	.525	0.711	0.249	2.033	–	–	–	–
AST abnormal	.121	1.733	0.864	3.473	–	–	–	–
ALP abnormal	**.009**	2.583	1.274	5.238	.768	0.756	0.118	4.845
BCr abnormal	.625	1.209	0.565	2.586	–	–	–	–
BUN abnormal	.891	1.110	0.250	4.931	–	–	–	–
AFP abnormal	**.003**	3.935	1.608	9.627	.057	4.509	0.958	21.219
CEA abnormal	**.004**	6.331	1.824	21.970	–	–	–	–
CA199 abnormal	.080	2.237	0.908	5.509	.553	1.785	0.264	12.079

Data was presented as *P* value, HR (hazards ratio) and 95% CI (confidence interval). Factors affecting OS (overall survival) were determined by univariate Cox's proportional hazards regression model analysis, while all factors with *P* value no more than .1 were further detected by multivariate Cox's proportional hazards regression analysis. *P* value <.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 Cox's proportional hazards analysis was performed based on these definitions. AFP = alpha fetoprotein, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, ANC = absolute neutrophil count, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, BCr = blood creatinine, BUN = blood urea nitrogen, CA199 = carbohydrate antigen199, CEA = carcino-embryonic antigen, cTACE = conventional transarterial chemo-embolization, DEB-TACE = drug-eluting bead transarterial chemoembolization, ECOG = Eastern Cooperative Oncology Group, Hb = hemoglobin, HB = hepatitis b, HC = hepatic c, PLT = platelet, RBC = red blood cell, RFA = radiofrequency ablation, TBA = total bile acid, TBIL = total bilirubin, TP = total protein, WBC = white blood cell.

3.7. Subgroup analysis of PFS and OS

Subgroup analysis of PFS revealed that the PFS of patients with largest nodule size >3.3 cm was more prolonged in DEB-TACE+RFA group compared with DEB-TACE group (*P* =.025) (Fig. 2F). However, the PFSs of 2 groups were similar in patients with no cirrhosis history (Fig. 2A, *P*=.283), cirrhosis history (Fig. 2B, *P*=.270), unilobar disease (Fig. 2C, *P*=.238), bilobar disease (Fig. 2D, *P*=.730), largest nodule size <3.3 cm (Fig. 2E, *P*=.471), no portal vein invasion (Fig. 2G, *P*=.328), portal vein invasion (Fig. 2H, *P*=.440), no hepatic vein invasion (Fig. 2I, *P*=.114), hepatic vein invasion (Fig. 2J, *P*=.227), Child-pugh stage A (Fig. 2K, *P*=.090), Child-pugh stage B-C (Fig. 2L, *P*=.779), BCLC stage 0-B (Fig. 2M, *P*=.949), BCLC stage C-D (Fig. 2N, *P*=.431), abnormal AFP (Fig. 2O, *P*=.081) and normal AFP (Fig. 2P, *P*=.631).

As presented in Figure 3, DEB-TACE+RFA accomplished increased OS in patients with unilobar disease (Fig. 3C, *P*=.009), no hepatic invasion (Fig. 3I, *P*=.019) and Child-pugh stage A

