Callispheres® Drug-Eluting Beads Transarterial Chemoembolization Might be an Efficient and Safety Down-Staging Therapy in Unresectable Liver Cancer Patients

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Research

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Abstract

Purpose: The purpose was to explore the effect of drug-eluting beads transarterial chemoembolization (DEB-TACE) on down-staging in unresectable liver cancer patients.

Methods: 15 unresectable liver cancer patients received DEB-TACE as a down-staging treatment before hepatectomy were enrolled. Data (including demographics, histories, clinical features at diagnosis and cycles of DEB-TACE before hepatectomy) were collected. Treatment response was evaluated at one month after DEB-TACE. Tumor diameter was evaluated by abdominal computed tomography scan. The residual liver volume was evaluated by IQQA liver system, Relapse-free survival (RFS) and overall survival (OS) were calculated by Kaplan-Meier curves.

Results: After DEB-TACE, 3 (20.0%) patients achieved complete response (CR) and 10 (66.7%) patients achieved objective response rate (ORR), meanwhile, 5 (27.8%) tumors achieved CR and 12 (66.7%) tumors achieved ORR. Tumor diameter was decreased after DEB-TACE compared to before DEB-TACE (9.4±3.3 *vs.* 5.4±3.5 cm) (P<0.01). As to residual liver volume, it was increased after DEB-TACE compared to before DEB-TACE (1066.2 cm^3 *vs.* 1172.5 cm^3) (P=0.007). More importantly, 15 (100%) patients could receive resection after DEB-TACE, (including 14 (93.3%) patients with curative resection and 1 (6.7%) patient with palliative resection). For survival, the median RFS was 26.0 months, and the percentage of 5-year accumulating RFS was 20%. As to OS, the median OS was 54.5 months, and the percentage of 5-year accumulating OS was 40%. For safety profiles, 5 patients had postoperative pain, 7 patients had fever, and 1 had nausea and vomiting.

Conclusion: DEB-TACE might be an efficient and safety down-staging treatment in unresectable liver cancer patients.

Introduction

Liver cancer is a kind of complex disease frequently arising in the setting of chronic liver disease and cirrhosis, which is considered as the sixth common diagnosed cancer and the second leading cause of death from cancer around the world, resulting in 841080 new cases and 781631 deaths during 2018 globally[1]. Despite the widespread use of surveillance programs (such as hepatic resection, liver transplantation and image-guided tumor ablation), not all liver cancer patients could get benefits. For instance, hepatic resection is the optimally curable choice for liver cancer patients, particular in these patients at early stage, whereas most patients diagnosed as liver cancer are at intermediate or advanced stages and lost the best time to receive surgery due to unbearable invasion [2, 3]. Although liver transplantation is another curable treatment for patients with small multinodular tumors or advanced liver dysfunction, it is still limitedly applicated owing to the shortage of donators and strict blood type matching requirements[2]. In regard to image-guided tumor ablation, its most procedures are done percutaneously, and it could achieve complete necrosis of almost 100% in liver tumors smaller than 2 cm, while less effectiveness occurs in larger tumors[2, 4, 5] .

For patients with unresectable liver cancer clinically, transarterial chemoembolization (TACE) is widely regarded as first-line therapy for sake of reduced collateral damage to tumor-free parenchyma and increased treatment effect, which is divided into two types according to different chemotherapy modalities (including conventional TACE (cTACE) and drug-eluting beads TACE (DEB-TACE))[6]. In detail, cTACE is a kind of conventional technology using lipiodol as chemotherapy drug carriers, while it has been determined to have high systemic toxicity[7]. So as to solve this problem, DEB-TACE has been introduced, which is a novel drug-delivery embolization system using microspheres as embolic agents and loading with chemotherapeutic drugs to gradually release them into the target tumor. Despite the benefits of DEB-TACE with accurate drug delivery and permanent vascular embolization, it is still not a curative treatment, and its disadvantages also contain liver function deterioration and incomplete tumor necrosis[8]. Therefore, convincing treatments combining with the advantages of DEB-TACE and other curable therapy are needed to be explored. Taken together with the above mentioned, we hypothesized DEB-TACE has down-staging effects for unresectable liver cancer patients, and after down staging, these patients could receive curable hepatic resection. However, little is known about the down-staging benefit in unresectable liver cancer patients. In an attempt to address this dilemma, we carried out this study with the purpose of investigating the effect of DEB-TACE on down-staging in unresectable liver cancer patients.

Methods

Patients selection

From May 2016 to June 2018, 15 unresectable liver cancer patients who received DEB-TACE as down-staging treatment before hepatectomy in The First Affiliated Hospital of Guangxi Medical University were enrolled in this study. The screening criteria were as follows: (i) diagnosed as primary hepatocellular carcinoma (HCC) or cholangiocarcinoma by postoperative pathological findings in accordance with American Association for the Study of the Liver Diseases (AASLD) guidelines, (ii) unable to receive resection due to the following reasons: (a) presenting with large and multiple tumors and insufficient residual liver; (b) presenting with poor liver function and potential risk of severe post-excision cirrhosis, incomplete compensation of residual liver function and post-excision liver failure; (c) coronary heart disease or other severe complications resulting in a higher surgical risk; (iii) The number of tumors ≤ 2, which were confined to the half liver and had no main portal vein invasion, underwent DEB-TACE as down-staging therapy, (iv) had no history of treatment for liver cancer before DEB-TACE, (v) clinical data and follow-up documents were complete, (vi) not complicated with other malignancies. The approval for this study was acquired from the Institutional Review Board of The First Affiliated Hospital of Guangxi Medical University, and the written informed consent or verbal agreement with tape recording was obtained from enrolled patients or their guardians.

