

# Efficacy and Safety of DEB-TACE for Patients With Hepatocellular Carcinoma With the Largest Tumor Diameter $\geq 7$ cm

Wei Chen (✉ [asdfg101a@126.com](mailto:asdfg101a@126.com))

Xingtai People's Hospital

Bei Lu

Xingtai People's Hospital

Mengzeng Zhang

Xingtai People's Hospital

Zhenguo Hou

Xingtai People's Hospital

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## Research Article

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# Abstract

**Objective:** To explore the effectiveness and safety of DEB-TACE in patients with primary huge hepatocellular carcinoma.

**Methods:** From January 2017 to January 2019, 87 patients with huge unresectable HCC were retrospectively analyzed. 48 cases received drug-eluted beads for transarterial chemoembolization (DEB-TACE group), and 39 cases received conventional transarterial chemoembolization (c-TACE group). The tumor treatment response, overall survival (OS), progression-free survival (PFS), the incidence of adverse events (AEs) were compared between the two groups and the factors influencing OS were analyzed.

**Results:** The median follow-up was 295 days (ranges 78 to 603 days). There was no statistical difference in baseline characteristics and follow-up treatment between the two groups. The objective response rate (ORR) of DEB-TACE group was higher than that of c-TACE group within 3 months after treatment. The change was similar in the incidence of AEs between the two groups; DEB-TACE group showed longer PFS and OS than c-TACE group. Cox-regression multivariate analysis showed that DEB-TACE was an important factor affecting the overall survival.

**Conclusion:** DEB-TACE prolonged the survival time of patients with huge unresectable HCC and could be a better choice than c-TACE without increasing the incidence of AEs.

## Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths in China [1]. Although high-risk patients are routinely screened, huge tumor with size of more than 7 cm are occasionally seen. Huge HCC has some special characteristics, which need to be considered in order to be successfully managed. First, HBV-related cirrhosis is the main potential cause of liver cancer in China [2]. Secondly, huge HCC always shows an incomplete capsule, easily to invade the local vascular system, increase the risk of tumor thrombosis and metastasis [3]. Third, the risk of huge HCC rupture increases, which may accelerate its local spread and deterioration of liver function [4]. Therefore, proper management of huge HCC is a challenge.

Transarterial chemoembolization (TACE) is considered to be the main treatment modality for the palliative treatment of huge unresectable liver cancer [1]. However, the efficacy of traditional TACE (cTACE) with lipiodol as an embolic agent is not ideal. Drug-eluted beads have been used in TACE treatment to further improve the clinical efficacy [4], and it has been clinically promoted in China. This study aims to investigate the effectiveness and safety of DEB-TACE in patients with primary huge hepatocellular carcinoma.

## Results

### Baseline data

The characteristics of patients are shown in Table 1. This study included 87 patients, including 48 patients receiving DEB-TACE (DEB-TACE group; 36 males and 12 females) and 39 patients receiving cTACE (cTACE group; 28 males and 11 females). There were no statistical differences in baseline characteristics between the two groups.

### **Follow-up treatment**

Patients underwent multiple cycles of TACE, ablation, hepatectomy, and targeted and immunotherapy. The average of TACE cycles received by patients in the DEB-TACE group decreased significantly compared with c-TACE group ( $3.35 \pm 1.082$  vs  $2.64 \pm 1.013$ ,  $P=0.002$ ). The change was similar between the two groups of other treatment (Table 2).

### **Outcome measures**

Compared with the c-TACE group, the percentage of patients who achieved ORR in the D-TACE group increased significantly one month after treatment. (39.6% vs 61.5%,  $P=0.046$ ) (Figure 1)

### **Adverse events**

All patients were monitored for adverse events 3 months after surgery. No deaths related to the TACE occurred. No serious AEs beyond CTCAE grade 3 were found. Most AEs were grade 1 or 2. There were 5 cases of liver abscess in DEB-TACE group and c-TACE group, respectively. The difference in the incidence of AEs between the two groups was not statistically significant. And the liver abscess was cured after ultrasound-guided puncture and drainage (Table 3).

### **PFS and OS**

The PFS and OS of DEB-TACE were remarkably higher than c-TACE group. The details were shown in Figure 2 and Figure 3

### **Analysis of Cox factors affecting overall survival**

There was no multivariate analysis, because in univariate analysis, only the P value of treatment selection is less than 0.05. The follow-up treatment cannot be analyzed because the number of patients is too small. DEB-TACE ( $HR=0.250$  ( $0.091-0.633$ ,  $P=0.004$ ) is a predictor of OS (Table 4).

