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Original Article

Drug-eluting bead transarterial chemoembolization is efficient and well-tolerated in treating elderly Chinese hepatocellular carcinoma patients

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Abstract: This study aimed to evaluate the efficacy and safety of drug-eluting bead transarterial chemoembolization (DEB-TACE), and to explore its prognostic factors in elderly Chinese hepatocellular carcinoma (HCC) patients. 93 elderly HCC patients undergoing DEB-TACE were prospectively enrolled. Treatment response was assessed by mRECIST criteriaat1 month post DEB-TACE treatment, and progression free survival (PFS) and overall survival (OS) were calculated. Liver function and adverse events (AEs) within 1 month post DEB-TACE were documented. Complete response (CR) rate and objective response rate (ORR) were 18.3% and 87.1%, respectively. Additionally, medians of PFS and OS were 9.0 months and 21.0 months, respectively. Multivariate logistic regression revealed that no factor independently predicted CR achievement, while tumor size ≥5.0 cm and AFP abnormal were independent factors for predicting both shorter PFS and OS, and higher BCLC stage was an independent predictive factor for unfavorable OS. As to safety profiles, the percentages of patients with abnormal TBIL, ALT, AST, and ALP were increased at 1 week, while they were not different at 1 month post DEB-TACE treatment compared with baseline. Most frequent AEs were pain, fever, nausea or vomiting; skin discolorations, myelosuppression, and other AEs were relatively rare. In conclusion, DEB-TACE was efficient and well tolerated in elderly HCC patients, and increased tumor size, abnormal AFP, as well as higher BCLC stage could be independent markers for predicting worse prognosis.

Keywords: Elderly, hepatocellular carcinoma (HCC), drug-eluting beads transarterial chemoembolization (DEB-TACE), efficacy, safety, prognostic factor

Introduction

Liver cancer is a common malignancy, ranking as the sixth most common neoplasm and the second leading cause of cancer death worldwide [1]. According to epidemiologic data, 782,500 new cases and 745,500 deaths of liver cancer occured during 2012 worldwide, with China alone accounting for about 50% of the total number of new cases and deaths [2]. Among all the liver cases, hepatocellular carcinoma (HCC) is the most frequent subtype accounting for about 90% of all primary cases [3]. It's considered that early diagnosis and early use of comprehensive treatments based on surgical resection are the keys to improve the long-term survival of HCC patients, but the early symptoms of HCC are occult, thus most patients are diagnosed in the intermediate or advanced stages which are not suitable for surgical treatment [4]. In addition, Asian patients tend to have chronic viral hepatitis and cirrhosis, which largely reduces the portion of patients suitable for resection [5, 6]. Thus, it is essential to explore more treatment options for HCC patients with intermediate or advanced stages.

Transarterial chemoembolization (TACE) is the most commonly used local-regional treatment for unresectable HCC [7-9]. Drug-eluting beads (DEB)-TACE, as developed in the latest decade, is one type of TACE that uses microbeads as carriers to deliver chemotherapeutic drugs and to embolize tumor feeding arteries [10]. Compared with traditional TACE, DEB-TACE has the unique properties of improving delivery efficiency and eliminating systemic toxicity [11, 12]. Several reports observe that DEB-TACE has good efficacy and safety in the treatment of

most HCC patients, while studies evaluating its application in treating elderly Chinese HCC patients is rare [13-15]. Therefore, this study aimed to investigate the efficacy and safety of DEB-TACE, and to explore its prognostic factors in elderly Chinese HCC patients.

Materials and methods

Patients

93 elderly Chinese HCC patients about to receive DEB-TACE treatment between Feb 2015 and Mar 2017 in Zhejiang Cancer Hospital were consecutively enrolled in this prospective cohort study. The inclusion criteria were: (1) Diagnosis as primary HCC confirmed by pathologic findings, clinical features, or radiographic examinations according to American Association for the Study of the Liver Diseases (AASLD) guidelines; (2) Age above 65 years; (3) About to receive DEB-TACE treatment with DC Beads® according to clinical needs and personal willingness; (4) Life expectancy more than 12 months. The exclusion criteria were as follows: (1) Contraindication for angiography, embolization procedure or artery punctures; (2) Severe liver dysfunction (Child-Pugh stage C) including jaundice, hepatic encephalopathy, refractory ascites, and hepatorenal syndrome; (3) History of liver transplantation; (4) Renal dysfunction: creatinine >2 mg/dL or creatinine clearance rate <30 mL/min; (5) History of severe infection or hematological malignances; (6) Unlikely to be followed up regularly.

Ethics

This study was approved by the Institution Review Board of Zhejiang Cancer Hospital and conducted in accordance with Declaration of Helsinki. All the patients or their legal guardians provided the written informed consent.

Data collection

Baseline characteristics of demography and clinical pathology were collected from all patients, which included age, gender, history of hepatitis B virus (HBV) and cirrhosis, cycles of TACE treatment, previous cTACE, previous surgery, previous systematic chemotherapy, previous radiofrequency ablation, Barcelona Clinic Liver Cancer (BCLC) stage, Child-Pugh stage, Eastern Cooperative Oncology Group (ECOG) performance status, tumor distribution, tumor size, tumor location, vein invasion, alpha fetoprotein (AFP), carcinoembryonic antigen (CEA) and carbohydrate antigen 199 (CA199).

