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ABOUT COVER

AIMS AND SCOPE

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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The *WJGO* is now abstracted and indexed in PubMed, PubMed Central, Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2024 edition of Journal Citation Reports® cites the 2023 journal impact factor (JIF) for *WJGO* as 2.5; JIF without journal self cites: 2.5; 5-year JIF: 2.8; JIF Rank: 71/143 in gastroenterology and hepatology; JIF Quartile: Q2; and 5-year JIF Quartile: Q2. The *WJGO*'s CiteScore for 2023 is 4.2 and Scopus CiteScore rank 2023: Gastroenterology is 80/167; Oncology is 196/404.

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ORIGINAL ARTICLE

Observational Study

Small particle drug-eluting beads-transarterial chemoembolization combined with targeted therapy in the clinical treatment of unresectable liver cancer

Jing-Song Qi, Peng Zhao, Xiao-Bo Zhao, Yong-Li Zhao, Ying-Chang Guo

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Abstract

BACKGROUND

Liver cancer is a highly malignant tumor with significant clinical impact. Chemotherapy alone often yields suboptimal outcomes in both the short and long term, characterized by high rates of local recurrence and distant metastasis, leading to a poor long-term prognosis.

AIM

To evaluate the clinical efficacy of small particle drug-eluting beads-transarterial chemoembolization (DEB-TACE) combined with targeted therapy for the treatment of unresectable liver cancer.

METHODS

We analyzed clinical data from 74 patients with unresectable liver cancer admitted between January 2019 and December 2020. Based on the different treatment regimens administered, patients were divided into the control (36 patients receiving sorafenib alone) and joint (38 patients receiving small particle DEB-TACE combined with sorafenib) groups. We compared liver function indicators [alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), albumin (ALB)] and serum tumor markers [alpha feto-protein (AFP)] before and after treatment in both groups. Short-term efficacy measures [complete response (CR), partial response, progression disease, stable disease, objective response rate (ORR), and disease control rate (DCR)] were assessed post-treatment. Long-term follow-up evaluated median overall survival (OS), progression-free survival (PFS), and adverse reaction rates between the two groups.

RESULTS

One month post-treatment, the joint group demonstrated significantly higher rates of CR, ORR, and DCR compared to the control group ($P < 0.05$). Three days after treatment, the joint group showed elevated levels of ALT, AST, and TBIL but reduced levels of ALB and AFP compared to the control group ($P < 0.05$). The median OS was 18 months for the control group and 25 months for the joint group, while the median PFS was 15 months for the control group and 22 months for the joint group, with significant differences observed (log-rank: $\chi^2 = 7.824$, 6.861, respectively; $P = 0.005$, 0.009, respectively). The incidence of adverse reactions was not significantly different between the groups ($P > 0.05$).

CONCLUSION

The combination of small particle DEB-TACE and sorafenib significantly improves both short- and long-term outcomes in the treatment of unresectable liver cancer while preserving liver function.

Key Words: Small particle; Drug-eluting beads-transarterial chemoembolization; Sorafenib; Treatment; Unresectable liver cancer

Core Tip: This study compared the efficacy of single-agent sorafenib targeted therapy and its combination with small particle drug-eluting beads-transarterial chemoembolization (DEB-TACE) in patients with unresectable liver cancer. The results demonstrate that combining small particle DEB-TACE with sorafenib significantly enhances both short- and long-term treatment outcomes compared to single-agent therapy. This combination approach improves liver function, reduces tumor marker levels, boosts overall treatment efficacy, and enhances patient prognosis. This approach is safe, reliable, and holds significant clinical utility.

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INTRODUCTION

Liver cancer is the most prevalent primary liver tumor and is associated with a poor prognosis and high mortality due to its asymptomatic nature and the presence of underlying liver cirrhosis, which facilitates rapid invasive growth[1,2]. Surgical intervention remains crucial for long-term survival; however, most patients are diagnosed at an advanced stage, limiting the possibility of surgical options[3]. Therefore, non-surgical treatments such as transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) have become standard therapies for unresectable liver cancer[4-7].