Baseline Data Collection

Data of enrolled patients were collected from medical documents, including (1) demographics (age, and gender), (2) histories (drink, hepatitis B (HB), hepatic encephalopathy, hypertension, heart disease, and liver cirrhosis), (3) clinical features at diagnosis (histological type, number of tumors, largest tumor size, portal vein invasion, lymphadenectasis, distant metastasis, liver involvement, Eastern Cooperative Oncology Group (ECOG) score, Barcelona clinic liver cancer (BCLC) stage, and Child-Pugh stage), (4) cycles of DEB-TACE before hepatectomy.

Treatment Process

The CalliSpheres® Microspheres (CSM) (Jiangsu Hengrui Medicine Co. Ltd., Jiangsu, China) were used as drug-eluting beads in the present study, which had the diameter ranging from 100 μm to 300 μm. Before operation, the CSM was loaded with pirarubicin (20~40 mg), which was prepared as previously described [9]. The DEB-TACE operation was conducted in the digital subtraction angiography (DSA) room. Briefly, the tumor supplying vessels were identified by the hepatic angiography using segment or subsegment super selective catheterization, and the femoral artery was punctured using microcatheter, which were performed in accordance with previous study[10]. When the microcatheter was precisely inserted into the tumor supplying vessel, 50 mg lobaplatin, 500 mg fluorouracil as well as 10 mL lipiodol were successively infused into the tumor supplying vessel, then, a bottle of CSM loading with pirarubicin were infused into the tumor supplying vessel. For patients with huge tumor, 1~3 bottle(s) of blank CSM (not loaded with drugs) were added additionally for embolization following the infusion of CSM loading with pirarubicin. Finally, a spot of lipiodol was injected into the tumor supplying vessel for preventing reverse flow of microspheres, resulting in a “sandwich” effect. Besides, pre-procedure and post-procedure treatments were carried out in line with the previous study[10]. With respect to the patients presenting limited efficacy by one cycle of DEB-TACE, if necessary, repeated DEB-TACE was administered for them. Finally, all patients underwent curative resection or palliative resection, which was depended on the efficacy of down-staging treatment by DEB-TACE.

Assessments

The sum of the largest diameters of target tumors in arterial enhancement on Computed Tomography (CT), the residual liver volume, the BCLC stage, the Child-Pugh stage, the tumor markers (including alpha fetoprotein (AFP), carcino-embryonic antigen (CEA) and carbohydrate antigen199 (CA199)) as well as the liver indexes (albumin (ALB), total protein (TP), total bilirubin (TBIL), total bile acid (TBA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP)) were examined and documented before and after down-staging treatment by DEB-TACE. The response to DEB-TACE therapy was evaluated at one month after DEB-TACE by enhanced CT or magnetic resonance imaging (MRI) examination, and the response criteria were in line with the modified Response Evaluation Criteria in Solid Tumors (mRECIST), as follows: (1) complete response (CR): disappearance of any intratumoral arterial enhancement in all target lesions; (2) partial response (PR): at least a 30% decrease

in the sum of diameters of viable (enhancement in the arterial phase) target lesions; (3) stable disease (SD): any cases that did not qualify either PR or progressive disease (PD); (4) PD: an increase of at least 20% in the sum of the diameters of the viable (enhancing) target lesions. Further, objective response rate (ORR) was defined as CR+PR. In addition, the patients' surgical type (curative resection or palliative surgery) was also recorded, and the adverse events occurred post DEB-TACE therapy were documented as well.

Follow-up

After surgery, patients were regularly followed up by clinic visits or telephone calls. The last follow-up date was 2021/09/31. The total follow-up duration was ranging from 12 to 38 months, and median follow-up duration was 23.2 months. Relapse-free survival (RFS) was calculated from the date of surgical resection to the date of disease relapse or death, whichever occurred first. Overall survival (OS) was calculated from the date of DEB-TACE therapy to the date of death or last follow-up.

Statistical analysis

The residual liver volume was evaluated by IQQA liver system (EDDA Technology, Inc, New Jersey, USA). Statistical data processing was conducted on SPSS 24.0 software (SPSS Inc, Chicago, USA), and the figure construction was performed on GraphPad Prism 7.01 software (GraphPad Software Inc, San Diego, USA). Continuous data were described as mean and standard deviation (SD), or median and interquartile range (IQR); categorical data were displayed as number (percentage). Comparison of the sum of target tumor largest diameters and residual liver volume before and after down-staging treatment by DEB-TACE was determined by paired-sample t test; Comparison of the BCLC stage, the Child-Pugh stage before and after down-staging treatment by DEB-TACE was determined by McNemar's test; Comparison of tumor markers and liver indexes before and after down-staging treatment by DEB-TACE was determined by Wilcoxon signed-rank test. RFS and OS were illustrated using Kaplan-Meier curves. *P* value <0.05 was considered significant.