Procedure of DEB-TACE treatment

In the present study, all patients received DEB-TACE treatment on demand according to clinical conditions and patients' willing, and the DC Beads (DC-Beads®, British Technology Group, UK) with the diameter of 100 μm to 300 μm were used as carriers, which were loaded with anthracyclines (80 mg). The detailed processes of DEB-TACE were as follows: (1) Loading of chemoembolization reagent: Before the start of loading, the chemoembolization reagent was dissolved to solution (20 mg/ml) and extracted into a 10 ml syringe. One bottle of DC beads was shaken and then the beads suspension was extracted into a 20 ml syringe, which was left at room temperature (RT) for 5 mins, after which the liquid supernatant was pushed out, so the beads remained in the syringe. Subsequently, the chemotherapy reagent solution was mixed with the beads by a tee joint, after which the non-ionic contrast agent was administered into the syringe containing beads and chemotherapy reagent solution at the ratio of 1:1, and the mixture was placed for 30 minutes at RT for further application. Ordinary embolization agents were used if the embolization point was not reached after a bottle of DC Beads was emptied. (2) Implement of DEB-TACE treatment: Digital subtraction angiography (DSA) was performed to exactly define the location of the tumor and its feeding arteries, and then a 2.4 F microcatheter (Merit Maestro®, Merit Medical System, Inc., USA) was inserted into the identified tumor feeding artery leaded by a microwire under the guidance of computer tomography (CT). Subsequently, the prepared beads were delivered at the speed of 1 ml/min through the microcatheter to the artery. As soon as stasis or reflux of the contrast agent was observed during the procedure, the chemoembolization was terminated, which was followed by a second angiography in order to detect the residual blush of tumor. The embolization procedure was repeated if the blush of tumor still occurred and stopped until no more blush of tumor was observed.

Table 1. Baseline characteristics of elderly patients with HCC who underwent DEB-TACE treatment

Measurement	Elderly HCC Patients (N=93)
Age (years)	70.4±4.6
Gender (male/female)	75/18
History of HBV (n/%)	76 (81.7)
History of cirrhosis (n/%)	58 (62.4)
Number of tumors (n/%)	
Unifocal	33 (35.5)
Multifocal	60 (64.5)
Tumor location (n/%)	
Unilobar	70 (75.3)
Bilobar	23 (24.7)
Tumor size ≥5.0 cm (n/%)	46 (49.5)
Vein invasion (n/%)	29 (31.2)
ECOG performance status (n/%)	
0	60 (64.5)
1	31 (33.3)
2	1 (1.1)
3	1 (1.1)
Child-Pugh stage (n/%)	
A	80 (86.0)
B	13 (14.0)
BCLC stage (n/%)	
A	24 (25.8)
B	38 (40.9)
C	31 (33.3)
Cycles of DEB-TACE treatment (n/%)	
1 cycle	75 (80.6)
≥2 cycles	18 (19.4)
AFP (n/%)	
Normal	29 (31.2)
Abnormal	51 (54.8)
Unknown	13 (14.0)
CEA (n/%)	
Normal	55 (59.1)
Abnormal	17 (18.3)
Unknown	21 (22.6)
CA199 (n/%)	
Normal	47 (50.5)
Abnormal	25 (26.9)
Unknown	21 (22.6)
Previous treatments (n/%)	
cTACE	34 (36.6)
Surgery	20 (21.5)
Systematic chemotherapy	2 (2.2)
Radiofrequency ablation	10 (10.8)

Data are presented as mean ± standard deviation or count (percentage). HCC, hepatocellular carcinoma; DEB-TACE, drug-eluting bead transarterial chemoembolization; HBV, hepatitis B virus; cTACE, conventional transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha fetoprotein; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199.

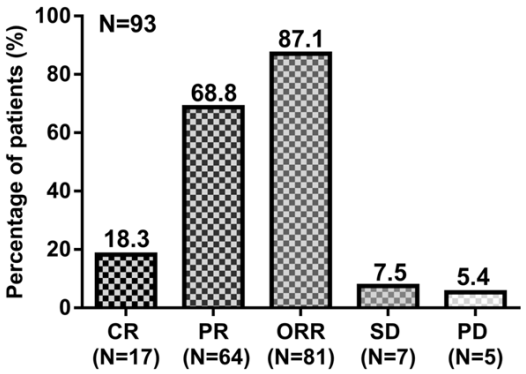

Figure 1. Treatment responses of DEB-TACE treatment in elderly HCC patients. The percentages of patients achieving CR, PR, ORR, SD and PD in elderly HCC patients 1 month after DEB-TACE treatment were 18.3%, 68.8%, 87.1%, 7.5% and 5.4%, respectively. DEB-TACE, drug-eluting bead transarterial chemoembolization; HCC, hepatocellular carcinoma; CR, complete response; PR, partial response; ORR, objective response rate; SD, stable disease; PD, progressive disease.

Assessment and definition of treatment response

One month after DEB-TACE treatment, all patients underwent enhanced magnetic resonance imaging (MRI) or CT examination. And the modified Response Evaluation Criteria in Solid Tumors (mRECIST) was used to assess treatment response of DEB-TACE treatment. The mRECIST embraced the following four response categories: Complete Response (CR), Partial Response (PR), Stable Disease (SD) and Progressive Disease (PD), which were defined as follows: (1) CR: no existence of arterial enhancement of targeted tumors; (2) PR: the decrease in diameter of targeted tumor (with arterial enhancement) ≤30%; (3) SD: the decrease in diameter of targeted tumor (with arterial enhancement) did not achieve PR or less than PD; (4) PD: the increase in diameter of targeted tumor (with arterial enhancement) ≥20% or new tumor existed. Moreover, objective response rate (ORR) was defined as the percentage of patients with CR plus patients with PR.

