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Drug-eluting bead transarterial chemoembolization with medium-sized versus small-sized CalliSpheres microspheres in unresectable primary liver cancer

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Abstract

Purpose: The optimal microparticle size for drug-eluting beads transarterial chemoembolization (DEB-TACE) remains unknown. This retrospective cohort study analyzed the efficacy and safety of CalliSpheres microsphere embolization in the treatment of unresectable hepatocellular carcinoma (HCC) to determine the influence of particle size on the results.

Patients and methods: Forty-two patients with unresectable HCC were enrolled in this retrospective study from January 2018 to January 2020. Patients received DEB-TACE with CalliSpheres of 100–300 μm (small-size, $n = 15$) or 300–500 μm (medium-size, $n = 27$). The tumor response was evaluated via enhanced CT or MRI at 1 month, 3 months, and 6 months after treatment, based on the Modified Response Evaluation Criteria in Solid Tumors. Adverse events after DEB-TACE were recorded.

Results: Complete response, partial response, stable disease, and progressive disease were recorded in 20%, 20%, 33.3%, 26.7%, respectively, of patients in the small-size group and 3.7%, 25.9%, 44.4%, 25.9% of patients in the medium-size group, respectively. No significant difference was found between the two groups ($p = 0.516$). Major adverse events, including grade three liver toxicity ($n = 4$) and liver abscess ($n = 3$), occurred significantly more in the small-size group, while none were reported in the medium size group ($p < 0.05$).

Conclusion: DEB-TACE with medium-size (300–500 μm) CalliSpheres microspheres had similar efficacy and a better safety profile than DEB-TACE with small-size (100–300 μm) CalliSpheres, indicating that medium-size microspheres may be a better choice for unresectable primary liver cancer.

KEYWORDS
chemoembolization, liver cancer, microspheres, size, unresectable

1 | INTRODUCTION

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths worldwide, with a 5-year survival rate of only 17.7%.[1] Primary liver cancer is characterized by rapid progression, low resection rate, high postoperative recurrence rate, and poor efficacy of conservative treatment.[2] Although the improvement of surgical techniques has increased the resection rate of liver cancer, it is still as low as 25%–40%.[3] As most patients with liver cancer are in BCLC stage B or C at the time of initial diagnosis, surgical resection, liver transplantation, or percutaneous ablation is not viable treatment option.[4] Transarterial chemoembolization (TACE) is the first-line treatment for unresectable liver cancer recommended by many norms and guidelines.[5] Compared with systematic conservative treatment, TACE can prolong the survival time of patients with advanced liver cancer and cirrhosis.[6]

Drug-eluting beads transarterial chemoembolization (DEB-TACE) is a form of therapy for HCC that has emerged in recent years. Theoretically, DEB-TACE not only embolizes the artery supplying blood to the tumor but also releases chemotherapeutic drugs loaded in microspheres continuously and gradually, thus maintaining the concentration of local chemotherapeutic drugs in tumors at a higher level. Results indicate that, because of these features, DEB-TACE achieves a better effect than conventional TACE (c-TACE).[7]

The optimal size of microsphere to use for DEB-TACE is still debated.[8,9] The normal diameter of hepatic capillaries is 5–8 μm[10]; thus, in theory, microspheres with diameters greater than 8 μm can be used for hepatic artery embolization. However, microspheres less than 40 μm in size were reported to be easily distributed to the spleen, lungs, and other organs when infused into the hepatic artery in rat liver cancer models.[11] The commonly used sizes of the DEB include 100–300 μm and 300–500 μm in current clinical practice. It is considered more dangerous to embolize with DEBs smaller than 100 μm.[12]

Theoretically, a smaller microsphere would more easily embolize the tumor precisely and achieve a better effect, but a higher incidence of complications, such as bile duct injury, can occur.[13] One study reported that more intense biliary toxicity was caused by the use of smaller microparticles.[14] For this reason, the most suitable microparticle size for DEB-TACE requires further investigation. This prospective cohort study aimed to analyze the efficacy and safety of CalliSpheres microsphere embolization using two different particle sizes for the treatment of advanced liver cancer.