Results

Patients' characteristics

There were 15 unresectable liver cancer patients (including 12 (80.0%) males and 3 (20.0%) females) with the mean age of 48.9±14.2 years old (Table 1). For clinical features, the mean value of largest tumor diameter was 8.8±3.9 cm. The numbers of patients with ECOG score at 0, 1, and 2 were 2 (13.3%), 11 (73.4%) and 2 (13.3%) respectively. Based on BCLC stage, 8 (53.3%) patients were at A stage, 3 (20.0%) at B stage, and 4 (26.7) at C stage. According to Child-Pugh stage, 14 (93.3%) patients were at A stage, and 1 (6.7%) patient was at B stage. In addition, there were 10 (66.6%) patients received 1 cycle of DEB-TACE, 4

(26.7%) patients received 2 cycles of DEB-TACE, and 1 (6.7%) patients received 3 cycles of DEB-TACE. The detailed information about others clinical characteristics of patients were shown in Table 1.

Table 1
Clinical characteristics of patients

Items	Patients (N=15)
Age (years), mean±SD	48.9±14.2
Gender, No. (%)	
Male	12 (80.0)
Female	3 (20.0)
History of drink, No. (%)	5 (33.3)
History of HB, No. (%)	12 (80.0)
History of hepatic encephalopathy, No. (%)	2 (13.3)
History of hypertension, No. (%)	3 (20.0)
History of heart disease, No. (%)	1 (6.7)
Liver cirrhosis, No. (%)	9 (60.0)
Histological type, No. (%)	
HCC	13 (86.7)
Cholangiocarcinoma	2 (13.3)
Number of tumors, No. (%)	
1	12 (80.0)
2	3 (20.0)
Largest tumor diameter (cm), mean±SD	8.8±3.9
Portal vein invasion, No. (%)	1 (6.7)
Lymphadenectasis, No. (%)	5 (33.3)
Distant metastasis, No. (%)	2 (13.3)
Liver involvement, No. (%)	
≤50%	1 (6.7)
50-70%	10 (66.7)
≥70%	3 (20.0)
Unknown	1 (6.7)

SD, standard deviation; HB, hepatitis B; HCC, hepatocellular carcinoma; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona clinic liver cancer; DEB-TACE, drug-eluting bead transarterial chemoembolization.

Items	Patients (N=15)
ECOG score, No. (%)	
0	2 (13.3)
1	11 (73.4)
2	2 (13.3)
BCLC stage, No. (%)	
A	8 (53.3)
B	3 (20.0)
C	4 (26.7)
Child-Pugh stage, No. (%)	
A	14 (93.3)
B	1 (6.7)
Cycles of DEB-TACE, No. (%)	
1	10 (66.6)
2	4 (26.7)
3	1 (6.7)

SD, standard deviation; HB, hepatitis B; HCC, hepatocellular carcinoma; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona clinic liver cancer; DEB-TACE, drug-eluting bead transarterial chemoembolization.

Treatment Response After Deb-tace

After DEB-TACE treatment at one month, in total patients, 3 (20.0%) patients achieved CR, 7 (46.7%) patients achieved PR and 10 (66.7%) patients achieved ORR (Figure 1A). As for PR patients, 2 (28.6%) patients presented with necrosis rate <50%, 4 (57.1%) patients presented with necrosis rate of 50-80%, and 1 (14.3%) patient presented with necrosis rate > 80% (Figure 1B). In total tumors, 5 (27.8%) tumors achieved CR, 7 (38.9%) tumors achieved PR and 12 (66.7%) tumors achieved ORR (Figure 1C). As for PR tumors, 2 (28.6%) tumors presented with necrosis rate <50%, 4 (57.1%) tumors presented with necrosis rate of 50-80%, and 1 (14.3%) tumors presented with necrosis rate > 80% (Figure 1D).

Comparison of tumor diameters, BCLC stage and Child-Pugh stage before and after DEB-TACE

For tumor diameters, it was decreased after DEB-TACE compared to before DEB-TACE (9.4±3.3 *vs.* 5.4±3.5 cm) (P<0.01) (Figure 2A). However, there was no difference in BCLC stage (P=0.317) (Figure 2B) and Child-Pugh stage (Figure 2C).

Comparison of the residual liver volume before and after DEB-TACE

The mean value of residual liver volume before and after DEB-TACE was 1066.2 cm^3 and 1172.5 cm^3 respectively (Table 2). Compared to before DEB-TACE, residual liver volume was increased after DEB-TACE (mean value of increased rate was 11.4%) (P=0.007). The detailed information about the residual liver volume in each patient before and after DEB-TACE was shown in Table 2.