Assessment of survival

Progression free survival (PFS) and overall survival (OS) were analyzed in this study. PFS was calculated from the date of DEB-TACE treatment to the date of progression or death from any cause, and OS was calculated from the

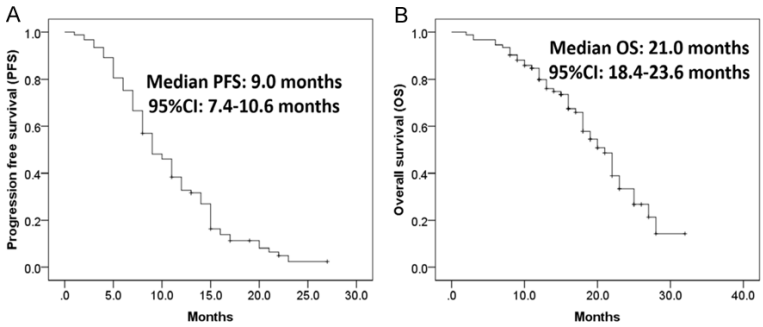

Figure 2. PFS and OS of DEB-TACE treatment. Median PFS was 9.0 months (95% CI: 7.4-10.6 months) (A), and median OS was 21.0 months (95% CI: 18.4-232.6 months) (B) in elderly HCC patients post DEB-TACE treatment. The PFS and OS were evaluated by K-M curve. PFS, progression free survival; OS, overall survival; DEB-TACE, drug-eluting beads transcatheter hepatic arterial chemoembolization; K-M, Kaplan-Meier.

date of DEB-TACE treatment to the date of death from any cause. The median follow-up duration was 16.0 months (range: 2.0-32.0 months) and the last follow up date was Oct 30th, 2017.

Liver function assessments and adverse events

Examinations of liver function indexes including total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were performed before DEB-TACE treatment, at 1 week and 1 month post DEB-TACE treatment to evaluate the influence of DEB-TACE on liver function. Assessments of liver function were based on the treatment records of DEB-TACE (N=121). In addition, adverse events (AEs) occurring within 1 month post DEB-TACE treatment were also recorded.

Statistics

Statistical analysis was performed using SPSS 22.0 software (IBM, USA), and graphs were drawn by Graphpad Prism 6.01 software (GraphPad Software Inc, USA). Data were mainly presented as mean value ± standard deviation or count (percentage). Kaplan-Meier (K-M) curve was used to describe the PFS and OS, and then comparison of PFS and OS between/among subgroups was determined by log-rank test. Univariate and multivariate logistic regression analysis was performed to determine the predicting value of baseline factors for CR achievement. Univariate and multivariate Cox regression analysis was used to evaluate the predictive factors for PFS and OS. P<0.05 was considered significant.

Results

Baseline characteristics of elderly HCC patients

As listed in **Table 1**, 93 elderly HCC patients (75 male and 18 female) with mean age 70.4±4.6 years were enrolled in this study. 76 (81.7%) cases had history of HBV and 58 (62.4%) cases had history of cirrhosis. There were 60 (64.5%) patients who had multifocal disease, 46 (49.5%) patients had tumor size ≥5.0 cm, and 29 (31.2%) patients had vein invasion. The numbers of patients in ECOG performance status 0, 1, 2 and 3 were 60 (64.5%), 31 (33.3), 1 (1.1%) and 1 (1.1%), respectively. 80 (86.0%) patients were at Child-Pugh stage A and 13 (14.0%) patients were at stage Child-Pugh B. In addition, there were 24 (25.8%), 38 (40.9%) and 31 (33.3%) patients at BCLC stage A, B and C, respectively. The other detailed clinicopathological characteristics, biochemical indexes and treatment history of elderly HCC patients were presented in **Table 1**.

Treatment response to DEB-TACE in elderly HCC patients

As displayed in **Figure 1**, after DEB-TACE treatment, 17 (18.3%) patients achieved CR and 64 (68.8%) patients achieved PR, and the ORR was 87.1%. Additionally, the numbers of patients were SD and PD were 7 (7.5%) and 5 (5.4%), respectively.

The PFS and OS of elderly HCC patients underwent DEB-TACE

K-M curve illustrated that the median PFS of elderly HCC patients was 9.0 months with 95% confidence interval (CI): 7.4-10.6 months (**Figure 2A**), and the median OS was 21.0 months with 95% CI: 18.4-23.6 months (**Figure 2B**).

