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Combining localised and systemic therapy options for advanced hepatocellular carcinoma

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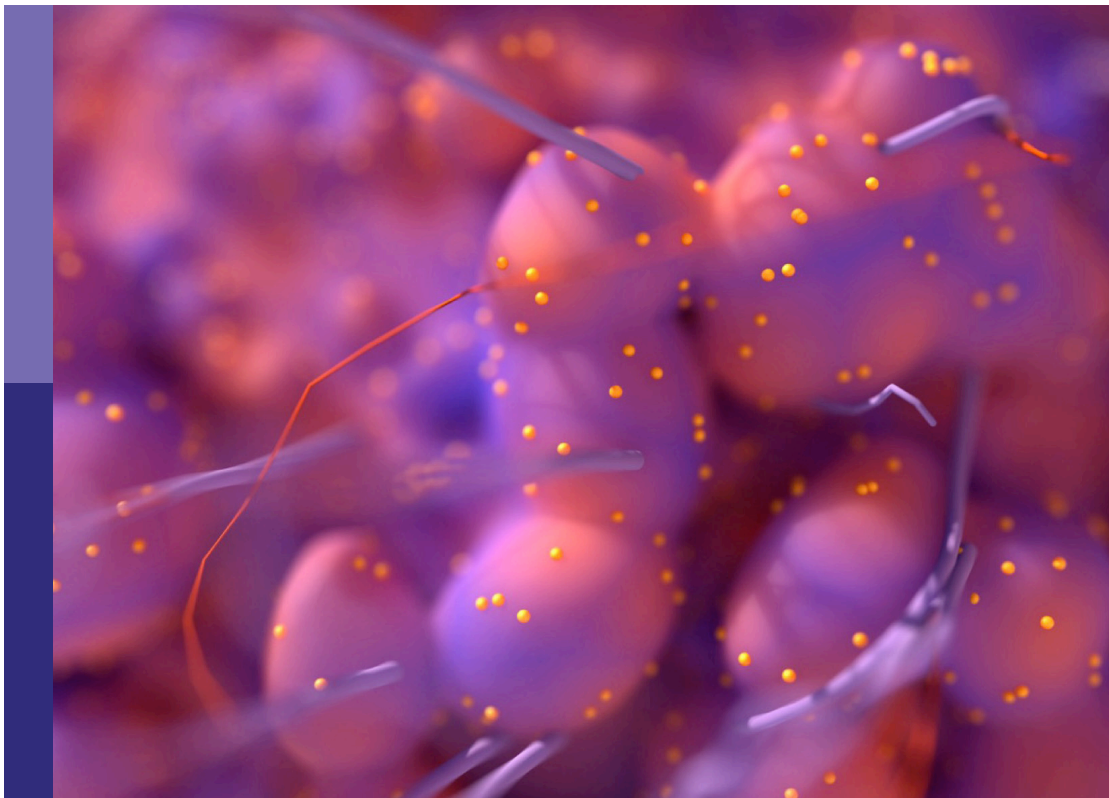

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Combining localised and systemic therapy options for advanced hepatocellular carcinoma

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Evaluation of D-TACE combined with endovascular brachytherapy for HCC with MPVTT

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Background: Hepatocellular carcinoma (HCC) patients with main portal vein tumor thrombus (MPVTT) may be able to have TACE through stent implantation into the portal vein with thrombosis to recover portal blood flow.

Purpose: The goal of this study was to compare clinical results of conventional transcatheter arterial chemoembolization (C-TACE) and doxorubicin-eluting bead transcatheter arterial chemoembolization (D-TACE) combined with endovascular brachytherapy in HCC patients with MPVTT.

Methods: This study was a retrospective controlled study with follow-up dates spanning from Mar 2015 to Feb 2020. Patients with both HCC and MPVTT were divided into two groups. Portal vein stents with iodine-125 seed strands were implanted first; then, C-TACE or D-TACE was administered to all patients. Objective response rates were assessed.

Results: A total of 26 patients were enrolled, with 13 in each group. During follow-up, the portal stent patency times were 112.3 ± 98.2 days in the C-TACE group and 101.7 ± 90.4 days in the D-TACE group. The time to disease progression was 42 days in the C-TACE group and 120 days in the D-TACE group (p=0.03). The overall survival time from the first intervention procedure was 216 days in the C-TACE group and 239 days in the D-TACE group (p=0.047). The D-TACE group was superior to the C-TACE group in terms of progression-free survival (PFS) and overall survival (OS) times.

Conclusion: Endovascular implantation of brachytherapy combined with TACE is safe and effective in HCC patients with MPVTT. This combination therapy may be helpful for survival benefits to patients with stage BCLC-C HCC.

KEYWORDS

hepatocellular carcinoma, portal vein, stents, endovascular brachytherapy, chemoembolization, doxorubicin-eluting beads

Background

Hepatocellular carcinoma (HCC) is a common malignant tumor. HCC patients with main portal vein tumor thrombus (MPVTT) often miss the opportunity for transcatheter arterial chemoembolization (TACE), a preferred nonsurgical option for liver cancer, because MPVTT is a relative contraindication for TACE. Previous studies have demonstrated that this type of patient may be able to have TACE through stent implantation into the portal vein with thrombosis to recover portal blood flow (1). The implantation of a radioactive seedling tent into the portal vein stent combined with TACE and MPVTT increases the stent patency rate and survival time (2, 3). Conventional TACE (C-TACE) embolic materials are always based on iodinated oil. A recent study reported the application of new embolic material loaded with doxorubicin class drug-eluting beads (DEB). Preliminary results show that the efficacy of DEB-TACE (D-TACE) in HCC is good and has low toxicity (4). However, whether D-TACE has greater survival benefits is still controversial (5). A DEB product, DC Bead™ (Biocompatibles UK Ltd.), has been officially approved by the China Food and Drug Administration and launched in China. However, few studies have examined the effects of radioactive seed stent implantation in a portal vein stent combined with D-TACE.

This preliminary study aimed to investigate the feasibility and safety of implanting a radioactive seed stent in a portal vein stent combined with TACE in HCC patients with MPVTT, and it compared the clinical effects of combined therapies with C-TACE or D-TACE.

Methods

Subjects

In this retrospective controlled study, 26 HCC patients with MPVTT were consecutively enrolled from March 1, 2015, to August 31, 2019 with subsequent follow-ups until February 29, 2020.

The included patients met the following conditions: age 18 to 80 years; diagnosis met the pathological or clinical diagnostic criteria of HCC; CT or MRI imaging showed that portal vein thrombosis involved the portal vein trunk and primary branch, but that the contralateral primary branch was not completely occluded; the liver function stage was Child-Pugh class A/B; patients had no extensive extrahepatic metastases; and the Eastern Cooperative Oncology Group (ECOG) score of the patient was 0–2. Due to economic constraints or concerns about the side effects of targeted drugs, these patients were not able to combine targeted drugs at the same time. All patients signed informed consent forms for this study.

Patients were excluded for the following reasons: the liver function stage was Child-Pugh class C; the patient had other serious diseases and could not complete treatment; or the patient had bleeding tendency with elongated coagulation time.

Intervention procedures

All patients underwent radioactive seeding in the portal vein immediately followed by C-TACE or D-TACE. First, under the guidance of ultrasound, the portal vein branch of the uninvolved liver lobe was percutaneously punctured and a vascular sheath was inserted. Second, angiography was performed over the main portal vein stenosis segment with a 4F pigtail catheter (Cordis, USA), and the pressure was measured. The diameter and length of the stent as well as the number of required iodine-125 (^{125}I) seeds were based on the stenosis segment length. The stents should extend 1 cm beyond each end of the tumor thrombus. The number of ^{125}I seeds (0.6 mCi/tablets, Shanghai Xinke Pharmaceutical Co., Ltd.) were calculated using the formula [stenosis length (mm)/4.5+2] to ensure that the radiation range of implanted ^{125}I seeds completely covered the portal vein thrombosis segment. The required ^{125}I seedlings were encapsulated in a 3F sterile sheath and developed into a seed strand. Third, the stents and the ^{125}I seed strips were placed into the portal vein vessels of the stenosis segments under the guidance of the X-ray perspective. Fourth, portal vein angiography was performed with the pigtail catheter; the pressure at this time was measured again. The liver puncture channel was blocked with a 5 mm × 5 cm coil (Cook Company, USA).

In the C-TACE group, the lipiodol dosage was based on lesion size. A tumor with a diameter of 1 cm corresponded to 1 ml of lipiodol with a maximum dose of 20 ml. Epirubicin (40 mg, Pharmorubicin, Pfizer) was mixed with the lipiodol, forming an emulsion. In the D-TACE group, the doxorubicin-eluting (DC) bead diameters were 300 μm to 500 μm. One to two bottles were used based on lesion size, each containing 40 mg epirubicin. After combining the epirubicin with DC beads, a nonionic contrast agent iopamidol injection (370 mg I/mL) was mixed at a 1:1 proportion. TACE was performed using the femoral artery approach. The abovementioned embolic agents were slowly injected into the tumor-feeding artery for embolization after superselective catheterization. Gelatin sponges were added to strengthen the embolism.

Patients received liver protection treatment with symptomatic and supportive treatment for 7 to 8 days after interventional procedures. Blood tests, liver renal function tests, and electrolytes were measured at 3 days, 7 days, 14 days and 30 days after the procedures. Complications were recorded and treated accordingly. Follow-up was performed every 3 months after the initial treatment. The clinical results mainly includes the changes of liver function, complications, the time to disease

progression (estimated using enhanced abdominal CT or abdominal MRI) and survival rate. Objective response rates were assessed, and TACE treatments were performed as needed. The patency of the portal stent was compared between the two groups. The median progression-free survival (PFS) and overall survival (OS) times were assessed after long-term follow-up.

Statistical analyses

The statistical analyses were performed using SPSS statistical software, version 23 (IBM, Armonk, NY, USA). A paired t-test was used to compare the changes in portal vein pressure before and after stent implantation. The Mann-Whitney test was used to compare the liver function and stent patency of the two groups. Progression-free survival and overall survival were analyzed with Kaplan–Meier and log-rank tests. All data are expressed as the mean ± SEM (standard error of the mean) of n independent measurements. GraphPad Prism 7 software (GraphPad, San Diego, CA, USA) was used to plot the graphs. A value of $P < 0.05$ was considered as statistically significant.

Results

Patients characteristics

Twenty-six patients (aged 40-78 years) were included in the analysis. Table 1 shows the patients' general information. The median age of the C-TACE group (9 men and 4 women) was 54.5 years; in the D-TACE group (11 men and 2 women), the median age was 56 years. Based on BCLC staging criteria, the all the patients were in stage C. Based on the Child-Pugh classification standard of liver function, in the C-TACE group, 9 cases were Child-Pugh class A, the other 4 cases were class B, and the mean Child-Pugh score was 6.15 ± 0.90. In the D-TACE group, 11 cases were Child-Pugh class A, the other 2 cases were class B, and the mean Child-Pugh score was 5.77 ± 0.73. No significant differences were found between the two groups (Mann-Whitney U=64.5, p=0.31). All patients had HCC lesions. In the C-TACE group, there were 4 cases in the left liver and 9 cases in the right liver. In the D-TACE group, there was one case in the left liver and all other cases were in the right liver. All the patients had tumor-side portal vein branch thrombus and MPVTT. Among these, 6 cases were accompanied by contralateral first level portal vein branch tumor thrombi in the C-TACE group and 4 cases were accompanied by contralateral first level portal vein branch tumor thrombi in the D-TACE group. There was no significant difference in post embolization syndrome between two groups.

Effect of interventional therapy

All the patients successfully underwent stent implantation of a radioactive seed into the portal vein followed by TACE treatment. In the C-TACE group (Figure 1), 13 stents were implanted (diameter: 8-14 mm, length: 60–90 mm), 13^{125}I radioactive seeds were used (a total of 204^{125}I seeds, with an average of 16 per strip), and 10.6 ml of lipiodol was used in each case on average. Fifty milligrams of epirubicin were mixed with lipiodol for each case, and 15 boxes of gelatin sponges were used to enhance embolization. In the D-TACE group (Figure 2), 13 stents were implanted (diameter: 8-14 mm, length: 40-94 mm), and 13^{125} I radioactive seeds were used (a total of 181^{125}I seeds, with an average of 14 per stripe); 18 bottles of DC beads were used; and five boxes of gelatin sponges were used to enhance embolization. Each bottle of DC beads contained a mixture of 40 mg of epirubicin.

Intraoperative angiography of the portal vein showed that the portal vein length of the tumor thrombus was 25.3 to 95.2 mm (average: 46.6 ± 19.1 mm) in the C-TACE group and 17.6 to 65.7 mm (average: 38.8 ± 16.5 mm) in the D-TACE group. In the C-TACE group, the average pressure of the distal main portal vein was 28.3 ± 11.2 cmH_2O and 23.6 ± 10.2 cmH2O before and after stent implantation, respectively, a decrease of 4.6 ± 3.0 cmH_2O,

TABLE 1 General information.

		C-TACE group	D-TACE group
Number of cases		13	13
Male: female		9:4	11:2
Average age (years)		54.5 ± 9.9	56.0 ± 9.2
CPC	A	9 (69.2%)	11 (84.6%)
	B	4 (30.8%)	2 (15.4%)
Primary tumor	left lobe: right lobe	4:9	1:10
	length (cm)	11.2 ± 1.3	10.0 ± 1.1
Other metastasis		none	none
VP class		VP 4 (100%)	VP 4 (100%)

CPC, Child-Pugh class; VP class, portal vein tumor thrombosis classification according to the Liver Cancer Study Group of Japan

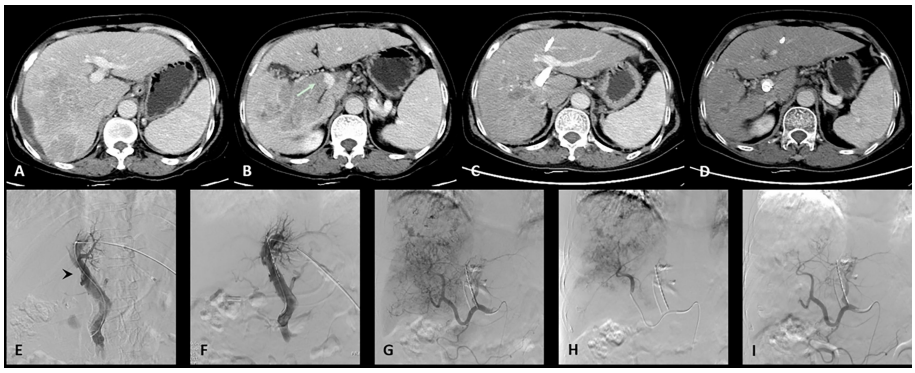

FIGURE 1
One case of the C-TACE group. The patient was a 60 years old female. **(A)**: Preoperative CT images showed a huge tumor in the right lobe of the liver. **(B)**: Tumor thrombus (arrow) was seen in the right branch and main portal vein. **(C)**: After 3 months follow up, the tumor was significantly reduced. **(D)**: The patency of portal vein stent was revealed after 3 months follow up. **(E)**: Filling defect was showed in the main portal vein (arrow head) during venography. **(F)**: Portal vein stent (diameter: 12 mm, length: 60 mm) was implanted and 12 125I radioactive seeds were used. **(G)**: Hepatic artery angiography showed large tumor staining of the right lobe of the liver. **(H)**: Superselective embolization of the tumor artery branches with 50 milligrams of epirubicin mixed with 10 ml lipiodol and 1 box of gelatin sponges was used to enhance embolization. **(I)**: Angiography after embolization, tumor blood supply was significantly reduced.

but the difference before and after stent implantation was not statistically significant (U=74.5, P=0.62). In the D-TACE group, the average pressures were 25.2 ± 12.3 cmH_2O and 20.2 ± 11.7 cmH_2O, respectively, a decrease of 5.0 ± 4.4 cmH2O, which was also not statistically significant (U=62.5, P=0.27). The difference in the magnitude of pressure decrease between the two groups was not statistically significant (U=74.5, P=0.62).

The alanine aminotransferase (ALT), aspartate aminotransferase (AST) and serum total bilirubin (TBil) levels significantly increased at 3 days and 7 days after the procedures but returned to preoperative levels after 30 days (Table 2). There were no significant differences in Child-Pugh scores between the two groups before the procedures (p=0.47) or at 3 days (p=0.77), 7 days (p=0.66), 14 days (p=0.47), and 30 days (p=0.56) after the procedures (Figure 3).

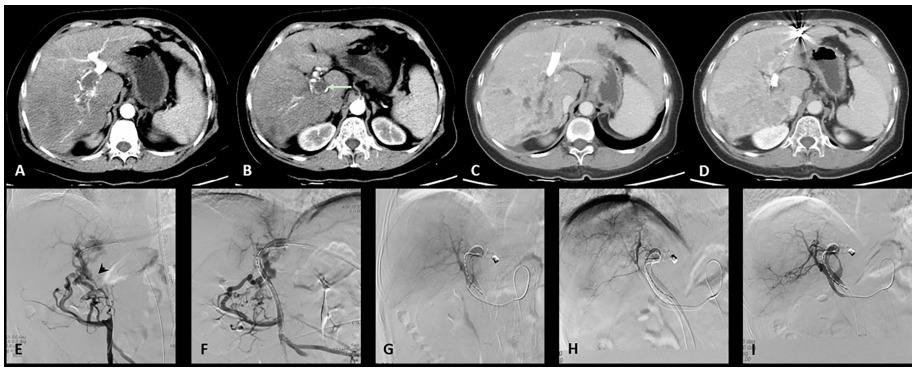

FIGURE 2
One case of the D-TACE group. The patient was a 69 years old female. **(A)**: Preoperative CT images showed a huge tumor in the right lobe of the liver. **(B)**: Tumor thrombus (arrow) was seen in the right branch and main portal vein. **(C)**: After 3 months follow up, the tumor was significantly reduced. **(D)**: The patency of portal vein stent was revealed after 3 months follow up. **(E)**: Filling defect was showed in the main portal vein (arrow head) during venography. **(F)**: Portal vein stent (diameter: 10 mm, length: 94 mm) was implanted and 20 125I radioactive seeds were used. **(G)**: Hepatic artery angiography showed large tumor staining of the right lobe of the liver. **(H)**: Superselective embolization of the tumor artery branches with 40 milligrams of epirubicin mixed with one bottle of DC beads. **(I)**: Angiography after embolization, tumor blood supply was significantly reduced.

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TABLE 2 Liver function parameters before and 3 days, 7 days, 14 days, 30 days after interventional procedures.

		ALT (IU/L)	AST (IU/L)	TBil (μmol/L)	Child-Pugh score
C-TACE group	pre	48.6 ± 28.9	84.6 ± 43.7	30.6 ± 19.1	5.7 ± 1.3
	3d	100.3 ± 151.0	210.0 ± 356.5	37.6 ± 19.9	6.8 ± 1.9
	7d	132.6 ± 154.7	176.1 ± 135.0	48.5 ± 42.9	6.8 ± 1.0
	14d	90.7 ± 29.9	106.0 ± 58.0	103.6 ± 122.9	6.8 ± 0.7
	30d	34.5 ± 54.7	108.8 ± 56.8	53.3 ± 94.2	6.3 ± 0.9
D-TACE group	pre	53.8 ± 42.8	93.2 ± 54.5	21.0 ± 7.0	5.3 ± 1.3
	3d	451.3 ± 462.8	590.3 ± 428.9	47.9 ± 26.9	6.7 ± 2.0
	7d	200.8 ± 222.6	116.2 ± 67.6	51.6 ± 27.9	6.6 ± 1.3
	14d	121.7 ± 75.7	127.0 ± 121.4	123.1 ± 165.2	6.5 ± 1.3
	30d	47.7 ± 45.1	117.5 ± 145.8	51.5 ± 77.7	6.0 ± 1.2

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBil, serum total bilirubin.

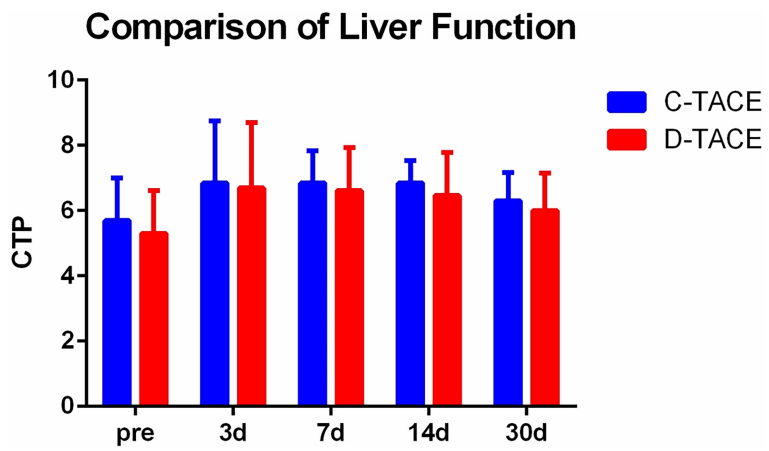

FIGURE 3
Comparison of liver function. There were no significant differences in Child-Pugh scores between the two groups before the procedures (p=0.47) or at 3 days (p=0.77), 7 days (p=0.66), 14 days (p=0.47), and 30 days (p=0.56) after the procedures.

No patient in either group had serious complications such as puncture bleeding, abdominal bleeding, tumor rupture, gastrointestinal bleeding, liver abscess, or bile aneurysm. Postoperative adverse reactions included postembolization syndrome, nausea, pain, fever and fatigue, all of which significantly improved after symptomatic treatment. Two patients with myocardial damage had chest discomfort and pain within 24 hours after the procedures in the D-TACE group treated with 80 mg (mixed with 2 bottles of DC beads) and 40 mg epirubicin (mixed with 1 bottle of DC beads), respectively. No abnormal electrocardiogram findings were observed, but the serum levels of AST, lactate dehydrogenase (LDH), and N-terminal pro B-type natriuretic peptide (NT-proBNP) within 24 hours after the procedures had transient increases. After oxygen therapy, sublingual nitroglycerin and other treatments, the indicators of myocardial damage gradually decreased after 3 days.

Results of follow-up

The stent patency time of the two groups was 112.3 ± 98.2 days in the C-TACE group and 101.7 ± 90.4 days in the D-TACE group, and there was no significant difference between the groups (U = 84, p> 0.99) (Figure 4).

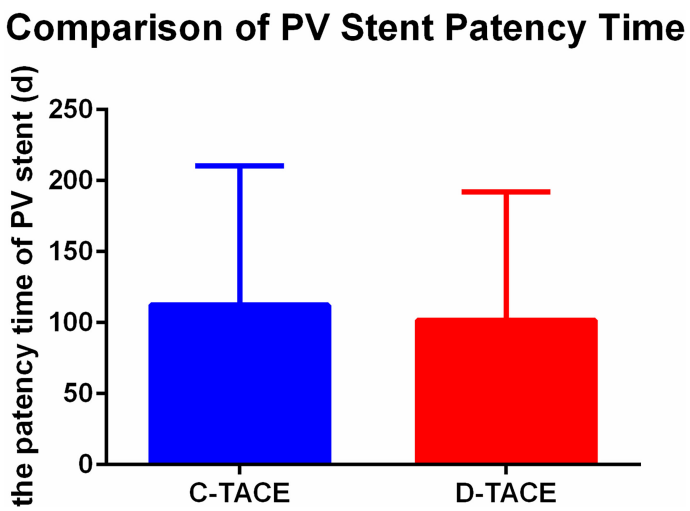

FIGURE 4
Comparison of PV stent patency time. The stent patency times of the two groups were 112.3 ± 98.2 days in the C-TACE group and 101.7 ± 90.4 days in the D-TACE group, and there was no significant difference between the groups (U = 84, p> 0.99).

According to the mRECIST criteria (6), the increased enhanced tumor tissue volume in CT or MRI images was used as the basis for evaluating disease progression. The median progression-free survival times of the two groups were 42 days and 120 days, respectively—significantly longer in the D-TACE group than in the C-TACE group (p = 0.03) (Figure 5A). By the end of the 5-year follow-up, 3 patients in the D-TACE group still survived. From the initial diagnosis, the overall survival times were 235 days and 357 days in the two groups (p=0.02) (Figure 5B). From the first interventional procedures, the overall survival times of the two groups were 216 days and 239 days, respectively (p=0.047) (Figure 5C). The difference was statistically significant: the D-TACE group was superior to the C-TACE group regarding both PFS and OS.

Discussion

Portal vein stents for HCC patients with MPVTT

This study demonstrated that endovascular implantation of a stent with a ^{125}I seed strand combined with D-TACE is a safe and effective option for managing HCC patients with MPVTT. Portal vein thrombosis is an important factor in the prognosis of HCC patients. For unresectable cases including those with major vessel invasion, many community hospitals do not attempt active oncologic therapy. Recently, some studies have suggested that local treatment including radiotherapy will have survival benefits for these patients (7, 8). Other methods based

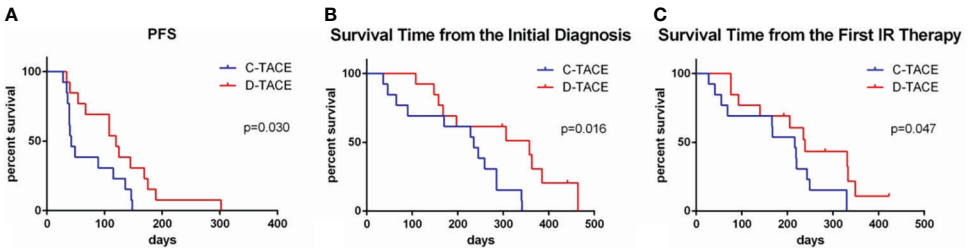

FIGURE 5
Comparison of PFS and OS in the two groups. The median progression-free survival times of the two groups were 42 and 120 days, respectively (p = 0.030). From the initial diagnosis, the overall survival times of the two groups were 235 days and 357 days (p=0.02). From the first interventional procedures, the overall survival times of the two groups were 216 days and 239 days, respectively (p=0.047).

on C-TACE combined with targeted drugs, radiation therapy, or thermal ablation also have been reported (9–11). Portal vein revascularization through endovascular stenting is also one of the ways to solve this difficult problem with improvement of liver parenchymal perfusion, relieving sequelae of portal hypertension and regaining of subsequent liver function (12). In this study, the mean stent portal vein pressure was 28.3 ± 11.2 cmH_2O in the C-TACE group and 25.2 ± 12.3 cmH_2O in the D-TACE group, which decreased to 23.6 ± 10.2 cmH2O and 20.2 ± 11.7 cmH_2O, respectively, after the stent implantations, suggesting that implanting portal vein stents may decrease the portal vein pressure and reduce the risk of secondary gastrointestinal bleeding in patients with MPVTT.

Impact of endovascular brachytherapy

Endovascular brachytherapy with ^{125}I seeds can be continuously performed and has a long half-life (approximately 60.1 d). Close contact with the tumor tissue under the continuous emission of X-rays and γ-rays from the ^{125}I seed can destroy the double-stranded DNA of tumor cells and inhibit the growth of tumor thrombi (13). Local irradiation can also inhibit vascular endothelial proliferation (14) and prolong the duration of stent patency. In this study, an appropriate amount of ^{125}I seeds were packaged into 3F sterile sheaths to develop seed strains based on tumor thrombus length (measured by main portal vein angiography); then, the patients were synchronously implanted with a portal vein stent and the stent was expanded. The ^{125}I seed strains were fixed to the tumor thrombus site, effectively preventing loss and displacement. Portal vein stent implantations were successfully completed in all the patients and the ^{125}I seed strains were implanted, suggesting that this combined therapy method is highly feasible. All patients successfully completed the procedures under local anesthesia with good tolerance in this study.

The combined toxicity of endovascular brachytherapy and TACE needs attention. Some literatures have confirmed that the combination of radiation therapy and TACE does not cause significant adverse effects on liver function with the grade 3 toxicity rates ranged from 3.5% to 5.7% (15, 16). Other studies have shown (17) that compared with C-TACE, patients' tolerance of D-TACE is better, with less-severe liver toxicity and fewer doxorubicin-related side effects. However, no study has reported the combination of endovascular brachytherapy and D-TACE in the treatment of HCC patients with MPVTT. The present study preliminarily explored the safety of this combination as well as the feasibility. Liver function was transiently abnormal but recovered gradually. The recovery of serum Tbil was slower than that of ALT and AST, which may be related to bile duct injury after embolism. The parameters of two patients with myocardial damage gradually decreased 2 to 3 days after oxygen therapy and nitroglycerin sublingual treatments. The epirubicin dosages of the two patients were 80 mg and 40 mg, respectively; based on patients' body surface area, these were not overdoses, suggesting the possible cardiotoxicity of D-TACE when loaded with epirubicin or doxorubicin. Therefore, patient heart function needs to be monitored closely and treated promptly. Overall, the combination of the implantation of radioactive seed stents into the portal vein and D-TACE in the treatment of HCC patients with MPVTT is both feasible and safe.

Comparison of C-TACE and D-TACE

D-TACE has been applied as a treatment for HCC for many years, and a number of clinical trials have demonstrated its safety (18) and effectiveness (4). A DC Bead® is a drug-loaded microsphere that was approved in China in August 2014. The bead can be loaded with doxorubicin, epirubicin, or irinotecan. After embolism, the drugs can be continuously released with a certain amount of compressibility, which can effectively block the target vessel. One prospective randomized controlled study (17) compared C-TACE with D-TACE in the treatment of HCC and found that the complete remission rate, objective response rate and disease control rate in the D-TACE group were higher than those in the C-TACE group (27% vs 22%, 52% vs 44%, and 63% vs 52%, respectively) but without significant differences. However, the objective response rate in the D-TACE group was significantly higher than that of the C-TACE group among cases with Child-Pugh grade B, ECOG score 1, involvement of two lobes, and relapse.

A randomized controlled study (19) compared the effectiveness of simple microembolization (BB group) and the drug doxorubicin in microsphere embolization (LCB group) in patients with HCC and found that the response rates (RECIST criteria) of the BB group and LCB group at the first revisit were 5.9% and 6.0%, respectively. The median PFS values of the BB group and LCB group were 6.2 months and 2.8 months, respectively, which were not significantly different. The median overall survival of the BB and LCB groups were 19.6 months and 20.8 months, respectively, which were not significantly different. The embolization effects of ordinary microspheres and drug-loaded adriamycin microspheres on HCC were not significantly different. Drug-loaded adriamycin microspheres may not be able to improve the effectiveness of liver cancer embolization. The long-term efficacy of D-TACE needs further investigation (20). Therefore, we followed up these cases for 5 years, a length of time that not only allows assessing the feasibility and safety of the combined treatment method but also objectively evaluating the long-term efficacy of the combined treatment. In our study, the D-TACE group was superior to the C-TACE group regarding both PFS and OS.

Compared with other studies, our patients had a relatively late disease course, showing that the combined treatment may have more advantages for patients with more severe disease.

Our study had some limitations. The sample size was relatively small. More cases are needed to reach more reliable results. All these patients were in the BCLC-C stage, and treatment with targeted drugs such as sorafenib may have yielded better results (21). However, due to economic constraints or concerns about the side effects of targeted drugs, these patients were not able to combine targeted drugs at the same time. Follow-up studies are also needed on patients who are being treated with combined targeted drug therapies.

In conclusion, the combination of the implantation of a radioactive seed stent to the portal vein and D-TACE in the treatment of HCC patients with MPVTT is both safe and feasible. This combination therapy may be helpful for survival benefits to patients with stage BCLC-C HCC.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZWu, WH and JGo contributed to conception and design of the study. JGu and QW organized the database. JL and QL performed the statistical analysis. WH and JGo wrote the first draft of the manuscript. JGu, XD and ZWa wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Clinical course and role of embolization in patients with spontaneous rupture of hepatocellular carcinoma

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Background: A diverse clinical course after the spontaneous rupture of hepatocellular carcinoma (HCC) renders nonstandardized treatment protocols.

Purpose: To evaluate clinical course and role of transcatheter arterial embolization (TAE) in patients with rupture of HCC.

Materials and methods: This retrospective study included 127 patients who were treated for ruptured HCC at single institution between 2005 and 2014. After multidisciplinary discussion, patients underwent medical management, TAE, emergency surgery or staged surgery. Patients were retrospectively divided into two groups based on the intent of treatment: curative and palliative. The rebleeding rate and 1-month and overall survival (OS) were compared between two groups. The incidence and survival of patients with intraperitoneal drop metastasis (IPDM) were also analyzed.

Results: The overall rebleeding rate in patients who underwent TAE was 3.1% (3/96). One-month mortality rate was 6.3% (8/127). The rebleeding and 1-month mortality rates were not significantly different between two groups. OS was significantly higher in the curative treatment group (median: 12.0 vs 2.2 months, $p<0.001$). Among 96 patients who initially received TAE, ten patients underwent staged operation (10.4%). The median OS for medical management, TAE, emergency surgery and staged surgery was 2.8, 8.7, 19.1 and 71.1 months, respectively. Of all patients, 15.2% developed IPDM mostly within 1 year and their survival was poorer than that of patients without IPDM (median: 6.3 vs. 15.1 months, $p<0.001$).

Conclusion: TAE provided effective immediate hemostasis with a low rebleeding rate and may serve as a bridge to elective surgery. IPDM frequently occurred within 1 year and manifested poor survival; thus, close surveillance should be considered for patients with spontaneous rupture of HCC.

KEYWORDS

hepatocellular carcinoma, spontaneous rupture, transcatheter arterial embolization, transcatheter arterial chemoembolization, intraperitoneal drop metastasis

Introduction

Spontaneous rupture of hepatocellular carcinoma (HCC) can manifest a wide spectrum of symptoms, from mild abdominal pain to abrupt hypovolemic shock, which result in a diverse clinical course. Its reported mortality rate is 25-75% (1, 2). Owing to the hypervascularity of HCC, timely intervention, including hemostasis and volume resuscitation in the acute phase, is vital to achieve hemodynamic stability in patients with ruptured HCC (3). Spontaneous rupture of the tumor also affects patients' long-term management plans even after successful recovery from acute hemodynamic instability. The incidence of intraperitoneal drop metastasis (IPDM) increases after HCC rupture because of potential tumor cell spillage in the peritoneal space, which hinders curative treatments after acute management (4–6). Therefore, patient management should be individualized in consideration of the initial manifestation, hepatic functional reserve, operability, and chance of IPDM.

Some studies have suggested treatment algorithms, but because of the lack of high-level evidence, the best treatment approach is still controversial, and patients with ruptured HCCs are largely treated using local protocols (3). Considering the high mortality rate (85-100%), conservative management should be reserved for patients in whom transarterial embolization (TAE) and surgery are not feasible because of poor liver function and advanced tumor stage (7, 8). Emergency surgery and TAE are the two main treatment modalities used to achieve immediate hemostasis. While surgery is advantageous for both hemostasis and tumor resection in a single operation procedure, TAE is less invasive, shows a relatively high success rate of hemostasis in the acute phase (53–100%) and has a lower 30-day mortality rate than surgery (0–37% vs. 28–75%) (9–13).

Considering the diverse clinical course following HCC rupture and various roles of TAE in each case, the effectiveness of TAE should be scrutinized separately for each situation. In addition, as the probability of IPDM is relatively high after spontaneous rupture of HCC, a longitudinal study on the development of IPDM is warranted. Therefore, this retrospective study was conducted to determine the role of TAE in acute management of HCC rupture and evaluate the development and clinical impact of IPDM.

Abbreviations: HCC, hepatocellular carcinoma; IPDM, intraperitoneal drop metastasis; OS, overall survival; TACE, transcatheter arterial chemoembolization; TAE, transcatheter arterial embolization.

Materials and methods

Patients

This retrospective study was approved by the institutional review board and the requirement for informed consent was waived. All patients diagnosed with HCC were retrospectively recorded in the institutional cohort, and the electronic database contained imaging findings from initial and subsequent studies. Among the 10536 patients who were initially diagnosed with HCC between January 2005 and December 2014, 133 were recorded as having imaging features suggestive of ruptured HCC. The patients' images were reviewed, and the records of 127 patients who met the imaging criteria for a ruptured HCC were finally analyzed (Figure 1).

Imaging evaluation of ruptured HCC

All patients underwent multiphase dynamic computed tomography (CT) or magnetic resonance (MR) imaging. The images were reviewed by two interventional radiologists (H.C.Kim and J.W.Choi with 15 and 4 years of experience in interventional oncology) in consensus. Ruptured HCC was diagnosed when a liver tumor with arterial-phase enhancement and portal- or delayed-phase washout abutted the liver surface and had one or more of the following findings: contrast media extravasation from the tumor to the peritoneum, tumor protrusion with hemoperitoneum, and focal discontinuity of the tumor surface with hemoperitoneum (14). In patients with ruptured HCC, the largest tumor size, number, distribution (unilobar and bilobar), vascular invasion, imaging signs of portal hypertension (ascites, varix, splenomegaly > 12 cm), extrahepatic

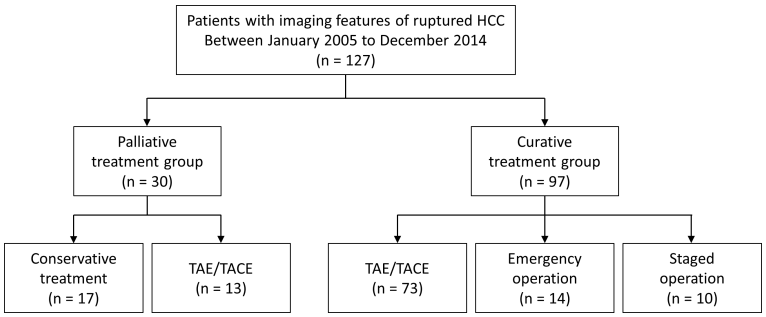

FIGURE 1
Flow chart of the study population. HCC, hepatocellular carcinoma; TAE, transcatheter arterial embolization; TACEm transcatheter arterial chemoembolization.

spread of HCC, and IPDM were also evaluated. IPDM was defined as a hypervascular intraperitoneal mass with or without central necrosis and engorgement of adjacent omental vessels (6). Two interventional radiologists also reviewed all follow-up liver CT and MRI scans of each patient to identify the occurrence of new or additional IPDMs.

Treatment of ruptured HCC

Tumor bleeding was initially managed by volume resuscitation, transfusion, or inotropic agents at the discretion of the attending physician. Emergency embolization was performed in patients with hemodynamic instability. Patients with terminal stage HCC and stable vital signs received supportive care only. Surgical resection was considered as the initial treatment for operable patients with stable vital signs. Operability was determined by consultation with hepatic surgeons or a multidisciplinary team. Interventional management was administered to patients who were not eligible for either surgery or supportive care. For these patients, interventional radiologists considered the vital signs, cancer stages, and liver functions, and performed transarterial chemoembolization (TACE) or TAE. TACE using iodized oil (Lipiodol Ultra-Fluid; Guerbet, Aulnay-Sous-Bois, France) plus doxorubicin chemoemulsion was primarily considered for most candidates, while TAE was preferred for patients with Child-Pugh class B or C, or hemodynamic instability. For both TACE and TAE, gelatin sponge particles were primarily used as embolic materials, but cyanoacrylate and iodized oil mixtures were also considered when contrast extravasation was evident on digital subtraction angiography and a microcatheter was advanced into the culprit arteries. After initial TACE or TAE, the operability of the patients was reassessed by a multidisciplinary conference of surgeons and interventional radiologists, and operable patients were treated with hepatic resection. The remaining patients were managed with subsequent TACE, systemic therapy, or supportive care at the discretion of the hepatologists.

Clinical data evaluation

Based on the review of electronic medical records, the management goal of ruptured HCCs was divided as curative treatment group and palliative treatment group. Surgical resection, staged surgical resection following TACE, and most TACE procedures were regarded as curative treatment, while selective TACE or TAE only for bleeding foci, and supportive care were considered as palliative treatment. With regard to the clinical course, two interventional radiologists (J.W.Chung and H.C.Kim with 27 and 15 years of experience in interventional oncology, respectively) reviewed all accessible medical records and images after tumor rupture to identify radiologically diagnosed rebleeding within 1 month, new development of IPDM within 5 years, and overall survival (OS). Anonymized survival data from the rupture of HCC were acquired from the Ministry of Interior and Safety of South Korea, which archives all citizens' survival data and updates them daily.

Statistical analysis

Demographic data of the curative treatment group and palliative treatment group were compared using the independent t-test and chi-square test. The 1-month rebleeding rates after interventional management with curative treatment (TACE) and palliative treatment (selective TACE only for bleeding foci, TAE) were compared using Fisher's exact test. The occurrence of IPDM in all patients and OS in each treatment group were evaluated using the Kaplan-Meier method and log-rank test. In the curative treatment group, the OS depending on each modality (TAE/TACE, surgery, and staged surgery) was also estimated for all patients. Statistical significance was set at $p < 0.05$. All statistical

analyses were performed using SPSS statistical software version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline patient characteristics

Among 127 patients with ruptured HCC, 97 and 30 were managed by curative treatment and palliative treatment, respectively (Table 1). Baseline laboratory findings, such as albumin, bilirubin, aspartate aminotransferase, and alkaline phosphatase levels were worse in the palliative treatment group (all $p < 0.05$). A higher proportion of patients in the palliative treatment group had ascites, portal hypertension and Child Pugh classes B and C (all $p < 0.001$). In terms of tumor characteristics, greater size, more infiltrative type of tumor, and more bilobar distribution were noted in the palliative treatment group (all $p < 0.01$). All these differences noted between the two groups were expected, considering that the patients in the palliative treatment group were treated with hemostasis as the main objective. Poor Child Pugh class, presence of ascites, portal hypertension, bilobar tumor distribution, and more infiltrative tumor type were noted in patients who underwent interventional treatment rather than emergency or staged surgery (all $p < 0.05$) (Table 2). Twelve patients (14.0%) who underwent TAE/TACE demonstrated contrast extravasation on digital subtraction angiography. In these cases, cyanoacrylate and iodized oil mixture was applied selectively to control the active bleeding.

In the curative treatment group, 14 (14.4%, 14/97), 10 (10.3%, 10/97), and 73 (75.3%, 73/97) patients underwent surgical resection as initial treatment, staged surgical resection following TACE, and TACE, respectively. In the palliative treatment group, 13 (43.3%, 13/30), and 17 (56.7%, 17/30) patients received TACE/TAE and supportive care, respectively (Supplementary Table 1).

TABLE 1 Characteristics of the study sample between curative and palliative treatment groups.

	Curative treatment group (n = 97)	Palliative treatment group (n = 30)	P value
Age	58 ± 13	59 ± 11	0.989
Sex (M/F)	88 (90.7)/9 (9.3)	26 (86.7)/4 (13.3)	0.504
Etiology			
HBV	60 (61.9)	26 (86.7)	**0.013**
HCV	7 (7.2)	2 (6.7)	1.000
Alcohol	18 (18.6)	1 (3.3)	**0.043**
Laboratory value			
Platelet ($\times 10^3/\mu\ell$)	223 ± 103	210 ± 98	0.531
Albumin (g/dL)	3.6 ± 0.6	3.0 ± 0.7	**<0.001**
Total bilirubin (mg/dL)	1.3 ± 0.8	2.2 ± 1.8	**0.011**
PT (INR)	1.15 ± 0.18	1.33 ± 0.49	0.060
Creatinine (mg/dL)	1.12 ± 0.73	1.13 ± 0.53	0.956
AST (IU/L)	112 ± 191	211 ± 232	**0.021**
ALT (IU/L)	70 ± 77	90 ± 89	0.231
ALP (IU/L)	133 ± 112	185 ± 123	**0.029**
GGT (IU/L)	201 ± 282	303 ± 177	0.174
AFP (ng/mL)	39016 ± 127314	97368 ± 339723	0.182
PIVKA (mAU/mL)	21634 ± 41490	39103 ± 34867	0.245
Ascites (absent/present)	13 (13.4) /84 (86.6)	16 (53.3)/14 (46.7)	**<0.001**
Portal hypertension (absent/present)	32 (33.0) /65 (67.0)	22 (73.3)/8 (26.7)	**<0.001**
Child Pugh class			
A	77 (79.4)	9 (30.0)	
B	19 (19.6)	15 (50.0)	**<0.001**
C	1 (1.0)	6 (20.0)	
Tumor size	9.4 ± 4.1	12.0 ± 5.5	**0.006**
Tumor type			
Single nodular	47 (48.5)	6 (20.0)	
Multinodular	20 (20.6)	5 (16.7)	**0.004**
Infiltrative	30 (30.9)	19 (63.3)	
Tumor distribution (uni-/bilobar)	66 (68.0)/31 (32.0)	7 (23.3)/23 (76.7)	**<0.001**

HBV, hepatitis B virus; HCV, hepatitis C virus; PT, prothrombin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl peptidase; AFP, alpha fetoprotein; PIVKA, prothrombin-induced by vitamin K absence or antagonist; AU, arbitrary unit.
The bold values are the parameters of statistically significant differences between the two groups.

TABLE 2 Characteristics of the study sample undergoing transcatheter arterial embolization or surgery in the curative treatment group.

	TAE/TACE (n = 73)	Emergency and Staged Surgery (n = 24)	P value
Age	59 ± 13	56 ± 13	0.317
Sex (M/F)	66 (90.4)/7 (9.6)	22 (91.7)/2 (8.3)	1.000
Etiology			
HBV	47 (64.4)	13 (54.2)	0.239
HCV	5 (6.8)	2 (8.3)	1.000
Alcohol	16 (21.8)	2 (8.3)	0.225
Laboratory value			
Platelet ($\times 10^3/\mu\ell$)	221 ± 109	228 ± 86	0.597
Albumin (g/dL)	3.5 ± 0.6	3.9 ± 0.5	**0.008**
Total bilirubin (mg/dL)	1.3 ± 0.7	1.2 ± 0.9	0.363
PT (INR)	1.16 ± 0.20	1.10 ± 0.09	0.130
Creatinine (mg/dL)	1.17 ± 0.82	0.98 ± 0.25	0.297
AST (IU/L)	126 ± 216	72 ± 57	**0.047**
ALT (IU/L)	73 ± 82	59 ± 57	0.431
ALP (IU/L)	143 ± 121	102 ± 67	**0.043**
GGT (IU/L)	236 ± 318	103 ± 93	0.118
AFP (ng/mL)	37574 ± 117588	43537 ± 157050	0.850
PIVKA (mAU/mL)	16744 ± 24966	32848 ± 65751	0.407
Ascites (absent/present)	60 (85.2)/13 (17.8)	24 (100.0)/0 (0.0)	**0.034**
Portal hypertension (absent/present)	42 (57.5)/31 (42.5)	23 (95.8)/1(4.2)	**<0.001**
Child Pugh class			
A	52 (71.2)	23 (95.8)	
B	20 (27.4)	1 (4.2)	**0.044**
C	1 (1.4)	0 (0.0)	
Tumor size	9.7 ± 4.3	8.4 ± 3.4	0.144
Tumor type			
Single nodular	29 (39.8)	16 (66.7)	
Multinodular	15 (20.5)	5 (20.8)	**0.032**
Infiltrative	29 (39.8)	3 (12.5)	
Tumor distribution (uni-/bilobar)	44 (60.2)/29 (39.8)	20 (83.3)/4 (16.7)	**0.048**

TAE, transarterial embolization; TACE, transcatheter arterial chemoembolization; HBV, hepatitis B virus; HCV, hepatitis C virus; PT, prothrombin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl peptidase; AFP, alpha fetoprotein; PIVKA, prothrombin-induced by vitamin K absence or antagonist; AU, arbitrary unit. The bold values are the parameters of statistically significant differences between the two groups.

Short-term outcome: Rebleeding and death within 1-month

Early rebleeding within 1-month from the initial management was observed in three patients (2.4%, 3/127); of these, two patients (2.1%, 2/97) were from the curative treatment group and one patient (3.3%, 1/30) was from the palliative treatment group (Supplementary Table 1). A total of 96 patients were initially treated with TACE or TAE, and the 1-month rebleeding rate of interventional management was 3.1% (3/96). Specifically, two (2.4%, 2/83) patients in the curative treatment group and one (7.7%, 1/13) in the palliative treatment group experienced rebleeding within 1 month, but the rebleeding rates were not significantly different (p = .357).

Eight out of 127 patients (1-month mortality rate, 6.3%) died 4–28 days after HCC rupture (median, 14.5 days): three (3.1%, 3/97) patients from the curative treatment group and five (16.7%, 5/30) from the palliative treatment group (p = 0.018) (Supplementary Table 1). Among the five patients (5.2%, 5/96) who underwent TACE or TAE for bleeding control, three patients died of early rebleeding after initial hemostasis. The remaining two patients succumbed to multiorgan failure, including severe deterioration of liver function.

