



# Efficacy and safety of CalliSpheres<sup>®</sup> drug-eluting beads transarterial chemoembolization in patients with secondary liver cancer: a preliminary result from CTILC study

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**Background:** This study aimed to assess the treatment response, short-term overall survival (OS) and safety profiles of drug-eluting beads transarterial chemoembolization (DEB-TACE) in patients with secondary liver cancer.

**Methods:** Fifty-five patients with secondary liver cancer underwent DEB-TACE were enrolled in this prospective cohort study. Treatment response was assessed by modified Response Evaluation Criteria in Solid Tumors (mRECIST). OS was calculated from the time of DEB-TACE operation until the date of death.

**Results:** The complete response (CR) and objective response rate (ORR) at 1–3 months post DEB-TACE were 12.7% and 67.3%. Mean OS was 383 d (95% CI: 360–406), and 6-month OS rate was 93.4%±3.7%.

Subgroup analysis revealed previous conventional TACE (cTACE) treatment was correlated with worse ORR ( $P=0.028$ ), and it was a risk factor for ORR achievement ( $P=0.021$ ). As for liver function, the percentages of abnormal TP ( $P=0.031$ ), TBIL ( $P=0.022$ ), ALT ( $P=0.002$ ) and AST ( $P=0.035$ ) were increased at 1 week post DEB-TACE compared to baseline, while these four indexes returned to baseline (all  $P>0.05$ ) at 1–3 months post DEB-TACE. As to safety profiles, 41 (66.1%), 28 (45.2%), 17 (27.4%), 8 (12.9%) and 6 (9.7%) cases had pain, vomiting, fever, nausea and other adverse events (AEs) respectively during DEB-TACE operation, while 26 (41.9%), 9 (14.5%), 8 (12.9%), 4 (6.5%), 1 (1.6%) and 2 (3.2%) cases had pain, fever, vomiting, nausea, bone marrow toxicity and other AEs respectively at 1 month after DEB-TACE operation.

**Conclusions:** DEB-TACE was efficient and well tolerated in treating patients with secondary liver cancer.

**Keywords:** Drug-eluting beads transarterial chemoembolization (DEB-TACE); secondary liver cancer; treatment response; overall survival; liver function; safety

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## Introduction

The liver is one of the most frequent sites of distant metastasis from various carcinomas due to its numerous supplying arteries, and its involvement has been considered to be a critical prognostic factor affecting patients' survival and quality of life (1,2). According to previous clinical reports, a significant number of patients with various carcinomas would also experience liver metastasis, including an estimated 50% of patients with colorectal cancer, 40% of patients with gastric cancer, and 25% to 50% of patients with pancreatic cancer. Furthermore, the 5-year survival rate dramatically decreases compared to patients without liver metastasis (3–5).

Despite the widespread use of transarterial chemoembolization (TACE), which contributes to antitumor effects and selective ischemia of a targeted tumor to kill the tumor cells (6,7), the conventional TACE (cTACE) is performed using lipiodol and chemotherapeutic agents. However, there still exist some limitations in containing the systemic toxicity caused by the flow of chemotherapeutics in the circulation system and the incapacity to precisely regulate drug release, thereby rendering cTACE ineffective (8,9). To reduce these drawbacks, the drug-eluting bead TACE (DEB-TACE), a novel drug delivery system using microspheres as embolic agents loaded with chemotherapy drugs, has been introduced into clinical practice, and offers higher intratumoral concentration and lower systemic drug concentrations when compared to cTACE, decreasing systemic adverse drug reactions and liver toxicity (10–13).

Although the benefits of DEB-TACE have been confirmed in patients with primary liver cancer, knowledge is still lacking regarding the efficacy and safety of DEB-TACE in patients with secondary liver cancer (14–17). Therefore, the purpose of this study was to assess the treatment response, short-term overall survival (OS), and safety profiles of DEB-TACE treatment in patients with secondary liver cancer.

## Methods

### Patients

Fifty-five patients with secondary liver cancer underwent DEB-TACE treatment between 2015/11/12 and 2016/11/04 from a CTILC study. The study was a multi-center, prospective cohort study which was registered on [clinicaltrials.gov](http://clinicaltrials.gov) (registry No. NCT03317483) and consecutively enrolled 367 liver cancer patients from 24 medical centers to investigate the efficacy, safety, and prognostic factors of DEB-TACE treatment in Chinese patients with liver cancer. It provided additional and convincing evidence for the role of DEB-TACE treatment in Chinese patients with liver cancer (18). The inclusion criteria for patients of the CTILC study were as follows: (I) diagnosed as primary HCC, primary ICC, or secondary liver cancer confirmed by pathological findings, clinical features, or radiographic examinations according to the American Association for the Study of the Liver Diseases (AASLD) guidelines; (II) age above 18 years; (III) about to receive DEB-TACE treatment with CalliSpheres®

according to clinical needs and patients' willingness; (IV) able to be followed up regularly; (V) life expectancy above 12 months. The exclusion criteria were as follows: (I) history of liver transplantation; (II) history of hematological malignancies; (III) severe hepatic failure (Child-Pugh score of  $\geq 10$ ) or renal failure; (IV) contraindication for angiography, embolization procedure, or artery puncture; (V) cognitive impairment, or unable to understand the study consents; (VI) women in gestation or lactation period. This study was approved by the Ethics committee of the Zhejiang Cancer Hospital. All the patients or their legal guardian provided the written informed consent. This study was conducted according to the Declaration of Helsinki.

### **Baseline data collection**

The following comprehensive baseline data of secondary liver cancer patients were collected: (I) demographic features including age and gender. (II) Clinical features including multifocal or unifocal tumor distribution (unifocal disease meant the single lesion, and unifocal disease patients could receive resection, while some of them might be unbearable for the surgery resection or unwilling to receive surgery due to other reasons (such as advanced age and severe cirrhosis). Thus, they chose DEB-TACE treatment, tumor location, largest nodule size, portal vein invasion status (the extent of portal vein thrombosis was incomplete occlusion of the portal vein trunk, and DEB-TACE treatment was suitable for patients with incomplete occlusion of portal vein trunk or the compensatory collateral vessel formation between the hepatic artery and the portal vein despite complete obstruction; meanwhile, patients whose portal vein trunk was completely embolized by tumor and had less collateral vessel formation were contraindicated for DEB-TACE treatment), hepatic vein invasion, ECOG performance status, primary cancer, and cycles of DEB-TACE treatment. (III) Blood routine indexes including white blood cell (WBC), red blood cell (RBC), absolute neutrophil (ANC), hemoglobin (Hb), and platelet (PLT) count. (IV) Liver function indexes including albumin (ALB), total protein (TP), total bilirubin (TBIL), total bile acid (TBA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). (V) Kidney function indexes including blood creatinine (BCr) and blood urea nitrogen (BUN); (VI) tumor markers including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and carbohydrate antigen 199 (CA199). (VII) Treatment history including cTACE history, surgery history, systematic

chemotherapy history, radiofrequency ablation history, and targeted therapy history. (VIII) Chemoembolization reagents and combination of ordinary embolization agent.

