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Drug-eluting beads transarterial chemoembolization by CalliSpheres is effective and well tolerated in treating intrahepatic cholangiocarcinoma patients

A preliminary result from CTILC study

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Abstract

This study aimed to investigate the efficacy and safety of drug-eluting beads (DEB) transarterial chemoembolization (TACE) treatment in Chinese intrahepatic cholangiocarcinoma (ICC) patients.

37 ICC patients underwent DEB-TACE treatment in CTILC study (registered on clinicaltrials.gov with registry No. NCT03317483) were included in this present study. Treatment response was assessed according to modified Response Evaluation Criteria in Solid Tumors (mRECIST). Overall survival (OS) was calculated from the time of DEB-TACE operation until the date of death from any causes. Liver function change and adverse events (AEs) were recorded during and after DEB-TACE operation.

3 (8.1%) patients achieved complete response (CR) and 22 (59.5%) patients achieved partial response (PR), with objective response rate (ORR) of 67.6%. After DEB-TACE treatment, mean OS was 376 days (95%CI: 341–412 days). Multivariate logistic regression analysis revealed that Bilobar disease ($P = .040$, OR: 0.105, 95% CI: 0.012–0.898) and portal vein invasion ($P = .038$, OR: 0.104, 95% CI: 0.012–0.881) could independently predict less possibility of ORR. Patients with ALB abnormal, TP abnormal, ALT abnormal and AST abnormal were increased at 1-week post DEB-TACE treatment ($P = .034$, $P = .001$, $P < .001$, $P = .006$,

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respectively), while returned to the levels at baseline after 1 to 3 months (all $P > .050$). Besides, most of the AEs were mild including pain, fever, vomiting, and nausea in this study.

DEB-TACE was effective and well tolerated in treating ICC patients, and bilobar disease as well as portal vein invasion were independently correlated with less probability of ORR achievement.

Abbreviations: AASLD = American Association for the Study of the Liver Diseases, ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CCA = Cholangiocarcinoma, CR = complete response, CR+PR = CR and PR, CT = computerized tomography, cTACE = conventional TACE, DEB-TACE = drug-eluting beads TACE, HCC = hepatocellular carcinoma, ICC = intrahepatic cholangiocarcinoma, mRECIST = Modified Response Evaluation Criteria in Solid Tumors, MRI = magnetic resonance imaging, ORR = objective response rate, OS = overall survival, PD = progressive disease, PR = partial response, SD = stable disease, TACE = transarterial chemoembolization, TBA = total bile acid, TBIL = total bilirubin, TP = total protein.

Keywords: drug-eluting beads transarterial chemoembolization, intrahepatic cholangiocarcinoma, overall survival, predictive factors, treatment response

1. 1. Introduction

Cholangiocarcinoma (CCA), with a preferential distribution among men rather than women, consists of intrahepatic, perihilar, and distal extrahepatic carcinomas,[1,2] among which intrahepatic cholangiocarcinoma (ICC) constitutes 5% to 15% of all cases.[3] The prognosis of the ICC patients is dismal, and surgery is the only curative treatment option with survival rates of 5 years ranging from 10% to 40%.[4,5] However, surgical therapy can only be carried out in about 30% of the cases due to most patients present at moderate to advanced stages with unspecific clinical symptoms.[6,7] Over the last decade, transarterial chemoembolization (TACE) as a palliative choice in ICC patients who are ineligible to receive curative treatments has become increasingly accepted and there is growing evidence for the ability of TACE to achieve high tumor response rates.[6,8]

TACE, of which the technology includes the obstruction of the tumor-supplying artery and infusion of chemotherapeutic, was mainly made up of conventional TACE (cTACE) and drug-eluting beads TACE (DEB-TACE).[9,10] DEB-TACE, in which the beads diameter varies from 100 μm to 900 μm, has not been commercially available until 2006.[11] Since then, DEB-TACE has become an option for unresectable liver cancer in many centers worldwide. Compared with cTACE, DEB-TACE reduces the risk of systemic chemotherapeutic distribution and increases intratumoral drug concentration. Despite of those benefits of DEB-TACE, little is known about the efficacy and safety of DEB-TACE treatment in Chinese ICC patients. Therefore, this study aimed to investigate the efficacy and safety of DEB-TACE treatment in Chinese ICC patients.