Correlation of baseline characteristics with PFS and OS by K-M curve analysis

In order to investigate the correlation of baseline characteristics with PFS and OS, patients

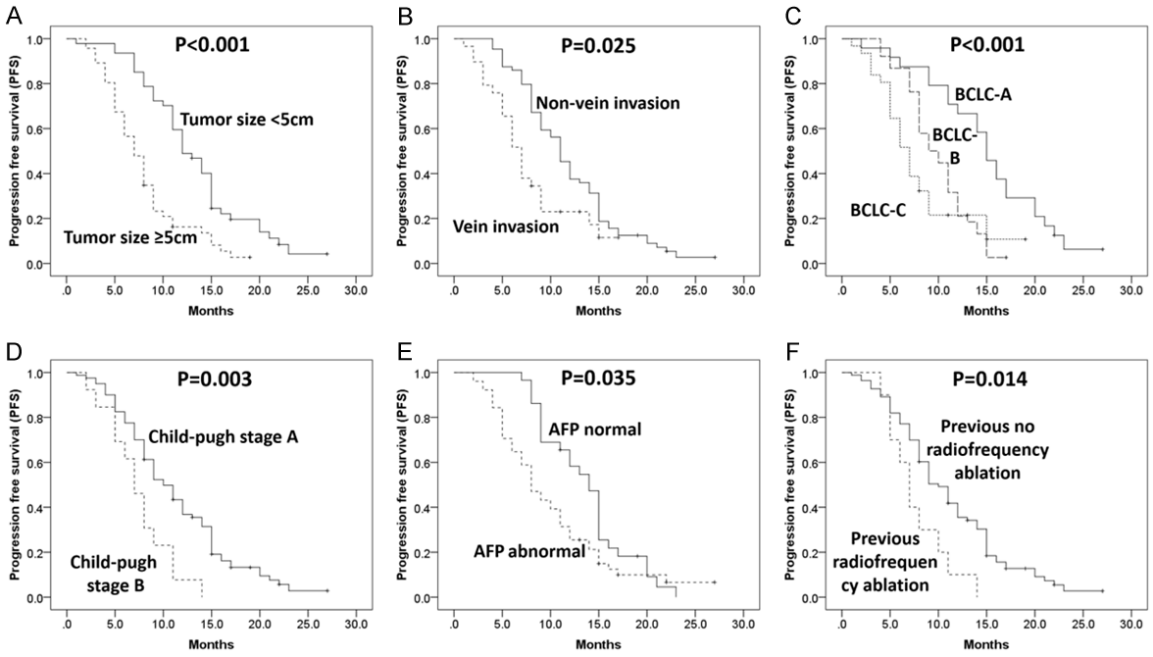

Figure 3. Comparison of PFS between/among subgroups. Elderly HCC patients with tumor size ≥5.0 cm (A), vein invasion (B), higher BCLC stage (C), Child-Pugh stage B (D), AFP abnormality (E) and previous radiofrequency ablation (F) had shorter PFS. Comparison of PFS between/among groups was determined by K-M curve and Log-rank test. P<0.05 was considered significant. HCC, hepatocellular carcinoma; PFS, progression free survival; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha fetoprotein; K-M, Kaplan-Meier.

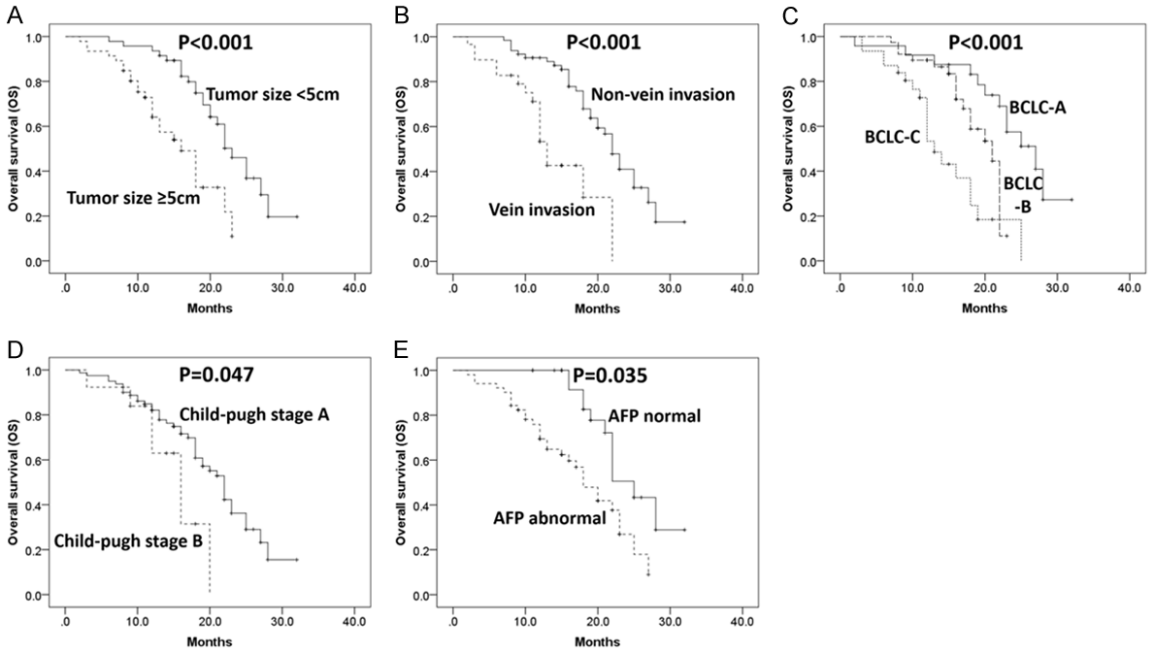

Figure 4. Comparison of OS between/among subgroups. Elderly HCC patients with tumor size ≥5.0 cm (A), vein invasion (B), BCLC stage B/C (C), Child-Pugh stage B (D) and AFP abnormality (E) were discovered to have poorer OS. Comparison of OS between/among groups was determined by K-M curve and Log-rank test. P<0.05 was considered significant. OS, overall survival; HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha fetoprotein; K-M, Kaplan-Meier.