### **Treatment**

TACE was carried out using a micro-puncture system via placing a 5F vascular introducer (Boston Scientific, USA) through a transfemoral arterial access route. Angiography of the hepatic artery was executed to provide the liver's vascular anatomy. The CalliSpheres<sup>®</sup> (Jiangsu Hengrui Medicine Co, Ltd., China) DEB loading was performed as follows: after the injection of CBs to the chemotherapy reagent solution was performed, the mixed solution was shaken up every 5 minutes for 30 minutes in an injector at a temperature of 23–28 °C. After that, adding non-ionic contrast agent into the same injector was performed at the ratio of (1–1.2):1 compared to the mixed solution and placed for 5 minutes at a temperature of 23–28 °C for use. Two mL 100–300  $\mu\text{m}$  CalliSpheres<sup>®</sup> DEBs (Jiangsu Hengrui Medicine Co, Ltd., China) loaded with 50–80 mg of anthracyclines (doxorubicin) for metastatic lung cancer and breast cancer patients, and 100–200 mg irinotecan for intestinal cancer, gastric cancer, and pancreatic cancer patients, were used and administered until stasis in each patient. After the procedure, patients were admitted and monitored to the hospital overnight.

### **Efficacy assessment**

Treatment response to DEB-TACE was performed at 1 to 3 months after DEB-TACE treatment by computerized tomography (CT) and magnetic resonance imaging (MRI) based on modified response evaluation criteria in solid tumors (mRECIST). The categories were defined as follows: as (I) complete response (CR), the disappearance of any arterial enhancement of targeted tumors; (II) partial response (PR), more than a 30% decrease in the sum of the diameter of targeted tumors (with arterial enhancement), using the baseline sum of diameter of targeted tumor as a reference; (III) stable disease (SD), the decrease in sum of the diameter of the targeted tumor with arterial enhancement) not reaching PR, with its increase less than progressive disease (PD); (IV) PD, more than 20% increase in the sum of diameter of targeted tumor (with arterial enhancement), taking the smallest diameter of the viable lesion as a reference. In addition, the objective response rate (ORR) was defined as the proportion of patients who

achieved CR and PR.

Overall survival (OS) was defined as the time from the DEB-TACE operation until the date of death from any causes. The median follow-up duration was 171 days (range, 38–404 days), and the last follow-up date was December 28<sup>th</sup>, 2016.

### **Safety assessment**

Liver function indexes including ALB, TP, TBIL, TBA, ALT, AST, and ALP were recorded before, 1-week post and 1–3 months post-DEB-TACE treatment to evaluate the influence of DEB-TACE on liver function. Adverse events (AEs) were recorded during DEB-TACE operation and 1 month after DEB-TACE operation.

### **Statistics**

Statistical analyses were performed using SPSS 22.0 (IBM, USA) and Microsoft Office 2010 software (Microsoft, USA). Data were shown as mean  $\pm$  standard deviation, median (25<sup>th</sup>–75<sup>th</sup>) or count (%). The Chi-Square test determined comparison between the two groups, and the McNemar test performed the comparison of liver function indexes between each visit. Kaplan-Meier (K-M) curves and log-rank test were performed to compare OS in the different groups. Factors affecting ORR achievement were determined by univariate logistic regression analysis, while all factors with a P value less than 0.1 were further detected by multivariate logistic regression analysis. Univariate Cox analysis determined factors affecting OS. A P value <0.05 was considered significant.

## **Results**

### **Baseline characteristics**

As listed in *Table 1*, the mean age of those 55 patients with secondary liver cancer undergoing DEB-TACE treatment was 64.33 $\pm$ 10.96 years. Female and male patient sample sizes were 25 and 30 respectively.

There were 39 (70.9%) patients with multifocal tumor distribution and 16 (29.1%) patients with unifocal tumor distribution. The percentage of patients with portal vein invasion and patients with hepatic vein invasion was the same at 10.9% (N=6). As for primary cancer, the numbers of patients with intestinal cancer, gastric cancer, pancreatic cancer, and other cancers were 34 (61.8%), 5 (9.1%), 7

(12.7%), and 9 (16.4%) respectively. Forty-eight (87.3%) patients achieved 1 cycle of DEB-TACE treatment, while 7 (12.7%) patients achieved 2 or more cycles. The median levels of ALB, TP, TBIL, TBA, ALT, AST, and ALP were 38.9 (interquartile range, 36.7–42.7) g/L, 68.9 (interquartile range, 64.3–73.6) g/L, 11.8 (interquartile range, 8.0–15.9)  $\mu$ mol/L, 6.0 (interquartile range, 3.8–10.6) I/L, 18.0 (interquartile range, 11.5–28.0) U/L, 27.0 (interquartile range, 21.0–37.5) U/L, and 112 (interquartile range, 83–155) U/L, respectively. As for tumor markers, the median levels of AFP, CEA, and CA199 were 2.6 (interquartile range, 2.2–3.9)  $\mu$ g/L, 12.1 (interquartile range, 2.9–89.7)  $\mu$ g/L, and 20.5 (interquartile range, 7.3–77.8) kU/L. Moreover, 11 (20.0%), 32 (58.2%), 33 (60.0%), 12 (21.8%), and 4 (7.3%) patients were previously treated with cTACE, surgery, systematic chemotherapy, radiofrequency ablation, and targeted therapy respectively. There were 62 DEB-TACE records, including 10 (16.1%) records used with anthracyclines and 52 (83.9%) records used with Irinotecan. Other baseline characteristics are shown in *Table 1*.

### **Treatment response of DEB-TACE treatment**

After DEB-TACE operation, the ORR of these 55 patients was 67.2 %, containing 12.7% of patients who achieved CR and 54.5% of patients who achieved PR. The SD rate was 23.6%, and the PD rate was 9.1% (*Figure 1A*). Among the patients who reached PR, the percentages of patients with necrosis rate of  $\geq$ 80%, 50% to 80% and <50% were 23.3 %, 70.0% and 6.7% respectively (*Figure 1B*).

As for treated nodules (N=102), the ORR was 64.7%, which consisted of CR (17.6%) and PR (47.1%), and 26.5% patients achieved SD and 8.8% patients achieved PD (*Figure 1C*). For those nodules reaching PR (N=48), 39.6% of nodules had a necrosis rate  $\geq$ 80%, 54.1% of nodules had a necrosis rate of 50% to 80%, while 6.3% of nodules had a necrosis rate <50% (*Figure 1D*).

### **OS of DEB-TACE treatment in secondary liver cancer patients**

K-M curves showed that mean OS of secondary liver cancer patients treated with DEB-TACE was 383 d (95% CI: 360–406), and the percentage of 6-month OS was 93.4% $\pm$ 3.7% (*Figure 2*).

