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ABOUT COVER

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The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

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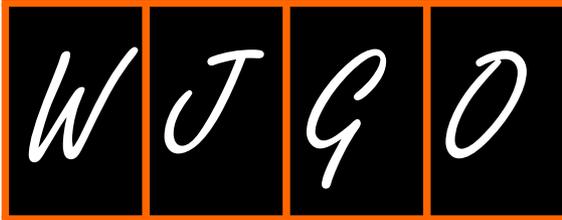
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Case Control Study

Comparison of ethanol-soaked gelatin sponge and microspheres for hepatic arterioportal fistulas embolization in hepatic cellular carcinoma

Guang-Sheng Yuan, Li-Li Zhang, Zi-Tong Chen, Cun-Jing Zhang, Shu-Hui Tian, Ming-Xia Gong, Peng Wang, Lei Guo, Nan Shao, Bin Liu

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Abstract

BACKGROUND

Hepatic arterioportal fistulas (APFs) are common in hepatocellular carcinoma (HCC). Moreover, correlated with poor prognosis, APFs often complicate anti-tumor treatments, including transarterial chemoembolization (TACE).

AIM

To compare the efficacy of ethanol-soaked gelatin sponges (ESG) and microspheres in the management of APFs and their impact on the prognosis of HCC.

METHODS

Data from patients diagnosed with HCC or hepatic APFs between June 2016 and December 2019 were retrospectively analyzed. Furthermore, APFs were embolized with ESG (group E) or microspheres (group M) during TACE. The primary outcomes were disease control rate (DCR) and objective response rate (ORR). The secondary outcomes included immediate and first follow-up APF improvement, overall survival (OS), and progression-free survival (PFS).

RESULTS

Altogether, 91 participants were enrolled in the study, comprising 46 in group E and 45 in group M. The DCR was 93.5% and 91.1% in groups E and M, respectively ($P = 0.714$). The ORRs were 91.3% and 66.7% in groups E and M, respectively ($P = 0.004$). The APFs improved immediately after the procedure in 43 (93.5%) patients in group E and 40 (88.9%) patients in group M ($P = 0.485$). After 2 mo, APF improvement was achieved in 37 (80.4%) and 33 (73.3%) participants in groups E and M, respectively ($P = 0.421$). The OS was 26.2 ± 1.4 and 20.6 ± 1.1 mo in groups E and M, respectively ($P = 0.004$), whereas the PFS was 16.6 ± 1.0 and 13.8 ± 0.7 mo in groups E and M, respectively ($P = 0.012$).

CONCLUSION

Compared with microspheres, ESG embolization demonstrated a higher ORR and longer OS and PFS in patients of HCC with hepatic APFs.

Key Words: Hepatocellular carcinoma; Arterioportal fistula; Ethanol; Gelatin sponge; Microsphere; Embolization

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Core Tip: Hepatocellular carcinoma (HCC) was considered the seventh most common cancer and the second leading cause of cancer-related deaths worldwide in 2020. Hepatic arterioportal fistulas (APFs) are common in HCC and often complicate anti-tumor treatments, including transarterial chemoembolization. The ethanol-soaked gelatin sponge combined the advantages of alcohol and gelatin sponges, contributed to better local control of hepatic APFs, and improved the survival of patients with HCC.

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INTRODUCTION

Hepatocellular carcinoma (HCC) was the seventh most common cancer and the second leading cause of cancer-related deaths worldwide in 2020, with 905677 new cases and 830180 deaths recorded annually[1]. Hepatic arterioportal fistulas (APFs), defined as fistulas between the hepatic artery and the neighboring portal vein[2,3], are common in HCC owing to tumor infiltration, vascular damage[4], or remodeling of the cirrhotic parenchyma.

Hepatic APFs may cause portal hypertension, ascites, and varices[5], which are strongly associated with poor prognosis[6]. The presence of hepatic APFs often complicates anti-tumor treatments, including transarterial chemoembolization (TACE). Chemotherapeutic agents and embolic materials run off through the fistulas, and tumor cells may detach from the hepatic artery, resulting in portal vein thrombosis[7].