Table 2
The residual liver volume before and after DEB-TACE

No.	Residual liver volume (cm^3)				*P* value
	Before DEB-TACE	After DEB-TACE	Increase	Increase rate (%)	
1	1182.0	1064.0	-118.0	-10.0	0.007
2	1006.0	1083.0	77.0	7.7	
3	1266.0	1407.0	141.0	11.1	
4	1021.8	972.8	-49.0	-4.8	
5	705.0	832.0	127.0	18.0	
6	1514.0	1659.0	145.0	9.6	
7	796.8	706.0	-90.8	-11.4	
8	784.0	1169.0	385.0	49.1	
9	1547.0	1740.0	193.0	12.5	
10	1266.0	1358.0	92.0	7.3	
11	1371.0	1371.0	0.0	0.0	
12	1127.0	1347.0	220.0	19.5	
13	944.0	1066.0	122.0	12.9	
14	909.0	1100.0	191.0	21.0	
15	554.0	713.0	159.0	28.7	
Mean	1066.2	1172.5	106.3	11.4	

Comparison was determined by Paired-sample t test. DEB-TACE, drug-eluting bead transarterial chemoembolization.

Comparison Of Liver Function Indexes Before And After Deb-tace

No difference was found in liver function indexes, including ALB (*P*=0.334), TP (*P*=0.256), TBIL (*P*=0.733), TBA (*P*=0.513), ALT (*P*=0.609) and AST (*P*=0.593) and ALP (*P*=0.050) (Table 3). The detailed information was shown in Table 3.

Table 3
The level of liver function indexes before and after DEB-TACE

Liver function indexes	Before DEB-TACE	After DEB-TACE	*P* value
ALB (g/L)	42.4 (38.2-44.7)	39.8 (37.0-42.3)	0.334
TP (g/L)	70.5 (63.2-76.0)	72.0 (63.8-79.0)	0.256
TBIL (μmol/L)	8.7 (7.3-10.9)	10.2 (7.0-13.0)	0.733
TBA (μmol/L)	7.3 (2.9-15.9)	6.2 (3.4-13.9)	0.513
ALT (U/L)	50.0 (22.0-59.0)	30.0 (24.0-46.0)	0.609
AST (U/L)	33.0 (26.0-59.0)	30.0 (26.0-37.0)	0.593
ALP (U/L)	109.0 (91.0-130.0)	120.0 (94.0-158.0)	0.050

Data were displayed as median (interquartile range). Comparison was determined by Wilcoxon signed-rank test. DEB-TACE, drug-eluting bead transarterial chemoembolization; ALB, albumin; IQR, interquartile range; TP, total protein; TBIL, total bilirubin; TBA, total bile acid; ALT, alanine transaminase; AST, aspartate aminotransferase; ALP, alkaline phosphatase.

Comparison Of Tumor Markers Before And After Deb-tace

For tumor markers, no difference was discovered in AFP (*P*=0.300) (Figure 3A), CEA (*P*=0.505) (Figure 3B) and CA191 (*P*=0.091) (Figure 3C).

Operation Types

In total patients, there were 14 (93.3%) patients received with curative resection, and 1 (6.7%) patient received palliative resection (Figure 4).

Rfs And Os

The median value of RFS was 26.0 months, and the percentage of 5-year accumulating RFS was 20% (Figure 5A). As to OS, the median value of OS was 54.5 months, and the percentage of 5-year accumulating OS was 40% (Figure 5B).

Adverse Events

After DEB-TACE, there were 5 patients presented with pain (NRS score ranging from 5 to 9), 7 patients presented with fever and 1 patient presented with nausea and vomiting (Table 4). The detailed information was shown in Table 4.

Table 4
Adverse events after DEB-TACE

No.	Pain	NRS score	Treatment	Fever	Treatment	Nausea and vomiting	Treatment
1	No	N/A	N/A	39.0℃	Ibuprofen	No	N/A
2	No	N/A	N/A	39.4℃	Ibuprofen+indometacin	No	N/A
3	No	N/A	N/A	39.0℃	Ibuprofen+indometacin	No	N/A
4	Yes	7	Flurbiprofen	No	N/A	No	N/A
5	No	N/A	N/A	No	N/A	No	N/A
6	No	N/A	N/A	39.0℃	Ibuprofen	No	N/A
7	Yes	8	Pethidine	No	N/A	No	N/A
8	Yes	8	Pethidine	38.6℃	Ibuprofen+indometacin	No	N/A
9	Yes	5	Tramadol	38.0℃	Ibuprofen	No	N/A
10	No	N/A	N/A	No	N/A	No	N/A
11	No	N/A	N/A	No	N/A	No	N/A
12	Yes	6	Tramadol	No	N/A	No	N/A
13	No	N/A	N/A	No	N/A	No	N/A
14	No	N/A	N/A	No	N/A	Yes	Palonosetron
15	Yes	9	Pethidine	38.4℃	Ibuprofen	No	N/A

DEB-TACE, drug-eluting bead transarterial chemoembolization; NRS, numerical rating scale.

Typical Case Report

Mr. Huang, a 56-year-old man was first diagnosed as HCC. Before DEB-TACE treatment, abdominal computed tomography (CT) scan showed that tumor size was 80.49mm*110.82mm (Figure 6A). After identifying the tumor supply artery by hepatic arteriography, DEB-TACE treatment was performed (Figure 6B). After the operation, hepatic arteriography was carried out immediately, which disclosed that the tumor was reduced and the tumor blood supply arteries were almost stagnant (Figure 6C).

Before the surgery, abdominal CT scan showed that tumor size was 40.22mm*64.38mm, which diameter was reduced nearly 5cm (Figure 6D). After resection (Figure 6E, F), the pathological examination was performed (Figure 6G), which discovered drug-loaded microspheres (Figure 6H). This patient was pathologically confirmed HCC with a trend of differentiation of bile duct cell carcinoma (Figure 6I).

