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350–560 μm gelatin sponge particles combined with transcatheter arterial chemoembolization for the treatment of elderly hepatocellular carcinoma

The safety and efficacy

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Abstract

To retrospectively analyze the safety and efficacy of 350–560 μm gelatin sponge particles combined with single-chemotherapy drug transcatheter arterial chemoembolization (Gs-TACE) for the treatment of elderly hepatocellular carcinoma without surgical resection.

Thirty elderly hepatocellular carcinoma patients without surgical resection, who received Gs-TACE in our hospital, were selected. Slowly injected gelatin sponge particles (350–560 μm)+ 10 mg lobaplatin injection into the regional embolization tumor target vessel. The Response Evaluation Criteria for Solid Tumors could be used to evaluate the tumor response after intervention surgery.

Eighty-nine times of intervention TACE were conducted on the 30 patients. The average size of tumor was 8.3 cm. The median survival time was 28 months, and the 1 and 2-year survival rates were 89% and 58%, respectively. The Response Evaluation Criteria for Solid Tumors was used to evaluate the tumor response, and found that the complete response, partial response, and OR were 30%, 56.67%, and 86.67%, respectively, at 1 month after intervention surgery. The patients were divided into groups: 60 to 65 years age group (A), >65 to 75 years age group (B), and >75 years age group (C); the median survival times were 16, 32, and 33 months, respectively, and there was statistical difference between A group, B group, and C group. The analysis of prognosis factors showed that there was statistical significance in age, Barcelona Clinic Liver Cancer stage, portal vein invasion, and alpha fetal protein (AFP), and age was the protective factor.

Gelatin sponge particles (350–560 μm), combined with transcatheter arterial chemoembolization, provide an alternative method for the treatment of elderly hepatocellular carcinoma without surgical resection.

Abbreviations: AFP = alpha fetal protein, CTCAE = Adverse Effects Evaluation Criteria, GSPs = gelatin sponge particles, Gs-TACE = gelatin sponge particles combined with single chemotherapy drug transcatheter arterial chemoembolization, mRECIST = Response Evaluation Criteria for Solid Tumors, PHC = primary hepatocellular carcinoma.

Keywords: elderly, gelatin sponge particles, hepatocellular carcinoma, survival rate, transcatheter arterial chemoembolization

1. Introduction

According to epidemiological survey, there is significant difference in primary hepatocellular carcinoma (PHC) occurrence, development, and prognosis between eastern and western countries, of which 60% PHC patients in China had a history of hepatitis B with liver cirrhosis, and pure alcoholic liver cirrhosis is rare; in Europe, United States, and Japan, 70% of liver cancer patients had hepatitis C,[1–3] and different types of hepatitis may lead to the difference in the prognosis of liver cancer. Studies have also reported that hepatitis B-related liver cancer has a worse outcome.[4] The incidence rate of elderly PHC showed upward trend,[5,6] and the incidence rate of liver cancer in China has been occupying the second place. At present, China has entered the aging society category (Chinese elderly standard is older or equal to 60 years) and China is a country where hepatitis occurrence is very much ; the treatment of elderly liver cancer should arouse our attention, especially the elderly liver cancer patients who cannot receive surgical resection, these elderly patients are not only the treatment problem, but also the social problem.

In recent years, more and more clinical research on elderly liver cancer have been reported, including surgical resection and radiofrequency ablation therapy,[7–10] both of which have confirmed its feasibility in their respective areas. Since most Chinese elderly PHC patients are already in middle and advanced stage when diagnosed, so they lose opportunity for surgery. Whereas, except for the shortage of liver source for liver transplantation, the costs and lifelong medication limit the clinical application.[11] A number of clinical studies have confirmed the feasibility and efficacy of TACE for the treatment

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of elderly hepatocellular carcinoma[12–15]; however, the research on gelatin sponge particles (GSPs) combined with TACE for the treatment of elderly hepatocellular carcinoma is rare at home and abroad.