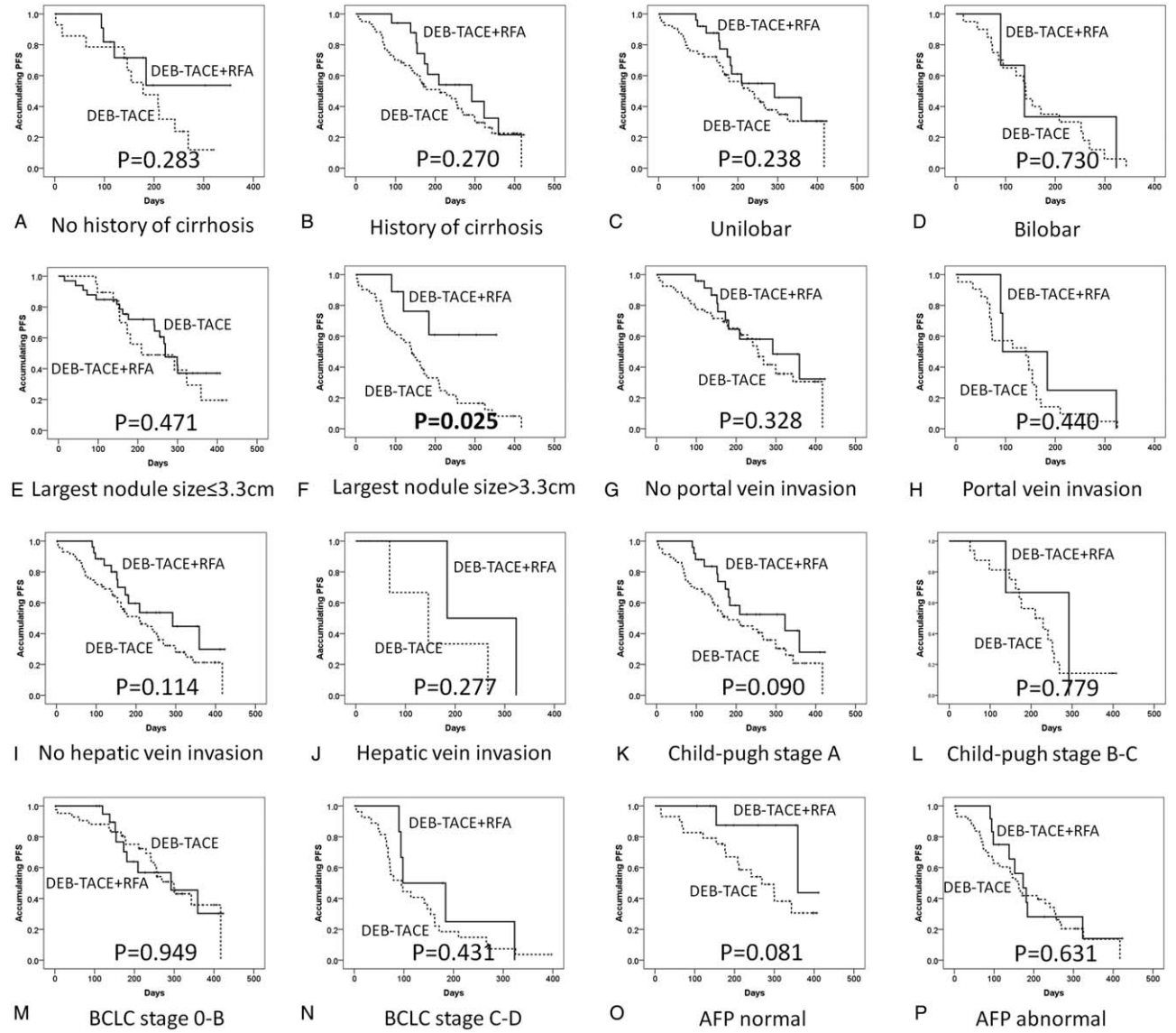

Figure 2. PFS in subgroups. Patients with largest nodule size >3.3 cm (F) had better PFS in DEB-TACE+RFA group compared with DEB-TACE group. While, the PFSs of 2 groups were similar in patients with other characteristics (A-E, G-P). K–M curve and log-rank test were conducted to evaluate the PFS and OS between 2 groups. $P<0.05$ was considered significant. AFP = alpha-fetoprotein, BCLC = Barcelona Clinic Liver Cancer, DEB-TACE = drug-eluting bead transarterial chemoembolization, K–M = Kaplan–Meier, PFS = progression free survival, RFA = radiofrequency ablation.

(Fig. 3K, $P=.037$). Nonetheless, the OS was of no difference in patients with other clinical characteristics (Fig. 3A-B, D-H, J, L-*P*, all $P>.05$).

4. Discussion

In this study, the results showed that:

(1) the CR and ORR were increased in DEB-TACE+RFA group compared with DEB-TACE group, and multivariate logistic regression revealed that DEB-TACE+RFA was independently associated with increased CR;
(2) subgroup analysis of CR achievement disclosed that the CR was increased in patients with history of cirrhosis, tumor located in right liver, bilobar disease, tumor size <3.3 cm, no portal vein invasion, no hepatic vein invasion, Child-pugh stage A, BCLC stage 0, A-B in DEB-TACE+RFA compared with DEB-TACE group;
(3) OS in DEB-TACE+RFA group was longer compared with DEB-TACE group, however, the PFSs were similar in 2 groups, and univariate as well as multivariate Cox's regression modal analysis illuminated that DEB-TACE +RFA was not independently associated with PFS or OS;
(4) subgroup analysis displayed that the PFS of patients with largest nodule size >3.3 cm was longer in DEB-TACE+RFA group compared with DEB-TACE group, and patients with unilobar disease, no hepatic vein invasion and Child-pugh stage A had more prolonged OS treated by DEB-TACE+RFA.