Discussion

DEB-TACE is a new type of embolization material involving the injection of a chemotherapeutic agent selectively into the feeding arteries of the tumor to not only potentially obtain higher intratumor drug concentrations and maintain lower plasma drug concentrations compared with cTACE, but also block the blood vessel effectively causing infarction and necrosis[8]. Accumulating evidence reveals that the 1-month CR rate ranges from 19.2–70.6% in tumors, and ORR ranges from 56.3–100% in tumors [11, 12]. In line with these previous data, we discovered that the 1-month CR rate and ORR in patients were 20.0% and 66.7%, respectively, while in tumors were 27.8% and 66.7%, respectively.

Based on the management guidelines published by the American Association for the Study of Liver Diseases, curative treatments have been only recommended to liver cancer patients who are with a single nodule <5 cm in diameter, three or fewer nodules <3 cm in diameter, or meet the Milan criteria [13, 14]. Although DEB-TACE is related to promising efficacy and low toxicity in unresectable liver cancer patients, which could effectively delay tumor progression or prevent recurrence during short-term (within 6 months), it is still less effective over longer periods, and could not achieve response rates and cure the tumor comparable to curative therapy [15]. There is therefore a requirement with additional and effective treatment strategies for unresectable liver cancer patients, including the optimization of DEB-TACE and its combination with other treatment modalities. TACE has been regarded as preoperative neoadjuvant chemotherapy to improve outcomes in patients with resectable hepatocellular carcinoma (HCC), which also is referred to as “bridging” therapy before liver transplantation for HCC[16, 17]. However, limited information about the down-staging effect of DEB-TACE in unresectable liver cancer patients. One previous study enrolling 30 unresectable liver cancer patients listed to liver transplantation discloses that after 30 times DEB-TACE successfully, 76.7% patients are down-staged to meet University of California, San Francisco (UCSF) criteria and 53.3% patients are down-staged to meet Milan criteria, meanwhile, there are 13 patients had been given liver transplantation successfully[18, 19] .

Considering the advantage of DEB-TACE, we hypothesized DEB-TACE might be used as a neo-adjuvant treatment for unresectable liver cancer patients, which might have down-staging effects for those patients, and made them receive curative treatment after DEB-TACE treatment. Whereas there was no evidence about whether DEB-TACE as down-staging therapy in unresectable liver cancer patients listed to receive surgery. Thus, we performed this study and discovered that DEB-TACE decreased tumor diameter in unresectable liver cancer patients, meanwhile, we found that DEB-TACE promoted the growth of residual liver volume in unresectable liver cancer patients. The possible explanations were that DEB-TACE is not only related to a high and sustained chemotherapy drug concentration, but also benefited for embolization of the small artery supplying tumor, which guaranteed the efficacy of DEB-TACE treatment on killing tumor cells and blocking tumor blood supply to promote tumor necrosis and inhibit tumor growth, thereby contributing to down-staging effect in unresectable liver cancer patients.

More importantly, we discovered that 15 (100%) patients could receive resection after DEB-TACE, suggesting that after DEB-TACE, the rate for unresectable patients received resection was 100%. The

probable causes were as follows: DEB-TACE presented with great efficiency in killing tumor cells and causing tumor avascular necrosis to devote into down-staging effect in unresectable liver cancer patients (above-mentioned), which made these patients have chance to receive resection again. In addition, we found the percentage of 1-year accumulating RFS was 64.6% as well as 2-year accumulating RFS was 55.4%. And the percentage of 1-year accumulating OS was 100.0% and 2-year accumulating OS was 77.8%. The median value of RFS was 26.0 months, and the percentage of 5-year accumulating RFS was 20%. As to OS, the median value of OS was 54.5 months, and the percentage of 5-year accumulating OS was 40%.These results were in line with a previous Chinese study disclosing the percentage of 1-year accumulating RFS of 92.3% and the percentage of 1-year accumulating OS of 100.0%[19] .

Like each invasive treatment, DEB-TACE undertakes the risk of AEs, including abdominal pain, fever, vomiting, and increased blood pressure[20]. In this study, we also discovered that 5 cases occurred pain, 7 cases occurred fever as well as nausea, and 1 case occurred vomiting, These results indicated that there were no serious complications occurring in these unresectable liver cancer patients after DEB-TACE, which showed the advantage of DEB-TACE with low systemic toxicity and good safety.

There were still several limitations in this study. The main limitation was a relatively small sample size of 15 unresectable liver cancer patients, which might lead to poor statistical power. Further validation is necessary in a larger sample size. In addition, the relatively short follow-up duration existed in this study, hence, long-term efficacy and safety were not able to be evaluated. Furthermore, all unresectable liver cancer patients were from one hospital, there might be selected bias. Further study with more patients from a multicenter is necessary.

In summary, DEB-TACE decreases tumor diameter and promotes the growth of residual liver volume in unresectable liver cancer patients. More importantly, after DEB-TACE treatment, 100% of patients could receive surgery. These data suggest that DEB-TACE might be effective and safety as a down-staging therapy in unresectable liver cancer patients.