2. Material and methods

2.1. Patients

This study was a part of CTILC study (Chinese CalliSpheres Transarterial chemoembolization In Liver Cancer) which was a multi-center, prospective cohort study aiming to investigate the efficacy and safety of DEB-TACE treatment by CalliSpheres in Chinese patients and to improve the prognosis and patients satisfaction. The inclusion criteria of CTILC were as follows:

1. Diagnosed as primary HCC, primary ICC or secondary liver cancer confirmed by pathological findings, clinical features, or radiographic examinations according to American Association for the Study of the Liver Diseases (AASLD) guidelines;
2. Age above 18 years;
3. About to receive DEB-TACE treatment with CalliSpheres according to clinical needs and patients' willing.
4. Able to be followed up regularly; (5) Life expectancy above 12 months.

The exclusions were as follows:

1. 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 understand the study consents.
6. Women in gestation or lactation period.

Other detailed information of CTILC study was available on clinicaltrials.gov with registry No. NCT03317483. 37 ICC patients underwent DEB-TACE treatment from 2015/11/12 to 2016/11/04 in CTILC study were included in this present study. This study was approved by Ethics committee of Zhejiang Cancer Hospital. All the patients or their legal guardian provided the written informed consents. This study was conducted according to the Declaration of Helsinki.

2.2. DEB-TACE procedure

DEB-TACE was performed using transfemoral arterial access route with a micro-puncture system by placing a 5F vascular introducer (Boston Scientific, Natick, MA, United States). CalliSpheres Beads (Jiangsu Hengrui Medicine Co, Ltd., Jiangsu, China) with the diameter between 100 μm to 300 μm were used as carriers. Beads were loaded with Adriamycin drug 50 to 80 mg, the mean dose was 60 mg for patients with ICC patients. Celiac and/or superior mesenteric arteriography was carried out to assess the arterial anatomy, tumor supplying vessel and patency of the portal vein. The lobar/segmental hepatic artery supplying the tumor was selectively cannulated with a microcatheter and embolized with DEB, which was loaded with the mixture of chemotherapy reagent solution and nonionic iodinated contrast material in a ratio of 1:1. The end point for embolization was stasis of blood flow in the tumor feeding artery.

2.3. Response assessment and follow ups

Modified Response Evaluation Criteria in Solid Tumors (mRECIST) was used to assess tumor response using enhanced

computerized tomography (CT) or magnetic resonance imaging (MRI)[12]:

1. Complete response (CR): no existence of arterial enhancement of targeted tumors;
2. Partial response (PR): the decrease in diameter of targeted tumor (with arterial enhancement) <=30%;
3. Stable disease (SD): the decrease in diameter of targeted tumor (with arterial enhancement) did not achieve PR or less than PD;
4. Progressive disease (PD): the increase in diameter of targeted tumor (with arterial enhancement) >=20% or new tumor existed. Objective response rate (ORR) was defined as the portion of patients achieved CR and PR (CR+PR).

Overall survival (OS) was calculated from the time of DEB-TACE operation to the date of death or last follow-up. Safety was assessed according to the change of liver function and the count and percentage of AEs during and after DEB-TACE. The median follow-up duration was 175 (range from 134 to 251) days, and the last follow-up date was December 27th, 2016.

2.4. Liver function and AEs

All patients were discharged after a brief observation period (48–72 hours). Clinical evaluation and assessment of liver function including albumin (ALB), total protein (TP), total bilirubin (TBIL), total bile acid (TBA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were recorded on an outpatient basis during 1 week and 1 to 3 months after DEB-TACE. AEs including pain, fever, nausea, vomiting, bone marrow toxicity, and other AEs were defined as treatment related if occurred during operations or within 1 month of treatment.

2.5. Statistics

Statistical analysis was performed using SPSS 22.0 software (IBM, USA). Data was presented as count (%), mean±standard deviation or median (25th–75th). Comparison between each visit was determined by McNemar test. K–M curve was drawn to analyze OS. Factors affecting ORR achievement in ICC patients were determined by 1 step enter univariate and multivariate logistic regression analysis. Factors affecting OS in ICC patients were determined by 1 step enter univariate Cox proportional hazards regression model analysis. $P < .05$ was considered significant.

3. Results

3.1. Baseline characteristics

37 ICC patients aged 62.9±13.4 years with 9 females and 28 males were included in this study. As to stages for ICC, 33 (89.2%) patients were categorized into child-pugh A stage while 4 (10.8%) patients were B stage, and 9 (24.3%), 11 (29.7%) as well as 17 (45.9%) patients were at BCLC stage A, B, and C respectively. In addition, 13 (35.1%) patients had history of HB. The other detailed information about clinicopathological features, biochemical indexes, previous treatments were presented in Table 1.

Table 1

Baseline characteristics of 37 ICC patients.