Many materials have been used to treat hepatic APFs, including gelatin sponges[8], microspheres[9], coils[10], histoacryl[10], absolute ethanol[10], polyvinyl alcohol particles[10], and ethanol-soaked gelatin sponges (ESG)[11,12]. Additionally, ESG combines the advantages of alcohol and gelatin sponges and provides convincing results at different APF stages[12]. However, to the best of our knowledge, no study has compared the efficacies of ESG and microspheres. We conducted a retrospective study to evaluate the efficacy of ESGs and microspheres for the treatment of HCC with hepatic APF.

MATERIALS AND METHODS

Patients with HCC and hepatic APF treated with TACE and ESG (group E) or microspheres (group M) were enrolled between June 2016 and December 2019. The study protocol was approved by the ethics committee of the leading center. The requirement for written informed consent was waived owing to the retrospective nature of the study. All the experiments were performed in compliance with the Ethical Principles for Medical Research Involving Human Subjects

outlined in the 1975 Declaration of Helsinki (revised in 2000).

The inclusion criteria were as follows: (1) Confirmed diagnosis of HCC based on the American Association for the Study of Liver Diseases practice guidelines[13]; (2) Hypervascular tumor with Barcelona Clinic Liver Cancer (BCLC) Staging A-C; (3) Hepatic APF confirmed by angiography; (4) Predicted life span ≥ 1 year; and (5) Karnofsky score > 70 .

The exclusion criteria were as follows: (1) Other malignancies within 5 years; (2) Child-Pugh score ≤ 10 ; and (3) Severe coagulopathy (prothrombin time > 17 s and/or platelet count $\leq 60 \times 10^9/L$).

Treatment of APF

For group E, an appropriate-sized gelatin sponge (Alicon Inc., Hangzhou, China) was mixed with 10 mL of iodixanol (Hengrui Co. Ltd, Lianyungang, China) and 10 mL of ethanol (Lingfeng Inc, Shanghai, China). For group M, appropriate-sized microspheres (Embosphere, Merit Medical, UT, United States) were mixed with 10 mL of iodixanol. Digital subtraction angiography (DSA) was performed after catheterization of the celiac or superior mesenteric artery to validate the location and size of the hepatic APFs (Figure 1). APFs were classified according to a previous study by Zhou *et al*[12] (Table 1). Each APF feeding artery was superselected using a 2.7-F microcatheter. ESG or the microspheres were injected under fluoroscopic guidance until the fistula was blocked. Coils were used if the fistula was not completely blocked. DSA was repeated to confirm the complete embolization of the APFs (Figure 2).

TACE procedure

After APF embolization, a microcatheter was advanced into each feeding artery of the HCC. An emulsion of poppy Lipiodol (Hengrui Co. Ltd., Lianyungang, China) and epirubicin (Qilu Co. Ltd., Jinan, China) was injected *via* a microcatheter until complete embolization of the tumor was achieved (Figure 3)[14].

Follow-up

Follow-up was conducted every 2 mo and included standard blood count, liver functional tests, alpha-fetoprotein (AFP), and abdominal contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI). The images were interpreted based on the consensus of three skilled interventional radiologists.

In case the tumor recurrence was detected on CECT or MRI, TACE was repeated. If APF recurrence with a grade ≥ 2 was observed, ESG or microsphere APF embolization was repeated; however, if APFs did not recur, TACE was the only procedure performed. Follow-up intervention was determined based on the tumor condition and general status.

Outcome measures

The modified Response Evaluation Criteria in Solid Tumors for HCC[15] were applied to assess tumor response after 4 mo. The primary outcomes were disease control rate (DCR) and objective response rate (ORR), and the secondary outcomes included immediate and first-time follow-up of APF improvement, overall survival (OS), and progression-free survival (PFS).

Immediate APF improvement was defined as a decrease in grade to 1 or 0. First-time follow-up APF improvement was defined as a decrease in at least two grades confirmed by angiography in the second session, whereas APF progression was defined as an increased grade on the first-time follow-up angiography. If the grade remained the same or decreased by one, the APFs were not considered to improve. Moreover, OS was defined as the time interval between the initial TACE and death or the last follow-up. Furthermore, PFS was defined as the time interval between initial TACE and disease progression or death.