Long-term outcome: Overall survival and IPDM

The median survival time and 1-year survival rate following HCC rupture were 8.4 months and 41.3%, respectively (Figure 2). The median survival of patients with conservative treatment only, TAE/TACE, emergency operation, and staged hepatectomy was 2.8, 8.7, 19.1 and 71.1 months, respectively (Figure 3A). Except for the comparison between patients who underwent emergency surgery and staged hepatectomy (p = 0.606), these differences were statistically significant (all p <

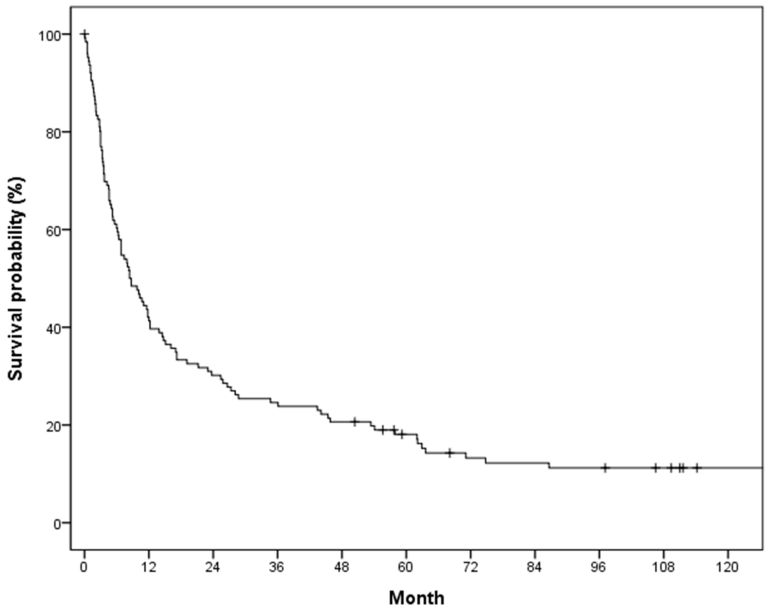

FIGURE 2
Overall survival in the study population.

0.05). OS was significantly longer in the curative treatment group (median, 12.0 months) than in the palliative treatment group (median, 2.2 months) (p <.001) (Figure 3B).

Regarding the development of IPDM, 105 patients underwent follow-up CT or MR images after HCC rupture, and 16 patients (15.2%, 16/105) experienced new development of IPDM. The incidence of IPDM gradually increased and reached a plateau from 1 year after HCC rupture (Figure 4A). The 1-year. 2-year, and 5-year IPDM rates were 15.2%, 15.2%, and 18.2%, respectively. OS in patients without IPDM was significantly higher than that in patients with IPDM (median, 15.1 vs. 6.3 months) (Figure 4B). A representative case of IPDM is shown in Figure 5.

Discussion

According to the results of this study, TAE/TACE provided effective immediate hemostasis with a low rebleeding rate and may serve as a bridge treatment before elective surgery. In addition, most cases of IPDM occur within 1 year; thus a more thorough surveillance should be considered for patients with spontaneous rupture of HCC, even after immediate hemostasis and eventual tumor control.

The characteristics of patients with ruptured HCC vary widely, and comparison of the treatment modalities in these patients most likely yield skewed results owing to the sampling bias. Commonly, patients with resectable tumors and preserved liver function undergo elective or staged surgery, whereas patients with unresectable tumors or poor liver function are more likely to undergo conservative treatment or TAE at best. Therefore, in our study, patients were divided into two groups: those who received treatment with palliative intent of immediate hemostasis and those who received treatment with therapeutic intent of hemostasis and ultimately tumor control. Laboratory results, tumor characteristics, and imaging findings were poorer in the palliative treatment group and those who received TAE/TACE than in the curative treatment group and those who underwent surgery (Tables 1, 2).

Previous studies have reported rebleeding rate varying from as low as 1% to as high as 20% (12, 15). In our study, the overall rebleeding rate in patients who underwent TAE or TACE was 3.1%. The rate of rebleeding was not significantly different between the two groups based on treatment intent. In addition, 1-month survival rate of patients who underwent TAE or TACE was 94.8%, which is much higher than the previously reported rates, which ranged from 28.6% to 87.5% (16). With the advent of cone-beam CT, which increases the sensitivity of tumor and feeding artery detection (17), TAE/TACE may have a larger than previously anticipated role in effective hemostasis in the acute management of ruptured HCC.

The prognosis of ruptured HCC is poorer than that of non-ruptured HCC (2). In a systematic review of ruptured HCC, the overall aggregate 1-year survival was 46.4% (range, 17.5% to 90.1%) (16), which is comparable to our result of 41.3%. Based on the treatment modality, TAE/TACE and emergency or staged operations provided better survival than conservative treatment. While there was no statistical difference between OS in patients

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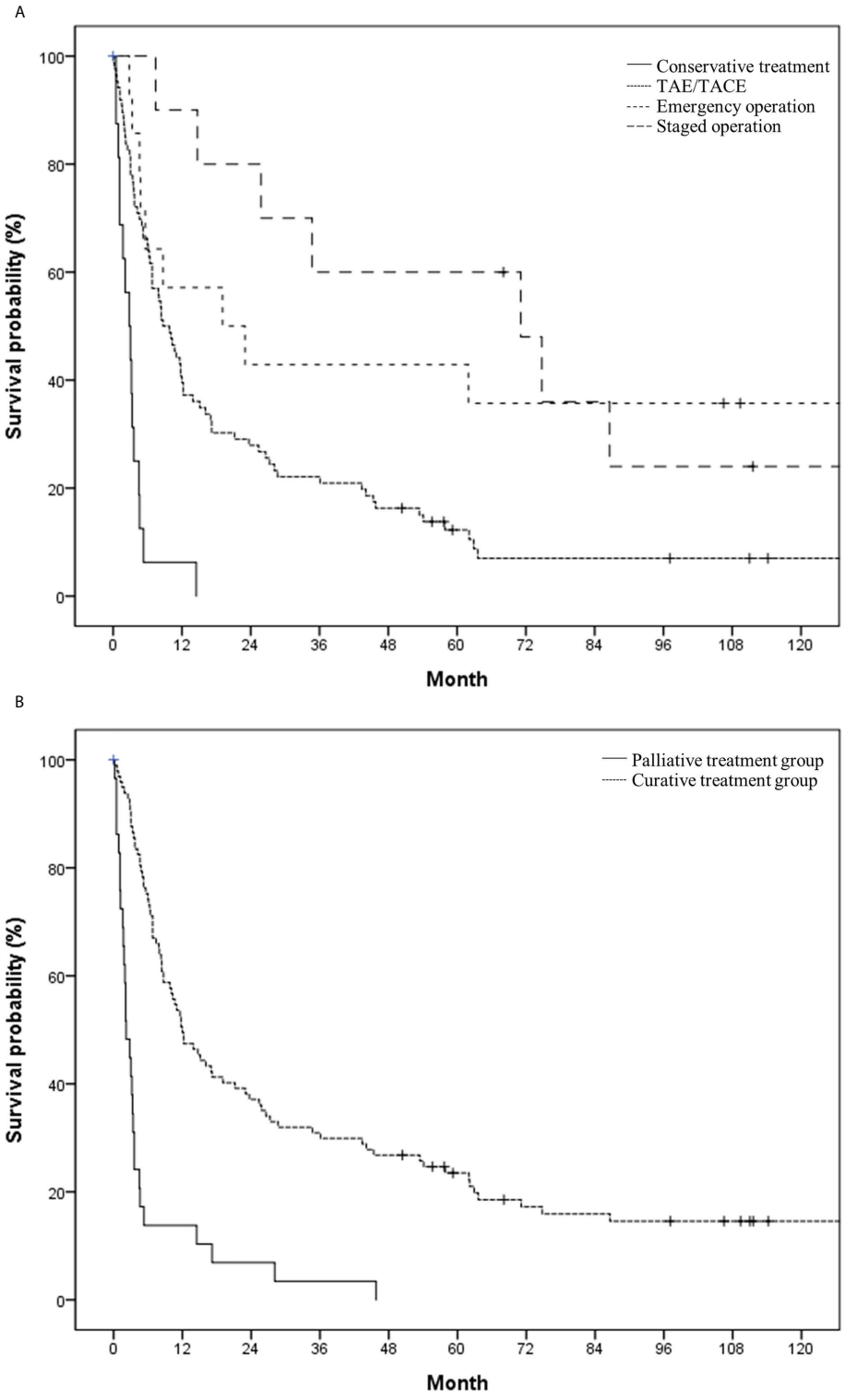

FIGURE 3
Overall survival in the study population based on **(A)** initial treatment modality (conservative treatment vs. transcatheter arterial (chemo-) embolization vs. emergency operation vs. staged operation) and **(B)** treatment intent (palliative vs. curative).

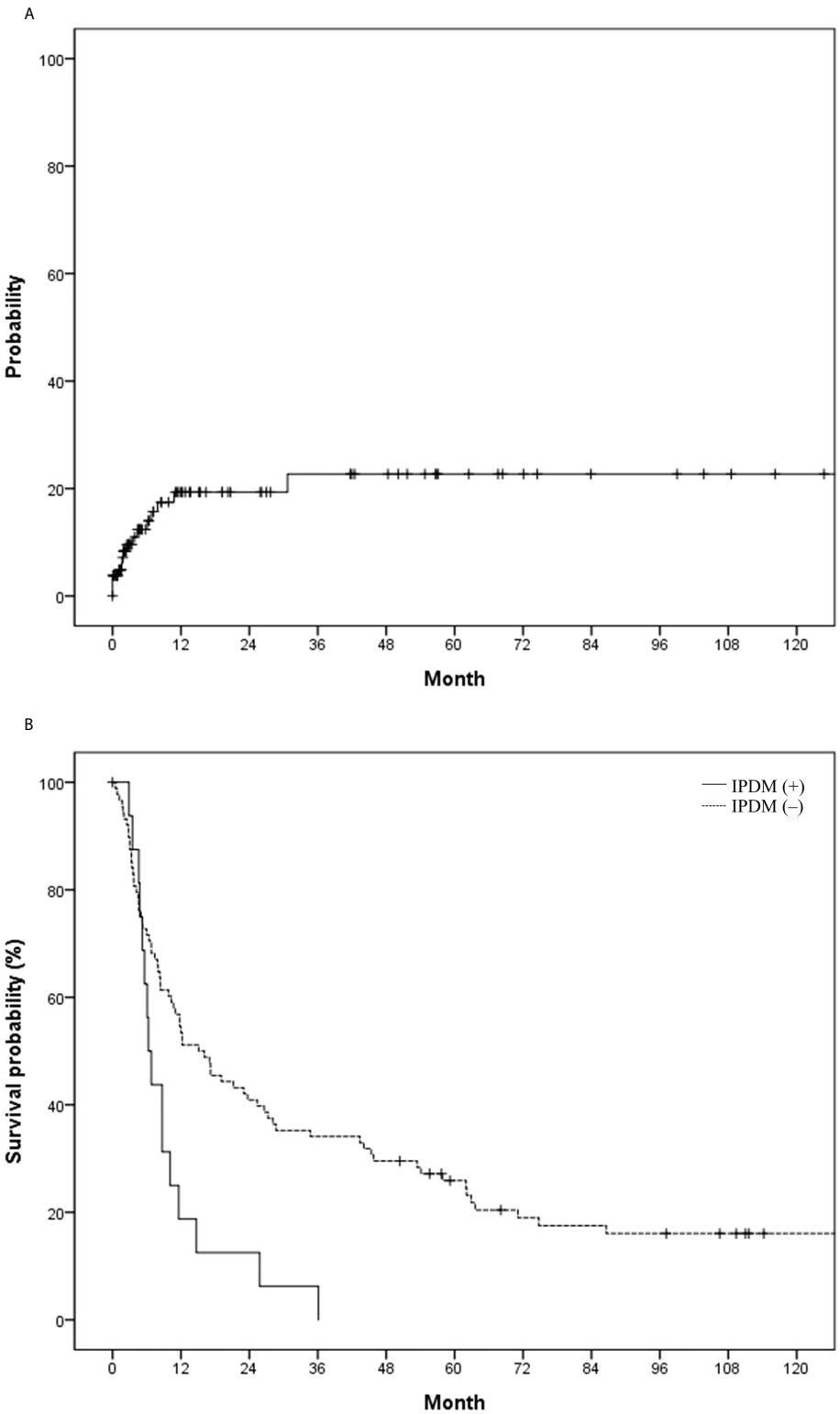

FIGURE 4
(A) Probability of intraperitoneal drop metastasis (IPDM) and **(B)** overall survival in the study population based on IPDM.

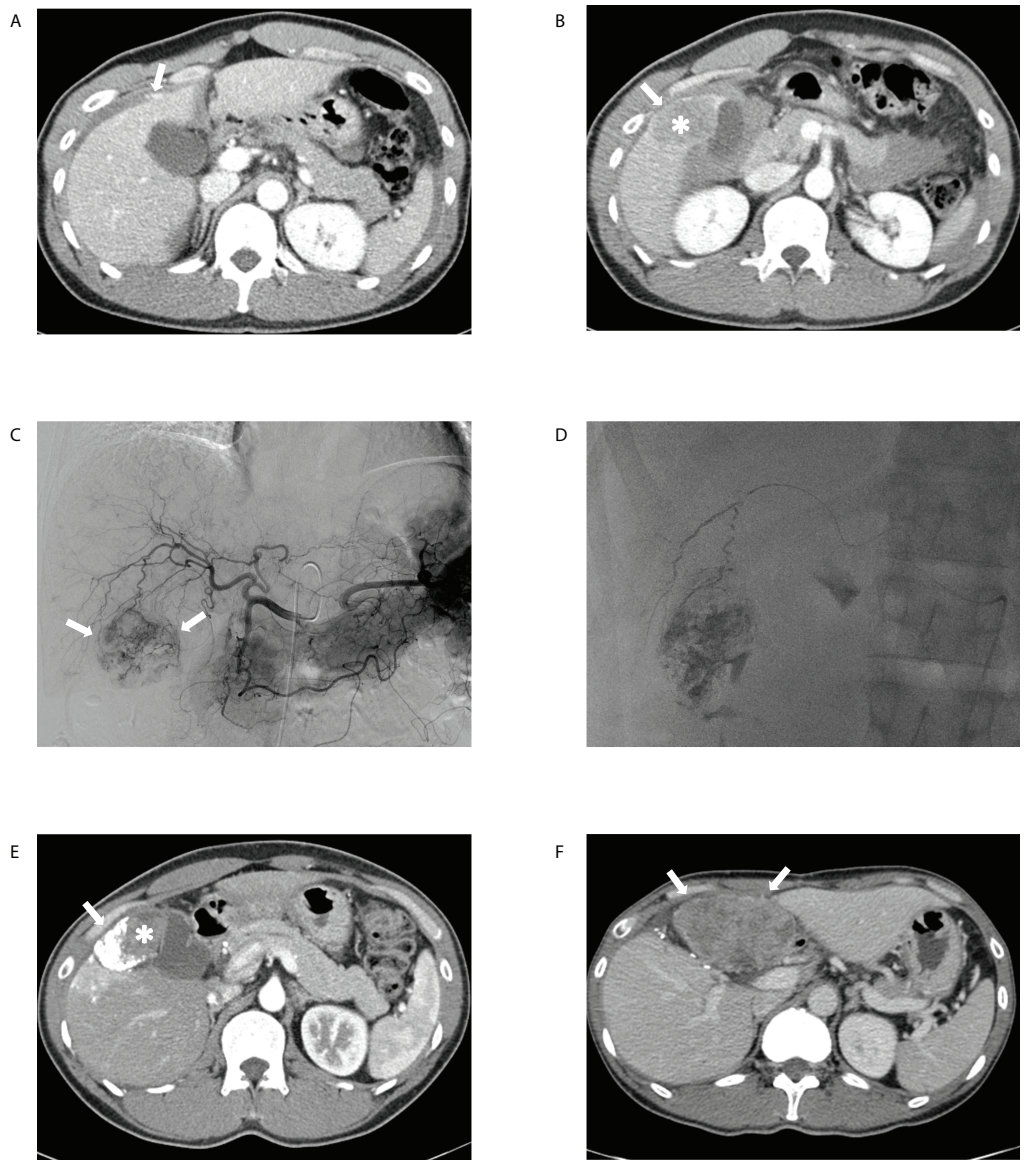

FIGURE 5
Transcatheter arterial chemoembolization (TACE) performed for ruptured hepatocellular carcinoma in a 41-year-old male patient. The portal phase of the initial computed tomography (CT) demonstrates **(A)** contrast media extravasation (arrow) from the tumor to the peritoneum and **(B)** washout lesion (asterisk) in segment 6 of the liver protruding to the peritoneum with focal discontinuity (arrow) of the liver surface, suggesting ruptured hepatocellular carcinoma. **(C)** Celiac angiography showing hypervascular tumor staining (arrows) corresponding to the CT findings. **(D)** Spot image of fluoroscopy demonstrating administration of iodized oil-doxorubicin mixture at the branch of S6 with partial uptake within the tumor. **(E)** Portal phase of the 1-month follow-up CT shows lipiodol-doxorubicin uptake (arrow) in the lateral aspect of the index tumor with a residual lesion (asterisk) in the medial portion. **(F)** Portal phase of the 11-month follow-up CT after tumorectomy performed at 6-month demonstrates a huge hypoattenuating mass (arrows) in the peritoneum, suggesting intraperitoneal drop metastasis.

who underwent emergency surgery and that in those who underwent staged surgery ($p < 0.606$), patients who underwent TAE/TACE had poorer OS than those who underwent either emergency or staged surgery ($p < 0.05$). This result was concordant with those of the previous studies that reported a more favorable long-term outcome with surgical intervention (16). However, since TAE/TACE was the only treatment option for patients with unresectable tumors or poor liver function, a selection bias might have occurred in favor of patients with better liver function and tumor characteristics to undergo surgical management (Table 2). Comparing patients who underwent emergency operations and patients who underwent staged operations in terms of median survival, the latter group demonstrated a longer median overall survival (19.1 vs. 71.1

months, $p = 0.606$). All the baseline statistics of these two groups were not significantly different except for the tumor size (9.64 ± 3.64 and 6.72 ± 2.09 for the emergency operation group and the staged operation group, respectively) ($p = 0.021$). This may have contributed to longer overall survival for the staged operation group. In addition, the number of patients in each group were relatively small (14 for emergency operation and ten for staged operation). Thus, a more comprehensive study is needed to compare the staged operation and the emergency operation in the setting of ruptured HCC. Considering that TAE/TACE may be the only option for most patients because of either poor liver function or unfavorable tumor characteristics for surgical options and that TAE/TACE may act as a bridge to staged surgery after initial hemostasis, TAE/TACE should be considered as a viable treatment option.

According to a previous study on the clinical course of patients with IPDM, 14.3% of the cases occurred after spontaneous rupture of HCC (5). In another study that compared peritoneal metastasis after emergency or delayed hepatectomy for spontaneous rupture of HCC, 35.3% and 40.7% of patients from each group, respectively, developed IPDM (4). Sixteen of 105 patients (15.2%) developed IPDM during the follow-up period in our study, and 11 patients (69%) developed IPDM within 1 year. After cytoreductive surgery, the survival rate in patients with IPDM was better than that in patients with other extrahepatic recurrences (1- and 2-year survival rates of 83% and 71%, respectively) (18). Nonetheless, the presence of IPDM in patients with spontaneous rupture rendered significantly worse survival in our study (median survival: 15.1 vs. 6.3 months). Thus, close surveillance of patients with spontaneous rupture of HCC for IPDM needs to be considered for up to at least 1 year.

This study has several limitations. First, it was a retrospective study and the number of patients included was small, especially those who underwent emergent and staged operations. Hence, an effective subgroup analysis comparing TAE/TACE, emergency surgery, and staged surgery could not be performed. Second, the intent of the treatment was retrospectively determined because of the emergent nature of the ruptured HCC. Finally, the baseline demographics of patients who underwent interventional procedures and surgical operations were different, which hindered the accurate depiction and comparison of these two treatment modalities.

In conclusion, TAE/TACE provided immediate effective hemostasis with a low rebleeding rate and adequate 1-month survival rate. In addition, TAE/TACE may serve as a bridge to staged surgery in patients with resectable HCC and good liver function. After initial treatment, a closer surveillance should be considered for up to at least 1 year for a high probability of IPDM.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Seoul National University of Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

The authors confirm contribution to the paper as follows: Study conception and design: JP and JWCho; data collection: YSS and YSJ; analysis and interpretation of results: JP, JWCho, HCK, and JWChu; draft manuscript preparation: JP and JWCho. All authors reviewed the results and approved the final version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.999557/full#supplementary-material

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Safety and efficacy of lenvatinib combined with camrelizumab plus transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma: A two-center retrospective study

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Objectives: To compare the safety and efficacy of lenvatinib (LEN) combined with camrelizumab plus transcatheter arterial chemoembolization (TACE-LEN-C) and TACE combined with LEN (TACE-LEN) in patients with unresectable hepatocellular carcinoma (uHCC).

Methods: Eighty-three patients with uHCC treated with TACE-LEN-C or TACE-LEN from September 2018 to May 2021 were enrolled in this retrospective study. Overall survival (OS), progression-free survival (PFS), local tumor response, and adverse events (AEs) were evaluated. Univariate and multivariate analyses were used to determine the factors affecting survival.

Results: There were 31 patients in the TACE-LEN-C group and 52 patients in the TACE-LEN group. The median follow-up period was 14.2 months (range 7.2–25.2 months) in the whole study. The combination of triple therapy was found to significantly prolong the PFS (12.5 months vs. 6.6 months, $P<0.001$) and OS (18.9 months vs. 13.9 months, $P<0.001$. In terms of tumor response, the combination demonstrated a higher objective response rate (71% vs. 42.3% by the modified Response Evaluation Criteria in Solid Tumors, $P=0.023$) without a statistically significant difference in the disease control rate (93.5% in TACE-LEN-C, 80.8% in TACE-LEN, $P=0.195$). In the multivariate analysis, two independent factors affecting PFS were identified: number of tumors and treatment. Three independent factors affected OS: number of tumors,

Barcelona Clinic Liver Cancer (BCLC) stage, and treatment. All the AEs were tolerable.

Conclusion: TACE-LEN-C is a safe and effective treatment for patients with uHCC, and could be a potential treatment option.

KEYWORDS

lenvatinib, transcatheter arterial chemoembolization, camrelizumab, hepatocellular carcinoma, efficacy, safety

Introduction

Hepatocellular carcinoma (HCC) accounts for nearly 85% of all liver cancer patients, and is the third leading cause of cancer-related death. (1) The prognosis of HCC remains poor, with the maximum 5-year survival estimated at 18%. (2) Surgery and radiofrequency ablation are the curative treatments for HCC patients; (3) however, approximately 70% of the HCC cases are unresectable at diagnosis. (4) The median survival of patients with unresectable HCC (uHCC) is 16 months. (5) Systemic treatment is the first-line treatment recommended for patients with advanced HCC, including sorafenib, Lenvatinib, and atezolizumab + bevacizumab. (6)

Transcatheter arterial chemoembolization (TACE) is the standard treatment for intermediate HCC recommended by most clinical practice guidelines. (7–9) TACE can cause tumor regression in up to 50% of the patients with HCC, resulting in survival benefits. (10) However, as a palliative approach, TACE has not been universally successful in controlling liver cancer growth because of the high rate of incomplete embolization and changes in the tumor microenvironment (TME) after embolization. (11) Thus, many combination strategies have been explored for the treatment of unresectable HCC to improve the long-term outcomes of HCC patients treated with TACE. Molecularly targeted drugs are common options for combination with locoregional therapy. (12–16) However, the results did not demonstrate the expected synergistic results of combining TACE with molecular targeted drugs versus TACE alone for uHCC. Although the TACTICS study demonstrated that concurrent sorafenib therapy might delay tumor progression following TACE, the latest results showed no survival benefits compared with TACE alone. (17, 18)

Tumor microenvironment in HCC is strongly immunosuppressive, expressing a high level of immune checkpoint inhibitors(ICIs), such as programmed death-1 (PD-1), cytotoxic T-lymphocyte antigen 4 (CTLA-4), lymphocyte activating gene 3 protein (LAG-3), and mucin domain molecule 3 (TIM-3). (19) The high levels of ICIs induce T cell inhibition and represent one of the major mechanisms of HCC immune escape. Thus, immune checkpoint inhibitors (ICIs) have rapidly progressed in the treatment of HCC, but monotherapy with programmed cell death protein-1 (PD-1) antibody only caused tumor regression in 20% of the patients. (20, 21) However, PD-1 combined with vascular endothelial growth factor (VEGF) inhibitors may improve the immune response of the tumor microenvironment. This combination could increase the infiltration of CD8+ T cells in the TME by temporarily normalizing the tumor vessels, an effect of blocking VEGF, and amplifying the value of PD-1 antibody. (22) In the IMbrave 150 research, the combination of PD-L1 antibody and VEGF inhibitor demonstrated a prolonged survival and higher response rate compared with sorafenib, causing a 42% risk reduction in mortality; thus, it is recommended as the first-line treatment for unresectable HCC. (23)

TACE, as an local-regional therapy (LRT), may induce "immunogenic cell death" by releasing tumor antigens and eliciting damage-associated molecular patterns, to facilitate antitumor immunity. (24, 25) In addition, TACE could cause an increase in VEGF and PD-L1 expression because of the hypoxic microenvironment after embolization. (26, 27) The molecularly targeted anti-cancer agents combined with the PD-1 antibody would be a promising complement to TACE. However, whether patients with uHCC can obtain core survival benefits from TACE combined with ICIs and molecularly targeted drugs remains unclear, and few studies have focused on this issue.

Lenvatinib is a novel tyrosine kinase inhibitor (TKI), which was approved in 2018 as the first-line treatment of uHCC, proven to be non-inferior to sorafenib in increasing the overall survival (OS) in patients with HCC in clinical trials. (28) Camrelizumab (AiRuiKa^{TM}) is a humanized high-affinity IgG4-kappa PD-1 monoclonal antibody being developed by Jiangsu Hengrui Medicine Co. Ltd (Jiangsu Hengrui Medicine, Jiangsu, China) for the treatment of various malignancies including HCC, exhibiting promising antitumor activity and an acceptable safety profile. (29, 30)

In this study, we assessed the efficacy and safety of lenvatinib combined with camrelizumab plus TACE (TACE-LEN-C) in

patients with uHCC in two centers in China and compared them with those of TACE combined with lenvatinib (TACE-LEN).

Patients and methods

Patients and study design

Patients who received TACE-LEN (n=52) or TACE-LEN-C (n=31) between September 2018 and May 2021 were enrolled in this retrospective observational study. All patients were pathologically or clinically diagnosed with HCC according to the guidelines of the American Association for the Study of Liver Diseases (31). All patients were confirmed unresectable by a multi-disciplinary team and all patients did not receive systematic anti-cancer therapy before the combination treatments.

The inclusion criteria were as follows: unresectable HCC treated with TACE-LEN-C or TACE-LEN; age between 18 and 75 years, and the presence of at least one target lesion with measurable diameter and arterial enhancement according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). (32) The exclusion criteria were as follows: presence of serious complications, such as severe dysfunction of the kidney, lung, or heart; having undergone other treatments during this period, such as thermal ablation, external beam radiotherapy, or percutaneous ethanol injection; the presence of other malignant tumors in addition to HCC; and incomplete data.

This study was approved by the ethics committee of the Wuhan Union Hospital, Huazhong University of Science and Technology and The Fifth Medical Center of Chinese, PLA General Hospital.

Treatment

TACE was performed by puncturing the right femoral artery. A 5-F catheter and 3-F microcatheter were used to identify the tumor-supplying artery. Lipiodol and doxorubicin hydrochloride were mixed and injected into the tumor-supplying artery *via* a microcatheter. Then, an appropriate amount of gelatin sponge was injected to seal the tumor's blood supplying artery.

In the TACE-LEN-C group, patients received camrelizumab and lenvatinib in one week after TACE. Patients received lenvatinib orally once daily at a dose of 8 mg (body weight <60 kg) or 12 mg (body weight ≥60 kg) and 200 mg camrelizumab intravenously once every 3 weeks until no clinical benefits be observed or unacceptable toxicity. (23) The mean time for patients receiving lenvatinib was 15.5 months (range 3-23 months) and 14.3 months for patients with camrelizumab (range 3.5-22 months). Patients receiving another TACE is according to the CT or MRI imaging evaluation based on the mRECIST criteria. The patients were recommended to receive another TACE if there were residual tumors (partial response, PR or stable disease, SD). However, patients were not recommended to receive TACE if the tumor continuously progressed after two TACEs because these patients were considered as TACE resistance. (17) For these patients, the lenvinib or camrelizumab should be taken if the investigators observed evidence of clinical benefits were absent. Lenvatinib and camrelizumab were discontinued for 3 days before and after TACE. In the TACE-LEN group, patients received lenvatinib, as in the TACE-LEN-C group.

Efficacy and safety

Adverse events (AEs) were monitored and recorded by experienced nurses who were blinded to the treatment, according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Treatment responses were assessed based on contrast-enhanced abdominal CT or MR imaging according to mRECIST. Complete response (CR) was defined as all target lesions disappeared, no new lesions appeared, and tumor markers were normal for at least 4 weeks. Partial response (PR) was defined as the reduction of the sum of the largest diameters of target lesions ≥30% and maintained for at least 4 weeks. Stable disease was defined as the sum of the largest diameters of target lesions did not shrink to the standard of PR, or enlarged to the standard of progressive disease (PD). PD was defined as the sum of the largest diameters of target lesions increased by at least ≥20%, or new lesions appear. The objective response rate (ORR) was defined as the incidence of complete response and partial response. The disease control rate (DCR) was defined as the incidence of complete response (CR), partial response (PR), and stable disease (SD). Progression-free survival (PFS) was defined as the time from the initiation of treatment to first tumor progression (first PD), death or the last follow-up in censored data. OS) was defined as the time from the initiation of treatment until death or the last follow-up in censored data.

Follow-up

The interval between the follow-ups was 4–6 weeks. During the follow-up, the patients underwent laboratory examinations, physical examinations and a thorough inquiry to record the AEs. Laboratory examinations included AFP, ALT, AST, and others. Contrast-enhanced CT or MRI was performed to identify the intrahepatic recurrent or residual tumors. Once an intrahepatic viable tumor appeared, another TACE was performed according to the consensus of the patient and their attending physician.

Statistical analysis

To compare the differences in baseline characteristics between the two groups of patients, Fisher's exact test or $\chi 2$ test was used for categorical variables, presented as numbers (percentages), and Student's t-test were used for continuous variables, presented as mean ± standard deviation. Kaplan–Meier analysis was used to plot the OS and PFS curves, and significance was calculated using the log-rank test. Cox proportional regression analysis was used to calculate potential factors that might influence the survival of all patients. Factors with p-values no more than 0.1 in the univariable analysis were included in the multivariate analysis. Differences were considered statistically significant when the bilateral p-value was ≤ 0.05. All statistical analyses were conducted using SPSS 24.0 and R.

Results

Baseline statistics

During the follow-up, there were a total of 109 patients (61 in Wuhan Union hospital, 48 in The Fifth Medical Center of Chinese, PLA General Hospital) with uHCC who received TACE-LEN-C (n=39) or TACE - LEN (n=70). However, 8 and 18 patients in the TACE-LEN-C and TACE-LEN groups, respectively were excluded according to the exclusion criteria. The flowchart is shown in Figure 1. Finally, 31 patients in the TACE-LEN-C group and 52 in the TACE-LEN group were enrolled in the study. There was no statistical difference in baseline variables between the two groups (Table 1).

Tumor response and patient survival

Tumor responses of the two groups were shown in Table 2. There were 3, 19, 7, 2 patients in the TACE-LEN-C group had CR, PR, SD, and progressive disease (PD), respectively, both PD patients were confirmed as immune-related confirmed progressed disease(iCPD) by immune-related response criteria in solid tumors (iRECIST) (33). There were 1, 21, 20, and 10 patients in the TACE-LEN group with CR, PR, SD, and PD. The patients in the TACE-LEN-C group had a better ORR than those in the TACE-LEN group (71% vs. 42.3% by the mRECIST, P=0.023). The DCR in the two groups demonstrated no statistical difference (93.5% in TACE-LEN-C, 80.8% in TACE-LEN, P= 0.195).

The median follow-up period of all the patients was 14.2 months (range 7.2–25.2 months). During the follow-up, 40 (76.9%) and 11(35.5%) patients died in the TACE-LEN and TACE-LEN-C groups, respectively. The median OS was significantly longer in the TACE-LEN-C group than that in the TACE-LEN group (18.9 vs. 13.9 months, P<0.001) (Figure 2A). The 6 and 12 months survival rates in the TACE-LEN-C and TACE-LEN-C groups were 96.7%, 95.7% and 88.2%, and 55.1%, respectively (Table 3). The median PFS of the TACE-LEN-C and TACE-LEN groups was 12.5 vs 6.6 months, respectively (Figure 2B). The 6 and 12 months progression-free rates of the TACE-LEN-C and TACE-LEN groups were 93.3%, 42.3% and 50%, 0%, respectively (Table 3).

Predictive factors affecting PFS and OS

In the univariate analysis, the number of tumors (hazards ratio [HR]: 3.192; 95% confidence interval [CI]: 1.570–6.492; P=0.001), BCLC stage (HR: 1.567; 95% CI: 0.939–2.615; P=0.085), and treatment (HR: 0.351; 95% CI: 0.211–0.584; P< 0.01) were the potential factors affecting PFS, and the potential factors associated with OS included age (HR: 0.967; 95% CI: 0.952–1.001; P=0.060), sex (HR: 0.366; 95% CI: 0.112–1.195; P=0.096), ECOG performance (HR: 2.926; 95% CI: 1.578–5.427; P=0.001), number of tumors (HR: 4.783; 95% CI: 1.476–15.513;

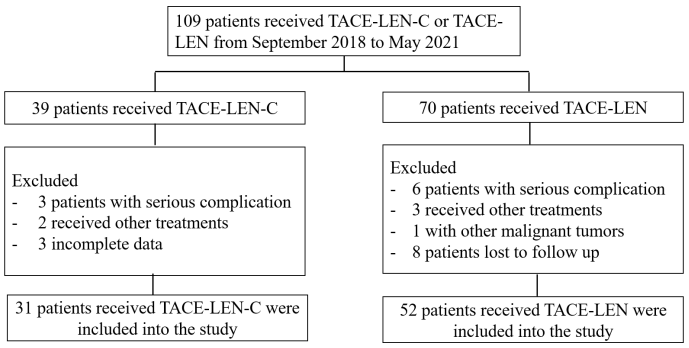

FIGURE 1
Flow chart illustrating the selection of patients; TACE-LEN-C, transcatheter arterial chemoembolization with lenvatinib plus camrelizumab; TACE-LEN, transcatheter arterial chemoembolization with LEN.

TABLE 1 Baseline characteristics of patients between the two groups.

Characteristics	TACE-LEN (N=52)	TACE-LEN-C (N=31)	*P* value
Age(years)	51.77 ± 9.791	54.84 ± 9.249	0.332
Genders			0.511
Male	46(88.5%)	25(80.6%)	
Female	6(11.5%)	6(19.4%)	
ECOG performance			0.115
0	22(42.3%)	19(61.3%)	
1	30(57.7%)	12(38.7%)	
BCLC stage			0.814
B	17(32.7%)	11(35.5%)	
C	35(67.3%)	20(64.5%)	
Extrahepatic metastases			0.548
Yes	32 (61.5%)	17 (54.8%)	
No	20 (38.5%)	14 (45.2%)	
HBV infection			0.389
Yes	44(84.6%)	29(93.5%)	
No	8(15.4%)	2(6.5%)	
AFP (ng/ml)			1.000
>400	21(40.4%)	12(38.7%)	
≤400	31(59.6%)	19(61.3%)	
Child-Pugh Class			0.576
A	43(82.7%)	24(77.4%)	
B	9(17.3)	7(22.6%)	
Tumors number			0.232
≤3	49(94.2%)	27(87.1%)	
>3	3(5.8%)	4(12.9%)	
ALT(IU/L)	37.90 ± 21.00	36.42 ± 24.67	0.443
AST(IU/L)	49.19 ± 26.44	42.03 ± 20.73	0.241
TB (μmol/L)	16.66 ± 6.60	16.83 ± 5.85	0.696
PLR	132.33 ± 70.49	119.13 ± 70.84	0.207
NLR	3.18 ± 2.38	2.80 ± 2.22	0.592
Albumin(g/dl)	37.70 ± 4.46	35.65 ± 4.85	0.085
PT(S)	13.46 ± 1.62	13.61 ± 2.97	0.226
Tumor size(cm)	7.65 ± 4.86	8.31 ± 4.80	0.392
TACE Sessions	4.38 ± 2.39	3.68 ± 2.01	0.951

ECOG, Eastern Cooperative Oncology Group; BCLC Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; AFP, a-fetoprotein; TACE, transarterial chemoembolization; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; PLR, platelet-to-lymphocyte; NLR, neutrophil-to-lymphocyte ratio; PT, prothrombin time; TACE-LEN, transcatheter arterial chemoembolization with Lenvatinib; TACE-LEN-C, transcatheter arterial chemoembolization with Lenvatinib plus camrelizumab.

TABLE 2 Tumor response in both groups.

Tumor response	TACE-LEN (N=52)	TACE-LEN-C (N=31)	*P* value
CR	1(1.9%)	3(9.7%)	
PR	21(40.3%)	19(61.3%)	
SD	20(38.5%)	7(22.6%)	
PD	10(19.2%)	2(6.5%)	
ORR	22(42.3%)	22(71.0%)	0.023
DCR	42(80.8%)	29(93.5%)	0.195

Data are presented as n (%), CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; TACE-LEN, transcatheter arterial chemoembolization with Lenvatinib; TACE-LEN-C, transcatheter arterial chemoembolization with Lenvatinib plus camrelizumab.

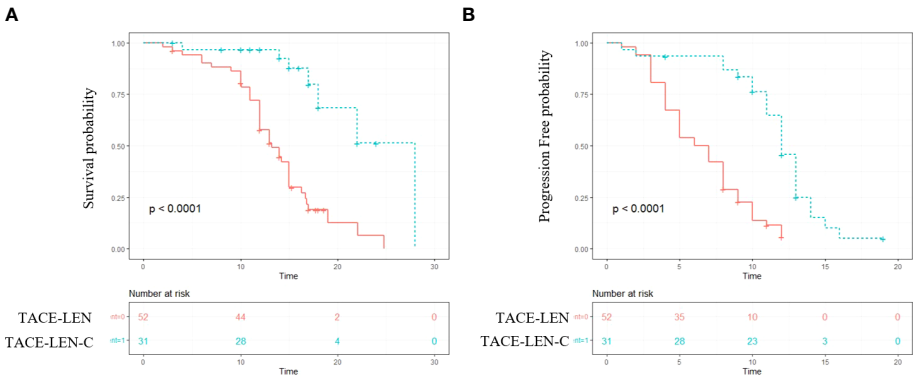

FIGURE 2
The Kaplan–Meier (KM) curves for patients with unresectable hepatocellular carcinoma who received the treatment of TACE-LEN-C or TACE-LEN (TACE-LEN-C, transcatheter arterial chemoembolization with lenvatinib plus camrelizumab; TACE-LEN, transcatheter arterial chemoembolization with LEN): **(A)** the KM curves of overall survival time; **(B)** the KM curves of profession-free time.

P=0.009), BCLC stage (HR: 1.911; 95% CI: 1.006–3.630; *P*=0.048), Extrahepatic metastases (HR: 0.578; 95% CI: 0.325~1.453; P=0.12) and treatment (HR: 0.171; 95% CI: 0.072–0.403; *P*<0.001). In the multivariate analysis, two independent factors affecting PFS were identified: number of tumors (HR: 2.212; 95% CI: 1.022–4.790; *P*=0.044) and treatment (HR: 0.451; 95% CI: 0.259–0.784; *P*=0.005). Three independent factors affected OS: number of tumors (HR: 2.250; 95% CI: 1.034–4.894; *P*=0.041), BCLC stage (HR: 1.738; 95% CI: 1.025–2.947; *P*=0.040) and treatment (HR: 0.381; 95% CI: 0.201–0.725; *P*=0.003). (Tables 4, 5)

Safety

The most common TACE-related AEs were post-embolization syndrome that induced fever (80.8% vs. 71%), pain (61.5% vs. 67.8), nausea (65.3% vs. 61.3%), and vomiting (32.6% vs. 35.4%) in the TACE-LEN and TACE-LEN-C groups. Grade 3 or 4 AEs with an incidence of more than 5% included fever in both groups and nausea in the TACE-LEN group. Drug-related AEs demonstrated a similar incidence in both groups, with no grade 3 or 4 AEs of > 5% (only two cases of hypertension in the TACE-LEN group and one case of hypertension in the TACE-LEN-C group). Drug-related AEs included elevated ALT levels (23.1% vs. 25.8%), insomnia (3.8% vs. 3.2%), proteinuria (17.3% vs. 19.4%), ventosity (13.5% vs. 11.8%), hypertension (25% vs. 25.8), hypothyroidism (0% vs. 12.9%) and hand-foot skin reaction (21.2% vs. 22.6%). All AEs are listed in Table 6.

TABLE 3 Rate of overall survival and progression free survival at 6 months and 12 months.

Rate, %	TACE-LEN (N=52)	TACE-LEN-C (N=31)
OS 6 months	88.2	96.7
OS 12 months	55.1	95.7
PFS 6 months	50	93.3
PFS 12 months	0	42.3

OS, overall survival; PFS, progression-free survival; TACE-LEN, transcatheter arterial chemoembolization with Lenvatinib; TACE-LEN-C, transcatheter arterial chemoembolization with Lenvatinib plus camrelizumab.

Discussion

In the past few years, many studies have been conducted to identify an appropriate systematic therapy protocol for patients with uHCC treated with TACE. The TACTICS trial with sorafenib and TACE in patients with uHCC indicated that TACE combined with antineoplastic agents is an independent predictor of prognosis for uHCC. (17) Several phase I or II trials have been conducted to evaluate the safety and efficacy of TACE plus ICIs (NCT03143270, NCT03572582, NCT03397654). In addition, there are some phase III RCTs on the combination of TKI and ICIs plus TACE, such as the LEAP-012 trial (NCT04246177) using lenvatinib plus pembrolizumab vs. placebo in combination with TACE, CheckMate 74W trial (NCT04340193) using nivolumab and ipilimumab plus TACE, and EMERALD study (NCT03778957) using durvalumab and bevacizumab plus TACE. However, these results remain unclear. Thus, we have summarized and described our experience of using lenvatinib and camrelizumab plus TACE in our centers.

Our results revealed that uHCC patients who received TACE combined with lenvatinib plus camrelizumab had prolonged OS and PFS compared with those who received TACE combined with lenvatinib. In the multivariate analyses, combination with camrelizumab was an independent predictor for better OS and

TABLE 4 Univariate and multivariate analysis of prognostic factors for PFS.

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age	0.992(0.972~1.013)	0.449		
Gender		0.158		
Male	Reference			
Female	0.587(0.280~1.229)			
ECOG performance		0.250		
0	Reference			
1	1.319(0.823~2.114)			
Number of tumors		**0.001**		**0.044**
>3	Reference		Reference	
≤3	3.192(1.570~6.492)		2.212(1.022~4.790)	
HBV infection		0.463		
No	Reference			
Yes	0.758(0.361~1.589)			
Child-Pugh class		0.210		
A	Reference			
B	0.651(0.333~1.274)			
BCLC stage		**0.085**		0.056
B	Reference		Reference	
C	1.567(0.939~2.615)		1.662(0.987~2.797)	
Extrahepatic metastases		0.153		
Yes	Reference			
No	0.845 (0.563~1.351)			
AFP (ng/ml)		0.806		
>400	Reference			
≤400	1.063(0.655~1.725)			
Tumor size (cm)	1.005(0.952~1.060)	0.862		
PLR	1.000(0.996~1.003)	0.929		
NLR	0.904(0.794~1.028)	0.124		
ALT(IU/L)	1.001(0.997~1.005)	0.512		
AST (IU/L)	1.001(0.992~1.009)	0.892		
Albumin (g/dL)	1.040(0.987~1.096)	0.144		
TB (μmol/L)	1.019(0.978~1.062)	0.370		
PT(s)	1.042(0.956~1.135)	0.348		
TACE Sessions	0.971(0.896~1.052)	0.468		
Treatment		**<0.001**		**0.005**
TACE-LEN	Reference		Reference	
TACE-LEN-C	0.351(0.211~0.584)		0.451(0.259~0.784)	

HR, hazard ratio; CI, confidence interval; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B; AFP, alpha-fetoprotein; ALT, alanine transaminase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; PFS, progression-free survival; TACE-LEN, transcatheter arterial chemoembolization with Lenvatinib; TACE-LEN-C, transcatheter arterial chemoembolization with Lenvatinib plus camrelizumab. Bold values signifies important information in the Statistical analysis section.

PFS. The combination also demonstrated a higher ORR (71% vs. 42.3%, *P*=0.023) in patients who received TACE-LEN-C than in those who received TACE-LEN. Interestingly, in a previous study, the ORR of lenvatinib plus pembrolizumab was 46%, lower than that of the TACE-LEN-C group. (34) Thus, this combination may result in an obvious improvement in controlling the tumor locally, which may result in an increase in patient's survival. In previous studies, the combination of TACE-LEN-C also demonstrated a significant increase in tumor responses and survival benefits for uHCC patients. (35–37) Although, in this study, there was no statistically significant difference in DCR (93.5% in TACE-LEN-C, 80.8% in TACE-LEN, *P*=0.195), the combination still deserves consideration as a prioritized treatment strategy for uHCC patients.

TABLE 5 Univariate and multivariate analysis of prognostic factors for OS.

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age	0.976(0.952~1.001)	**0.060**	1.004(0.980~1.028)	0.753
Gender		**0.096**		0.168
Male	Reference		Reference	
Female	0.366(0.112~1.195)		0.589(0.277~1.250)	
ECOG performance		**0.001**		0.276
0	Reference		Reference	
1	2.926(1.578~5.427)		0.735(0.422~1.279	
Number of tumors		**0.009**		**0.041**
>3	Reference		Reference	
≤3	4.785(1.476~15.513)		2.250(1.034~4.894)	
HBV infection		0.345		
No	Reference			
Yes	0.654(0.271~1.577)			
Child-Pugh class		0.299		
A	Reference			
B	0.651(0.290~1.463)			
BCLC stage		**0.048**		**0.040**
B	Reference		Reference	
C	1.911(1.006~3.630)		1.738(1.025~2.947)	
Extrahepatic metastases		0.120		
Yes	Reference			
No	0.578(0.325~1.453)			
AFP (ng/ml)		0.734		
>400	Reference			
≤400	0.901(0.494~1.643)			
Tumor size (cm)	1.007(0.943~1.076)	0.827		
PLR	1.001(0.996~1.006)	0.677		
NLR	1.002(0.895~1.166)	0.750		
ALT(IU/L)	1.007(0.996~1.019)	0.216		
AST (IU/L)	1.006(0.996~1.016)	0.243		
Albumin (g/dL)	1.037(0.970~1.109)	0.290		
TB (μmol/L)	1.026(0.977~1.077)	0.303		
PT(s)	1.018(0.897~1.156)	0.783		
TACE Sessions	1.035(0.933~1.148)	0.514		
Treatment		**<0.001**		**0.003**
TACE-LEN	Reference		Reference	
TACE-LEN-C	0.171(0.072~0.403)		0.382(0.201~0.725)	

HR, hazard ratio; CI, confidence interval; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B; AFP, alpha-fetoprotein; ALT, alanine transaminase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; OS, overall survival; TACE-LEN, transcatheter arterial chemoembolization with Lenvatinib; TACE-LEN-C, transcatheter arterial chemoembolization with Lenvatinib plus camrelizumab. Bold values signifies important information in the Statistical analysis section.

These encouraging effects may be attributed to a stronger local and systematic immune response. A recent study demonstrated that the failure of anti-PD-1 partly results from the imbalance between CD8+ T cells and tumor burden, and the therapeutic efficacy of anti-PD-1 is positively associated with the ratio of CD8+ T cell invigoration to the tumor burden (measured as the sum of the long axis of all lesions, cm). (38) TACE can reduce tumor burden and elicit a response against cell death antigens, causing immunogenic cell death(ICD). (27) In addition, emerging evidence suggests that the ectopic overexpression of VEGF results in a highly abnormal vasculature, preventing the infiltration of immune effector cells

TABLE 6 The adverse events of patients after receiving TACE-LEN or TACE-LEN-C.

Adverse event	TACE-LEN(n=52)		TACE-LEN-C(n=31)	
	Any grade (n, %)	Grade 3 or 4 (n, %)	Any grade (n, %)	Grade 3 or 4 (n, %)
Fever	42(80.8)	5(9.6)	22(71.0)	3(9.7)
Pain	32(61.5)	2(3.8)	21(67.8)	1(3.2)
Nausea	34(65.3)	3(5.8)	19(61.3)	1(3.2)
Vomiting	17(32.6)	3(3.8)	11(35.4)	1(3.2)
Elevated ALT	12 (23.1)	1 (1.9)	8 (25.8)	0 (0)
Insomnia	2 (3.8)	0 (0)	1 (3.2)	0 (0)
Proteinuria	9 (17.3)	0 (0)	6 (19.4)	0 (0)
Ventosity	7 (13.5)	0 (0)	4 (11.8)	0 (0)
Hypertension	13(25.0)	2(3.8)	8(25.8)	1(3.2)
Hypothyroidism	0(0)	0(0)	4(12.9)	0(0)
Hand-foot skin reaction	11(21.2)	0(0)	7(22.6)	0(0)

(especially CD8+T cells). (39, 40) Thus, TACE-LEN-C could reduce tumor burden, increase the infiltration of CD8+T cells, and alleviate the inhibitory effect of CD8+T cells, leading to local and systemic immune activation. Further studies are required to verify this hypothesis.

Tumor burden has been proven to lead to poor prognosis in patients with uHCC who received TACE or immunotherapy. (41, 42) In our study, the Cox model was used to reduce potential factors that might influence the outcomes. Patients with ≤ 3 tumors could increase the all-cause mortality risk and tumor progression risk compared to patients with > 3 tumors. There were 3 patients (5.8%) in the TACE-LEN group and 4 patients (12.9%) in the TACE-LEN group with tumor number > 3. The number of patients was small which might lead to statistical bias. Thus, wo hope the future studies conducted by us or other studies can include more patients with tumor number > 3 to confirm the results generated by the current study. Patients with BCLC stage C could increase all-cause mortality risk compared to patients with BCLC stage B. However, after excluding other factors that might influence the outcomes, TACE-LEN-C could reduce tumor progression risk and the all-cause mortality risk compared to TACE-LEN, which might indicate that patients with uHCC could get more survival benefits from TACE-LEN-C than TACE-LEN.