## **Discussion**

For patients with huge HCC, hepatectomy is the preferred treatment when their liver function is well-preserved. Only a small number of patients with huge HCC have the chance of hepatectomy. A large number of patients presented with invading the liver parenchyma in patients with huge HCC. Compared with patients with small tumors, intrahepatic metastasis is more frequent and the survival is worse in patients with huge tumors [6]. TACE is one of the important methods for the treatment of huge HCC. It can block the tumor blood supply and increase the drug concentration in the target vessel [7]. However,

the traditional TACE with lipiodol as the embolization agent don't achieve the ideal curative efficacy. It often requires repeated embolization to achieve a better treatment response, and multiple cycles of TACE will cause hepatic blood vessel and liver dysfunction, which has a bad effect on the next embolization treatment [8]. The CalliSpheres drug-eluted beads can not only load and release chemotherapeutics slowly in local area but can also embolize the tumor feeding vessels permanently [9]. Multiple clinical trials have shown that DOX loaded DEB-TACE can increase the intra-tumoral drug concentrations and reduce systemic toxicity [10-11]. Many studies showed that while TACE treatment causes hypoxia in tumor cells and surrounding liver tissues, it also up-regulates vascular endothelial growth factor and promotes the proliferation and metastasis of remaining tumor cells [12]. Obviously, the restoration of the blood supply of tumor tissue is an important cause of tumor cell survival [13]. Tsai et al. [14] have compared the short-term effect of HAIC and TACE in the treatment of large liver cancer, and the result showed that HAIC provide better survival compared with c-TACE. However, the effect of survival in between c-TACE and DEB-TACE doesn't be compared. Therefore, we conducted this study to further explore its potential in HCC patients with the largest tumor size greater than 7cm.

In our study, patients in DEB-TACE group achieved higher ORR, PFS and OS compared with c-TACE group, and the difference was significant. The possible reasons are as follows: (1) DEB-TACE reduced tumor size by increasing local drug concentration and drug retention time in HCC tumors. According to previous studies, DEB-TACE shrunk tumor size resulted from increasing the localized drug concentration and drug retention time inside the tumors [15,16]. (2) Moreover, apart from the tumor-selective drug delivery, DEB-TACE has extra embolization effect, which result in the synergies of local cytotoxic activity and ischemia in the all feeding arteries of the tumor, so as to make the treatment more effective in unresectable huge HCC patients.(3) At the same time, compared with the lipiodol used in c-TACE, the dose of chemotherapeutic drugs adsorbed by CalliSpheres drug-loaded microspheres is significantly increased, and the adsorbed chemotherapeutic drugs can be released under control. And the DEB-TACE group underwent less cycles of TACE compared with DBE-TACE. This may be due to the fact that patients in the DEB-TACE group had longer PFS, which would reduce the cycles of TACE during the whole follow-up period.

In this study, the two groups had more adverse reactions due to the larger target lesions. These adverse reactions are mainly manifested as pain, nausea, vomiting and fever, which considered as post-embolization syndrome [17]. The results showed that incidence of AEs does not have the remarkable difference between the two groups, and these adverse reactions can be improved after symptomatic treatment. There were no serious complications such as liver failure, gastrointestinal hemorrhage or ectopic embolism in the two groups. However, there were 5 cases of liver abscesses in the study group and the control group, respectively. Liver abscess is considered to be caused by excessive DEBs embolization or tumor vascular reflux. The abscess was punctured and drained under ultrasound guidance. In order to prevent this complication, surgeons must strictly abide by aseptic operation in TACE treatment, and the embolization can be enforced in different times. Postoperative anti infection treatment is feasible after surgery.

There are some limitations in this study, it is a retrospective study and there may be bias in case selection; most of the cases received multiple TACE or systemic treatments after the first TACE treatment. As the limited of less cases number, subgroup analysis was not carried out about the follow up therapy, which is also key directions for our future research.

In general, DEB-TACE is a clinically effective and safe treatment choice for patients with huge HCC either alone or combined with other systemic therapies. Our findings provide the theoretical basis for further studies of TACE treatment strategy for huge HCC. The therapeutic effect of DEB-TACE combined with other therapies should be further explored and compared for patients with huge HCC in future studies.

## Materials And Methods

### General information

This is a single-center study, which analyzed the medical records of patients with huge unresectable HCC treated from January 2017 to January 2019 at Xingtai People's Hospital retrospectively. This study was approved by the Ethics Committee of Xingtai People's Hospital and carried out according to the Declaration of Helsinki. Written informed consent was obtained from all patients.

All patients met the following criteria:(1) HCC was diagnosed by imaging, serological, and pathological examinations; (2) Patient with the tumor diameter  $\geq 7$  cm (3) Patients with tumors less than 3; (4) Patients with no extrahepatic metastasis.