In this study, we analyzed the safety and efficacy of 350–560 μm GSPs combined with TACE for the treatment of elderly hepatocellular carcinoma without surgical resection from June 2010 to June 2014.

2. Materials and methods

2.1. Case selection

The inclusion criteria were as follows: patients older than 60 years; no limitation in male and female patients; hepatocellular carcinoma (HCC) diagnosed, and treated with TACE, and the patients who can not or do not receive surgical resection; liver function Child-Pugh A to B grade, Barcelona Clinic Liver Cancer (BCLC) A to C grade; patients who did not received other anticancer therapy before surgery; expected survival time >3 months; and patients who signed the informed consent voluntarily.

The exclusion criteria were as follows: patients who were allergic to contrast agents and chemotherapeutic drugs; patients who had significant heart, kidney, and brain dysfunction; patients who had portal vein tumor thrombus.

The exit criteria were as follows: patients who had liver failure and liver function Child-Pugh C grade; patients with combined obstructive jaundice or other tumor-related serious complications; and patients who refused TACE treatment, lost or dead.

The study has been approved by our institutional review board, and all patients provided informed written consent before the TACE procedure.

2.2. TACE technology

Seldinger method was used to puncture the right femoral artery, and routine abdominal angiography and hepatic arteriography were conducted with 5F-RH hepatic duct, and auxiliary conducted phrenic artery, superior mesenteric artery, left gastric artery, and right renal artery ectopic angiography according to tumor location, size, and tumor staining complete or not, to confirm all feeding arteries of tumor. The operation method was similar to TACE, and the difference is that TACE technology selected the blended microparticle suspension of 350 to 560 μm GSPs (Hangzhou Yili Kang Pharmaceutical Co., Ltd., specification: 100 mg) and 10 to 20 mg lobaplatin injection (specifications: 10 mg/support, Hainan Chang'an International Pharmaceutical Co., Ltd.) based on the tumor size, then slowly injected the microparticle suspension of GSPs and chemotherapy drug into the feeding artery in tumor region under the guidance of digital subtraction angiography through catheter. Embolism stopping criteria were as follows: disappearance of tumor staining and regional arterial blood stagnation. Supplement embolization or not was decided according to the intraoperative angiography or DynaCT angiography.

2.3. Evaluation of the effect and observation of adverse reaction

Computed tomography (CT) scan was conducted at 4 days after surgery, and enhanced CT was conducted the next month after surgery, to observe the lesion size, necrosis degree, and the presence of new lesions. The blood routine, AFP, and liver function were reviewed at 4 and 7 days, and every month after surgery. The intervention effect was comprehensively assessed and whether to accept intervention therapy again was determined.

For evaluation of tumor response reference to the Response Evaluation Criteria for Solid Tumors (mRECIST 1.1), all patients received abdominal enhanced CT/magnetic resonance imaging (MRI) every 1 to 2 months after surgery to evaluate the efficacy, observe the tumor progression, and determine whether to conduct interventional therapy again or not.

The adverse reaction was evaluated according to the Adverse Drug Reaction Evaluation Criteria in 2010.

2.4. Statistical analysis

SPSS16.0 statistical software was used for statistical analysis. The count data were tested using chi-square test, $P < .05$ was considered statistically significant, and the survival rate was calculated using Kaplan–Meier statistics.