### **Comparison of ORR between/among subgroups**

Chi-Square test was used to compare ORR in subgroups

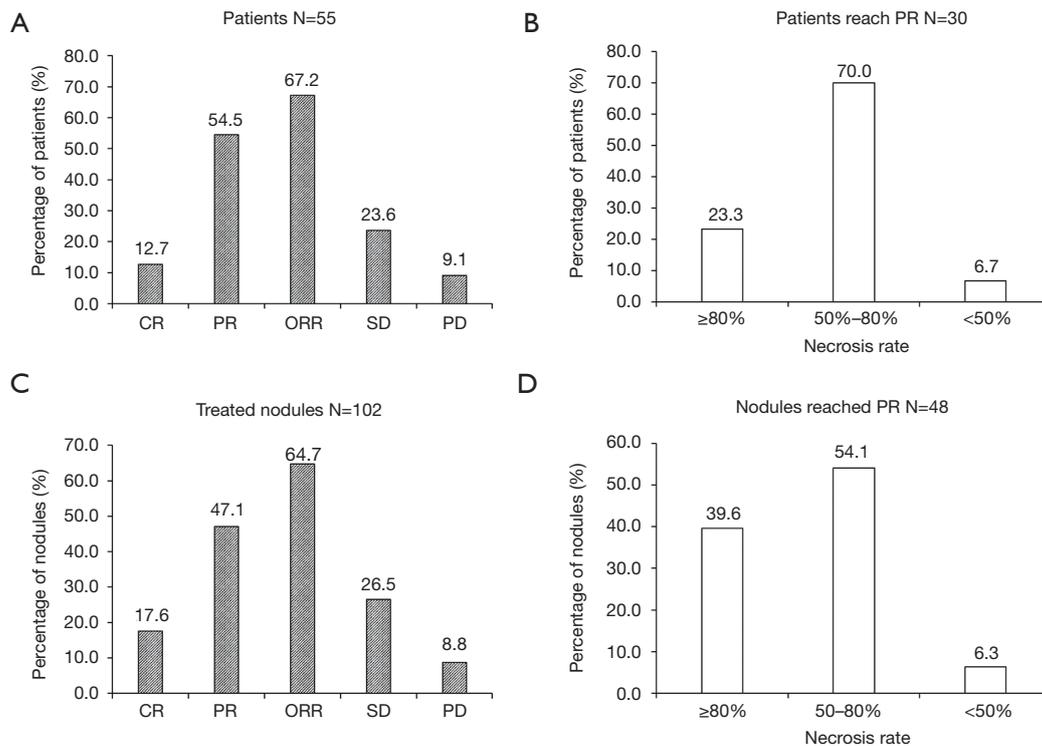
**Table 1** Baseline characteristics of 55 patients with secondary liver cancer underwent DEB-TACE treatment

Parameters	Patients (n=55)
Age (years)	64.33±10.96
Gender (female/male)	25/30
Tumor distribution, n (%)	
Multifocal	39 (70.9)
Unifocal	16 (29.1)
Tumor location, n (%)	
Left liver	6 (10.9)
Right liver	20 (36.4)
Bilobar	29 (52.7)
Largest nodule size (cm)	5.0 (2.6–6.7)
Portal vein invasion, n (%)	6 (10.9)
Hepatic vein invasion, n (%)	6 (10.9)
ECOG performance status, n (%)	
0	12 (21.8)
1	29 (52.7)
2	11 (20.0)
3	3 (5.5)
Primary cancer, n (%)	
Intestinal cancer	34 (61.8)
Gastric cancer	5 (9.1)
Pancreatic cancer	7 (12.7)
Others (lung cancer, breast cancer and so on), n (%)	9 (16.4)
Cycles of DEB-TACE treatment, n (%)	
1 cycle	48 (87.3)
2 or more cycles	7 (12.7)
Blood routine	
WBC ( $\times 10^9$ cell/L)	5.6 (4.3–7.6)
RBC ( $\times 10^{12}$ cell/L)	3.9 (3.6–4.3)
ANC%	62.7 (53.3–70.6)
Hb (g/L)	116 (100–128)
PLT ( $\times 10^9$ cell/L)	159 (120.5–226.5)

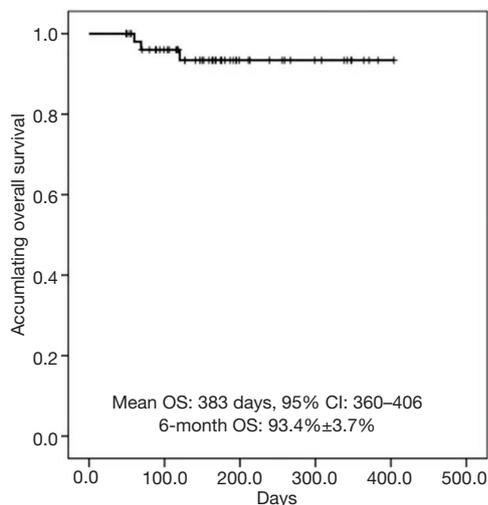
**Table 1** (continued)**Table 1** (continued)

Parameters	Patients (n=55)
Liver function	
ALB (g/L)	38.9 (36.7–42.7)
TP (g/L)	68.9 (64.3–73.6)
TBIL ( $\mu\text{mol/L}$ )	11.8 (8.0–15.9)
TBA (I/L)	6.0 (3.8–10.6)
ALT (U/L)	18.0 (11.5–28.0)
AST (U/L)	27.0 (21.0–37.5)
ALP (U/L)	112 (83–155)
Kidney function	
BCr ( $\mu\text{mol/L}$ )	60 (49.4–73.1)
BUN (mmol/L)	4.5 (3.6–5.4)
Tumor markers	
AFP ( $\mu\text{g/L}$ )	2.6 (2.2–3.9)
CEA ( $\mu\text{g/L}$ )	12.1 (2.9–89.7)
CA199 (kU/L)	20.5 (7.3–77.8)
Previous treatments, n (%)	
cTACE	11 (20.0)
Surgery	32 (58.2)
Systematic chemotherapy	33 (60.0)
Radiofrequency ablation	12 (21.8)
Targeted therapy	4 (7.3)
Chemoembolization reagents (62 DEB-TACE records), n (%)	
Anthracyclines	10 (16.1)
Irinotecan	52 (83.9)
Combination of ordinary embolization agent, n (%)	8 (14.5)

Data was presented as mean  $\pm$  standard deviation, median (25<sup>th</sup>–75<sup>th</sup>) or count (%). DEB-TACE, drug-eluting bead transarterial chemoembolization; ECOG, Eastern Cooperative Oncology Group; WBC, white blood cell; RBC, red blood cell; ANC, absolute neutrophil count; Hb, hemoglobin; PLT, platelet; ALB, albumin; TP, total protein; TBIL, total bilirubin; TBA, total bile acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BCr, blood creatinine; BUN, blood urea nitrogen; AFP, alpha fetoprotein; CEA, carcino-embryonic antigen; CA199, carbohydrate antigen199; cTACE, conventional transarterial chemo-embolization.



**Figure 1** Treatment response of DEB-TACE treatment in secondary liver cancer patients. CR, PR, ORR, SD and PD were 12.7%, 54.5%, 67.2%, 23.6% and 9.1% respectively (A); as to PR, the percentages of patients with necrosis rate  $\geq 80\%$ , 50% to 80% and  $< 50\%$  were 23.3%, 70.0% and 6.7% respectively (B). As to treated nodules (N=102), CR, PR, ORR, SD and PD were 17.6%, 47.1%, 64.7%, 26.5% and 8.8% (C). For nodules reached PR, necrosis rate  $\geq 80\%$ , 50% to 80%,  $< 50\%$  were 39.6%, 54.1% and 6.3% (D). DEB-TACE, drug-eluting bead transarterial chemoembolization; CR, complete response; PR, partial response; ORR, objective response rate; SD, stable disease; PD, progressive disease.



**Figure 2** OS of DEB-TACE treatment in secondary liver cancer patients. Mean OS was 383 days (95% CI: 360–406), and the percentage of 6-month OS was  $93.4\% \pm 3.7\%$ . Kaplan-Meier curve was used to evaluate OS. OS, overall survival; DEB-TACE, drug-eluting bead transarterial chemoembolization.

divided by demographic and clinical characteristics. Previous cTACE treatment was correlated with worse ORR ( $P=0.028$ ), while no difference of ORR in subgroups divided by other demographic and clinical characteristics was found (Table 2).

