



Hepatic fibrosis and short-term clinical efficacy after hepatic artery embolization for unresectable hepatocellular carcinoma using doxorubicin-eluting HepaSpheres

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Background: Hepatocellular carcinoma (HCC) is most common malignancies around world. Transcatheter arterial chemoembolization (TACE) is recognized as the first-line treatment for HCC by NCCN, and its efficacy is widely reported. However, repeated TACE induces hepatic fibrosis. How to reduce hepatic fibrosis and retard cirrhosis is an urgent problem in treatment of HCC. To verify the efficacy of doxorubicin-eluting HepaSpheres for TACE in the treatment of unresectable HCC.

Methods: We retrospectively analyzed 91 patients with unresectable HCC underwent TACE from June 2015 to June 2018. Among which, 51 cases were treated with HepaSpheres and 40 cases were treated with iodized oil. The primary endpoint was got according to the Modified Response Evaluation Criteria in Solid Tumors (mRECIST). Type IV collagen (IV-C), layer mucin (LN), amino-terminal propeptide of type III procollagen (PIIINP), and hyaluronic acid (HA) were tested before and after TACE treatment.

Results: Serologic factors of the groups were re-examined 3 days after TACE, which showed higher ALT and AST in the conventional TACE group than in the HepaSpheres-TACE group ($P < 0.05$). The postoperative efficacies were evaluated according to the mRECIST criteria. No difference in the short-term efficacy between these two groups ($P > 0.05$) were found. Moreover, serologic factors for fibrosis were further re-examined 6 months later, showing no differences for IV-C and PIIINP ($P = 0.906$ and 0.574 , respectively). However, LN and HA were slightly higher in C-TACE group than HepaSpheres-TACE group ($P = 0.045$ and 0.048 , respectively).

Conclusions: HepaSpheres-TACE prevents the occurrence of late hepatic fibrosis effectively.

Keywords: Hepatocellular carcinoma (HCC); HepaSpheres; iodized oil; hepatic fibrosis; hepatic cirrhosis; transarterial chemoembolization

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies in the world, and its mortality has risen to second place in cancer-related deaths (1,2). About 800,000 patients die each year from HCC, and more than

50% of new or fatal cases occur in China (3). Due to the imperceptible early symptoms, most patients have lost the optimal time for radical ablation or surgical resection at the time of diagnosis (1,3). According to the NCCN guidelines, transcatheter arterial chemoembolization (TACE) is the

first-line treatment for patients with advanced HCC, and its efficacy has been widely recognized.

Conventional transcatheter arterial chemoembolization (C-TACE) is a mixed emulsion of iodized oil and chemical agents, which could embolize the tumor supplying artery and cause hypoxia and local high concentrations of chemotherapeutic agents to induce tumor necrosis (4,5). However, patients with HCC often need to undergo repeated TACE treatment, in which the hepatic fibrosis may be induced by the repeated lipiodol embolization (6). Cirrhosis is the last stage of hepatic fibrosis and it is one of the independent predictors of long-term efficacy for HCC (7). How to reduce hepatic fibrosis and slow the progression of cirrhosis is still an urgent problem to be solved in the comprehensive diagnosis and treatment of liver cancers.

Here, in this study, we included 91 cases of HCC that were treated with doxorubicin-loaded HepaSphere and traditional iodized oil-loaded drugs, respectively. The short-term efficacy and postoperative hepatic fibrosis between these two groups were analyzed. The results indicated that doxorubicin-loaded HepaSphere might reduce hepatic fibrosis after repeated TACE.

Methods

Study design

This single-center retrospective study was conducted at the Guangdong Provincial People's Hospital. The study has been approved by the Ethics Committee of the Guangdong Provincial People's Hospital, and all patients or their families have signed relevant informed consent. The number of the ethical approval is No. GDREC 2016437H. All surgeries were performed by a surgeon with more than 20 years of treatment experience, and postoperative efficacy evaluation was performed by two or more senior clinicians.