Parameters	Patients (N=37)
Age (years)	62.9±13.4
Gender (Female/Male)	9/28
History of HB (n/%)	13 (35.1)
History of drink (n/%)	15 (40.5)
History of cirrhosis (n/%)	9 (24.3)
Multifocal disease (n/%)	25 (67.6)
Tumor location	
Left (n/%)	8 (21.7)
Right (n/%)	19 (51.4)
Bilobar (n/%)	10 (27.0)
Largest nodule size (cm)	5.700 (3.0–8.3)
Portal vein invasion (n/%)	15 (40.5)
Hepatic vein invasion (n/%)	5 (13.5)
ECOG performance status	
0 (n/%)	16 (43.2)
1 (n/%)	15 (40.5)
2 (n/%)	5 (13.5)
3 (n/%)	1 (2.7)
Child-pugh Stage	
A (n/%)	33 (89.2)
B (n/%)	4 (10.8)
BCLC Stage	
A (n/%)	9 (24.3)
B (n/%)	11 (29.7)
C (n/%)	17 (45.9)
Cycles of DEB-TACE treatment	
1 cycle (n/%)	30 (81.0)
2 or more cylces (n/%)	7 (18.9)
Tumor markers	
AFP (μg/L)	3.4 (2.2–6.5)
CEA (μg/L)	3.0 (2.1–7.5)
CA199 (ku/L)	40.5 (8.3–242.9)
Previous treatments	
cTACE (n/%)	9 (24.3)
Surgery (n/%)	9 (24.3)
Systematic chemotherapy (n/%)	5 (13.5)
Radiofrequency ablation (n/%)	5 (13.5)
Targeted therapy (n/%)	0 (0.0)
Combination of ordinary embolization agent (n/%)	8 (21.6)

Data was presented as mean±standard deviation, median (25th–75th) or count (%).
ICC = intrahepatic cholangiocarcinoma, AFP = alpha fetoprotein, BCLC = Barcelona Clinic Liver Cancer, 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 = hepatitis B.

3.2. Treatment response of DEB-TACE treatment

As shown in Figure 1A, 3 (8.1%), 22 (59.5%), 9 (24.3%) and 3 (8.1%) patients achieved CR, PR, SD, and PD, respectively, and ORR was 67.6%. As to treated nodules (Fig. 1B), 4 (8.9%), 26 (57.8%), 10 (22.2%), and 5 (11.1%) nodules achieved CR, PR, SD, and PD respectively, and ORR was 66.67%.

3.3. OS analysis

As presented in Figure 2, after DEB-TACE treatment, mean OS of ICC patients was 376 days (95%CI: 341–412 days), which revealed a great therapeutic effect for ICC patients by using DEB-TACE.

3.4. Comprehensive analysis of factors predicting ORR

Drink ($P=.031$, OR: 0.194, 95% CI: 0.044–0.858), bilobar disease ($P=.037$, OR: 0.190, 95% CI: 0.040–0.904) and portal vein invasion ($P=.031$, OR: 0.194, 95% CI: 0.044–0.858) were predictors for less probability of ORR in univariate logistic