As to subgroups divided by biochemical indexes, abnormal AST ( $P=0.080$ ), ALP ( $P=0.073$ ), CEA ( $P=0.076$ ), and CA199 ( $P=0.059$ ) were correlated with numerically worse ORR but without statistical significance (Table 3). No difference of ORR between/among subgroups divided by other biochemical indexes was observed (Table 3).

#### Factors affecting ORR achievement by logistic regression model analysis

Univariate logistic regression was used to analyze the factors affecting ORR achievement, which indicated that previous cTACE treatment ( $P=0.021$ ) was negatively correlated with ORR achievement (Table 4). Multivariate logistic

**Table 2** Comparison of ORR in subgroups divided by demographic and clinical characteristics

Parameters	n	Not ORR	ORR	P value
Age, n (%)				0.196
≥60 years	37	10 (27.0)	27 (73.0)	
<60 years	18	8 (44.4)	10 (55.6)	
Gender, n (%)				0.495
Male	30	11 (36.7)	19 (63.3)	
Female	25	7 (28.0)	18 (72.0)	
Tumor distribution, n (%)				0.157
Multifocal	39	15 (38.5)	24 (61.5)	
Unifocal	16	3 (18.8)	13 (81.3)	
Tumor location, n (%)				0.569
Left liver	6	1 (16.7)	5 (83.3)	
Right liver	20	6 (30.0)	14 (70.0)	
Bilobar	29	11 (37.9)	18 (62.1)	
Largest nodule size, n (%)				0.631
≥5 cm	28	10 (35.7)	18 (64.3)	
<5 cm	27	8 (29.6)	19 (70.4)	
Portal vein invasion, n (%)				1.000
Yes	6	2 (33.3)	4 (66.7)	
No	49	16 (32.7)	33 (67.3)	
Hepatic vein invasion, n (%)				0.381
Yes	6	3 (50.0)	3 (50.0)	
No	49	15 (30.6)	34 (69.4)	
ECOG performance status				0.505
0	12	4 (33.3)	8 (66.7)	
1	29	8 (27.6)	21 (72.4)	
2	11	4 (36.4)	7 (63.6)	
3	3	2 (66.7)	1 (33.3)	
Primary cancer, n (%)				0.321
Intestinal cancer	34	10 (29.4)	24 (70.6)	
Gastric cancer	5	3 (60.0)	2 (40.0)	
Pancreatic cancer	7	1 (14.3)	6 (85.7)	
Others	9	4 (44.4)	5 (55.6)	
Cycles of DEB-TACE treatment, n (%)				0.671
1 cycle	48	15 (31.3)	33 (68.8)	
2 or more cycles	7	3 (42.9)	4 (57.1)	

**Table 2** (continued)

Table 2 (continued)

Parameters	n	Not ORR	ORR	P value
Previous cTACE treatment, n (%)				0.028
Yes	11	7 (63.6)	4 (36.4)	
No	44	11 (25.0)	33 (75.0)	
Previous surgery, n (%)				0.561
Yes	32	9 (28.1)	23 (71.9)	
No	23	9 (39.1)	14 (60.9)	
Previous systematic chemotherapy, n (%)				0.481
Yes	33	12 (36.4)	21 (63.6)	
No	22	6 (27.3)	16 (72.7)	
Previous radiofrequency ablation, n (%)				1.000
Yes	12	4 (33.3)	8 (66.7)	
No	43	14 (32.6)	29 (67.4)	
Previous targeted therapy, n (%)				0.291
Yes	4	0 (0.0)	4 (100)	
No	51	18 (35.3)	33 (64.7)	
Combination of ordinary embolization agent, n (%)				1.000
Yes	8	2 (25.0)	6 (75.0)	
No	47	16 (34.0)	31 (66.0)	

Data was presented as count (%). Comparison between two groups was determined by Chi-square test.  $P < 0.05$  was considered significant. ORR, objective response rate; ECOG, Eastern Cooperative Oncology Group; DEB-TACE, drug-eluting bead transarterial chemoembolization; cTACE, conventional transarterial chemo-embolization.

regression was further performed to analyze all factors with a P value no more than 0.1. It revealed that previous cTACE treatment ( $P=0.057$ ) and CEA ( $P=0.096$ ) seemed to be independent factors for ORR achievement in secondary liver cancer patients but without statistical significance.

#### Comparison of OS between/among subgroups

No difference in OS was found between or among the subgroups divided by clinicopathological characteristics, including unifocal disease and multifocal disease ( $P=0.292$ ); single-side and bilobar disease ( $P=0.636$ ); tumor size  $< 5$  cm and tumor size  $\geq 5$  cm ( $P=0.582$ ); no portal vein invasion and portal vein invasion ( $P=0.279$ ); no hepatic vein invasion and hepatic vein invasion ( $P=0.313$ ); ECOG 0 to 3 performance status ( $P=0.135$ ); primary intestinal cancer, primary pancreatic cancer, primary gastric cancer and other disease ( $P=0.588$ ); primary intestinal cancer and no primary

intestinal cancer ( $P=0.165$ ); and 1 cycle of DEB-TACE treatment and 2 or more cycles of DEB-TACE treatment ( $P=0.402$ ) subgroups (Figure 3).

#### Factors affecting OS

Factors affecting OS were determined by the univariate Cox proportional hazards regression analysis, which suggested that no factor (all  $P > 0.05$ ) could predict OS in patients with secondary liver cancer post-DEB-TACE. Owing to no factor with  $P < 0.1$  in univariate Cox proportional hazards regression analysis, multivariate Cox proportional hazards regression analysis was not performed (Table 5).

#### Liver function before and after DEB-TACE treatment

Compared to baseline, the percentages of abnormal TP ( $P=0.031$ ), TBIL ( $P=0.022$ ), ALT ( $P=0.002$ ), and AST

**Table 3** Comparison of ORR in subgroups divided by biochemical indexes

Parameters	n	Not ORR	ORR	P value
Blood routine				
WBC				0.244
Abnormal	9	1 (11.1)	8 (88.9)	
Normal	46	17 (37.0)	29 (63.0)	
RBC				0.495
Abnormal	30	11 (36.7)	19 (63.3)	
Normal	25	7 (28.0)	18 (72.0)	
ANC				0.331
Abnormal	17	4 (23.5)	13 (76.5)	
Normal	38	14 (36.8)	24 (63.2)	
Hb				0.933
Abnormal	31	10 (32.3)	21 (67.7)	
Normal	24	8 (33.3)	16 (66.7)	
PLT				0.701
Abnormal	14	4 (28.6)	10 (71.4)	
Normal	41	14 (34.1)	27 (65.9)	
Liver function				
ALB				0.925
Abnormal	27	9 (33.3)	18 (66.7)	
Normal	28	9 (32.1)	19 (67.9)	
TP				0.434
Abnormal	16	4 (25.0)	12 (75.0)	
Normal	39	14 (35.9)	25 (64.1)	
TBIL				0.200
Abnormal	7	4 (57.1)	3 (42.9)	
Normal	48	14 (29.2)	34 (70.8)	
TBA				1.000
Abnormal	6	2 (33.3)	4 (66.7)	
Normal	41	12 (29.3)	29 (70.7)	
ALT				1.000
Abnormal	11	4 (36.4)	7 (63.6)	
Normal	44	14 (31.8)	30 (68.2)	
AST				0.080
Abnormal	16	8 (50.0)	8 (50.0)	
Normal	39	10 (25.6)	29 (74.4)	

Table 3 (continued)