Inclusion and exclusion criteria

Before being included in the analysis, patients must meet all the following criteria: (I) age >18 years, the patient was diagnosed as HCC according to the histological examination or imaging criteria of the European Association of Liver Research (EASL); (II) tumor diameter ≤150 mm, Child-Pugh of Liver function ≤7 points, Eastern Cancer Cooperative Group (ECOG) score: 0–2 points; (III) patients were BCLC stage B or BCLC stage A without radical treatment and the liver function Child-Pugh ≤7 points,

patients were BCLC C stage, ECOG ≤2, and the expected survival period ≥6 months.

Patients were excluded from the study if any of the following criteria were met: (I) presence of clinically serious vascular diseases such as cerebrovascular accident (within 6 months prior to TACE), myocardial infarction (within 6 months prior to TACE), uncontrollable hypertension after appropriate medical treatment, unstable angina pectoris, congestive heart failure (NYHA class 2–4), arrhythmia requiring medication; (II) allergic to pirarubicin or contrast media; (III) pregnant or lactating women; (IV) patients with other concomitant malignancies.

Procedure of hepatic artery embolization

A venous access was established on the day of surgery. In addition, the patients were given antiemetic (Dolasetron, 25 mg, IV, Haisco Pharmaceutical Group, Tibet, China) and antibiotic (Cefazoline, 1 g, IV, China Resources Group, Beijing, China). Surgery was performed under local anesthesia (or general anesthesia if necessary). Seldinger technology was used for femoral artery puncture. RH or YASHIRO catheters (TERUMO, Tokyo, Japan) were used for hepatic artery angiography, and Finecross microcatheters (TERUMO, Tokyo, Japan) were used to select HCC-fed arteries. The drug-loaded microsphere suspension/iodinated oil emulsion was injected in a pulsed manner to embolize the tumor supplying artery. The injection rate was 1 mL per minute until the end of embolization was reached (tumor blood flow slowed down and the contrast agent disappeared after 2–5 heartbeats). For tumors involving 2 hepatic lobes, the more severe hepatic lobe was treated first, then the contralateral lobe was treated after a 2–4-week interval, and liver function must be restored to baseline levels prior to treatment.

In the HepaSphere-TACE group, all patients underwent TACE surgery using 50–100 μm HepaSphere microspheres (Merit Medical, USA). Pirarubicin was loaded using a two-step technique and the embolization procedure was shown in *Figure 1*. In the C-TACE group, all patients were treated with iodized oil (Guerbet, France) injection as an embolic material. The dosage of iodized oil was determined according to the size and vascular supply of the tumor, but the maximum dose did not exceed 20 mL. Pirarubicin (50 mg), iodized oil and a nonionic contrast agent (1:1) were emulsified. If the end of embolization was not reached after all of the iodized oil emulsion had been injected, appropriate doses of 100–300, 300–500, and 500–700 μm