Exclusion criteria: (1) Patients with extrahepatic liver cancer metastasis; (2) Patients with severe organic dysfunction of other important organs; (3) Patients with previous treatment for HCC; (4) Patients with the expected survival time less than 3 months.

### TACE procedure

1) c-TACE group: A solution of pirarubicin (10-40 mg, Meile, China), lobaplatin (50 mg / m<sup>2</sup>, Changan, China), 10 mg mitomycin C (Haishun,China) and iodized oil (Hengrui, China) were mixed. According to the number and size of the lesions, the mixture were injected into the tumor-feeding vessels as described in previous studies [9].

2) DEB-TACE group:100-300  $\mu$ m or 300-500 $\mu$ m CalliSpheres® beads (Jiangsu Hengrui Pharmaceutical Co., Ltd., China) were loaded with pirarubicin (60 mg). Dissolve Pirubicin to a concentration of in the 20mg/ml solution, the microspheres and the pirarubicin solution were mixed with a three-way tube, and then the non-ionic contrast agent was added to the mixed solution. The tumor supply vessels were detected by digital subtraction angiography (DSA). And the microcatheter and microwire were superselectively guided into the tumor-feeding vessels for the embolization. The indication of the end of the injection is a stagnant flow of contrast media, and angiography is performed again after 5 minutes to detect the blushed/ tinted tumor. Stop embolization if there was no more blushed tumor. Besides, if a

bottle of CalliSpheres® beads are not sufficient for embolization, add 8Spheres (Jiangsu, China) with sizes of 100-300 µm or 300-500 µm as appropriate.

### **Treatment response and safety evaluation**

Tumor response was evaluated by dynamic CT or MRI performed 1-3 months after TACE treatment based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST) evaluation[5]:(1) complete response (CR): the disappearance of any intratumoral arterial enhancement in all target nodules; (2) partial response (PR): reduction of the total diameters of viable (enhancement in the arterial phase) target nodules by at least 30% based on the baseline sum of target nodule diameters; (3) stable disease (SD): any patient that do not achieve either PR or progressive disease (PD); (4) PD: an increase of at least 20% in the sum of the diameters of viable (enhancing) target nodules, taking the smallest sum of the diameters of viable (enhancing) target nodules recorded since treatment started as reference. Objective response rate (ORR) was defined as the percentage of patients achieving CR or PR.

### **Statistical analysis**

SPSS software 22.0 (IBM, USA) and Office 2016 software (Microsoft, USA) were used for the statistical analysis. Data were expressed as count (%), mean±standard deviation. Chi-square test was performed to compare the categorical data. An independent-sample t-test was applied to compare the average between the two groups. Kaplan–Meier method was used to analyze progression-free survival (PFS) and overall survival (OS) after the first DEB-TACE procedure, and log-rank test was applied for comparison. Cox proportional hazards model was used for univariate analyse.  $P < 0.05$  was considered statistically significant.

## **Declarations**

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None.

### **Competing interests**

The author(s) declare no competing interests.

### **Author contributions**

Wei Chen and Bei Lu designed the study and wrote the manuscript; Mengzeng Zhang collected and analyzed the data; Zhenguo Hou revised the manuscript.

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Tables

Due to technical limitations, table 1,2,3,4 is only available as a download in the Supplemental Files section.