Table 2. Factors affecting CR achievement by univariate and multivariate logistic regression analysis

Measurement	Univariate logistic regression				Multivariate logistic regression			
	P value	OR	95% CI		*P* value	OR	95% CI	
			Lower	Higher			Lower	Higher
Age (≥70 years vs <70 years)	0.512	0.700	0.241	2.031	0.481	0.562	0.113	2.798
Gender (male vs female)	0.388	2.000	0.414	9.662	0.601	2.034	0.142	29.115
History of HBV	0.448	1.844	0.380	8.952	0.394	0.345	0.030	3.998
History of cirrhosis	0.441	1.565	0.501	4.895	0.069	6.303	0.868	45.764
Number of tumors (multifocal vs unifocal)	0.031	0.304	0.103	0.897	0.649	0.636	0.091	4.458
Tumor location (bilobar vs unilobar)	0.899	0.923	0.268	3.174	0.545	1.908	0.236	15.432
Tumor size ≥5.0 cm	0.451	0.664	0.229	1.927	0.848	0.834	0.130	5.352
Vein invasion	0.035	0.107	0.013	0.852	0.275	0.238	0.018	3.128
Higher ECOG performance status	0.843	1.095	0.444	2.703	0.639	1.535	0.256	9.194
Child-Pugh stage (B vs A)	0.308	0.333	0.040	2.756	0.704	0.433	0.006	32.641
Higher BCLC stage	0.014	0.388	0.182	0.828	0.265	0.408	0.085	1.973
DEB-TACE treatment (≥2 cycles vs 1 cycle)	0.631	1.363	0.386	4.813	0.420	2.491	0.270	22.941
AFP abnormal	0.299	0.563	0.190	1.668	0.948	0.944	0.167	5.341
CEA abnormal	0.079	0.152	0.019	1.247	0.219	0.150	0.007	3.093
CA199 abnormal	0.273	0.498	0.143	1.731	0.371	0.448	0.077	2.602
Previous cTACE	0.905	0.935	0.312	2.805	0.862	1.165	0.207	6.541
Previous surgery	0.384	1.694	0.517	5.550	0.254	3.428	0.413	28.463
Previous systematic chemotherapy	0.284	4.687	0.278	78.946	-	-	-	-
Previous radiofrequency ablation	-	-	-	-	-	-	-	-

Data are presented as *P* value, OR (odds ratio) and 95% CI (confidence interval). BCLC stage was scored as: A=1, B=2, C=3. For the variable "Previous radiofrequency ablation", "-" indicated that there was no statistical effectiveness in univariate and multivariate logistic regression model analysis due to the lack of effective events. For the variable "Previous systematic chemotherapy", "-" indicated that there was no statistical effectiveness in multivariate logistic regression model analysis due to the lack of effective events. *P* value <0.05 was considered significant. CR, complete response; DEB-TACE, drug-eluting bead transarterial chemoembolization; cTACE, conventional transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha fetoprotein; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199.

were divided into subgroups according to their baseline parameters, and K-M curves were drawn and log-rank test was performed. As listed in **Figure 3**, tumor size ≥5 cm (P<0.001, **Figure 3A**), vein invasion (P=0.025, **Figure 3B**), higher BCLC stage (P<0.001, **Figure 3C**), Child-Pugh stage B (P=0.003, **Figure 3D**), AFP abnormal (P=0.035, **Figure 3E**) and previous radiofrequency ablation (P=0.014, **Figure 3F**) were associated with worse PFS.

As to OS (**Figure 4**), tumor size ≥5 cm (P<0.001, **Figure 3A**), vein invasion (P<0.001, **Figure 4B**), higher BCLC stage (P<0.001, **Figure 3C**), Child-Pugh stage B (P=0.047, **Figure 4D**) and AFP abnormal (P=0.035, **Figure 4E**) were correlated with unfavorable OS. No correlation of other baseline characteristics with PFS and OS was observed.

Factors affecting CR achievement in elderly HCC patients

As listed in **Table 2**, univariate logistic regression and multivariate logistic regression analysis was used to detect the factors affecting CR achievement and the results showed that multifocal (P=0.031), vein invasion (P=0.035) and higher BCLC stage (P=0.014) were factors that predicted absence of CR, but no independent predictive factor for CR achievement was found according to multivariate logistic regression analysis.

Factors affecting PFS in elderly HCC patients

To explore the factors for predicting PFS, univariate Cox regression was performed, and tumor size ≥5.0 cm (P<0.001), vein invasion (P=0.013), higher BCLC stage (P<0.001), Child-

Table 3. Factors affecting PFS by univariate and multivariate Cox proportional hazards regression model analysis