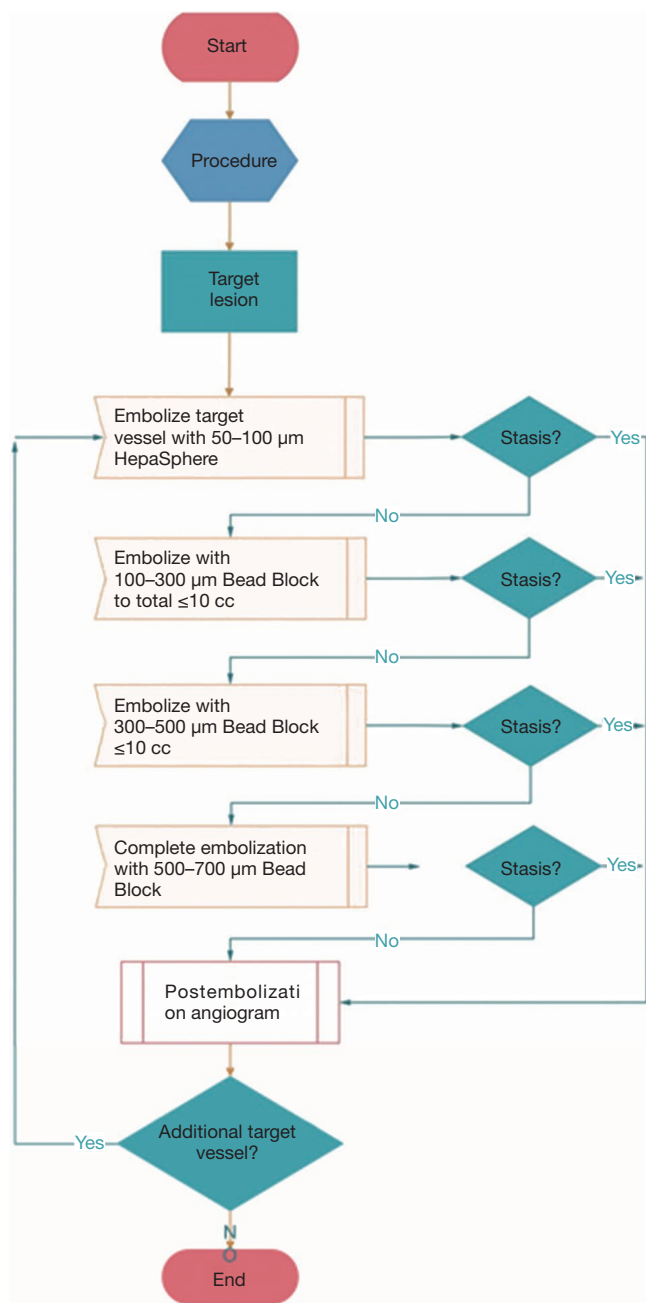


Figure 1 Procedure of HepaSphere-TACE for HCC. In the HepaSphere-TACE group, Pirarubicin 50 mg was loaded onto HepaSphere (25 mg). The nutrient vessel of tumor was embolized using HepaSphere microspheres loaded with pirarubicin. After all the microspheres were injected, added Bead Block of appropriate specifications necessary to achieve stasis, depending on assessment of a combination of tumor volume and vascularity. Stasis was defined as the absence of antegrade flow within a vessel such that contrast filling the target vessel persisted, without washout, five cardiac beats after the injection of contrast.

blank microspheres were administered to embolize the blood supply to the tumor until the end reached. Hepatic fibrosis (IV-C, LN, PIIINP and HA) were determined using chemiluminescence immunoassay. All kits were purchased from Sigma, USA.

Peripheral venous blood was collected from all patients three days before and after the surgery for the corresponding blood test. The decision regarding retreatment or not was based on enhanced CT/MR obtained every other month. And the internationally recognized solid tumor improvement response assessment (mRECIST) was used for efficacy evaluation. Patients with CR (complete response) entered the follow-up system. In the case of PR (partial response) or SD (stable disease), repeated treatment was considered, but a 4–6-week interval from the last treatment was required, and liver function must be restored to baseline before the repeated treatment. If PD (progressive disease) persisted after TACE treatment for the same lesion twice, patients should no longer receive TACE. Changes of liver function were compared at 3 days and 1 month before and after the treatment, and the treatment effects were evaluated at 1, 3, and 6 months later, respectively. The severity of hepatic fibrosis was compared within 6 months after treatment between the two groups.

Statistical analysis

Data analysis was performed using SPSS 20.0 statistical analysis software (IBM, Armonk, New York, USA). Data are expressed as mean ± SD. Inter-group comparisons were performed using independent sample t-tests. The calculated data were described using the number of cases or percentages and compared using the χ^2 -test. The test level was set to $\alpha=0.05$, and a P value <0.05 indicated statistical significance.

Results

Baseline of the patients

We included a total of 91 patients with advanced liver cancer who were treated in this hospital between May 2015 and May 2018 in this study. These patients were divided into groups as follows: 51 patients in trial group receiving HepaSphere-TACE and 40 patients in control group receiving C-TACE. The details were shown in *Table 1*. There were no significant differences in age, gender constituent ratio, histories of hepatitis, drinking or Hepatic