The CR and ORR of DEB-TACE in HCC patients realize a range of approximately 32% to 42.4% and 51% to 94.5% in several previous studies, displaying good treatment responses.[15–

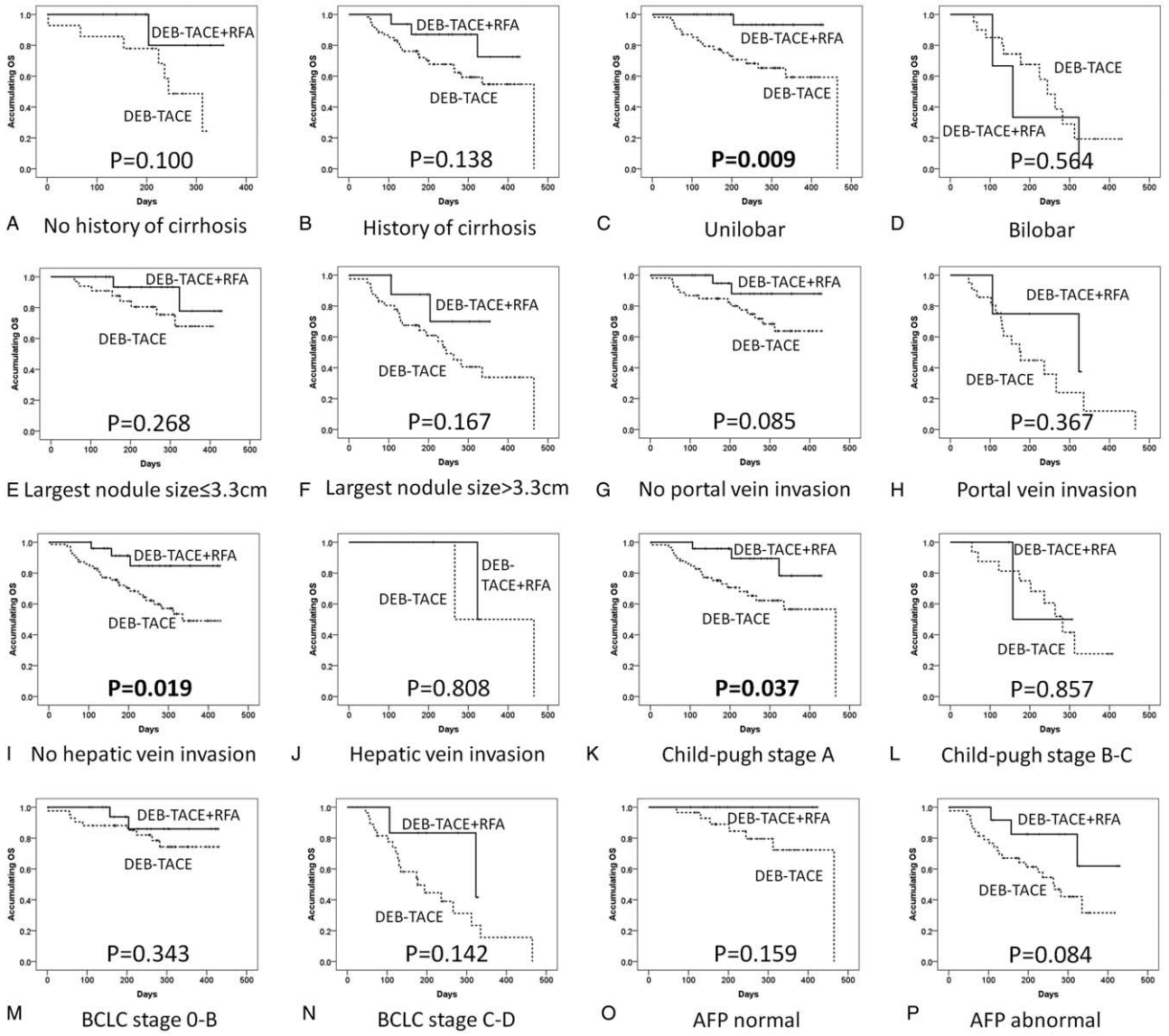

Figure 3. OS in subgroups. Unilobar disease (C), no hepatic invasion (I) and Child-pugh stage A (K) associated with more favorable OS treated by DEB-TACE+RFA compared with DEB-TACE alone. However, the OS was of no difference in patients with other clinical characteristics (A-B, D-H, J, L-P). K–M curve and log-rank test were conducted to evaluate the PFS and OS between 2 groups. $P < .05$ was considered significant. DEB-TACE = drug-eluting bead transarterial chemoembolization, K–M = Kaplan–Meier, OS = overall survival, RFA = radiofrequency ablation.

17] While for RFA, previous studies indicate responses rates of RFA in HCC patients with a CR range roughly at 20% to 90%.[18–20] Prior studies show that combining TACE with RFA realizes relatively encouraging treatment responses. For instance, in the study of Yan JY et al, TACE is combined with RFA in HCC patients have large tumor beyond 7 cm, and at 1 month after treatment, the CR and ORR achieve 87.4% and 96.6%, respectively.[21] However, to our best knowledge, the studies evaluating the efficacy of DEB-TACE +RFA in HCC patients are few. One study evaluated the treatment response of DEB-TACE +RFA in HCC patients, the prospective study enrolls 40 patients with single HCC and tumor size larger than 3 cm treated by DEB-TACE+RFA and 20 patients treated by single DEB-TACE and discloses a better CR in HCC patients treated by DEB-TACE +RFA (80% vs 40%, $P < .001$).[22] In our study, DEB-TACE +RFA achieved more favorable CR (78.6% vs 33.8%) and ORR (92.9% vs 78.4%) in HCC patients compared with DEB-TACE alone, and multivariate logistic regression revealed that DEB-TACE+RFA was independently correlated with increased CR. The results in our study suggest that DEB-TACE+RFA might have a more pleasant efficacy than using DEB-TACE alone in HCC patients. RFA is a potentially curative therapy for HCC patients and displays satisfying tumor control according to numerous previous studies, which might be able to explain why DEB-TACE+RFA achieved better treatment responses in our study.[23]