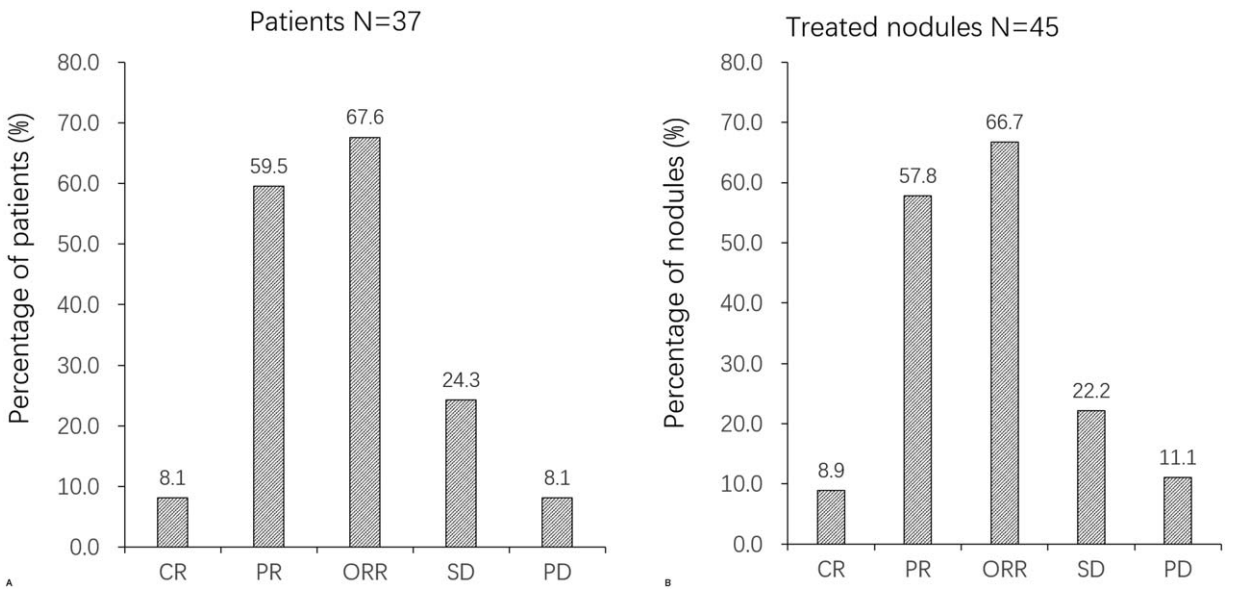

Figure 1. Treatment response of DEB-TACE in ICC patients. (A) Treatment response of DEB-TACE in patients. (B) Treatment response of DEB-TACE in treated nodules. Comparison among groups was determined by Chi-Squared test. $P < .05$ was considered significant.

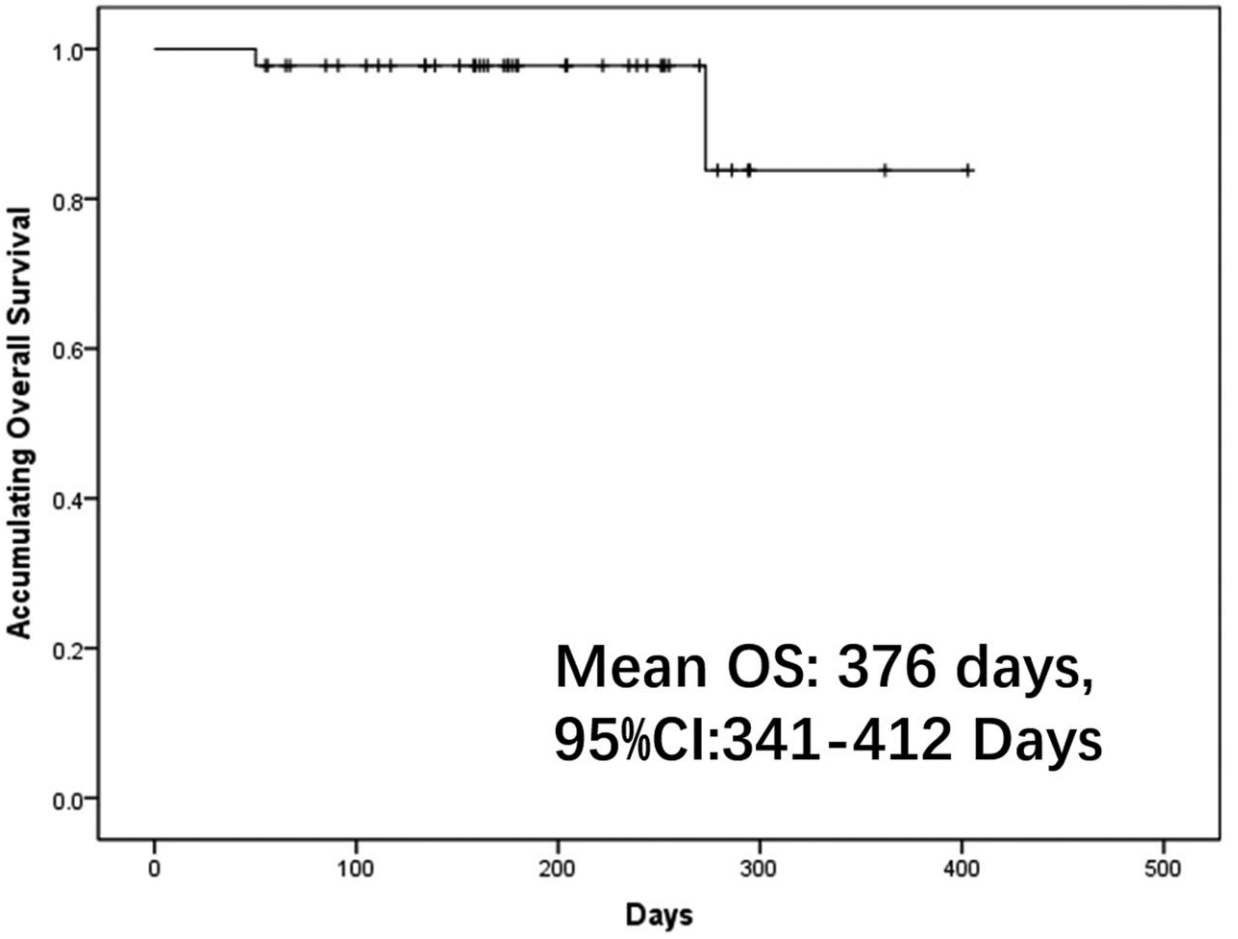

Figure 2. OS of DEB-TACE treatment in ICC patients. K–M curve was performed to evaluate the OS.