Statistical analysis

Continuous variables were analyzed using Student's *t*-test to determine whether the variables were normally distributed; otherwise, the Mann-Whitney U test was used. Categorical variables were analyzed using the χ^2 or Fisher's exact tests.

Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. Statistical significance was defined as a two-tailed $P < 0.05$. All statistical analyses were conducted using the SPSS software (version 24.0; IBM Inc., Armonk, NY, United States).

RESULTS

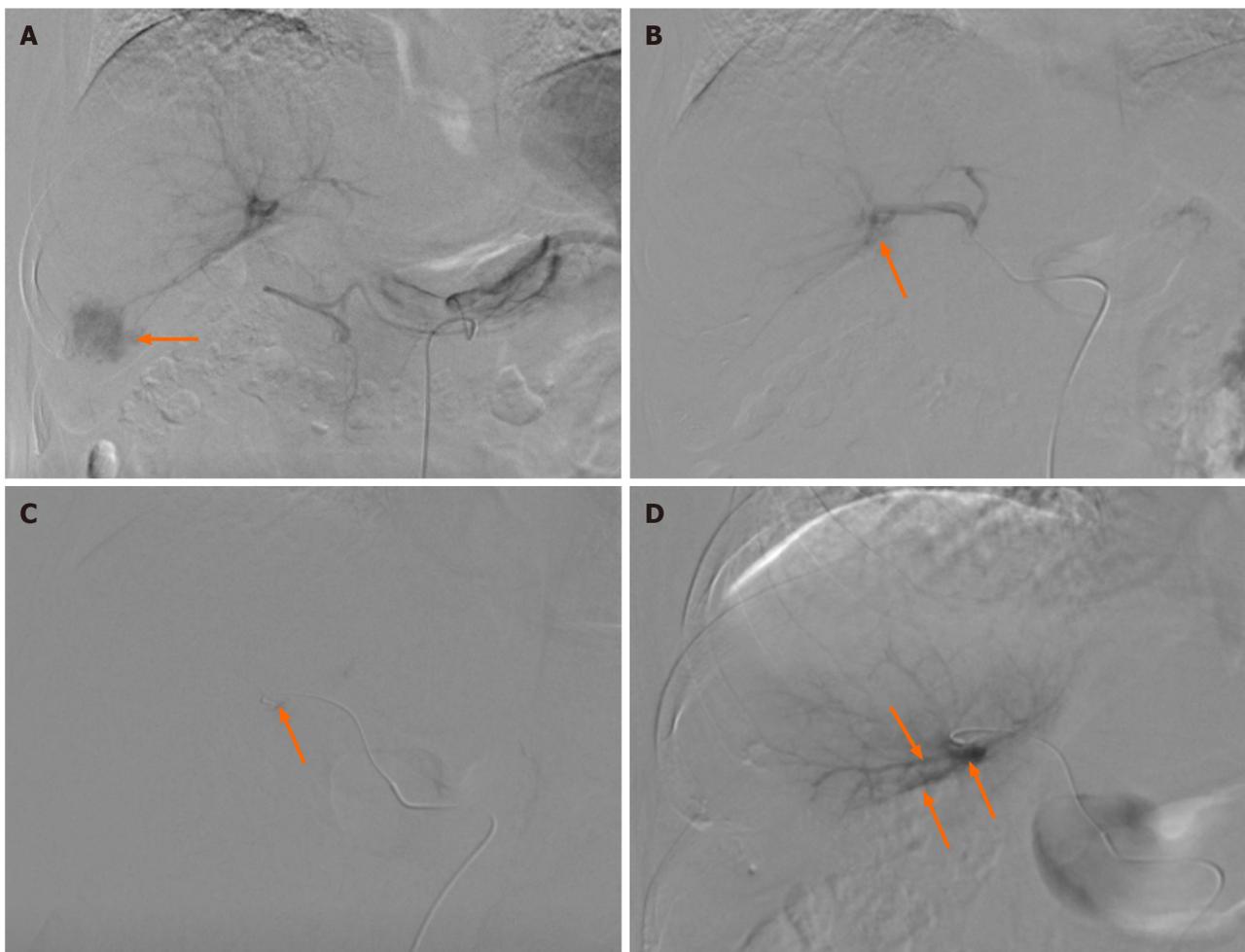
Participant characteristics

A consecutive series of 91 patients were enrolled in the study. During TACE, APFs were embolized using ESG in 46 participants and microspheres in 45 participants. The ratios of men to women were 33/13 in group E and 33/12 in group M ($\chi^2 = 0.029$, $P = 0.865$), with a mean age of 63.4 ± 8.5 and 58.4 ± 10.1 years ($P = 0.092$), respectively. The etiologies included hepatitis B virus (HBV) (38/46, 82.6% in group E; 39/45, 86.7% in group M), hepatitis C (4/46, 8.7% in group E; and 2/45, 4.4% in group M), HBV + hepatitis C virus (2/46, 4.3% in group E; 2/45, 4.4% in group M), and alcohol consumption (2/46, 4.3% in group E; 2/45, 4.4% in group M) ($P = 0.952$). No significant differences in the Child-Pugh stage, BCLC stage, or tumor location were observed between the two groups. The mean tumor diameters were 6.8 ± 2.9 mm and 7.1 ± 1.6 mm in groups E and M ($P = 0.765$), respectively. Portal vein thrombi were identified in 24 participants (24/46, 52.2%) in group E and 22 participants (22/45, 48.9%) in group M ($\chi^2 = 0.098$, $P = 0.754$), respectively. The treatments administered before TACE included surgery, microwave ablation (MWA), radiofrequency ablation (RFA), TACE, radiation, and TACE + MWA/RFA. We observed no significant differences in previous treatments between the