As to the survival profile in our study, the OS in DEB-TACE +RFA group was prolonged (mean OS 380 days vs 320 days), and there was no difference of PFS between 2 groups. In a previous prospective single-center pilot study comparing DEB-TACE+FA and DEB-TACE alone in HCC patients with cirrhosis and single tumor, the OS rate is markedly higher in patients

treated by DEB-TACE+RFA, which is in accordance with our study.[22] In another single arm retrospective study, the cumulating survival rates at 1, 3 and 5 years are 90%, 50%, 27%, and the median value of survival is 37.4 months.[24] In addition, the cumulating recurrence-free survival (RFS) rates at 1, 3, and 5 years are 48%, 16%, and 16%, and the median RFS time was 10.7 months.[24] Those studies suggest DEB-TACE+RFA might be able to accomplish a satisfying survival in HCC patients. Due to the relatively short follow up time, the long-term survival was not assessed in our study; however, the results regarding survival in our study might provide information to the future studies, which could extend the follow-up time of survival in the future.

There were still several limitations to our study:

(1) the short follow up time resulted in that the long-term efficacy was not assessed in our study;
(2) as a retrospective cohort study, there were several confounding factors in our study, such as cirrhosis and the ALP level at baseline;
(3) the sample size was relatively small, which could lead to less statistical power and the magnify of some bias in our study;
(4) our study was conducted in a single center, which causes selection bias. In order to further validate our results, more clinical trials which could avoid the confounding factors and bias should be conducted. Thus, a multicenter, prospective study with larger sample size and increased follow up time, or a multicenter, randomized clinical trial with larger sample size and longer follow up duration are needed in the future.

In conclusion, DEB-TACE+RFA achieved better treatment responses and OS compared with DEB-TACE alone in Chinese HCC patients.

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Writing – review & editing: Dedong Zhu, Denggao Yuan, Zhe Wang, Sihan Chen.

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