3. Results

In all, 30 elderly hepatocellular carcinoma patients were included in the intervention therapy in this study (26 males and 4 females), and the patients were divided into groups according to their age: 60 to 65 years age group (n = 8), >65 to 75 years age group (n = 15), and >75 years age group (n = 7). The average age was 70.23 ± 7.56 (60–88) years, and 20 patients had a history of hepatitis B, 5 patients had a history of hepatitis C, 1 patient with the history of alcoholic liver disease, and 4 patients had no history of hepatitis. AFP was <400 ng/mL in 18 patients and ≥400 ng/mL in 12 patients; Child-Pugh grade (A/B) was 19/11, and BCLC stage (A/B/C) was 5/18/7. According to the Expert Consensus on Standardization of The Management of Primary Liver Cancer made by Chinese Society of Liver Cancer,[5] all the patients were confirmed after ultrasonography, abdominal enhanced CT, or pathological biopsy. All the patients were fully informed before surgery and had signed the informed consent. In all, 89 times of GSMs-TACE procedures were conducted on the 30 patients (average 3.0 times; 1–8), and the average tumor size was 8.3 cm (range 5.0–15.5 cm) (Table 1).

3.1. Tumor response after intervention therapy

At 4 days after intervention therapy, liver CT scan was reviewed, and it was found that tumor showed uniformly distributed low-density honeycomb necrosis, and obvious tumor liquefaction necrosis could be observed in 1 patient at 3 hours after surgery. In this study, we used mRECIST to evaluate tumor response after intervention, and the results showed that the tumor response: complete response, partial response and overall response rates at 1 month after intervention were 56.67%, 30%, and 86.67% respectively.

3.2. Survival time and survival curves

Till January 2015, the follow-up time was 12 to 54 (average 29.4) months. The 1 and 2-year survival rates were 89% and 58%, and the median survival time was 28 months (Fig. 1). Grouping according to age, the median survival time of 60 to 65 years age group (group A), >65 to 75 years age group (group B), and >75 years old group (group C) were 16, 32, and 33 months, respectively, and there were significant differences between group A and group B, and group A and group C; namely the survival time of groups B and C was longer (Fig. 2).

Table 1

Baseline characteristics and features of 30 patients.

Clinical characteristic	Value
Mean age, y (range)	70.23±7.56 (60–88)
60–65	8
66–75	15
≥75	7
Sex (male/female)	26/4
Etiology (HBV/HCV/alcoholic /others)	20/5/1/4
Child-Pugh grade (A/B)	19/11
BCLC stage (A/B/C)	5/18/7
ECOG performance status (0/1/2)	8/20/2
Number of tumors (1/≥2)	6/24
Extrahepatic metastasis (−/+)	25/5
Pulmonary metastasis	2
Lymphatic metastasis	3
Portal vein invasion (−/+)	(28/2)
Mean largest tumor size in cm (range), cm	8.3 (5.0–15.5)
Size of tumor, cm (5–10/≥10)	14/16
AFP, ng/mL (0–400/≥400)	18/12

BCLC = Barcelona Clinic Liver Cancer, ECOG = Eastern Cooperative Oncology Group, HBV = hepatitis B virus, HCV = hepatitis C virus.

3.3. Adverse reactions and complications

After surgery, the patients had varying degrees of fever, and between 37.5 and 39.5°C; it was considered to be related with tumor necrosis and absorption, and eased gradually within 5 to 10 days. Upper abdominal pain occurred in 16 patients (>50%), and nausea and vomiting occurred in 13 patients (<50%), but the degree was less; the patients were generally relieved of the discomfort within 24 hours. All the patients had transient liver damage after intervention surgery, and recovered to the preoperative level within 7 to 10 days after liver protection therapy (Table 2). In this study, 5 patients had acute cholecystitis, and the reason was considered to be ectopic embolism. As GSPs are the absorbable particles embolic agents, all patients had complete remission after symptomatic treatment, and there was no gallbladder perforation or gallbladder gangrene. No acute liver failure, gastrointestinal ulcer or bleeding, and liver abscess and other sever complications occurred (Table 3).