Table 1 The physiological baseline characteristics of the study cohort

Items	HepaSphere-TACE (n=51)	C-TACE (n=40)	P value
Age (years)	59.00±10.828	56.98±12.939	0.419
Gender (female/male/N)	9/42/51	7/33/40	1.000
History of HB, n (%)	23 (45.1)	22 (55.0)	0.402
History of HC, n (%)	2 (3.9)	1 (2.5)	1.000
History of drink, n (%)	7 (13.7)	4 (10.0)	0.750
History of cirrhosis, n (%)	17 (33.3)	12 (30.0)	0.822
Child-Pugh stage, n (%)			0.793
A	42 (82.4)	32 (80.0)	
B	9 (17.6)	8 (20.0)	
C	0	0	
BCLC stage, n (%)			0.919
A	9 (17.6)	7 (17.5)	
B	37 (72.5)	28 (70.0)	
C	5 (9.8)	5 (12.5)	
D	0	0	
ECOG performance status, n (%)			0.777
0	35 (68.6)	26 (65.0)	
1	11 (21.6)	11 (27.5)	
2	5 (9.8)	3 (7.5)	
Tumor distribution, n (%)			0.962
Unifocal	9 (17.6)	7 (17.5)	
2–3 tumors	28 (54.9)	23 (57.5)	
Multifocal	14 (27.5)	10 (25.0)	
Largest nodule size (mm)	59.35±30.537	69.88±36.609	0.139
Vascular invasion or distant metastasis	5 (9.8)	5 (12.5)	0.744

Prior therapy includes surgical or medical therapy not directed toward current tumor burden or systemic therapy. BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group.

cirrhosis, liver function Child-Pugh scoring, BCLC staging, ECOG staging, and tumor condition between the two groups (all P value >0.05).

Peripheral venous blood was collected from all included cases within 3 days before surgery for the determination of corresponding factors (albumin, ALT, AST, total bilirubin, cholinesterase, prothrombin activity, platelets and alpha-fetoprotein) and serologic factors for hepatic fibrosis. None of the results showed any significant differences in the corresponding blood indexes between these two groups (all

P value >0.05). See *Tables 2* and *3* for details.

Liver function after treatment

Liver function and other serological factors were re-examined in all patients within 3 days after TACE treatment. The results showed changes in postoperative liver function in both groups. In the TACE treatment group, the changes in patients' albumin, total bilirubin, cholinesterase, prothrombin activity, platelet and alpha-

Table 2 The serological baseline characteristics of the study cohort

Items	HepaSphere-TACE (n=51)	C-TACE (n=40)	P value
Albumin	35.047±4.7322	36.245±4.9931	0.245
ALT	40.08±28.334	46.40±52.698	0.466
AST	53.90±38.139	64.75±66.883	0.332
Total bilirubin	21.645±11.5814	19.015±10.5462	0.267
Cholinesterase	5,458.86±1,823.515	5801.45±2,106.660	0.408
Prothrombin activity	89.45±14.492	92.90±13.046	0.242
Platelet	138.84±55.434	169.28±96.212	0.061
Alpha-fetoprotein	6,776.664±16,295.5952	6,217.937±14,888.1539	0.867

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 3 The hepatic fibrosis baseline of the study cohort

Parameters	HepaSphere-TACE (n=51)	C-TACE (n=40)	P value
IV-C	110.3714±74.37717	131.5425±153.96306	0.391
LN	64.1035±39.78016	74.6697±61.97047	0.327
PIIINP	12.3882±5.130032	13.7607±7.21875	0.292
HA	239.6320±305.93052	208.8608±242.33391	0.604

IV-C, type IV collagen; LN, layer mucin; PIIINP, amino-terminal propeptide of type III procollagen; HA, hyaluronic acid.

fetoprotein were not significantly different from those before treatment ($P>0.05$). However, there was a significant difference ($P<0.05$) for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Moreover, changes in ALT and AST were more significant in C-TACE group than in HepaSphere-TACE group (Table 4).

We also reviewed the relevant factors one month after the patient was treated. The results showed that albumin, ALT, AST, total bilirubin, cholinesterase, prothrombin activity, platelet, alpha-fetoprotein and other factors were not significantly different ($P>0.05$, Table 5).

Short-term efficacy of HepaSphere-TACE and C-TACE

We used mRECIST to evaluate the treatment efficacy in surgery for both groups one, three and six months later (Figure 2), and used the χ^2 test to analyze short-term postoperative outcomes. The results showed that all P values were >0.05 , indicating there was no significant difference in short-term efficacy between the HepaSphere-TACE group and the C-TACE group (Table 6). The chi-square test was used for comparison between the two

groups. $P<0.05$ was considered significant. There was no difference between the first month, the third month, and the sixth month between the two groups (OR: objective response rate = CR + PR, DC: disease control rate = CR + PR + SD).