Abbreviations

DEB-TACE
Drug-eluting beads transarterial chemoembolization
RFS
Relapse-free survival
OS
Overall survival
CR
Complete response
ORR
Objective response rate
HCC

Hepatocellular carcinoma
PR
Partial response
CT
Computed Tomography
AFP
alpha fetoprotein
CEA
Carcino-embryonic antigen
CA199
Carbohydrate antigen199
ALB
Albumin
TP
Total protein
TBIL
Total bilirubin
TBA
Total bile acid
ALT
Alanine aminotransferase
AST
Aspartate aminotransferase
ALP
Alkaline phosphatase
MRI
Magnetic resonance imaging.

Declarations

Authors' contributions

N.P. and K.X. conceived this study, S.H. directed the study. N.P. and K.X. performed most of the experiments. N.P. drafted the manuscript. N.P., L.M. and Y.T. analyzed the data and performed the statistical analyses. L.M., G.Y. and Y.T.participated in some experiments. S.H., N.P., K.X. and L.M. provided critical intellectual revision. S.H. provided financial support.

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Availability of data and materials

Datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of The First Affiliated Hospital of Guangxi Medical University.

Consent for publication

Not applicable

Conflict of interest

The authors declare no potential conflicts of interest.

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Figures

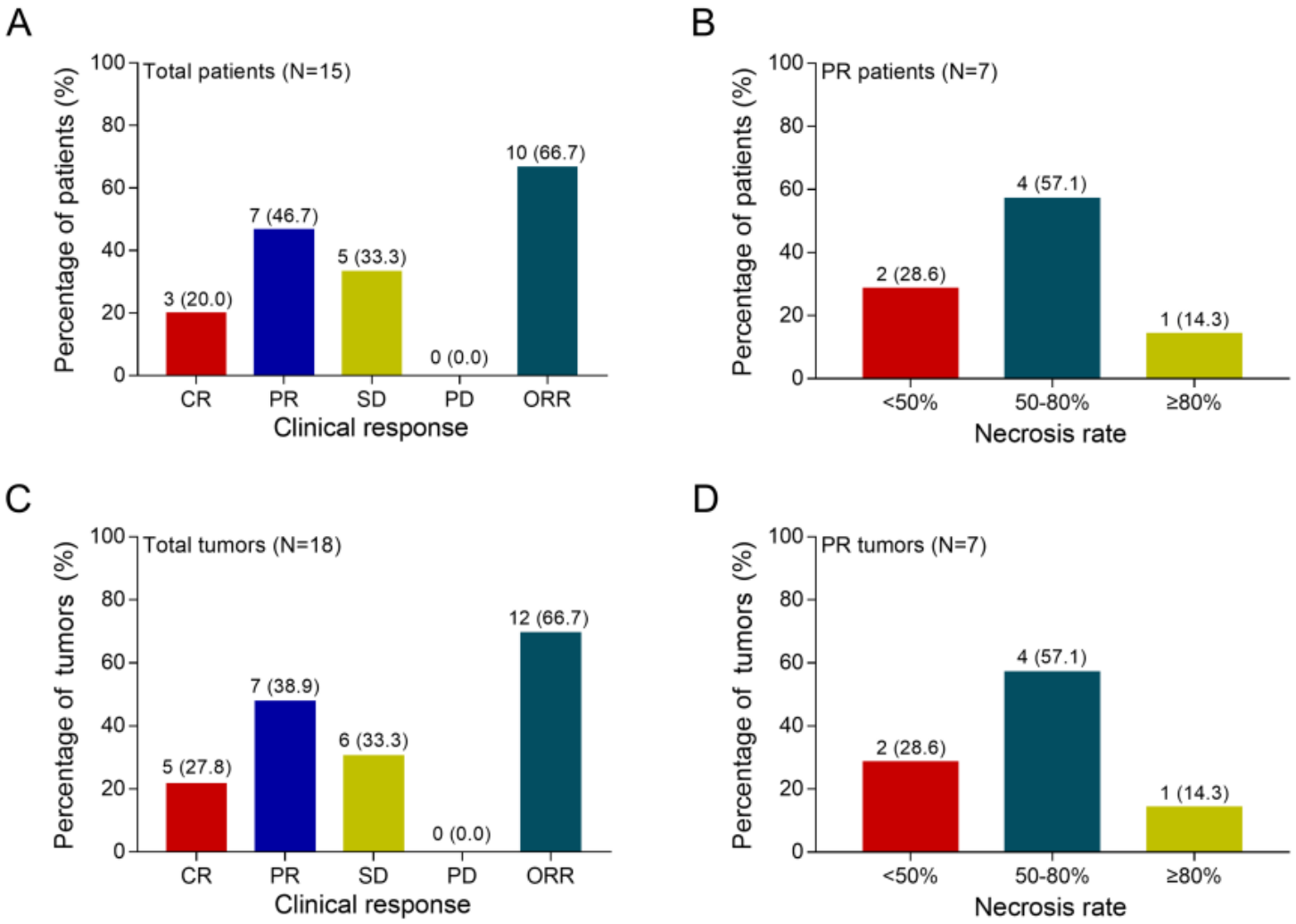

Figure 1

Treatment response after DEB-TACE treatment at one month A: The percentage of patients achieved clinical response in total patients; B: The percentage of patients achieved different necrosis rate in PR patients; C: The percentage of tumors achieved Clinical response in total tumors; D: The percentage of patients achieved different necrosis rate in PR tumors.