In terms of AEs, our study suggested that TACE-LEN-C was well-tolerated and led to manageable side effects in patients with uHCC. The most commonly reported drug-related toxicities were elevated ALT, insomnia, proteinuria, ventosity, hypertension, hypothyroidism and hand-foot skin reaction, similar to previous studies. (35, 36) Furthermore, TACE-LEN-C did not increase TACE-related complications in patients with uHCC, specifically post-embolization syndrome. No permanent adverse sequelae or treatment-related deaths were reported. Thus, these results suggest that TACE-LEN-C was well-tolerated by patients with uHCC.

Our study had some limitations. This was a retrospective study with a small sample size, and further prospective studies are needed to confirm the efficacy of TACE-LEN-C. In addition, a recent study indicated that lenvatinib is better than sorafenib in patients with hepatitis B virus (HBV), (43) and most patients in our study had HBV. Thus, more studies need to be conducted to confirm the efficacy in other types of patients and more types of TKI +PD-1 antibody combinations need to be tested to determine the best combination as a supplementary systematic therapy to TACE.

Conclusion

Our study showed that patients who received TACE-LEN-C demonstrated a better tumor response and survival benefits with tolerable AEs. TACE-LEN-C is a safe and effective treatment for patients with uHCC and deserves consideration as a prioritized option.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Wuhan Union Hospital, Huazhong University of Science and Technology and The Fifth Medical Center of Chinese, PLA General Hospital. The ethics committee waived the requirement of written informed consent for participation.

Author contributions

Conception and design: CZ, FX, and LC; administrative support: CZ; provision of the study materials or patients: CZ and FX; collection and assembly of data: BS, LCZ, TS, YR, YC, YXG, and YSG; data analysis and interpretation: BS, TS, and LJZ; Manuscript writing: All authors. Final approval of manuscript: All authors.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Percutaneous thermal ablation combined with transcatheter arterial chemoembolization for hepatitis C virus-related hepatocellular carcinoma: Efficacy and survival

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Objective: The aim of this study was to investigate the efficacy and survival of Hepatitis C virus (HCV) -related hepatocellular carcinoma (HCC) undergoing percutaneous thermal ablation combined with transcatheter arterial chemoembolization (TACE).

Methods: A total of 83 HCV-related HCC patients who were treated with percutaneous thermal ablation combined with TACE were retrospectively analyzed. The demographic and clinical data were collected. The overall survival (OS) and recurrence free survival (RFS) rates were assessed by the Kaplan-Meier method. Univariate and multivariate Cox regression analysis was used to assess independent risk factors of OS and RFS.

Results: 92.8% patients (77/83) and 96.6% (170/176) tumor lesions achieved complete response (CR) 1 month after all treatment, and 10.8% (9/83) patients had minor complications. The median OS was 60 months (95% confidence interval (*CI*)= 48.0-72.0), and the 1-, 2-, 3-, 5- and 10-year cumulative OS rates were 94%, 78.3%, 72.3%, 43.4% and 27.5%, respectively. The cumulative RFS rates at 1-, 2-, 3- and 5-year were 74.7%, 49.3%, 30.7% and 25.3%, respectively. Sex (*HR* =0.529, *P*=0.048), ablation result (*HR*=5.824, *P*=0.000) and Albumin-bilirubin (ALBI) score (*HR*=2.725, *P*=0.011) were independent prognostic factors for OS. Alpha-fetoprotein (AFP) (*HR* =2.360, *P* = 0.005) and tumor number(*HR*=2.786, *P*=0.000) were independent prognostic factors for RFS.

Conclusions: Percutaneous thermal ablation combined with TACE is a safe and effective treatment for HCV-related HCC. Sex, ablation result and ALBI are

significant prognostic factors for OS. AFP and tumor number are significant prognostic factors for RFS.

KEYWORDS

hepatocellular carcinoma, transcatheter arterial chemoembolization, percutaneous thermal ablation, overall survival, recurrence, prognosis

Introduction

Primary liver cancer is the sixth most common cancer in the world, accounting for the fourth cause of cancer death worldwide in 2018, with about 841000 new cases and 782000 deaths each year (1). Hepatocellular carcinoma (HCC) accounts for about 85-90% of all primary liver cancers (2). Hepatitis virus B Virus (HBV) and Hepatitis C virus (HCV) are the main risk factors for HCC (3, 4). Although the incidence of HCV-related HCC is lower than that of HBV-related HCC, with the aging and population growth, the expected burden of HCV-related HCC in China is rising (5). Curative therapies for early-stage HCC includes surgical resection, liver transplantation and percutaneous ablation. Owing to cirrhosis almost accompanying all HCV-related HCC, percutaneous ablation, especially thermal ablation is usually useful alternative modalities for these patients. Recent studies have showed that percutaneous ablation combined with transcatheter arterial chemoembolization (TACE) may have synergistic effect in the treatment of early and intermediate stages HCC (6). However, there are few studies focused on the efficacy and prognosis of HCV-related HCC receiving percutaneous thermal ablation combined with TACE.

In this study, we aimed to identify the efficacy, safety and survival of HCV-related HCC after percutaneous thermal ablation with TACE in HBV-endemic area.

Material and methods

Patients

We retrospectively reviewed a total of 507 consecutive treatment-naive patients with HCC who underwent percutaneous thermal ablation combined with TACE at Beijing You An Hospital, Capital Medical University from July 2006 to January 2016. Inclusion criteria for this study were as follows: (1) HCV-infected patients; (2) a single tumor with a maximum size smaller than 7 cm and tumor number less than 5; (3) no invasion of adjacent organs or tumor thrombi in portal, vein and bile ducts system, and no extrahepatic metastasis; (4) no serious non-liver underlying illness including heart, brain, lung, kidney and other organs dysfunction, and no other tumor diseases; (5) liver function of Child-Turcotte-Pugh (CTP) class A and B; ECOG (Eastern Cooperative Oncology Group) performance status score 0~1; (6) platelet count ≥50 × 10^9/L for percutaneous thermal ablation, prothrombin time ratio ≥ 50% and total bilirubin<50umol/L for both TACE and percutaneous thermal ablation; (7) no upper digestive track bleeding due to portal hypertension within 1 month before TACE; (8) no uncontrolled infection; (9) complete case and follow-up data. This research scheme has been exempted from the requirement of informed consent and approved by the Ethics Committee of our hospital. As summarized in Figure 1, among the 507 patients, the remaining 83 patients met the inclusion criteria, including 30 patients who were diagnosed with HCC histologically by liver biopsy, and another 53 patients, who were diagnosed by imaging diagnosis.

Pretreatment evaluation

The pretreatment assessment of each patient included spiral computed tomography (CT) of chest, either Contrast-enhanced CT (CECT) or contrast-enhanced magnetic resonance imaging (CEMRI) of the abdomen, electrocardiogram, complete blood count (CBC), liver and renal function tests, prothrombin time, alpha-fetoprotein (AFP), HCV RNA. According to the guidelines for diagnosis and treatment of primary liver cancer (China, 2017 edition) (7), patients with maximum tumor diameter 1-2cm confirmed by 2 typical contrast enhancement imaging presentations, or maximum tumor diameter more than 2cm confirmed by 1 typical contrast enhancement imaging presentations or histopathological examinations were diagnosed with HCC.

We collected baseline clinical data including: age, gender, CBC, albumin (ALB), total bilirubin(TBIL), glutamic pyruvic transaminase(ALT), glutamic oxaloacetic transaminase(AST), cholinesterase(CHE), prothrombin time(PT), AFP, CTP grade, tumor characteristics. We calculated Albumin-bilirubin (ALBI) score as follows, ALBI = 0.66 × Log10(TBIL μmol/L) -0.085 × (ALB g/L). ALBI grade was classified as grade 1 (≤−2.60), grade 2 (−2.60 to −1.39), or grade 3 (>−1.39), respectively.

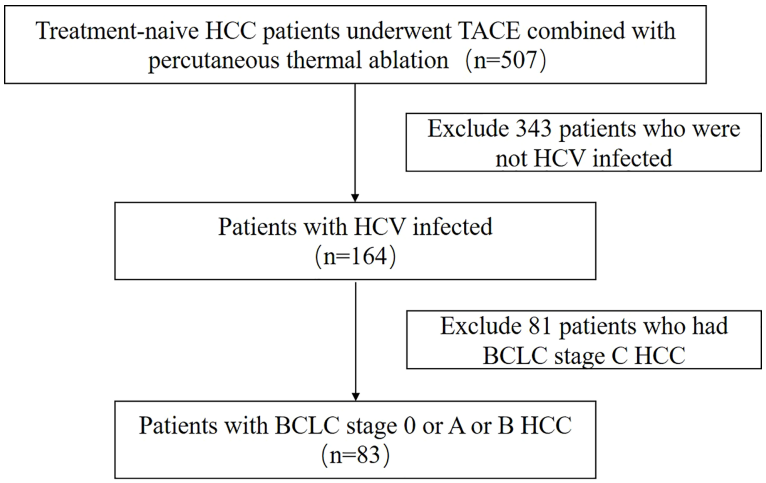

FIGURE 1
Patient flowchart.

TACE

All TACE are conventional-TACE(c-TACE). TACE was performed first.Seldinger catheterization was used to intubate the right femoral artery, and angiography of the hepatic artery was performed to observe the location, size, number, arterial supply of tumors. Catheters and microcatheters (Asahi Intecc Co., Ltd., Japan) was inserted into the target branch. Iodized oil (Guerbet, Villepinte, Seine-Saint-Denis, France), and doxorubicin (Pfizer Inc., NY, USA) suspension emulsion were injected into the arterial branches followed by injection of gelatin sponge particles (350~560um, Hangzhou Alicon Pharmaceutical Technology Co., Ltd. Hangzhou, China). The dose of the drugs depended on the tumor size, liver function, white blood cell count and platelet count of the patient. One week later, CT scan of the abdomen was performed to evaluate the effect of TACE. The TACE procedure was repeated if the effect was not satisfactory.

Radiofrequency ablation/microwave ablation

Thermal ablation was carried out within 2 weeks after TACE. CT scanning was performed to determine the puncture site and approach. After routine sterilization and focal anesthesia, the RFA electrode needle or microwave antenna was used to puncture the tumor under CT guidance. The ablation was performed according to the predetermined ablation conditions. According to the ablation range of each tumor, the RFA electrode needles or microwave antennas were adjusted to achieve an overlapping ablative margin that would theoretically include the tumor and 0.5~1 cm of surrounding tissue. After the ablation range was satisfied, the electrode needle or microwave antennas were withdrawn, and the needle tunnel was ablated at 70°C-90°C to reduce the risk of hemorrhage or implantation metastasis *via* the needle tunnel. CECT or CEMRI of the abdomen was performed within 1 week after ablation to evaluate technique effectiveness. If the imaging examination showed an enhanced area within or around the original tumor, we suspected that incomplete ablation portions remained, and the RFA/MWA procedure was repeated if the liver function met the requirements.

Treatment was continued until CT or MRI imaging demonstrated necrosis of the entire tumor. CECT or CEMRI was performed one month after the treatment to determine the effects of ablation, which were classified as complete response (CR) or incomplete response (ICR). CR was defined as CECT or CEMRI detection of a non-enhanced area with necrosis at the ablation site of the HCC nodules. Patients with CECT or CEMRI evidence lacking CR were defined as ICR and received repeated salvage RFA/MWA treatment. The evaluations were repeated 1month after salvage treatment. Those who failed to obtain CR after repeated salvage RFA/MWA were regarded as treatment failure (TF). In these cases, liver transplantation, resection, TACE, or other treatments were considered.

Follow-up

The follow-up protocol included AFP assays, CECT or CEMRI of the abdomen and liver function every 3 months after treatment and more frequently when needed. CT of chest was performed every 6 months or if tumor recurrence was

suspected. Tumor recurrence includes local recurrence, intrahepatic recurrence and extrahepatic recurrence. Overall survival (OS) was defined as the interval between the date of the initial TACE and the death, or the end of the study for patients who survived. Recurrence free survival (RFS) was defined as the interval between the date of the CR and the recurrence or death or the end of the study for patients who did not experience recurrence.

Statistical analysis

SPSS software version 22.0 (SPSS, Inc., Chicago, IL, USA) was used to statistically analyze data. Quantitative variables were expressed as mean ± standard deviation or as medians, ranges. Survival rates were estimated using the Kaplan-Meier method and compared using the log-rank test. The OS and RFS rates were assessed by the Kaplan-Meier method with the log-rank test. Univariate and multivariate analysis was carried out by Cox proportional hazards regression model to assess independent risk factors of OS and recurrence. $P<0.05$ was defined as statistically significant.

Results

Characteristics of the patients

Baseline characteristics of the 83 patients who underwent percutaneous thermal ablation combined with TACE were showed in Table 1.

Treatment response

Among the 83 treated patients, 80 patients underwent a single TACE, and 3 patients underwent two TACE for successful embolization of the tumor artery. We performed 110 thermal ablation including 89 RFA and 21 MWA for 176 tumor lesions in 83 patients. 58 patients underwent a single thermal ablation, 23 patients underwent two thermal ablation and 2 patients were treated with three thermal ablation in order to achieve the complete response. 92.8% patients (77/83) and 96.6% (170/176) tumor lesions achieved CR 1 month after all treatment, and 7.2% (6/83) patients and 3.4% (6/176) tumor lesions were identified as ICR. 100% patients in the BCLC-0 group, 97.9% (46/47) in the BCLC-A group and 81.5% (22/27) in the BCLC-B group achieved CR.

During treatments, there were no serious adverse reactions such as liver failure, biliary bleeding, abdominal bleeding, pericardial tamponade, liver abscess and treatment-related death. 10.8% (9/83) patients had minor complications such as puncture point pain, liver pain, fever, nausea and vomiting, abdominal distension, mild liver function injury, ascites or pleural effusion, and recovered by conservative treatment.

Follow-up results

Until January 31st 2020, the median follow-up period was 73months (ranging from 7-139months). At the end of follow-up, 57.8%(48/83) patients died and 42.2%(35/83) patients survived. The median OS was 60 months (95% confidence interval (*CI*)= 48.0-72.0), and the 1-, 2-, 3-, 5- and 10-year cumulative OS rates were 94%, 78.3%, 72.3%, 43.4% and 27.5%, respectively. The 1-, 2-, 3-, 5- and 10-year cumulative OS rates in patients with BCLC−0/A HCC were 98.2%, 89.3%, 83.9%, 51.4%, 32.7%, and 85.2%, 55.6%, 48.1%, 27.2% in patients with BCLC−B. There was significant difference in OS among the two groups (χ^2 = 10.134, P=0.001)(Figure 2).

During the follow-up period, 77.9%(60/77) patients who achieved CR from the thermal ablation combined with TACE experienced recurrence. The cumulative RFS rates at 1-, 2-, 3- and 5-year were 74.7%, 49.3%, 30.7% and 25.3%, respectively. The median RFS of BCLC BCLC-0/A/B HCC was 32 months (95% *CI*= 23.1-40.9), 28 months (95% *CI*= 18.9-37.1) and 18 months (95% *CI*= 15.9-20.1), respectively.

Multivariate analysis

The factors associated with OS were summarized in Table 2. Univariate analysis

indicated 8 factors were related with OS, and multivariate analysis confirmed that only three factors including sex (*HR* =0.529, *P*= 0.048), ablation result (*HR*=5.824, *P*=0.000), ALBI (*HR*=2.725, *P*=0.011)were independent prognostic factors for OS.

The factors associated with RFS were summarized in Table 3. Univariate analysis

indicated 4 factors were related with RFS, and multivariate analysis confirmed that two factors including AFP (*HR* =2.360, *P* = 0.005) and tumor number (*HR*=2.786, *P*=0.000) were independent prognostic factors for RFS.

Discussion

Percutaneous thermal ablation is considered to be the optimum local treatment for patients with early-stage unresectable lesions, liver cirrhosis or elderly patients. Percutaneous MWA had similar therapeutic effects and complication rate compared with RFA for HCC (8). Recent studies revealed that combination of thermal ablation and TACE

TABLE 1 Clinical characteristics of patients.

Variable	Value
Age (years)	
Mean (range)	61.83 ± 8.49 (40-84)
Sex	
Males	49 (59.04%)
Females	34 (40.96%)
Cirrhosis	
No	7 (8.43%)
Yes	76 (91.57%)
Ablation result	
CR	75 (90.36%)
ICR	8 (9.64%)
HCV-RNA	
Positive	69 (83.13%)
Negative	14 (16.87%)
ALBI	
Grade 1	24 (28.92%)
Grade 2	52 (62.65%)
Grade 3	7 (8.43%)
CTP	
A	70 (84.34%)
B	13 (15.66%)
AFP levels(ng/ml)	
≤7	26 (31.33%)
>7	57 (68.67%)
Tumor number	
≤1	37 (44.58%)
>1	46 (55.42%)
Diameter of largest tumor (cm mean (range))	2.77 ± 1.19 (1.00-7.00)
≤3.0	53 (63.86%)
>3.0	30 (36.14%)
Tumor location	
Right lobe of liver	49 (59.04%)
Left lobe of liver	15(18.07%)
Right and left lobe of liver	19(22.89%)
BCLC stage	
0	9 (10.84%)
A	47 (56.63%)
B	27 (32.53%)

SD, standard deviation; HCV, hepatitis C viruses; ALB, albumin; TBIL, total bilirubin; ALT, glutamic pyruvic transaminase; AST, glutamic oxaloacetic transaminase, CHE, cholinesterase; AFP, alpha fetoprotein.

is an effective option for patients with early or intermedium stage HCC (6, 9). TACE prior to percutaneous ablation can not only block the feeding arteries to reduce tumor burden, but also detect satellite nodules and label range of carcinoma. This treatment mode can increase complete ablation rate and reduce the risk of ablation-related bleeding (10). Zhen et al. (11) divided 189 patients into two groups (RFA group, TACE-RFA group); they found that the 1-, 3-, and 4-year OS for the RFA group and the TACE-RFA group were 85.3%, 59%, and 45.0% and 92.6%, 66.6%, and 61.8%, respectively (*HR*=0.525, 95% *CI*:0.335-0.822, *P*=0.002), and the corresponding RFS were 66.7%, 44.2%, and 38.9% and 79.4%, 60.6%, and 54.8%, respectively(*HR*=0.575, 95% *CI*:0.374 to 0.897, *P* = 0.009).

In this study, the CR rate at 1 month was 96.6% in the combination treatment similar to the obtained in previous studies (12). In subgroup analysis, CR rate of BCLC 0 was 100%, and that of BCLC A was 97.9%. The reason that one patient belonged to BCLC A did not achieve CR was considered that tumors was close to portal vein. In addition, there were only minor complications in 10.8% patients. These data suggest that TACE combined with thermal ablation was safe and effective in the treatment of HCV-related hepatocellular carcinoma, although this is an observational study without control.

It is reported that the long-term prognosis of HCV-related HCC is about 50% with the 5-year OS rate after curative treatment (13). Ren Y et al (9) analyzed 128 HCC patients mainly including HBV-HCC (85.2%) and showed the 1-, 3-, 5- and 8-year survival rates were 90.6%, 76.6%, 68.0%, 68.0%. In our study, after long-term follow-up, the 1-year, 2-year, 3-year, 5-year and 10-year cumulative OS rate were 94%, 78.3%, 72.3%, 43.4% and 27.5%, respectively, and the curative effect in first three years is similar to that reported in HBV-HCC. However, the long term outcome was poorer than that of HBV-HCC reported before. This finding may be attributed to different tumor characteristics or hepatocarcinogenesis between HCV-HCC and HBV-HCC (14, 15).

Previous studies have shown that liver function and field factors might play an important role in prognosis of patients with HCV-related HCC. Due to the subjective judgment of ascites and hepatic encephalopathy, the CTP system was not accurate. Johnson et al. (16) established a novel and objective evaluation model for liver functional reserve assessment called ALBI grade composed of albumin and bilirubin. A number of retrospective studies further confirmed that ALBI grade can predict the prognosis patients with HCC after hepatectomy, liver transplantation, RFA or TACE (17–20). An C et al. (21) recruited 183 patients of HCV-related HCCs and constructed a nomogram which was based on ALBI grade and could provide prediction of long-term outcomes for HCV-related HCC patients after US-PMWA. In the current study, we also identified that ALBI grade determined prognosis for OS of patients with HCV-related HCC underwent thermal ablation combined with TACE. In addition, Univariate and multivariate analysis demonstrated that incomplete ablation of tumors and male were also independent unfavorable prognostic factors for poor OS. Among the 3 factors, incomplete ablation was the most important prognostic factor. Considered reasons of incomplete

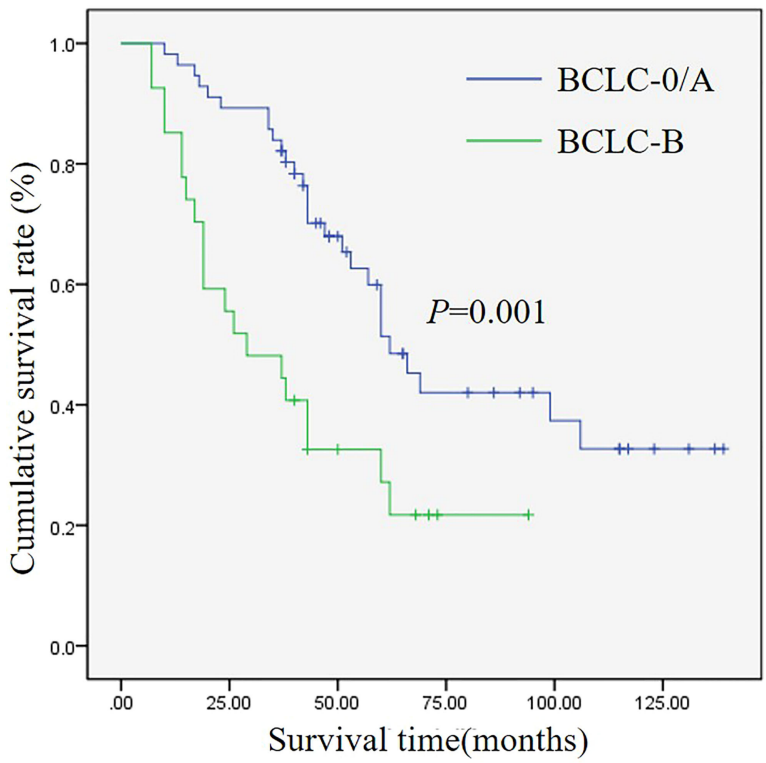

FIGURE 2
Kaplan-Meier analysis of OS for patients with different BCLC stages.

TABLE 2 Univariate and multivariate analysis of overall survival after percutaneous thermal ablation combined with TACE in patients with HCV-related HCC.

Variable		Case No.	Univariate Analysis		Multivariate Analysis	
			HR (95%CI)	P	HR (95%CI)	P
Sex	Males/Females	49/34	0.466 (0.254-0.853)	0.013	0.529 (0.281-0.944)	0.048
Age (years)	<60/≥60	34/49	1.384 (0.767-2.50)	0.281		
cirrhosis	Yes/No	76/7	0.295 (0.071-1.219)	0.092		
HCV-RNA	Positive/Negative	69/14	0.949 (0.421-2.137)	0.899		
Ablation result	CR/ICR	75/8	5.606(2.408-13.052)	0.000	5.824 (2.436-13.926)	0.000
WBC ($\times10^9$)	<4.0/≥4.0	45/38	1.000 (0.565-1.768)	0.999		
PLT ($\times10^9$)	<100/≥100	51/32	0.645 (0.352-1.180)	0.155		
ALT(U/L)	<45/≥45	41/42	1.199 (0.676-2.129)	0.535		
AST(U/L)	<37/≥37	17/66	2.047 (0.869-4.820)	0.101		
ALB(g/L)	<35/≥35	30/53	0.551 (0.308-0.986)	0.045		
TBIL (umol/L)	≤21/>21	58/25	1.831 (1.024-3.274)	0.041		
ALBI	Grade 1	24	1		1	
	Grade 2	52	3.035 (1.437-6.409)	0.004	2.725 (1.263-5.881)	0.011
	Grade 3	7	3.859 (1.145-12.998)	0.029	3.059 (0.881-10.617)	0.078
CHE(U/L)	<4000/≥4000	36/47	0.429 (0.242-0.760)	0.004		

(Continued)

TABLE 2 Continued

Variable		Case No.	Univariate Analysis		Multivariate Analysis	
			HR (95%CI)	P	HR (95%CI)	P
PT(s)	≤12.8/>12.8	64/19	1.934 (1.012-3.697)	0.046		
CTP	A/B	70/13	2.712 (1.319-5.580)	0.007		
AFP (ng/ml)	<7/≥7	26/57	1.448 (0.766-2.740)	0.255		
Tumor number	<1/≥1		0.564 (0.312-1.019)	0.058		
Diameter of largest tumor (cm)	≤3/>3	53/30	1.029 (0.569-1.864)	0.924		
Tumor location	Right lobe of liver	49	1			
	Left lobe of liver	15	1.208 (0.549-2.661)	0.639		
	Right and left lobe of liver	19	1.564 (0.803-3.046)	0.188		
Ablation type	RFA/MWA	70/13	1.086 (0.456-2.590)	0.852		

ablation, except for the fact that it is difficult to achieve CR for tumors close to the large vessels, it may be related to poor differentiation of tumor or microvascular invasion in some patients before therapy. It is suggested to enlarge the cohort and collect the pathological results. The decreased expression of estrogen receptor alfa (ERα) in male patients may explain the worse prognosis of HCV-related cirrhosis and HCC in men than in women (22).

TABLE 3 Univariate and multivariate analysis of RFS after percutaneous thermal ablation combined with TACE in patients with HCV-related HCC.

Variable		Case No.	Univariate Analysis		Multivariate Analysis	
			HR(95%CI)	P	HR (95%CI)	P
Sex	Males/Females	44/31	0.492 (0.285-0.849)	0.011		
Age (years)	<60/≥60	31/44	0.964 (0.574-1.616)	0.888		
cirrhosis	Yes/No	68/7	1.454 (0.621-3.401)	0.388		
HCV-RNA	Positive/Negative	61/14	0.872 (0.426-1.783)	0.707		
WBC ($\times10^9$)	<4.0/≥4.0	41/34	1.639 (0.976-2.753)	0.062		
PLT ($\times10^9$)	<100/≥100	45/30	1.471 (0.873-2.477)	0.147		
ALT (U/L)	<45/≥45	37/38	1.345 0.805-2.248)	0.258		
AST (U/L)	<37/≥37	15/60	1.130 (0.595-2.148)	0.708		
ALB (g/L)	<35/≥35	25/50	0.889 (0.492-1.606)	0.697		
TBIL (umol/L)	≤21/>21	53/22	0.764 (0.425-1.376)	0.371		
ALBI	Grade 1	23	1			
	Grade 2	48	1.919 (1.052-3.502)	0.034		
	Grade 3	4	1.617 (0.467-5.597)	0.448		
CHE (U/L)	<4000/≥4000	30/45	0.866 (0.500-1.501)	0.608		
PT (s)	≤12.8/>12.8	59/16	0.848 (0.439-1.637)	0.624		
CTP	A/B	66/9	1.386 (0.622-3.087)	0.424		
AFP (ng/ml)	<7/≥7	23/52	2.055 (1.148-3.678)	0.015	2.360 (1.300-4.284)	0.005
Tumor number	<1/≥1	35/40	2.488 (1.446-4.281)	0.001	2.786 (1.599-4.856)	0.000
Diameter of largest tumor (cm)	≤3/>3	53/22	1.258 0.726-2.180)	0.413		
Tumor location	Right lobe of liver	46	1			
	Left lobe of liver	14	0.463 (0.213-1.008)	0.052		
	Right and left lobe of liver	15	0.964 (0.510-1.821)	0.911		
Ablation type	RFA/MWA	63/12	1.333 (0.671-2.647)	0.412		

Several studies showed that sustained virological response (SVR) is associated with the favorable long-term survival after curative resection or ablation (23, 24). However, in this study, HCV-RNA is not related to OS of patients after thermal ablation combined with TACE. We consider that there were only few cases (14/69) achieve virological response when antiviral therapy was applied.

The 1-year, 2-year, 3-year and 5-year RFS rates of patients in this study were 74.7%, 49.3%, 30.7% and 25.3%, respectively, similar to those previously reported (25). It is reported that, tumor-related factors were risk factor for recurrence of HCC patients after curative treatment, such as AFP, tumor size, tumor number, pathological type, etc. (25–27). In this study, we identified only AFP levels and tumor number were associated with RFS probability in HCV-related HCC patients after thermal ablation combined with TACE. Tumor size was not risk factor for recurrence of HCC, probably because of the low proportion of patients with tumors larger than 3 cm (n=30, 36.14%).

There were some limitations in this study. First of all, this was a single-center and retrospective study, and we could not completely avoid referral bias. Second, this was a single-arm study. The effects of combined therapy on the survival of patients between HCV-related HCC and HBV-related HCC were not compared. Finally, the sample of this study is relatively small. Further prospective randomized controlled trials are necessary to validate our observations.

Conclusions

The data of our study indicated that percutaneous thermal ablation combined with TACE is an effective and safe ablation modality for patients with HCV-related HCC. Sex, ablation result and ALBI were independent prognostic factors for survival after percutaneous thermal ablation combined with TACE for HCC.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Capital Medical University affiliated Beijing Youan Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceived and designed the protocol: CY. Collected data: YS and JL. Wrote the manuscript: YS and HZ. Analyzed data: JZ and YZ. Critically revised and approved the final version of manuscript: CY. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Hepatic arterial infusion chemotherapy combined with PD-1 inhibitors and tyrosine kinase inhibitors for unresectable hepatocellular carcinoma: A tertiary medical center experience

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Background: Unresectable hepatocellular carcinoma (u-HCC) still accounts for the majority of newly diagnosed HCC which with poor prognosis. In the era of systemic therapy, combination therapy with programmed cell death protein-1 (PD-1) inhibitors and tyrosine kinase inhibitors (TKIs) has become mainstream. Hepatic arterial infusion chemotherapy (HAIC) as a local treatment has also shown a strong anti-tumor effect. This study aimed to investigate the efficacy and safety of HAIC, PD-1 inhibitors plus TKIs for u-HCC.

Methods: This retrospective study included patients with initially u-HCC between October 2020 to April 2022 who had received at least one cycle of therapy with HAIC, PD-1 inhibitors plus TKIs. The primary outcome included overall response rate (ORR), the disease control rate (DCR), surgical conversion rate, progression-free survival (PFS) and treatment-related adverse events.

Results: A total of 145 patients were included in the study. The median treatment cycle of HAIC and PD-1 inhibitors were 3 and 4, respectively. According to the modified RECIST criteria, the best ORR was 57.2% (83/145), 9 had achieved complete response (CR), DCR was 89.7% (130/145). Median time to achieve CR or PR was 65 days. Surgical conversion rate was 18.6% (27/145), seven patients (7/27,25.9%) achieved pathological complete response (pCR). The median follow-up was 12.5 months (4.5-20 months), and the

median PFS was 9.7 months. Subgroup analysis showed that Child-pugh A patients had higher DCR (92.2% vs 79.3%, p=0.041) than Child-pugh B patients, as well as increased successful conversion rate (22.4% vs 3.4%, p=0.019). Patients without vascular invasion and extrahepatic metastases showed higher PR (63.4% vs 43.3%, p<0.05) and ORR (73.2% vs 50.0%, p<0.05) than those with vascular invasion. The ORR (73.2% vs 45.5%, p<0.05) and DCR (95.1% vs 78.8%, p<0.05) were also significantly better than those of patients with extrahepatic metastases. HAIC regimen was not related to efficacy (All p>0.05). The incidence rate of grade 3/4 treatment-related AEs was 17.7% without fatal events.

Conclusion: The triple combination therapy of HAIC and PD-1 inhibitors plus TKIs for patients with initially unresectable HCC exhibited satisfactory efficacy with tolerable toxicity.

KEYWORDS

unresectable hepatocellular carcinoma, hepatic arterial infusion chemotherapy, programmed cell death protein-1, tyrosine kinase inhibitors, conversion therapy

Introduction

Hepatocellular carcinoma (HCC) is still the most common kinds of malignant tumors worldwide, although the morbidity is decreasing stably in China (1). The prognosis of HCC remains poor, and approximately 830000 newly deaths every year (2). Although progress has been made in early screening for HCC, the majority have lost the chance of cure at the time of diagnosis. These so called "unresectable HCC" (u-HCC) have worse prognosis with the median overall survival (OS) ranging from 1 to 2 year (3).

Systemic therapy is the preferred option for u-HCC patients with the advent of sorafenib, but the objective response rate (ORR) remains far from satisfactory. With the publications of REFLECT, RESORCE, CELESTIAL and REACH-2 study, more novel tyrosine kinase inhibitors (TKIs) have been the alternative modality of sorafenib, such as lenvatinib, apatinib, cabozantinib, and ramucirumab, but the outcomes remain poor with the ORR of 4% to 18.8% (4). Trial of CheckMate040 has ushered the era of immunotherapy for HCC in the recent years, but phase III CheckMate459 trials of PD-1 inhibitors monotherapy for HCC have all failed to meet the primary endpoints (5). Dual combination regimen, such as lenvatinib plus pembrolizumab, camrelizumab plus apatinib, and sintilimab plus anlotinib, have yielded promising clinical efficiency and safety, but the prognosis for those u-HCC patients is still unsatisfactory with the median OS of 20.1 to 20.4 months (6–8).

IMbrave150 trial has not only opened the era of molecular target and immunotherapy, but also shed light on the triple combination of local regional therapy, TKIs, and immunotherapy. In the trial of IMbrave150, about 40% patients received previous transarterial chemoembolization (TACE) before enrollment (9). In the recent years, hepatic arterial infusion chemotherapy (HAIC) has been identified to be alternative strategy of TACE in the management of advanced HCC, which has the advantage over TACE for those with extrahepatic metastasis or macrovascular invasion (10, 11). Combination of HAIC and sorafenib has exhibited significant survival benefit compared with sorafenib or HAIC alone, but the 2-year survival rate remains low (12, 13).

In addition, "conversion therapy" has been well concerned in the field of HCC, which needs a more aggressive strategy. In the past two years, triple therapy of TACE/HAIC, TKIs, and immune checkpoint inhibitors (ICIs) have been tried with encouraging results, but most of the studies were retrospective with small sample size. In this study, we aimed to evaluate the clinical efficacy and safety of the triple regimen of HAIC, PD-1 inhibitors and TKIs for u-HCC patients in a retrospective study of single-center.

Patients and methods

Patients selection

All consecutive patients in our hospital diagnosed as u-HCC and received triple therapy of HAIC, PD-1 inhibitors and TKIs from October 2020 to April 2022 were enrolled in this study. The exclusion criteria were as followed: 1) age <18 years old, 2) recurrent HCC, 3) receiving other antitumor treatment, 4)

postoperative adjuvant HAIC, 5) terminated treatment, and 6) without treatment evaluation. Of note, the definition of u-HCC in this study was oncologically or biologically unresectable: technically resectable, but resection does not result in a better outcome than non-surgical treatment.

This study was approved by the Ethics Committee of The First Affiliated Hospital of Nanchang University, Nanchang, China. No (2022). CDYFYYLK (06–009). Considering that patients medical records were analyzed retrospectively and no patient-identifiable information was utilized, the ethics committee waived the need for individual consent.

HAIC procedure

The procedure of HAIC was similar as previous report and the regimens in this study included FOLFOX (HAIC with oxaliplatin, 5-fluorouracil, and leucovorin) and RALOX (HAIC with raltitrexed plus oxaliplatin). Briefly, the femoral artery was punctured by the Seldinger technique after local anesthesia, then the blood supply of the tumor was determined using the digital subtraction angiography, and at last a 2.7-F microcatheter was maintained at the tumor-feeding arteries for HAIC. HAIC was carried out in the ward within two days, during which the microcatheter was connected externally to an artery infusion pump. Notably, the dose of drugs would be adjusted according to the Child–Pugh grade and tolerance to chemotherapy.

Tyrosine kinase inhibitors and PD-1 inhibitors

Considering the accessibility of drugs, TKIs in this study were sorafenib, apatinib and lenvatinib, and PD-1 inhibitors were camrelizumab, stintilimab and tislelizumab. The dose of these agents was administrated according to the guidelines, which would also be adjusted according to the performance status, liver function, and treatment tolerance.

Data collection

Collecting clinical data of patients during each hospital admission. Baseline clinical characteristics including: age, gender, Eastern Cooperative Oncology Group Performance Status (ECOG PS) score, positive or negative of hepatitis B surface antigen, liver cirrhosis, Child-Pugh classification, ALBI* grade, total bilirubin, albumin,α-fetoprotein (AFP) level, Barcelona Clinic Liver Cancer (BCLC) stage, Chinese Liver Cancer (CNLC) stage, American joint Committee on cancer (AJCC) stage, size of largest nodule, tumor number, tumor distribution, absence or presence of macroscopic vascular invasion (portal vein tumor thrombus or hepatic vein tumor thrombus), absence or presence of extrahepatic metastasis. At the same time, the imaging examination results of each patient were collected to evaluate the efficacy response. The patient's follow-up treatment was also collected.

* ALBI: albumin-bilirubin; Calculated using the following equation: linear predictor = ($\log_{10}$ bilirubin μmol/L×0.66) + (albumin g/L×−0.085). The continuous linear predictor was further categorized into three different grades for prognostic stratification purposes: grade 1 (less than −2.60), grade 2 (between −2.60 and −1.39) and grade 3 (above −1.39) (14).

Follow-up

The triple therapy was terminated if complete response (CR) was achieved, the patient received surgery, the disease progressed or the patient experienced intolerable toxicity. Blood examination including blood cell analysis, biochemistry, and AFP were performed before and after each cycle of treatment. Abdominal contrast-enhanced CT scan or MRI and chest computed tomography (CT) every cycle (4–6 weeks) after initial treatment. Patients were followed up every 3 months until death or censored.

Outcomes

The primary end points of this study were safety and PFS. The complete response (CR), objective response rate (ORR), disease control rate (DCR) and successful conversion rate were also recorded.

The tumor response was assessed by two independent experienced radiologists according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria and RECIST 1.1 criteria based on the abdominal enhanced CT or MRI and chest CT, as well as AFP levels. CR was defined as the disappearance of all lesions or no enhancement by enhanced CT/MRI for at least 4 weeks and normal AFP levels. If there were discrepancies in the assessments between the two independent radiologists, another radiologist was asked to evaluate the response to determine the tumor response rate.

PFS was defined as the time from initial treatment to disease progression or death from any reason. Disease progression included intrahepatic tumor and/or extrahepatic tumor progression.

Safety was assessed among all the patients treated, and all the treatment-related adverse events (AEs) were determined by the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0), but the immune-related AEs (irAEs) were diagnosed, managed and followed-up according

to the European Society for Medical Oncology Clinical Practice Guidelines.

Statistical analyses

Continuous variables including age, AFP level, ALBI grade, total bilirubin, albumin, tumor size, and tumor number were categorized as previously reported, all the variables in this study were presented as n (%). Survival analysis was calculated using the Kaplan-Meier method. Subgroup analysis was conducted stratified by different Child-pugh classification, BCLC stage and regimen. All the statistical tests were two-tailed, and $p<0.05$ was considered to be statistically significant. Statistical tests were conducted using RStudio, including the Table 1, survminer, rms, and survival packages.

Results

Patient clinic characteristics

Initially, 235 patients receiving HAIC+PD-1+TKIs were identified. 90 patients were excluded as followed: 1) receiving postoperative recurrence therapy (n=35), 2) receiving postoperative adjuvant therapy (n=32), 3) combined with other types of malignant tumor (n=3), 4) lost to follow up (n=14),5) terminated treatment (n=3) and 6) efficacy not evaluated (n=3). And at last, 145 patients were eligible for further analysis (Figure 1).

The baseline characteristics of the included patients were depicted in Table 1. Of note, 29 (20%) patients were present with Child-Pugh B, 109 (75.1%) were with ALBI grade 2 and 3, 75 (51.7%) were with macrovascular invasion, and 33 (22.8%) were with extrahepatic metastasis.

Table 2 exhibited the regimens of the triple combination therapy, including the HAIC regimen, PD-1 inhibitors scheme and TKIs prescription. Briefly, the median cycle teratment of HAIC and PD-1 inhibitors were 3 and 4, respectively. Specially, TKIs and PD-1 inhibitors regimens were diverse,lenvatinib+camrelizumab (n=91), lenvatinib +stintilimab (n=16), lenvatinib+tislelizumab (n=6), sorafenib +camrelizumab (n=19), sorafenib+stintilimab (n=4), and apatinib+camrelizumab (n=9), respectively.

Outcomes

The median follow-up was 12.5 months (4.5-20 months), and the median PFS was 9.7 months (1-16.1 months, Figure 2). The corresponding PFS rates at 6-months, 9-months, 12-months and 15-months were 66.9%, 55.2%, 51.7%, and 48.3%, respectively.

Figure 3 summarized the results of the best response (mRECIST and RECIST 1.1). For consistency, tumor response was only depicted using mRECIST in the following section. During the follow-up period, 9 (6.2%) patients achieved CR, 74 (51%) achieved PR, 47 (32.5%) achieved SD, and 15 (10.3%) achieved PD. The ORR reached 57.2%, as well as increased DCR of 89.7%. The median time to achieve CR or PR was 65 days (21-175 days). A waterfall plot showed the change in the intrahepatic target lesion size of patients (Figure 4).

Twenty-seven patients received surgery, and the successful conversion rate was 18.6% (27/145) with the median duration of triple therapy was 91 days. All 27 patients underwent open hepatectomy and recovered well after surgery. Two patients developed serious complications, including postoperative liver failure, massive pleural effusion, and dyspnea, but were recovered after symptomatic treatment. All (100%) patients achieved R0 resection, and 7 (25.9%) were confirmed to achieve pathological CR (pCR). Until June 2022, 9 (33.3%) patients had tumor recurrence or metastasis.

Subgroup analysis

According to Child-Pugh classification, 116 (80.0%) patients were graded A and 29 (20.0%) were B, respectively. Subgroup analysis showed that the best response was in favor of patients with Child-Pugh A in terms of PD, DCR, and successful conversion rate compared with those with Child-Pugh B (all $p<0.05$, Table 3A).

In this study, 60 patients with macrovascular invasion (no extrahepatic metastasis), 33 patients had extrahepatic metastasis. Results showed that the best PR (63.4% vs 43.3%, $p<0.05$) and ORR (73.2% vs 50.0, $p<0.05$) in the subgroup of patients with macrovascular invasion was significantly lower than that without macrovascular invasion. The ORR (73.2% vs 45.5%, $p<0.05$) and DCR (95.1% vs 78.8%, $p<0.05$) of patients without extrahepatic metastases were significantly higher than those with extrahepatic metastases (Table 3B).

According to the regimen of HAIC, 113 (77.9%) patients received FOLFOX regimen and 32 (22.1%) received RALOX regimen, respectively. No differences were observed between the two subgroups in terms of all the best response (all $p>0.05$, Table 3C).

Adverse events

The majority of patients experienced treatment-related AEs (Figure 5), but most of the AEs were mild or curative after treatment. The top three most common treatment-related AEs were elevated ALT, elevated AST, and fatigue, respectively. The incidence of grade 3/4 AEs were 17.7%, but none of the fatal AEs was reported. The top three most common grade 3/4 AEs were

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TABLE 1 Baseline clinical characteristics.

Characteristics		No. (%)
Age, years		
	≤50	61 (42.1)
	>50	84 (57.9)
Gender		
	Male	121 (83.4)
	Female	24 (16.6)
ECOG		
	0	138 (95.2)
	1	7 (4.8)
Hepatitis B virus infection		
	Positive	133 (91.7)
	Negative	12 (8.3)
Liver cirrhosis		
	Absent	30 (20.7)
	Present	115 (79.3)
Child-Pugh classification		
	A	116 (80.0)
	B	29 (20.0)
ALBI grade		
	1	36 (24.8)
	2	104 (71.7)
	3	5 (3.4)
Total bilirubin (μmol/L)		
	≦20	88 (60.7)
	>20	57 (39.3)
Albumin (g/L)		
	<40	114 (78.6)
	≧40	31 (21.4)
AFP (ng/ml)		
	≦400	63 (43.4)
	>400	82 (56.6)
BCLC stage		
	B	41 (28.3)
	C	104 (71.7)
CNLC stage		
	IIa	5 (3.4)
	IIb	36 (24.8)
	IIIa	71 (50.0)
	IIIb	33 (22.8)
AJCC stage		
	II	8 (5.5)
	IIIA	33 (22.8)
	IIIB	65 (44.8)
	IVA	22 (15.2)
	IVB	17 (11.7)
Size of largest nodule (cm)		
	<10	72 (49.7)
	≥10	73 (50.3)
Tumor number		
	Solitary	37 (25.5)
	Multiple	108 (74.5)
Tumor distribution		
	Uni-lobar	71 (49.0)
	Bi-lobar	74 (51.0)
Macrovascular invasion		
	Absent	70 (48.3)
	Present	75 (51.7)
	PVTT	66
	HVTT	7
	PVTT+HVTT	2
Extrahepatic metastasis		
	Absent	112 (77.2)
	Present	33 (22.8)

ECOG; Eastern Cooperative Oncology Group. ALBI, albumin-bilirubin; Calculated using the following equation: linear predictor = ($\log_{10}$ bilirubin μmol/L×0.66) + (albumin g/L×−0.085). The continuous linear predictor was further categorized into three different grades for prognostic stratification purposes: grade 1 (less than −2.60), grade 2 (between −2.60 and −1.39) and grade 3 (above −1.39);AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CNLC, China Liver Cancer; AJCC, American Joint Committee on Cancer; PVTT, Portal vein tumor thrombus; HVTT, Hepatic vein tumor thrombus.

hyperbilirubinemia, myelosuppression, and abdominal pain, respectively.

Subsequent therapy

A total of 79 patients continued to receive follow-up treatment (Table 4). Systemic therapy was still the first choice for these patients, the vast majority of patients continued to combine targeted and immunotherapy, and some patients added local therapy (TACE, HAIC). For metastases, microwave ablation and radiation therapy were also options.

Discussion

In this study, we reported 145 patients with initially unresectable HCC who received HAIC plus PD-1 inhibitors and TKIs with CR of 6.2%, ORR of 57.2%, DCR of 89.7%, and successful conversion rate of 18.6%. The median follow-up was 12.5 months, and the median PFS was 9.7 months. In addition, the triple combination therapy regimen has controllable toxic and side effects.

In the era of lack of systemic therapy, TACE is the main means of conversion therapy for u-HCC with the ORR of 12.0% 18.1% (15). With the publication of IMbrave150 trial, the treatment combination of TKIs and ICIs has become

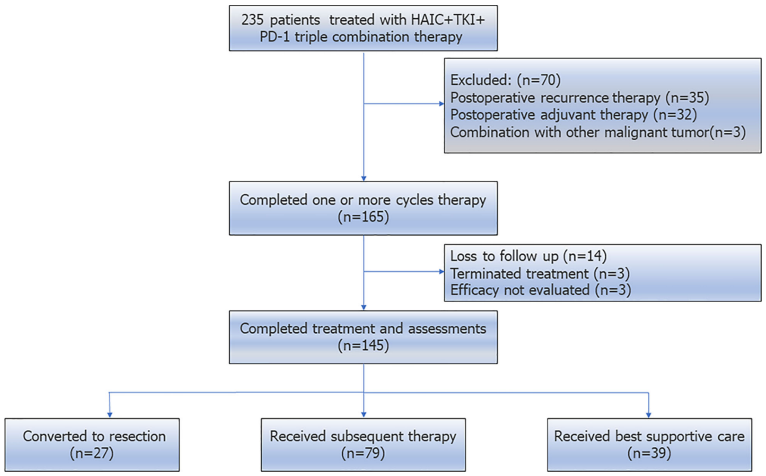

FIGURE 1
Patient selection flow. Initially, 235 patients receiving HAIC+TKIs+PD-1 were identified. And at last, 145 patients were eligible for further analysis.

mainstream, and the ORR has also reached 28.1%-38.6% (9). In addition, IMbrave150 also gave birth of an aggressive treatment for u-HCC, triple modality of arterial directed therapy (ADT), ICIs, and TKIs. Zheng, et al (16) firstly reported the combination treatment of TACE+sorafenib+ICIs for 29 u-HCC patients, and results showed that the triple therapy exhibited significant advantage over TACE+sorafenib in terms of DCR (81.82% vs. 55.17%, $p = 0.046$). This finding was verified by the subsequent studies and was also confirmed in the latest systematic review.

Recently, HAIC-based combination therapy has received increasing attention due to encouraging tumor response rates and patient survival rates. Table 5 depicted all the published reports of combination of HAIC and TKIs plus ICIs. The published studies were almost come from small size sample of 25 to 84, and the results varied greatly from each study with the CR ranging from 0% to 48%, ORR from 40% to 96%, and DCR from 77.6% to 100%, respectively (17–21). This divergence might be contributed to the difference in study population (macrovascular invasion or not, extrahepatic metastasis or not) and therapy regimen (sorafenib, apatinib or lenvatinib, toripalimab, sintilimab, pembrolizumab or camrelizumab). In the present study of 145 patients in a single center, the corresponding CR, ORR, and DCR were 6.1%, 57.2% and 89.7%, respectively. And the median PFS was 9.7 months in the whole cohort, but with 18.6% achieved successful conversation. These findings were coincident with previous studies, but limitations were: 1) the heterogneity of study population, 51.7% were present with macrovascular invasion and 22.8% were with extrahepatic metastasis; 2) the divergence of liver function, the ALBI ranged from grade 1 to 3 regard less of 80% grading Child-Pugh A.