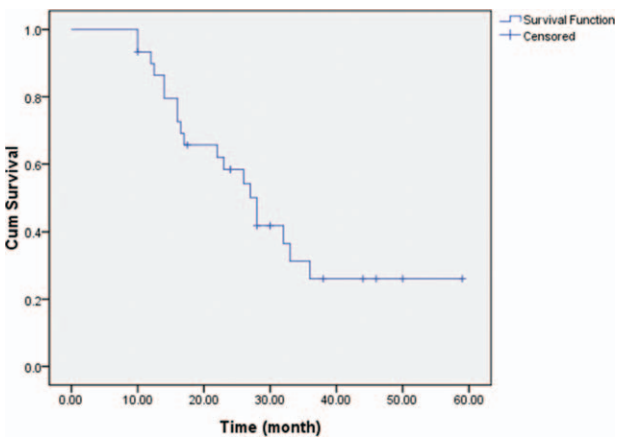

Figure 1. Kaplan–Meier graph depicting overall survival in the whole cohort (N = 30).

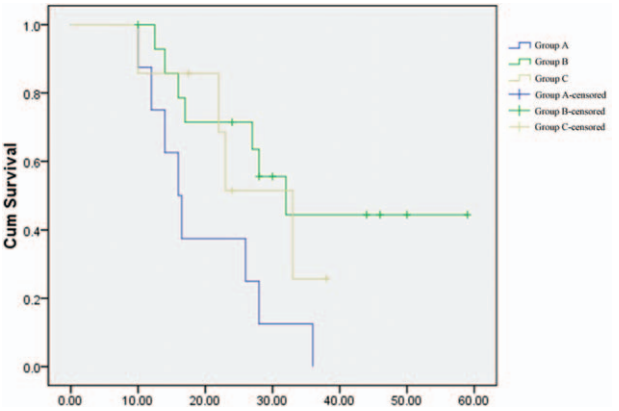

Figure 2. Kaplan–Meier curves for all patients in 3 groups, censored data come from patients who were still alive at the end of the study (group A: 60–65 years age group; group B: >65 to 75 years age group; group C: >75 years ages group).

3.4. Prognosis factor analysis

Prognosis factor analysis was conducted after intervention surgery, including 10 indicators, such as age, sex, Child-Pugh grade, BCLC stage, number of tumors, AFP level, and so on, of which 4 factors (age, BCLC stage, portal vein invasion, and AFP) were statistically significant; they were considered as prognosis factors, and age was considered as the protective factor (Table 4, Fig. 3).

4. Discussion

At present, there is no consent on the prognosis of elderly hepatocellular carcinoma. In A cohort study on the treatment of early hepatocellular carcinoma of average 70 years old patients with TACE, the results showed that the 1, 2, and 3-year survival rates were 91%, 86%, and 80%, respectively.[8] Another study showed that the 1-, 2, and 3-year survival rates were 51%, 36%, and 23%, respectively, and the age of hepatocellular carcinoma patients was 70 to 75 years old.[13] In a Japanese study on 136 cases of hepatocellular carcinoma patients who more than 70 years old, the results showed the 3-year survival rate was 80%.[14] Studies suggested that compared with the elderly hepatocellular carcinoma patients, disease stage, but not age, is the main independent prognosis indicator.[9,12,14,15] Dohmen et al[16] found that among the 36 cases of hepatocellular carcinoma patients older than 80 years, 20 cases received TACE, and part of other patients received surgery, ablation, chemotherapy, and other comprehensive therapy at the same time, and there were no significant differences compared with the patients who were younger than 80 years. Other studies reported that both the

Table 2

Change of liver function before and after GSMs-TACE ($\bar{x} \pm s$).

	Pre-TACE	7 d after TACE	*P*
ALT, U/L	55.57±25.05	67.66±26.53	.054
AST, U/L	64.94±35.11	77.83±34.10	.124
TBIL, μmol/L	25.13±14.23	31.63±15.81	.075
ALB, g/L	36.04±5.13	30.19±4.06	.000

ALB = albumin, ALT = glutamic pyruvic transaminase, AST = lutamic oxaloacetic transaminase, TBIL = total bilirubin.