2 | MATERIALS AND METHODS

2.1 | Patient population

This study was conducted according to the Declaration of Helsinki and approved by the Institutional Ethics Committee of our hospital. Patient database was retrospectively analyzed.

Written informed consent forms were signed by the patients or their authorized trustee.

Inclusion criteria for TACE were as follows: 1. primary liver cancer diagnosed according to the American Association for the Study of the Liver Diseases guidelines; 2. age 18–80 years, physical condition score ECOG $\leq$ 2, and liver function classified as grade Child–Pugh A or B; 3. expected survival time $\geq$ 3 months; 4. signed informed consent and accepted the embolization treatment with CalliSpheres microspheres; and 5. liver cancer unresectable after a multidisciplinary comprehensive evaluation.

The exclusion criteria for TACE were as follows: 1. a history of hepatic encephalopathy; 2. refractory pleural effusion, abdominal effusion, or pericardial effusion; 3. cancer thrombi of the main portal vein involving bilateral portal vein branches at the same time; 4. liver and/or kidney failure; 5. complications associated with severe cardiovascular and cerebrovascular diseases and coagulation dysfunction; 6. Malignant tumors with other systems; and 7. patients who have a history of psychotropic drug abuse or have mental disorders.

A total of 170 patients with unresectable HCC were treated with TACE from January 2018 to January 2020. A total of 112 patients opted to undergo c-TACE. The remaining 58 patients who received DEB-TACE were screened. Eight patients refused to sign the informed consent. Ultimately, 50 patients were enrolled in the study. Six patients were lost to follow-up, and two patients withdrew from the study. The final data analysis included 42 patients.

2.2 | DEB-TACE

All DEB-TACE was performed using a super-selective embolization technique by two interventional radiologists with more than 10 years of experience. The diameter of the embolic microspheres (Hengrui Pharmaceutical Co., Ltd. Jiangsu, China) used was 100–300 μm or 300–500 μm. Epirubicin hydrochloride (Pfizer Pharmaceuticals Ltd) was selected as the chemotherapy drug.

The following drug loading method was employed. The microspheres were drawn into a 20 ml syringe and left to sit at room temperature for 5 min. After the blue microspheres were separated from the solution, the syringe was loaded with a filter needle, and the supernatant was pushed out through the filter needle. Then, 60 mg of epirubicin hydrochloride was dissolved in 5 ml of sterilized water and injected into the syringe containing the drug-loaded microspheres through the tee joint. The drug and the microsphere were mixed thoroughly by gently shaking the mixture every 5 min. The absorption time for microspheres with the particle size of 100–300 μm and 300–500 μm was 15 min and 30 min, respectively. Completion of drug absorption was indicated when the microspheres changed color from blue to red. The same amount of iodixanol was then added to form a suspension including the drug-loaded microspheres.

The procedures for the DEB-TACE were as follows. The patient was placed in the supine position, and the right femoral artery was punctured using the Seldinger technique. A 5F vascular sheath was inserted into the femoral artery. An RH catheter was selectively inserted into the hepatic artery. Arteries supplying the tumor were identified by angiography. A 2.7F microcatheter (Terumo Cooperation, Tokyo,