**Table 3** (continued)

Parameters	n	Not ORR	ORR	P value
ALP				0.073
Abnormal	20	10 (50.0)	10 (50.0)	
Normal	34	8 (23.5)	26 (76.5)	
Kidney function				
BCr				1.000
Abnormal	6	2 (33.3)	4 (66.7)	
Normal	49	16 (32.7)	33 (67.3)	
BUN				1.000
Abnormal	8	3 (37.5)	5 (62.5)	
Normal	47	15 (31.9)	32 (68.1)	
Tumor markers				
AFP				1.000
Abnormal	6	2 (33.3)	4 (66.7)	
Normal	40	11 (27.5)	29 (72.5)	
CEA				0.076
Abnormal	33	13 (39.4)	20 (60.6)	
Normal	19	3 (15.8)	16 (84.2)	
CA199				0.059
Abnormal	20	9 (45.0)	11 (55.0)	
Normal	30	6 (20.0)	24 (80.0)	

Data was presented as count (%). Comparison between two groups was determined by Chi-Square test.  $P < 0.05$  was considered significant. ORR, objective response rate; WBC, white blood cell; RBC, red blood cell; ANC, absolute neutrophil count; Hb, hemoglobin; PLT, platelet; ALB, albumin; TP, total protein; TBIL, total bilirubin; TBA, total bile acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BCr, blood creatinine; BUN, blood urea nitrogen; AFP, alpha fetoprotein; CEA, carcino-embryonic antigen; CA199, carbohydrate antigen199.

**Table 4** Factors affecting ORR achievement by logistic regression model analysis

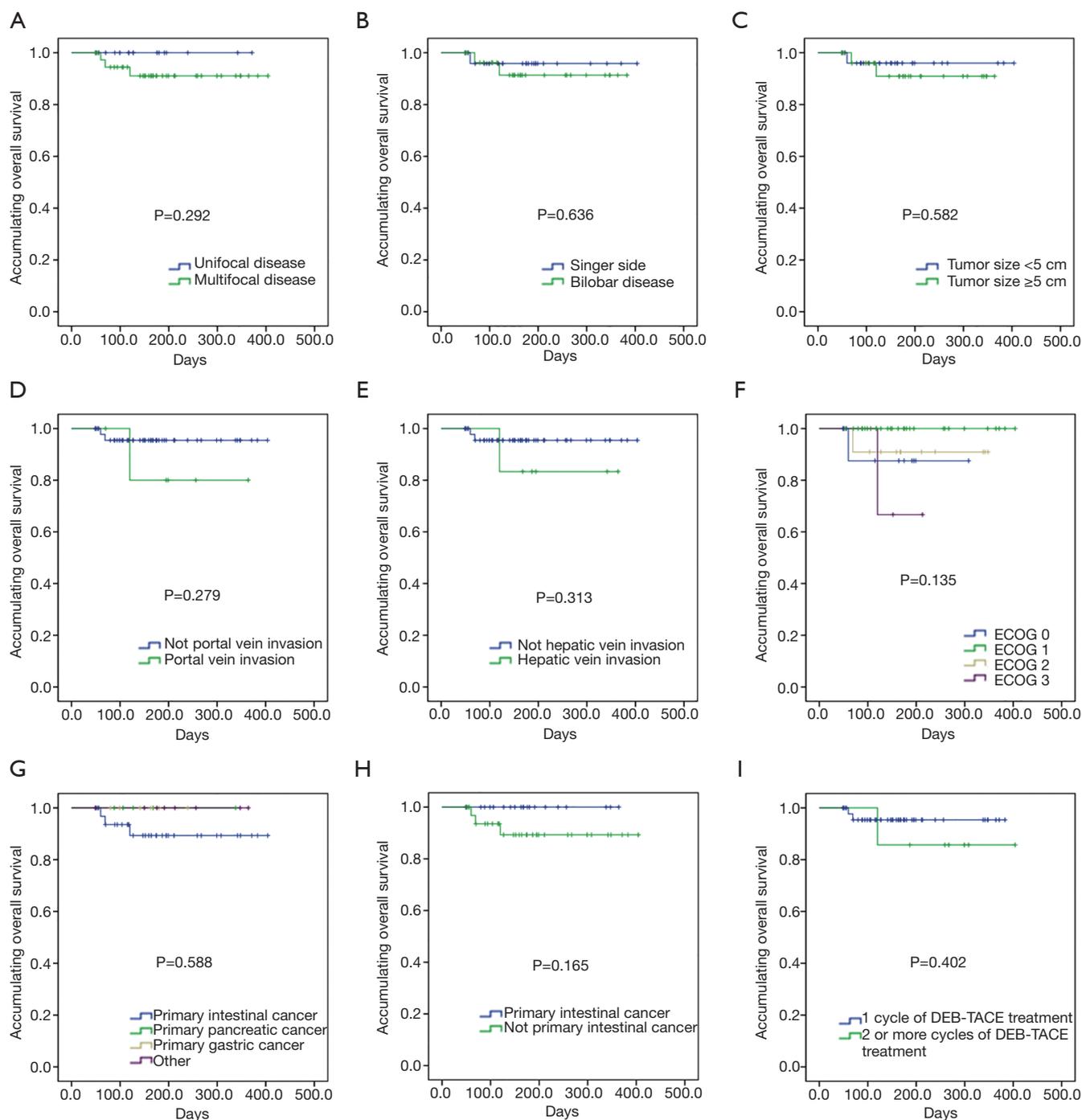
Parameters	Univariate logistic regression				Multivariate logistic regression			
	P value	OR	95% CI		P value	OR	95% CI	
			Lower	Higher			Lower	Higher
Age $\geq 60$ years	0.201	2.160	0.664	7.025	–	–	–	–
Male	0.496	0.672	0.214	2.113	–	–	–	–
Multifocal disease	0.166	0.369	0.090	1.515	–	–	–	–
Tumor location-left liver	0.390	2.656	0.287	24.608	–	–	–	–
Tumor location-right liver	0.745	1.217	0.373	3.978	–	–	–	–
Tumor location-Bilobar	0.387	0.603	0.192	1.897	–	–	–	–
Largest nodule size $\geq 5$ cm	0.631	0.758	0.244	2.349	–	–	–	–

**Table 4** (continued)

Table 4 (continued)

Parameters	Univariate logistic regression				Multivariate logistic regression			
	P value	OR	95% CI		P value	OR	95% CI	
			Lower	Higher			Lower	Higher
Portal vein invasion	0.973	0.970	0.160	5.862	–	–	–	–
Hepatic vein invasion	0.349	0.441	0.080	2.443	–	–	–	–
Higher ECOG performance status	0.395	0.735	0.361	1.495	–	–	–	–
Primary intestinal cancer	0.506	1.477	0.468	4.659	–	–	–	–
Primary gastric cancer	0.194	0.286	0.043	1.889	–	–	–	–
Primary pancreatic cancer	0.288	3.290	0.365	29.638	–	–	–	–
2 or more cycles of DEB-TACE treatment	0.544	0.606	0.120	3.052	–	–	–	–
Previous cTACE treatment	0.021	0.190	0.047	0.776	0.057	0.153	0.022	1.056
Previous Surgery	0.393	1.643	0.526	5.127	–	–	–	–
Previous systematic chemotherapy	0.483	0.656	0.202	2.128	–	–	–	–
Previous radiofrequency ablation	0.960	0.966	0.248	3.759	–	–	–	–
Previous targeted therapy	–	–	–	–	–	–	–	–
Combination of ordinary embolization agent	0.616	1.548	0.280	8.563	–	–	–	–
WBC abnormal	0.161	4.690	0.539	40.801	–	–	–	–
RBC abnormal	0.496	0.672	0.214	2.113	–	–	–	–
ANC abnormal	0.335	1.896	0.517	6.957	–	–	–	–
Hb abnormal	0.933	1.050	0.338	3.265	–	–	–	–
PLT abnormal	0.702	1.296	0.344	4.887	–	–	–	–
ALB abnormal	0.925	0.947	0.307	2.923	–	–	–	–
TP abnormal	0.437	1.680	0.455	6.208	–	–	–	–
TBIL abnormal	0.155	0.309	0.061	1.562	–	–	–	–
TBA abnormal	0.839	0.828	0.133	5.138	–	–	–	–
ALT abnormal	0.774	0.817	0.205	3.255	–	–	–	–
AST abnormal	0.086	0.345	0.102	1.163	0.309	0.404	0.071	2.316
ALP abnormal	0.051	0.308	0.094	1.003	0.567	0.643	0.142	2.913
BCr abnormal	0.973	0.970	0.160	5.862	–	–	–	–
BUN abnormal	0.756	0.781	0.165	3.707	–	–	–	–
AFP abnormal	0.768	0.759	0.121	4.747	–	–	–	–
CEA abnormal	0.086	0.288	0.070	1.190	0.096	0.176	0.023	1.358
CA199 abnormal	0.064	0.306	0.087	1.072	0.119	0.301	0.067	1.362