Table 1 Grading of arterioportal fistula

Grade	Definition	Class
0	APFs were not observed	-
1	APFs flow to the subsegmental portal branch	Mild
2	APFs flow to the segmental portal branch	Moderate
3	APFs flow into the main portal branch of the ipsilateral lobe	Moderate
4	APFs flow into the main portal branch of the contralateral lobe and/or the main portal vein	Severe
5	APFs flow into the main portal vein presenting with hepatofugal portal venous flow	Severe

APF: Arterioportal fistula.



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Figure 1 Digital subtraction angiography of the tumor and shunt. A: Angiography of the celiac artery shows liver tumor staining (orange arrow) in segment VI; B: Angiography of the proper hepatic artery shows hepatic arterioportal shunt. The orange arrow indicates the branch of the portal vein; C: The feeding artery (orange arrow) of the shunt is super-selected with a microcatheter; D: Angiography with the microcatheter shows the branches of the portal vein (orange arrow).

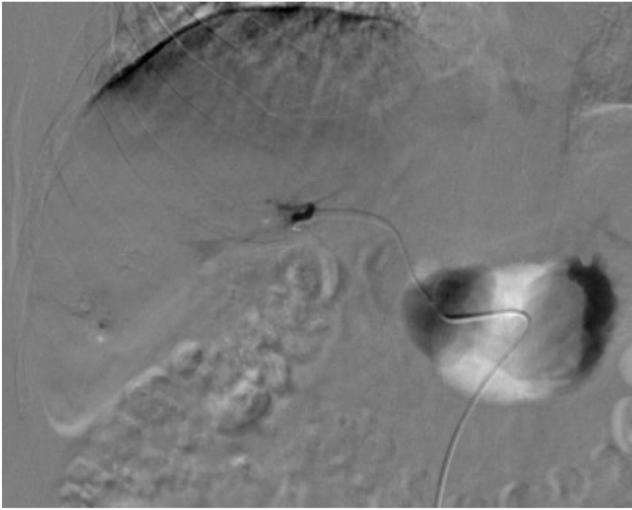
two groups ($P = 0.925$). The median levels of AFP were 137 [interquartile range (IQR): 9.8, 970.1] and 114.9 (IQR: 3.7, 725.7) ng/mL in groups E and M, respectively ($P = 0.734$). APF grades 1, 2, 3, 4, and 5 were recorded in 5 (5/46, 10.9%) and 6 (6/45, 13.3%); 15 (15/46, 32.6%) and 16 (16/45, 35.6%); 11 (11/46, 23.9%) and 14 (14/45, 31.1%); 9 (9/46, 19.6%), and 7 (7/45, 15.6%); and 6 (6/46, 13%) and 2 (2/45, 4.4%) participants in groups E and M, respectively ($P = 0.636$) (Table 2).