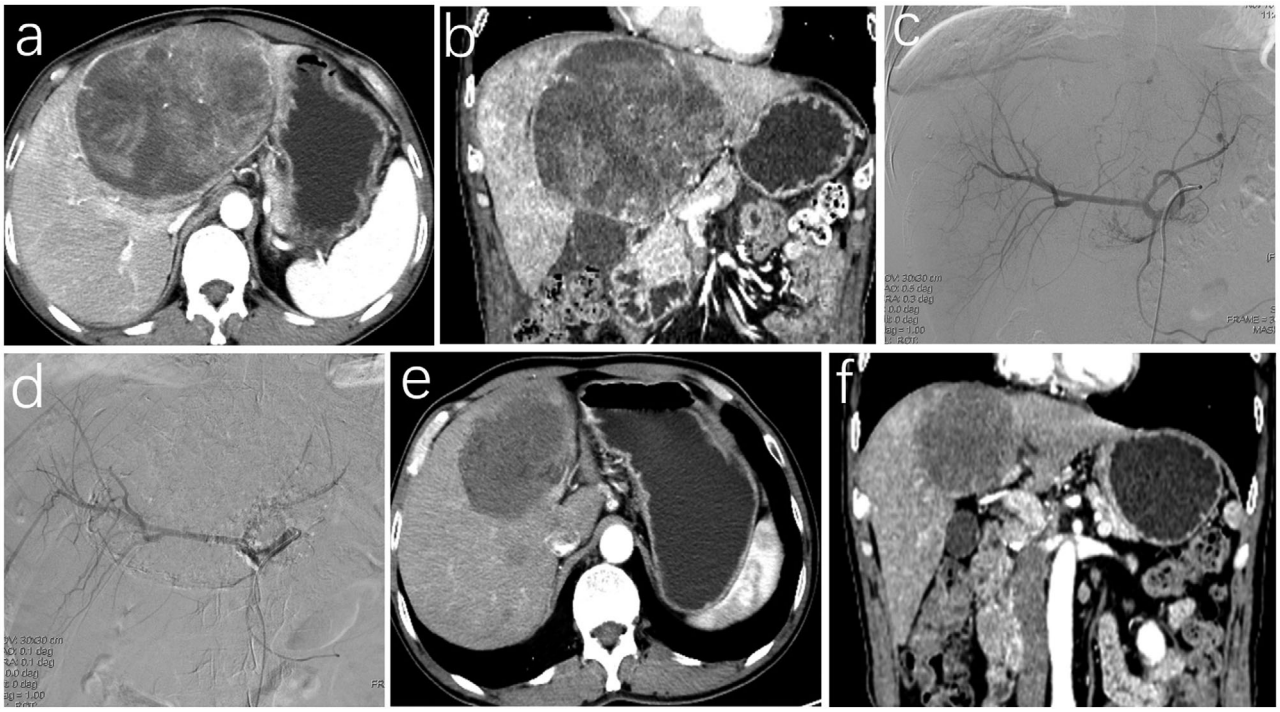

FIGURE 1 Images of a male patient diagnosed with HCC. (A) Transverse section CT image showed a large tumor in the left liver lobe. (B) Coronal section CT image. (C) Arteries supplying the tumor were identified by angiography. (D) Repeat angiography showed the blood supply of the tumor disappeared after DEB-TACE with CalliSpheres of 300–500 μm. (E) Transverse section CT image showed CR was achieved 3 months later. (F) Coronal section CT image

Japan) was coaxially inserted to specifically select the target vessels. The drug-loaded microspheres were slowly injected using a 1 ml syringe at a speed of 1 ml/min until the blood flow stagnated. Repeat angiography was performed 5 min later. Embolization was resumed if the tumor was still stained. Because there may be multiple blood supply for liver tumors, the aim is to embolize all arteries supplying blood to the tumor as completely as possible during the operation. According to the tumor location, angiography of the left gastric artery, internal thoracic artery, right renal artery, and inferior phrenic artery should be selectively imaged to avoid missing any feeding vessels.

2.3 | Endpoint definition

The Modified Response Evaluation in Solid Tumors (mRECIST) was used to evaluate the curative effect. Complete response (CR) is defined as the enhancement and disappearance of the tumor. Partial response (PR) is defined as a reduction of at least 30% of the diameter of the enhanced part of the tumor compared to baseline. Progressive disease (PD) is defined as an increase of at least 20% in the diameter of the enhanced part of the tumor compared to baseline. Stable disease (SD) is defined as the condition where PR or PD is not satisfied. Objective response rate (ORR) is defined as the proportion of the sum of CR and PR patients. Disease control rate (DCR) is defined as the total proportion of CR, PR, and SD patients. Safety evaluation is based on Common Terminology Criteria for Adverse Events (CTCAE) 4.0 standard.