Data was presented as P value, odds ratio (OR) and 95% confidence interval (CI). Factors affecting objective response rate (ORR) achievement were determined by univariate logistic regression analysis, while all factors with P value no more than 0.1 were further detected by multivariate logistic regression analysis. P value <0.05 was considered significant. ECOG, Eastern Cooperative Oncology Group; DEB-TACE, drug-eluting bead transarterial chemoembolization; cTACE, conventional transarterial chemo-embolization; WBC, white blood cell; RBC, red blood cell; ANC, absolute neutrophil count; Hb, hemoglobin; PLT, platelet; ALB, albumin; TP, total protein; TBIL, total bilirubin; TBA, total bile acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BCr, blood creatinine; BUN, blood urea nitrogen; AFP, alpha fetoprotein; CEA, carcino-embryonic antigen; CA199, carbohydrate antigen199.



**Figure 3** Comparison of OS between/among subgroups divided by clinicopathological characteristics. No difference in OS was found in all subgroups. (A) unifocal disease and multifocal disease ( $P=0.292$ ); (B) single side and bilobar disease ( $P=0.636$ ); (C) tumor size  $<5$  cm and tumor size  $\geq 5$  cm ( $P=0.582$ ); (D) not portal vein invasion and portal vein invasion ( $P=0.279$ ); (E) not hepatic vein invasion and hepatic vein invasion ( $P=0.313$ ); (F) ECOG 0 to 3 performance status ( $P=0.135$ ); (G) primary intestinal cancer, primary pancreatic cancer, primary gastric cancer and others ( $P=0.588$ ); (H) primary intestinal cancer and not primary intestinal cancer ( $P=0.165$ ); (I) 1 cycle of DEB-TACE treatment and 2 or more cycles of DEB-TACE treatment ( $P=0.402$ ). Kaplan-Meier curves and log-rank test were used to evaluate OS.  $P<0.05$  was considered significant.

**Table 5** Factors affecting OS by Cox's regression analysis

Parameters	Univariate Cox's regression			
	P value	HR	95% CI	
			Lower	Higher
Age ≥60 years	0.912	1.146	0.103	12.691
Male	0.651	1.740	0.158	19.213
Multifocal disease	0.526	33.047	0.001	1,642,247
Tumor location-left liver	0.673	0.040	0.000	120,151
Tumor location-right liver	0.970	0.954	0.086	10.538
Tumor location-Bilobar	0.641	1.771	0.161	19.538
Largest nodule size ≥5 cm	0.589	1.938	0.176	21.375
Portal vein invasion	0.309	3.475	0.315	38.362
Hepatic vein invasion	0.341	3.225	0.290	35.813
Higher ECOG performance status	0.318	1.968	0.522	7.426
Primary intestinal cancer	0.437	45.056	0.003	671,987
Primary gastric cancer	0.656	0.040	0.000	60,048
Primary pancreatic cancer	0.717	0.043	0.000	1,056,651
2 or more cycles of DEB-TACE treatment	0.420	2.691	0.242	29.901
Previous cTACE treatment	0.671	1.682	0.152	18.561
Previous Surgery	0.414	0.366	0.033	4.074
Previous systematic chemotherapy	0.749	1.481	0.133	16.480
Previous radiofrequency ablation	0.558	0.033	0.000	2,992
Previous targeted therapy	0.738	0.044	0.000	3,864,701
Combination of ordinary embolization agent	0.500	2.291	0.206	25.467
WBC abnormal	0.405	2.777	0.251	30.705
RBC abnormal	0.620	1.836	0.166	20.255
ANC abnormal	0.349	236.360	0.003	2,174,933
Hb abnormal	0.651	1.740	0.158	19.213
PLT abnormal	0.558	0.033	0.000	2,992
ALB abnormal	0.355	84.331	0.007	1,012,513
TP abnormal	0.408	605.75	0.000	2,372,162
TBIL abnormal	0.673	0.040	0.000	120,151
TBA abnormal	0.700	0.042	0.000	417,666
ALT abnormal	0.540	2.119	0.192	23.381
AST abnormal	0.487	0.027	0.000	719.253
ALP abnormal	0.305	3.511	0.318	38.785
BCr abnormal	0.673	0.040	0.000	120,151

**Table 5** (continued)

Table 5 (continued)

Parameters	Univariate Cox's regression			
	P value	HR	95% CI	
			Lower	Higher
BUN abnormal	0.630	0.038	0.000	23,118
AFP abnormal	0.662	0.040	0.000	74,272
CEA abnormal	0.846	1.269	0.115	14.014
CA199 abnormal	0.854	0.799	0.072	8.817

Data was presented as P value, HR (hazards ratio) and 95% CI (confidence interval). P Value <0.05 was considered significant. ECOG, Eastern Cooperative Oncology Group; DEB-TACE, drug-eluting bead transarterial chemoembolization; cTACE, conventional transarterial chemo-embolization; WBC, white blood cell; RBC, red blood cell; ANC, absolute neutrophil count; Hb, hemoglobin; PLT, platelet; ALB, albumin; TP, total protein; TBIL, total bilirubin; TBA, total bile acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BCr, blood creatinine; BUN, blood urea nitrogen; AFP, alpha fetoprotein; CEA, carcino-embryonic antigen; CA199, carbohydrate antigen199.

( $P=0.035$ ) at 1 week post-DEB-TACE were increased, while these four indexes returned to the percentage at baseline (all  $P>0.05$ ) 1–3 months post-DEB-TACE (Table 6). However, abnormal ALP ( $P=0.006$ ) at 1 week post-DEB-TACE was similar to baseline, while it was increased at 1–3 months post-DEB-TACE compared to baseline levels. The percentages of ALB and TBA in 1 week and 1–3 months were similar to those of baseline (all  $P>0.05$ ) in secondary liver cancer patients.

### Safety profiles of DEB-TACE treatment

As for the safety profiles, 41 (66.1%), 28 (45.2%), 17 (27.4%), 8 (12.9%), and 6 (9.7%) cases occurred with pain, vomiting, fever, nausea and other AEs during DEB-TACE respectively, while 26 (41.9%), 9 (14.5%), 8 (12.9%), 4 (6.5%), 1 (1.6%), and 2 (3.2%) cases occurred with pain, fever, vomiting, nausea, bone marrow toxicity and other AEs after 1-month DEB-TACE operation respectively (Table 7).