The mean follow-up period was 35.3 ± 2.7 mo in group E and 30.9 ± 3.8 mo in group M ($P = 0.195$). After 4 mo, complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were achieved in 18 (18/46, 39.1%) and 8 (8/45, 17.8%) patients; 21 (21/46, 45.7%) and 18 (18/45, 40%) patients; 4 (4/46, 8.7%) and 15 (15/45, 33.3%) patients; and 3 (3/46, 6.5%) and 4 (4/45, 8.9%) participants in groups E and M, respectively ($P = 0.014$). The DCR

Table 2 Demographic and baseline characteristics

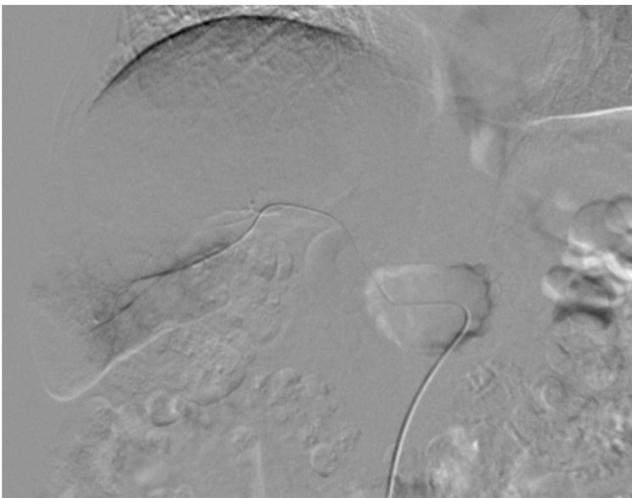
Characteristics	E group (n = 46)	M group (n = 45)	χ^2	P value
Sex, n (%)			0.029	0.865
Male	33 (71.7)	33 (73.3)		
Female	13 (28.3)	12 (26.7)		
Age (yr)	63.4 ± 8.5	58.4 ± 10.1	-	0.092
Etiology, n (%)			0.909	0.952
HBV	38 (82.7)	39 (86.8)		
HCV	4 (8.7)	2 (4.4)		
HBV + HCV	2 (4.3)	2 (4.4)		
Alcohol	2 (4.3)	2 (4.4)		
Child-Pugh stage, n (%)			0.297	0.586
A	25 (54.3)	27 (60)		
B	21 (45.7)	18 (40)		
BCLC stage, n (%)			0.271	0.873
A	7 (15.2)	6 (13.3)		
B	19 (41.3)	21 (45.7)		
C	20 (43.5)	18 (40)		
Tumor location			0.837	0.658
Right lobe	30 (65.2)	28 (62.2)		
Left lobe	9 (19.6)	10 (22.2)		
Right and left lobes	7 (15.2)	7.1 ± 1.6		
Mean tumor diameter (cm)	6.8 ± 2.9		-	0.765
Portal vein thrombus			0.098	0.754
Present	24 (52.2)	22 (48.9)		
Absent	22 (47.8)	23 (51.1)		
Previous treatment			1.639	0.925
Surgery	7 (15.2)	6 (13.3)		
MWA/RFA	9 (19.6)	7 (15.6)		
TACE	4 (8.7)	5 (11.1)		
Radiation	4 (8.7)	6 (13.3)		
TACE + MWA/RFA	2 (4.3)	3 (6.7)		
None	20 (43.5)	18 (40)		
AFP [ng/mL, median (IQR)]	137 (9.8, 970.1)	114.9 (3.7, 725.7)	-	0.734
APF grade, n (%)			2.689	0.636
1	5 (10.9)	6 (13.3)		
2	15 (32.6)	16 (35.6)		
3	11 (23.9)	14 (31.1)		
4	9 (19.6)	7 (15.6)		
5	6 (13)	2 (4.4)		

HCV: Hepatitis C virus; BCLC: Barcelona Clinic Liver Cancer; MWA: Microwave ablation; RFA: Radiofrequency ablation; TACE: Transcatheter arterial chemoembolization; AFP: Alpha-fetoprotein; IQR: Interquartile range; APFs: Arterioportal fistulas.