2.4 | Follow-up

The patients were examined with enhanced CT or MRI at 1 month, 3 months, and 6 months after DEB-TACE (Figure 1). The diameter of the largest intrahepatic tumor was measured and used as a benchmark to evaluate the curative effect on postoperative follow-up. The preoperative and postoperative imaging data were evaluated independently by two experienced imaging experts who had no prior knowledge of the location of the intrahepatic tumors.

2.5 | Statistical methods

SPSS 24.0 software was used for statistical analysis. The measurement data are expressed as the mean +/− standard deviation. Fisher's exact test was used to compare the classified variables. The Mann–Whitney *U* test or *t*-test were used to compare continuous variables, and $p < 0.05$ was statistically significant.

3 | RESULTS

3.1 | Patients and treatment

Among the 42 patients (mean age, 61.43 ± 11.5 years old; range, 42–77 years), 34 (81%) were male, and eight (19%) were female. More than half of the patients had a history of hepatitis B infection (54.8%) or

TABLE 1 Patient characteristics of the two groups

Parameters	Small size group ($n = 15$)	Medium size group ($n = 27$)	p value
Age	59.2 ± 9.8	62.7 ± 12.3	0.136[&]
Sex			0.605[#]
Male	12 (80%)	22 (81.5%)	
Female	3 (20%)	5 (18.5%)	
Number of nodules			0.258[Θ]
≤3	3 (20%)	10 (37%)	
>3	12 (80%)	17 (63%)	
Size of target tumor (cm) (range)	5.7 ± 2.9 (1.8–12.4)	6.9 ± 2.6 (2–14.7)	0.165[&]
ECOG performance status			0.737[Θ]
0	4 (26.7%)	7 (25.9%)	
1	5 (33.3%)	11 (40.7%)	
2	6 (40%)	9 (33.3%)	
Child-Pugh stage			0.927[Θ]
A	8 (53.3%)	14 (51.9%)	
B	7 (46.7%)	13 (48.1%)	
BCLC stage			0.122[Θ]
A	4 (26.7%)	4 (14.8%)	
B	10 (66.7%)	16 (59.3%)	
C	1 (6.6%)	7 (25.9%)	

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
[#]Fisher's exact test, [&] Independent-samples t-test.
[Θ]Independent sample Mann–Whitney U test.

TABLE 2 Tumor response for whole group

Parameters	1 month	3 months	6 months
CR	9 (21.4%)	7 (16.7%)	4 (9.5%)
PR	20 (47.6%)	18 (42.9%)	10 (23.8%)
SD	9 (21.4%)	13 (31%)	17 (40.5%)
PD	4 (9.5%)	4 (9.5%)	11 (26.2%)
ORR	29 (69%)	25 (59.6%)	14 (33.3%)
DCR	38 (91.5%)	38 (91.5%)	31 (73.8%)

Abbreviations: CR, complete response; DCR, disease control rate; ORR, objective response rate, PD, progressive disease; PR, partial response; SD, stable disease.

TABLE 3 Tumor response at 6 months

Parameters	Small size group ($n = 15$)	Medium size group ($n = 27$)	p value
Tumor response (mRECIST)			0.516
CR	3 (20%)	1 (3.7%)	
PR	3 (20%)	7 (25.9%)	
SD	5 (33.3%)	12 (44.4%)	
PD	4 (26.7%)	7 (25.9%)	
ORR	6 (40%)	8 (29.6%)	
DCR	11 (73.3%)	20 (74%)	

p value was calculated by independent sample Mann–Whitney U test.
Abbreviations: CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

alcohol abuse (52.4%), and the majority of patients were BCLC stage B (61.9%). All patients were successfully embolized with drug-loaded microspheres, among which 27 (64.3%) patients were embolized with microspheres of 300–500 μm (medium-size group) and 15 (35.7%) with microspheres of 100–300 μm (small-size group). There was no significant difference in baseline data between the two groups. The baseline data of the 42 patients are shown in Table 1.