Comparison of hepatic fibrosis changes in the two groups

There were no significant differences in preoperative IV-C, LN, PIIINP and HA between HepaSphere-TACE group and C-TACE group. After 6 months of continuous treatment, hepatic fibrosis was reviewed in both groups, showing no significant difference in CIV and PIIINP levels between the two groups ($P=0.906$, 0.574 , respectively). However, LN and HA levels were slightly higher than in the C-TACE group than that of HepaSphere-TACE group ($P=0.045$ and 0.048 , respectively) (Table 7).

Discussion

Compared to the traditional TACE technology, HepaSphere-TACE has the advantages of non-degradability

Table 4 Comparison of liver function on the 3rd day after operation in both groups

Parameters	HepaSphere-TACE (n=51)	C-TACE (n=40)	P value
Albumin	34.151±6.5111	34.830±4.8015	0.583
ALT	43.81±32.624	71.78±87.484	0.038
AST	57.69±40.446	101.28±101.161	0.006
Total bilirubin	24.113±14.6082	26.305±29.0519	0.640
Cholinesterase	5,359.59±1,845.067	5,244.88±2,109.668	0.783
Prothrombin activity	88.41±15.326	90.90±13.700	0.423
Platelet	156.75±167.664	159.50±86.094	0.925
Alpha-fetoprotein	6,730.908±16,291.0440	8,319.067±1,7305.4600	0.654

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 5 Comparison of liver function in 1 month after operation in both groups

Parameters	HepaSphere-TACE (n=51)	C-TACE (n=40)	P value
Albumin	34.584±4.6584	34.678±5.2043	0.928
ALT	41.312±31.4322	60.228±64.6390	0.070
AST	76.882±122.9738	113.475±154.0055	0.211
Total bilirubin	30.584±52.3265	26.452±26.5851	0.650
Cholinesterase	5,268.82±2,198.602	5,105.25±2,462.365	0.739
Prothrombin activity	88.71±16.199	87.25±15.400	0.665
Platelet	138.39±64.772	172.88±103.282	0.055
Alpha-fetoprotein	7,067.283±16,734.9663	9,964.659±19,047.7122	0.443

Comparison among two groups was performed by Student's *t*-test. $P < 0.05$ was considered significant. No difference of liver function index among two groups was shown.

of the embedded microspheres and sustained release of the drug. HepaSphere-TACE up-regulates the concentration of chemotherapeutic drugs at the site of tumor embolization under the premise of reliable embolization. In addition, according to meta-analysis, the side effects of HepaSphere-TACE, including fever, fatigue, abdominal pain, nausea, alopecia, myelosuppression and other common adverse reactions, are less than traditional embolization treatments of iodized oil (8).

In this study, we found that patients with HepaSphere-TACE and C-TACE treatments both induced reversible liver function changes, mainly in the reduction of albumin and cholinesterase, as well as increase of ALT and AST. However, after C-TACE treatment, patients with increased higher ALT and AST, which may be related to the rapid release of chemotherapy drugs caused by C-TACE.

However, drug-loaded microspheres currently used in clinical (such as HepaSphere and DC-bead) are mostly non-degradable microspheres (9). Therefore, there is an urgent demand to find new materials that are more susceptible to degradation than iodized oil. Otherwise, ectopic embolization of the microspheres would result in irreversible damage. In general, HepaSphere microspheres are TACE safe and effective embolic agents. Its effects on liver function and postoperative complications are within acceptable limits, but more attention should be paid to selecting the blood supply artery to avoid ectopic embolization.

Currently, researches about drug-loaded microspheres and traditional lipiodol have been reported. Although drug-loaded microspheres are significantly superior to iodized oil in pharmacokinetics, there is no strong evidence for