Measurement	Univariate Cox's regression				Multivariate Cox's regression			
	P value	HR	95% CI		*P* value	HR	95% CI	
			Lower	Higher			Lower	Higher
Age (≥70 years vs <70 years)	0.867	1.037	0.677	1.589	0.871	0.950	0.508	1.773
Gender (male vs female)	0.735	0.905	0.507	1.615	0.846	1.085	0.476	2.472
History of HBV	0.729	1.102	0.638	1.903	0.922	0.949	0.327	2.747
History of cirrhosis	0.918	0.977	0.627	1.523	0.689	0.865	0.424	1.762
Number of tumors (multifocal vs unifocal)	0.207	1.334	0.852	2.090	0.682	0.871	0.449	1.690
Tumor location (bilobar vs unilobar)	0.102	1.522	0.920	2.519	0.777	1.130	0.485	2.630
Tumor size ≥5.0 cm	<0.001	2.594	1.650	4.079	0.002	3.179	1.504	6.716
Vein invasion	0.013	1.856	1.142	3.017	0.981	0.991	0.466	2.109
Higher ECOG performance status	0.144	1.317	0.910	1.908	0.651	1.144	0.639	2.047
Higher BCLC stage	<0.001	1.775	1.327	2.375	0.060	1.759	0.977	3.167
Child-Pugh stage (B vs A)	0.007	2.336	1.265	4.315	0.087	2.840	0.858	9.398
DEB-TACE treatment (≥2 cycles vs 1 cycle)	0.729	1.102	0.636	1.910	0.576	1.273	0.547	2.963
AFP abnormality	0.050	1.614	1.000	2.607	0.038	2.026	1.038	3.951
CEA abnormality	0.256	0.701	0.379	1.294	0.253	0.588	0.236	1.463
CA199 abnormality	0.966	0.989	0.585	1.669	0.884	1.053	0.524	2.117
Previous cTACE	0.500	1.164	0.749	1.810	0.412	1.300	0.695	2.433
Previous surgery	0.782	1.075	0.643	1.798	0.339	1.516	0.646	3.554
Previous systematic chemotherapy	0.592	1.474	0.357	6.077	0.263	0.233	0.018	2.982
Previous radiofrequency ablation	0.022	2.213	1.122	4.364	0.849	1.121	0.345	3.639

Data are presented as *P* value, HR (hazards ratio) and 95% CI (confidence interval). BCLC stage was scored as: A=1, B=2, C=3. *P* value <0.05 was considered significant. PFS, progression free survival; DEB-TACE, drug-eluting bead transarterial chemoembolization; cTACE, conventional transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha fetoprotein; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199.

Pugh stage B (P=0.007), AFP abnormality (P=0.050), and previous radiofrequency ablation (P=0.022) were disclosed to be correlated with worse PFS, while multivariate Cox regression revealed that only tumor size ≥5.0 cm (P=0.002) and AFP abnormality (P=0.038) were independent factors for predicting shorter PFS (**Table 3**).

Factors affecting OS in elderly HCC patients

As shown in **Table 4**, univariate Cox regression analysis was performed showing that tumor size ≥5.0 cm (P<0.001), vein invasion (P< 0.001), higher BCLC stage (P<0.001) and AFP abnormality (P=0.005) were associated with poorer OS. Multivariate Cox regression analysis revealed that tumor size ≥5.0 cm (P=0.001), higher BCLC stage (P=0.022), and AFP abnormality (P=0.001) were independent factors for predicting worse OS.

Influence of DEB-TACE treatment on liver function in elderly HCC patients

In this study, the liver function related laboratory indexes of 121DEB-TACE records before, after 1 week and 1 month of treatment DEB-TACE were documented, and the results are shown in **Table 5**. The percentage of patients with TBIL abnormality (P=0.002), ALT abnormality (P<0.001), AST abnormality (P<0.001) and ALP abnormality (P<0.001) were all increased at 1 week post DEB-TACE treatment compared with baseline, while no difference of the percentage of patients with abnormal TBIL, ALT, AST and ALP at 1 month after DEB-TACE treatment compared to baseline was found (all P>0.05).

Safety assessment

The AEs of 121 DEB-TACE records during 1 month post DEB-TACE treatment were record-

Table 4. Factors affecting OS by univariate and multivariate Cox proportional hazards regression model analysis

Measurement	Univariate Cox regression				Multivariate Cox regression			
	P value	HR	95% CI		*P* value	HR	95% CI	
			Lower	Higher			Lower	Higher
Age (≥70 years vs <70 years)	0.433	1.255	0.712	2.214	0.301	1.547	0.677	3.539
Gender (male vs female)	0.270	0.682	0.345	1.347	0.810	1.150	0.368	3.593
History of HBV	0.834	0.930	0.473	1.829	0.188	0.433	0.124	1.505
History of cirrhosis	0.945	1.021	0.566	1.842	0.489	0.691	0.242	1.971
Number of tumors (multifocal vs unifocal)	0.494	1.236	0.673	2.270	0.433	0.659	0.232	1.870
Tumor location (bilobar vs unilobar)	0.123	1.703	0.865	3.353	0.979	0.982	0.246	3.917
Tumor size ≥5.0 cm	<0.001	3.058	1.643	5.693	0.001	6.454	2.057	20.248
Vein invasion	<0.001	3.770	1.921	7.400	0.410	1.570	0.537	4.589
Higher ECOG performance status	0.303	1.312	0.782	2.200	0.409	1.467	0.591	3.643
Higher BCLC stage	<0.001	2.436	1.635	3.629	0.022	2.606	1.151	5.898
Child-Pugh stage (B vs A)	0.057	2.252	0.976	5.196	0.330	2.229	0.445	11.164
DEB-TACE treatment (≥2 cycles vs 1 cycle)	0.818	1.090	0.523	2.270	0.751	1.233	0.339	4.483
AFP abnormality	0.005	2.816	1.366	5.805	0.001	7.180	2.205	23.385
CEA abnormality	0.532	1.274	0.596	2.727	0.495	1.467	0.488	4.408
CA199 abnormality	0.768	1.108	0.561	2.191	0.969	1.021	0.362	2.878
Previous cTACE	0.576	0.839	0.453	1.553	0.922	0.953	0.359	2.527
Previous surgery	0.752	1.116	0.566	2.198	0.769	1.108	0.558	2.200
Previous systematic chemotherapy	0.853	1.207	0.165	8.837	0.889	1.154	0.154	8.643
Previous radiofrequency ablation	0.360	1.637	0.570	4.706	0.406	0.496	0.095	2.592