3.2 | Tumor response

After 6 months of follow-up, the tumor response was evaluated according to the mRECIST standard. All patients survived until the end of follow-up. In 42 patients, the ORR and DCR of 1 month, 3 months, and 6 months after the procedure were 69% (29/42), 59.6% (25/42), 33.3% (14/42), 91.5% (38/42), 91.5% (38/42), and 73.8% (31/42), respectively (Table 2).

Complete response, partial response, stable disease, and progressive disease were recorded in 20%, 20%, 33.3%, 26.7%, respectively, of patients in the small-size group and 3.7%, 25.9%, 44.4%, 25.9% of patients in the medium-size group, respectively. There was no significant difference in tumor response between the medium-size group and the small-size group ($p = 0.516$) (Table 3).

3.3 | Adverse events

The most common adverse events within 1 month after procedure included abdominal pain (45.2%), nausea and vomiting (40.5%), and fever (31%). The degree of these adverse events was grade 1 or grade 2 according to the CTCAE 4.0 standard. Three patients from the small-size group developed liver abscess, which was diagnosed by CT examination and cured by percutaneous catheter drainage. Compared with the medium-size group, there was no significant difference in the incidence of mild adverse events, such as abdominal pain, fever, and nausea, in the small-size group, but there was a significant difference in the incidence of grade 3 liver toxicity ($p = 0.012$) and liver abscess ($p = 0.040$) (Table 4).

4 | DISCUSSION

Although TACE is more popular in Eastern than Western medicine, it is still considered as first-line palliative care in treating unresectable HCC.[15] TACE has a high level of repeatability and is less invasive, which can slow down tumor progression and improve the long-term survival of patients with liver cancer.[16] Multi-center randomized controlled studies and meta-analyses have confirmed that the effective rate of

TABLE 4 Adverse events

Parameters	Small size group ($n = 15$)	Medium size group ($n = 27$)	p value
Abdominal pain	10 (66.7%)	13 (48.1%)	0.337
Fever	12 (80%)	17 (62.9%)	0.314
Nausea/vomiting	9 (60%)	16 (59.3%)	0.613
Myelosuppression	3 (20%)	5 (18.5%)	0.605
Grade 3 liver toxicity	4 (26.7%)	0 (0%)	0.012
Liver abscess	3 (20%)	0 (0%)	0.040

Comparison between two groups was determined by Fisher's exact test.

TACE in treating liver cancer can reach 55%, which can increase the survival benefit of liver cancer patients by 4 months.[17,18]

Several therapeutic strategies for TACE are used in clinical practice, including c-TACE, balloon-assisted TACE, transarterial radioembolization, and DEB-TACE.[19] Traditional embolization uses lipiodol mixed with chemotherapeutic drugs as embolic material. This mixed emulsion has poor stability and is easy to dissociate and stratify. Some chemotherapeutic drugs can enter the systemic circulation through blood flow, which reduces the local curative effect. However, drug-loaded microspheres are combined with chemotherapeutic drugs through ion exchange, and the chemotherapeutic drugs can be released slowly after the microspheres are injected into the tumor through a catheter, which has better pharmacokinetic advantages.[20] Although the clinical efficacy of DEB-TACE and c-TACE remains controversial, growing evidence has shown that the former obtained better survival benefits for advanced liver cancer. Results from a meta-analysis including 3438 patients with liver cancer treated with TACE showed that DEB-TACE had better 1-year, 2-year, and 3-year survival rates than cTACE, with relative risk ratios of 0.79, 0.89, and 0.89, respectively.[21] DEB-TACE achieved significant improvement in overall survival and progression-free survival in another meta-analysis including 1832 patients with metastatic liver cancer (DEB-TACE $n = 822$; c-TACE $n = 1010$).[22] These studies showed that DEB-TACE has good prospects for the treatment of advanced liver cancer.