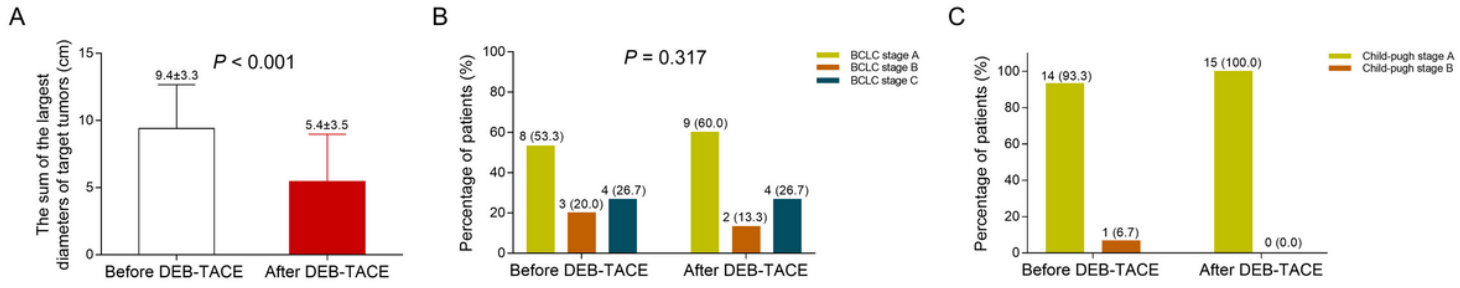

Figure 2

Tumor diameters, BCLC stage and Child-pugh stage before and after DEB-TACE A: Comparison of tumor diameters before and after DEB-TACE; B: Comparison of BCLC stage before and after DEB-TACE; C:

Comparison of Child-pugh stage before and after DEB-TACE.

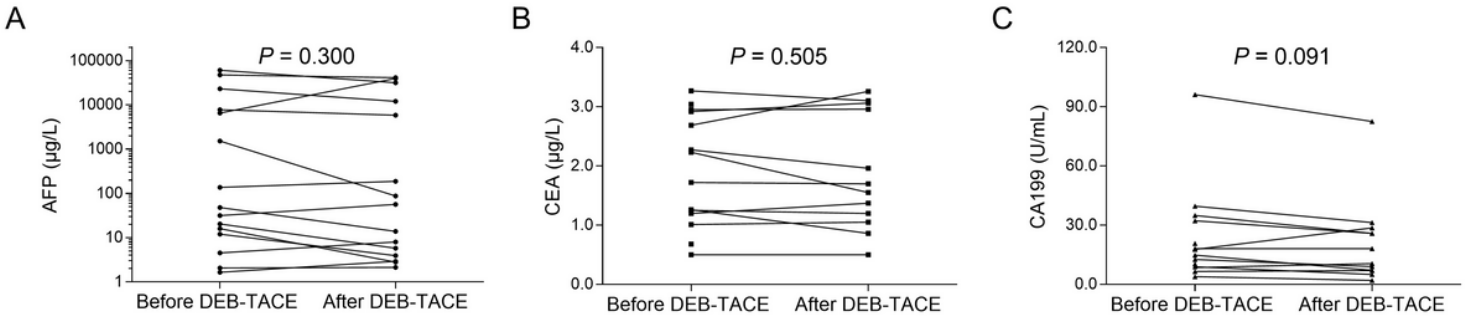

Figure 3

Tumor markers before and after DEB-TACE A: Comparison of serum AFP concentration before and after DEB-TACE; B: Comparison of serum CEA concentration before and after DEB-TACE; C: Comparison of serum CA191 concentration before and after DEB-TACE.