Figures

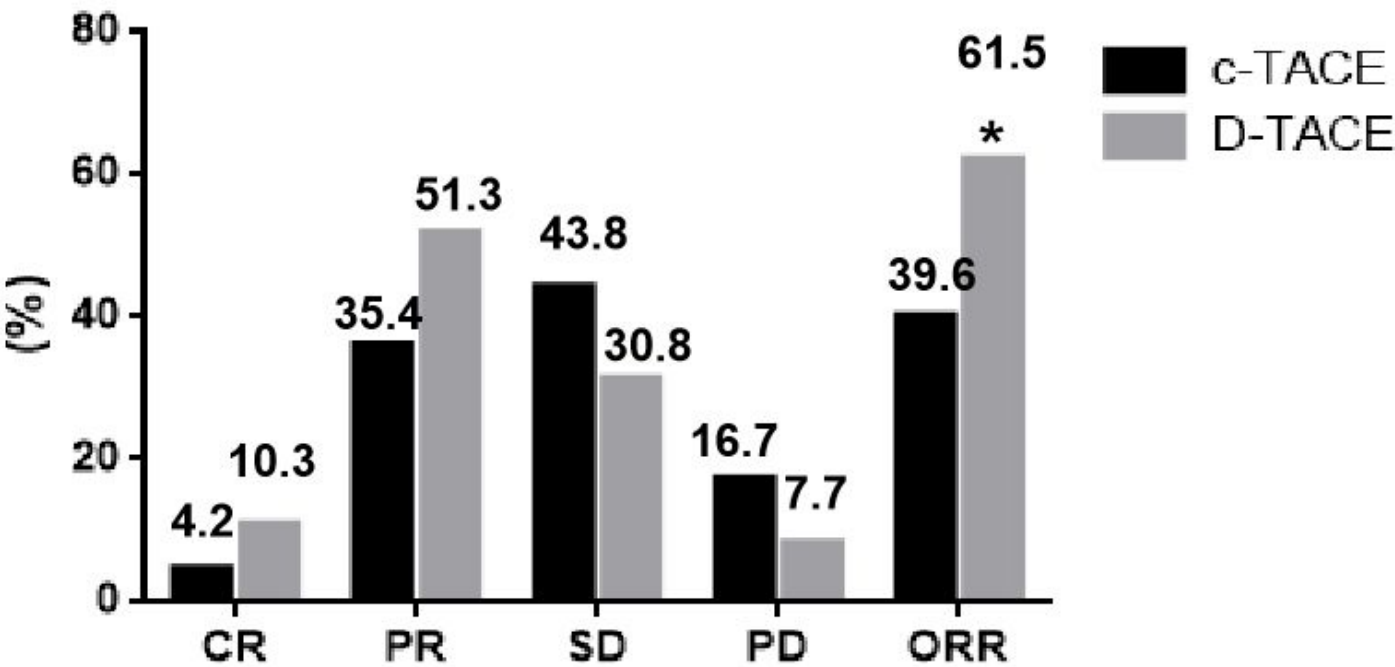
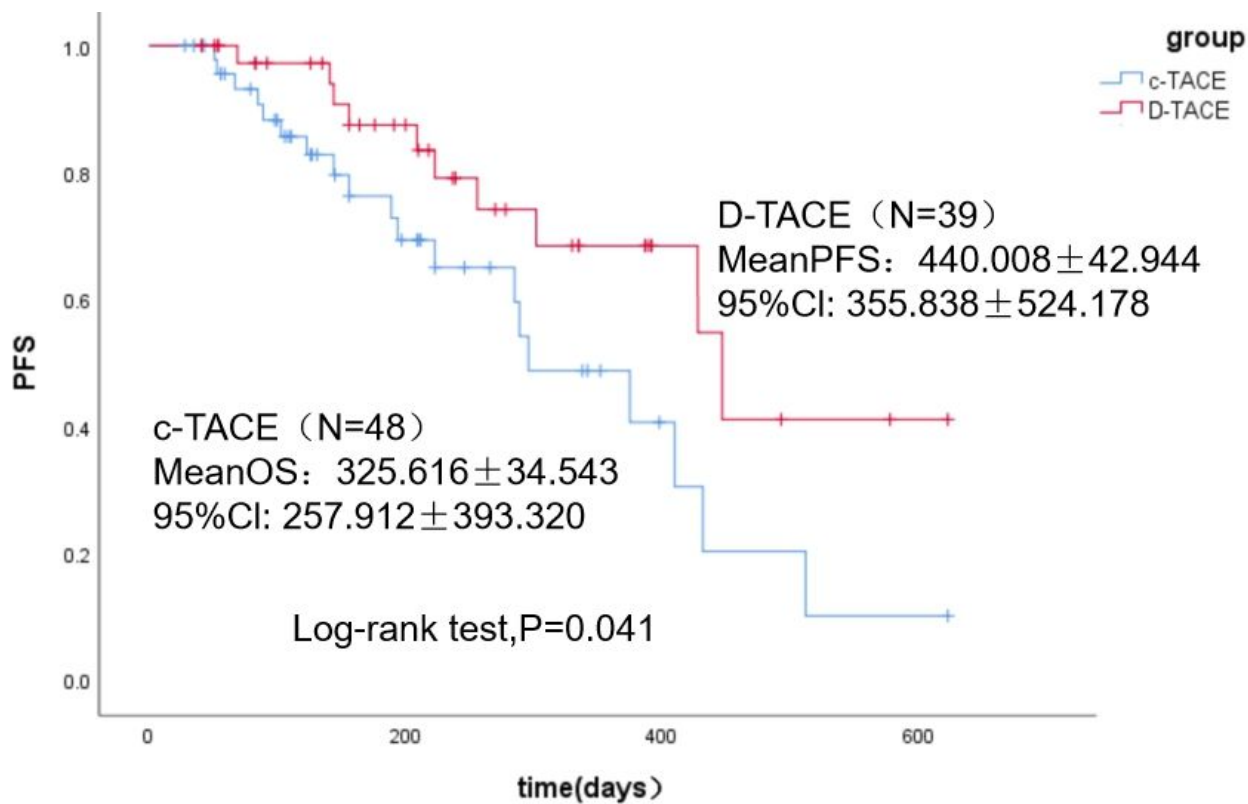