Table 2

Factors affecting ORR achievement to DEB-TACE treatment in ICC patients 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
Age>=60 years	.935	1.062	0.245	4.599	–	–	–	–
Male	.457	0.514	0.089	2.963	–	–	–	–
History of HB	.874	1.125	0.263	4.804	–	–	–	–
History of drink	**.031**	0.194	0.044	0.858	.084	0.160	0.020	1.279
History of cirrhosis	.381	0.500	0.106	2.355	–	–	–	–
Multifocal disease	.169	0.300	0.054	1.669	–	–	–	–
Tumor location-Bilobar	**.037**	0.190	0.040	0.904	**.040**	0.105	0.012	0.898
Largest nodule size>=5 cm	.893	0.909	0.226	3.661	–	–	–	–
Portal vein invasion	**.031**	0.194	0.044	0.858	**.038**	0.104	0.012	0.881
Hepatic vein invasion	.530	2.095	0.208	21.099	–	–	–	–
Higher ECOG performance status	.179	2.018	0.724	5.620	–	–	–	–
Higher Child-pugh Stage B (VS A)	.436	0.435	0.053	3.536	–	–	–	–
Higher BCLC Stage	.303	0.622	0.252	1.534	–	–	–	–
2 or more cycles of DEB-TACE treatment	.277	3.474	0.369	32.743	–	–	–	–
Previous cTACE treatment	.947	0.947	0.192	4.677	–	–	–	–
Previous Surgery	.381	0.500	0.106	2.355	–	–	–	–
Previous systematic chemotherapy	.530	2.095	0.208	21.099	–	–	–	–
Previous radiofrequency ablation	.530	2.095	0.208	21.099	–	–	–	–
Previous targeted therapy	–	–	–	–	–	–	–	–
Combination of ordinary embolization agent	.239	0.381	0.076	1.901	–	–	–	–
AFP abnormal	.955	0.947	0.145	6.169	–	–	–	–
CEA abnormal	.660	1.436	0.286	7.212	–	–	–	–
CA199 abnormal	.064	0.188	0.032	1.105	.290	0.343	0.047	2.495

Data was presented as *P* value, OR (odds ratio) and 95% CI (confidence interval). Factors affecting ORR (objective response rate) 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. BCLC stage was scored as 1-Stage A, 2-Stage B, 3-Stage C, the logistic analysis was performed based on these definitions.

AFP = alpha fetoprotein, BCLC = Barcelona Clinic Liver Cancer, 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 = hepatitis B, ICC = intrahepatic cholangiocarcinoma.

regression analysis. Factors with $P<.100$ were further detected by multivariate logistic regression analysis which illuminated that bilobar disease ($P=.040$, OR: 0.105, 95% CI: 0.012–0.898) and portal vein invasion ($P=.038$, OR: 0.104, 95% CI: 0.012–0.881) could independently predict less possibility of ORR (Table 2).

3.5. Comprehensive analysis of factors predicting OS

In order to investigate influence of the baseline factors on OS, Cox proportional hazards regression model analysis was performed and the results were showed in Table 3. However, no association was observed between each factor and OS in univariate Cox regression (all $P>.050$), thus multivariate Cox regression was not performed.

3.6. Comparison of liver function before and after DEB-TACE treatment

The percentage of ALB abnormal, TP abnormal, ALT abnormal and AST abnormal patients were increased at 1-week post DEB-TACE treatment ($P=.034$, $P=.001$, $P<.001$, $P=.006$, respectively), while returned to the levels at baseline after 1 to 3 months (all $P>.050$). No difference of other liver function indexes between each visit were observed (Table 4).

3.7. AEs of 45 DEB-TACE records

AEs of 45 records during operation and at 1 month post DEB-TACE operation were presented in Table 5. During operation, 35 (77.8%) patients felt pain, 21 (46.7%) patients had fever, 12 (26.7%) patients had vomiting, 10 (22.2%) patients had nausea and 6 (13.3%) patients with other AEs. While at 1-month post DEB-TACE treatment, pain occurred in 11 (24.4%) patients, fever in 6 (13.3%) patients, nausea in 6 (13.3%) patients, vomiting in 1 (2.2%) patients, bone marrow toxicity in 1 (2.2%) patients and other AEs in 3 (6.7%) patients.