Table 3

Adverse events after GSPs-TACE treatment.

	G1	G2	G3	G4	G5	G3+4+5, %
WBC	10	5	3	0	0	3 (16.7)
PLT	6	2	2	0	0	2 (20)
Fever	14	11	5	0	0	5 (10.6)
Pain	9	4	2	1	0	3 (18.8)
Nausea and vomiting	9	2	2	0	0	2 (15.4)
Abscess	0	0	0	0	0	0 (0)
Cholecystitis	3	1	1	0	0	1 (20)
Pancreatitis	0	0	0	0	0	0 (0)
Renal insufficiency	2	1	0	0	0	0 (0)

PLT = platelet, WBC = white blood cell.

patients who were older than 70 years and those who were younger than 70 years could obtain the same survival benefit after oral sorafenib.[17] Studies also reported that the hepatocellular carcinoma patients who were older than 75 years had worse prognosis. Kao et al[18] recently reported the results of a radiofrequency ablation therapy, indicating that elderly patients had a worse outcome. Hsu et al[19] also reported that old age could increase the mortality of TACE patients.

At present, in the field of clinical medicine, the definition of "elder" is not clear; it is usually defined as greater than 60 years or more than 65 years old. In China, the elder is defined as more than 60 years old, and 60 years is also defined as the legal age of retirement; so in this study, elderly hepatocellular carcinoma patients who were older than 60 years were included as the research subjects. In this study, the elderly patients were divided into groups according to their age: 60 to 65 years age group (group A), >65 to 75 years age group (group B), and >75 years age group (group C); the median survival time of these 3 groups were 16, 32, and 33 months, respectively, and there was significant difference between group B and group A, and group C and group A; namely the survival time was longer in group B and group C, and there was no significant difference between group B and group C. According to data analysis results, we found that age was the protective factor, and it seemed that elderly patients had a better prognosis; this is inconsistent with the former 2 points.[8,9,12–16]

As the hepatocellular carcinoma patients in our country generally have the background of liver cirrhosis, and because of the neglect or no medical examination conditions, the patients are usually in the middle and advanced stage when diagnosed, and the tumor is larger. In this study, the tumor size of the patients is greater than 5 cm, the average size of tumor is 8.3 cm, these characteristics or specificity of tumor size could not be found it the patients of other countries, and the tumor size directly affects the survival time of HCC patients,[20] although the data of this study dose not show the correlation between tumor size the prognosis.

Transcatheter arterial chemoembolization can cause liver damage and lead to liver fibrosis progression,[21] although the rate of complications after TACE can go up to 2% to 80%[22,23]; there is no significant correlation between age and the probability

Table 4

Multivariate survival analyses with Cox model adjusting for all important covariates.

		Univariate			Multivariable		
Clinical Characteristic	**No.**	**HR**	**95%**	***P***	**HR**	**95%**	***P***
Age, y							
60–65	8	1			1		
>65–75	15	0.78	0.36–1.28	.03*	3.75	1.26–11.11	.02*
>75	7	0.53	0.29–0.98	.02*	0.24	0.08–0.71	.01*
Sex							
Male	29	1			1		
Female	1	1.68	0.96–3.28	.07	2.14	1.03–4.25	.18
Child-Pugh grade							
A	19	1			1		
B	11	1.24	0.12–2.51	.58	1.24	0.12–2.51	.58
BCLC stage							
A	5	1			1		
B	18	0.98	0.50–1.92	.01*	1.38	0.99–2.73	.02*
C	7	2.33	0.92–5.94	.03*	2.33	1.52–4.44	.03*
Number of tumors							
1	6	1			1		
≥2	24	0.63	0.30–1.92	<.001*	2.24	1.52–3.96	.08
Extrahepatic metastasis							
−	25	1			1		
+	5	2.16	0.78–3.29	.56	0.86	0.45–1.93	.46
Portal vein invasion (−/+)							
−	28	1			1		
+	2	0.45	0.32–1.09	.02*	0.35	0.17–0.98	.01*
Mean largest tumor size, cm							
5–10	14	1			1		
≥10	16	1.25	0.83–3.25	.134	1.76	1.14–3.77	.39
AFP, ng/mL							
0–400	18	1			1		
≥400	12	0.95	0.85–2.36	<.001*	0.68	0.69–2.02	<.001*