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Figure 2 Repeated angiography confirmed completed embolization of the shunt.



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Figure 3 Angiography performed to confirm complete embolization of the tumor.

was 93.5% (43/46) in group E and 91.1% (41/45) in group M ($P = 0.714$). The ORRs were 91.3% (42/46) and 66.7% (30/45) in groups E and M, respectively ($P = 0.004$).

The APFs immediately improved after the procedure in 43 (43/46, 93.5%) and 40 (40/45, 88.9%) participants in groups E and M, respectively ($P = 0.485$). After 2 mo, APF improvement was achieved in 37 (37/46, 80.4%) and 33 (33/45, 73.3%) participants in groups E and M, respectively ($P = 0.421$). The median AFP levels at 4 mo after the procedure were 28.48 (IQR: 4, 257.9) and 45.25 (IQR: 4.43, 359.5) ng/mL in groups E and M, respectively ($P = 0.045$). After 4 mo, the difference in Child-Pugh class distribution between the two groups was not significant ($P = 0.083$) (Table 3).

The OS was 26.2 ± 1.4 and 20.6 ± 1.1 mo in groups E and M, respectively ($\chi^2 = 10.3$, $P = 0.004$; Figure 4A) (Table 3). The PFS was 16.6 ± 1.0 and 13.8 ± 0.7 mo in groups E and M, respectively ($P = 0.012$; Figure 4B) (Table 3).