Recent advancements in embolization materials have introduced drug-eluting beads (DEBs), which carry anti-tumor agents such as doxorubicin and epirubicin. DEBs offer a prolonged and localized release of high-concentration drugs, leading to improved therapeutic outcomes compared to traditional TACE, effectively compensating for its shortcomings [8,9]. Small particle (70-150 μm) drug-eluting beads-transarterial chemoembolization (DEB-TACE) has shown promising results in the interventional treatment of tumors such as liver cancer[10]. Sorafenib, a widely used first-line therapy, targets and inhibits programmed death 1, demonstrating significant therapeutic effects in primary liver cancer[11,12]. This study aimed to evaluate the clinical efficacy of combining small particle DEB-TACE with sorafenib in treating unresectable liver cancer, assessing the potential benefits of this combined treatment regimen.

MATERIALS AND METHODS

Patient data

We collected clinical data from 74 individuals with unresectable liver cancer who were admitted to our hospital's inpatient department between January 2019 and December 2020. Patients were divided into two groups based on their treatment regimens: The control group (36 patients receiving sorafenib alone) and the joint group (38 patients receiving small particle DEB-TACE combined with sorafenib). Table 1 displays the clinical characteristics of all patients, revealing no statistically significant differences in baseline data between the two groups ($P > 0.05$), indicating their comparability [13,14].

Table 1 Comparison of baseline data in the two groups

Characteristics		Control group, *n* = 36	Joint group, *n* = 38	χ^2/t	*P* value
Sex	Male	19	21	0.046	0.830
	Female	17	17		
Age in years	-	54.26 ± 6.18	53.99 ± 6.03	0.190	0.850
Number of tumors	1	12	15	0.820	0.664
	2	7	9		
	≥ 3	17	14		
Maximum tumor diameter in cm	-	8.13 ± 0.65	8.40 ± 0.72	1.690	0.095
HBV-DNA in IU/mL	≤ 100	20	15	1.918	0.166
	> 100	16	23		
Child-Pugh grading[13]	A	28	24	1.891	0.169
	B	8	14	1.921	0.383
ECOG scores in points[14]	0	15	20		
	1	16	11		
	2	5	7		
PVTT	Presence	9	12	0.394	0.530
	Absence	27	26		

Data are *n* or mean ± SD. ECOG: Eastern Cooperative Oncology Group performance status; HBV: Hepatitis B virus; PVTT: Portal vein tumor thrombus.

Inclusion and exclusion criteria

Inclusion criteria: Patients diagnosed with unresectable liver cancer according to established diagnostic criteria[15], confirmed by imaging or clinical pathology, with at least one measurable lesion; Child-Pugh liver function classification of grade A or B; Eastern Cooperative Oncology Group performance status scores between 0 and 2; No complete occlusion of the main portal vein; expected survival of more than 6 months; age 18 years or older; complete case data and ability to comply with follow-up requirements.

Exclusion criteria: Patients with concurrent malignancies at other sites; patients with local or systemic liver infections; Child-Pugh liver function classification of grade C; coagulation abnormalities; previous anti-tumor treatments such as radiotherapy or ablation therapy; contraindications to chemotherapy or targeted drugs; contraindications to interventional surgery; pregnancy; missing clinical data, mental abnormalities, or inability to comply with the study or follow-up. This study was approved by the medical ethics committee of our hospital, and all patients provided written informed consent.

Methods

In the control group, patients received oral sorafenib, specifically Sorafenib Tosylate Tablets (Decamet, Chongqing Yaoyou Pharmaceutical Co., Ltd., NMPA approval number: H20203403), with a dosage of 200 mg per tablet. The daily dose was 400 mg (2 tablets) administered once daily.

In the joint group, patients were treated with DEB-TACE in combination with sorafenib. The procedure was performed with the patient in a supine position using routine disinfection and draping and local anesthesia. A 5F vascular sheath was inserted into the right femoral artery *via* the Seldinger percutaneous surgical technique, followed by catheterization with a 5F RH catheter for angiography of the abdominal cavity. Digital subtraction angiography images were obtained during the arterial, parenchymal, and venous phases to assess tumor location, size, number, and arterial blood supply. Under fluoroscopic guidance, 1 g fluorouracil and 8 mL iodinated oil were injected through the catheter for infusion chemotherapy with a perfusion duration of 20 min, resulting in visible iodinated oil deposition in the liver lesions. Subsequently, a mixture of DEBs (70-150 μm in diameter, containing 60 mg epirubicin) was infused through the catheter at a rate of 1 mL/min until tumor vascular enhancement was no longer visible, indicating successful embolization. After embolization, the catheter sheath was removed, and the patient was kept supine postoperatively. The puncture site was compressed for hemostasis for 8 h and then bandaged. The right lower limb was immobilized for 24 h with careful monitoring for bleeding at the puncture site. Postoperative care included hydration, diuresis, pain relief, acid suppression, liver protection, and other symptomatic treatments. The nursing care level was adjusted based on the patient's condition 24 h later, with observation for adverse reactions and timely management. If the target dose was fully infused without reaching the embolization endpoint, additional blank microspheres were administered until the embolization endpoint was achieved.