TABLE 2 Regimens of the triple combination therapy.

Treatment		No. (%)
HAIC regimen	FOLFOX	113 (77.9)
	RALOX	32 (22.1)
TKI+PD-1 regimen	Lenvatinib+Camrelizumab	91 (62.8)
	Lenvatinib+ Stintilimab	16 (11.0)
	Lenvatinib+ Tislelizumab	6 (4.1)
	Sorafenib+ Camrelizumab	19 (13.1)
	Sorafenib+ Stintilimab	4 (2.8)
	Apatinib+ Camrelizumab	9 (6.2)
HAIC treatment cycle		
	Median (range)	3 (1-6)
PD-1 treatment cycle		
	Median (range)	4 (1-10)

HAIC, hepatic arterial infusion chemotherapy; FOLFOX, HAIC with oxaliplatin, 5-fluorouracil, and leucovorin; RALOX, HAIC with raltitrexed plus oxaliplatin; TKIs, tyrosine kinase inhibitors; PD-1, programmed cell death protein-1.

The underlying mechanism of the synergistic antitumor effect of the HAIC plus TKI and PD-1 might be as follows: 1) HAIC induces tumor antigen exposure through persistent high-concentration chemotherapeutic drug penetration, increases antigenicity through immunogenic cell death of tumor cells, and improves the tumor immune microenvironment to reduce off-targets, thereby enhancing the efficacy of systemic therapy (22); 2) chemotherapy drugs may activate adaptive immunity by increasing leukocyte antigen expression and enhancing T cell stimulation, and restore immune surveillance by disrupting signal transduction and immunosuppression (23); 3) combination of PD-1 inhibitor and anti-VEGF drug may promote normalization of blood vessels breaks the hypoxic microenvironment of tumors and convert cold tumors into

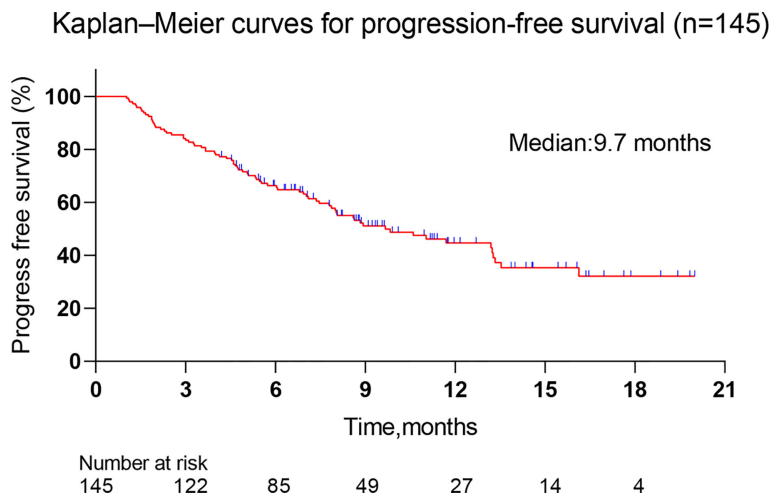

FIGURE 2
Kaplan–Meier curves for progression-free survival. The median follow-up was 12.5 months (4.5-20 months), and the median PFS was 9.7 months (1-16.1 months).

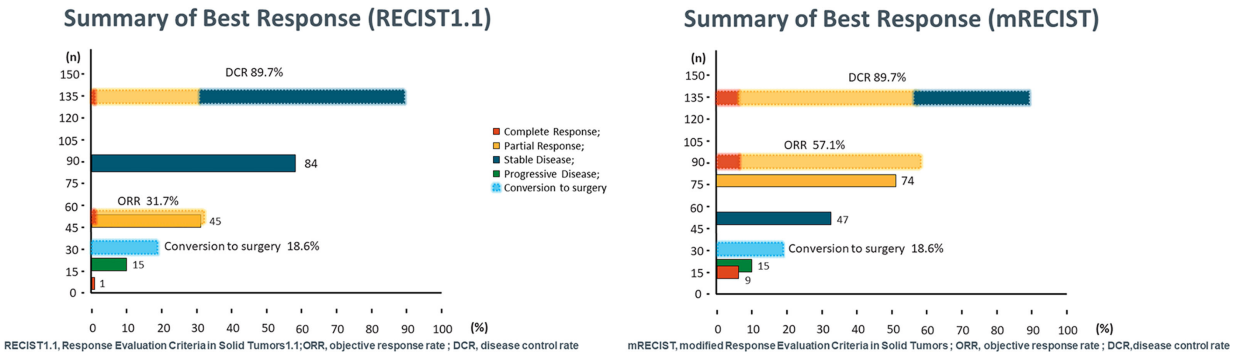

FIGURE 3
Summarized the results of the best response according RECIST1.1 and mRECIST criteria. RECIST1.1, Response Evaluation Criteria in Solid Tumors1.1; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

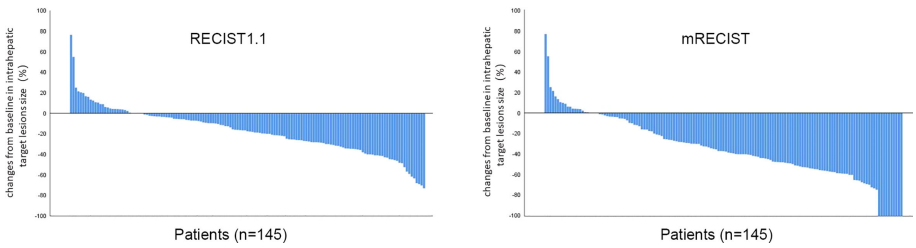

FIGURE 4
Best percentage changes from baseline in size of the intrahepatic target lesions of patients. RECIST1.1, Response Evaluation Criteria in Solid Tumors1.1; mRECIST, modified Response Evaluation Criteria in Solid Tumors.

TABLE 3A Subgroup analysis according to liver function (Child-pugh A vs Child-pugh B).

	Child-pugh A (n = 116)	Child-pugh B (n = 29)	*p* value
	mRECIST		
Best response (n, %)			
CR	9 (7.8)	0 (0)	0.205
PR	60 (51.7)	13 (44.8)	0.506
SD	38 (32.7)	10 (34.5)	0.860
PD	9 (7.8)	6 (20.7)	0.041
ORR (CR+PR)	69(59.5)	13 (44.8)	0.154
DCR (CR+PR+SD)	107 (92.2)	23 (79.3)	0.041
Conversion rate (n, %)	26 (22.4)	1 (3.4)	0.019

mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

TABLE 3B Subgroup analysis according to macrovascular invasion and extrahepatic metastasis (Group A vs Group B; Group A vs Group C).

	Group A(n = 41)	Group B(n = 60)	*p* value	Group A(n = 41)	Group C(n = 33)	*p* value
	mRECIST			mRECIST		
Best response (n, %)						
CR	4 (9.8)	4 (6.7)	0.712	4 (9.8)	1 (3.0)	0.373
PR	26 (63.4)	26 (43.3)	0.047	26 (63.4)	14 (42.5)	0.072
SD	9 (21.9)	25 (41.7)	0.039	9 (21.9)	11 (33.3)	0.273
PD	2 (4.9)	5 (8.3)	0.698	2 (4.9)	7 (21.2)	0.033
ORR (CR+PR)	30 (73.2)	30 (50.0)	0.020	30 (73.2)	15 (45.5)	0.015
DCR (CR+PR+SD)	39 (95.1)	55 (91.7)	0.698	39 (95.1)	26 (78.8)	0.033
Conversion rate (n, %)	11 (26.8)	9 (15.0)	0.143	11 (26.8)	5 (15.2)	0.280

Group A: No macrovascular invasion and extrahepatic metastasis; Group B: Macrovascular invasion (no extrahepatic metastasis); Group C: Extrahepatic metastasis.
mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response;PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

TABLE 3C Subgroup analysis according to HAIC regimen (FOLFOX vs RALOX).

	FOLFOX (n = 113)	RALOX(n = 32)	*p* value
	mRECIST		
Best response (n, %)			
CR	5 (4.4)	4 (12.5)	0.109
PR	59(52.2)	14 (43.8)	0.398
SD	36 (31.9)	12 (37.5)	0.549
PD	13 (11.5)	2 (6.2)	0.523
ORR (CR+PR)	64 (56.6)	18 (56.3)	0.670
DCR (CR+PR+SD)	100 (88.5)	30 (93.8)	0.523
Conversion rate (n, %)	22 (19.5)	5 (15.6)	0.622

FOLFOX: HAIC with oxaliplatin, 5-fluorouracil, and leucovorin; RALOX: HAIC with raltitrexed plus oxaliplatin; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

hot tumors (24); and 4) anti-angiogenic effects of TKIs and ICIs will help to eliminate tumor angiogenesis and tumor recurrence.

Another strength in this study was that we performed subgroup analysis to verify whether the efficacy of triple therapy would be influenced by other factors. Liver function is the premise of all treatments, and triple therapy means higher requirements for liver function (25). In the present study, we found that Child-pugh A patients had higher DCR (92.2% vs

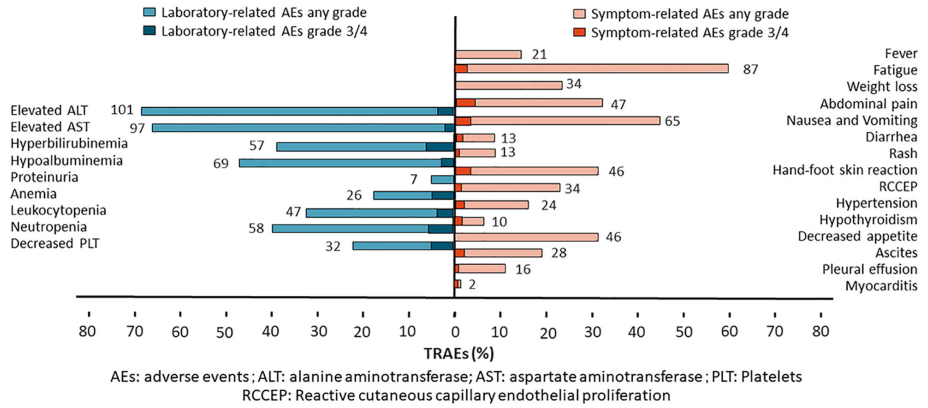

FIGURE 5
Summary of treatment-related adverse events.

79.3%, p=0.041) than Child-pugh B patients, as well as increased successful conversion rate (22.4% vs 3.4%, p=0.019). These findings indicated that liver function must be taken as an important decision-making factor of triple therapy.

Macrovascular invasion and extrahepatic metastasis are both two aggressive hallmarks of HCC, and patients combined with macrovascular invasion or extrahepatic metastasis generally mean adverse prognosis (4). Systematic therapy is the preferred option for patients with macorvascular invasion and/or extrahepatic metastasis, although many novel modalities such as surgical resection combined with local regional therapy have been tried with encouraging results (26, 27). In the present study, subgroup analysis showed that patients with macrovascular invasion have significantly lower rates PR and ORR (both p<0.05) compared with the patients with no macrovscular invasion and extrahepatic metastasis, and similar disadvantage was observed in patients with extrahepatic metastasis in terms of ORR and DCR (both p<0.05). These results suggested that the current modality might not be appropriate for this population. Considering that tumor thrombus is much more sensitive to radiotherapy (RT), RT-based comprehensive treatment might be ideal option for patients with macrovascular invasion (28). As is known to all, good local control (LC) is positively correlated with improved prognosis, and RT or radiofrequency ablation offer superior LC to ADT for patients with metastasis, such as oligo-metastasis in lung, brain, and bone. As one saying goes, one size does not fit for all. In future, more modalities combined with local treatment and systematic therapy should be worth trying for u-HCC.

As for the choice of the HAIC regimen, there is still no answer. The oxaliplatin-based FOLFOX regimen is currently the mainstream HAIC chemotherapy regimen in China (29), which could regulate the function of immune response, thereby improving the ability of dendritic cells to recognize tumor cells, activating cytotoxic T lymphocytes to attack tumor cells, and leading to tumor immune death (30). While evidences revealed that RALOX was not inferior to FOLFOX in efficacy but with shorter infusion period, which might improve

TABLE 4 Subsequent therapy.

Subsequent therapy	N=79
TKI	8 (10.1)
PD-1	5 (6.3)
HAIC	5 (6.3)
TKI+PD-1	30 (37.9)
MWA+TACE	1 (1.3)
RFA+ Radiotherapy	1 (1.3)
TACE+ TKI+PD-1	9 (11.4)
HAIC+ TKI+PD-1	8 (10.1)
MWA+ TKI+PD-1	1 (1.3)
TKI+PD-1+ Radiotherapy	3 (3.8)
HAIC+TACE+ TKI+PD-1	4 (5.0)
TACE+ TKI+PD-1+Radiotherapy	1 (1.3)
TACE+ TKI+PD-1+Radiotherapy	1 (1.3)
MWA+ TKI+PD-1+ Radiotherapy	1 (1.3)
HAIC+TACE+ TKI+PD-1+Radiotherapy	1 (1.3)

TKIs, tyrosine kinase inhibitors; PD-1, programmed cell death protein-1; HAIC, hepatic arterial infusion chemotherapy; MWA, microwave ablation; TACE, transcatheter arterial chemoembolization. RFA, radiofrequency ablation.

TABLE 5 Published literature for HCC patients received HAIC+TKIs+PD-1 treatment.

Study (Year), Design	Treatment	Patients	BCLC stageB/C	HAIC	TKIs	PD-1/PD-L1	CR	ORR	DCR	Conversion rate	MedianOS (months)	MedianPFS (months)	AE rate (Grade≥3)
1 (2021), Retrospective	HAIC+TKIs+PD-1	25	0/25	FOLFOX	Apatinib Lenvatinib Sorafenib	Camrelizumab Sintilimab	48%	96%	100%	56%	Not reached (median follow-up 12.53)	not reached	28%
2 (2021), Retrospective	HAIC+Lenvatinib+ Toripalimab Lenvatinib	71 86	0/71 0/86	FOLFOX	Lenvatinib	Toripalimab	14.1% vs 0%	67.6% vs 14.3%	90.1% vs 72.1%	/	Not reached vs 11	11.1 vs 5.1	Combination therapy group higher
3 (2021), Retrospective	HAIC+PD1+Lenvatinib Lenvatinib+PD-1	45 25	5/40 3/22	FOLFOX	Lenvatinib	Nivolumab Keytruda Toripalimab Sintilimab	0% vs 0%	40.0% vs 16.0%	77.6% vs 44.0%	/	15.9 vs 8.6	8.8 vs 5.4	22.2% vs 36.0%
4 (2021), Retrospective	HAIC+TKIs+PD-1	27	0/27	FOLFOX	Lenvatinib Regorafenib Sorafenib Apatinib	Camrelizumab Sintilimab Toripalimab Nivolumab	22.2%	63.0%	92.6%	/	Not reached (median follow-up 12.9)	12.9	55.6% (All grade 3)
5(2021), Retrospective	HAIC+ Pembrolizumab + Lenvatinib Lenvatinib +Pembrolizumab	84 86	22/62 21/65	FOLFOX	Lenvatinib	Pembrolizumab	15.5% vs 9.3%	59.5% vs 41.9%	89.3% vs 86.1%	/	17.7 vs 12.6	10.9 vs 6.8	4.8% vs 2.3%
6 Ours, Retrospective	HAIC+PD-1+TKIs	145	41/104	FOLFOX RALOX	Sorafenib Lenvatinib Apatinib	Camrelizumab Stintilimab Tislelizumab	6.1%	57.2%	89.7%	18.6%	not reached (median follow-up 12.5)	9.7	17.7%

1、Surgical Conversion for Initially Unresectable Locally Advanced Hepatocellular Carcinoma Using a Triple Combination of Angiogenesis Inhibitors, Anti-PD-1 Antibodies, and Hepatic Arterial Infusion Chemotherapy:A Retrospective Study.
2、Lenvatinib, toripalimab, plus hepatic arterial infusion chemotherapy versus Lenvatinib alone for advanced hepatocellular carcinoma.
3、Hepatic Arterial Infusion Chemotherapy Combined With PD-1 Inhibitors Plus Lenvatinib Versus PD-1 Inhibitors Plus Lenvatinib for Advanced Hepatocellular Carcinoma.
4、Real-world study of hepatic artery infusion chemotherapy combined with anti-PD-1 immunotherapy and tyrosine kinase inhibitors for advanced hepatocellular carcinoma.
5、Pembrolizumab plus Lenvatinib with or without hepatic arterial infusion chemotherapy in selected populations of patients with treatment-naive unresectable hepatocellular carcinoma exhibiting PD-L1 staining: a multicenter retrospective study.
TKIs, tyrosine kinase inhibitors; HAIC, hepatic arterial infusion chemotherapy; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1FOLFOX Regiment, oxaliplatin+leucovorin+5-fluorouracil; RALOX Regiment, raltitrexed + oxaliplatin; BCLC, Barcelona Clinic Liver Cancer; CR, complete response; DCR, disease control rate; ORR, objective response rate.

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compliance of patients to treatments (31). In the present study, we found that there was no significant differences between the two HAIC regimen in CR, ORR, DCR, and successful conversion rate (all $p>0.05$), which was coincident with previous studies (32). But considering feasibility and compliance, RALOX could be taken as an alternation for selected patients, especially for those with poor performance status.

Safety is a key concern for the triple therapy protocol. In this study, the most common AEs were impaired liver function, myelosuppression, fatigue, nausea and vomiting and abdominal pain. Although the vast majority of patients experienced treatment-related AEs, grade 3/4 treatment-related AEs was 17.7% and no deaths were reported. But this does not mean that we can relax our vigilance. Late onset AEs deserve much more attentions, especially to those related to ICIs. In addition, high rates of impaired liver function damage also indicated the need of adequate liver reserve function for triple therapy, and patients with impaired liver function should be excluded or taken much more carefully.

There were several limitations in this study. Firstly, this was a retrospective, single center, and single-arm study. Although our sample size was large, we did not provide a control group, which is what we need to do next. Second, our treatment regimens were not uniform as depicted in other published studies, which may have some impact on efficacy. Third, median OS could not be derived due to short follow-up time, the choice of subsequent treatment regimens could also have an impact on OS. Fourth, the number of patients in the subgroup analysis may be insufficient, and the conclusions drawn may not be accurate. Prospective randomized controlled trials with large sample sizes are needed to verify the efficacy of triple therapy, and Table 6 lists ongoing clinical trials.

TABLE 6 Ongoing clinical trials for HCC patients with HAIC+TKIs+PD-1/PD-L1 treatment.

	NCT Number	Phases	Title	Experimental: Treatment Group	Contral Group	Disease stage	Primary end point	Enrollment
1	04961918	Phase 2	The Efficacy of Hepatic Arterial Infusion Chemotherapy (HAIC) Combine Lenvatinib and Durvalumab (HILL) in Advanced Hepatocellular Carcinoma (HCC)	HAIC+Lenvatinib +Durvalumab	None	Advanced HCC	PFS	36
2	05029973	Phase 2	HAIC Combined With Sintilimab and Bevacizumab Biosimilar for Advanced Unresectable HCC	HAIC+Sintilimab +Bevacizumab Biosimilar	None	Advanced unresectable HCC	ORR	30
3	04814043	Phase 2	PD-1 Antibody and Lenvatinib Plus TACE-HAIC for Potential Resectable HCC: a Single-arm, Phase 2 Clinical Trial	Lenvatinib+PD-1 inhibitor	None	Potential resectable HCC	Conversion rate to resection	57
4	05198609	Phase 3	Camrelizumab, Apatinib Plus HAIC Versus Camrelizumab and Apatinib for HCC With Portal Vein Invasion: a Randomized Trial	FOLFOX-HAIC +Camrelizumab +Apatinib	Camrelizumab +Apatinib	HCC With PVTT	OS	214
5	05166239	Phase 2	HAIC Combine With Lenvatinib and Camrelizumab for Advanced HCC With PVTT	HAIC+Lenvatinib +Camrelizumab	Lenvatinib +Camrelizumab	HCC with PVTT	6 months PFS rate	66
6	05135364	Phase 2	HAIC Combined With Camrelizumab and TKI for Unresectable Hepatocellular Carcinoma After TACE Failure	HAIC+TKI +Camrelizumab	None	Unresectable HCC	PFS	48
7	05099848	Phase 2	A Trial of Conversion Treatment of HAIC Combined With Camrelizumab and Apatinib for Unresected Hepatocellular Carcinoma	HAIC+Apatinib +Camrelizumab	None	Unresected HCC	R0 resection rate	20
8	04191889	Phase 2	A Trial of Hepatic Arterial Infusion Combined With Apatinib and Camrelizumab for C-staged Hepatocellular Carcinoma in BCLC Classification	HAIC++Apatinib +Camrelizumab	None	BCLC C-stage HCC	ORR	84
9	04618367	Not Applicable	HAIC Combined With Lenvatinib and Sintilimab for Hepatocellular Carcinoma With PVTT	HAIC+Lenvatinib +Sintilimab	None	HCC With PVTT	PFS rate at 6 months	30
10	05003700	Phase 2	Hepatic Arterial Infusion Combined With Lenvatinib and Camrelizumab for Unresectable Hepatocellular Carcinoma	HAIC+Lenvatinib +Camrelizumab	None	Unresectable HCC	ORR	48

HCC, Hepatocellular Carcinoma; HAIC, hepatic arterial infusion chemotherapy; TKIs, tyrosine kinase inhibitors; PD-1, programmed cell death protein-1; TACE, transarterial chemoembolization; BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombus; FOLFOX HAIC, Oxaliplatin+Leucovorin+5-fluorouracil; ORR, objective response rate; OS, overall survival; PFS, progression free survival.

Conclusion

In this real-world series, triple combination of HAIC plus PD-1 inhibitors and TKIs was feasible and efficient in the treatment for patients with initially unresectable HCC. However, more attentions should be paid to screening of potential beneficiary, optimal regimen of triple therapy, timing of treatment response evaluating, standard of successful conversion, subsequent therapy, and late onset AEs. In future, cross-regional centers RCTs with a larger sample size will be helpful in clarifying the role of the triple modality for unresectable HCC.

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the first affiliated hospital of Nanchang University, Nanchang, China. No. (2022) CDYFYYLK (06-009). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

LL, RS and RW: study concept and design. YX, GZ and AH: acquisition and analysis or interpretation of data. LL, TW and XG: drafting of the manuscript. LL, ZH and WW: critical revision of the manuscript. JX and WD: statistical analysis. HM and SS: administrative and technical support. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Lenvatinib plus transarterial chemoembolization with or without immune checkpoint inhibitors for unresectable hepatocellular carcinoma: A review

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Lenvatinib plus transarterial chemoembolization (TACE)have become the first choice for patients with hepatocellular carcinoma (HCC) that are unsuitable for TACE. Sorafenib plus TACE therapy for patients with portal vein tumor thrombus (PVTT) achieved positive results. However, Lenvatinib plus TACE appeared to achieve a more advantageous result for these patients based on the phase 3 REFLECT trial. Both TACE and lenvatinib therapy have immune-stimulating effects, so would lenvatinib plus TACE and immune checkpoint inhibitors be an advantageous therapy for unresectable HCC (uHCC)? Thirteen articles from PubMed were explored to determine the efficacy and safety of lenvatinib plus TACE with or without PD-1 inhibitors therapy. Most of the adverse events (AEs) were manageable. Lenvatinib plus TACE therapy was superior to lenvatinib monotherapy with intermediate stage HCC especially beyond up-to-seven criterion and was superior to TACE monotherapy in patients with uHCC or sorafenib plus TACE therapy in patients with PVTT. Objective response rates (ORRs) of 53.1%–75%, median progression free survival (PFS) of 6.15–11.6 months, and median overall survival (OS) of 14.5–18.97 months were achieved in the lenvatinib plus TACE group. Levatinib plus TACE and PD-1 inhibitors achieved ORRs of 46.7% –80.6%, median PFS of 7.3–13.3 months, and median OS of 16.9–24 months. Control studies also confirmed the triple therapy was superior to lenvatinib plus TACE in patients with uHCC. Overall, the triple therapy is a promising treatment for patients with uHCC, including main PVTT and extrahepatic metastasis. Lenvatinib plus TACE therapy was also preferable for intermediate stage HCC beyond up-to-seven criterion and for patients with PVTT.

KEYWORDS

lenvatinib, transarterial chemoembolization, immune checkpoint programmed death factor 1 inhibitors, immune checkpoint inhibitors, unresectable hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is malignant, and the median overall survival (OS) of HCC with Barcelona clinic liver cancer (BCLC) 0/A, B, C, and D was longer than 5 years, 2.5 years, 2 years and 3 months, respectively (1). Additionally, the poorer the liver function, the higher the incidence of treatment-related poisoning events (2–5). Transarterial chemoembolization (TACE) was the first choice for patients at the intermediate stage (BCLC stage B). However, repeated TACE treatment could decrease the liver function and cause failure to accept follow-up systematic treatment. The increased times of TACE treatment resulted in the decline in the response rate of tumor tissue to treatment (6–9). The phenomenon was known as TACE refractoriness/TACE failure, which was defined by the Japan Society of Hepatology in 2010 (7). What occurs if systemic therapy is applied before TACE treatment? The results of a prospective study of lenvatinib as initial treatment in HCC at BCLC substage B2 showed the median OS and progression free survival (PFS) were 17.0 and 10.4 months, and objective response rate(ORR)was 70.0%, respectively (10). The albumin-bilirubin (ALBI)score was sustained in the lenvatinib group, whereas it declined in the TACE group after the treatment (8). Kudo et al. also published an article explaining that HCC at BCLC stage B, especially HCC with multiple heterogeneous nodules, need lenvatinib pretreatment before TACE to achieve a high tumor response rate, preserve liver function, and prolong PFS and OS (11–13). The first choice of the treatment of intermediate HCC with a high tumor burden, especially beyond the up-to-seven criterion, is no longer TACE (11, 14–17). The intermediate stage of HCC sank and became multifocal, with preserved liver function, and had considerable heterogeneity: from the Child-Pugh score 5 to Child-Pugh score 9, tumor size from ≥5 cm to >10 cm, and the number of nodules from 4 to >10 (1, 11, 18–20). According to the 2022 BCLC version stratifications, TACE is suitable for HCC with well-defined nodules, preserved portal flow, and selective access. Systemic therapy is suitable for the BCLC stage B HCC that are diffuse and infiltrative, with extensive liver involvement, but there was no clear dividing line between the two (1, 21). HCC in an advanced-stage (BCLC stage C) with vascular invasion or extrahepatic spread, ECOG PS ≤ 2, and preserved liver function should be evaluated for systemic therapy (1). The combination of atezolizumab with bevacizumab is the first-line treatment, exhibiting a breakthrough ORR of 33.2% and median PFS of 6.8 months and proving the superiority compared to sorafenib in survival benefit (22–24). According to Maesaka et al., although the median PFS was significantly longer in the atezolizumab plus bevacizumab group (8.8 months vs. 5.2 months), there were no significant differences in terms of median OS (not reached vs. 20.6 months) or ORR (43.8% vs. 52.4%) (25). If lenvatinib plus TACE therapy can improve PFS, and achieve results matching the atezolizumab plus bevacizumab therapy requires further study.

The TACTICS trial confirmed the advantage of sorafenib plus TACE compared to TACE alone for patients with unresectable hepatocellular carcinoma (uHCC) (18 at BCLC stage C), with a better PFS (25.2 vs 13.5months) and a higher ORR (71.3% vs 61.8%) (26). According to the phase 3 REFLECT trial, the OS of lenvatinib and sorafenib was 13.6 and 12.3 months, and patients in the lenvatinib group exhibited a longer median time to progression (TTP) compared with sorafenib (8.9 vs. 3.7 months), a higher ORR (21.4% vs. 9.2%), and a longer PFS (7.2 vs. 4.6 months) (8, 13). However, there was no comparison between lenvatinib plus TACE therapy and sorafenib plus TACE therapy. Patients with liver occupation greater than 50%, bile duct invasion, a Child-Pugh class B, or main portal vein tumor thrombus (PVTT) were excluded from the phase 3 REFLECT trial (13). We need to verify the efficacy of these two tyrosine kinase inhibitors (TKIs) plus TACE treatments at various tumor stages.

The occurrence and progression of HCC are based on the inflammatory environment of the liver. Many immune related factors or cells provide a immunosuppression tumor microenvironment (TME) for tumor cells (5, 27). Immune checkpoint inhibitors (ICIs) is a research hotspots, including the inhibition of immune checkpoint programmed death factor 1 (PD-1), programmed death factor ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (5). PD-1, a transmembrane receptor, is expressed by activated T cells, B cells, natural killer cells, and antigen-presenting cells. PD-L1 is expressed by cancer cells, which would combine with PD-1 and escape from immunosurveillance (5, 27–29). The inhibition of these two targets destroy the immunosuppression TME of tumors. However, approximately two-thirds of HCC did not respond to immunotherapy alone, which illustrated the complex interaction of multiple immunosuppressive mechanisms in the TME. More optimized treatment strategies need to be formulated, and combination therapy is the first choice (30). The combination therapy of lenvatinib plus

pembrolizumab produced an ORR of 46% and a median OS of 22.0 months, according to a Phase Ib Study. The FDA approved lenvatinib plus pembrolizumab as a first-line treatment for uHCC that is not amenable to locoregional therapy (31–33). This indicated that lenvatinib had synergistic effects with PD-1 inhibitors. Whether lenvatinib plus TACE combined with PD-1 inhibitors, such as pembrolizumab, is better than lenvatinib plus TACE therapy and what synergistic effects exist among TACE, lenvatinib, and PD-1 inhibitors are also the key points to be discussed in this review.

Based on the above, this review embodied 13 studies by the end of April 2022 through PubMed to explore the advantages of lenvatinib plus TACE therapy and lenvatinib plus TACE and PD-1 inhibitors in patients with uHCC.

Therapeutic responses of lenvatinib plus TACE therapy versus lenvatinib or TACE monotherapy

First, we determine whether lenvatinib plus TACE therapy has advantages over TACE or lenvatinib monotherapy. This chapter covers 3 articles comparing lenvatinib plus TACE therapy with TACE monotherapy for patients with uHCC, lenvatinib monotherapy for intermediate HCC mostly beyond up-to-seven criterion, and one demonstrated the therapeutic effect of lenvatinib plus TACE on uHCC with PVTT, in a total of 218 people (2, 17, 34, 35).

Objective response rate

Four studies reported response assessments based on the modified Response Evaluation Criteria in Solid Tumors (mRECIST), classified as complete response (CR), partial response (PR), stable disease (SD), and progression of disease (PD). The ORR (CR + PR) was reported in three studies, and the outcomes are shown in Table 1. ORR of the lenvatinib plus TACE group vs. the lenvatinib-alone group was 63.2% vs. 63.2%, p = 1.0, respectively. However, CR was 15.8% in the lenvatinib plus TACE group and was 10.5% in the lenvatinib-alone group (17). ORR of the lenvatinib plus TACE group vs. TACE-alone group was 68.3% vs. 31.7%, p<0.001 (34). Chen et al. reported that the ORR of the lenvatinib plus TACE group was 75%, significantly better than the phase 3 REFLECT trial, even when including 25% HCC with main PVTT (35).

Progression free survival and overall survival

Ando et al. reported that the median PFS of the lenvatinib plus TACE group vs. lenvatinib-alone group was 11.6 vs. 10.1 months, p = 0.019, respectively. Child-Pugh score 5 and lenvatinib followed by TACE were the predictive factors of PFS in a multivariate analysis (17). A prospective study also showed that the Child-Pugh score was a momentous factor for the prognosis (10). The 1-year and 2-year PFS rates were 78.4% and 45.5% vs. 64.7% and 38.0%, p<0.001, in the TACE plus lenvatinib group vs. TACE alone, respectively (34). Chen et al. reported that the median PFS of lenvatinib plus TACE group was 6.15 months (35). Shimose et al. and Ando et al. reported that the median OS of the lenvatinib plus TACE group vs. lenvatinib-alone group were not reached vs. 16.3 months, P = 0.01 and not reached vs. 16.9 months, p = 0.007, respectively (2, 17). The independent predictive factors of OS were transarterial therapy and ALBI grade 1 according to Shimose et al. (2). Child-Pugh score 5, serum AFP level <400 ng/mL, and lenvatinib followed by TACE were the independent predictive factors of a longer OS in multivariate analysis according to Ando et al. (17). According to Yao et al., a high level of AFP was correlated with poor prognosis in HCC. This was possibly because it was positively correlated with the weakening of the immune stimulation effect of dendritic cells (DCs) on T cells (36). The 1-year and 2-year OS rates were 88.4% and 79.8% vs. 79.2% and 49.2%, p=0.047, in the TACE plus lenvatinib group vs. TACE monotherapy, respectively (34). A treatment option was identified as an independent prognostic factor for OS in the multivariate analysis and the benefits of the total population were consistent with BCLC stage B and C in the lenvatinib plus TACE group (34). The relative dose intensity (RDI) was relevant to the therapeutic response of lenvatinib, including the PFS and OS (8).Chen et al. reported the median OS of the lenvatinib plus TACE group was 16.9 months (35). This is slightly lower than the results published by Shimose et al. and Ando et al. However, the patients included in Shimose et al. and Ando et al. had HCC at BCLC stage B, whereas Chen et al. included patients with HCC and PVTT (2, 17, 35).Table 1 shows the details.

Change of liver function and adverse events

ALBI grade was an important factor associated with survival in patients with HCC (37, 38). According to Shimose et al., age and ALBI were the first and second splitting variables for arterial therapy (AT), respectively (2). The median ALBI score in the TACE plus lenvatinib group before TACE, and 1 and 2 months after TACE, and at the end of treatment was −2.52, −2.48, −2.51, and −2.44, respectively, and there was no significant difference (17). According to Fu et al., there was no dramatical change in the Child-Pugh score between the baseline and the first follow-up after treatment in the TACE plus lenvatinib group and TACE group (34). Common adverse events (AEs) included hypertension, hemorrhage of the digestive tract, liver dysfunction, ascites, proteinuria, fatigue, anorexia, hand-foot

TABLE 1 Lenvatinib plus TACE therapy compared with lenvatinib or TACE monotherapy.

Author/ Reference numbers	Year	Country	Treatment (number of patients)	Follow-up time	Median OS/OS rate	Median PFS/PFS rate	TTP	ORR	Main characteristics of patients
Shigeo Shimose (2)	2021	Japan	Lenvatinib+AT (24) or lenvatinib (24)	NA	not reached vs. 16.3 months	NA	NA	NA	BCLC stage B (100%); Beyond up-to-seven criteria (87.5% vs. 91.6%); ALBI grade 2 (54.17% vs. 66.67%)
Yuwa Ando (17)	2021	Japan	Lenvatinib +TACE (19) vs lenvatinib (19)	14.8 vs. 14.3 months	not reached vs. 16.9 months	11.6 vs. 10.1 months	NA	63.2% vs. 63.2%	BCLC stage B (100%); Beyond up-to-seven criteria (68.4% vs. 63.16%); ALBI grade 2 (31.58% vs. 31.58%)
Zhigang Fu (34)	2021	China	Lenvatinib +TACE (60)/ TACE (60)	11.6 vs. 17.5 months	The 1-year and 2-year OS rates were 88.4% and 79.8% vs. 79.2% and 49.2%	The 1-year and 2-year PFS rates were 78.4% and 45.5% vs. 64.7% and 38.0%	NA	68.3% vs. 31.7%	Child-Pugh grade B (6.7% vs. 5.0%); PVTT (35.0% vs. 45.0%); Extrahepatic spread (15.0% vs. 15.0%); AFP≥400(45.0% vs. 45%); BCLC stage A (3.3% vs. 5.0%)/B (55.0%vs43.3%)/ C (41.7% vs. 51.7%); ALBI grade 2-3 (68.33% vs. 73.33%)
Ruiqing Chen (35)	2022	China	Lenvatinib +TACE (12)	15.2 months	16.9 months	6.15 months	NA	75%	PVTT type II (75.0%), III (25.0%); Extrahepatic spread (58.3%); BCLC stage C(100%)

OS, overall survive; PFS, progression-free survival; TTP, time to progression; ORR, objective response rate; AT, trans-arterial therapy; NA, not available; BCLC, Barcelona clinic liver cancer; ALBI, albumin-bilirubin; TACE, transarterial chemoembolization; PVTT, portal vein tumor thrombus; AFP, alpha-fetoprotein.

skin reaction (HFSR), hypothyroidism, diarrhea, and hoarseness. There was no obvious difference in AEs between the groups. Hypertension, gingiva bleeding, diarrhea, fatigue, dysphonia, HFSR, and anorexia were likely caused by lenvatinib (2, 17, 34, 35). TACE is mostly related to elevated liver enzymes and post-embolism syndrome. However, there were no significant differences between groups in any parameter and they were manageable (2, 17, 34, 35).

In summary, there was no difference in the ORR between the lenvatinib plus TACE and lenvatinib monotherapy, according to Ando et al. (17). One possible reasons was that all HCC lesions of the included patients could be controlled by lenvatinib. A multicenter retrospective study showed that only the type of TKI was associated with tumor response (36). However, the OS of combined therapy was significantly longer for intermediate-stage HCC (17). The alternative lenvatinib plus TACE therapy improved the overall prognosis of patients compared with lenvatinib monotherapy, possibly because liver function could be preserved. The same result for the median OS was confirmed by Shimose et al. (2). According to Chen et al., the lenvatinib plus TACE group had significantly better ORR and OS than the lenvatinib monotherapy group in the REFLECT study, in spite that all included patients had HCC with PVTT; however, a larger sample size is needed for additional validation (35). Furthermore, we confirmed the superiority of lenvatinib plus TACE over TACE monotherapy in regard to ORR, PFS, and OS for uHCC (34). In addition, lenvatinib plus TACE is tolerable. The lenvatinib plus TACE group also confirmed its superiority in the following aspects. Shimose et al. reported that TACE is helpful in prolonging the administration time of lenvatinib. The administration time of lenvatinib in the AT group and non AT group was 13.7 months and 8.6 months, respectively (2). According to Kawamura et al., patients who achieved the lenvatinib-TACE sequential therapy after progression during lenvatinib therapy exhibited better post-progression survival (PPS), regardless of the CT enhancement pattern, whereas the heterogeneous enhancement pattern with irregularly shaped ring structures was correlated with a poorer PPS (39). Receiving TACE immediately after lenvatinib treatment could be an intense physical burden for patients (2). The median interval between TACE treatments was 74.7 d and 60.0% patients received TACE more than twice in the TACE group. However, the median interval between TACE treatments was 103.3 d and only 40.0% patients received TACE more than twice

in the TACE plus lenvatinib group. Thus, the TACE plus lenvatinib therapy could decrease the number of TACE sessions and extend the interval time, which could be conducive to maintaining liver function, according to Fu et al. (34). Additionally, lenvatinib-TACE sequential therapy achieved tumor control even if the dose of lenvatinib was reduced or the drug was suspended, and the subsequent TACE treatment achieved tumor shrinkage (17). After the lenvatinib-TACE sequence therapy, a 78-year-old and an 80- year-old patient with HCC at BCLC stage C received hepatectomy, which showed coagulative necrosis of the entire HCC in one case and a small amount of surviving HCC cells in the other case (40).

However, according to Matsuda et al., the diameter of the hepatic artery after TKI treatment, such as lenvatinib or sorafenib, decreased significantly, which may be caused by the normalization of tumor blood vessels, which limited TACE treatment after TKI treatment, even if the TACE treatment did not cause any complications (41). This could be a technical limitation and according to Xue et al., the decrease of hepatic vessel diameter will strengthen the effect of embolization and improve the survival benefit (42).

Eight clinical trails have been registered in ClinicalTrials. gov website to study the effect of TACE plus lenvatinib on uHCC, including preoperative treatment, prevention of postoperative recurrence. The registration time of the experiments is from January 2019 to May 2022, and the expected completion time is from August 2022 to March 2027.Two of them are from United States, six of them are from China, and two of them are multicenter studies. Whether lenvatinib and TACE are applied simultaneously or sequentially is also an urgent problem to be solved.

Therapeutic responses of lenvatinib plus TACE therapy versus sorafenib plus TACE therapy

Whether lenvatinib plus TACE has advantages over sorafenib plus TACE is the subject of this section. Three studies with a total of 292 people were included (42–44). Two of them were prospective studies that explored the effect of TACE plus lenvatinib or sorafenib for patients with uHCC with PVTT (43, 44) and one propensity score matching retrospective study that addressed TACE with drug-eluting beads plus lenvatinib vs. sorafenib for advanced HCC (42). The outcomes are shown in Table 2.

Objective response rate

The response assessments were reported based on mRECIST. The ORR (CR + PR) of the sorafenib plus TACE

TABLE 2 Lenvatinib plus TACE therapy compared with sorafenib plus TACE therapy.

Author/ Reference numbers	Year	Country	Treatment (number of patients)	Follow-up time	Median OS/OS rate	Median PFS/PFS rate	TTP	ORR	Main characteristics of patients
Xiaoyan Ding (43)	2021	China	Lenvatinib+TACE (32)/ sorafinib+TACE (32)	16.1 months	14.5 vs. 10.8 months	NA	4.7 vs. 3.1 months	53.1% vs. 25.0%	Tumor size (cm) >7.0(78.1% vs. 71.2%); Child-Pugh grade B (6.7% vs. 5.0%); PVTT I/II (65.6%vs78.1%), III/IV (34.4% vs. 21.9%); Extrahepatic spread (40.6% vs. 28.1%); AFP≥400(50% vs. 56.2%); BCLC stage C (100%) ALBI grade 2-3 (62.5% vs. 65.6%)
Biao Yang (44)	2021	China	Lenvatinib + TACE (38)/sorafenib + TACE (38)	NA	18.97 vs. 10.77 months	10.6 and 5.4 months	NA	66.8% vs. 33.3%	Tumor size (cm) >7 (63.2% vs. 68.4%); Child-Pugh grade B (2.6% vs. 2.6%); PVTT type I (52.6% vs. 52.6%), II (28.9% vs. 34.2%), III/IV (18.4% vs. 13.2%); Extrahepatic spread (15.8% vs. 15.8%); AFP≥400(63.2% vs. 60.5%); BCLC stage C (100%); ECOG PS 2 (28.9% vs. 23.7%)
Miao Xue (42)	2021	China	Lenvatinib+TACE (50)/ sorafenib+TACE(100)	NA	14.9 vs. 12.3 months	NA	8.4 vs. 6.0 months	64.0% vs. 33.3%	Tumor size (cm) >5 (74.0% vs. 81.0%); Child-Pugh grade B (18% vs. 16%); PVTT (72.0% vs. 81.0%); Extrahepatic spread (54.0% vs. 45.0%); BCLC stage C (100%)

OS, overall survive; PFS, progression-free survival; TTP, time to progression; ORR, objective response rate; NA, not available; BCLC, Barcelona clinic liver cancer; ALBI, albumin-bilirubin; TACE, transarterial chemoembolization; PVTT, portal vein tumor thrombus; AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status.

group vs. lenvatinib plus TACE group was reported in three articles by Ding et al., Yang et al., and Xue et al., as 25% vs. 53.1%,P =0.039; 33.3% vs. 66.8%, p = 0.037; and 33.3% vs. 64%, P=0.008, respectively (42–44). These results verified that the ORR with the TACE plus lenvatinib treatment was superior to that of the TACE plus sorafenib treatment.

Progression free survival or time to progression and overall survival

The PFS of the lenvatinib plus TACE and sorafenib plus TACE therapy was reported by Yang et al. as 10.6 vs. 5.4 months, p = 0.002 (44). The TTP of lenvatinib plus TACE therapy and sorafenib plus TACE therapy was reported by Ding et al. and Xue et al. as 4.7 vs. 3.1 months, P = .029 and 8.4 vs. 6.0 months, P=0.023, respectively (42, 43). The OS of lenvatinib plus TACE therapy and sorafenib plus TACE therapy was reported by Ding et al., Yang et al., and Xue et al. as 14.5 vs. 10.8 months, P = 0.17; 18.97 vs. 10.77 months, p = 0.022; and 14.9 vs. 12.3, P=0.043, respectively (42–44).The studies by Yang et al. and Xue et al. reported significant differences in the OS and PFS between the two groups, as noted above, after propensity score matching (PSM) (42, 44). Although Ding et al. reported no significant difference in OS between the two groups, the median OS for patients with advanced HCC including main PVTT receiving lenvatinib plus TACE was 14.5 months, which was longer than 13.6 months in the REFLECT trial (43). According to Ding et al., reasons why OS was not significantly different between the two groups could have been that a high proportion of patients with HCC (40.6%) in the sorafenib plus TACE group were switched to lenvatinib, and there were no PSM and few samples (43).

Univariable and multivariable analyses showed that the TACE frequency < 3, ECOG < 2, and treatment method were significantly important factors for longer OS according to Yang et al. (44). Ding et al. also reported that TACE plus lenvatinib significantly improved the TTP and OS. It was reported that a maximum liver tumor >7 cm was a critically negative prognostic factor and patients with HCC who achieved an objective response had significantly improved TTP and OS as well. However, according to this study, no significant lengthening or shortening of OS or TTP by AFP level, ECOG PS, type of PVTT, or extrahepatic metastasis differed from that in previous studies (43). We require larger sample sizes and more sophisticated experimental designs to explore this problem. Subgroup analysis showed that OS and PFS were significantly prolonged in the TACE plus lenvatinib group in patients with HCC with PVTT, especially PVTT type I/II, according to Ding et al., Yang et al., and Xue et al. (42–44). A retrospective study found that lenvatinib monotherapy increased both median OS (not reached vs. 187 d, p=0.0040) and ORR (53.8% vs. 14.3%, p=0.0193) compared with sorafenib in patients with HCC and PVTT type II/III (45). This further demonstrated the superiority of lenvatinib plus TACE in the treatment of various types of PVTT. TACE frequency < 3, ECOG < 2, larger and multiple tumors, cases with extrahepatic metastasis, and a higher AFP level appeared to benefit more from TACE plus lenvatinib (43, 44). Furthermore, in patients with FGF21 amplification, median OS was longer in the lenvatinib plus TACE group (10.4 months) than the sorafenib plus TACE group (5.7 months) according to Xue et al. (42). This result was in accordance with Finn et al. wherein a higher baseline FGF21 was related to longer OS with lenvatinib than sorafenib (46).

Change in liver function and adverse events

There are no treatment-related deaths reported in these three articles, and AEs could also be controlled through drug reduction, drug withdrawal, and symptomatic treatment. Higher incidences of proteinuria, ascites, hoarseness, elevated bilirubin, decreased albumin, and hypothyroidism were observed in the lenvatinib plus TACE group compared with the sorafenib plus TACE group (42, 43). Higher incidences of HFSR and rash were observed in the sorafenib plus TACE group (42–44).The structural characteristics and different drug targets of sorafenib and lenvatinib played an important role (42). However, lenvatinib caused more AEs and a lower transition rate to second-line TKIs compared to sorafenib (2). A significantly higher incidence of ascites, decreased albumin, and elevated bilirubin suggested that lenvatinib has greater hepatic toxicity (43). According to Ding et al., lenvatinib plus TACE was tolerated in patients with HCC with the Child-Pugh classes A or B ≤7 (43).

The above results confirm the superiority of lenvatinib plus TACE over sorafenib plus TACE in terms of PFS, OS, and ORR. Lenvatinib led to greater AEs and hepatotoxicity. However, the lenvatinib plus TACE treatment is generally tolerable. Additionally, digital subtraction angiography (DSA) imaging authenticated that lenvatinib has a greater effect on vasoconstriction compared to sorafenib, which indicated that subsequent TACE treatment has a better embolic effect (42).According to a multicenter cohort study by Shimose et al., the median PFS time was 5.8, 3.2, and 2.4 months in the lenvatinib, sorafenib, and TACE groups in patients with intermediate-stage HCC refractory to TACE, respectively (47).Ding et al. also identified the use of the camrelizumab (a kind of ICI) after disease progression as a positive predictive factor for survival (43). This leads to the next topic to be discussed, the suitability and efficacy of lenvatinib plus TACE combined with immunotherapy.

Therapeutic responses of lenvatinib plus TACE with PD-1 inhibitors

In the previous section, we explained the advantages of lenvatinib plus TACE over TACE alone in patients with uHCC, lenvatinib monotherapy in patients with intermediate-stage HCC, and sorafenib plus TACE in patients with advanced-stage HCC, especially with PVTT. However, these advantages were inconspicuous and the most research was imperfect. Whether lenvatinib plus TACE and PD-1 inhibitors can play a greater role is discussed in this section. Our review embodied 6 studies on lenvatinib plus TACE and PD-1 inhibitors in a total of 465 people with uHCC, of which only 2 studies were randomized and controlled, and the other four were single arm studies, indicating the effectiveness and safety of the triple therapy (31–33, 48–50). All of the articles here were from China, and the PD-1 inhibitors are developed in China: toripalimab,camrelizumab, pembrolizumab,sintilimab,tislelizumab (31–33, 48–50). The outcomes are shown in Table 3. Immunotherapy had a longer onset period than TACE, but lasted longer (51).