3.8. Description of 2 typical cases

In patient 1, tumor-supplying arteries were completely embolized by DEB-TACE according to DSA images (Fig. 3A and B), and the tumor was totally necrotic after DEB-TACE (Fig. 3C and D). In patient 2, arteries were greatly embolized by DEB-TACE (Fig. 3E and F), and tumor was necrotic post DEB-TACE operation (Fig. 3G and H). The results showed a good effect of DEB-TAEC in treating ICC patients.

4. Discussion

In this study, we found:

1. 8.1% and 67.6% ICC patients achieved CR and ORR respectively by DEB-TACE treatment, and mean OS was 376 days (95%CI: 341–412 days).
2. Bilobar disease and portal vein invasion were independent factors for predicting less probability of ORR;
3. DEB-TACE was well tolerated in treating ICC patients regarding to liver function change and mild AEs.

Table 3

Factors affecting OS to DEB-TACE treatment in ICC patients by Cox proportional hazards regression model analysis.

	Univariate Cox's regression			
	P value	HR	95% CI	
Parameters			Lower	Higher
Age>=60 years	.418	0.310	0.018	5.295
Male	.655	29.142	0.000	77274823.610
History of HB	.459	462.690	0.000	5.317E9
History of drink	.452	82.228	0.001	8052226.250
History of cirrhosis	.521	2.494	0.153	40.561
Multifocal disease	.418	0.310	0.018	5.295
Tumor location-Bilobar	.733	1.643	0.094	28.626
Largest nodule size>=5 cm	.577	41.822	0.000	20910376.59
Portal vein invasion	.704	1.713	0.106	27.611
Hepatic vein invasion	.800	0.040	0.000	2.850E9
Higher ECOG performance status	.502	0.059	0.000	231.155
Higher Child-pugh Stage B (VS A)	.907	76963.333	0.000	1.286E87
Higher BCLC Stage	.511	1.950	0.267	14.247
2 or more cycles of DEB-TACE treatment	.545	0.020	0.000	6308.229
Previous cTACE treatment	.521	2.494	0.153	40.561
Previous Surgery	.591	0.029	0.000	12125.659
Previous systematic chemotherapy	.705	0.039	0.000	788767.023
Previous radiofrequency ablation	.221	5.657	0.352	90.918
Previous targeted therapy	–	–	–	–
Combination of ordinary embolization agent	.665	1.904	0.103	35.186
AFP abnormal	.795	0.039	0.000	1.519E9
CEA abnormal	.520	0.020	0.000	3069.562
CA199 abnormal	.793	0.687	0.041	11.379

Data was presented as *P* value, HR (hazards ratio) and 95% CI (confidence interval). Factors affecting OS (overall survival) were determined by univariate Cox proportional hazards regression model analysis, while no factors with *P* value no more than .1 were found thus multivariate Cox proportional hazards regression analysis was not performed. *P* value < .05 was considered significant. BCLC stage was scored as 1-Stage A, 2-Stage B, 3-Stage C, the logistic analysis was performed based on these definitions.

ICC = intrahepatic cholangiocarcinoma, AFP = alpha fetoprotein, BCLC = Barcelona Clinic Liver Cancer, 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 = hepatitis B.

ICC, counts for 10% to 20% of all primary liver cancers, is the second most common primary liver malignancy after hepatocellular carcinoma (HCC).[13] The incidence of ICC has been increasing worldwide at a growing rate greater than that of HCC.[14,15] The disease often presents symptoms in an advanced state, which precludes surgical resection in about 50% to 70% of patients at the time of diagnosis. DEB-TACE, a novel drug delivery system, uses microspheres as embolic agents and ensures the slow and sustained release of the drug locally in addition to causing ischemic injury to the tumor.[11,16] Some studies illustrate that, compared to cTACE, DEB-TACE does not improve the treatment response or survival rate but achieves less liver toxicity and better tolerance in HCC patients,[17,18] while several recent meta-analysis articles disclose DEB-TACE could achieve a higher response rate and survival profiles.[19–21]

A great number of studies reveal that DEB-TACE shows good efficacy in treating HCC patients, and the ORR is 64% or higher,[22–24] which is similar to our results that ORR of ICC patients was 67.6%. However, a study that is conducted on patients with HCC receiving DEB-TACE therapy elucidates a CR rate of 58%,[25] which is better compared to ours (8.1%). The reasons might be that ICC is very different from HCC in the type

Table 4

Liver function before and after DEB-TACE treatment (45 DEB-TACE records in cholangiocarcinoma patients).