Data were presented as *P* value, HR (hazards ratio) and 95% CI (confidence interval). BCLC stage was scored as: A=1, B=2, C=3. *P* value <0.05 was considered significant. OS, overall survival; DEB-TACE, drug-eluting bead transarterial chemoembolization; cTACE, conventional transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha fetoprotein; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199.

ed, and the results exhibited that 83 (68.6%) cases had pain, 51 (42.1%) cases presented with fever, and 38 (31.4%) cases had nausea or vomiting (**Table 6**). In addition, there were 3 (3.0%), 2 (2.0%) and 10 (8.3%) cases presented with skin discoloration, myelosuppression, and other AEs, respectively.

Discussion

This study illuminated that: (1) DEB-TACE treatment achieved 18.3% CR rate and 87.1% ORR in elderly HCC patients. (2) Elderly HCC patients had median PFS 9.0 months (95% CI: 7.4-10.6 months) and median OS 21.0 moths (95% CI: 18.4-23.6 months) post DEB-TACE. (3) Subgroup analysis of PFS and OS exhibited that elderly HCC patients with tumor size ≥5.0 cm, vein invasion, higher BCLC stage, Child-Pugh stage B, and AFP abnormal had both shorter PFS and OS, and the patients with previous radiofrequency ablation had worse PFS. The multivariate Cox regression analysis elucidated that tumor size ≥5.0 cm and AFP abnormal were independent predicting factors for both poorer PFS as well as OS, and higher BCLC stage was an independent factor for predicting worse OS. (4) Compared with baseline, elderly HCC patients'liver function related laboratory indexes deteriorated after 1 week of DEB-TACE treatment, while no change in liver function related laboratory indexes was observed after 1 moth of treatment. (5) The most common AEs within 1 month after treatment were pain, fever, nausea and vomiting, while skin discoloration and myelosuppression were rare in our study.

TACE is one of the most commonly used treatments for HCC patients who are not suitable for surgery. It aims to realize tumor necrosis effect by blocking the tumor supplying vessel and delivering antitumor drugs [8, 9]. Conventional TACE involves the use of lipiodol, chemotherapy drugs, and embolization of the tumor-supplying vessel with gel-foam or particles [16]. However, the liquid motility of lipiodol reduces the effec-

Table 5. Liver function before and after DEB-TACE treatment (121 DEB-TACE records)

	Baseline	1 week post DEB-TACE	1 months post DEB-TACE	*P* value*	*P* value#
TBIL abnormal (n/N/%)	40/120 (33)	53/105 (51)	28/113 (25)	0.002	0.064
ALT abnormal (n/N/%)	23/120 (19)	59/105 (56)	18/113 (16)	<0.001	0.383
AST abnormal (n/N/%)	50/120 (42)	67/102 (66)	42/112 (38)	<0.001	0.281
ALP abnormal (n/N/%)	41/119 (35)	61/112 (55)	42/102 (41)	<0.001	0.143

Data are presented as count (percentage). Comparison was determined by McNemar test. P<0.05 was considered significant. *P value: 1 week post DEB-TACE vs baseline; #P value: 1 months post DEB-TACE vs baseline. DEB-TACE, drug-eluting bead transarterial chemoembolization; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

Table 6. Adverse events occurring within one month after DEB-TACE treatment (121 DEB-TACE records)

Items	n (%)
Pain	83 (68.6)
Fever	51 (42.1)
Nausea or vomiting	38 (31.4)
Skin discoloration	3 (3)
Myelosuppression	2 (2)
Others	10 (8.3)

Data are presented as count (percentage). DEB-TACE, drug-eluting bead transarterial chemoembolization.

tive concentration of antitumor drugs, and the inability to control drug release precisely renders the conventional TACE ineffective in many cases [17-19]. DEB-TACE, a modified version of conventional TACE, uses antitumor drug loaded microbeads with diameter of 100-1000 μm to slowly release drugs to the targeted tumor and meanwhile blocks the tumor-supplying vessel, achieving increased and more sustained drug concentration and less systemic toxicity in HCC patients compared with conventional TACE [20]. Cumulative studies show that DEB-TACE has a good efficacy in treating patients with HCC. For example, a single-center, prospective cohort study reveals a midterm CR rate of 28.6% and an ORR of 71.4% in 28 HCC patients treated with DEB-TACE [21]. Another prospective cohort study illuminates that the ORR is 60% at 1 month post DEB-TACE treatment in 57 HCC patients [22]. In a study aimed to evaluate the efficacy of DEB-TACE as bridge therapy for HCC patients undergoing liver transplantation, 40% and 73% of the patients achieves CR and ORR, respectively [23]. However, since these previous studies did not enroll entirely elderly HCC patients, to our knowledge, there is still no study aiming to evaluate the treatment response of elderly HCC patients to DEB-TACE. In the present study, we found that the CR and ORR were 18.3% and 87.1% to DEB-TACE treatment in elderly Chinese HCC patients. The discrepancy of treatment response rates between our study and previous studies might be derived from the distinct eligibility criteria, different patients with distinctive disease conditions, and the different time of response assessment among studies.