Objective response rate

The reported tumor responses were assessed by mRECIST. The ORR (CR + PR) of the lenvatinib plus TACE and PD-1 inhibitors group vs. the lenvatinib plus TACE group was reported by Chen et al. and Cai et al., being 47.1% vs. 27.8%, p=0.017; 56.1% vs. 32.5%, P=0.033, respectively (32, 48). The ORR in the remaining three articles was 54.9%, 46.7%, as well as 80.6% assessed by an investigator and 77.4% assessed by a blinded independent central reviewer (BICR) (31, 33, 50).

Progression free survival and overall survival

The PFS of the lenvatinib plus TACE and PD-1 inhibitors group vs. the lenvatinib plus TACE group was reported as 9.2 vs. 5.5 months, p=0.006 and 7.3 vs. 4.0 months, P=0.002, respectively (32, 48). The PFS of the remaining three articles was 8.5, 11.4, and 13.3 months (33, 49, 50).The median OS of the lenvatinib plus TACE and PD-1 group vs. the lenvatinib plus TACE group was reported as 18.1 vs. 14.1 months, p=0.004; 16.9 vs. 12.1 months, P=0.009, respectively (32, 48). The median OS of the remaining two studies was 24 months and 23.6 months reported by Liu et al., Cao et al. (49, 50).

Change of liver function and adverse events

According to Teng et al., 3.8% patients with HCC experienced upper gastrointestinal bleeding and died; however, it is unknow if this was related to treatment (33). Furthermore, this occurred in 7% patients in the IMbrave 150 trial (24). Cao et al. reported that a total of 3.8% of patients with HCC experienced grade 5 AEs, including one developed abnormal liver function, upper gastrointestinal bleeding and death on day 134 (50).Significant differences occurred in terms of hypertension, nausea, and rash in the lenvatinib plus TACE and pembrolizumab group vs. in the lenvatinib plus TACE group according to Chen et al. (48). Liu et al. reported that 1 week after the triple therapy, the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were elevated, However, there was no significant change in total bilirubin. All of these levels returned to baseline 1 month after the triple therapy (49).

In summary, despite having a higher tumor burden, higher level of AFP, larger proportion of patients with Child-Puge grade B, ECOG PS 2, PVTT, and extrahepatic metastasis, the studies confirmed superior PFS, OS, or ORR compared with Phase Ib Study and the IMbrave150 trial (31, 49, 50). According to Cai et al. and Chen et al., lenvatinib plus TACE and PD-1 inhibitors therapy had advantages in ORR, PFS, and OS compared with lenvatinib plus TACE therapy. However, the PFS and OS in the triple therapy group in these two studies were relatively short. A considerable proportion of patients with HCC and extrahepatic metastasis (41.5% and 68.6%), AFP levels ≥400ng/ml (51.2% and 64.3%) could have been the reasons (32, 48). Furthermore, a significant proportion of patients have main PVTT (36.6%), the heavy tumor burden (largest tumor size of 12.3 ± 4.8 cm) could also lead to the limited survival benefit of the triple therapy, according to Cai et al. (32). Despite improvements in ORR compared with the Phase Ib Study and the IMbrave150 trial, according to Teng et al., the median PFS and OS was shorter than that of lenvatinib plus pembrolizumab (33, 49, 50, 52). The reasons could include the high proportion of patients with HCC with TACE failure, previous TKI treatment failure (45.3%), and inadequate follow-up. The median PFS was 11.2 months for patients with HCC after first-line treatment with PD-1 inhibitors, which was longer than that of second-line therapy (6.2 months) and that of PFS reported by Phase Ib Study which suggested that the triple therapy should be used in patients with HCC as early as possible (33, 49, 50). Lenvatinib after failure of PD-1 inhibitors was longer than that of lenvatinib as the first-line therapy. The effect of PD-1 inhibitors binding to CD8+T cells being sustained for more than several months might be one of the reasons (53). However, different results were reported by Yao et al., in which changes in signaling pathway, epigenetics, and the upregulation of other checkpoints (such as T-cell immunoglobulin and mucin domain 3 (TIM3) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)), the history of PD-1 inhibitors resulted in a poorer PFS (36). This is another problem that needs to be addressed in the future. Additionally, a study for patients with uHCC with 69.6% in BCLC stage C, macroscopic vascular invasion (33.9%) and extrahepatic metastasis (51.8%) achieved an ORR of 67.9%, a median PFS of 11.9 months, and a median OS of 23.9 months in the triple therapy group (54). Xiang et al. reported that the triple

TABLE 3 Lenvatinib plus TACE combined with PD-1 inhibitors.

Author/ Reference numbers	Year	Country	Treatment (number of patients)	Follow-up time	Median OS/OS rate	Median PFS/ PFS rate	TTP	ORR	Main characteristics of patients
Mingyue Cai (32)	2022	China	Lenvatinib+TACE+PD-1 inhibitors (sintilimab/tislelizumab/camrelizumab) (41) vs lenvatinib+TACE (40)	13.7 months	16.9 vs. 12.1months.	7.3 vs. 4.0 months	NA	56.1% vs.32.5%	Tumor size (cm) 12.3 ± 4.8/13.6 ± 5.1; Child-Pugh grade B (9.8% vs. 17.5%); PVTT type III (36.6% vs. 45.0%); Extrahepatic spread (41.5% vs. 47.5%); AFP≥400(51.2% vs. 55.0%); BCLC stage C (100%)
Song Chen (48)	2021	China	Lenvatinib+TACE+ PD-1 inhibitors (pembrolizumab) (n=70) vs. lenvatinib +TACE (n=72)	27 months	18.1 vs. 14.1 months	9.2 vs. 5.5 months	NA	47.1% vs. 27.8%	Brain metastasis (68.6% vs.72.2%); AFP≥400(64.3% vs. 61.1%); BCLC stage B (67.1% vs.62.5%), C (32.9% vs. 37.5%) ALBI grade 2 (65.7% vs. 70.8%)
Ying Teng (33)	2021	China	Lenvatinib+TACE+PD-1 inhibitors (sintilimab/camrelizumab)(53)	15.4 months	not reached	8.5 months	NA	54.9%	Child-Pugh grade B (35.8%); Vascular invasion (47.2%); Extrahepatic spread (79.2%); AFP≥400(34.0%); BCLC stage B (43.4%), C (56.6%)
Juanfang Liu (49)	2021	China	Lenvatinib+TACE+PD-1 inhibitors (camrelizumab) (22)	NA	24 months	11.4 months	NA	NA	Tumor burden >50% (36.4%); Child-Pugh grade B (27.3%); PVTT (50.0%); AFP≥400(68.2%); BCLC stage B (54.5%)/C (45.5%); ECOG PS 2 (36.4%)
Fei Cao (50)	2021	China	Lenvatinib+TACE+PD-1 inhibitors (sintilimab) (52)	12.5 months	23.6 months	13.3 months	NA	46.7%	Child-Pugh grade B (11.5%); Macroscopic vascular invasion (36.5%); Extrahepatic spread (40.4%); AFP≥400 (34.6%); BCLC stage B (25.0%)/C (75.0%); ALBI grade 2-3 (80.8%)
JiaYi Wu (31)	2021	China	Lenvatinib+TACE+PD-1 inhibitors (sintilimab/tislelizumab/camrelizumab/ toripalimab/pembrolizumab)(62)	12.2 months	not reached	not reached	NA	Investigator and BICR-assessed ORR were 80.6% and 77.4%	Tumor size (cm) ≥10 (50%); Child-Pugh grade B (6.7% vs. 5.0%); PVTT type I

(Continued)

TABLE 3 Continued

Author/ Reference numbers	Year	Country	Treatment (number of patients)	Follow-up time	Median OS/OS rate	Median PFS/ PFS rate	TTP	ORR	Main characteristics of patients
									(6.5%), II (19.4%), III/IV(17.7%); Extrahepatic spread (9.7%); AFP≥400(51.6%); BCLC stage A (9.7%)/B (33.9%)/C (56.5%)

OS, overall survive; PFS, progression-free survival; TTP, time to progression; ORR, objective response rate; PD-1, programmed death factor 1; NA, not available; BCLC, Barcelona clinic liver cancer; ALBI, albumin-bilirubin; TACE, transarterial chemoembolization; PVTT, portal vein tumor thrombus; AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status; BICR, blinded independent central review.

therapy for patients with intermediate-stage HCC had an ORR of 64.3%, median OS of 26.0 months, and median PFS of 22.5 months (55). In addition, a global randomized Phase 3 LEAP-012 Study conducted in the United States is ongoing to compare TACE with or without lenvatinib plus pembrolizumab for intermediate-stage HCC that are not amenable to curative treatment. The research plans to include 950 patients from different countries and was expected to be completed in 2029.Ten clinical trails have also been registered in ClinicalTrials. gov website to study the effect of TACE plus lenvatinib and ICIs on uHCC, including conversion therapy. The registration time of the experiments were from May 2020 to May 2022, and the expected completion time is from December 2022 to January 2027.Nine experiments are from China and one is from the United States. ICIs planned to be used include sintilimab, tislelizumab, camrelizumab, toripalimab, pembrolizumab, envafolimab, tremelimumab and durvalumab. The choice of ICIs is a problem, the application sequence of triple therapy is also urgent problems to be solved.

PVTT and extrahepatic metastasis indicated a lower OS in patients with advanced HCC and extrahepatic metastasis indicated a shorter PFS (49). Cai et al. also reported similar results, wherein the main PVTT, extrahepatic metastasis, and treatment options were identified as the independent prognostic factors for OS. Treatment option and extrahepatic metastasis were identified as the independent prognostic factors for PFS (32). Combined positive score (CPS)>1 indicated PD-L1 positivity (56). Chen et al. reported that a higher PD-L1 CPS was associated with a longer OS with anti-PD-L1 treatment (48). In addition, a high conversion rate was related to PD-L1 positive expression (57, 58). However, PD-L1 expression was related to tumor aggressiveness based on tumor resection specimens (59). OS and ORR in patients with HCC treated with nivolumab affected the expression of tumor PD-1 and PD-L1 at baseline (60). Subgroup analyses indicated that the triple therapy might be better employed for patients with HCC before the main PVTT and having a tumor number >3 or extrahepatic metastasis. The reasons could be that TACE acted on intrahepatic tumors rather than extrahepatic metastases and the effect of TACE on multiple tumors was constrained (32). Immune evasion in extrahepatic tumors could be another reason (34). According to Chen et al., a distinct, durable response was observed in patients with HCC with intrahepatic tumors who recieved lenvatinib plus TACE, suggesting that lenvatinib plus TACE therapy has a short-term anticancer effect for these patients, but the effect on patients with distant metastasis was limited (48). The higher the ORR of overall tumor (56.1% vs. 32.5%, P=0.033) and intrahepatic tumor (65.9% vs. 37.5%, P=0.011) in the lenvatinib plus TACE and PD-1 inhibitor group and lenvatinib plus TACE group was reported by Cai et al., which indicated that PD-1 inhibitors improved ORR than lenvatinib plus TACE therapy, both for the intrahepatic tumor and overall tumor (32). Wu et al. reported an ORR of 66.7% at BCLC stage A, 76.2% at BCLC stage B, and 80% at BCLC stage C. ORRs were not different at various BCLC stages (31).

Chen et al. reported a tumor reduction rate of 90.0% in the lenvatinib plus TACE and pembrolizumab group vs. 72.2% in the lenvatinib plus TACE group, p=0.007 (48). The study of Wu et al. showed a tumor reduction rate was 91.9% in the lenvatinib plus TACE and PD-1 inhibitor group (31). The rate of conversion therapy in Chen et al. was 25.7% vs. 11.1%, p=0.025. Among patients undergoing surgery, 22.2% died in the triple therapy group and 75.0% died in the duplex group, p=0.012 (48). These data corroborated that triple therapy hindered the progression of uHCC more compared than the duplex therapy (48). Wu et al. reported that a total of 33 patients with HCC reached the resectable standard (3 with BCLC stage A, 11 with BCLC stage B, and 19 with BCLC stage C). Twenty-nine patients underwent resection (31). Pathological CR and major pathological response (no active tumor cells were found in the resected specimens, and less than or equal to 10%, respectively) were observed in 16 and 24 patients, respectively (31). The 5-year survival rate of patients who underwent surgical resection

after downstaging conversion therapy was similar to that of patients who underwent surgical resection at the beginning (48).

Why the combination therapy of lenvatinib plus TACE with PD-1 inhibitors is promising

Combination of TACE and lenvatinib

TACE only worked on intrahepatic lesions, and had no effect on extrahepatic metastasis; thus, combination with systemic therapy is necessary (61). In addition, TACE could lead to necrosis of tumor tissue and upregulate the expression of hypoxia-inducible factor 1-α (HIF-1α), vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF), which could stimulate tumor recurrence or growth (2, 34, 42, 61). However, lenvatinib administration after TACE could suppress the effects of angiogenic factors (2, 40). Lenvatinib pretreatment could promote the normalization of tumor feeding arteries, lessen the pressure of intertumoral interstitial, and reduce vascular permeability. This change could improve the distribution of lipiodol and drug loaded microspheres mixed with chemotherapy drugs, to enhance the therapeutic effects of TACE (26, 40). Additionally, the shrinkage and reduction of tumor feeding arteries led to the reduction of the embolic material and lipiodol dose, which could be helpful in maintaining liver function. As compared with lenvatinib, TACE has been reported to worsen the hepatic functional reserve (40). However, not all lesions responded to lenvatinib because of the high heterogeneity of the HCC. Tumor progression after lenvantinib therapy, and second-line drugs were used. However, if TACE could control these "no response" lesions, lenvatinib could continue to be used. Compared with other drugs, lenvatinib had a higher tumor response rate (2, 17, 62). Thus, the purpose of lenvantinib plus TACE therapy is to provide a continuous deep response without deterioration of liver function, improve the prognosis of patients with intermediate-stage hepatocellular HCC, and prolong the time of transformation to advanced HCC (17).

Compared with sorafenib, lenvatinib had advantages in combining with TACE

The possible mechanisms of the different effects of lenvatinib and sorafenib are described next. First, the two drugs have different targets., lenvatinib acted as an inhibitor of VEGF receptors (VEGFR) 1–3, FGF receptors (FGFR) 1–4, platelet-derived growth factor receptor (PDGFR) -α, proto-oncogenes KIT, and RET (8, 63). Sorafenib primarily suppressed the function of Raf kinase, VEGF, and PDGF (64, 65). The FGF/FGFR signaling pathway led to the activation of multiple downstream pathways, such as Ras/MAPK and PI3K/AKT signaling pathways, which promoted cell proliferation and angiogenesis. Abnormal expression of FGF19/FGFR4 accelerated HCC progression (63). In addition to the VEGF/VEGFR signaling pathway, the FGF/FGFR signaling pathway also works on tumor progression in HCC. The dual inhibition of lenvatinib on VEGFR and FGFR signaling pathways enhanced its antitumor effect in HCC (42, 63). Furthermore, according to previous studies, FGF 19, 21, and 23 could be tied to OS in patients with uHCC treated with lenvatinib or sorafenib (42, 63, 64, 66, 67). The development of HCC is promoted by FGF21 amplification *via* the TGF-β signaling pathway and patients having higher baseline FGF21 appeared to have better OS with lenvatinib than sorafenib (42).Cell survival, growth, proliferation, and differentiation was also limited by lenvatinib *via* blocking the RET receptor, which is associated with numerous signaling pathways, including PI3K/AKT and RAS/MAPK pathways (42, 63). Second, the two drugs also bind to target kinases in different ways: the binding mode of lenvatinib to VEGFR2 is Type V, and of sorafenib is Type II. The former binding mode is more closely related to VEGFR2 (67). VEGFR2 has a high-affinity with VEGF on vascular endothelial cells and HCC cells. The binding of VEGFA and VEGFR2 causes activation of the phospholipase-Cγ (PLCγ), Ras/MAPK, and PI3K/AKT signaling pathways. These signaling pathways are involved in the proliferation of tumor cells, endothelial cells, and an increase in vascular permeability (63). Lenvatinib significantly reduced the tumor microvessel density in HCC by blocking VEGFR and had a stronger effect than sorafenib in various preclinical models (63). Finally, the immunomodulatory activity of lenvatinib targeting FGFR has been demonstrated in recent studies. There were no differences in antitumor activity between lenvatinib and sorafenib in immunodeficient mice, although lenvatinib was confirmed to have additional antitumor activity in immunocompetent mice (68).

Immune response activated by TACE

According to Montasser et al., tumor specimens from patients with TACE therapy showed substantially higher PD-L1 expression in cells. PD-1 and PD-L1 expression in inflammatory cells were higher in TACE-resected tumors than non-TACE group (29). According to this report, TACE therapy was related to the increase of PD-1 and PD-L1 expression in HCC, and could be a promising therapeutic option in combination with immunotherapy (29). Chen et al. reported that a higher PD-L1 CPS was associated with a longer OS with anti-PD-L1 treatment (48). A high conversion rate was related to PD-L1 positive expression in the previous studies (57, 58). Membranous PD-1/PD-L1 (mPD-1/mPD-L1) and soluble PD-1/PD-L1 (sPD-1/sPD-L1) are the two forms of the PD-1/PD-L1 molecules. SPD-L1 is mainly separated from mPD-L1, partly reflects the level of mPD-L1,

and was easy to measure. Studies have found that the expression of PD-L1 was related to tumor staging, prognosis, and could be potential biomarker of the onset, development, and prognosis of HCC guiding to immunotherapy. SPD-L1 level was higher in patients with BCLC stage C, PVTT, or beyond the up-to-seven criterion. According to Ma et al., the level of sPD-L1 in CR patients receiving TACE therapy was lower than that of PR and SD patients, which further confirmed that the level of sPD-L1 was related to the prognosis and responsiveness to treatment of patients (69). Tumor apoptosis or necrosis caused by TACE promoted the release of chemokines and inflammatory mediators, which increased the level of sPD-L1 (29, 69). When the tumor burden was reduced by TACE, the level of sPD-L1 decreased (69). Approximately 1 week after TACE therapy, the immune inhibition becomes increasingly dominant in TME, because sPD-L1 continues to increase. This period is the best time to apply ICIs and fully activate the immune system for the eradication of tumor cells (69, 70).

Additionally, TACE was reported to promote T-cell activation. Tumor cell necrosis caused by TACE increased the release of tumor-associated antigens, recruited DCs and increased CD4+T cells (57). According to Ren et al., 1 to 5 weeks after TACE, the proportion of Treg cells was significantly lower than before TACE, and this result indicated that a positive regulatory effect on immune function should occur after TACE. This study also showed that the proportion of CD4+T cells and the ratio of CD4+/CD8+T cells prominently increased in HCC from 1 to 5 weeks after TACE, CD8 +T cells slightly increased; however, there was no statistical significance and these data confirmed that the immune function was restored in HCC after TACE (71). The increase of CD4+ and CD8+ cells after TACE has also been reported in previous studies and it was related to a better response to TACE therapy (69). The above confirmed the improvement of immune function within 1 month after TACE (71). Yang et al. reported that CD4+T cells and the ratio of CD4+/CD8+T cells decreased in 1 month after lenvatinib plus TACE and PD-1 inhibitor therapy. Nevertheless, CD8+ T, CD3+ T, and NK cells increased from 1 to 4 months. In general, triple therapy could activate immune function and maintained it for a long time (6). However, hypoxia and overexpression of VEGF as a result of TACE led to an immunosuppressive TME by increasing Treg cells, myeloid-derived suppressor cells (MDSCs), and mast cells, recruiting monocytes from bone marrow, and raising tumor-infiltrating macrophages. Moreover, VEGF inhibited the development of T cells and the maturation of DCs (50, 58, 66). VEGF was also reported to modulate the checkpoint expression of CD8+T cells in HCC (72). The expression of PD-1 increased in peripheral mononuclear cells (6, 7). ICIs activate interferon-γ (IFN-γ)+ Type 1 T helper (Th1) cells to normalize the tumor vasculars and improve hypoxic environments (6). TACE synergized with PD-1 inhibitors and increased T lymphocytes (57). The immune response induced by TACE is complex, but there was indeed a synergistic effect with PD-1 inhibitors.

Studies on the mechanisms of lenvatinib combined with PD-1 inhibitors therapy

In addition to the role of TACE, the oxygen content of tumor cells was dramatically lower than that of normal liver cells, which increased the angiogenic growth factors, including VEGF and FGF and led to immune disorders (73). The expression of PD-1, CTLA-4, and Tim-3 were upregulated by FGF and VEGF on T cells. TIM-3 also promoted the exhaustion of T cells (70). When FGF and VEGF were combined, these effects were strengthened (30). After PD-1 inhibitors therapy, the expression of VEGF and FGF in patients with PD was significantly higher than that of SD patients (30). Lenvatinib inhibited these angiogenic growth factors and was associated with T-cell activation, enhanced the antitumor immunity, and increased the efficacy of PD-1 inhibitors (54, 55, 74). Additionally, the JAK/STAT3 signaling pathway was activated by FGFR2 signals accompanied with increasing PD-L1 expression according to Li et al. FGFR2 was inhibited by lenvatinib (75). Yi et al. showed that PD-1 inhibitors increased the level of interleukin 2 (IL-2); nevertheless, lenvatinib inhibited IL-2-mediated Treg differentiation by targeting FGFR4 and restrained STAT5 phosphorylation. Lenvatinib and FGFR4 knockdown lead to the activation of GSK3β, which destabilized PD-L1 *via* proteasome degradation (76). Lenvatinib decreased the expression of PD-L1 on human umbilical vein endothelial cells (HUVEC). However, it did not affect the expression of PD-L1 on tumor cells and restored T-cell function and retained the sensitivity of tumor cells to PD-1inhibitors (30). Adachi et al. reported that the activation of FGFR inhibited the IFN-γ-signaling pathways in mouse and human renal cell carcinoma (RCC) cell lines (66). IFN-γ could enhance the immune response by recruiting other leukocytes (76). The IFN-γ signaling pathway also facilitated tumor recognition by cytotoxic CD8+T cells, increased tumor immunogenicity, and caused rejection of the tumor by the host immune system. An active IFN-γ-signaling pathway enhances antitumor activity of lenvatinib plus PD-1 inhibitors. IFN-γalso activated the JAK/STAT1 signaling pathway and increased its target genes, including PD-L1. Lenvatinib blocked FGFR, which also led to an increase in PD-L1 (66). The increased PD-L1-positive area after PD-1 inhibitor monotherapy further extended after lenvatinib plus PD-1 inhibitors. Adachi et al. held that the increase of PD-L1 will enhance the effect of PD-1 inhibitors (66). Lenvatinib also increased neutrophil and upregulated PD-L1 expression on neutrophils in the TME (77). In conclusion, the effect of lenvatinib on PD-L1 expression remains controversial and has not been finalized. Koganemaru et al. reported that PD-L1 overexpression on tissue-infiltrating mononuclear cells was related to a good prognosis yet poor prognosis of tumor cells (78). PD-L1 overexpression on tumor cells or inflammatory cells had a considerable relationship with tumor aggressiveness, such as poor differentiation, high AFP levels, satellite nodules, and vascular invasion. However, PD-L1 expression was thought to represent a

biomarker predictive of drug sensitivity (59). Although according to the current study, PD-L1 expression was closely related to a poor prognosis, it also promoted antitumor activity of lenvatinib plus PD-1 inhibitor therapy according to Adachi et al. (66). The role of PD-L1 in the prognosis of HCC and in the prediction of lenvatinib treatment effect needs further verification, but the superiority of lenvatinib combined with PD-1 inhibitors should not be ignored. In addition to the above mechanisms, lenvatinib also enhanced the efficacy of PD-1 inhibitors by increasing the proportion of activated CD8+T cells and secreting IFN-γ and granzyme B. IFNγ+ CD8+ T cells increased more in the combination therapy group. Moreover, in immunodeficient mice, the antitumor activity of lenvatinib decreased because of the absence of CD8+T cells. CD4+ T cells also increased with lenvatinib therapy. Furthermore, lenvatinib decreased monocytes, macrophages, and TAMs (30, 66, 68, 79). A low concentration of lenvatinib acted as an immunoregulator (30). Long-term immune memory was formed with lenvatinib plus PD-1 inhibitor therapy, the TME was modulated, and the cytotoxic effect of T cells enhanced (30). Lenvatinib plus PD-1 inhibitor therapy also reduced tumor vessel density (30, 42).

According to the article published by Yang et al., CD8+ T cells increased significantly after 1 month of the TKIs plus TACE and inhibitor therapy, which reflects the activation of cellular immunity. However, CD8+T cells were relatively stable after PD-1 inhibitor monotherapy or TACE therapy alone (80). A significant increase in circulating CD8+ T cells was observed until 3 months after tremelimumab plus TACE therapy (81). Patients receiving PD-1 inhibitors-based combination immunotherapy, appeared to experience a decrease in B cells accompanied by an increase in Ig G, kappa light chains (Ig κ), and lambda light chains (Ig λ). B cells migrated from the bone marrow to the secondary lymphoid organs, activated by antigens and underwent isotype switching to Ig G. Therefore, the reduction in circulating B cells likely occurred because of the isotype switch to antibodies, indicating that humoral immunity plays an important role in TKIs plus TACE and inhibitors therapy (6). Additionally, Ig G, Ig κ, and Igλ increased at the time of response, and decreased to the baseline with tumor progression. CD8+ T and B cells did not show this trend. Therefore, circulating Ig G, Ig κ, and Igλ could serve as potential biomarkers (6).

Conclusions

The advantages of lenvatinib plus TACE over lenvatinib monotherapy in patients with HCC in intermediate stage, especially beyond the up-to-seven criterion, over TACE in patients with uHCC, and over sorfenib plus TACE in patients with advanced-stage HCC, especially with PVTT, are described in detail in this review. Lenvatinib plus TACE therapy is preferable in patients with HCC with high tumor burden, poor liver function, and numerous heterogeneous lesions in the intermediate stage and has advantages over sorafenib plus TACE in patients with PVTT. Lenvatinib plus TACE and PD-1 inhibitors therapy improved OS, PFS, and ORR compared with lenvatinib plus TACE therapy, and is a promising treatment for patients with uHCC at various BCLC stages.

Author contributions

FC and LS proposed ideas and completed outline of this review. FM, XX and QL found out the relevant literatures and carried out data collection. HW and XL performed data analysis. LS wrote the original draft and edited the manuscript. GL and FC supervised. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Prospective study of TACE combined with sorafenib *vs* TACE combined with ^{125}I seed implantation in the treatment of hepatocellular carcinoma with portal vein tumor thrombus and arterioportal fistulas

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Purpose: To compare the efficacy of TACE combined with sorafenib and TACE combined with ^{125}I seed implantation in the treatment of hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT) combined with arterioportal fistulas (APFs), and discuss the efficacy and safety of TACE combined with ^{125}I seed implantation.

Patients and methods: Between January 2017 and December 2018, the clinical data of patients with HCC complicated with PVTT and APFs who were admitted to the Affiliated Cancer Hospital of Zhengzhou University, First Affiliated Hospital of Zhengzhou University, and Henan Provincial People's Hospital were prospectively collected. The patients were divided into the TACE+sorafenib (TACE-S) group based on their treatment willingness. There were 26 and 32 patients in the TACE-S and TACE-^{125}I groups, respectively. Both groups of patients underwent APFs occlusion during TACE therapy. The embolization effect of APFs was observed and recorded in the two groups, the efficacy of intrahepatic lesions and PVTT was evaluated, and the effects of different treatment methods on the efficacy were analysed.

Results: All patients completed the 3 months follow-up. The improvement rates of APFs in TACE-S and TACE-^{125}I groups were 30.77% (8/26) and 68.75% (22/32), respectively, and difference was statistically significant ($\chi 2$ = 8.287,

P=0.004). The median survival time of TACE-S and TACE-^{125}I groups was 8.00 months and 12.8 months, respectively ($\chi 2$ = 7.106, P=0.008). Multivariate analysis showed that the PVTT subtype (IIa/IIb) and treatment method (TACE-S or TACE-^{125}I) were independent factors affecting the recanalization of APFs in patients (P<0.05).

Conclusion: For patients with HCC with PVTT and APFs, TACE combined with ^{125}I seed implantation can effectively treat portal vein tumor thrombus, thereby reducing the recanalization of APFs and prolonging the survival time of patients.

KEYWORDS

hepatocellular carcinoma, arterioportal fistulas, portal vein tumor thrombus, ^{125}I seed, transarterial chemoembolization, sorafenib

1 Introduction

The proportion of portal vein tumor thrombus (PVTT) in patients with advanced hepatocellular carcinoma (HCC) in China is high, ranged 44%–62.2% (1, 2). PVTT has been recognized as an independent risk factor for poor prognosis in HCC patients (3). Median overall survival (OS) was only 2.7-4 months in patients with HCC with PVTT with best supportive care only, compared with 10-24 months in patients without PVTT (4). Arterioportal shunts have been reported in 27-63.2% (5) of advanced HCC cases and may be caused by PVTT. The emergence of arterioportal fistulas (APFs) increases the risk of serious complications such as esophageal varices, ascites, and hepatic encephalopathy (6, 7), which seriously affects the prognosis and survival of patients.

The Barcelona Clinic Liver Cancer (BCLC) system recommends sorafenib alone for HCC patients with PVTT (8). In the Asia-Pacific region, transarterial chemoembolization combined with sorafenib (TACE-S) is the more commonly used treatment for such patients (9, 10). In TACE procedures, APFs are frequently seen by digital subtraction angiography (DSA) (7), which is also the gold standard for diagnosis. In addition, multi-slice CT angiography (MSCTA) can also detect the presence of APFs (11, 12). However, because of poor control of PVTT, even if the APFs are blocked, most patients recanalize the APFs on subsequent follow-up examinations.

In addition, direct puncture implantation of ^{125}I seeds can be used to treat tumor thrombus in portal vein branches (12–14). A prospective study in China reported that TACE-^{125}I was superior to TACE-S in the treatment of HCC patients with branch portal vein tumor thrombus (12). There are no studies to prove that implantation of ^{125}I in PVTT can lead to favorable APFs response. Therefore, we designed this prospective, non-randomized controlled study to compare the efficacy and safety of TACE combined with sorafenib and TACE combined with PVTT ^{125}I seed implantation for the treatment of HCC patients with PVTT and APFs.

2 Material and methods

2.1 Patient information

This prospective controlled study complies with the ethical guidelines of the World Medical Association Declaration of Helsinki. The overall clinical trial has been registered in the Chinese Clinical Trials Database (number ChiCTR-ONN-16007929). This study was reported as a subgroup of the overall clinical trial from which the data were derived. All patients signed informed consent and had the right to withdraw from the study at any time.

Between January 2017 and December 2018, 127 patients with HCC and PVTT were treated in our department. A total of 58 patients were found to have APFs during hepatic angiography, and they were immediately included in this study. The inclusion criteria were as follows (1): Diagnosis according to the criteria of the European Association for the Study of Liver Disease/American Association for the Study of Liver Disease (15), diagnosis of HCC complicated with PVTT (Figure 1), and only included in Cheng's classification Type II PVTT (16); (2) Hepatic artery DSA confirmed APFs; (3) Child-Pugh class A or B. Exclusion criteria: (1) patients who had received anti-tumor therapy such as surgery, radiofrequency or microwave ablation, systemic chemotherapy, and intra-arterial chemoinfusion, or TACE; (2) severe concomitant diseases, such as severe heart failure or respiratory diseases; (3) hepatic encephalopathy or extrahepatic metastasis; (4)

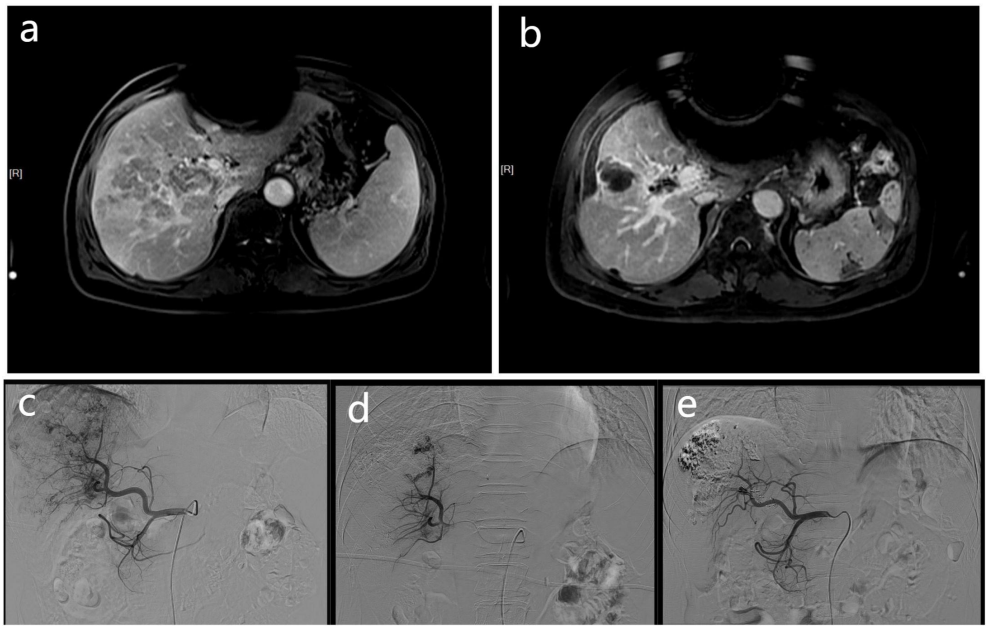

FIGURE 1
These MR and DSA images show the imaging data of a 68-year-old men with HCC complicated by portal vein tumor thrombosis in the right branch. Contrast-enhanced MR scan showing a tumor thrombus in right portal vein **(A)**. The contrast-enhanced MR of the patient 3 months later shows a significant reduction in PVTT volume **(B)**, and the previously blocked portal vein due to PVTT also restores blood flow. At the same time, according to the mRECIST criteria, there was no activity in the intrahepatic lesions, and no activity was found in the PVTT, which was judged as CR. The DSA image of the patient undergoing embolization of the APFs and obvious portal vein development can be seen during angiography of the proper hepatic artery **(C)**. The angiographic image of the patient taken at a time after treatment, showing that the APFs are completed by sealing **(D)**. A follow-up DSA image of the patient three months later showed no APFs **(E)**.

Child-Pugh grade C; and (5) uncorrectable renal and coagulation dysfunction.

Based on fully introducing the two treatment methods and respecting the wishes of the patients, they were divided into two groups. A group of patients received TACE + sorafenib (TACE-S) treatment, which consisted of a total of 26 cases. The other group received TACE+PVTT ^{125}I seed implantation (TACE-^{125}I), which consisted of a total of 32 patients. A total of 58 patients were included in the study.

2.2 TACE procedure

As previously reported (12, 14), routine celiac arteriography and hepatic arteriography were performed to confirm the diagnosis of HCC and the specific conditions of the APFs. If the presence of APFs was confirmed, a 2.7 F coaxial microcatheter (Terumo, Japan) was used to select the corresponding artery for superselective arteriography to determine the location of the APFs and determine the flow. After hepatic arteriography, there are two types of embolization according to whether the microcatheter can pass through the APFs area: (1) if the microcatheter can pass through the APFs area, tumor embolization should be performed first. A volume of 5–20 ml Lipiodol (Lipiodol Ultrafluide, Laboratoire Guerbet, France) and doxorubicin (50–75 mg/m2) (Haizheng Pharmaceutical Co. Ltd., China) were mixed to prepare a lipiodol emulsion. After tumor chemoembolization was completed, the microcatheter was returned to the APFs area, and polyvinyl alcohol of different diameters (polyvinyl alcohol foam embolization particles; Cook Medical Inc., Bloomington, IN, USA) was selected to embolize the fistula; (2) if the microcatheter could not pass through the APFs area, chemoembolization was performed in a certain area of the supplying artery, and the target tumor and APFs were simultaneously embolized. When it was found that APFs still existed during the re-imaging, a spiral steel ring (China, Cook Medical Trading Co., Ltd.) was chosen. Angiography showed that the APFs disappeared or most of the shunt disappeared, and the operation was ended.

2.3 Sorafenib treatment

All patients in the TACE-S group started sorafenib (400 mg, bid) 3-7 days before the first TACE treatment. Therefore, patients should continue sorafenib treatment. If there is an obvious clinical toxicity related to the treatment, the dose can be reduced or discontinued depending om the situation. After

the toxicity subsided or disappeared, the original dose or resumed medication was restored.

2.4 ^{125}I seed implantation procedure

The liver functions of patients in the TACE-^{125}I group were followed up 3-7 days after the first TACE treatment. An enhanced CT scan was performed before surgery, the image was imported into the treatment planning system (TPS) (FTT Technology Ltd. Co, Beijing, China), the ^{125}I seed implantation plan was planned to calculate the formula dosage, number, spatial distribution, intensity of radioactivity, and matched peripheral dosage of seeds before implantation so that 95% of the tumor target volume reached the prescribed dose, and the target volume ratio reaches 1.5–2.0. According to the TPS system, an 18 G seed implantation needle was used to puncture the target lesion, and ^{125}I seeds were implanted in different layers and positions of the tumor. According to the spacing of the 5 mm cloth source, the particle distribution was uniform. A CT scan was performed immediately after surgery to observe the particle distribution.

2.5 Evaluation indicators

According to the time of appearance of AFPs, they are divided into three categories: (1) Mild: no fistula shape is shown on angiography, and when bolus injection of lipiodol is used for embolization, the small branches of the portal vein can be seen. (2) Moderate: the main or branch of the portal vein is visualized in the middle and late stages of tumor staining. (3) Severe: the portal vein is visible when the main and branches of the hepatic artery are visualized. At this time, tumor staining was absent or was at an early stage.

MSCTA diagnostic criteria for AFPs (11, 12): (1) the main portal vein or first-order branches in the hepatic arterial phase are visualized early, while the splenic vein and superior mesenteric vein have not been enhanced; (2) the hepatic arterial phase peripheral portal vein secondary or secondary and distal branches are visualized early, while the proximal main portal vein and left and right branches are not yet enhanced. The diagnostic criteria for APFs include the early development of hepatic vein branches in the hepatic arterial phase, while the portal vein and liver parenchyma have not yet been enhanced.

Criteria for evaluating the therapeutic effect of APFs were as follows: (1) changes in APFs classification: ① Cure, APFs disappear completely; ② Relief, APFs degree is reduced or time delay occurs; ③ Stabilize, APFs level remains unchanged; ④ Progress, APFs level increase in flow rate. DSA angiography images of all patients were re-examined 3 months after the first treatment, and the effect of fistula embolization was observed according to the arterial angiography images. Among them, ① and ② were considered effective, and ③ and ④ were considered ineffective. (2) Changes in liver function indices, including Child-Pugh grade and total bilirubin and albumin levels, were found.

The modified response evaluation criteria in solid tumors (mRECIST) were used to evaluate the efficacy of tumor embolization three months after the first treatment (17), including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Intrahepatic tumor lesions and portal vein tumor thrombus were evaluated separately.

2.6 Study objectives and follow-up

All patients were re-examined 4-6 weeks after the first TACE with plain upper abdominal MRI plus dynamic enhancement. Repeat TACE is feasible for residual tumor lesions. APF assessment of APFs is based on DSA angiography as the gold standard. Some patients no longer receive TACE after their condition has stabilized. Therefore, there is no direct evidence to prove recanalization of APFs, and the judgment is based on the performance of the MSCTA.

The improvement rates of APFs was defined as the percentage of responders (① and ②). The disease control rate (DCR) was defined as the percentage of CR+PR+SD patients. The time from treatment to the last follow-up or death was defined as overall survival (OS). The main objectives were to evaluate the improvement rates of APFs, changes in liver function indices, and DCR of intrahepatic lesions and PVTT after the first TACE. The secondary endpoint was OS.

2.7 Statistical analysis

All statistical analyses were performed using SPSS version 25.0 (SPSS, Chicago, IL, USA). To determine significant differences between groups, Student's t-test, chi-squared test, or Fisher's exact test was used. Factors affecting recanalization of APFs were analysed using univariate and multivariate logistic regression analyses. Survival analysis was performed using the Kaplan-Meier method, and an OS curve was drawn. The difference in survival between the two groups was analysed using the log-rank test. Statistical significance was set at $P< 0.05$.

3 Results

3.1 Basic characteristics

A comparative analysis of the TACE-S and TACE-^{125}I groups is shown in (Table 1). There were no significant differences in gender, age, ECOG score, Child-Pugh score, tumor number, largest tumor diameter, total tumor diameter, type of PVTT (IIa or IIb), AFP level, or blood test results ($P> 0.05$).

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TABLE 1 Comparison of general data of patients in the TACE-^{125}I group and the TACE-S group.

Variable	Grading	TACE-^{125}I group n=32	TACE-S group n=26	P value
Gender	Male	27 (84.4)	23 (88.5)	0.947
	Female	5 (15.6)	3 (11.5)	
Age	≤60	17 (53.1)	13 (50.0)	1.000
	>60	15 (46.9)	13 (50.0)	
ECOG Score	0	9 (28.1)	12 (46.2)	0.252
	1	23 (71.9)	14 (53.8)	
Child-Pugh classification	Class A	29 (90.6)	20 (76.9)	0.285
	Class B	3 (9.4)	6 (23.1)	
Number of liver tumors	1	10 (31.2)	12 (46.2)	0.373
	≥2	22 (68.8)	14 (53.8)	
Maximum tumor diameter	<60	19 (59.4)	18 (69.2)	0.616
	≥100	13 (40.6)	8 (30.8)	
Total tumor diameter	<100	24 (75.0)	23 (88.5)	0.335
	≥100	8 (25.0)	3 (11.5)	
Tumor location	Single leaf	8 (25.0)	9 (34.6)	0.610
	Futaba	24 (75.0)	17 (65.4)	
PVTT type	IIa	18 (56.2)	17 (65.4)	0.662
	IIb	14 (43.8)	9 (34.6)	
APFs classification	Mild	17 (53.1)	13 (50.0)	0.949
	Moderate	11 (34.4)	10 (38.5)	
	Severe	4 (12.5)	3 (11.5)	
AFP(ng/ml)	<400	15 (46.9)	16 (61.5)	0.396
	≥400	17 (53.1)	10 (38.5)	
TBL (g/L)		21.51 (11.13)	19.24 (11.71)	0.453
ALB (μmol/L)		38.77 (5.31)	37.96 (4.54)	0.540
PT(s)		12.97 (1.17)	13.30 (1.80)	0.415
WBC(10×12/L)		4.94 (1.87)	5.31 (1.60)	0.423
RBC(10×9/L)		4.33 (0.50)	4.17 (0.49)	0.238
HGB(g/L)		132.53 (15.83)	130.12 (12.38)	0.528

Unless otherwise indicated, data are presented as numbers of patients.
TACE, transarterial chemoembolisation; ECOG, Eastern Cooperative Oncology Group; PVTT, portal vein tumor thrombosis; AFP, alpha-fetoprotein; TBL, total bilirubin; ALB, albumin; PT, prothrombin time; WBC, white blood cell; RBC, red blood cell; HGB, haemoglobin.

3.2 Evaluation of the therapeutic effect of APFs

All 58 patients were followed up for 3 months after treatment, and there were statistically significant differences in APFs grading between the two groups before treatment and 3 months after treatment (Table 2). After 3 months of treatment, 22 patients in the TACE-^{125}I group were effective for APFs occlusion, while 10 were ineffective. In the TACE-S group, 8 were effective and 18 were ineffective. The improvement rates of

TABLE 2 Comparison of APFs grades before and 3 months after treatment between the TACE-^{125}I group and the TACE-S group.

Groups	Before treatment				After treatment				χ^2	P *value*
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe		
TACE-^{125}I group (n=32)	0	17	11	4	16	11	1	4	29.010	0.001
TACE-S group (n=26)	0	13	10	3	5	5	12	4	8.750	0.029
X^2			0.158				17.317			
P value			0.949				0.001			

APFs in the TACE-S group and TACE-^{125}I group were 30.77% (8/26) and 68.75% (22/32), respectively, and the difference was statistically significant ($\chi2$ = 8.287, P=0.004) (Table 2). There were no differences in Child-Pugh grade and albumin and bilirubin levels between the TACE-S and TACE-^{125}I groups before and after treatment (Table 3).

3.3 Efficacy assessment of intrahepatic lesions and PVTT

The DCR of intrahepatic lesions in the TACE-^{125}I group and TACE-S group were 84.38% and 60.71%, respectively, and this difference was statistically significant ($\chi2$ = 4.275, P=0.039) (Table 4). The DCR of PVTT in TACE-^{125}I group and TACE-S group were 81.25% and 53.57% , respectively, and the difference was statistically significant ($\chi2$ = 5.287, P= 0.021) (Table 5).

3.4 Analysis of factors affecting APFs recanalization

Univariate and multivariate analyses showed that PVTT subtype (IIa/IIb) and treatment method (TACE-S or TACE-^{125}I) were factors affecting the recanalization of APFs (Table 6).

3.5 Subsistence analysis

As of 31 December 2020, the 12-month survival rates were 12.2% in the TACE-S group and 53.1% in the TACE-^{125}I groups. The median overall survival (mOS) of the TACE-S group and TACE-^{125}I group were 8.00 months and 12.8 months, respectively ($\chi2$ = 7.106, P=0.008) (Figure 2A). Survival analysis of patients with successful APFs recanalization and occlusion in each group. TACE-S group: 8.7 months *vs* 6.9 months ($\chi2$ = 3.155, P=0.08) (Figure 2B); TACE-^{125}I group: 13.9 months *vs* 9.1 months ($\chi2$ = 1.454, P=0.228) (Figure 2C).

TABLE 4 Efficacy assessment for intrahepatic lesions.

	TACE-^{125}I group	TACE-S group	χ^2	P *value*
CR	1 (3.12%)	0 (0.0%)		
PR	12 (37.50%)	7 (25.00%)		
SD	14 (43.75%)	10 (35.71%)		
PD	5 (15.63%)	11 (39.29%)		
DCR	84.38%	60.71%	4.275	0.039

3.6 Adverse reactions

Some patients experienced adverse reactions related to TACE treatment and post-embolization syndromes of varying degrees, such as abdominal pain, nausea, and vomiting. After to 3-7 days of symptomatic treatment, the patient's symptoms were relieved. The overall incidence of adverse events or toxic effects related to sorafenib use was 84.61% (22/26). The most common grade 3 to 4 adverse events were diarrhoea (7.69%, 2/26) and hand-foot skin reactions (3.85%, 1/26). Adverse effects of PVTT^{125}I seed implantation included haemorrhage and pneumothorax, which were relieved by symptomatic treatment. No serious adverse reactions, such as surgery-related deaths, were observed.

4 Discussion

Previous studies have shown that PVTT is an independent risk factor for recanalization (18). In our study, the APFs occlusion rate of patients in the TACE-^{125}I group was high (68.75%) and one-time intraoperative occlusion rate was 100%. Our study analysed the occlusion effect of APFs 3 months after TACE, and confirmed that compared with TACE-S, TACE combined with portal vein tumor thrombus ^{125}I seed implantation can control the recanalization of APFs.

Previous studies have shown that embolic materials for the treatment of hepatic arterial shunt (APS) include ethanol-soaked gelatin sponge (ESG) and polyvinyl alcohol (PVA) particles. On the basis of TACE-based therapy, aggressive and thorough APS embolization during surgery can reduce the occurrence of fistula recanalization (19, 20). In our study, all patients achieved

TABLE 3 Comparison of Child-Pugh classification, as well as total bilirubin and albumin levels, before treatment and 3 months after treatment in the TACE-^{125}I group and the TACE-S group.

Variable		TACE-S group			TACE-^{125}I group		
		Before therapy	After treatment	P value	Before therapy	After treatment	P value
Child-Pugh classification	A	20 (76.9)	18 (69.23)	0.532	29 (90.6)	30 (93.75)	1.000
	B	6 (23.1)	8 (30.77)		3 (9.4)	2 (6.25)	
Total bilirubin (g/L)		19.24 ± 11.71	18.37 ± 10.12	0.766	21.51 ± 11.13	18.7 7 ± 10.17	0.291
Albumin (μmol/L)		37.96 ± 4.54	37.72 ± 5.16	0.866	38.77 ± 5.31	38.62 ± 4.81	0.907

complete occlusion by using PVA particles during TACE procedure. The final results showed that the recanalization rate of APFs in the TACE-S group was still high, even when the APFs were blocked with the same material. The results of the APS study combined with PVTT showed that there were differences in the survival of patients with different PVTTs (21). Therefore, for patients with APF and PVTT, it is important to control the progression of PVTT after complete occlusion therapy. This will further prolong patient survival.

In previous studies, APS improvement was shown to be an independent prognostic factor (6). However, most studies focus on materials for the treatment of APS, ignoring the specificity of APS with PVTT. As we believe, fistula and tumor thrombus are mutually causal and mutually reinforcing results. The mechanism may be: the formation of PVTT is mainly related to portal venous reflux. About 47%-63% of liver cancers are associated with hepatic arteriovenous fistula (22), mainly the hepatic artery-portal communicating branch. 90% of the blood supply of HCC comes from the hepatic artery, and the liver cancer cells are directly injected into the small branch of the portal vein with low pressure through the blood flow of the hepatic artery with higher pressure, and stay and implant in the portal vein to form PVTT. The formation of PVTT results in the obstruction of the portal vein, resulting in the opening of extensive anastomotic branches between the hepatic artery and the portal vein in normal liver tissue to form fistulas, further aggravating the occurrence of intrahepatic decompensation events.

In terms of related indicators before and after treatment, the results of this study showed that the proportion of patients with Child-Pugh A grade in the TACE-^{125}I group did not change significantly (90.6% *vs* 93.75%) 3 months after treatment, and the proportion of those with Child-Pugh B grade in the TACE-S group increased (23.1% *vs*. 30.77%), although no statistical difference was observed. However, the control of PVTT by ^{125}I particles relieves clogging of the portal vein, and is more important for the relief of liver function, which is consistent with previous studies (12).