AFP = alpha fetal protein, BCLC = Barcelona Clinic Liver Cancer, HR = hazard ratio.
* $P < 0.05$.

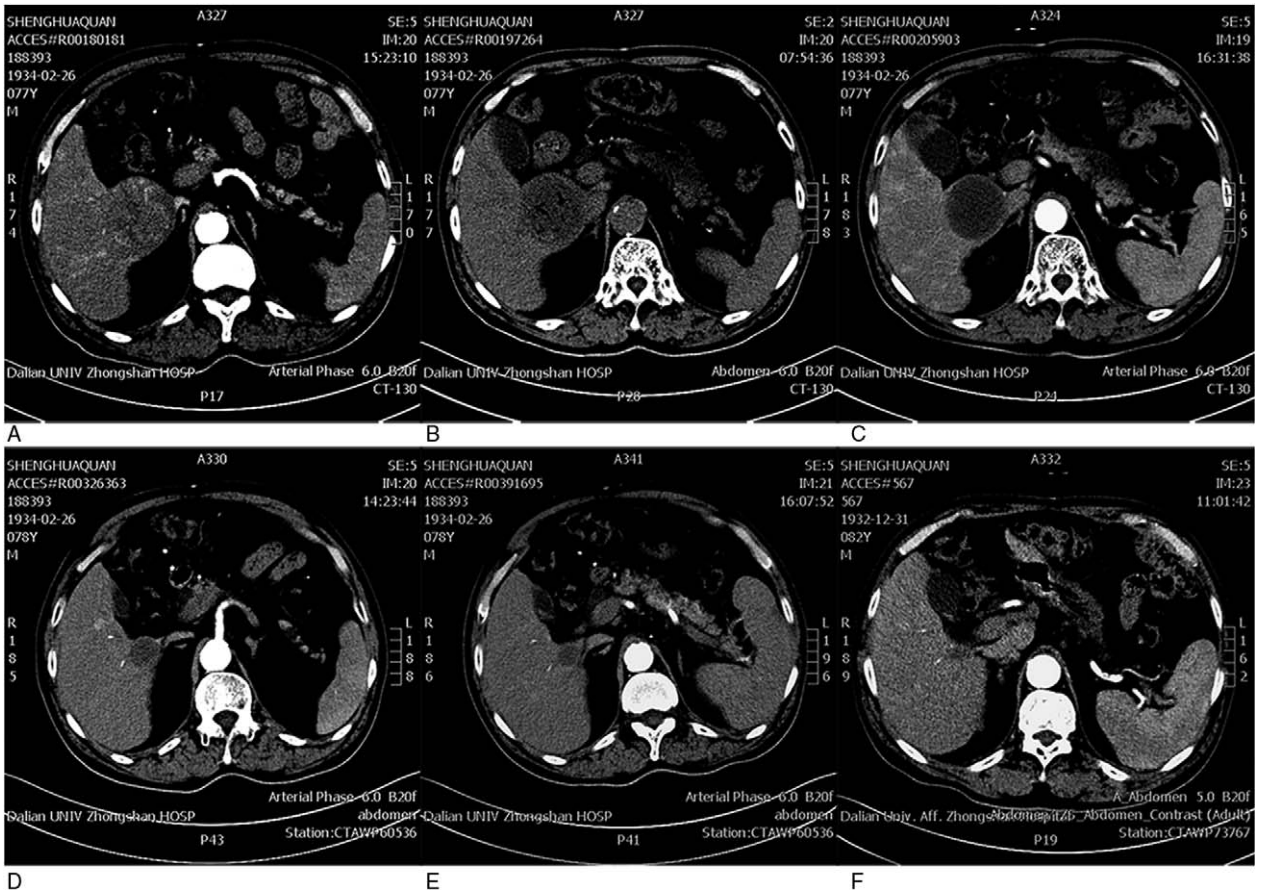

Figure 3. Computed tomography (CT) image of liver of a 78-year-old patient with primary liver cancer. (A) CT image of liver before surgery; (B) review CT image at 7 days after GS-TACE; (C) review CT image at 1 month after GS-TACE; (D) review CT image at 8 months after GS-TACE; (E) review CT image at 12 months after GS-TACE; CT image after 3-year follow-up.

of complications.[19] The results of this study showed that the application of 350 to 560 μm GSPs combined with single chemotherapy drug had ideal medium and long-term efficacy in the treatment of elderly hepatocellular carcinoma, and the patients could tolerate TACE-related complications; the 1 and 2-year survival rates were 89% and 58%, respectively, and the overall median survival time was 28 months, which was higher than the results of global multicenter reports made by Matan et al.[15]

This research achieved better results, which considered related with the following factors. Firstly, there was significant tumor necrosis in the near future after GSPs embolization.[24] We conducted reviewed CT scan at 4 days after intervention surgery, and showed that 100% patients had varying degrees evenly and consistent honeycomb necrosis on liver tumors, of which, one patient appeared significant tumor liquefaction necrosis at 3 hours after intervention, and as the tumor necrosis was rapid and significant, tumor can shrink recently after intervention surgery, thereby reducing tumor burden in patients.[25] Secondly, GSPs, as the absorbable mid-embolic agent, is generally believed that the average degradation time is 2 weeks, so regional tumor embolization can be conducted, which is equivalent to surgical resection, and GSPs is more suitable for the treatment of malignant tumor, as we all know that tumor surrounding has stronger activity, and it is also the common site of tumor recurrence.