At present, the published literature mainly consists of the application of drug-loaded microspheres in European and American populations, while research on the efficacy of CalliSpheres in patients with advanced liver cancer in China is relatively lacking. A multi-center study from the United States revealed that the overall ORR and DCR of beads loaded with doxorubicin were 47.6% and 76.8%, respectively, for advanced HCC.[20] Another single-center study in Greece showed ORR and SD was seen in 68.9% and 20% of 45 HCC patients using HepaSphere DEB-TACE.[23] Urbano et al conducted a prospective multicenter study in Spain, including 131 patients with liver cancer receiving 214 times of D-TACE treatment. The objective remission rates at 6 months, 1 year, and 2 years were 74.6%, 45.7%, and 44.1%, respectively.[24] In this study, CalliSpheres microspheres loaded with epirubicin hydrochloride were used for arterial embolization, and the curative effect was evaluated using the mRECIST standard. The ORR and DCR of 1, 3, and 6 months were 69%, 59.6%, 33.3%, and 91.5%, 91.5%, and 73.8%, respectively. These results were consistent with those of previous studies.

The size of the DEBs is a key parameter for DEB-TACE. However, no standard exists currently on the optimal size of DEBs, and creating a standardized approach could achieve better curative efficacy and lower incidence of adverse reactions. Compared with the DEBs of 700–900 μm, 100–300 μm showed higher adriamycin concentration and larger necrosis range in tumors when used to embolize hepatic tumors in pigs.[25] Hasmukh et al used DEBs to embolize 94 patients with unresectable hepatocellular carcinoma, among which 59 patients received 100–300 μm and 35 patients received a mixture of 300–500 μm and 500–700 μm. A longer median survival time was achieved in the small-size group (15.1 months vs. 11.1 months).[26] A recent study compared the efficacy of DEB-TACE with 100–300 μm or 300–500 μm for liver cancer and reported that the small-size group achieved higher CR rates (56.0% vs 33.3%).[27] However, the smaller size of DEBs was also related to higher adverse events. Bhagat et al reported that more than half of the patients embolized with DEBs of 100–300 μm developed post-embolization syndrome. Liver abscess occurred in 23% of these patients.[13] In this study, we compared the clinical responses of embolization with DEBs of 100–300 μm or 300–500 μm. The results demonstrated that the two groups had no difference in local control rate. However, the major complication rate of liver abscess and grade 3 toxicity was higher in the small-size group. All three patients who developed liver abscess were in the small-size group and were cured with catheter drainage. The high incidence of complications with the use of small-size CalliSpheres microspheres may be attributed to the characteristics of this DEB. CalliSpheres microspheres were made of non-degradable polyvinyl alcohol, which had good deformability and could shrink and deform under a certain pressure with a maximum compression rate of 50%. During injection, the compression deformation of the drug-loaded microspheres made it easier to penetrate the tumor through the blood vessels. Then, the recovery of the original diameter facilitated complete embolization.[28] This elastic deformation characteristic of CalliSpheres microspheres makes it possible to achieve good results in tumor embolization, but at the same time, the normal liver tissue and blood supply of the biliary tract around the tumor may be affected by embolization, resulting in irreversible ischemia and necrosis and further development of biloma or liver abscess.[29]

There are some limitations to this study. First, the sample size of this study was small. The insufficient number of cases may affect the statistical analysis, resulting in false positive or false negative results. Furthermore, this study had a short follow-up time (6 months); therefore long-term survival was not analyzed. Although some studies have shown that there is an important relationship between the control rate of lesions and long-term survival, the long-term survival is still the key factor in determining the curative effect.

5 | CONCLUSIONS

CalliSpheres microsphere embolization was a safe and effective method for advanced HCC. DEB-TACE with CalliSpheres microspheres

of 300–500 μm had similar tumor response and lower rate of serious adverse event compared with 100–300 μm. The medium-size CalliSpheres microspheres may be a better choice for unresectable primary liver cancer. Long-term prospective multicenter clinical studies are needed to further analyze the long-term efficacy and safety of CalliSpheres microspheres with different sizes.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

All data included in this study are available upon request by contact with the corresponding author.

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