As for survival profiles, a retrospective cohort study enrolling 143 HCC patients who underwent DEB-TACE treatment disclosed that DEB-TACE treatment realizes a median OS of 12.53 months [24]. Another retrospective cohort study conducted in 147 unresectable HCC patients revealed that the median survival by single-drug DEB-TACE treatment was 15.00±1.50 months [25]. Also, a retrospective cohort study showed that the median PFS and OS of patients who underwent DEB-TACE were 5.1 months and 13.3 months in 80 advanced stage HCC patients, respectively [26]. These results from the prior studies suggest that DEB-TACE could achieve a good efficacy regarding patients' survival in HCC patients. In this study, we found that the median PFS of elderly Chinese HCC patients post DEB-TACE treatment was 9.0 months (95% CI: 7.4-10.6 months), and the median OS was 21.0 months (95% CI: 18.4-23.6 months). Compared with previous studies, the PFS and OS of in our study were numerically increased. This disparity might mainly result from the follow-up time in our study being longer and the technology skills were improved along with time, as well as the disease conditions that differed.

In clinical practice, a proportion of elderly HCC patients appear to have a poor response to DEB-TACE, hence, investigating prognostic fac-

tors in elderly HCC patients undergoing DEB-TACE treatment is necessary. However, few studies explored the prognostic factors in elderly HCC patients undergoing DEB-TACE therapy until now. The published reports only evaluated the prognostic factors in general HCC patients but not in the elderly HCC patients specifically. For instance, a previous cohort study reports that higher Child-Pugh stage and portal vein invasion are independent factors for predicting unfavorable OS in HCC patients treated by DEB-TACE [27]. Another prospective cohort study discloses that higher ECOG performance score, elevated serum albumin, and multifocal disease independently correlate with worse OS in both DEB-TACE and cTACE treated HCC patients [28]. In addition, a retrospective cohort study reveals that multifocal disease and maximum tumor diameter above 3.5 cm are associated with shorter OS in early/intermediate HCC patients [29]. To our best knowledge, this was the first study evaluating the predictive factors for efficacy in elderly HCC patients receiving DEB-TACE, and we found that tumor size ≥5.0 cm as well as AFP abnormality were independently correlated with unfavorable PFS, and tumor size ≥5.0 cm, higher BCLC stage as well as AFP abnormality were independent factors for predicting worse OS in elderly patients treated by DEB-TACE. Several possible explanations for our results were as follows: (1) largest tumor size ≥5.0 cm and higher BCLC stage indicated more severe disease and decreased liver function, which might lead to a poorer prognosis and a less favorable tolerance to the treatment. (2) AFP, secreted by HCC cells, is a typical biomarker of HCC, and it is reported that early increased serum AFP level is associated with disease progression in advanced HCC patients treated with sorafenib [30]. AFP also participates in the pathogenesis of HCC by promoting HCC cells growth, proliferation, metastasis, repressing cell apoptosis, and evading immune surveillance through a variety of mechanisms [31-35]. Therefore, high AFP level was detrimental to elderly HCC patients' prognosis.

Liver function assessment is routine in patients with HCC before performing resections, transplantation, chemotherapy, radiotherapy or TACE treatments. The results in our study showed that the proportions of patients with abnormal liver function related indexes were elevated at 1 week while they were similar to that of baseline at 1 month after DEB-TACE treatment, which indicated that there was a rapid worsening of the liver function in elderly HCC patients treated by DEB-TACE in our study. However, their liver function recovered at 1 month post treatment, suggesting that DEB-TACE did not cause long-term damage of liver function in elderly HCC patients. For the purpose of evaluating the safety of DEB-TACE in treating elderly HCC patients, we also recorded the AEs occurred within one month post DEB-TACE. According to previous studies, the most common AE in HCC patients treated by DEB-TACE is embolization syndrome, including pain, fever, nausea and vomiting [25, 26, 36]. Unfortunately, there are very limited studies aiming to evaluate safety in the elderly HCC patients receiving DEB-TACE. In our study, the most common AEs in elderly HCC patients who underwent DEB-TACE were pain, fever, nausea and vomiting, which were mainly mild and manageable. There were only a few severe AEs associated with chemotherapeutic agents such as skin discoloration, myelosuppression and other AEs, which suggested that DEB-TACE was well tolerable in elderly HCC patients.

There were several limitations in this study: (1) The sample size of this study was relatively small, which might cause insufficient statistical power, thus, it is necessary to include more patients in future studies. (2) The treatment response in our study was assessed at 1 month post DEB-TACE, therefore, the long-term response was not evaluated, which should be performed in future studies. (3) The single center design of our study might cause selection bias, thus a future study should be conducted in multiple centers in different areas.

In conclusion, DEB-TACE was efficient and well tolerated in elderly HCC patients, and increased tumor size, abnormal AFP, and higher BCLC stage could be independent markers for adverse prognosis.

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Disclosure of conflict of interest

None.

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