### Discussion

In the present study, we observed that in patients with secondary liver cancer after DEB-TACE treatment, (I) the CR and ORR were 12.7% and 67.3% respectively, and the mean OS was 383 d (95% CI: 360–406). (II) Also, previous cTACE treatment was associated with a worse ORR, and univariate and multivariate logistic analyses revealed that previous cTACE treatment and CEA were likely to be independent risk factors for ORR but without

statistical significance, while Cox analysis indicated that no predictive factor of OS in patients with secondary liver cancer was found. (III) Additionally, liver function indexes were deteriorative 1 week post-DEB-TACE, while at 1–3 months post-DEB-TACE, most of liver function indexes returned to baseline levels.

Liver metastases frequently occurred in a large number of patients with primary cancers; these patients' metastatic process typically occurs with invasive tumor cells being separated from the primary site into circulation, with these circulating cancer cells subsequently adhering to sinusoidal endothelial cells by specific sets of adhesion molecules, thereby arresting at the site of the liver and finally colonizing in the liver (19). TACE with drug-eluting microspheres, serving as a new therapeutic approach, is characterized by delivering the chemotherapeutics through microspheres to achieve ischemic tumor effect, and a more controlled release of chemotherapeutic and sustained drug concentration (16,17). However, few studies have explored the role of DEB-TACE in patients with secondary liver cancer; thus, our study enrolled 55 patients with secondary liver cancer and evaluated the efficacy of DEB-TACE in treatment response and OS.

Prior studies have found a CR and ORR of 28.6% and 71.4% respectively, in HCC patients 1–3 months after DEB-TACE (20). Also, DEB-TACE achieved a CR of 40% and ORR of 73.3% in HCC patient at 1–3 months (21). Another interesting study reported that at 1-month follow up, CR and ORR were 48% and 64% respectively in HCC patients receiving DEB-TACE (22). However, knowledge about the treatment response of DEB-

**Table 6** Liver function before and after DEB-TACE treatment in secondary liver cancer patients (62 DEB-TACE records)

Variables	Baseline	1 week post DEB-TACE	1–3 months post DEB-TACE	P value*	P value <sup>#</sup>
ALB abnormal, n/N (%)	31/62 (50.0)	31/51 (60.8)	30/57 (52.6)	0.227	0.754
TP abnormal, n/N (%)	20/62 (32.3)	27/51 (52.9)	17/57 (29.8)	0.031	0.774
TBIL abnormal, n/N (%)	7/62 (11.3)	15/51 (29.4)	11/57 (19.3)	0.022	0.424
TBA abnormal, n/N (%)	7/53 (13.2)	9/42 (21.4)	13/48 (27.1)	0.774	0.180
ALT abnormal, n/N (%)	13/62 (21.0)	26/51 (51.0)	21/57 (36.8)	0.002	0.093
AST abnormal, n/N (%)	17/62 (27.4)	23/49 (46.9)	26/56 (46.4)	0.035	0.052
ALP abnormal, n/N (%)	25/61 (41.0)	24/48 (50.0)	33/56 (58.9)	0.219	0.006

Data was presented as count. Comparison among groups was determined by McNemar test.  $P < 0.05$  was considered significant. Analysis was based on 62 DEB-TACE records. \*, 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. DEB-TACE, drug-eluting bead transarterial chemoembolization; ALB, albumin; TP, total protein; TBIL, total bilirubin; TBA, total bile acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

**Table 7** Safety profiles of DEB-TACE treatment in secondary liver cancer patients (62 DEB-TACE records)

Parameters	N (%)
During DEB-TACE operation	
Pain	41 (66.1)
Vomiting	28 (45.2)
Fever	17 (27.4)
Nausea	8 (12.9)
Others	6 (9.7)
1 month after DEB-TACE operation	
Pain	26 (41.9)
Fever	9 (14.5)
Vomiting	8 (12.9)
Nausea	4 (6.5)
bone marrow toxicity	1 (1.6)
Others	2 (3.2)

Description was based on 62 DEB-TACE records. DEB-TACE, drug-eluting bead transarterial chemoembolization.

TACE in patients with secondary liver cancer is lacking. In our study, the CR was 12.7% and the ORR was 67.3% in patients with secondary liver cancer at 1 to 3 months post-DEB-TACE, which were numerically lower compared to HCC patients treated with DEB-TACE in previous studies. This might result from the fact that patients in our study

were all secondary liver cancer patients, while all patients enrolled in those previous studies were primary liver cancers, which would lead to the difference in treatment response of DEB-TACE.

Regarding OS, a previous short-term study with a 12-month follow-up duration revealed that DEB-TACE (loaded with irinotecan) led to a mean OS of 11.7 months, which is better than a mean OS of 5.7 months in HCC patients treated with cTACE (23). In another study, survival rates of HCC patients receiving DEB-TACE at 1 and 2 years were 65% and 55% respectively (24). As for patients with colorectal liver metastasis, the percentage of 1-year OS occurring post-DEB-TACE was found to be 75% (25). However, for patients with secondary liver cancer treated with DEB-TACE, we observed a mean OS of 383 days (95% CI: 360–406), and a rate of 6-month OS of 93.4%±3.7%. Therefore, OS observed in this study was numerically similar to that in HCC patients after DEB-TACE, while it was numerically better compared to patients with liver metastasis in previous studies. However, the follow-up duration was short in the present study. Thus, a longer follow-up duration is much needed in further study.

In the present study, we also observed that previous cTACE treatment was a risk factor for ORR achievement. The possible reasons were as follows: (I) retreatment with TACE might accumulate liver deterioration, leading to worse treatment response; (II) previous cTACE treatment might increase drug resistance, thereby resulting in worse treatment response. However, no other predictive

factor for ORR achievement was identified in this study apart from previous cTACE treatment in secondary liver cancer patients post-DEB-TACE. Recent data illustrates that tumor size and tumor location serve as independent predictive factors for treatment response to DEB-TACE in HCC patients (26). The possible reasons are that the sample size in our study was relatively small, leading to lower statistical efficiency compared to more extensive sample size studies. Thus, the predictive effects of these baseline factors were not apparent. However, we did not find any potential factor predicting OS in patients with secondary liver cancer post-DEB-TACE. These might partially result from the relatively small sample size and short follow-up duration, leading to a lack of death events.

The effect of DEB-TACE on liver function was also evaluated, which suggested abnormal TP, TBIL, ALT, and AST were increased 1 week post-DEB-TACE compared to baseline, while, at 1–3 months post-DEB-TACE, these four indexes returned to baseline. This rapid worsening of liver function in patients might result from the fact that liver function can be impaired by invasion, and healthy liver tissue can be damaged by vascular occlusion during a DEB-TACE procedure. On the other hand, the liver has the self-recovery capability and regeneration capacity that contributes to the recovery of liver impairment caused during DEB-TACE procedure; thus, liver function indexes would return to baseline after the short-term deterioration. Moreover, we also observed that the percentage of abnormal ALP was similar to baseline, while it notably increased at 1–3 months post-DEB-TACE. ALP is an important enzyme known to catalyze the hydrolytic removal of phosphate from a variety of molecules, and its concentration may be affected by some drugs, such as anthracyclines and irinotecan which were loaded into the DEBs used in this study; these might partially explain the increase of ALP post procedures. However, according to a previous meta-analysis, the results of liver function indexes, including AST, TBIL, ALB, and prothrombin (PT), increased compared to baseline in HCC patients after the procedure of both DEB-TACE and cTACE (27).