Multivariate logistic analysis showed that the type of PVTT and treatment were prognostic factors affecting recanalization of APFs. In our study, there were statistically significant differences in the DCR for both intrahepatic lesions and PVTT. The median survival times of patients in the two groups were 8.00 months and 12.80 months, respectively. Compared with previous results, the tumor response in our study was poor, which may be related to the effect of APFs on TACE efficacy (12, 23). In addition, studies have shown that DEB-TACE and Y-90 radioembolization have good efficacy and safety in HCC patients with PVTT (24, 25). However, Y-90 radioembolization is not feasible for the appearance of APFs.

Further analysis of our study revealed the results. Under the same treatment modalities, the survival of patients with fistula recanalization was worse than that of patients with fistula closure (TACE-S group: 8.7 months *vs* 6.9 months, P=0.08; TACE-^{125}I group: 13.9 months *vs* 9.1 months, P=0.228), although no statistical difference was shown (P>0.05). This may be related to our limited sample size. APFs interact with PVTT to make the prognosis of patients worse, and further research is needed to prove this inference.

In terms of safety, previous studies have also shown that TACE combined with sorafenib has no unexpected toxicities (23), and this study did not show any additional adverse reactions. The adverse reactions related to ^{125}I seed implantation are mainly caused by puncture and subcapsular haemorrhage. Only part of the puncture route passes through the lung tissue, and the pneumothorax caused by it is mild.

This study has certain limitations. First, although this study is a prospective multicentre study, it is a non-randomized control, it may cause statistical bias. Additionally, the small sample size is an important limitation. Secondly, considering that previous studies have shown that different materials have different effects on APFs (19, 20), and to avoid confounding factors, all patients were treated with PVA particles. Further research on the efficacy of different blocking materials for APFs is necessary after actively controlling PVTT.

5 Conclusion

In conclusion, from the perspective of fistula recanalization, this study found that in patients with HCC complicated with PVTT and APFs, TACE combined with ^{125}I seed implantation can more effectively reduce the occurrence of APFs

TABLE 5 Efficacy assessment for PVTT.

	TACE-^{125}I group	TACE-S group	χ^2	P *value*
CR	1 (3.13%)	0 (0.0%)		
PR	13 (40.635%)	6 (21.43%)		
SD	12 (37.50%)	9 (32.14%)		
PD	6 (18.75%)	13 (46.43%)		
DCR	81.25%	53.57%	5.287	0.021

Unless otherwise indicated, data are numbers of patients.
CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; PVTT, portal vein tumor thrombosis; SD, stable disease; TACE, transarterial chemoembolisation.

TABLE 6 Multivariate Analysis of Influencing APFs Recanalization.

variable	RR	95% confidence interval	P value
PVTT type (IIa/IIb)	15.88	2.99-84.34	0.001
Treatment (TACE-S group/ TACE-^{125}I group)	13.07	2.54-67.16	0.002

The binary logistic regression model was used.

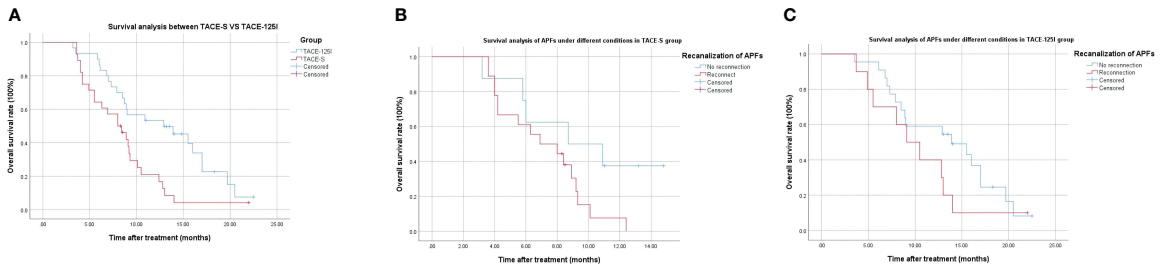

FIGURE 2
Survival curve of patients in TACE-S group and TACE-^{125}I group.

recanalization. In such patients, the control of PVTT progression may be more important. TACE combined with portal vein tumor thrombus ^{125}I seed implantation is effective and safe in the treatment of advanced HCC patients with type II PVTT, and can significantly prolong patient survival.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was reviewed and approved by The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki, was approved by the Ethics Committee of our institution (2016ct005) and was registered in the Chinese Clinical Trials Database (number ChiCTR-ONN-16007929). This study was reported as a subgroup of the overall clinical trial from which the data were derived. All patients provided written informed consent for participation in this study. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Conception and design: H-TH. Patient selection and treatment: X-HZ, HY, W-LX, H-TH,G-SC, ZL, Hai-LL, C-YG, Q-JY and W-BZ. Data collection, analysis, and interpretation: X-HZ, HY, W-LX and L-LZ. Data interpretation: X-HZ, H-TH, and Hai-LL. Undertook steering committee activities and critical statistical processing: H-TH and Hai-LL . Manuscript writing: X-HZ, HY, W-LX and L-LZ. Manuscript reviewing: H-TH, W-JF and Hong-LL . All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Application of systemic treatment in conversion therapy options for liver cancer

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Radical hepatectomy is the main treatment method to improve the prognosis of patients with intermediate and early-stage liver cancer. Most liver cancer patients in China are in the advanced stage at the initial diagnosis, losing the opportunity for surgical treatment. Therefore, it is essential to down-stage unresectable liver cancer to resectable liver cancer clinically, which is an important way to improve patients' survival and a hotspot of current clinical research. In recent years, with the increase in effective treatment methods for liver cancer, the resection rate of conversion surgery for unresectable advanced liver cancer has been significantly improved, and a growing number of patients benefit from conversion therapy. This article mainly reviews the connotation of conversion therapy for liver cancer, the patient selection, the selection of conversion strategy, the timing of sequential operations, the scheme and safety, etc.

KEYWORDS

primary liver cancer, systemic treatment, conversion therapy, downstaging, surgical resection

Introduction

As one of the most common malignant tumors in the world, primary liver cancer ranks sixth in the incidence of malignant tumors worldwide in 2018, and is the fourth leading cause of tumor death (1). Primary liver cancer is the fourth most common malignant tumor and the second leading cause of tumor death in China, which seriously threatens the lives and health of the Chinese people. Hepatocellular carcinoma (HCC) (hereafter referred to as liver cancer) accounts for 75% of 85% of primary liver cancer cases. Risk factors for liver cancer include chronic viral hepatitis (hepatitis B virus infection, hepatitis C virus infection), alcoholic liver disease, consumption of food contaminated by aflatoxin, obesity and diabetes, etc. Among them, chronic hepatitis B virus (HBV) infection is the main risk factor for HCC in China (2). For patients with early-stage liver cancer, the main treatment methods include surgical resection, local

ablation and liver transplantation. However, due to the latent onset and rapid progress of liver cancer, most patients are diagnosed at the intermediate and advanced stages including Barcelona Clinic Liver Cancer(BCLC) stage B, C or China liver cancer staging (CNCL) stage IIIa, IIIb and some stage IIb, when the surgical effect is poor or the opportunity for surgery is lost, and the median survival time is only 1 year (3). For such patients, the most important thing is to transform unresectable liver cancer into resectable liver cancer and perform successful surgery, which is also the key to long-term survival. In recent years, the development of tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) has brought opportunities for the treatment of liver cancer at intermediate and advanced stages, and conversion therapy has become one of the current research hotspots.

As a treatment method for unresectable liver cancer, conversion therapy for liver cancer mainly adopts systematic drug therapy and or non-surgical local therapy to inhibit tumor progression, reduce tumor burden and improve clinical tumor staging, thereby providing patients the opportunity to undergo radical surgery (4, 5). The other category of conversion therapy is neoadjuvant therapy, which refers to HCC patients with technically resectable tumors and a high risk of recurrence. It aims to shrink the tumor, improve the radical resection rate, and reduce recurrence. When the treatment is applied to patients with surgically resectable but oncologically unresectable HCC, both treatments may be overlapped in the target population (5). At present, the commonly used conversion therapy methods in clinic include targeted therapy, immunotherapy, local therapy, radiotherapy and other combination therapy methods. With the in-depth investigation of various clinical studies, more and more patients with liver cancer at intermediate and advanced stages have benefited from conversion therapy. The regimen and efficacy of conversion therapy are described as follows:

Application of drug therapy in conversion therapy

Effect of drug therapy

Targeted therapy

Mainly TKIs drugs with representatives including sorafenib, lenvatinib, apatinib, etc. Sorafenib can directly inhibit tumor cell proliferation by inhibiting the rat sarcoma virus (Ras)/rapidly accelerated fibrosarcoma (Raf)/mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling pathway, which was used in the treatment of renal cell carcinoma at first. It was approved by the U.S. Food and Drug Administration (FDA) in 2007 for the treatment of advanced HCC. In a large randomized controlled international multicenter clinical trial (SHARP study), 602 patients with advanced liver cancer who had not received systemic treatment were included and randomized to receive sorafenib or placebo. The results showed that the median overall survival (mOS) in the sorafenib group (n1 = 299) and the placebo group (n2 = 303) was 10.7 months vs. 7.9 months (P<0.001), and the median time to progression (mTTP) was 5.5 months vs. 2.8 months (P<0.001), indicating that sorafenib can postpone the progression of advanced liver cancer and prolong the survival of patients (6). Another clinical study on sorafenib (Oriental study) also came to similar conclusions (7). Sorafenib, as the first molecular targeted drug for the treatment of advanced liver cancer, has made a certain contribution to prolonging the survival of patients. However, due to its low objective response rate (ORR) (about 2.3%), significant adverse reactions, no obvious improvement in the overall survival rate in hepatitis B virus-positive patients, it still cannot fulfill the current needs for treatment of advanced liver cancer.

Lenvatinib is an oral multi-receptor tyrosine kinase inhibitor developed by Eisai. Its main targets are: vascular endothelial growth factor receptor (VEGFR) 1-3, fibroblast growth factor receptor (FGFR) 1-4, platelet-derived growth factor receptor (PDGFR) α, c-Kit, RET etc. A phase III randomized controlled global multicenter non-inferiority clinical study, the REFLECT trial (8), compared lenvatinib with sorafenib. For the primary endpoint of the trial, the mOS in the lenvatinib group was non-inferior to the sorafenib group with a trend of prolongation (13.6 months vs. 12.3 months, P>0.001); in terms of secondary endpoints comparing the lenvatinib with sorafenib, the median progression-free survival (mPFS) (7.4 vs. 3.7 months), mTTP (8.9 vs. 3.7 months), and ORR (24% vs. 9%) all improved. In terms of safety, there was no significant difference between lenvatinib and sorafenib with the incidences of treatment-related adverse events similar between the two groups. Meanwhile, for HBV-related HCC, lenvatinib showed more advantages in prolonging the survival. These data indicated that lenvatinib was not inferior to sorafenib in the efficacy for advanced HCC patients, was superior to sorafenib in secondary endpoints such as ORR and mPFS, and was applicable to a wider population. Therefore, it is recommended by many first-line guidelines to be used in the first-line treatment of unresectable HCC. Tomoko's team (9) also conducted a clinical study of lenvatinib treatment after failure of PD-1/PD-L1 treatment for liver cancer, finding that the mPFS after lenvatinib treatment was 10 months, mOS was 15.8 months, ORR reached 55.6%, and Disease control rate (DCR) reached 86.1%. It showed that the use of lenvatinib could still increase the chance of conversion and prolong the survival after failure of immunotherapy.

Other drugs, for example, apatinib, a new small-molecule targeted drug independently developed by Jiangsu Hengrui Pharmaceuticals, was initially used for the treatment of advanced gastric cancer, and is now also used in patients with advanced liver cancer who fail or are intolerable to first-line systemic anti-tumor treatment, as a second-line therapeutic

regimen for advanced liver cancer. The results of a phase III clinical study of advanced liver cancer in China showed that apatinib, compared with placebo, significantly prolonged the median survival in patients with advanced liver cancer receiving second-line treatment or above, and the ORR reached 10.7%. The risk of death was reduced by 21.5%, and the risk of disease progression was reduced by 52.9% (10).

Targeted drugs combined with immunotherapy

Currently, targeted drugs combined with immunotherapy has become the first-line treatment strategy for advanced HCC. In the IMbrave150 study, atezolizumab combined with bevacizumab (T+A) achieved better positive results compared with sorafenib, showing significantly improved mOS (19.2 months vs. 13.4 months $p < 0.001$) and mPFS (6.9 months vs. 4.3 months $p < 0.001$) in liver cancer patients after treated with the T+A regimen (11). In addition to the T+A regimen, the combination of TKI drugs with PD-1/PD-L1 has also achieved good results. In the phase Ib study Keynote524 (12), the mPFS of lenvatinib combined with pembrolizumab was 9.7 months, the mOS was 20.4 months, and the ORR was 46.3%. In 2019, this regimen was used as the first-line treatment regimen for liver cancer at advanced stage. At the 2020 ASCO-GI meeting, a phase Ib study of lenvatinib combined with nivolumab as the first-line treatment for patients with unresectable liver cancer (13) was reported with the results showing the overall ORR 76.7%, DCR 96.7%, and the clinical benefit rate 83.3%. In the study reported by Zhongshan Hospital affiliated to Fudan University using lenvatinib combined with PD-1 monoclonal antibodies (including nivolumab, camrelizumab, pembrolizumab, sintilimab and toripalimab) in the treatment of advanced HCC (14), the results showed that 6 patients (10.2%) underwent the surgical resection as the tumor had shrunk. Another clinical study of lenvatinib combined with pembrolizumab and apatinib combined with toripalimab in the treatment of unresectable liver cancer was published (15), wherein 10 patients (15.9%) underwent surgical resection 3.2 months (2.4-8.3 months) after the start of treatment and 6 patients (60%) achieved pathological complete response (pCR). In a prospective, uncontrolled, open-label study led by Professor Lu Shichun (16), PD-1 monoclonal antibodies combined with lenvatinib were investigated for the efficacy in the treatment of liver cancer with macrovascular invasion, and the results showed that the ORR was 53.1%(26/49), and the imaging-based conversion rate reached 51.0%, and 15 patients (30.6%) underwent R0 surgical resection. In a retrospective analysis of lenvatinib combined with camrelizumab versus lenvatinib alone, the efficacy in the combination group was improved compared with the single agent group, showing mPFS increasing from 7.5 months to 10.3 months ($P<0.05$), ORR increasing from 20.5% to 41.7% ($P<0.05$) (17). It showed that TKI drugs combined with PD-1 is a more effective conversion regimen.

Targeted therapy combined with local therapy

As the most commonly used local treatment method and one of the most common non-surgical treatment methods for liver cancer, Transarterial Chemoembolization (TACE) has certain effects in reducing tumor burden and prolonging patient survival, which is also recommended by many guidelines as the standard treatment for intermediate-stage liver cancer (18–20). However, when it is used alone, the conversion efficiency of TACE is low and recurrence often happens, moreover, multiple TACE can lead to poor efficacy or even resistance (21). Studies have shown that TACE combined with targeted therapy can improve the efficacy of TACE. A retrospective study led by Professor Shi Ming compared the efficacy of TACE combined with sorafenib versus sorafenib monotherapy in the treatment of advanced liver cancer complicated with hepatic vein tumor thrombus. The results showed that the OS and TTP in the TACE combined with sorafenib group were superior to sorafenib monotherapy (22). Ding et al. (23) conducted a study comparing the efficacy of sorafenib combined with TACE (TACE-S) and lenvatinib combined with TACE (TACE-L) in the treatment of advanced liver cancer complicated with portal vein tumor thrombus (PVTT). The results showed that TACE-L was superior to TACE-S in both mOS (14.5 months vs. 10.8 months) and mTTP (4.7 months vs. 3.1 months), and 17 patients (53.1%) in the TACE-L group achieved partial response, compared to 12 (25.0%) in the TACE-S group. Another study has also found that hepatic arterial infusion chemotherapy (HAIC) based on FOLFOX regimen is superior to TACE in efficacy, and HAIC combined with targeted therapy has also achieved good results. A prospective study found that sorafenib combined with HAIC significantly improved the survival and conversion rate compared with sorafenib alone, increasing mOS from 7.13 months to 13.37 months ($p<0.05$), PFS from 2.6 months to 7.03 months ($p<0.05$), and improving ORR from 5.7% to 54.4% (24). In a retrospective study reported by Mai at the American Society of Clinical Oncology in 2020 (25), 24 patients with advanced liver cancer who received FOLFOX regimen based HAIC combined with lenvatinib were analyzed showing that ORR and DCR were 66.7% and 79.2%, respectively. Among the targeted treatment combined with local treatment regimens, lenvatinib combined with HAIC achieved the best conversion effect.

Targeted therapy, immunotherapy combined with local therapy

Recent studies have shown that targeted immunotherapy combined with local therapy (TACE or HAIC) can further improve the surgical conversion rate of advanced unresectable liver cancer. In a study conducted to explore the efficacy of lenvatinib combined with TACE and pembrolizumab versus lenvatinib combined with TACE in the treatment of unresectable

liver cancer, Chen et al. (26) found that the OS and PFS of triple therapy were 18.1 months and 9.2 months respectively, superior to 14.1 months and 5.5 months of dual therapy, and 18 patients (25.7%) in the triple therapy group were successfully downstaged to undergo surgery, while 8 (11.1%) in the dual therapy group underwent surgery. Another retrospective analysis investigating the conversion of triple therapy using anti-angiogenic drugs combined with PD-1 and HAIC for unresectable liver cancer showed that the objective response rate was 96% (24/25) with 14 patients (56%) undergoing surgical resection, including 7 cases achieving pathologic complete response (27). In the retrospective analysis to investigate the efficacy of TACE combined with lenvatinib and sintilimab, the mOS of this regimen was 23.6 months, the mPFS was 13.3 months, and the ORR was 46.7% (28). In the LTHAIC study, a prospective, single-arm phase II clinical study (29), the treatment regimen of lenvatinib + toripalimab + HAIC showed to have an ORR of 66.7% (95% CI, 43.3-75.1), including 5 (13.9%) patients achieving complete radiographic response and 8 patients successfully downstaged to meet the criteria for surgical resection (Table 1). At present, the triple therapy shows the highest conversion efficiency.

In addition, as portal vein metastasis is prone to occur for liver cancer, many patients complicated with portal vein tumor thrombus cannot undergo surgical resection or the resection effect is poor. Some studies have found that when liver cancer is complicated with portal vein tumor thrombus, combination with radiotherapy can make the tumor thrombus shrink or even disappear, creating conditions for surgery and improving patients' survival. A large randomized controlled trial (RCT) comparing the efficacy of neoadjuvant radiotherapy followed by resection with direct resection in liver cancer patients with portal vein tumor thrombus showed that the 1-year survival rates of the two groups were 75.2% vs. 43.1%, and the 1-year tumor-free survival rates were 33.0% vs. 14.9%, respectively (30). Toshiya et al. compared the efficacy of radiotherapy followed by surgery with direct surgery. The pathological results after surgery showed that 83.3% of patients in the radiotherapy followed by surgery group achieved pathologically complete necrosis of the main portal vein tumor thrombus with the 5-year survival rate of 34.8%, compared to only 13.1% in the surgery alone group (31). There are also clinical data confirming the efficacy of Transarterial Radioembolization (TARE) in shrinking tumors and its role in the conversion therapy for liver cancer. For cases complicated with portal vein tumor thrombus, TARE shows higher local dose and more precise location than external beam radiotherapy, and also reduces radiation damage to normal liver tissue, with less effect on reserve function (32). Therefore, combination with radiotherapy can further improve the conversion rate and prolong the survival in patients withadvanced liver cancer complicated with portal vein tumor thrombus.

Decades ago, for patients with significant tumor load, many lesions, vascular invasion, or distant metastases, the only therapeutic options were TACE, sorafenib, or symptomatic therapy, and the prognosis was dismal, with a median overall survival rate of 6.5-10.7 months (6, 7, 33). Nowadays, In the era of systematic treatment, the application of TKI drugs and PD-1/PD-L1 has enriched the treatment of liver cancer, expanded the beneficiary group of patients, and median OS has reached 18.1 months or even longer (13, 14, 24, 26). Due to the decrease in tumor volume and stage(reducing the volume and number of primary lesions and eliminating portal vein tumor thrombus and metastatic lesions), part of advanced HCC patients have obtained the opportunity for radical surgery (Table 2) (34).

Conversion that increases liver volume

Liver failure caused by insufficient residual liver volume after surgery has become a major restraining factor affecting the surgical resection for liver cancer. For patients undergoing surgery after conversion, the residual liver volume should be maintained over 40% as far as possible. When the requirements cannot be met, portal vein thrombosis (PVE) and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) can be considered. The complications of PVE were mild, but it took 4-6 weeks to wait for the growth of liver. For some patients who may lose the opportunity for surgery due to tumor progression or insufficient growth of liver, combination with TACE therapy may be considered (35, 36). ALPPS can induce a 47%-192% increase in liver volume within 1-2 weeks, which is much higher than PVE, and the tumor resection rate can also reach 95-100% (37), but it has high incidence of perioperative complications. Therefore, it is necessary to comprehensively evaluate the patient's condition before surgery, such as level of liver cirrhosis, patient age, the capacity to withstand two surgeries in a short period of time, and the rapid tumor progression (38).

Management of adverse reactions

While conversion therapy has achieved promising efficacy results, we need to pay attention to the adverse reactions during the treatment. Common adverse reactions of TKI drugs include hypertension, palmar-plantar erythrodysesthesia syndrome (PPES), loss of appetite, nausea, vomiting and fatigue (39). Immune-related adverse events (irAEs) caused by immune checkpoint inhibitors (ICIs) involve almost all organs, and common adverse reactions include rash and itching, diarrhea and colitis, hepatotoxicity, pneumonia, and thyroiditis (40, 41). The adverse reactions of TACE and HAIC are similar with post-embolization syndrome the most common, mainly manifested as fever, hepatalgia, nausea and vomiting, etc (42), and some adverse reactions caused by chemotherapeutic drugs. The

TABLE 1 Clinical studies of conversion therapy in unresectable HCC patients.

Medicine	Case	mOS (month)	mPFS (month)	ORR %	DCR %	CR (%)	Surg (%)	TRAE %	Outcome
TKIs									
Sor (SHARP) [6]	299	10.7	5.5[e]	2.0[a]	43[a]	–	–	80	sorafenib improves overall survival by nearly 3 months.
Sor (Oriental) [7]	150	6.5	2.8[e]	3.3[a]	53[a]	–	–	98.0[c]	Sorafenib prolongs OS, TTP and improves DCR.
LEN (REFLECT) (8)	478	13.6	7.4	24.1[b]	75.5[b]	–	–	94	lenvatinib is non-inferiority of sorafenib in OS, and improves PFS, TTP and ORR.
Apatinib (AHELP) (10)	267	8.7	4.5	11.0[a]	61[a]	–	–	97	Apatinib significantly improves OS in patients with pretreated HCC.
TKIs+ICIs									
T+A (IMbrave150) (11)	336	19.2	4.3	30.0[a]	74[a]	25 (7.4)[a]	–	86	T+A maintained clinically survival benefits over sorafenib.
LEN+Pembrolizumab (12)	104	22.0	9.3	46[b]	88[b]	5(4.8)[b]	–	99	LEN plus pembrolizumab improves antitumor activity in uHCC.
LEN +NIV (13)	30	–	–	76.7[b]	96.7[b]	4 (13.3)[b]	9 (30.0)	100	LEN + NIV has encouraging anti-tumor activity in uHCC.
LEN +PD-1 (14)	59	–	–	55.9[b]	76.2 [b]	9 (15.3)[b]	10 (16.9)	–	LEN+PD-1 is effective and may convert unresectable HCC into resectable.
TKIs+PD-1 (15)	63	–	–	–	–	–	–	–	TKI+PD-1 is a feasible to convert unresectable HCC into resectable.
LEN +PD-1 (16)	46	NR	NR	53.1	69.4	5 (10.8)	–	–	LEN+PD-1 could benefit unresectable HCC patients to achieve curative surgery.
LEN +Cam (17)	48	NR	10.3	41.7[b]	75.0[b]	4(8.3)[b]	–	–	LEN+Cam might benefit patients with unresectable HCC more than lenvatinib monotherapy
TKIs+local therapy									
Sor+TACE (22)	20	14.9	4.9[e]	50[b]	80[b]		–	–	Sor+TACE is effective in treating advanced HCC and HVTT
LEN+TACE (23)	32	14.5	4.7[e]	53.1[b]	90.6[b]		–	100	LEN+TACE is more effective than Sor+TACE in advanced HCC with PVTT
Sor+HAIC (24)	125	13.37	7.03	40.8[b]	75.2[b]	10 (8.0)[b]	16 (10.0)	95.16	Sor+HAIC improves OS in patients with HCC and portal vein invasion
LEN+HAIC (25)	24	–	8.1	66.7[b]	79.2[b]	–	–	–	6-, 9-, and 12-months OS rates were 91.7, 83.3%, and 75%, respectively.
TKIs+ICIs+local therapy									
LEN+TACE+Pembrolizumab (26)	70	18.1	9.2	47.1[b]	70.0[b]	7 (10.0)[b]	18 (25.7)	–	Pembrolizumab+LEN+ TACE contribute to a higher rate of conversion therapy and longer survival time than the lenvatinibTACE regimen
TIKs+PD-1+HAIC (27)	25	–	–	96[b]	100[b]	12 (48.0)[b]	16 (64.0)	92	TIKs+PD-1+HAIC showed significant therapeutic effect with an extremely high surgical conversion rate.
LEN+TACE+sintilimab (28)	60	23.6	13.3	46.7[b]	85.0[b]	6(10)[b]	–	84.6[d]	LEN+TACE+sintilimab is a promising therapeutic regimen in unresectable HCC
LEN+toripalimab+HAIC (29)	36	NR	10.5	66.7[b]	–	5 (13.9)[b]	8 (22.2)	–	LEN+toripalimab+HAIC shows promising antitumor activity

TKIs, tyrosine kinase inhibitors; ICIs, immune checkpoint inhibitors; Sor, sorafenib; LEN, lenvatinib; PD-1, programmed cell death 1; TACE, Transarterial Chemoembolization; HAIC, hepatic arterial infusion chemotherapy. pCR, pathological complete response. NR, not reached; pts: Patients; TRAE: treatment-related adverse events; TTP, time to progression; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; DCR, Disease control rate; T+A, atezolizumab plus bevacizumab; NIV, nivolumab; Cam, camrelizumab; HVTT, hepatic vein tumor thrombus; PVTT, portal vein tumor thrombus; HCC; [a]According to RECIST; [b]According to mRECIST; [c]treatment-emergent adverse events (TEAE); [d]AEs, adverse events; [e]TTP, time to progress.

assessment of the above adverse events (AEs) should be performed according to the Common Terminology Criteria for Adverse Events Version 5.0 (CTCEA Version 5.0). For mild adverse reactions, symptomatic treatment can be given. For severe adverse reactions, it is necessary to fully evaluate the patient's condition, discontinue the current treatment and perform active symptomatic treatment, adjust the treatment dose or even change the regimen, etc. (40–43) Most cases are transient or can be resolved through dose reduction or symptomatic treatment. It has been reported in literature that

TABLE 2 Summary of the advantages and disadvantages of monotherapy and combination therapy.

	Advantage	Disadvantage
Monotherapy (6–8, 10)	Compared with a placebo, a monotherapy regimen prolongs the survival of patients with advanced liver cancer, with lenvatinib being the most effective.	Adverse reactions to monotherapy are between 80% to 98%, and every monotherapy regimen has a similar incidence of severe adverse reactions, which is manageable.
Bigeminy therapy		
TKIs+ICIs (11–17)	TKIs combined with ICIs are more effective in conversion therapy than monotherapy. In addition, some patients were successfully downstaged, underwent surgical resection, and achieved a complete pathological response (pCR).	There are no statistically significant differences between targeted immunotherapy and monotherapy in the incidence of most adverse events. In general, toxicities are manageable, with no unexpected safety signals.
TKIs+local therapy (22–25)	Compared with monotherapy, TKIs combined with local therapy had better conversion effectiveness and improved OS and PFS in patients with HCC and portal vein invasion.	Some grade 3 to 4 adverse events are more frequent in TKIs combined with local therapy groups than in the monotherapy group. The overall incidence of adverse events is similar and well tolerated.
Triple therapy (26–29)	Triple therapy shows promising antitumor activity and contributes to a higher conversion rate than Bigeminy therapy for patients in advanced HCC and PVTT.	There were no significant differences in majority grade ≥ 3 AEs between triple therapy and bigeminy therapy, and toxic side effects were manageable.

TKIs, tyrosine kinase inhibitors; ICIs, immune checkpoint inhibitors; OS, overall survival; PFS, progression-free survival; AEs, adverse events; PVTT, portal vein tumor thrombus.

the occurrence of some TKI-related AEs indicated favorable prognosis (44). Therefore, during the conversion therapy, the tolerance to some adverse reactions can be enhanced for patients, and at the same time, serious adverse reactions that occur during the treatment should be alerted for early detection and timely intervention to ensure the efficacy and safety of conversion.

Patient assessment and regimen selection

Radical operation is the essential means of treating primary liver cancer, which is also a necessary means of achieving long-term survival. It is also the core of conversion therapy, which transforms unresectable liver cancer into resectable liver cancer for surgical resection. Usually, there are two reasons for unresectability: surgically unresectable and oncologically unresectable. The former is widely accepted, including the patient's inability to withstand surgical trauma regarding their general condition, liver function, and insufficient remaining liver volume (surgically unresectable). The latter means Technically resectable but cannot acquire better effectiveness after resection than non-surgical treatment, which is dynamic and controversial (5). Clinically, for unresectable liver cancer, TKIs combined with ICIs can be used initially for conversion attempt, and the reasons for unresectable tumor should be analyzed and evaluated. In case of excessive tumor burden, TACE or HAIC can be added for tumor shrinkage (45, 46); in case of complication with portal vein tumor thrombus, HAIC or TARE can be added (47, 48), or external beam/Stereotactic Body Radiation Therapy (SBRT) radiotherapy can be combined (49) to achieve tumor thrombus shrinkage or even complete disappearance; in case of complication with extrahepatic oligometastasis, radical resection of the primary tumor + resection or ablation of metastasis can be selected if tolerable after sufficient assessment (50, 51).

Since conversion therapy methods can affect tumor, liver, and other organ functions, patients who have the opportunity for surgery after conversion therapy must be evaluated for organ function, target tumor burden, high-risk factor conversion, residual liver volume, and liver function (52). The evaluation includes regular review of enhanced CT, MRI and other imaging data to dynamically compare the changes of lesions and intra- and extra-hepatic metastasis; completion of the Child-Pugh (CTP) grading, indocyanine green (ICG) clearance test, and model for end-stage liver disease (MELD) score, HBV DNA level, etc. to assess liver function and tolerance to surgery; making full use of 3D visualization technology to use a wide incisal margin with tumor boundary >1 cm as the resection range as far as possible, and ensure that FLR accounts for more than 40% of the standard liver volume so as to ensure the safe implementation of surgery (3).

The treatment regimen should not be selected solely based on the staging of liver cancer as some patients with BCLC stage A (or some CNLC stage Ib), who are not suitable for surgical treatment due to excessive tumor burden at the initial diagnosis, should receive conversion therapy before radical resection; some patients with BCLC stage B/C (CNLC stage IIb/IIIa/IIIb) should not be completely considered as equivalent to the advanced stage for systemic therapy alone, but can undergo radical surgery after conversion therapy. It is recommended to use the multidisciplinary team (MDT) model (5) to fully assess the condition and formulate individualized follow-up and treatment strategies. Combined with the current research results, when the liver function, performance status, general condition is favorable, and the patient can tolerate the treatment, try to choose a regimen combining multiple treatment methods, such as targeted treatment combined with local therapy, to improve the tumor response rate and surgical conversion rate.

Others

Surgical resection after conversion

Surgical resection is an important way for patients to obtain long-term survival after successful conversion. An important condition for conversion resection is to achieve tumor response, or at least to keep the lesions stable for a period of time (3~4 months) (42). Studies have shown that the tumor-free survival of patients after liver cancer conversion resection is related to the degree of pathological response, and the postoperative tumor-free survival is longer in patients with pathological response. In addition, tumor response is only based on imaging, not equivalent to pathological response, and there may be residual cancer cells. Therefore, when the transformed patients achieve the surgically resectable criteria, concurrent surgical treatment should be evaluated as soon as possible to clear necrotic tumor cells or viable tumor cells to achieve the pathological response criteria (52, 53). Timely surgery can also avoid tumor drug resistance and achieve better survival (54).

After the conversion is assessed to be successful, the timing of surgery should also be determined according to the preoperative conversion regimen. Expert consensus recommends: Before surgery, small-molecule targeted drugs (lenvatinib, apatinib, sorafenib, etc.) should be discontinued for more than 1~2 weeks; PD-1 inhibitors should be discontinued for more than 2-4 weeks, bevacizumab should be discontinued for >6 weeks, and bevacizumab should not be used until the wound fully recovers; if TACE or radiotherapy is performed, the surgery should be performed 4 weeks after the last treatment to reduce perioperative complications incidence and ensure the safety of surgery (5).

Postoperative adjuvant therapy

There is still a lack of sufficient data and high-level evidence-based medical evidence to guide the selection of postoperative adjuvant therapy. However, the success of conversion implies that the tumor is sensitive to the regimen. Therefore, experts recommend that the original regimen or part of the drugs in the original regimen should be used for more than 6 months as appropriate according to the patient's physical condition, adverse reactions and treatment tolerance. Re-examination should be performed every 3 months, and drug withdrawal can be considered when there is no tumor recurrence or metastasis in two consecutive imaging examinations, and tumor markers are normal for 3 consecutive months without upward trend (5).

MDT is an important method to ensure the quality of conversion therapy

Due to the complex pathogenic factors, highly malignant biological behavior of liver cancer, great differences in liver disease backgrounds and prognosis, as well as different individual responses to treatment and the multiple disciplines involved (55), a multidisciplinary team (MDT) is required to evaluate the patients based on the imaging results to further provide individualized treatment regimen. During the treatment, the tumor response should be actively monitored, and the conversion regimen should be adjusted if necessary to create the opportunity for radical surgery with the ultimate goal to enable high-quality long-term survival for patients.

Discussion

Molecule targeted drugs, represented by TKIs, have achieved promising therapeutic efficacy in existing clinical trials. Combined immunotherapy and local treatment may improve the ORR, increase the proportion of conversion resection rate, and prolong the survival time to benefit more patients with advanced HCC. In addition, PVE and ALPPS increase the residual liver volume, reduce the risk of postoperative liver failure, and ensure the safety of resection. Before choosing the treatment regimen, evaluating the cause of the unresectable, the patient's liver function and performance status, and selecting an appropriate conversion method are necessary. The application of systemic treatment provides an opportunity for conversion and downstaging for patients with liver cancer at an intermediate and advanced stage and provides the possibility for surgical resection after conversion, thereby bringing hope to prolong overall survival and tumor-free survival.

At present, the research on systemic treatment is in the ascendant, but there are still many problems and challenges: (1) How to better screen the population with efficacy? (2) How to better arrange systemic treatment and local therapy to achieve downstaging effect? (3) How to choose a combination regimen to improve the conversion rate? (4) How to determine the conversion therapy time and arrange the operation time window? (5) Can ctDNA dynamic monitoring make up for the detection effect in patients with negative tumor indicators. More high-quality RCT studies are still needed to provide evidence-based medical data. In the future, higher-definition imaging technology, in conjunction with liquid biopsy, next-generation sequencing (NGS), and other techniques, could be used to assess the liver cancer tumor burden and metastasis in a more accurate and detailed manner in order to create a reasonable, individualized treatment plan for patients, thereby further improving the success rate of conversion and survival rate.

Author contributions

HB, WM, and WC wrote the paper. ML and YY conceived the idea and supervised the manuscript. HB and WM contributed equally to this work. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Transarterial chemoembolization plus apatinib with or without camrelizumab for unresected hepatocellular carcinoma: A two-center propensity score matching study

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Purpose: To compare the effectiveness and safety of transarterial chemoembolization (TACE) combined with apatinib and camrelizumab with those of TACE as well as apatinib among patients with unresectable hepatocellular carcinoma (HCC).

Materials and methods: The data of patients with unresectable HCC (uHCC) who received TACE-apatinib-camrelizumab combination (TACE + AC group) and TACE-apatinib combination (TACE + A group) were collected from two centers between January 2018 and January 2022. Propensity score matching (PSM) was conducted to diminish the bias between the two groups. The primary outcome measures of the study were overall survival (OS) and progression-free survival (PFS), and the secondary outcome measures were response rate (ORR), disease control rate (DCR), and adverse events (AEs).

Results: A total of 102 patients were enrolled in this study after PSM, with 34 patients in the TACE + AC group and 68 patients in the TACE + A group. Compared to the TACE + A group, TACE + AC had a significantly longer median OS (25.5 months, interquartile range [IQR], 23.5–33.0) than 18.5 months (IQR, 13.0–25.0; P = 0.001). Similarly, the PFS of the TACE + AC group was significantly improved (14.0 months, IQR, 9.0–NA) compared to that of the TACE + A group (5.0 months, IQR, 2.5–9.0; P = 0.001). The ORR rates (55.9% vs. 51.5%), and DCR rates (79.4% vs. 72.1%) were comparable between groups (P > 0.05). All treatment-related adverse events were tolerable and manageable, and no serious adverse events were observed.

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Conclusion: TACE combined with apatinib plus camrelizumab demonstrated superior efficacy to TACE plus apatinib for patients with unresectable HCC. The two combination therapies showed similar safety profiles.

KEYWORDS

apatinib, immunotherapy, transarterial chemoembolization, hepatocellular carcinoma, PD-1, prognosis

Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related deaths worldwide and is often diagnosed at an advanced stage because of its insidious onset and nonspecific symptoms. Transarterial chemoembolization (TACE) and systematic therapy are considered standard therapeutic methods for patients with intermediate and advanced HCC, respectively (1–3). As a widely accepted and proven treatment strategy for HCC, TACE could effectively inhibit tumor progression. However, TACE could cause hypoxia in tumor tissue, which ultimately induces the expression of vascular endothelial growth factor (VEGF) and increases tumor angiogenesis (4), and consequently, mediates tumor growth and/or metastasis. Moreover, repeated TACE procedures can gradually impair liver function and aggravate liver cirrhosis.

Apatinib (Jiangsu Hengrui Medicine Co., Ltd., Jiangsu, China), a novel targeted agent, has higher selectivity to VEGFR-2 than sorafenib. Qiu et al (5) proposed that TACE combined with apatinib can improve the efficacy of unresectable HCC compared to TACE alone. Meanwhile, camrelizumab (SHR-1210, Jiangsu Hengrui Medicine Co., Ltd., Jiangsu, China) is a humanized monoclonal antibody against PD-1. According to the RESCUE trial (6), camrelizumab in combination with apatinib has an efficacy profile of 34.3% for advanced HCC. Moreover, with the continuation of the IMBrave150 study (7) and several clinical trials (8, 9), immunotherapy in combination with antiangiogenic drugs is known to significantly improve the outcome of patients with advanced HCC. Furthermore, evidence (10) shows that TACE is an inducer of immunogenic cell death, resulting in facilitating antigen presentation and priming of antitumour lymphocytes (11). Thus, there is an appealing rationale for the combination of TACE, tyrosine kinase inhibitors (TKIs), and immune checkpoint inhibitors (ICIs) (12).

Several studies (13, 14) have shown that TACE combined with anti-angiogenic therapy and immunotherapy can improve the treatment efficacy of patients with unresectable HCC, with an ORR of approximately 35%–59% and median overall survival (OS) of approximately 13–35 months. Few studies have been conducted using TACE along with apatinib and camrelizumab for patients with unresectable HCC. Therefore, we conducted this retrospective study to determine the efficacy and safety of TACE combined with apatinib and camrelizumab (TACE + AC) therapy compared to TACE combined with apatinib (TACE + A) therapy.

Materials and methods

Study design and patient selection

This retrospective analysis was conducted between January 2018 and January 2022, on all patients with unresectable HCC from the First Affiliated Hospital of Nanjing Medical University and the Affiliated Hospital of Nanjing University of Chinese Medicine who received TACE plus apatinib with/without camrelizumab. The study was approved by the Institutional Ethics Review Boards of both hospitals, and the procedures followed in this study were conducted in accordance with the guidelines of the World Medical Association Declaration of Helsinki. The requirement for informed consent was waived due to the retrospective nature of the study. According to the Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China, HCC was diagnosed pathologically or clinically. The inclusion criteria for the study were as follows: (1) Barcelona Clinic Liver Cancer (BCLC) stage B or C; (2) Child–Pugh class A5–B7; (3) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1; and (4) ≥ 1 cycle of TACE and apatinib with or without camrelizumab. The exclusion criteria were as follows: (1) < 1 month of apatinib or camrelizumab treatment; (2) appearance of secondary primary malignant tumors; (3) contraindication to camrelizumab (an allergy to the active ingredient and excipients of camrelizumab); and (4) incomplete data or loss to follow-up.

TACE procedure

TACE was initiated before apatinib and camrelizumab administration. Under local anesthetic, TACE treatment was conducted through the femoral artery. To determine the number, size, location, and feeding arteries of the tumors, a 5-F

catheter (COOK) was inserted and angiography was performed. Then, an emulsion of chemotherapeutic drugs (lobaplatin, 30–50 mg; epirubicin, 10–30 mg) mixed with lipiodol was administered through the hepatic artery. Thereafter, embolization *via* a microcatheter (2.7 F; Terumo Medical Corp., Tokyo, Japan; or 2.4 F; Merit Maestro, South Jordan, Utah, USA) was performed either selectively or superselectively. Selective embolization with 300 μm polyvinyl alcohol particles (Biosphere Medical, Paris, France; or Jiangsu Hengrui Medicine Co., Ltd., Jiangsu, China) or gelatin sponge particles was performed to achieve blood flow stasis in the tumor-feeding artery. Post-TACE syndrome was recorded, and liver function indices were assessed within 1 week of each TACE session.

Apatinib and camrelizumab administration

Apatinib was administered orally 250 mg once a day within 1 week of the initial TACE and was suspended 3 days before and after repeated TACE procedures. Camrelizumab was administered 200 mg intravenously within 1 week of the initial TACE and then every 3 weeks continuously (maximum of 24 months of camrelizumab treatment). The doses of camrelizumab and apatinib were reduced, suspended, or discontinued in patients who experienced severe adverse events (AEs).

Follow-up

All patients were followed up constantly until death or the end of the study (March 1, 2022). To track treatment-related adverse events (AEs), blood tests, including complete blood counts, liver, kidney, cardiac biomarkers, and thyroid functions, were conducted approximately every 3 weeks. Tumor markers and contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) were performed every 2 months to assess the treatment response. TACE was repeated in keeping with the tumor status, liver function, and patient's general condition when residual viable tumors were detected or new lesions emerged after a multidisciplinary team discussion.

Assessment and outcomes

The primary measure outcomes were OS and progress-free survival (PFS). OS was defined from the date of the first TACE therapy to the date of death arising from any cause or the date of the last contact in both groups. PFS was defined as the time between the beginning of TACE treatment and the first sign of tumor progression or death. Secondary measure outcomes of this study included the objective response rate (ORR), disease control rate (DCR), and AEs. The tumor response was evaluated by two experienced radiologists using the modified Response Evaluation Criteria in Solid Tumors (mRECIST, version 1.1), including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The ORR was defined as CR + PR, and the DCR was defined as CR + PR + SD. AEs were assessed based on the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03).

Statistical analyses

Propensity score matching (PSM) was performed to minimize the effects of selection bias and potential confounders. Categorical data are expressed as the number of patients (percentage). Quantitative data were expressed as mean ± standard deviation and median (range) for normally and nonnormally distributed variables. Categorical data between the two groups were compared using the c2 test or Fisher's exact test, as appropriate. Quantitative data were compared using Student's t-test or Mann–Whitney U test, as appropriate. Survival curves were analyzed by Kaplan–Meier method using the log-rank test. All statistical analyses were performed using SPSS Statistics version 26 (IBM, Armonk, New York, USA). All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Patient demographics

Between January 2018 and January 2022, 147 patients with BCLC stage B or C were considered eligible for this study, including the TACE + AC group (n = 34) and TACE + A group (n = 113). The median follow-up time is 22.8 months in the TACE + AC group, while 29.3 months in the TACE + A group. The flow diagram is displayed in Figure 1. The baseline characteristics of the patients are summarized in Table 1. Before PSM, BCLC stage (B/C, $P = 0.003$) and tumor distribution (single/multiple, $P = 0.02$) showed statistically significant differences in the two groups. Groups were matched strictly in age, gender and grade of BCLC classification (caliper = 0.1). After PSM at a 1:2 radio, there were no statistically significant differences in the baseline characteristics between the two groups. A total of 102 patients were included after PSM, among whom, 34 were in the TACE + AC group and 68 were in the TACE + A group.

Efficacy

Before PSM, Patients in the TACE + AC group had a median OS of 25.5 (IQR: 23.5–33) months and a median PFS of 14.0 (IQR:

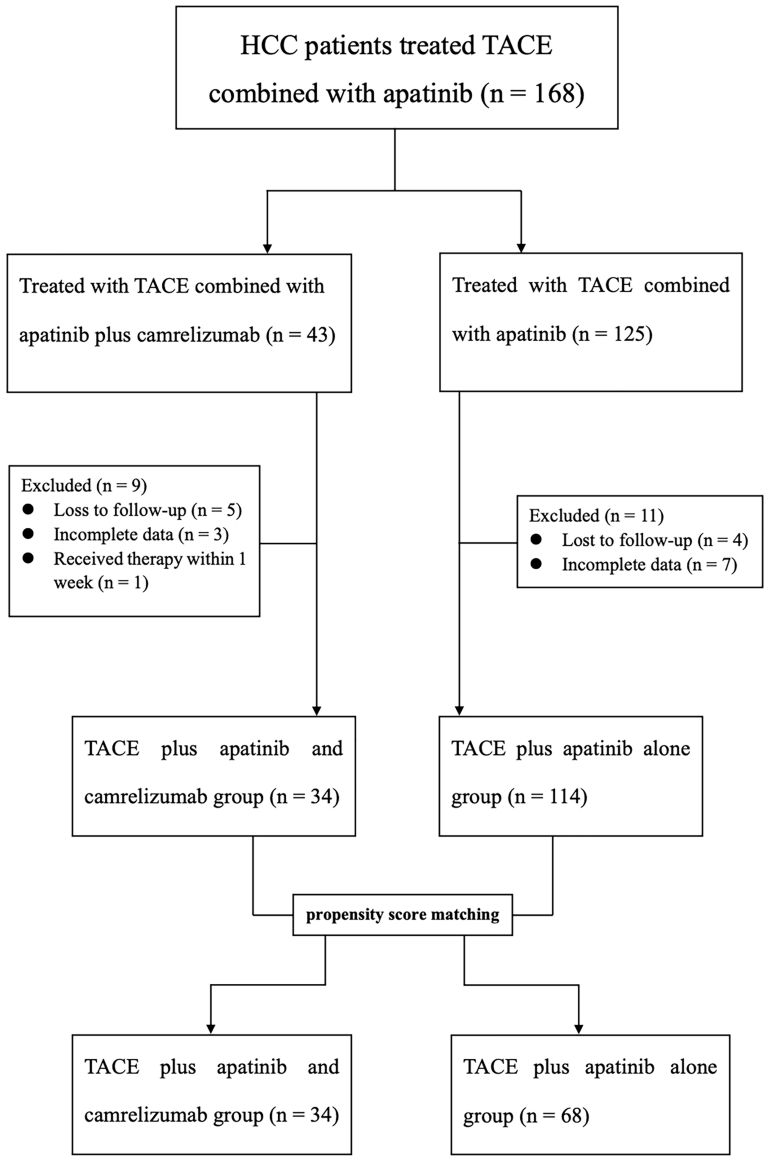

FIGURE 1
Flow diagram of patient enrollment. HCC, Hepatocellular carcinoma; TACE, Transarterial chemoembolization.

9.0–NA) months, while 19.1 (IQR: 2.5–27.5) months and 5.1 (IQR: 2.7-8.1) for those in the TACE + A group, respectively. Patients in the TACE + AC group had a median OS of 25.5 (IQR: 23.5–33) months compared to 18.5 (IQR: 13.0–25.0) months for those in the TACE + A group (HR = 0.312, 95%CI = 0.162–0.602; Figure 2); and a median PFS of 14.0 (IQR: 9.0–NA) months compared to 5.0 (IQR: 2.5–9.0) months for those in the TACE + A group. The survival rates of the TACE + AC group were 91.1%, 63.2%, and 48.6% at 1, 2, and 3 years, while those of the TACE + A group were 76.3%, 27%, and 18.2%, respectively. Figure 3 is the representative MR imaging figures from 1 case of CR. All data and results are available in Supplementary Tables 1, 2.

Tumor responses

The tumor responses at the 1-year rate of the two groups of patients are shown in Table 2. For the TACE + AC group, 4 (11.8%) patients achieved CR, 15 (44.1%) achieved PR, 8 (23.5%) patients were in the SD state, and 7 (20.6%) patients had PD. However, in the TACE + A group, 4 (5.9%) patients achieved CR, 31 (45.6%) patients achieved PR, 14 (20.6%) patients were in the SD state, and 19 (27.9%) had PD. The ORR rates (55.9% vs. 51.5%) and DCR rates (79.4% vs. 72.1%) of the TACE + AC group were numerically higher than those of the TACE + A group, and neither showed a statistically significant difference ($P > 0.05$).