[26] Thirdly, due to the characteristics of 350–560 μm GSPs, the patients can tolerate the liver dysfunction after intervention, while for other complications, such as the occurrence of cholecystitis, is transient and recoverable, and can be avoided by using microcatheter technology, but after that, regional embolization can not be conducted. GSPs has the sustained effects of chemotherapy drugs, which make the less chemotherapy drugs maintain longer period of drug concentration, and this may be one of the reasons to achieve better efficacy in this study.[27]

The GSPs, as the absorbable particles, have no mass effect compared with iodized oil, and is beneficial to efficacy evaluation after intervention therapy, whereas easy to observe tumor activity, to timely conduct necessary TACE consolidation treatment. In summary, the tumor intervention treatment is reduced; meanwhile, because of this, the liver damage is reduced, the process of cirrhosis is slowed down, the liver function is further protected, and it provides a guarantee for the prognosis of patients. Meanwhile, as the embolic agents have no mass effect, it is beneficial to imaging evaluation after tumor intervention therapy.

Outcomes of elder patients with HCC in this study are encouraging; the reasons probably are related to following factors: firstly, due to the GSMs' absorbable feature, all of tumor feeding arteries and some branches of hepatic arteries around the tumor were completely blocked during 1 GSMs-TACE procedure in patient with good liver function. Secondly, our previous study

had documented the significantly higher chemotherapeutic drug concentration in tumor tissue and lower chemotherapeutic drugs in peripheral plasma compared with intra-arterial infusion in the VX2 animals model treated with GSMs-TACE.[27] That may be one of therapeutic mechanisms of GSMs-TACE for HCC.

In conclusion, 350 to 560 μm combined with single chemotherapy drugs TACE is safe and effective in the treatment of elderly hepatocellular carcinoma without surgical resection, and more elderly patients may have better prognosis.

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