The initial DEB-TACE treatment was scheduled 2-3 weeks after starting sorafenib therapy, which was maintained at the same dosing regimen as the control group. Sorafenib was temporarily discontinued 2 days before and after the interventional treatment and resumed on the third postoperative day. The daily dose was gradually increased from 400 mg/day to 800 mg/day. In the event of adverse reactions, the dose was reduced back to 400 mg/day or administered every other day based on patient tolerance. DEB-TACE was repeated if imaging showed incomplete tumor necrosis, tumor regrowth, or new lesions during follow-up with intervals longer than 2 months.

Post-operation follow-up

Patients were first re-examined 1 month after surgery, with subsequent examinations every 3 months. These examinations included routine blood tests, upper abdominal computed tomography (CT) or magnetic resonance imaging (MRI) scans, liver function tests, kidney function tests, and liver cancer marker assays.

Postoperative follow-up was conducted *via* telephone or hospital visits to monitor disease progression and adverse events. The follow-up period for this study concluded on April 30, 2024.

Evaluation of short-term efficacy

Following the Response Evaluation Criteria in Solid Tumors[16], short-term efficacy was assessed 1 month after surgery. Complete response (CR): disappearance of enhancement in target lesions during the arterial phase; partial response (PR): total sum of the longest diameters of target lesions reduced by ≥ 30%; progression disease (PD): total sum of the longest diameters of target lesions increased by at least 20%, with an absolute increase in the total sum of the longest diameters > 5 mm, or appearance of new lesions; stable disease (SD): Disease status that does not meet the criteria for CR, PR, or PD.

Objective response rate (ORR) = (CR + PR)/total number of cases × 100%. Disease control rate (DCR) = (CR + PR + SD)/total number of cases × 100%.

Long-term efficacy assessment

Long-term efficacy was evaluated by calculating progression-free survival (PFS) and overall survival (OS) for patients in both groups. PFS refers to the time from the start of treatment until disease progression, death due to any cause, or the end of follow-up. OS refers to the time from the start of treatment until death due to any cause or the end of follow-up.

Safety evaluation

Safety was assessed according to the Common Terminology Criteria for Adverse Events 5.0[17] developed by the National Cancer Institute of the United States. Adverse events such as embolism syndrome, fatigue, abnormal liver function, rash, bone marrow suppression, gastrointestinal reactions, and hand-foot syndrome were recorded. The overall incidence rate of these adverse events was calculated for both groups.

Statistical analysis

Data were analyzed using SPSS 22.0 software. Measurement data were represented as mean ± SD. One-way analysis of variance was used for comparisons among multiple groups, and *t*-tests were employed for comparisons between two groups. Enumeration data were presented as percentages, and the χ^2 test was used for comparisons. A significance level of $P < 0.05$ was considered statistically significant.

RESULTS

Short-term efficacy in both groups

According to the criteria for assessing tumor efficacy, the efficacy of both groups of patients was evaluated 1 month after surgery using enhanced X-ray CT or MRI. In the joint group, the outcomes were as follows: 19 patients achieved CR, 13 achieved PR, 4 had SD, and 2 experienced PD. The ORR and DCR rates in the joint group were 81.58% and 84.74%, respectively, which were significantly higher than those in the control group ($P < 0.05$), as shown in Table 2 and Figure 1A. These results indicate that the combination of small particle DEB-TACE and sorafenib provided superior short-term efficacy compared to sorafenib alone.