	Baseline	1-week post DEB-TACE	1–3 months post DEB-TACE	*P* value*	*P* value#
ALB abnormal (n/N/%)	14/45 (31.1)	22/41 (53.6)	18/44 (40.9)	**.034**	.336
TP abnormal (n/N/%)	9/45 (20.0)	23/41 (56.1)	10/44 (22.7)	**.001**	.754
TBIL abnormal (n/N/%)	9/45 (20.0)	13/41 (31.7)	13/44 (29.5)	.214	.297
TBA abnormal (n/N/%)	12/42 (28.6)	12/38 (31.6)	14/42 (33.3)	.769	.637
ALT abnormal (n/N/%)	10/45 (22.2)	28/41 (68.3)	11/44 (25.0)	**<.001**	.758
AST abnormal (n/N/%)	18/44 (40.9)	29/41 (70.7)	19/44 (43.2)	**.006**	.829
ALP abnormal (n/N/%)	19/43 (44.2)	24/41 (58.5)	25/44 (56.8)	.118	.239

Data was presented as count. Comparison among groups was determined by McNemar test. *P* < .05 was considered significant. Analysis was based on 45 DEB-TACE records in ICC (intrahepatic cholangiocarcinoma) patients.

* *P* value of liver function related biochemical indexes of patients from baseline to 1 week post treatment.

\# *P* value of liver function related biochemical indexes of patients from baseline to 1–3 months post treatment.

ALB = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DEB-TACE = drug-eluting bead transarterial chemoembolization, TBA = total bile acid, TBIL = total bilirubin, TP = total protein.

Table 5

Adverse events of DEB-TACE treatment (45 DEB-TACE records in cholangiocarcinoma patients).

Parameters	n (%)
During DEB-TACE operation	
Pain (n/%)	35 (77.8)
Fever (n/%)	21 (46.7)
Vomiting (n/%)	12 (26.7)
Nausea (n/%)	10 (22.2)
Others (n/%)	6 (13.3)
1 month after DEB-TACE operation	
Pain (n/%)	11 (24.4)
Fever (n/%)	6 (13.3)
Nausea (n/%)	6 (13.3)
Vomiting (n/%)	1 (2.2)
bone marrow toxicity (n/%)	1 (2.2)
Others (n/%)	3 (6.7)

Data was presented as count (%). Description was based on 45 DEB-TACE records in ICC (intrahepatic cholangiocarcinoma) patients.
DEB-TACE = drug-eluting bead transarterial chemoembolization.

of vascularization, tumor dimensions and sensitivity to the toxic drug, which lead to more dismal outcome than HCC.[26]

Studies investigating DEB-TACE treatment in ICC patients were seldom reported, a prospectively cohort study enrolling 20 ICC patients, among which 11 cases choose the TACE with microspheres treatment and other 9 cases choose palliative care or chemotherapy, discloses that TACE with microspheres achieves extremely high response rate with 10% CR and 90% PR, and realized a favorable OS (median 13 months) compared to palliative care or chemotherapy patients.[27] Another recent published study which recruits 109 ICC patients underwent DEB-TACE treatment reveals the CR, ORR, disease control rate (DCR) are 0%, 7% and 95% respectively.[28] While in this present study, 8.1% and 67.6% ICC patients achieved CR and ORR and mean OS was 376 days (95%CI: 341–412 days) by DEB-TACE treatment. The primary cause of this controversy might result from the gap of technical ability between operators and differences of the population.

In order to improve the prognosis of ICC patients, it is essential to explore novel and convincing biomarker for both treatment response and survival in ICC patients by DEB-TACE treatment. A prospective historical cohort illustrates that nodule size 5 cm and tumor location in the segments 1 and 4 are correlated with more probability of CR in HCC patients.[29] And several retrospective studies reveal that portal vein tumor thrombus is an independent prognostic factor for survival according to uni- and multivariate analysis in TCAE treated patients.[30,31] These studies suggest that tumor location and portal vein invasion could predict less probability of CR, and our results suggested that drink, bilobar disease, and portal vein invasion were associated with less possibility of ORR. The possible explanation of the predictive value of these factors might be: drink could induce pancreatitis, which is a relatively rare but potentially lethal complication after DEB-TACE[32]; (2) severe disease condition with poor liver function including bilobar disease and portal vein invasion led to a worse treatment response.