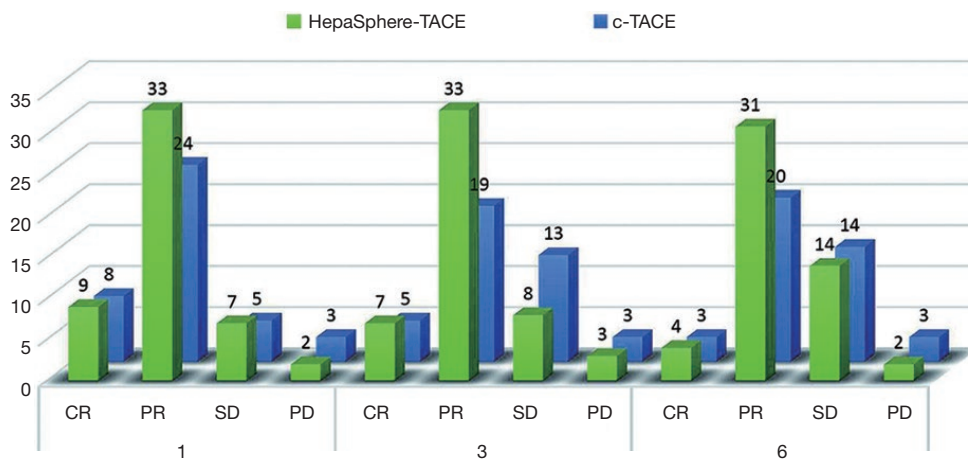


Figure 2 Comparison among two groups was performed by Chi-square test. $P < 0.05$ was considered statically significant. No differences were found in 1st, 3rd and 6th months after treatment in both groups ($P = 0.875, 0.259, 0.704$, respectively).

Table 6 Comparison of recent treatment efficiency between the two groups

Month	Efficacy assessment	HepaSphere-TACE (n=51)	C-TACE (n=40)	P value
1st	OR	42	32	0.793
	DC	49	37	0.651
3rd	OR	40	24	0.067
	DC	48	37	1.000
6st	OR	35	23	0.283
	DC	49	37	0.651

Comparison among two groups was performed by Chi-square test. $P < 0.05$ was considered significant. No difference in 1st, 3rd, 6th month among two groups was shown. OR, objective response; DC, disease control.

Table 7 Comparison of liver fibrosis after 6 months in the two groups

Parameters	HepaSphere-TACE (n=51)	C-TACE (n=40)	P value
IV-C	137.9990±111.31665	140.8385±115.39194	0.906
LN	77.3522±45.9516	104.3360±79.19955	0.045
PIIINP	15.9671±8.36818	17.0202±9.38048	0.574
HA	216.3737±238.43665	339.4758±346.31562	0.048

IV-C, type IV collagen; LN, layer mucin; PIIINP, amino-terminal propeptide of type III procollagen; HA, hyaluronic acid.

the superiority of drug-loaded microspheres to iodized oil in HCC treatment. Here, we retrospectively analyzed 91 patients treated with different TACE (including 51 cases with HepaSphere-TACE, 40 cases with C-TACE). The results showed no significant difference in short-term efficacy between the two methods at the first month, the third month, and the sixth month after treatment. In

a meta-analysis of 1,449 patients, there was no significant difference in tumor response rate or survival between the DEB-TACE group and the C-TACE group (10). And in a comparative study of the efficacy of commonly used drug-loaded microspheres, there was no significant difference in the short-term efficacy of DC-Bead TACE, HepaSphere-TACE and C-TACE (11). In addition, in a prospective study

conducted by Brown *et al.* (9), 101 patients with HCC were randomized to receive drug-loaded microspheres or blank microspheres as embolic material. The overall survival rates for the two groups were 20.8 and 19.6 months, respectively ($P=0.64$). However, in this study, 34 patients were BCLC patients with stage C, 60 patients had multiple intrahepatic lesions, and 19 patients had portal vein tumor thrombus. According to NCCN guideline, the first-line therapeutic regimen for patients with BCLC stage C was targeted and drug-based comprehensive treatment (10), but all patients enrolled in this study received TACE, without mentioning essential basic targeted therapy, and the number of cases enrolled in this study was another limitation.