Comparison of liver function and tumor markers between the two groups before and after treatment

There were no significant differences in liver function tests (ALT, AST, TBIL, ALB) and tumor marker AFP levels between the two groups before treatment ($P > 0.05$). Three days post-treatment, the joint group showed elevated levels of ALT, (49.63 ± 5.18 U/L), AST (65.71 ± 7.04 U/L), and TBIL (30.08 ± 4.11 μmol/L), while ALB (28.73 ± 2.99 g/L) and AFP (114.65 ± 12.05 μg/L) were lower compared to the control group with statistically significant differences ($P < 0.05$), as detailed in Table 3. These findings suggest that the combination therapy with small particle DEB-TACE more efficaciously protected liver function, attenuated serum tumor marker levels, and exhibited superior anti-tumor and hepatoprotective effects.

Comparison of long-term prognosis between the two groups

Both patient groups were followed for over 3 years to assess long-term prognosis. The median OS was 18 months in the control group and 25 months in the joint group (log-rank: $\chi^2 = 7.824$, $P = 0.005$), as illustrated in Figure 1B. The median PFS was 15 months in the control group and 22 months in the joint group (log-rank: $\chi^2 = 6.861$, $P = 0.009$), as shown in Figure 1C. These results confirm that the combination of small particle DEB-TACE with sorafenib not only achieves better

Table 2 Comparison of tumor response 1-month postoperatively between the two groups, *n* (%)

Efficacy	Control group, *n* = 36	Joint group, *n* = 38	χ^2	*P* value
CR	9 (25.00)	19 (50.00)	4.912	0.027
PR	14 (38.89)	13 (34.21)	0.175	0.676
SD	5 (13.89)	4 (10.53)	0.196	0.658
PD	8 (22.22)	2 (5.26)	4.549	0.033
ORR	23 (63.89)	32 (81.58)	4.000	0.045
DCR	28 (77.78)	36 (94.74)	4.549	0.033

CR: Complete response; DCR: Disease control rate; ORR: Objective response rate; PD: Progression disease; PR: Partial response; SD: Stable disease.

Table 3 Comparison of liver function and tumor markers between the two groups before and after treatment

Indicator	Treatment period	Control group, *n* = 36	Joint group, *n* = 38	χ^2/t	*P* value
ALT in U/L	Pre	39.41 ± 4.28	38.89 ± 4.55	0.506	0.615
	Post	45.12 ± 5.37	49.63 ± 5.18	3.677	0.001
AST in U/L	Pre	52.76 ± 8.33	53.02 ± 6.74	0.148	0.883
	Post	58.35 ± 6.92	65.71 ± 7.04	7.532	< 0.001
TBIL in μmol/L	Pre	20.01 ± 3.16	19.66 ± 2.25	0.551	0.583
	Post	25.41 ± 3.79	30.08 ± 4.11	5.073	< 0.001
ALB in g/L	Pre	37.85 ± 4.01	37.99 ± 3.32	0.164	0.870
	Post	32.66 ± 3.45	28.73 ± 2.99	5.245	< 0.001
AFP in μg/L	Pre	215.43 ± 20.77	218.96 ± 23.63	0.681	0.498
	Post	186.75 ± 15.46	114.65 ± 12.05	22.442	< 0.001

Data are mean ± standard deviation. AFP: Alpha fetoprotein; ALB: Albumin; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin.

short-term efficacy but also offers significant benefits in long-term prognosis.

Comparison of the occurrence of adverse reactions between the two groups

Common adverse reactions included embolism syndrome, fatigue, abnormal liver function, rash, bone marrow suppression, gastrointestinal reactions, and hand-foot syndrome. The total incidence of adverse reactions within the control group reached 19.44%, whereas in the joint group, it was 28.95%. However, this difference was not statistically significant ($P > 0.05$), as presented in Table 4. This suggests that the addition of small particle DEB-TACE does not significantly increase the incidence of adverse reactions in individuals with unresectable liver cancer, indicating that the combined regimen is relatively safe and manageable.

DISCUSSION

Surgical resection remains the most conventional and direct method for treating liver cancer. However, due to the propensity for early dissemination within the liver, to the capsule, abdominal lymph nodes, and blood vessels in the early stages, many patients are diagnosed at a stage where surgical intervention is no longer feasible[18,19]. Conversion treatment represents a promising approach for advanced liver cancer, aiming to transform unresectable liver cancer into resectable cancer through various strategies. These include local treatments [TACE, TARE, or hepatic artery infusion chemotherapy (HAIC)], systemic treatments (targeted therapy or combination immunotherapy), and combination therapies (TACE combined with radiotherapy, TACE combined with targeted therapy, TAIC combined with targeted therapy or immunotherapy) to optimize patient survival outcomes[20,21].