As to liver function before and after DEB-TACE, a prospective and single-center study illustrate that liver function is not remarkably affected by DEB-TACE in most HCC patients assessed by the image with 2 years follow-up.[33] And a comprehensive review reveals that DEB-TACE has remarkably reduced liver toxicity.[34] In our study, the liver function indexes such as ALB, TBIL, TBA, and ALP became better after DEB-TACE, with no change of ALT at 1week and 1 to 3 months post DEB-TACE compared to baseline, which was consistent with those 2 former studies. However, the percentage of patients with abnormal liver function at 1 to 3 months post DEB-TACE seemed to be larger than that at 1 week. The reason might be that ICC was a malignant tumor leading to persistent deterioration of liver function, of which the speed was higher than that of liver recovery treated by DEB-TACE. Besides, our study illustrated a good safety with mild AEs during operation and 1 month after DEB-TACE operation, which was consistent with the previous

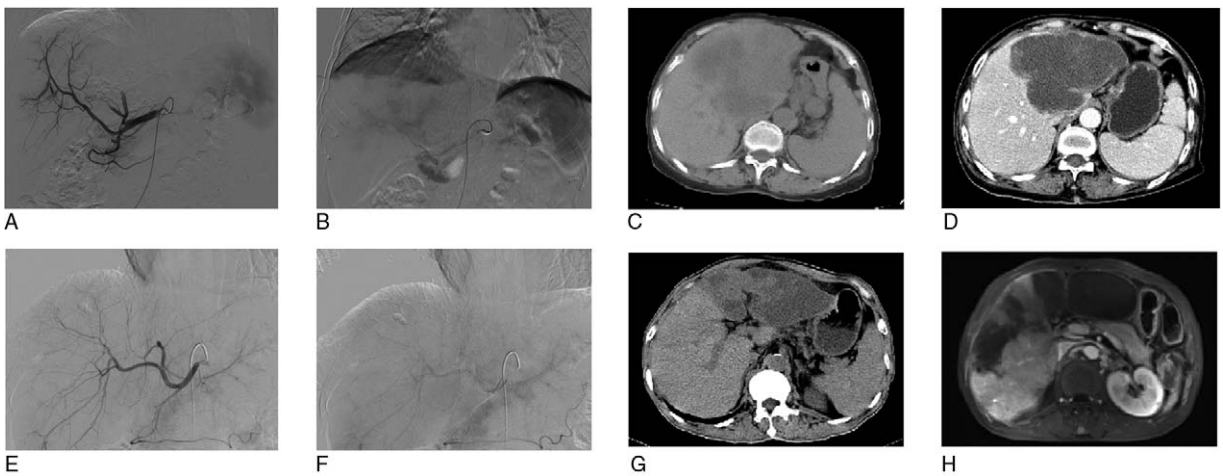

Figure 3. CT and DSA images of 2 patients at pre-operation and post-operation. (A–D) CT and DSA images of 1 patient at preoperation and postoperation. (E–H) CT and DSA images of another patient at preoperation and postoperation. Scan parameters were that: tube voltage was 120 kv; automatic pipe technology to adjust current; collimator width was 128 × 0. 625 mm; the reconstruction was 5 mm; a thick layer of reconstruction interval was 5 mm; screw pitch was 0.914. Enhanced scan USED MEDRAD double cylinder of high-pressure syringe injected iodine alcohol (containing iodine 300 mg/ml) from peripheral vein intravenous (dose of 1.5 ml/kg). When abdominal aorta CT value arrive to 100 HU, it delays after 5 seconds and begins to scan, and after arterial phase late 30 seconds and 150 seconds, respectively, it began to scan portal venous phase and delayed phase.

study of DEB-TACE treatment in ICC patients which illuminates that the most common AEs are pain, fever, nausea.[28]

Some limitations still existed in our study:

1. lack of a proper control group of ICC patients (for instance, ICC patients with cTACE treatment only or ICC patients who did not accept any treatment) was still a main limitation in this study. Further study is needed.
2. Owning to that most ICC patients enrolled in this study were ecdemic patients, the majority of them received 1 time of DEB-TACE or multiple times of continue DEB-TACE in our hospital. After receiving DEB-TACE, some patients would continue to receive consolidation therapy according to their own conditions in our hospital; whereas most patients would go back to the local place, and they would receive additional treatments in the local hospital when their disease progressed. Thus, we could not collect the detailed information about their tumor progression free survival, recurrence with CR as well as metastasis. Further study investigating the efficacy of DEB-TACE on progression free survival, recurrence with CR as well as metastasis in ICC patients is greatly needed.
3. whether other multiple approaches (eg cTACE, surgery, RFA, etc) after DEB-TACE affect the effiacy and safty of DEB-TACE was not explored in this study, further study is needed.
4. sample size with 37 ICC patients was relatively small and study with a larger sample size is needed in the future;
5. most patients (75.7%) in our study had treatment history before DEB-TACE, of which the efficacy and safety in treatment-naive ICC patients could not be evaluated.
6. The follow-up duration was relatively small thus long-term benefit of DEB-TACE in ICC patients was not assessed.

In conclusion, DEB-TACE was effective and well tolerated in treating ICC patients, and bilobar disease as well as portal vein invasion were independantly correlated with less probability of ORR achievement.

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