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TABLE 1 Patient characteristics at baseline.

Characteristic		Before PSM			After PSM		
		TACE+AC	TACE+A	p	TACE+AC	TACE+A	p
Age (years)				0.32			0.52
	< 60	23	65		23	41	
	≥ 60	11	48		11	27	
Sex				0.25			1
	Male	29	84		29	58	
	Female	5	29		5	10	
ECOG PS				1			0.67
	0	19	62		19	34	
	1	15	51		15	34	
Etiology				0.47			0.78
	HBV	29	89		29	56	
	Other	5	24		5	12	
Child–Pugh class				0.79			0.57
	A	30	105		30	56	
	B	4	18		4	12	
AFP				0.84			0.40
	< 200 ng/ml	21	67		21	35	
	≥ 200 ng/ml	13	46		13	33	
Tumor distribution				0.02			0.55
	Single	12	14		12	22	
	Multiple	22	99		22	46	
Tumor size				0.82			0.35
	< 10 cm	27	85		27	47	
	≥ 10 cm	7	28		7	21	
Extrahepatic metastases				0.07			0.51
	Yes	13	24		13	21	
	No	21	89		21	47	
Macrovascular invasion				0.01			0.2
	Yes	17	17		17	24	
	No	17	96		17	44	
BCLC stage				0.00			1
	B	13	73		13	26	
	C	21	40		21	42	

Data are presented as the median (range) or N (%). PSM: Propensity score matching, TACE, Transcatheter arterial chemoembolization; TACE + A, TACE plus apatinib; TACE + AC, TACE plus apatinib and camrelizumab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; AFP, Alpha-fetoprotein.

Safety

No treatment-related deaths were observed and the treatment-related adverse events (TrAEs) are listed in Table 3. All toxicities were manageable. AEs of any grade during the TACE procedure included abdominal pain (65.1%), transaminitis (46.1%), fever (53.9%), lymphopenia (10.8%), decreased appetite (29.4%), nausea/vomiting (58.5%), diarrhea (25.5%), fatigue (13.7%), leukopenia (14.7%), neutropenia (11.8%), and anemia (13.7%). There were no significant differences in AEs resulting from TACE between the groups. In contrast, hand-foot syndrome (29.4%), hypertension (44.1%), and reactive cutaneous capillary endothelial proliferation (RCCEP) (23.5%) were the most common AEs in the period of apatinib and camrelizumab administration. In the TACE + AC group, apatinib administration was suspended in five patients and camrelizumab administration was suspended in one patient. In the TACE + A group, apatinib administration was suspended in 10 patients due to intolerance. Grade 4 myelosuppression occurred in one patient after the TACE procedure and recovered after symptomatic management.

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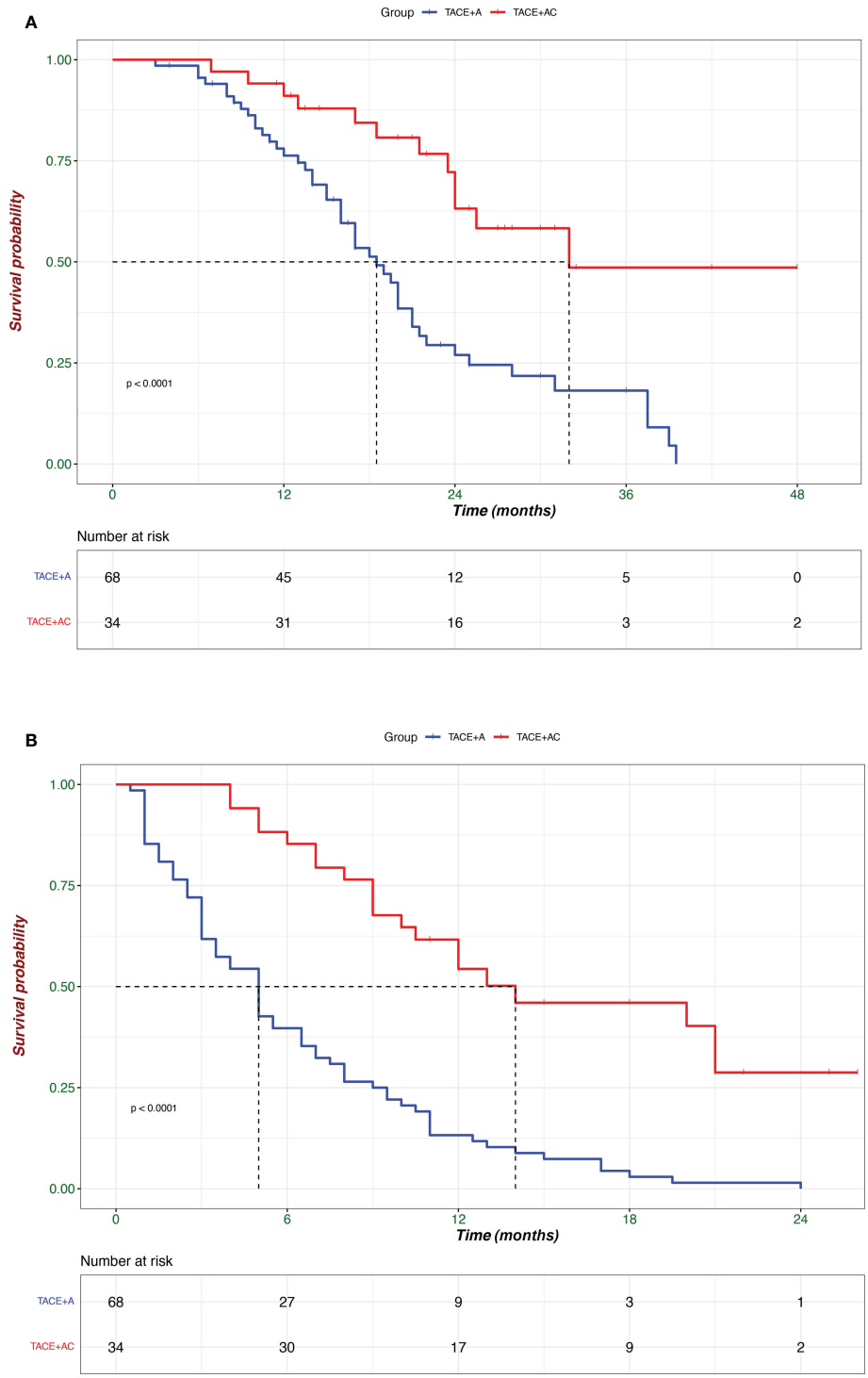

FIGURE 2
Kaplan–Meier analyses of overall survival **(A)** and progression-free survival **(B)** according to treatment groups. TACE + A, Transarterial chemoembolization combined with apatinib; TACE + AC, Transarterial chemoembolization combined with apatinib plus camrelizumab.

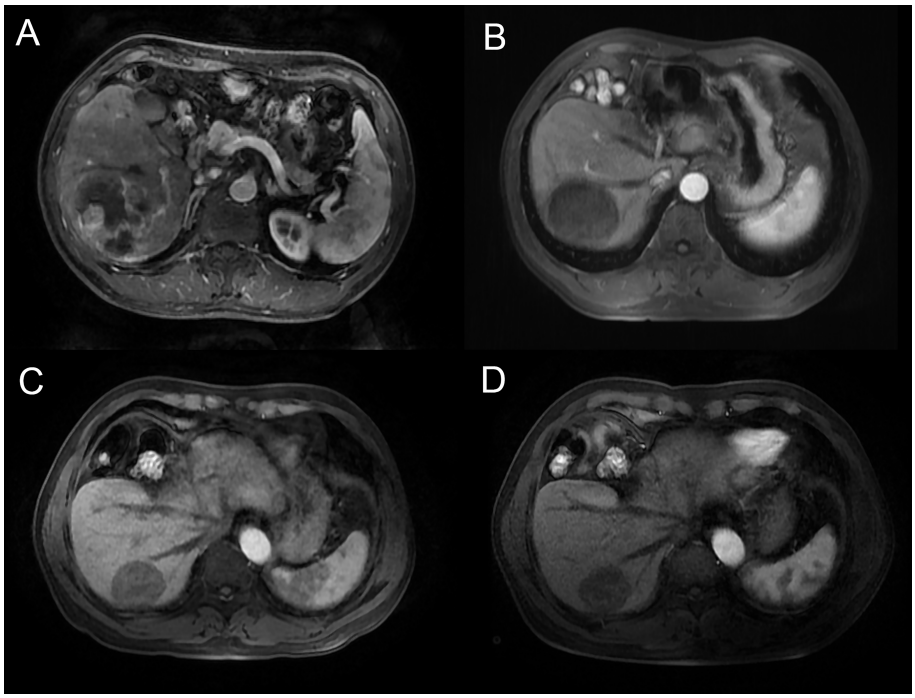

FIGURE 3
Male, 58y, BCLC B stage, Child-Pugh grade A6, massive and ruptured HCC. MR images (arterial phase) were acquired. **(A)** before TACE treatment, **(B)** 6 months after the combination treatment, **(C)** 12 months after the combination treatment, **(D)** 18 months after the combination treatment, demonstrating complete response, with a reduction in tumor size, the patient was classified as CR according to mRECIST. TACE, transarterial chemoembolization.

Discussion

Our study revealed that TACE + AC therapy was more effective than TACE + A therapy in patients with unresectable HCC. Patients who received the TACE + AC modality had a median OS of 25.5 (IQR: 23.5–33.0) months and a median PFS of 18.5 (IQR: 13.0–25.0) months, which yielded a sufficient edge over the TACE + A modality and was comparable to the results of previous studies (15, 16).

The combination of TACE with immunotherapy modalities has shown promising clinical efficacy. Regarding the survival time, several retrospective studies have shown that TACE combined with TKIs and ICIs demonstrated superior OS (18–24 months) and PFS (5.5–13.3 months) than TACE combined with TKIs or TKIs combined with ICIs, which were not better than our outcomes. In our study, the median OS and PFS in the TACE + AC group were numerically higher than those in the TACE + A group. Of note, Ju et al. (17, 18) reported comparable

TABLE 2 Tumor response at 1 year between the two groups based on mRECIST1.1.

	TACE+AC group (n = 34, %)	TACE +A group (n = 68, %)	X^2	P-value	Overall (n = 102,%)
Tumor response					
CR	4 (11.8)	4 (5.9)	0.99	0.44	13 (12.6)
PR	15 (44.1)	31 (45.6)	0.20	1.00	41 (40.2)
SD	8 (23.5)	14 (20.6)	0.12	0.80	22 (21.6)
PD	7 (20.6)	19 (27.9)	0.71	0.47	26 (25.5)
ORR (CR+PR)	19 (55.9)	35 (51.5)	0.18	0.84	54 (52.9)
DCR (CR+PR+SD)	27 (79.4)	49 (72.1)	0.64	0.48	76 (74.5)

mRECIST, Modified Response Evaluation Criteria in Solid Tumors; CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease; ORR, Objective response rate; DCR, Disease control rate.

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TABLE 3 Treatment-related adverse events in the two groups.

		TACE+AC (n = 34)				TACE+A (n = 68)				*P* value
Adverse events										
	Toxicity grade	1/2		3/4		1/2		3/4		
TACE-related										
	Diarrhea	6	17.6%	1	2.9%	14	20.6%	5	7.4%	0.268
	Transaminitis	13	38.2%	3	8.8%	26	38.2%	5	7.4%	1
	Rash	4	63.7%	0	0.0%	11	16.1%	3	4.4%	0.409
	Nausea with/without vomiting	22	64.7%	2	5.9%	31	45.6%	5	7.4%	0.135
	Abdominal pain	19	55.9%	4	11.7%	42	61.7%	9	13.2%	0.641
	Fatigue	7	29.0%	0	0.0%	4	5.8%	3	4.4%	0.221
	Fever	19	26.5%	3	8.8%	33	48.5%	0	0.0%	0.144
	Leukopenia	6	17.6%	1	2.9%	8	11.7%	0		0.249
	Neutropenia	5	14.7%	1	2.9%	6	8.8%	0		0.208
	Lymphopenia	4	11.8%	1	2.9%	5	7.4%	1	1.5%	0.499
	Thrombopenia	7	20.6%	0	0.0%	12	17.6%	0	0.0%	0.789
	Anemia	6	17.6%	0	0.0%	8	11.7%	0	0.0%	0.543
	Decreased appetite	6	17.6%	0	0.0%	24	35.2%	0	0.0%	0.071
Apatinib and Camrelizumab -related	Hand-foot skin reactions	7	11.7%	3	8.8%	20	29.4%	8	11.7%	0.283
	Hypertension	11	32.4%	4	11.7%	16	23.5%	11	16.1%	0.676
	REECP	7	29.0%	1	2.9%	0		0		–
	all	34	100.0%	11	32.3%	64	100.0%	16	23.5%	0.298

results of TACE combined with apatinib and camrelizumab; thus, our findings demonstrated a substantial and synergistic improvement in survival for patients with unresectable HCC treated with TACE + AC. Several possible explanations exist for this finding (1) TACE can induce the up-regulation of VEGF and neovascularization, and apatinib can inhibit tumor angiogenesis by targeting VEGFR-2 (12); (2) TACE can cause tumor cell necrosis and neoangiogenesis, while the immune tolerance induced by TACE can be attenuated by TKI and PD-1 inhibitors (19, 20); and (3) the combination of ICIs with TKIs can convert "cold tumors" into "hot tumor" by T cell activation (11), which may restore exhausted T cells and facilitate anti-tumor immunity (21). Therefore, patients with unresectable HCC may experience superior clinical results when applying TACE, apatinib, and camrelizumab in combination.

For the tumor response, the RESCUE trial (6) disclosed an ORR of 34.3% and a DCR of 77.1% following combined apatinib and camrelizumab therapy. The TACE + AC group had a greater ORR compared to those reported by the IMbrave150 trial (7) (atezolizumab plus bevacizumab: ORR = 33.2%), the phase 1b KEYNOTE-524 trial (22) (lenvatinib plus pembrolizumab: ORR = 46.0%), and the ORIENT-32 trial (sintilimab plus bevacizumab: ORR = 24%); this was likely because the addition of TACE is thought to be related to immune activation and can induce low expression of Tregs *via* modulating pro-inflammatory pathways. In our study, the CR, ORR, and DCR rates of the TACE + AC group were numerically greater than those of the TACE + A group (11.8% vs. 5.9%, 55.9% vs. 51.5%, and 79.4% vs. 72.1%, respectively), although the difference did not reach statistical significance. Simultaneously, Ju et al. reported an ORR of 58.8% and a DCR of 81.2% in the TACE + AC group, which is similar to our findings. However, our results did not achieve statistical significance, likely for the following reasons: (1) the intervals between TACE were believed to affect the results, (2) some patients in the TACE + AC group were newly included in the cohort and had comparatively fewer cycles of camrelizumab, and (3) PVTT and subsequent metastasis can induce tumor cells to spread, which may reduce the efficacy of immunotherapy in patients with PVTT. These findings and views were similarly shared by Cai et al. (23).

Regarding AEs, the most common AEs were hand-foot skin reaction and hypertension, which were predominantly related to apatinib. Moreover, the incidence of apatinib-related AEs (grade ≥ 3) was 11%–16%, whereas events such as increased AST/ALT and RCCEP were related to camrelizumab. According to previous studies, the most common AE in patients with HCC treated by TACE is embolization syndrome, including pain, fever, nausea, and vomiting. Altogether, TACE + AC therapy for patients with unresectable HCC presented a safe profile.

This study also has some limitations. First, this is a retrospective study with a small sample of enrolled patients and a short follow-up period. Therefore, the results may not be generalizable and should be interpreted with caution. Second, although we performed PSM to avoid selection bias, our analyses may still be influenced by some inherent biases, such as regional bias and population and tumor-related factors; indeed, the

etiology of HCC, prevalence of cirrhosis, comorbidities, and overall treatment approach differs in some regions of the world. Thirdly, the subgroup analyses were lacked in this study. Lastly, some patients did not achieve endpoint events throughout the limited follow-up period.

In conclusion, this study showed that TACE combined with apatinib and camrelizumab therapy demonstrated superior efficacy to TACE combined with apatinib for patients with unresectable HCC. Although promising, our results need to be validated by more studies in the future.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Designing and instructing the study: WZZ. Collecting the data: DZ, YGX, JWR and QS. Analyses and interpretation of data: WY and HFZ. Dradting of manuscript: DZ and KM. Critical revision of manuscript: SL, HBS and WZZ. All authors contributed to the article and approved the submitted version. DZ and KM contributed equally this work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.1057560/full#supplementary-material

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Lenvatinib as second-line treatment in patients with unresectable hepatocellular carcinoma: A retrospective analysis

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Objective: The purpose of this study is to determine the efficacy and safety of lenvatinib as second-line therapy in Chinese patients with unresectable hepatocellular carcinoma (HCC).

Methods: We performed a retrospective analysis of Chinese patients with unresectable HCC who received second-line treatment of lenvatinib at three institutions from November 2018 to February 2022. Demographic and clinicopathologic characteristics, data on the treatment regimens were obtained from medical records. Tumor response was evaluated every 4-6 weeks by modified Response Evaluation Criteria in Solid Tumors (mRECIST).

Results: In total, 50 patients with unresectable HCC who received second-line treatment of lenvatinib were enrolled in this study. The objective response rate (ORR) was 18.0% and the disease control rate (DCR) was 74.0%, respectively. The duration of response (DoR) was 6.0 months. The median progression-free survival (PFS) and overall survival (OS) were 5.0 and 8.5 months, respectively. Patients who received ICIs combined with anti-angiogenic inhibitors as first-line therapy, achieving CR/PR at first-line therapy, with PFS≥6months at first-line therapy had a higher DCR. Univariate and multivariate analysis showed that AFP (ng/ml)<400, absence of extrahepatic metastasis, Child-Pugh A, tumor number<3, ICIs combined with anti-angiogenic inhibitors as first-line therapy, CR/PR to first-line therapy, and PFS≥6months at first-line therapy were independent factors of favorable PFS. Univariate analysis showed that absence of extrahepatic metastasis, tumor number<3, ICIs combined with anti-angiogenic inhibitors as first-line therapy, and PFS≥6months at first-line therapy were significantly associated with longer OS. Multivariate analysis showed that absence of extrahepatic metastasis, Child-Pugh A, tumor number<3, CR/PR to first-line therapy and PFS≥6months at first-line therapy were independent prognostic factors of OS. The majority of AEs were grade 1-2, and were reversible. Grade 3/4 AEs occurred in 12 patients (24.0%) and were mostly connected with hand-foot skin reactions (10.0%), and 10 patients had

lenvatinib dose reductions. Two toxicity-related treatment interruptions were attributed to grade 3 hand-foot skin reaction, and grade 4 proteinuria, respectively.

Conclusion: This study confirms the efficacy and safety of lenvatinib as second-line therapy after progression on sorafenib or ICIs combined with anti-angiogenic inhibitors.

KEYWORDS

lenvatinib, hepatocellular carcinoma, second-line treatment, efficacy, safety

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide (1). Over half of all HCC patients globally are from China, where the prognosis is extremely poor, with a 5-year survival rate of only 12.1% (2). The liver is the body's major immune organ, and its anatomical structure and physiological functions contribute to chemoresistance and poor prognosis of HCC (3). Until 2007, there were no effective treatment options for patients with unresectable HCC. Systemic treatment, especially with conventional cytotoxic drugs, is usually ineffective. Sorafenib was the first and only systemic drug approved by the Food and Drug Administration (FDA) as standard treatment for advanced HCC between 2007 and 2016. However, since more than 80% of HCC patients in China have hepatitis B virus (HBV) infection, the survival benefits imparted by sorafenib are limited in comparison to HCC patients in Europe and the United States (4, 5).

Lenvatinib is a small molecular inhibitor targeting vascular endothelial growth factor receptors 1-3, fibroblast growth factor receptors 1-4, platelet-derived growth factor receptors, and the RET as well as KIT (6). In the phase III REFLECT study, lenvatinib showed non-inferiority in terms of overall survival (OS) compared with sorafenib in the first-line therapy of unresectable HCC (7). In the subgroup analysis, lenvatinib was superior to sorafenib in Asia-Pacific patients, with substantial improvements in overall survival (OS), progression-free survival (PFS), and time to progression (TTP) (8). Based on the REFLECT results, the FDA approved lenvatinib for the first-line treatment of patients with advanced HCC.

However, the rapid progress of immunotherapy therapies has dramatically changed the treatment landscape for advanced HCC in recent years. Immune checkpoint therapies are now being incorporated into HCC therapies, and their combination with molecular targeted therapy is emerging as a tool to enhance the immune response. In the phase III IMbrave 150 trial, which was published in 2021, atezolizumab plus bevacizumab showed significant OS and PFS benefits compared to sorafenib in patients with advanced HCC (9). This allows for a new shift in the patterns of first-line treatment in advanced HCC.

Overall, the new combination treatment paradigm appears to be promising, and as a result, an increasing number of patients are opting for immunotherapy combined with anti-angiogenic agents as their first-line treatment. Meanwhile, sorafenib is still being used as the first-line treatment for some individuals with advanced HCC in China (10). The efficacy and safety of lenvatinib as a second-line treatment for individuals who did not receive lenvatinib as a first-line treatment are unknown. Furthermore, little is known about the clinical features of advanced HCC patients who may benefit from second-line lenvatinib treatment. This study aimed to investigate the efficacy, safety, and potential beneficiaries of lenvatinib in patients with unresectable HCC who received sorafenib or immune checkpoint inhibitors (ICIs) combined with antiangiogenic inhibitors for first-line therapy.

Materials and methods

Patient selection and diagnosis of hepatocellular carcinoma

The study included patients with advanced HCC who received lenvatinib monotherapy as a second-line treatment in 3 institutions (The First Affiliated Hospital of Dalian Medical University, The Second Affiliated Hospital of Dalian Medical University, and Dalian Friendship hospital) from November 2018 to February 2022. The eligible patients must have at least one measurable target lesion for response evaluation, an Eastern Cooperative Oncology Group Performance Status score of 0–2, Barcelona Clinic Liver Cancer Stages (BCLC) B or C categorization, and Child-Pugh class A or B. We excluded patients with a history of second primary malignancy, concurrent cholangiocarcinoma, and patients who underwent TACE therapy. In addition, patients with incomplete clinical

records and those lost to follow-up were excluded. 74 patients who received lenvatinib as second-line therapy were screened according to the inclusion and exclusion criteria, and a total of 50 patients were enrolled (Figure 1). The diagnosis of HCC was confirmed *via* histology or characteristic radiologic findings, such as dynamic computed tomography (CT) or magnetic resonance imaging (MRI) of the liver. Staging was determined according to the Barcelona Clinic Liver Cancer (BCLC) staging classification at the time of lenvatinib treatment initiation. Alpha-fetoprotein (AFP) was measured at baseline.

Lenvatinib treatment

The respective standard starting doses of lenvatinib for Child-Pugh A patients weighing 60 kg or more and less than 60 kg were 12 and 8 mg orally once per day. The starting dose of lenvatinib for Child-Pugh class B patients was 8 mg orally once per day[6]. The attending physician decided the dose of lenvatinib according to the grades of adverse events (AEs) or ECOG PS. Treatment was discontinued due to tumor progression, intolerable toxicity, and patient decision.

Response evaluation and study endpoint

Tumor response was evaluated every 4-6 weeks by modified Response Evaluation Criteria in Solid Tumors (mRECIST) and was assessed as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) (11, 12). The primary endpoint was PFS, defined as the period from the administration of lenvatinib to disease progression or death from any cause. The secondary endpoints were OS, ORR (objective response rate), DCR (disease control rate), and safety. OS is defined as the period from the administration of lenvatinib to death from any cause. ORR is defined as the percentage of patients with a best overall response of CR or PR. DCR is defined as the percentage of patients with the best overall response of CR, PR, or SD. The AEs were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, and the worst grade for each AE was recorded. Bone marrow suppression, liver function, renal function, heart function, and thyroid function were assessed routinely every 2-4 weeks. The patients were followed-up for OS every 30 days until death or study completion. The final follow-up was scheduled for April 2022. The protocol used in this study was approved by the Institutional Ethics Committee, IRB No. PJ-KS-KY-2020-112(X).

Statistical analysis

The chi-squared test was used to compare the differences between the various patient groups. The Kaplan-Meier method was used to assess the PFS and OS. The hazard ratio

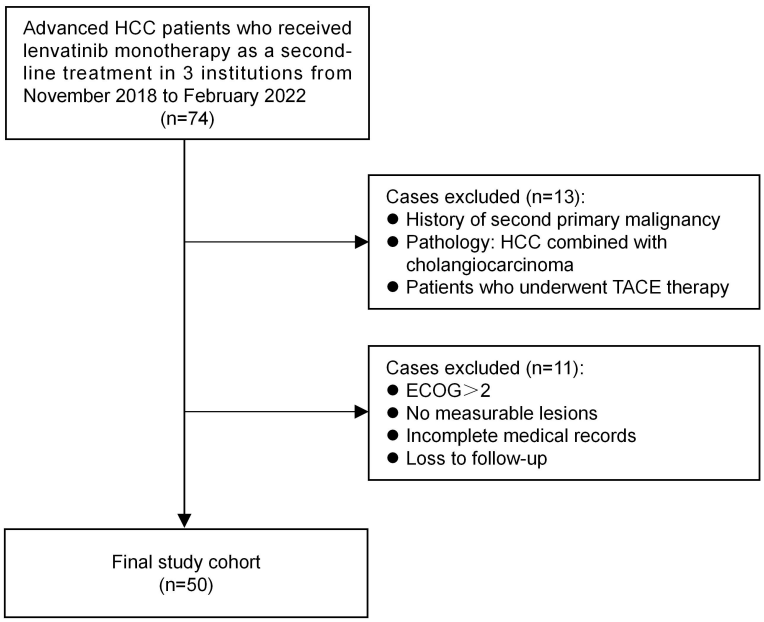

FIGURE 1
Study flow chart: Flow diagram of patient selection steps.

(HR) and confidence intervals (CI) were calculated. Univariate analysis was allowed to enter into a multivariable Cox proportional hazards model at a p-value <0.10. A P-value of <0.05 was considered significant. The statistical software used to perform the analyses was SPSS 22.0 and GraphPad Prism 7.0.

Results

Baseline characteristics of patients with lenvatinib as second-line treatment

A total of 50 patients with advanced HCC who were treated with lenvatinib as a second-line treatment were enrolled in this study. Baseline patient characteristics are shown in Table 1. The majority of patients (62.0%) were male, and the median age was 63.0 years (44–88). Regarding viral hepatitis, 29 patients (58.0%) had HBV infection, 5 patients (10.0%) had hepatitis C virus (HCV) infection, and 16 patients (32.0%) were negative for HBV or HCV, including 10 patients (20.0%) with hepatocirrhosis. 32 patients (64.0%) had an ECOG PS score of 0-1, and 18 patients (36.0%) had a score of 2. The majority of patients (36 patients, 72.0%) had an AFP level of >400ng/ml at baseline, and 24 patients (28.0%) had an AFP response after the initiation of lenvatinib (>20% decrease in AFP serum level from baseline after 4 weeks of lenvatinib treatment). The Child-Pugh classification was A in 27 patients (54.0%) and B in 23 patients (46.0%), whereas the BCLC stage was C in all patients. 34 patients (68.0%) had portal vein tumor thrombus (PVTT), and 35 patients (70.0%) had extrahepatic spread. In the first-line treatment, 20 patients (40.0%) received ICIs combined antiangiogenic inhibitors (atezolizumab plus bevacizumab, 7 patients; sorafenib plus pembrolizumab, 3 patients; apatinib plus camrelizumab, 10 patients), and 30 patients (60.0%) received sorafenib. During the first-line treatment, 1 patient (2.0%) had CR, 15 patients (30.0%) had PR, and 25 patients (50.0%) had SD, 9 patients (18.0%) had PD, and the 3-month and 6-month PFS rates were 86.0% and 50.0%.

Up to the date of data cutoff, 38 of 50 patients (76.0%) had discontinued lenvatinib, and all had confirmed radiological progression according to mRECIST. 6 of 38 patients (15.8%) received third-line therapy (regorafenib, 3 patients; PD-1 inhibitors, 2 patients; chemotherapy, 1 patient). 5 of 38 patients (13.2%) received TACE, and the others received best supportive care.

Efficacy of lenvatinib as second-line treatment

The median observation period after initiation of lenvatinib was 6.3 (5.5-8.0) months. The median treatment duration of lenvatinib was 4.5 months (95% CI, 4.0-5.0). As per mRECIST, no patients had CR, 9 patients (18.0%) had PR, 28 patients (56.0%) had SD, and 13 patients (26.0%) had PD (Table 2). The objective response rate (ORR) and disease control rate (DCR) were 18.0% and 74.0% (Figure 2A). The duration of response (DoR) was 6.0 months (Figure 2B). The median PFS was 5.0 months (95% CI, 4.5-6.5 months, Figure 3A). The median OS was 8.5 months (95% CI, 7.5–10.5 months, Figure 3B).

The efficacy of first-line treatment and its effect on second-line lenvatinib

Notably, the modality of first-line therapy may affect the efficacy and outcome of second-line treatment with lenvatinib (Table 3). Sorafenib was used as first-line therapy in 30 patients. There were 7 patients with PR to sorafenib previously, and they all achieved SD. Among 14 patients with SD in response to sorafenib, 3 (21.4%) had PR to lenvatinib, and 5 (35.7%) remained SD. Among 9 patients who had PD with sorafenib, none achieved CR/PR to lenvatinib, and 3 (33.3%) had SD. ICIs combined antiangiogenic inhibitors were used as first-line treatment in 20 patients. Among 9 patients with CR/PR in response to ICIs combined antiangiogenic inhibitors, 2(22.2%) had PR to lenvatinib, and 7 (77.8%) remained SD. Among 11 patients with SD in response to ICIs combined antiangiogenic inhibitors, 4 (36.4%) achieved PR to lenvatinib, and 6 (54.5%) had SD.

The DCR for lenvatinib second-line therapy was 95.0% in patients who received ICIs combined with anti-angiogenic inhibitors as first-line therapy, which was significantly higher than 60.0% in those who received sorafenib (p=0.006). In patients who achieved CR/PR at first-line therapy, the DCR for lenvatinib second-line therapy was 100.0%, which was significantly higher than those with SD and PD. The efficacy was also significantly different according to the period of progression. In patients with PFS≥6months at first-line therapy, the DCR was 84.0%, which was significantly higher than the 60.0% in those with PFS< 6months (p= 0.024). No statistical difference was observed in ORR.

Univariate and multivariate analyses of PFS and OS in patients with lenvatinib as second-line treatment

The results of univariate and multivariate analyses of PFS and OS are listed in Tables 4, 5, respectively. Regarding PFS, univariate analysis showed that AFP (ng/ml)<400 (HR=0.279, 95%CI, 0.102-0.722, p=0.009), absence of extrahepatic metastasis (HR=0.314, 95%CI, 0.136-0.725, p=0.007), Child-Pugh A (HR=0.505, 95%CI, 0.981-0.260, p=0.044), tumor number<3 (HR=0.394, 95%CI, 0.185–0.842, p=0.016), ICIs combined with anti-angiogenic inhibitors as first-line therapy

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TABLE 1 Clinical characteristics in the 50 patients with unresectable HCC who received lenvatinib as second-line treatment.

Characteristics	All (n=50)	First-line treatment		P value
		Sorafenib (n=30)	ICIs+anti-angiogenic inhibitors (n=20)	
Age (years)				0.774
<65	31 (62.0%)	18 (60.0%)	13 (65.0%)	
≥ 65	19 (38.0%)	12(40.0%)	7 (35.0%)	
Gender				0.387
male	31 (62.0%)	17(56.7%)	14 (70.0%)	
female	19 (38.0%)	13(43.3%)	6 (30.0%)	
ECOG-PS				0.765
0-1	32 (64.0%)	20 (66.7%)	12 (60.0%)	
2	18 (36.0%)	10 (33.3%)	8 (40.0%)	
AFP (ng/ml)				1.000
<400	14 (28.0%)	8 (26.7%)	6 (30.0%)	
≥400	36 (72.0%)	22 (73.3%)	14 (70.0%)	
AFP response				0.779
present	24 (48.0%)	15(50.0%)	9 (45.0%)	
absent	26 (52.0%)	15(50.0%)	11 (55.0%)	
Hepatitis				0.312
negative	16 (32.0%)	12(40.0%)	4 (20.0%)	
HBV	29 (58.0%)	15(50.0%)	14 (70.0%)	
HCV	5 (10.0%)	3(10.0%)	2 (10.0%)	
Hepatocirrhosis				0.494
absent	40 (80.0%)	25(83.3%)	15 (75.0%)	
present	10 (20.0%)	5(16.7%)	5 (25.0%)	
Tumor size				0.567
≤3cm	22 (44.0%)	12(40.0%)	10 (50.0%)	
>3cm	28 (56.0%)	18(60.0%)	10 (50.0%)	
Tumor number				0.237
<3	32 (64.0%)	17(56.7%)	15 (75.0%)	
≥3	18 (32.0%)	13(43.3%)	5 (25.0%)	
PVTT				1.000
absent	16 (32.0%)	10(33.3%)	6 (30.0%)	
present	34 (68.0%)	20(66.7%)	14 (70.0%)	
Extrahepatic metastasis				0.114
absent	15 (30.0%)	6(20.0%)	9 (45.0%)	
present	35 (70.0%)	24(80.0%)	11 (55.0%)	
BCLC				–
B	0 (0.00%)	0	0	
C	50 (100.0%)	30(100.0%)	20(100.0%)	
Child-pugh				0.569
A	27 (54.0%)	15(50.0%)	12 (60.0%)	
B	23 (46.0%)	15(50.0%)	8 (40.0%)	
Response to first-line treatment				0.019
CR+PR	16 (32.0%)	7(23.3%)	9 (45.0%)	
SD	25 (50.0%)	14(46.7%)	11 (55.0%)	
PD	9 (18.0%)	9(30.0%)	0	
PFS of first-line treatment				1.000
≥ 6 months	25 (50.0%)	15(50.0%)	10 (50.0%)	
<6 months	25 (50.0%)	15(50.0%)	10 (50.0%)	

ECOG-PS, Eastern Cooperative Oncology Group performance status; AFP, α-fetoprotein; HBV, Hepatitis B virus; PVTT, Portal vein tumor thrombus; BCLC, Barcelona Clinic Liver Cancer; NLR, Neutrophil to lymphocyte ratio, ICIs, immune checkpoint inhibitors, VEGFR, Vascular Endothelial Growth Factor Receptor; PFS, Progression-free survival.

TABLE 2 ORR and DCR in the 50 patients with unresectable HCC who received lenvatinib as second-line treatment.

Response to lenvatinib	All (n=50)
CR	0
PR	9
SD	28
PD	13
ORR	18.0%
DCR	74.0%

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

(HR=0.277, 95%CI, 0.131-0.585, p=0.001) (Figure 4A), CR/PR to first-line therapy (HR=0.455, 95%CI, 0.222-0.933, p=0.031) (Figure 4B) and PFS≥6months at first-line therapy (HR=0.496, 95%CI, 0.251-0.983, p=0.045) (Figure 4C) were significantly associated with longer PFS (Table 4).

Multivariate analysis revealed that AFP (ng/ml)<400 (HR=0.140, 95%CI, 0.042-0.463, p=0.001), absence of extrahepatic metastasis (HR=0.250, 95%CI, 0.084-0.743, p=0.013), Child-Pugh A (HR=0.316, 95%CI, 0.154-0.650, p=0.002), tumor number<3 (HR=0.337, 95%CI, 0.147-0.776, p=0.011), ICIs combined with anti-angiogenic inhibitors as first-line therapy (HR=0.303, 95%CI, 0.107-0.861, p=0.025), CR/PR to first-line therapy (HR=0.308, 95%CI, 0.122-0.773, p=0.012) and PFS≥6months at first-line therapy (HR=0.093, 95%CI, 0.034-0.258, p=0.001) were independent prognostic factors of favorable PFS (Table 4).

Regarding OS, univariate analysis revealed that absence of extrahepatic metastasis (HR=0.268, 95% CI, 0.081-0.885, p=0.031), tumor number<3 (HR=0.320, 95% CI, 0.148-0.694, p=0.004), ICIs combined with anti-angiogenic inhibitors as first-line therapy (HR=0.326, 95% CI, 0.132-0.806, p=0.015) (Figure 5A) and PFS≥6months at first-line therapy (HR=0.251, 95% CI, 0.113-0.560, p <0.001) (Figure 5C) were significantly associated with longer OS and CR/PR to first-line therapy (HR=0.460, 95%CI, 0.208-1.019, p=0.056) was not associated with OS (Figure 5B). Multivariate analysis showed that absence of extrahepatic metastasis (HR=0.196, 95% CI, 0.043-0.884, p=0.034), Child-Pugh A (HR=0.421, 95%CI, 0.184-0.963, p=0.041), tumor number<3 (HR=0.277, 95% CI, 0.111-0.688,p =0.006), CR/PR to first-line therapy (HR=0.206, 95%CI, 0.070-0.605, p=0.004) and PFS≥6months at first-line therapy (HR=0.147, 95%CI, 0.054-0.397, p<0.001) were independent prognostic factors of OS (Table 5).

Safety of lenvatinib as second-line treatment in patients with unresectable HCC

In total, Table 6 shows the frequency of adverse events (AEs) after the initiation of lenvatinib treatment in all 50 patients. Treatment-related AEs (TRAEs) were acceptable and no toxicity-related death events occurred. Diarrhea (all grades, 36.0%) and hand-foot skin reaction (all grades, 26.0%) events were the most common toxicities of lenvatinib. The majority of AEs were grade 1-2, and were reversible. Grade 3/4 AEs occurred in 12 patients (24.0%) and were mostly associated with hand-foot skin reactions (10.0%), and 10 patients had lenvatinib dose reductions. Two toxicity-related treatment interruptions were attributed to grade 3 hand-foot skin reaction, and grade 4 proteinuria, respectively. All of the AEs were resolved with the appropriate measures, and most cases were reversible following adequate medical therapy.

Discussion

The purpose of this study was to determine the efficacy and safety of lenvatinib in the second-line setting of unresectable

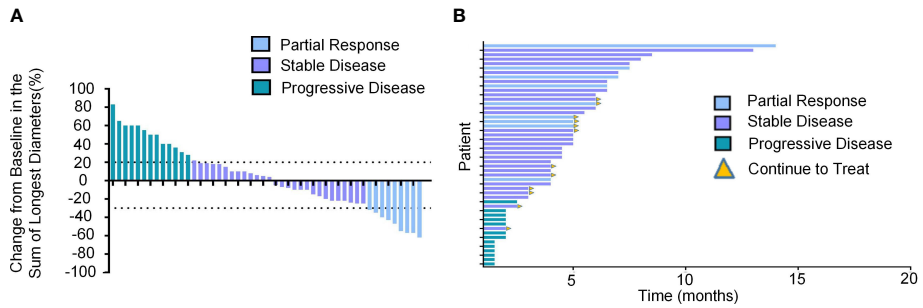

FIGURE 2
Tumor response of unresectable HCC patients treated with lenvatinib as the second-line treatment. **(A)** Best percentage change from baseline in the sum of the longest diameters of target lesions per response assessment in unresectable HCC patients (n=50). **(B)** DoR in unresectable HCC patients treated with lenvatinib as the second-line treatment.

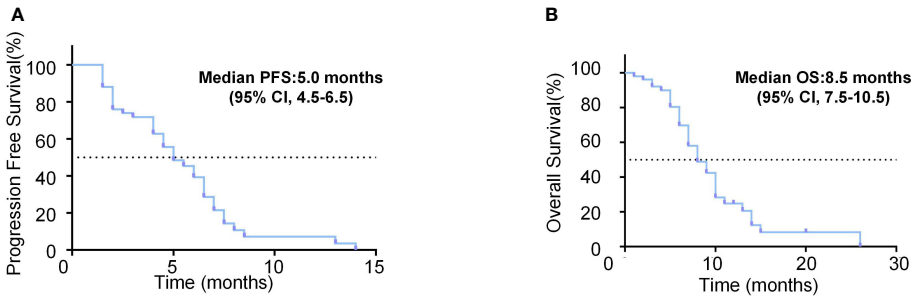

FIGURE 3
Survival analysis of unresectable HCC patients treated with lenvatinib as the second-line treatment. **(A)** Kaplan-Meier curves of PFS for the unresectable HCC patients treated with lenvatinib as the second-line treatment. **(B)** Kaplan-Meier curves of OS for the unresectable HCC patients treated with lenvatinib as the second-line treatment.

HCC. In our study, patients who received lenvatinib as second-line therapy after sorafenib or ICI in combination with an anti-angiogenic inhibitor had an ORR and DCR of 18.0% and 74.0%, and median PFS and OS of 5.0 months and 8.5 months, respectively. The modalitis of first-line therapy, response to first-line therapy, and PFS of first-line therapy were significantly associated with the outcome of lenvatinib second-line therapy.

In recent years, advances in targeted therapy and immunotherapy have led to an annual increase in treatment options for patients with advanced HCC. The expansion of treatment options complicates systemic HCC treatment, particularly in the selection of second-line treatment options (13). Lenvatinib, a multi-tyrosinase inhibitor with a unique binding mechanism to vascular endothelial growth factor receptor (VEGFR) and fibroblast growth factor receptor (FGFR), has exhibited outstanding antitumor effectiveness and safety in the first-line treatment of unresectable HCC (6). However, clinical data is inadequate to determine if lenvatinib can be utilized as a second-line treatment once sorafenib or ICIs combined with anti-angiogenic therapy fails.

Since 2017, the FDA has granted approval to regorafenib and cabozantinib for advanced HCC following progression on sorafenib. In the phase III RESORCE study, the ORR and DCR in patients who received regorafenib after sorafenib were 10.6% and 65.1%, respectively. Regorafenib was associated with a substantial improvement in PFS (3.1 months vs 1.5 months) and OS (10.6 months vs 7.8 months) when compared to placebo (14). The CELESTIAL study demonstrated a significant survival benefit with cabozantinib in patients previously treated with sorafenib, showing a significant increase versus placebo in PFS (5.2 months vs 1.9 months) and OS (10.2 months vs.

TABLE 3 The association between the efficacy of first-line treatment and lenvatinib.

Response to lenvatinib	CR+PR	SD	PD	ORR	*P value*	DCR	*P value*
Response to sorafenib							
CR+PR (n=7)	0 (0%)	7 (100%)	0 (0%)	0%	0.149	100%	0.025
SD (n=14)	3 (21.4%)	5 (35.7%)	6 (42.9%)	21.4%		57.1%	
PD (n=9)	0 (0%)	3 (33.3%)	6 (66.7%)	0%		33.3%	
Response to ICIs combined antiangiogenic inhibitors							
CR+PR (n=9)	2 (22.2%)	7 (77.8%)	0 (0%)	22.2%	0.642	100%	1.000
SD (n=11)	4 (36.4%)	6 (54.5%)	1 (9.1%)	36.4%		90.9%	
PD (n=0)	0(0%)	0(0%)	0(0%)	0%		0%	
All							
CR+PR (n=16)	2 (12.5%)	14 (87.5%)	0(0%)	12.5%	0.136	100%	0.001
SD (n=25)	7 (28.0%)	11 (44.0%)	7(28.0%)	28.0%		72.0%	
PD (n=9)	0(0%)	3 (33.3%)	6 (66.7%)	0%		33.3%	
PFS at first-line therapy							
PFS≥6months (n=25)	4(16.0%)	17(68.0%)	4(16.0%)	16.0%	0.714	84.0%	0.024
PFS<6months (n=25)	5(20.0%)	10(40.0%)	10(40.0%)	20.0%		60.0%	

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

TABLE 4 Univariate and multivariate analysis of PFS in the 50 patients with unresectable HCC who received lenvatinib as second-line treatment.

Factors	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Gender (female/male)	0.658 (0.329-1.316)	0.237		
Age (<65 vs. ≥65)	0.788 (0.408-1.522)	0.479		
Hepatitis (absent vs. HBV/HCV)	0.805 (0.402-1.610)	0.538		
Hepatocirrhosis (absent vs. present)	0.787 (0.341-1.815)	0.574		
ECOG-PS (0/1 vs. 2)	0.760 (0.385-1.500)	0.429		
AFP (ng/ml) (<400 vs. ≥400)	0.279 (0.102-0.722)	**0.009**	0.140 (0.042-0.463)	**0.001**
AFP response (ng/ml) (≥20%vs. <20%)	0.637 (0.331-1.227)	0.177		
Extrahepatic metastasis (absent vs. present)	0.314 (0.136-0.725)	**0.007**	0.250 (0.084-0.743)	**0.013**
Child-pugh (A vs. B)	0.505 (0.981-0.260)	**0.044**	0.316 (0.154-0.650)	**0.002**
PVTTs (absent vs. present)	0.880 (0.437-1.771)	0.720		
Tumor size (≤3 vs. >3)	0.911 (0.464-1.789)	0.786		
Tumor number (<3 vs. ≥3)	0.394 (0.185-0.842)	**0.016**	0.337 (0.147-0.776)	**0.011**
First-line treatment (Antiangiogenic inhibitor+ICIs vs. Sorafenib)	0.277 (0.131-0.585)	**0.001**	0.303 (0.107-0.860)	**0.025**
Response to first-line treatment (CR/PR vs. SD/PD)	0.455 (0.222-0.933)	**0.031**	0.308 (0.122-0.772)	**0.012**
PFS of first-line treatment (≥3months vs. <3 months)	0.473 (0.204-1.095)	0.080	0.698 (0.265-1.841)	0.468
PFS of first-line treatment (≥6 months vs. <6 months)	0.496 (0.251-0.983)	**0.045**	0.093 (0.034-0.258)	**0.001**

ECOG-PS, Eastern Cooperative Oncology Group performance status; AFP, α-fetoprotein; HBV, Hepatitis B virus; PVTT, Portal vein tumor thrombus; BCLC, Barcelona Clinic Liver Cancer; NLR, Neutrophil to lymphocyte ratio, ICIs, immune checkpoint inhibitors, VEGFR, Vascular Endothelial Growth Factor Receptor; PFS, Progression-free survival. Bold values, data with p<0.05 in Table.

TABLE 5 Univariate and multivariate analysis of OS in the 50 patients with unresectable HCC who received lenvatinib as second-line treatment.

Factors	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Gender (female vs.male)	0.635 (0.280-1.437)	0.276		
Age (<65 vs. ≥65)	0.754 (0.365-1.558)	0.446		
Hepatitis (absent vs. HBV/HCV)	0.978 (0.455-2.105)	0.955		
Hepatocirrhosis (absent vs. present)	0.891 (0.339-2.342)	0.815		
ECOG-PS (0/1 vs. 2)	0.959 (0.444-2.072)	0.916		
AFP (ng/ml) (<400 vs. ≥400)	0.306 (0.072-1.295)	0.108		
AFP response (ng/ml) (≥20%vs. <20%)	0.694 (0.333-1.449)	0.331		
Extrahepatic metastasis (absent vs. present)	0.268 (0.081-0.885)	**0.031**	0.196 (0.043-0.884)	**0.034**
Child-pugh (A vs. B)	0.469 (0.217-1.016)	0.055	0.421 (0.184-0.963)	**0.041**
PVTTs (absent vs. present)	0.759 (0.344-1.676)	0.495		
Tumor size (≤3 vs. >3)	0.938 (0.445-1.980)	0.867		
Tumor number (<3 vs. ≥3)	0.320 (0.148-0.694)	**0.004**	0.277 (0.111-0.688)	**0.006**
First-line treatment (Antiangiogenic inhibitor+ICIs-1inhibitor vs. Sorafenib)	0.326 (0.132-0.806)	**0.015**	0.839 (0.260-2-703)	0.769
First-line treatment response (CR/PR vs. SD/PD)	0.460 (0.208-1.019)	0.056	0.206 (0.070-0.605)	**0.004**
PFS of first-line treatment (≥3months vs. <3 months)	0.452 (0.170-1.203)	0.112		
PFS of first-line treatment (≥6 months vs. <6 months)	0.251 (0.113-0.560)	**0.001**	0.147 (0.054-0.397)	**<0.001**

ECOG-PS, Eastern Cooperative Oncology Group performance status; AFP, α-fetoprotein; HBV, Hepatitis B virus; PVTT, Portal vein tumor thrombus; BCLC, Barcelona Clinic Liver Cancer; NLR, Neutrophil to lymphocyte ratio, ICIs, immune checkpoint inhibitors, VEGFR, Vascular Endothelial Growth Factor Receptor; PFS, Progression-free survival. Bold values, data with p<0.05 in Table.

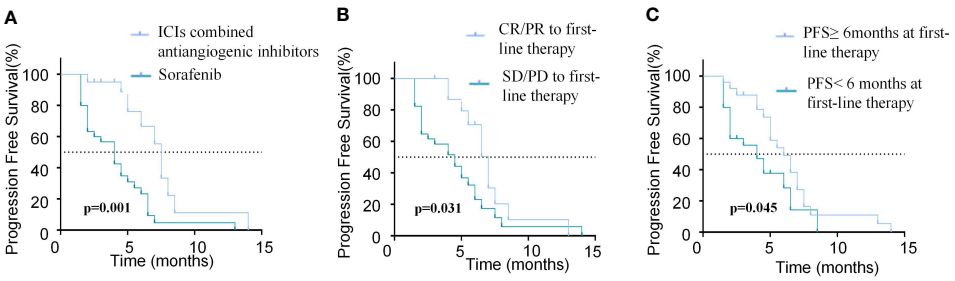

FIGURE 4
Comparison of PFS in patients with different modalities and efficacy of first-line treatment. **(A)** Kaplan-Meier curves of PFS between patients with ICIs combined antiangiogenic inhibitors or sorafinib for the first-line treatment. **(B)** Kaplan-Meier curves of PFS between patients who achieved CR/PR or SD/PD in the first-line treatment. **(C)** Kaplan-Meier curves of PFS between patients with PFS≥6months or PFS<6months in the first-line treatment.