It has been demonstrated that, in safety profiles for post-DEB-TACE, the most common AEs were abdominal pain, transient fever, fatigue, and nausea (16,17). In line with these studies, we also observed that during DEB-TACE, pain, vomiting, and fever were the most frequent AEs, while at 1-month DEB-TACE operation pain was the most common AE and only 1 case of bone marrow toxicity occurred. There were no severe AEs during and 1 month

after DEB-TACE operation. Therefore, these results suggest that DEB-TACE was well-tolerated in patients with secondary liver cancer.

Despite these new findings, some limitations still exist. First, the sample size in this study was relatively small, and so further study should recruit more patients with secondary liver cancer. Second, this was a cohort study with a single arm; an RCT study enrolling more than 1,000 patients that explores the comparison of effects in treatment responses and OS between DEB-TACE and cTACE is much needed. Third, the follow-up duration was relatively short; analysis of the long-term efficacy of DEB-TACE in patients with secondary liver cancer is necessary.

In conclusion, DEB-TACE was efficient and well tolerated in treating patients with secondary liver cancer.

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### Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2019.06.44>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics committee of the Zhejiang Cancer Hospital. All the patients or their legal guardian provided the written informed consent. This study was conducted according to the Declaration of Helsinki (as revised in 2013).

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## References

1. Ferreira A, Pereira P, Rolanda C. Diffuse hepatic metastasis--or not? *Gastroenterology* 2012;142:1070, 257.
2. Reddy SK, Clary BM. Neuroendocrine liver metastases. *Surg Clin North Am* 2010;90:853-61.
3. De Greef K, Rolfo C, Russo A, et al. Multidisciplinary management of patients with liver metastasis from colorectal cancer. *World J Gastroenterol* 2016;22:7215-25.
4. Negoii I, Runcanu A, Paun S, et al. Resection of Large Metachronous Liver Metastasis with Gastric Origin: Case Report and Review of the Literature. *Cureus* 2016;8:e814.
5. Fukumitsu N, Okumura T, Numajiri H, et al. Follow-up study of liver metastasis from breast cancer treated by proton beam therapy. *Mol Clin Oncol* 2017;7:56-60.
6. Sieghart W, Hucke F, Peck-Radosavljevic M. Transarterial chemoembolization: modalities, indication, and patient selection. *J Hepatol* 2015;62:1187-95.
7. Imai N, Ishigami M, Ishizu Y, et al. Transarterial chemoembolization for hepatocellular carcinoma: A review of techniques. *World J Hepatol* 2014;6:844-50.
8. Korean Liver Cancer Study G, National Cancer Center K. 2014 KLCSSG-NCC Korea Practice Guideline for the Management of Hepatocellular Carcinoma. *Gut Liver* 2015;9:267-317.
9. Xie ZB, Wang XB, Peng YC, et al. Systematic review comparing the safety and efficacy of conventional and drug-eluting bead transarterial chemoembolization for inoperable hepatocellular carcinoma. *Hepatol Res* 2015;45:190-200.
10. Kim JH, Sinn DH, Shin SW, et al. The role of scheduled second TACE in early-stage hepatocellular carcinoma with complete response to initial TACE. *Clin Mol Hepatol* 2017;23:42-50.
11. Zhou X, Tang Z, Wang J, et al. Doxorubicin-eluting beads versus conventional transarterial chemoembolization for the treatment of hepatocellular carcinoma: a meta-analysis. *Int J Clin Exp Med* 2014;7:3892-903.
12. Kettenbach J, Stadler A, Katzler IV, et al. Drug-loaded microspheres for the treatment of liver cancer: review of current results. *Cardiovasc Intervent Radiol* 2008;31:468-76.
13. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol* 2010;33:41-52.
14. Cucchetti A, Trevisani F, Cappelli A, et al. Cost-effectiveness of doxorubicin-eluting beads versus conventional trans-arterial chemo-embolization for hepatocellular carcinoma. *Dig Liver Dis* 2016;48:798-805.
15. Suk Oh J, Jong Chun H, Gil Choi B, et al. Transarterial chemoembolization with drug-eluting beads in hepatocellular carcinoma: usefulness of contrast saturation features on cone-beam computed tomography imaging for predicting short-term tumor response. *J Vasc Interv Radiol* 2013;24:483-9.
16. Facciorusso A, Mariani L, Sposito C, et al. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma. *J Gastroenterol Hepatol* 2016;31:645-53.
17. Song MJ, Chun HJ, Song DS, et al. Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. *J Hepatol* 2012;57:1244-50.
18. Zhang X, Zhou J, Zhu DD, et al. CalliSpheres(R) drug-eluting beads (DEB) transarterial chemoembolization (TACE) is equally efficient and safe in liver cancer patients with different times of previous conventional TACE treatments: a result from CTILC study. *Clin Transl Oncol* 2019;21:167-77.
19. Ma R, Feng Y, Lin S, et al. Mechanisms involved in breast cancer liver metastasis. *J Transl Med* 2015;13:64.
20. Kloth C, Thaiss WM, Kargel R, et al. Evaluation of Texture Analysis Parameter for Response Prediction in Patients with Hepatocellular Carcinoma Undergoing Drug-eluting Bead Transarterial Chemoembolization (DEB-TACE) Using Biphasic Contrast-enhanced CT Image Data: Correlation with Liver Perfusion CT. *Acad Radiol* 2017;24:1352-63.
21. Yu CY, Ou HY, Weng CC, et al. Drug-Eluting Bead Transarterial Chemoembolization as Bridge Therapy for Hepatocellular Carcinoma Before Living-Donor Liver Transplantation. *Transplant Proc* 2016;48:1045-8.
22. Grosso M, Vignali C, Quaretti P, et al. Transarterial chemoembolization for hepatocellular carcinoma with drug-eluting microspheres: preliminary results from an Italian multicentre study. *Cardiovasc Intervent Radiol* 2008;31:1141-9.
23. Kuhlmann JB, Euringer W, Spangenberg HC, et al. Treatment of unresectable cholangiocarcinoma:

- conventional transarterial chemoembolization compared with drug eluting bead-transarterial chemoembolization and systemic chemotherapy. *Eur J Gastroenterol Hepatol* 2012;24:437-43.
24. Reyes DK, Vossen JA, Kamel IR, et al. Single-center phase II trial of transarterial chemoembolization with drug-eluting beads for patients with unresectable hepatocellular carcinoma: initial experience in the United States. *Cancer J* 2009;15:526-32.
25. Martin RC, Joshi J, Robbins K, et al. Hepatic intra-arterial injection of drug-eluting bead, irinotecan (DEBIRI) in unresectable colorectal liver metastases refractory to systemic chemotherapy: results of multi-institutional study. *Ann Surg Oncol* 2011;18:192-8.
26. Cavalcante RN, Nasser F, Motta-Leal-Filho JM, et al. Occurrence of Vascular Lake Phenomenon as a Predictor of Improved Tumor Response in HCC Patients That Underwent DEB-TACE. *Cardiovasc Intervent Radiol* 2017;40:1044-51.
27. Huang K, Zhou Q, Wang R, et al. Doxorubicin-eluting beads versus conventional transarterial chemoembolization for the treatment of hepatocellular carcinoma. *J Gastroenterol Hepatol* 2014;29:920-5.

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