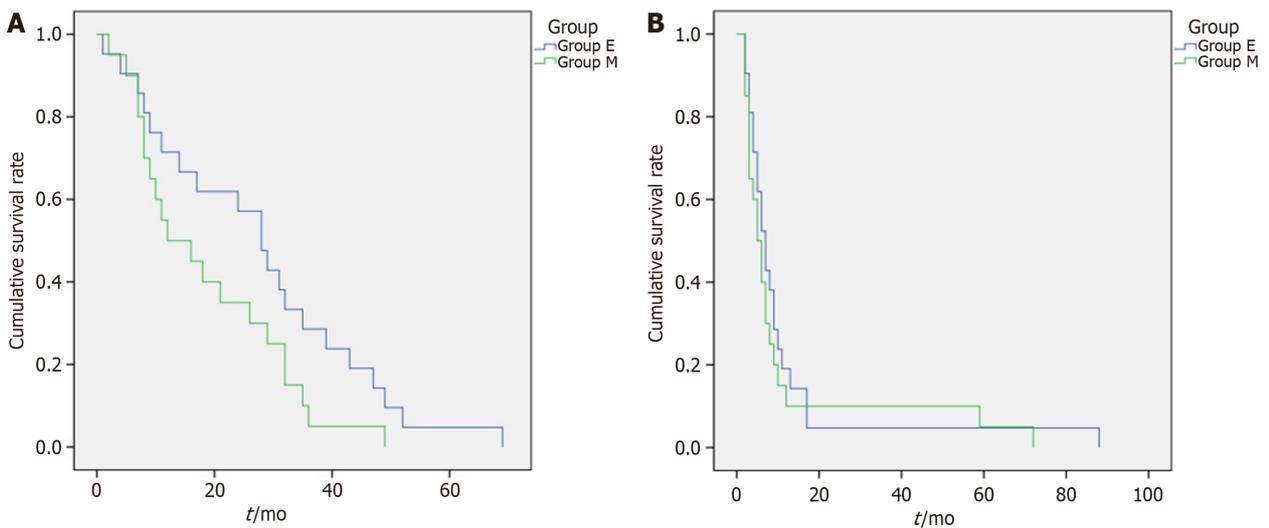
DISCUSSION

According to the updated BCLC prognosis and treatment strategy[16], TACE is recommended for intermediate-stage B HCC. With its tendency to infiltrate the portal and hepatic venous structures, HCC is often accompanied by APFs, which may reduce the therapeutic benefits of TACE[7]. Our study focused on comparing ESG and microspheres for the treatment of hepatic APFs. The DCRs were 93.5% (43/46) in group E and 91.1% (41/45) in group M ($P = 0.714$). The ORRs were 91.3% and 66.7% in groups E and M, respectively ($P = 0.004$). The OS was 26.2 ± 1.4 and 20.6 ± 1.1 mo in groups E and M, respectively ($P = 0.004$). The PFS was 16.6 ± 1.0 and 13.8 ± 0.7 mo in groups E and M, respectively ($P = 0.012$; Figure 4B) (Table 3).

Table 3 Outcome characteristics

Characteristics	E group (n = 46)	M group (n = 45)	χ^2	P value
Tumor response after four months (%)			10.578	0.014
CR	18 (39.1)	8 (17.8)		
PR	21 (45.7)	18 (40)		
SD	4 (8.7)	15 (33.3)		
PD	3 (6.5)	4 (8.9)		
DCR	43 (93.5)	41 (91.1)		0.714
ORR	42 (91.3)	30 (66.7)	8.358	0.004
Immediate improvement of APF (%)			-	0.485
Yes	43 (93.5)	40 (88.9)	-	
No	3 (6.5)	5 (11.1)		
First-time follow-up APF improvement (%)			0.646	0.421
Improved	37 (80.4)	33 (73.3)		
Not improved	9 (19.6)	12 (26.7)		
AFP after 4 mo [ng/mL, median (IQR)]	28.48 (4, 257.9)	45.25 (4.43, 359.5)		0.045
Child-Pugh score after 4 mo (%)			5.321	0.083
A	33 (71.7)	23 (51.1)		
B	10 (21.7)	20 (44.4)		
C	3 (6.6)	2 (4.5)		
OS, months (mean \pm SD)	26.2 \pm 1.4	20.6 \pm 1.1	10.3	0.004
PFS, months (mean \pm SD)	16.6 \pm 1.0	13.8 \pm 0.7	6.3	0.012

CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; DCR: Disease control rate; ORR: Objective response rate; APFs: Arterioportal fistulas; AFP: Alpha-fetoprotein; AP: Arterioportal; IQR: Interquartile range; OS: Overall survival; PFS: Progression-free survival.



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Figure 4 The Kaplan-Meier curve. A: Overall survival; B: Progression-free survival.

Gelatin sponges and microspheres have several disadvantages in the treatment of hepatic APF. Gelatin sponges are absorbed 2-3 wk after the procedure, and APFs can be recanalized. Microspheres exerted a physical embolic effect without causing protein degradation in the vascular wall. Ethanol has been widely used in the embolization of arteriovenous malformations[17], which can denature blood proteins, dehydrate vascular endothelial cells, and cause segment fractures in the vascular wall[18-20]. Compared to gelatin sponges alone, ethanol demonstrated an improved long-term effect on hepatic APFs[21]. However, because of its liquid properties, ethanol alone is not suitable for shunts with high blood flow. ESG combines the advantages of ethanol and gelatin sponges, promoting local control of hepatic APFs and liver tumors[12].

In our study, the immediate improvement and first-time follow-up rates of APFs in group E were not significantly higher than those in group M (93.5% and 88.9%, $P = 0.485$, 80.4% and 73.3%, $P = 0.421$, respectively). Thus, ESG and microspheres may have similar short-term effects on the treatment of hepatic APFs. The immediate improvement rate in group E was comparable to the 97% reported by Zhou *et al*[12], whereas the first follow-up APF improvement rate was higher in both groups than that reported by Zhou *et al*[12] (54%). This discrepancy may be attributed to the higher proportion of patients with grades 1-3 APFs in our study.