Figure 1

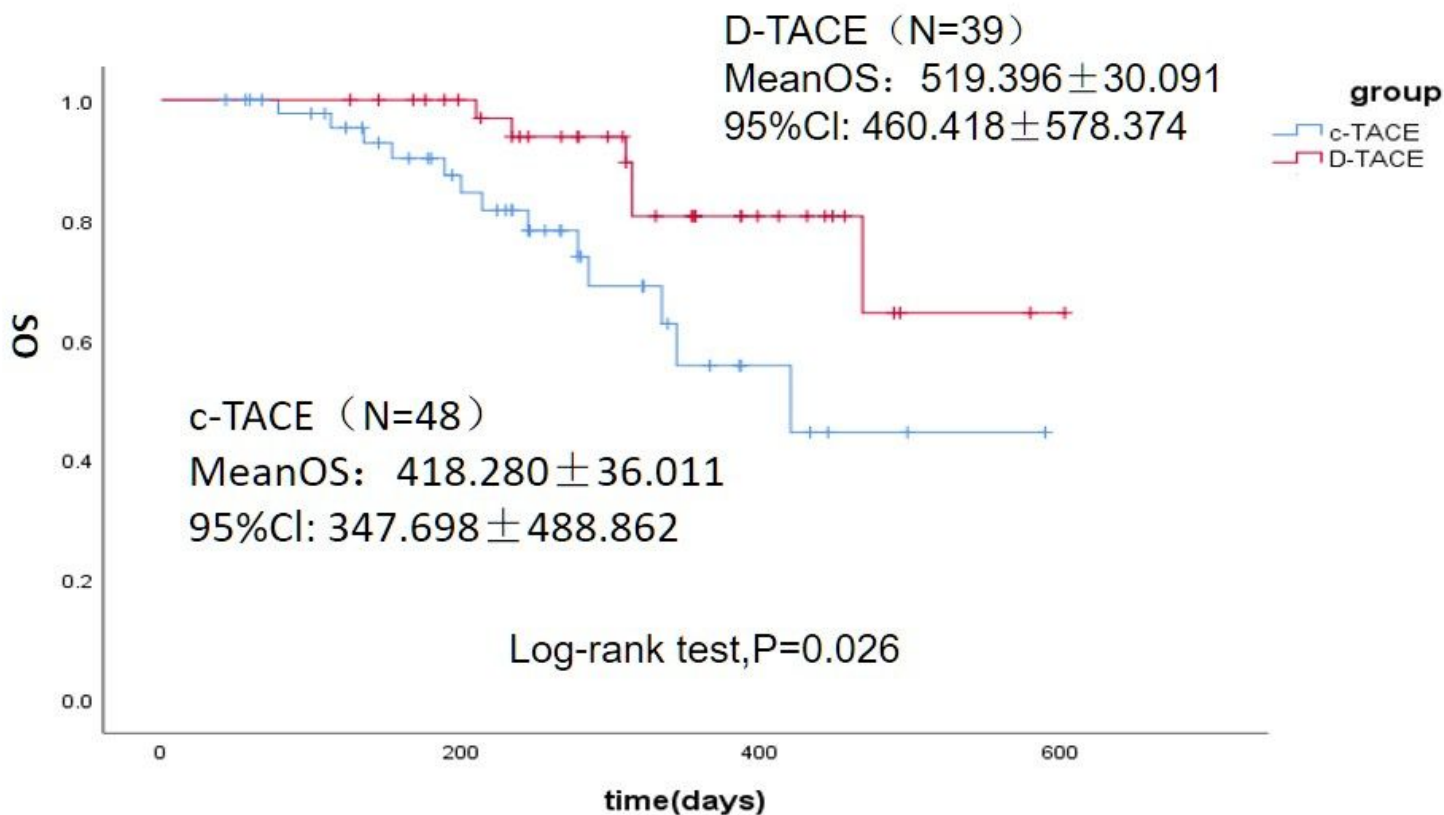
Comparison of Treatment Response of two groups.





**Figure 2**

Progression-free survival (PFS) in two groups.



**Figure 3**

Overall survival (OS) in two groups.

## Supplementary Files

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