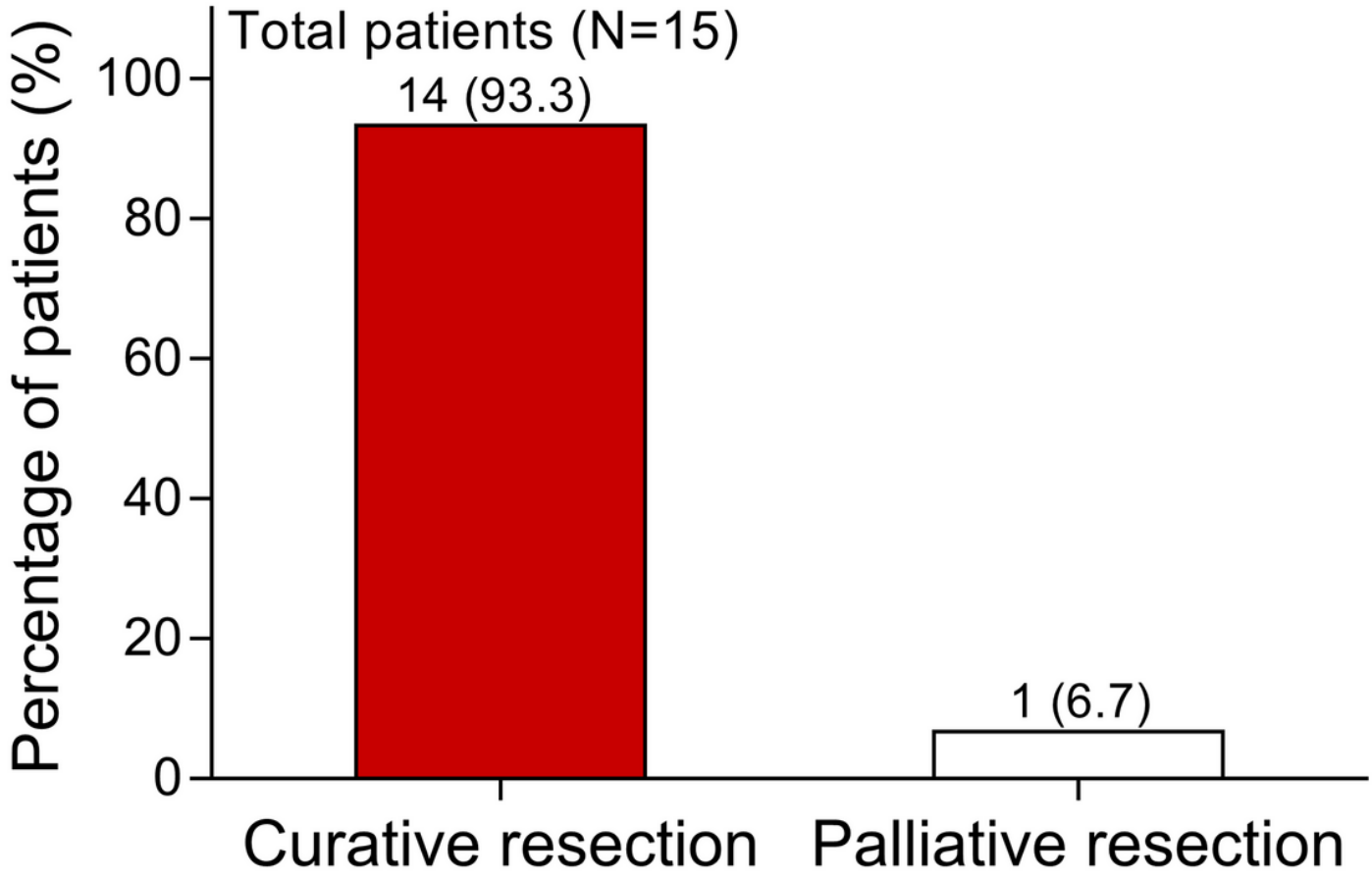

Figure 4

Operation types The percentage of patients achieved curative resection or palliative resection in total patients;

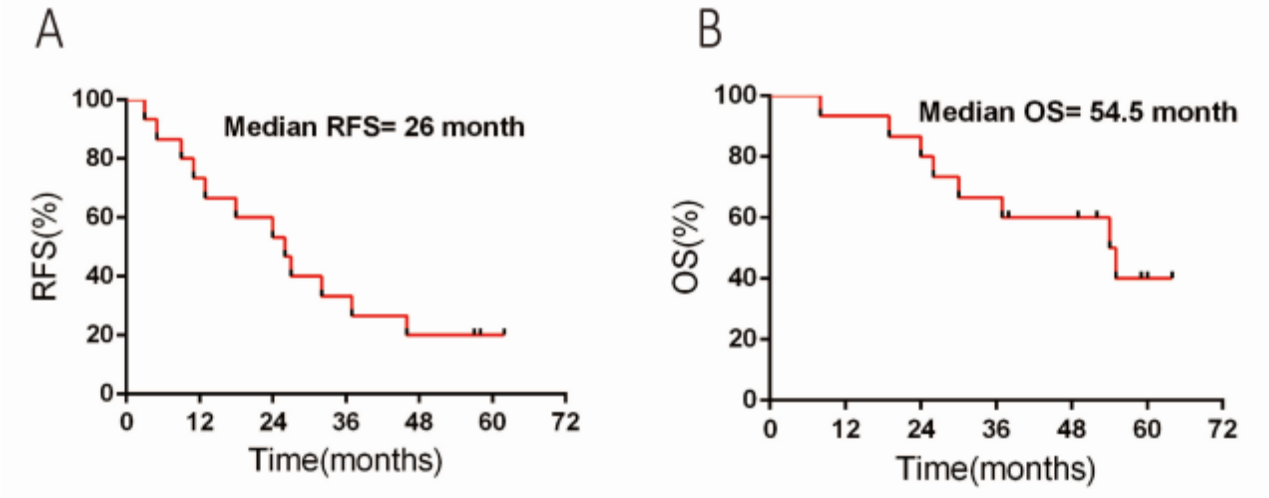

Figure 5

Survival A: The patients' RFS analyzed by Kaplan–Meier Survival curve; B: The patients' OS analyzed by Kaplan–Meier Survival curve.

Figure 6

Typical Case report A: Representative images of tumor by abdominal computed tomography scan before DEB-TACE treatment; B: Representative images of DEB-TACE treatment; C: Representative images of Hepatic arteriography during DEB-TACE; D: Representative images of tumor Abdominal computed tomography scan after DEB-TACE treatment; E-F: Representative images of tumor during resection; G: Representative images of resected tumor; H-I: Representative images of tumor pathological examination.