Traditional TACE employs iodinated oil as an embolic agent mixed with chemotherapy drugs, selectively injected into tumor-feeding arteries to induce ischemic damage, hypoxic damage, and cytotoxic effects on tumors[22,23]. However, the iodinated oil emulsion can facilitate the systemic dissemination of chemotherapy drugs, potentially increasing systemic adverse reactions and reducing drug concentration at the tumor site, which may diminish overall efficacy[24]. In contrast,

Table 4 Comparison of adverse reaction occurrence between the two groups, *n* (%)

Adverse reaction	Control group, *n* = 36	Joint group, *n* = 38	χ^2	*P* value
Embolism syndrome	0 (0)	2 (5.26)		
Fatigue	1 (2.78)	1 (2.63)		
Abnormal liver function	2 (5.56)	1 (2.63)		
Rash	1 (2.78)	2 (5.26)		
Bone marrow suppression	0 (0)	1 (2.63)		
Gastrointestinal reaction	2 (5.56)	2 (5.26)		
Hand-foot syndrome	1 (2.78)	2 (5.26)		
Total incidence	7 (19.44)	11 (28.95)	0.907	0.341

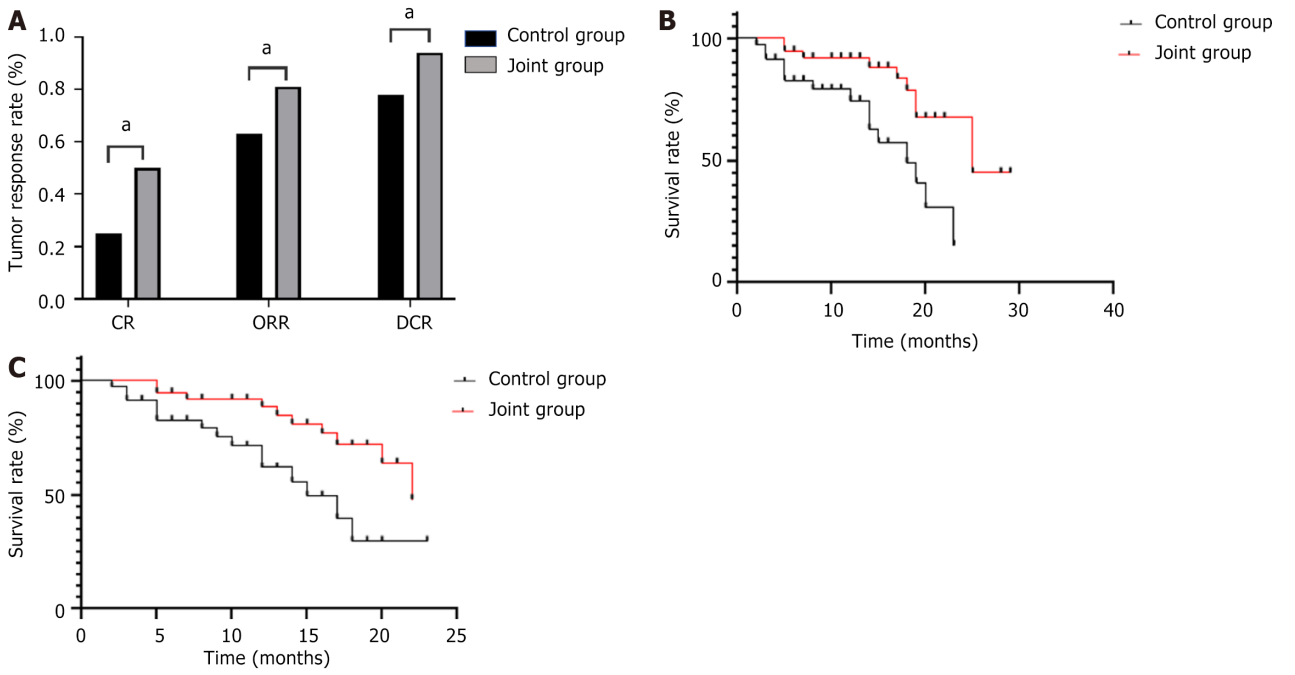

Figure 1 Tumor response 1 month after surgery in the two groups and survival curve graph. A: Tumor response 1-month postoperatively in the two groups. [a]*P* < 0.05; B: Survival curve graph of overall survival in both groups; C: Survival curve graph of progression-free survival in both groups. CR: Complete response; DCR: Disease control rate; ORR: Objective response rate.