Our study investigated tumor response 4 mo after the procedure and revealed that the CR, PR, SD, and PD rates were 39.1% and 17.8%, 45.7% and 40%, 8.7% and 33.3%, and 6.5% and 8.9% in groups E and M, respectively ($P = 0.014$). Moreover, the ORR was 84.8% and 57.8% in groups E and M, respectively ($P = 0.004$). Compared with microspheres, ESG led to complete long-term control of hepatic APF, including physical blockade and chemical destruction and yielded a significantly better local tumor response. Both the DCRs (93.5%) and ORRs (84.8%) in group E patients were higher than those reported in Zhou *et al*'s study (81.9% and 42.6%, respectively)[12]. This has three possible reasons. First, the tumor response in our study was evaluated 4 mo after the procedure, which provided an additional opportunity for tumor control. Second, the percentage of participants with portal vein thrombus (52.5%) was lower than that reported by Zhou *et al*'s study[12]. Third, the proportion of grade 1-3 APFs in our study was higher, resulting in a better embolic response.

The OS, PFS, and median AFP levels at 4 mo after the procedure in group E were significantly better than those in group M. The aforementioned outcome may be attributed to the complete blockage of hepatic APFs and well-controlled tumors. Compared with microspheres, ESG embolization demonstrated complete long-term blockade of hepatic APFs and therefore improved the local control of HCC and survival of patients with HCC.

Nevertheless, the study had some limitations. As this was a retrospective study, selection bias may have reduced the value of the results. However, further prospective studies are required to validate the findings.

CONCLUSION

Compared to microsphere embolization, ESG embolization resulted in a higher ORR and longer OS and PFS. The findings may contribute to the selection of embolic agents for treating hepatic APFs in patients with HCC.

ARTICLE HIGHLIGHTS

Research background

Hepatic arterioportal fistulas (APFs) are common in hepatocellular carcinoma (HCC) because of tumor infiltration, vascular damage, and remodeling of the cirrhotic parenchyma. The presence of hepatic APFs often complicates anti-tumor treatments, including transarterial chemoembolization (TACE).

Research motivation

Ethanol-soaked gelatin sponges (ESG) combine the advantages of alcohol and gelatin sponges, demonstrating a convincing effect at different stages of hepatic APFs. However, to date, no study has compared the efficacy of ESG and microspheres.

Research objectives

This retrospective study aimed to compare the efficacy of ESG and microspheres in the management of APFs, and their impact on the prognosis of HCC.

Research methods

The APFs were embolized using ESG (group E) or microspheres (group M) during TACE. The disease control rate (DCR) and objective response rate (ORR) were considered the primary outcomes. The secondary outcomes included immediate and first follow-up APF improvement, overall survival (OS), and progression-free survival (PFS).

Research results

The DCR was 93.5% and 91.1% in groups E and M, respectively ($P = 0.714$). The ORRs were 91.3% and 66.7% in groups E and M, respectively ($P = 0.004$). In 43 (93.5%) patients in group E and 40 (88.9%) patients in group M, the APFs improved immediately after the procedure ($P = 0.485$). After 2 mo, APF improvement was achieved in 37 (80.4%) and 33 (73.3%) participants in groups E and M, respectively ($P = 0.421$). The OS was 26.2 ± 1.4 and 20.6 ± 1.1 mo in groups E and M,

respectively ($P = 0.004$). The PFS was 16.6 ± 1.0 and 13.8 ± 0.7 mo in groups E and M, respectively ($P = 0.012$).

Research conclusions

Compared with microspheres, ESG embolization demonstrated a higher ORR and longer OS and PFS in patients with HCC with hepatic APFs.

Research perspectives

The findings may aid the selection of embolic agents for the treatment of hepatic APFs in patients with HCC.

FOOTNOTES

Author contributions: Yuan GS and Zhang LL have contributed equally to this work; Yuan GS and Liu B performed the conception and design; Guo L and Liu B contributed to the administrative support; Zhang LL, Chen ZT, and Zhang CJ performed the provision of study materials and patients; Chen ZT, Tian SH, Gong MX, Wang P, Guo L, and Shao N performed the data collection and assembly; Chen ZT and Zhang CJ contributed to the data analysis and interpretation; All authors wrote the manuscript and performed the final approval of manuscript.

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