In addition, cirrhosis is one of the factors that affect the prognosis of liver cancer, and liver fibrosis is an important cause of cirrhosis. Repeated TACE treatment may lead to hepatocyte damage and hepatic fibrosis in HCC patients, which would further impair liver function and lead to chronic decompensation of liver (10). Currently, the best method for clinically determining the severity of hepatic fibrosis is liver biopsy. However, due to its invasiveness and poor reproducibility, repeated biopsy monitoring during long-term treatment is difficult. "APASL consensus guideline: Invasive and non-invasive assessment of hepatic fibrosis: a 2016 update" (4) and "2015 EASL-ALEH clinical practice guideline: Non-invasive tests for evaluation of liver disease severity and prognosis" (12), serologic markers of hepatic fibrosis provide high-quality evidence in the diagnosis or exclusion of significant hepatic fibrosis and cirrhosis. Recent studies that have shown that compared with transient elastography (FibroScan), type IV collagen (IV-C), laminin (LN), type III procollagen N-terminal peptide (PIIINP), serum hyaluronic acid (HA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and other hepatic fibrosis serological markers have equally good performance in predicting hepatic fibrosis (13). Thus, the combination of serologic markers for fibrosis test maybe a reliable non-invasive method for the prediction of hepatic fibrosis. In this study, we compared the changes in hepatic fibrosis markers before and after surgery in the two groups. The results showed no significant difference in IV-C and PIIINP levels between the two groups ($P=0.906$ and 0.574 , respectively), but the LN and HA levels in the C-TACE group were slightly higher than those in the HepaSphere-TACE group ($P=0.045$ and 0.048 , respectively). Therefore, repeated C-TACE surgery in HCC patients is more likely to increase liver fibrosis and affect liver reserve function. Inflammation occurs in all tissues in response to injury or

stress, and it is also a key factor in hepatic fibrosis (14). At the same time, hepatic fibrosis represents the liver tissue wound repair process, which indirectly objectively reflects the severity of pathological damage to liver (15,16). High-concentration chemotherapeutic drugs in patients with HCC after treatment with TACE are the main cause of postoperative liver inflammation. Under the premise of ensuring the therapeutic effect, thus, how to reduce the concentration of chemotherapeutic drugs in normal liver is an effective measure to slow the progression of hepatic fibrosis. Kong *et al.* applied low-dose and conventional-dose chemotherapy drugs to 50 patients with HCC during C-TACE. After C-TACE, four serological markers of hepatic fibrosis were significantly increased in the conventional dose group, while there was no significant difference in the low dose group (17). In another study, 36 patients with HCC who received TACE were included in low-dose ($n=15$) and conventional-dose ($n=21$) chemotherapeutic groups for analysis. In conventional-dose group, IV-C, LN, hPC-III (human pro-collagen type-III), HA and transforming growth factor-beta 1 (TGF- β 1) significantly increased after surgery ($P<0.01$), while no significant differences were observed in low-dose group except for TGF- β 1 (18).

In a pharmacokinetic study of HepaSphere (19), 45 HCC patients received TACE using HepaSphere microspheres or iodized oil emulsions. The doxorubicin AUC of the HepaSphere-TACE group ($35,195\pm 27,873$ ng \times min/mL) was significantly lower than that of the conventional C-TACE group ($103,960\pm 16,652$ ng \times min/mL; $P=0.009$). At the same time, the C_{max} of the HepaSphere-TACE group (83.9 ± 32.1 ng/mL) was also significantly lower than that of the C-TACE group (761.3 ± 58.8 ng/mL; $P=0.002$). HepaSphere may be one of the best embolic materials for TACE in the treatment of patients with Hepatic cirrhosis by its locally sustained release action and reliable embolization efficacy. However, regardless of HepaSphere-TACE or C-TACE, embolization-induced hepatic hypoxia will inevitably aggravate the fibrosis process of liver tissues; accordingly, selecting tumor blood-feeding vessels as far as possible is an effective method to reduce normal liver injuries.

In summary, although there may not be any significant difference between the short-term and long-term effects of drug-loaded microspheres (such as HepaSphere and C-TACE), HepaSphere may have better application prospects in patients with liver cirrhosis compared to other drug-loaded microspheres. In addition, by repeatedly

receiving C-TACE, DEB-TACE treatment may achieve better results in patients who have no response or even disease progression (20). In the embolization treatment of HCC, the relevant factors for drug-loaded microspheres have not been determined, and more relevant studies should be done to explore whether the efficacy is related to genotyping, tumor pathological type, and tumor anatomy, as well as HCC primary and metastasis.

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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.2020.01.15>). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study has been approved by the Ethics Committee of the Guangdong Provincial People's Hospital, and all patients or their families have signed relevant informed consent. The number of the ethical approval is No. GDREC 2016437H.

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