small particle DEB-TACE represents an advanced TACE technology that delivers chemotherapy drugs continuously through small particle DEBs, extending the duration of drug action. This approach generally yields superior treatment outcomes compared to traditional TACE. Research by Kondo *et al*[25] demonstrated that DEB-TACE combined with low-dose HAIC significantly improves ORR and OS in individuals with advanced liver cancer, positioning it as an economical and effective treatment option for patients with advanced HCC. Wen *et al*[26] identified DEB-TACE as an independent predictor for achieving CR in patients with liver cancer, and univariate Cox regression analysis further indicated that DEB-TACE is a predictor of prolonged PFS and OS. These findings underscore the efficacy of DEB-TACE in treating liver cancer, consistent with the results of our study.

Our research findings indicate that patients receiving combined treatment with small particle DEB-TACE and sorafenib showed significantly improved outcomes compared to those receiving sorafenib monotherapy. Specifically, the joint group exhibited higher rates of CR, ORR, DCR, ALT, AST, and TBIL levels compared to the control group, whereas ALB and AFP levels were lower in the joint group. The median OS and PFS in the joint group were 25 months and 22 months, respectively, both of which were significantly longer than those observed in the control group ($P < 0.05$). Although the incidence of adverse reactions was slightly higher in the combined treatment group compared to the control group, the difference was not statistically significant ($P > 0.05$). These results underscore that combining small particle DEB-TACE with sorafenib significantly improved short-term efficacy in patients with unresectable liver cancer. Additionally, this combination effectively protects liver function, reduces tumor marker levels, and improves both short-term and long-term prognoses without significantly increasing adverse reactions. This treatment approach proves to be safe, reliable, and efficient in treating unresectable liver cancer, demonstrating substantial clinical value. Our findings are consistent

with those of Wang *et al*[27], who reported that small particle DEB-TACE combined with irinotecan provided superior ORR and PFS compared to C-TACE combined with irinotecan in unresectable intrahepatic cholangiocarcinoma. Moreover, studies also report that compared to TACE patients receiving conventional treatment, patients receiving sorafenib DEB-TACE exhibit better prognosis and survival rates, attenuated tumor volume, and decreased tumor marker levels. Furthermore, DEB-TACE with Callispheres has been shown to preserve liver function and mitigate irinotecan toxicity without increasing adverse reactions[28]. The superior efficacy and safety of our study protocol may be attributed to several factors: (1) Small particle DEB-TACE addresses the limitations of traditional embolic agents by improving efficacy for tumors with challenging blood supply patterns or suboptimal outcomes from iodinated oil deposition[29,30]; and (2) Oral administration of sorafenib for at least 2 weeks before the first small particle DEB-TACE enhances tumor blood supply and reduces postoperative hypoxia-induced factors, laying the foundation for improved therapeutic effects and greater treatment efficacy[31,32].

While this study confirms the value of combining small particle DEB-TACE with targeted therapy in unresectable liver cancer, it has certain limitations. For instance, it is a single-center retrospective study with a small sample size, which may introduce potential biases. Further research should aim to validate these findings through large-sample, multicenter, prospective studies.

CONCLUSION

In conclusion, the combination of small particle DEB-TACE and sorafenib therapy demonstrates precise efficacy in treating unresectable liver cancer, offering significant improvements in both short-term and long-term outcomes, prolonged patient survival, preserving liver function, and enhancing prognosis. This approach provides a safe, reliable, and effective treatment option with considerable therapeutic value. Furthermore, these findings enable clinicians to tailor strategies based on individual patient conditions and tumor characteristics to enhance patient prognosis.

FOOTNOTES

Author contributions: Qi JS conceptualized the study and supervised the project; Qi JS and Zhao P collected data, preformed the research, wrote the manuscript and prepared the original draft; Zhao XB, Zhao YL and Guo YC did the validation, investigation, and analysis of the data; All authors have reviewed, edited, read and approved the final manuscript.

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