8.0months), while the ORR (4% vs <1%) and DCR (64% vs 33%) were also better in the cabozantinib arm (15, 16). Immune checkpoint inhibitors have been approved as a second-line treatment for advanced HCC in recent years. In the KEYNOTE-224 study, pembrolizumab has shown clinical activity in patients with advanced HCC previously treated with sorafenib. The ORR and DCR were 17% and 62%, respectively, and the median PFS and OS were 4.9 months and 13.2 months. Unfortunately, pembrolizumab failed to show superiority compared to placebo in terms of OS and PFS in the KEYNOTE-240 study (17, 18). The CheckMate 040 study showed that the ORR and DCR of nivolumab for second-line treatment following progression on sorafenib was 15-20% and 58-64%, while the median PFS and OS were 2.1 months and 13.8 months, respectively (19, 20). Camrelizumab, another PD-1 inhibitor, was approved as a second-line therapy in Chinese patients with advanced HCC (21). However, these earlier clinical studies only enrolled patients who had failed to sorafenib in first-line therapy, and did not represent the optimal second-line treatment option in the current HCC treatment landscape. The efficacy of either targeted agents or checkpoint inhibitors in these studies was not very satisfactory. Our study showed a median PFS and OS of 5.0 and 8.5 months for lenvatinib as second-line treatment after progression on sorafenib or ICIs combined with anti-angiogenic inhibitors. But the clinical benefit of second-line lenvatinib treatment needs to be further validated in randomized controlled trials.

In addition, recent studies have evaluated the efficacy of combination therapy modalities in the second-line treatment of advanced HCC, including dual checkpoint inhibitors and ICIs combined with anti-angiogenic agents. In the CheckMate 040 trial, the ORR of nivolumab plus ipilimumab was between 31% and 32%, with DOR ranging between 4.6 and 30.5 months (22). However, combination treatment had more serious AEs compared to the monotherapy arm. Similarly, although the combination of tremelimumab plus durvalumab had an ORR of up to 22.7% and a median OS of up to 18.7 months, it should be noted that the incidence of grade 3 or 4 TRAEs was as high as

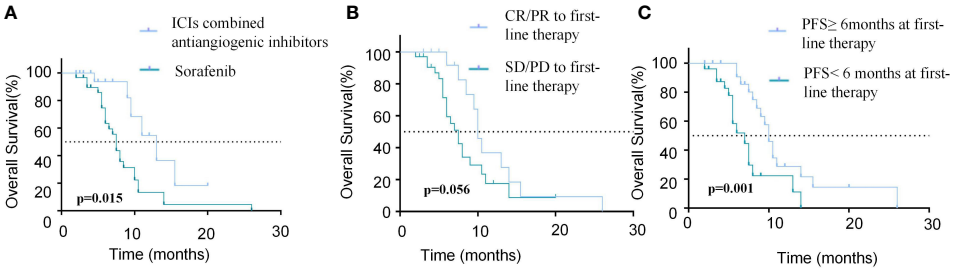

FIGURE 5
Comparison of OS in patients with different modalities and efficacy of first-line treatment. **(A)** Kaplan-Meier curves of OS between patients with ICIs combined antiangiogenic inhibitors or sorafinib for the first-line treatment. **(B)** Kaplan-Meier curves of OS between patients who achieved CR/PR or SD/PD in the first-line treatment. **(C)** Kaplan-Meier curves of OS between patients with PFS≥6months or PFS<6months in the first-line treatment.

TABLE 6 TRAEs of lenvatinib as second-line treatment in patients with unresectable HCC.

TRAEs	All (n=50)		
	Any Grades	Grade 1/2	Grade 3/4
Hand-foot skin reaction	13 (26.0%)	8 (16.0%)	5 (10.0%)
Hypertension	12 (24.0%)	10 (20.0%)	2 (4.0%)
Rash	8 (16.0%)	7 (14.0%)	1 (2.0%)
Fatigue	9 (18.0%)	9 (18.0%)	0 (0.0%)
Hoarseness	4 (8.0%)	4 (8.0%)	0 (0.0%)
Diarrhea	18 (36.0%)	18 (36.0%)	0 (0.0%)
Increased ALT	3 (6.0%)	2 (4.0%)	1 (2.0%)
Increased AST	3 (6.0%)	2 (4.0%)	1 (2.0%)
Increased TB	5 (10.0%)	4 (8.0%)	1 (2.0%)
Decreased WBC	8 (16.0%)	6 (12.0%)	2 (4.0%)
Decreased PLT	2 (4.0%)	2 (4.0%)	0 (0.0%)
Increased creatinine	1 (2.0%)	1 (2.0%)	0 (0.0%)
Proteinuria	1 (2.0%)	0 (0.0%)	1 (2.0%)
Gastrointestinal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; WBC, white blood cell; PLT, platelet count.

35.1%. The phase II RESCUE study showed that the ORR of apatinib in combination with camrelizumab for second-line treatment of advanced HCC was 22.5%, with a median PFS of 5.5 months and a 12-month survival rate of 68.2%. However, the proportion of grade 3 or 4 TRAEs was as high as 77.4% (23, 24). Thus, although the combination treatment modality appears to improve efficacy, the higher incidence of serious adverse effects limits its clinical application in the real world. In our study, lenvatinib showed favorable safety and tolerability.

It is critical to identify the group that will benefit from second-line lenvatinib treatment. Our study revealed that the modality of first-line therapy may affect the efficacy and outcome of second-line treatment with lenvatinib. First-line treatment with ICIs combined with anti-angiogenic agents, CR/PR to first-line therapy, and PFS≥6months at first-line therapy were significantly associated with better DCR, PFS, and OS. Given that anti-angiogenic agents may reprogram the suppressive tumor immune microenvironment by affecting infiltration of immune cells and the expression of immune checkpoints, anti-angiogenic agents combined with ICIs may exert synergistic effects. Previous studies have shown that residual effects persist after discontinuation of ICIs in patients who previously benefited from ICIs, which may explain the better efficacy of second-line treatment with lenvatinib in HCC patients who received ICIs in the first-line treatment (25, 26). In a retrospective analysis, Chen et al. found that response to first-line treatment with sorafenib in patients who failed sorafenib correlated with the efficacy of second-line lenvatinib, which is consistent with the findings of this study, but the study did not analyze the relationship between the PFS of sorafenib first-line therapy and the efficacy of lenvatinib (27). In addition, we found that AFP level, with or without extrahepatic metastasis, Child-Pugh, tumor number, was associated with the efficacy of lenvatinib.

The AEs for lenvatinib in this study were similar to those in the REFLECT study, without unreported AEs (8). Lenvatinib was well tolerated and no treatment-related deaths occurred. The most common adverse events with lenvatinib included diarrhea, hand-foot skin reactions, hypertension, and dermatitis, and most AEs are reversible. This suggests that lenvatinib monotherapy is a relatively well-tolerated treatment option for the second-line HCC population with poor PS scores and more comorbidities.

Our study is a retrospective analysis of real-world data, which includes patients with Child-Pugh B as well as primary PVTT, and presents a more objective overview of the current status of second-line therapy for advanced HCC. Due to the fact that previous trials of second-line treatment for HCC did not enroll patients receiving first-line treatment with ICIs, there is an urgent need to explore the optimal modality for second-line treatment of advanced HCC in the era of immunotherapy. This study confirms the efficacy and safety of lenvatinib as second-line therapy after progression on sorafenib or ICIs combined with anti-angiogenic inhibitors. However, this study has some limitations. First, this was a retrospective analysis with a small sample size, and confounding factors and bias were inevitable. Secondly, some patients received regorafenib, ICIs, or other treatments in third-line therapy after progression on lenvatinib, which may have affected OS outcomes. Thirdly, the AEs of levatinib may have been underestimated due to the nature of retrospective data. Finally, the follow-up period of this study was short, and PFS and OS data need to be updated with further long-term follow-up. Further studies with a larger

population or a randomized controlled trial are warranted to validate the findings of this study.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the First Affiliated Hospital of Dalian Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

J-wL and A-mW conceived the project, and J-wL supervised the project. H-nQ and ZN designed and performed most of analysis. RS, C-xJ, and XG provided significant intellectual input. H-nQ, ZN, and A-mW wrote the manuscript with input from all other authors. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Lenvatinib plus anti-PD-1 therapy represents a feasible conversion resection strategy for patients with initially unresectable hepatocellular carcinoma: A retrospective study

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Purpose: We aimed to investigate the feasibility of lenvatinib plus anti-PD-1 therapy as a conversion therapy for initially unresectable hepatocellular carcinoma (HCC).

Methods: Patients with initially unresectable HCC who received combined lenvatinib and anti-PD-1 antibody between May 2020 and Jan 2022 in Zhongshan Hospital were retrospectively analyzed. Tumor response and resectability were assessed by imaging every two months according to RECIST version 1.1 and modified RECIST (mRECIST) criteria.

Results: A total of 107 patients were enrolled. 30 (28%) of them received conversion surgery within 90.5 (range: 53–456) days after the initiation of lenvatinib plus anti-PD-1 therapy. At baseline, the median largest tumor diameter of these 30 patients was 9.2 cm (range: 3.5-15.0 cm), 26 patients had Barcelona Clinic Liver Cancer stage B-C, and 4 had stage A. Prior to surgery, all cases displayed tumor regression and 15 patients achieved objective response. Pathological complete response (pCR) was observed in 10 patients. No severe drug-related adverse events or surgical complications were observed. After a median follow-up of 16.5 months, 28 patients survived and 11 developed tumor recurrence. Survival analysis showed patients achieving tumor response before surgery or pCR had a longer tumor-free survival.

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Notably, patients with microvascular invasion (MVI) had significantly higher recurrence rate and poorer overall survival than patients without.

Conclusions: Lenvatinib combined with anti-PD-1 therapy represents a feasible conversion strategy for patients with initially unresectable HCC. Patients achieving tumor responses are more likely to benefit from conversion resection to access a longer term of tumor-free survival.

KEYWORDS

hepatocellular carcinoma, lenvatinib, Anti-PD-1 therapy, conversion resection, objective response

Introduction

Hepatocellular carcinoma (HCC), more than 50% cases of which occurs in China, ranks the sixth most prevalent cancer and the fourth leading cause of cancer death globally (1). Despite the developing technology for detecting early-stage HCC, more than 50% HCC patients are still diagnosed at an advanced stage when the opportunity for radical surgical resection has been already lost, resulting in a poor clinical outcome (2). For these HCC patients, systemic therapies including multi-kinase inhibitors, intra-arterial therapy, chemotherapy, and immunotherapy, are beneficial but still not optimistic (3).

The concept of conversion therapy has been proposed with the aim of downstaging tumor to convert initially unresectable tumor into resectable and improving the long-term survival of patients with advanced tumors. This treatment strategy has also been widely practiced in HCC for more than 30 years, using several locoregional therapies like transcatheter arterial chemoembolization and associating liver partition and portal vein ligation for staged hepatectomy to reduce tumor burden and increase the feasibility of surgery (4–7). However, currently potential conversion regimens still need to be further supported by sufficient clinical evidence to facilitate their routine application in clinical practice.

Systemic therapies for HCC mainly include tyrosine kinase inhibitors (TKIs), immunotherapy and chemotherapy. Traditional sorafenib treatment had a relatively low tumor response rate and thus was not considered as part of conversion therapy for advanced HCC (8–10). Lenvatinib has been approved as a new first-line option for advanced HCCs and is associated with significantly higher overall response rates than sorafenib in unresectable HCC (11, 12). In addition, immune checkpoint inhibitors (ICIs) have proved to have an effective anti-tumor activity in advanced HCC patients. Furthermore, pre-clinical and clinical studies prove that lenvatinib plus pembrolizumab has higher objective response rate (ORR) than single-agent treatment, and is one of the most promising therapies among all the regimen of combinations (13–16). Notably, a small sample study from our institution has reported that anti-PD-1 therapy combined with TKIs can improve the rate of conversion resection in initially unresectable HCC (17). Thus, advances in systemic therapy, represented by lenvatinib combined with anti-PD-1 therapy, have led clinicians to reassess the value of systemic therapy in the conversion therapy of HCC.

Herein, we report 30 initially unresectable HCC patients who received lenvatinib and anti-PD-1 combination therapy, followed by successful surgical resection. To the best of our knowledge, this study represents the largest cohort of HCC patients undergoing conversion rection following systemic therapy. Furthermore, we performed survival analysis of the 30 patients and revealed the association between patient clinical outcomes and treatment response as well as microvascular invasion (MVI). Our study provides clinical evidence to evaluate the efficacy and safety of systemic therapy for HCC in the conversion therapy setting.

Abbreviations: AEs, Adverse events; BCLC, Barcelona Clinic Liver Cancer; CNLC, China Liver Cancer; CR, Complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBsAg, Hepatitis B surface antigen; HCC, Hepatocellular carcinoma; ICIs, Immune checkpoint inhibitors; IIR, Independent imaging review; INR, Investigator review; mRECIST, Modified response evaluation criteria in solid tumors; ORR, Objective response rate; OS, overall survival; PD, Progressive diseases; PR, Partial response; SD, Stable disease; TKI, Tyrosine kinase inhibitors.

Materials and methods

Study design and patient population

A total of 107 patients with unresectable or advanced HCC who received lenvatinib with anti-PD-1 antibodies at Zhongshan Hospital, Fudan University between May 2020 and Jan 2022

were retrospectively analyzed in this study. The inclusion criteria comprised the following (1): Clinically confirmed HCC based on the domestic guideline and American Association for the Study of Liver Diseases criteria (18, 19) (2); Tumor was considered unresectable either due to intermediate to advanced HCC or insufficient postoperative remnant liver volume (3); At least one measurable tumor lesion according to modified Response Evaluation Criteria in Solid Tumors (mRECIST) (20). The presence of vascular invasion was diagnosed using the Magnetic Resonance Imaging (MRI). The clinical data of these patients were obtained from the medical record system. This study was approved by the Ethics Committee of Zhongshan Hospital and conducted conformed to the standards set by the Declaration of Helsinki. All patients signed the written informed consent before systemic therapy or surgery.

Systemic therapy

Systemic therapy included lenvatinib plus intravenous anti-PD-1 antibody. Lenvatinib was orally administered once daily (body weight ≥60 kg, 12 mg; <60 kg, 8 mg; Eisai, Inc., Tokyo, Japan). Anti-PD-1 antibody like camrelizumab (Hengrui Medicine, Jiangsu, China) 200 mg (21), was administered every two weeks, and sintilimab (Innovent Biologics, Suzhou, China and Eli Lilly and Company, Inc., Indianapolis, IN, USA) 200 mg (22), or toripalimab (Junshi Bioscience, Shanghai, China) 240 mg (23), or pembrolizumab (MSD, State of New Jersey, USA) 200 mg, or tislelizumab (BeiGene, Beijing, China) 200 mg (24), was administered every three weeks. During the study period, all anti-PD-1 antibodies were off-label regimens for HCC and could not be covered by the medical insurance system in China. Thus, anti-PD-1 antibodies were utilized based on patient preference, mainly due to the economic cost and the updated information from ongoing clinical trials. Patients were monitored for hematuria routine, tumor markers, liver, kidney, thyroid, adrenal and cardiac functions every 2-3 weeks prior to the anti-PD-1 antibody treatment.

Treatment response evaluation

Tumor responses were evaluated using abdominal MRI and chest computed tomography (CT) every two months, and determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (25) and mRECIST (20). Both investigator review (INR) and independent imaging review (IIR) were conducted for all evaluation. Briefly, complete response (CR) was defined as a complete disappearance of all tumor lesions, partial response (PR) as the sum of tumor diameters were reduced by ≥ 30% from baseline, progressive diseases (PD) as the sum of tumor diameters were increased by ≥ 20% from baseline, and stable diseases (SD) as neither CR, PR nor PD. The ORR was calculated as the sum of percentage of patients who achieved CR and PR. All image processing and measurement were performed by two independent radiologists, who were blinded to the patient information. Safety evaluations were performed according to the Common Terminology Criteria for Adverse Events version 4.03.

Surgical resection procedure

Tumor resectability was assessed based on the imaging results with the following criteria (1): R0 resection could be achieved with residual liver volume more than 35% and no contraindications to hepatic resection (2); intrahepatic lesions were assessed as CR, PR, or regressed SD without severe drug-related adverse events (AEs). The surgical procedure was conducted as previously reported (26). Tumor resectablility was discussed and passed by the Multidisciplinary Team (MDT) composed of senior surgeons and radiologists in Zhongshan Hospital. Completely resected tumor samples without residual viable tumor cells after hematoxylin and eosin staining were considered as pathological complete response (pCR). Combination therapy was resumed 4 weeks after surgery and follow-up imaging and serum tumor biomarkers were performed every 2-3 months. Overall survival (OS) was determined as the interval between the date of surgery and the date of death or study endpoint. Recurrence-free survival (RFS) was defined as the interval between the date of surgery and the date of tumor recurrence or study endpoint.

Statistical analysis

Statistical analyses were conducted using SPSS v.25 (IBM Inc., Armonk, NY, USA). Categorized variables were summarized as frequencies (proportion). The value and 95% confidence interval (CI) of ORR was calculated by the Clopper-Pearson algorithm. Survival differences were analyzed by the Kaplan-Meier method. Two-sided P value < 0.05 was considered statistically significant.

Results

Baseline characteristics of the study cohort

From May 2020 to Jan 2022, 107 consecutive HCC patients who received lenvatinib plus anti-PD-1 antibodies as first-line systemic therapy were retrospectively analyzed. Of these patients, 32 were evaluated as resectable and 30 (30/107, 28%) successfully underwent R0 conversion resection. Other 2 patients refused surgery and continued to receive the systemic therapy

(Figure 1). The baseline demographic and clinical characteristics of the 30 patients are summarized in Table 1. Briefly, the median age of these patients was 56.0 (range: 40–70) years, and 83.3% of them were male. As for Eastern Cooperative Oncology Group (ECOG) performance status, 63.3% of them had a score of 0. Twenty-four (80%) patients had an etiology of chronic HBV infection. Twenty (20/30, 66.7%) patients had macrovascular invasion, including portal vein or hepatic vein tumor thrombus in 19 patients and intrahepatic bile duct tumor thrombus in 1 patient. Four patients had Barcelona Clinic Liver Cancer (BCLC) stage A disease but were evaluated as unresectable, consisting of 2 patients due to anatomical constraints removing the tumor, and 2 patients with insufficient functional hepatic reserve.

Treatment efficacy of lenvatinib combined with anti-PD-1 therapy

Tumor responses were evaluated *via* preoperative radiographic imaging (Table 2). According to the criteria of RECIST Version 1.1, the ORR was 50% (95% CI, 31.3%-68.7%) by both INR and IIR assessment. PR was achieved in 15 patients (50%) and SD was observed in the rest of the patients. By mRECIST criteria, 7 (23.3%), 8 (26.7%), and 15 (50%) patients had CR, PR, and SD respectively. All cases displayed tumor regression and a decrease in tumor size compared with that at baseline (Figure 2).

Surgery and perioperative findings

The median diameter of the major liver tumor was 9.2 cm (range: 3.5–15 cm), and 5 patients had multiple intrahepatic lesions (Table 3). The median interval from the initiation of systemic therapy to surgery was 90.5 (range: 53–456) days. All patients received at least 3 infusions of anti-PD-1 antibodies, with a median infusion of 4 (range: 3–21) times. All patients underwent open surgery. The median time of surgery was 180 (range: 150–220) minutes, and the median volume of blood loss was 400 (range: 100–1500) milliliters. Three patients received intraoperative blood transfusion. The median postoperative hospital stay was 14 (range: 9–31) days. All patients recovered well and no major postoperative complications occurred. A total of 10 patients (10/30, 33.3%) achieved a pathological complete

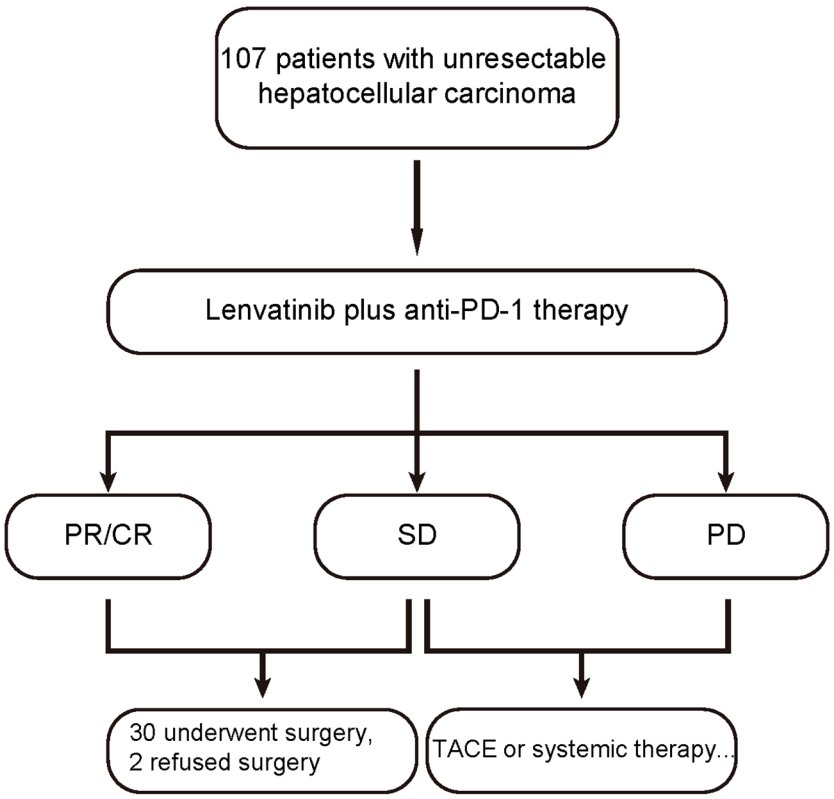

FIGURE 1
Patient flowchart.

TABLE 1 Baseline demographic and clinical characteristics of HCC patients receiving surgery after treatment with lenvatinib plus anti-PD-1 antibody (n = 30).

Characteristics	Number (%)
Age, years	
Median	56
Range	40-70
Gender	
Male	25 (83.3%)
Female	5 (16.7%)
ECOG PS score	
0	19 (63.3%)
1	11 (36.7%)
HBsAg	
Positive	24 (80.0%)
Negative	6 (20.0%)
Alpha-fetoprotein, ng/mL	
≤ 300	17 (56.7%)
> 300	13 (43.3%)
PIVKA-II, mAU/mL	
≤ 1000	5 (16.7%)
> 1000	25 (83.3%)
Macrovascular invasion[a]	20 (66.7%)
BCLC stage	
0-A	4 (13.3%)
B-C	26 (86.7%)
CNLC stage	
I a	1 (3.3%)
I b	3 (10.0%)
II b	6 (20.0%)
III a	17 (56.7%)
III b	3 (10.0%)

BCLC, Barcelona Clinic Liver Cancer; CNLC, China National Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HBsAg, Hepatitis B surface antigen; HCC, Hepatocellular carcinoma; PD-1, Programmed death receptor 1; PIVKA-II, protein induced by vitamin K absence-II.
[a]Indicators based on radiographic evidence.

response (pCR) in all surgical specimens, and MVI was detected in 8 (8/30, 26.7%) patients (Table 3).

Two representative cases were shown in Figure 3. Patient 8 was diagnosed with BCLC stage C HCC, with tumor invading into the right hepatic vein and inferior vena cava (Figure 3A). 12 weeks after the treatment with lenvatinib plus tislelizumab, MR scans showed significant necrosis in both the tumor and tumor thrombi (Figure 3B). Massive necrosis of tumor cells and infiltration of inflammatory cells were observed in the resected tumor samples. Moreover, complete necrosis of the macrovascular tumor thrombi observed by pathological study indicated a downstaging from BCLC stage C to stage A (Figures 3C, D). Patient 17 was classified as BCLC stage A, while the tumor compression on nearby hepatic vein and the first porta hepatis, and its proximity to inferior vena cava increased the risk for complete resection, making it surgically unresectable. After the combination therapy with lenvatinib plus toripalimab for 18 weeks, obvious tumor shrinkage and thickening of tumor encapsule decreased the risk of severe bleeding and tumor dissemination during resection, offering this patient an opportunity for surgery (Figures 3E, F).

Typical MR or CT imaging scans of other patients (besides patients 8 and 17) before systemic treatment and before surgery were also listed in Figures 4, 5. The major reason for unresectability were tumor invasion into major portal vein (patients 12, 18 and 22) and the main branches of the portal vein (patients 2, 7, 9, 11, 14, 20, 24, 25, 26, 27 and 28), into hepatic vein or inferior vena cava (patients 5, 21, 29 and 30), into right hepatic bile duct (patient 3), multiple intrahepatic lesions (patients 1, 6, 15, 16, 19 and 23), insufficient remnant liver volume (patients 4 and 13), anatomical constraints for curative resection (patient 10), concomitant hilar or retroperitoneal lymph node metastasis (patients 7, 20 and 21). Obvious tumor regression was observed in all these cases before surgery.

Safety

The treatment-related AEs were summarized in Table 4. Most patients experienced mild, tolerable, and controllable AEs. The most common AEs of any grade were decreased platelet count (n = 14, 46.7%), proteinuria (n = 10, 33.3%), decreased white blood cell count (n = 8, 26.7%), hypertension (n = 6, 20.0%), hypothyroidism (n = 5, 16.7%), and palmar-plantar erythrodysesthesia syndrome (n = 4, 13.3%).

TABLE 2 Efficacy of lenvatinib plus anti-PD-1 antibody in patients receiving surgery (n = 30).

Response	RECIST Version 1.1		mRECIST	
	INR	IIR	INR	IIR
Objective response rate, %	50.0	50.0	50.0	50.0
95% CI[a]	31.3-68.7	31.3-68.7	31.3-68.7	31.3-68.7
Complete response	0 (0%)	0 (0%)	7 (23.3%)	7 (23.3%)
Partial response	15 (50.0%)	15 (50.0%)	8 (26.7%)	8 (26.7%)
Stable disease	15 (50.0%)	15 (50.0%)	15 (50.0%)	15 (50.0%)

IIR, Independent imaging review; INR, Investigator review; mRECIST, modified response evaluation criteria in solid tumors.
[a]Calculated using the Clopper-Pearson method.

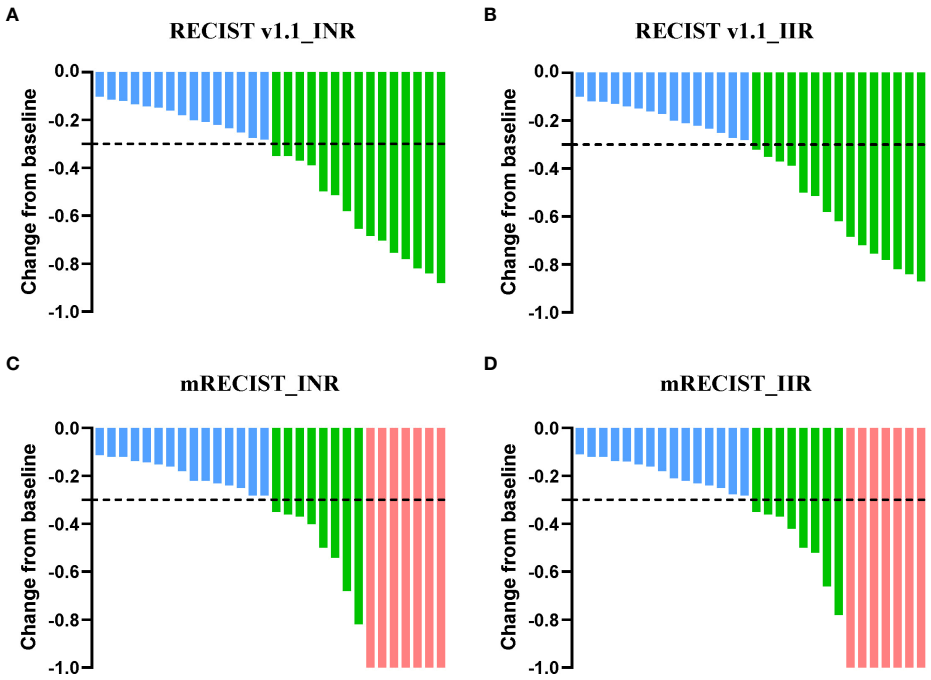

FIGURE 2
Percent change of the sum of tumor diameters from baseline. Percent change of total tumor diameters from baseline by INR **(A)** and IIR assessment **(B)** according to RECIST Version 1.1. Overall percent change from baseline in tumor size by INR **(C)** and IIR assessment **(D)** according to mRECIST criteria. Each bar represents one patient. INR, Investigator review; IIR, Independent imaging review; mRECIST, modified response evaluation criteria in solid tumors.

TABLE 3 Surgical and pathological features of patients receiving conversion surgery (n = 30).

Characteristics	Total (n = 30)
Days from systemic therapy to surgery, days (median, range)	90.5 (53–456)
Anti-PD-1 antibody used	
Sintilimab	14 (46.7%)
Toripalimab	8 (26.7%)
Tislelizumab	4 (13.3%)
Camrelizumab	3 (10%)
Pembrolizumab	1 (3.3%)
Infusions of anti-PD-1 antibody, times (median, range)	4 (3-21)
Major tumor size, cm (median, range)	9.3 (3.5-15)
Tumor number	
Solitary	25 (83.3%)
Multiple	5 (16.7%)
Open surgery, n (%)	30 (100%)
Time of surgery, mins (median, range)	180 (150–220)
Blood loss, mL (median, range)	400 (100-1500)
Blood transfusion	3 (10.0%)
Postoperative hospital stay, days (median, range)	14 (8-31)
Micro-vascular invasion, n (%)	8 (26.7%)
Pathological complete response, n (%)	10 (33.3%)

Follow-up and survival analysis

The cutoff date for the present analysis was July 1, 2022. After a median follow-up of 16.5 months since the date of surgery, 28 patients remained alive and 11 patients developed tumor recurrence (Figure 6). All surviving patients continued the combination therapy, with a median time of 12 months. 10 (10/30, 33.3%) patients had a dose reduction of lenvatinib due to its related toxicities. The 12-month overall survival rate of the 30 patients after surgery was 95.7% (standard error, 4.3%), and 12-month disease-free survival rate after surgery was 61.6% (standard error, 9.6%).

Postoperative survival analysis demonstrated that there was a significant difference in DFS between patients who did and did not achieve a treatment response before surgery (Figure 7A; P = 0.037). Compared with patients with SD, patients who achieved CR or PR had a longer DFS, while no statistically significant difference in OS was observed among patents with and without tumor response (Figure 7B; P = 0.43). Similar results were found when performing survival analysis between patients who achieved pCR in resected samples and those did not (Figures 7C, D; P=0.0041 for DFS, P=0.31 for OS). Notably, patients with the presence of MVI in resected tumor specimens had significantly higher recurrence risk and poorer overall

survival than patients without after surgery (Figures 7E, F; both P <0.05). This indicated that MVI still acts as a vital prognostic risk factor for HCC patients who received conversion surgery.

Discussion

Our present study showed that lenvatinib plus anti-PD-1 antibodies allowed successful R0 resection in 28% (30/107) of patients with initially unresectable HCC, indicating this combination therapy is a feasible conversion strategy for converting HCC patients from unresectable to resectable.

Conversion resection aims to achieve downstaging of tumors and allow patients with advanced or initially unresectable cancers to obtain curative resectability. The role of conversion therapy in HCC patients has long been neglected due to lack of effective systemic therapies. Recently, systemic therapeutic agents especially the combination of TKIs with ICIs have shown promising anti-tumor efficacy, reviving the idea of conversion therapy in HCC. Several studies have explored the feasibility of different combination therapies as conversion therapy in HCC. A previous study from our liver cancer institute reported that 15.9% (10/63) of patients with initially unresectable HCC received conversion surgery after combination treatment with TKI and anti-PD-1 antibodies (17). The combination of TKIs, ICIs and local regional therapy has been reported to convert 9 (9/38, 23.7%) HCC patients with extrahepatic metastases from unresectable to resectable (27). A multi-center retrospective study showed that the ORR of triple combination therapy with lenvatinib, toripalimab plus hepatic arterial infusion chemotherapy (HAIC) was as high as 67.6%, and its conversion resection rate was higher than that of lenvatinib alone (12.7% vs 0) (28). In our study, lenvatinib plus PD-1 inhibitors led to an ORR of 50% (15/30) in HCC

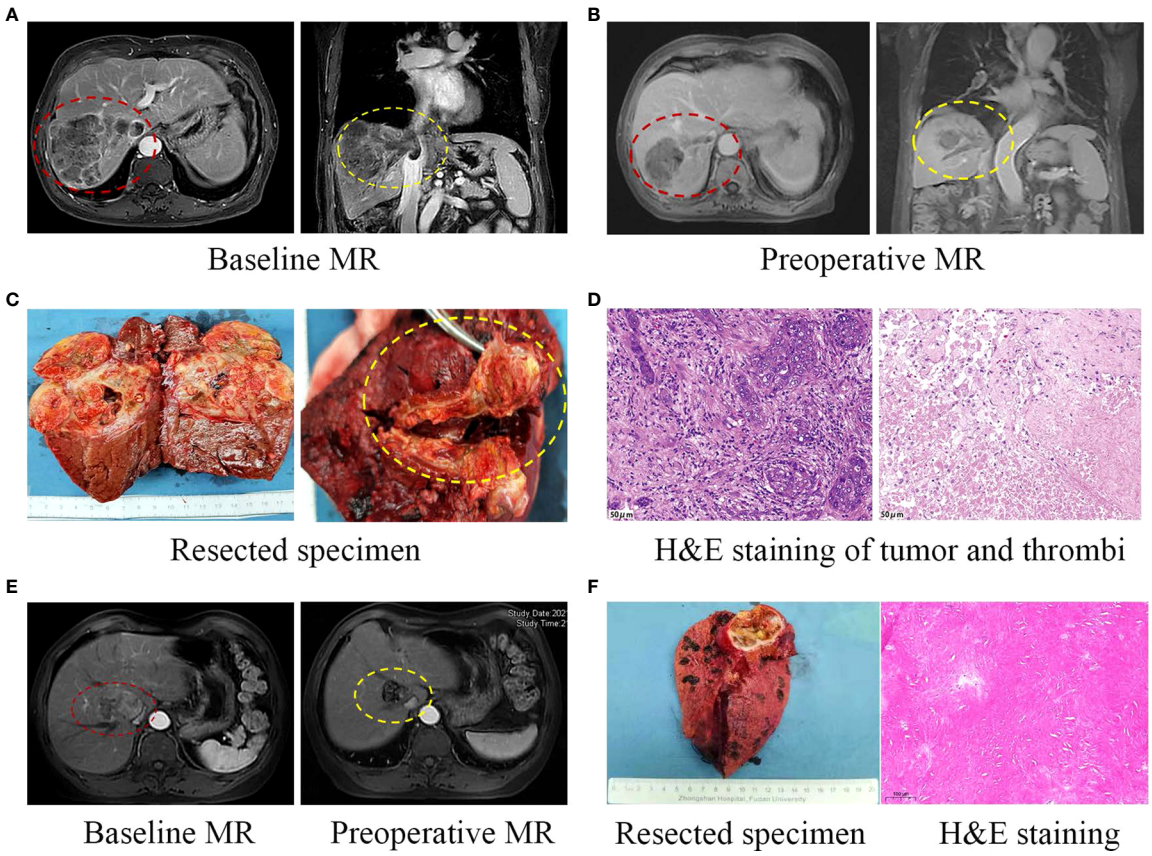

FIGURE 3
Two representative cases. **(A)** Pre-treatment MR showing both the liver tumor and macrovascular tumor thrombi. **(B)** Preoperative MR showing the regression of liver tumor and tumor thrombi following systemic therapy. **(C)** Curative resection of liver tumor and tumor thrombi in right hepatic vein and inferior vena cava. **(D)** HE staining of surgically resected tumor samples (left) and complete necrosis of the macrovascular tumor thrombi with infiltration of inflammatory cells (right, 200×). **(E)** This case was classified as BCLC stage A, with tumor compression on hepatic vein and inferior vena cava. After the combination therapy, obvious regression of the tumor was observed. The patient underwent curative liver resection and HE staining of resected tumor samples showed massive necrosis without viable tumor cells **(F)**.

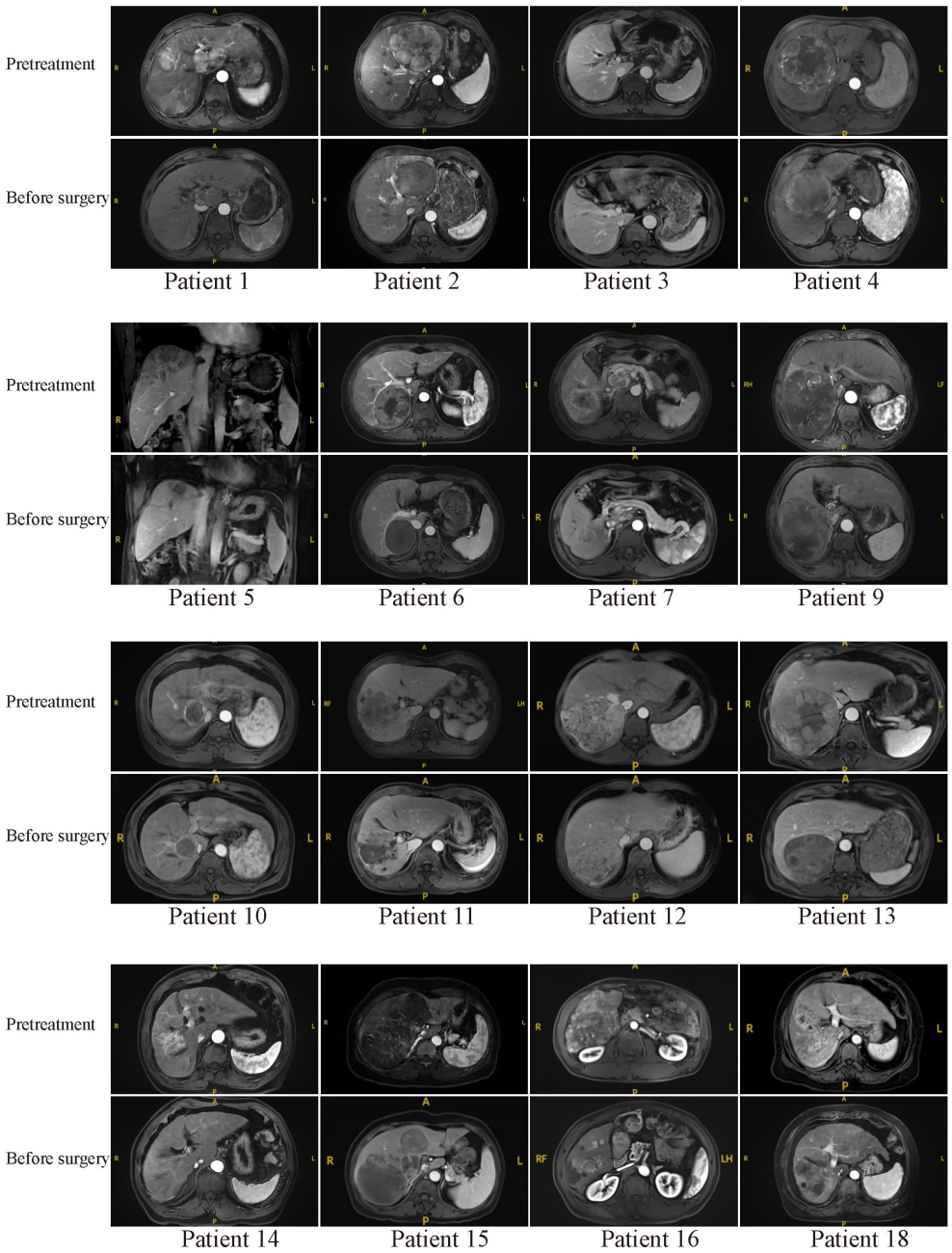

FIGURE 4
Pretreatment and preoperative MR scans of patients 1-18 (except patients 8 and 17).

patients who underwent conversion surgery and the conversion resection rate was 28% (30/107). Notably, the treatment efficacy of the combination therapy could still be underestimated because surgical resection was considered for patients who achieved tumor regression whenever feasible. For example, patients with regressed SD could regress to PR if they continued the systemic therapy rather than surgery. No major postoperative adverse events occurred in these cases. Therefore, lenvatinib plus PD-1 inhibitors can result in downstaging and increase the likelihood of surgical resection in advanced HCC patients, with high potential to prolong their survival.

Postoperative follow-up of the 30 patients revealed that the one-year overall survival rate was 95.7% and the one-year disease-free survival rate was 61.6%, highlighting the

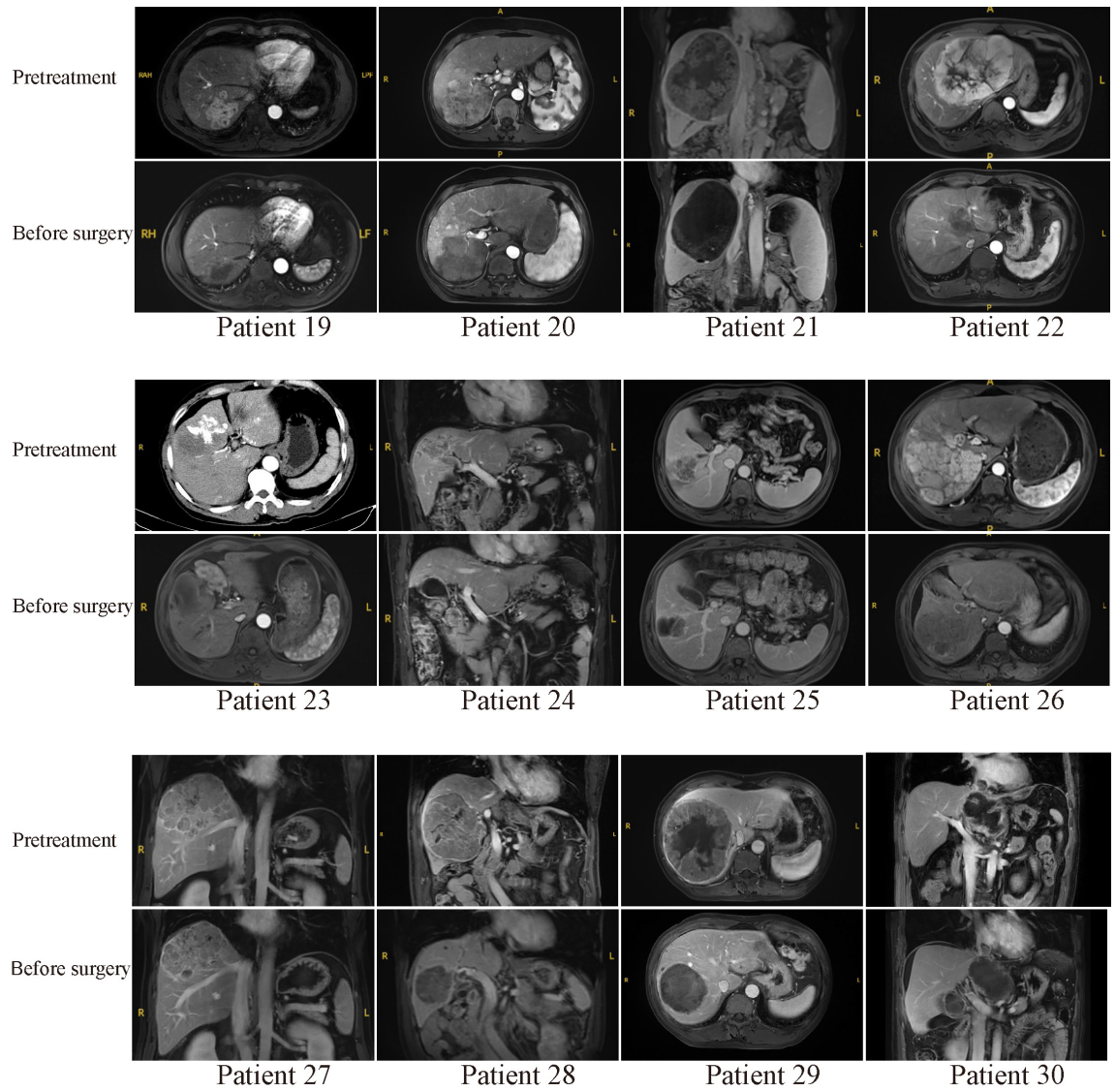

FIGURE 5
Pretreatment and preoperative MR or CT scans of patients 19-30. Patient 23 received emergency hepatic arterial chemoembolization due to rupture of hepatocellular carcinoma in other hospital before combination therapy.

significance of surgical resection in improving survival outcomes. Remarkably, while all these patients displayed tumor shrinkage and underwent conversion surgery, patients achieving CR or PR before surgery had a significantly longer DFS compared with those with SD. The pCR rate was 33.3% (10/30) compared with 60% (6/10) reported before (17) and patients who achieved pCR also had better DFS than those did not. These results suggested that patients with tumor responses, whether evaluated by preoperative imaging or by pathological findings of resected specimens, are more likely to benefit from conversion resection to access a longer term of tumor-free survival.

Tumor recurrence often occurs because micro-metastasis persists even after curative resection. The presence of MVI has been determined to accurately predict the early recurrence and

TABLE 4 Treatment-related AEs in patients receiving lenvatinib plus anti-PD-1 antibody (n = 30).

Preferred AE Term	No. (%)			
	Any Grade[a]	Grade 1	Grade 2	Grade 3
Decrease in platelet count	14 (46.7%)	5 (16.7%)	4 (13.3%)	5 (16.7%)
Proteinuria	10 (33.3%)	1 (3.3%)	6 (20.0%)	3 (10.0%)
Decrease in white blood cell count	8 (26.7%)	2 (6.7%)	3 (10.0%)	3 (10.0%)
Hypertension	6 (20.0%)	0	4 (13.3%)	2 (6.7%)
Hypothyroidism	5 (16.7%)	3 (10.0%)	0	2 (6.7%)
Palmar-plantar erythrodysesthesia syndrome	4 (13.3%)	1 (3.3%)	1 (3.3%)	2 (6.7%)
Increased transaminase	4 (13.3%)	0	2 (6.7%)	2 (6.7%)
Weight decreased	3 (10.0%)	0	3 (10%)	0
Hypoadrenalism	3 (10.0%)	0	0	3 (10.0%)
Myocarditis	3 (10.0%)	2 (6.7%)	0	1 (3.3%)
Gastrointestinal bleeding	2 (6.7%)	0	0	2 (6.7%)
Hyperthyroidism	2 (6.7%)	2 (6.7%)	0	0
Abdominal distension	2 (6.7%)	2 (6.7%)	0	0

[a]Adverse events were graded in accordance with the Common Terminology Criteria for Adverse Events v4.0.

adverse clinical outcomes of HCC patients undergoing liver resection (29–32). In this study, pre-treatment MR scans showed that 20 (20/30, 66.7%) patients had macrovascular invasion, which was not recommended for resection by BCLC guideline. After surgery, MVI was detected in 8 (8/30, 26.7%) resected tumor samples, compared with the MVI incidence of 63% with tumor size larger than 6.5cm reported previously (33), suggesting that lenvatinib plus PD-1 inhibitors could effectively eradicate microvascular tumor thrombi and decrease the positive rate of MVI. Moreover, patients with MVI had significantly shorter tumor-free survival and OS than patients without MVI. This indicated that MVI retained its vital prognostic value in patients receiving conversion surgery. Surgical resection, followed by adjuvant intervention therapy and systemic therapy, could be utilized to reduce the burden of MVI and prolong the survival of this subgroup of patients with MVI, although further investigation is warranted in real world studies.

Safety evaluations revealed that there were no severe (grade 4 or 5) treatment-related adverse events in these patients during the systemic treatment period. Most treatment-related AEs were mild and tolerable, indicating that the drug toxicity can be well addressed and controlled by dynamic monitoring and dose modification in the clinical practice (15).

Several limitations of this study should be noted. First, our study enrolled a relatively small number of HCC patients from a single center although it represented the largest reported cohort of HCC patients receiving conversion

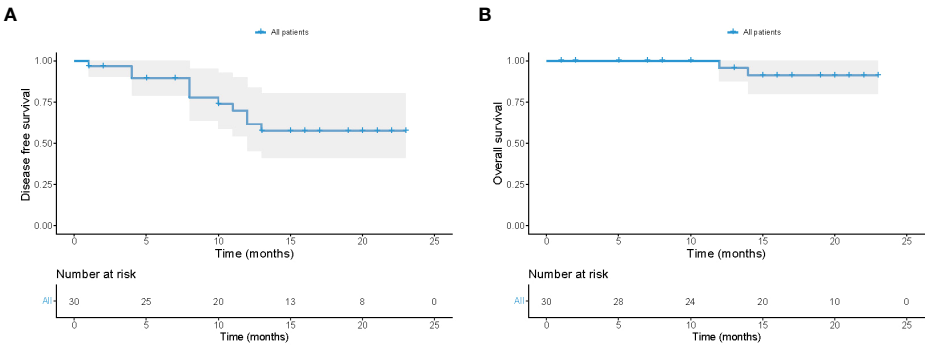

FIGURE 6
Follow-up of all 30 patients receiving conversion surgery. Kaplan-Meier plots of disease-free survival **(A)** and overall survival **(B)** in all 30 patients.

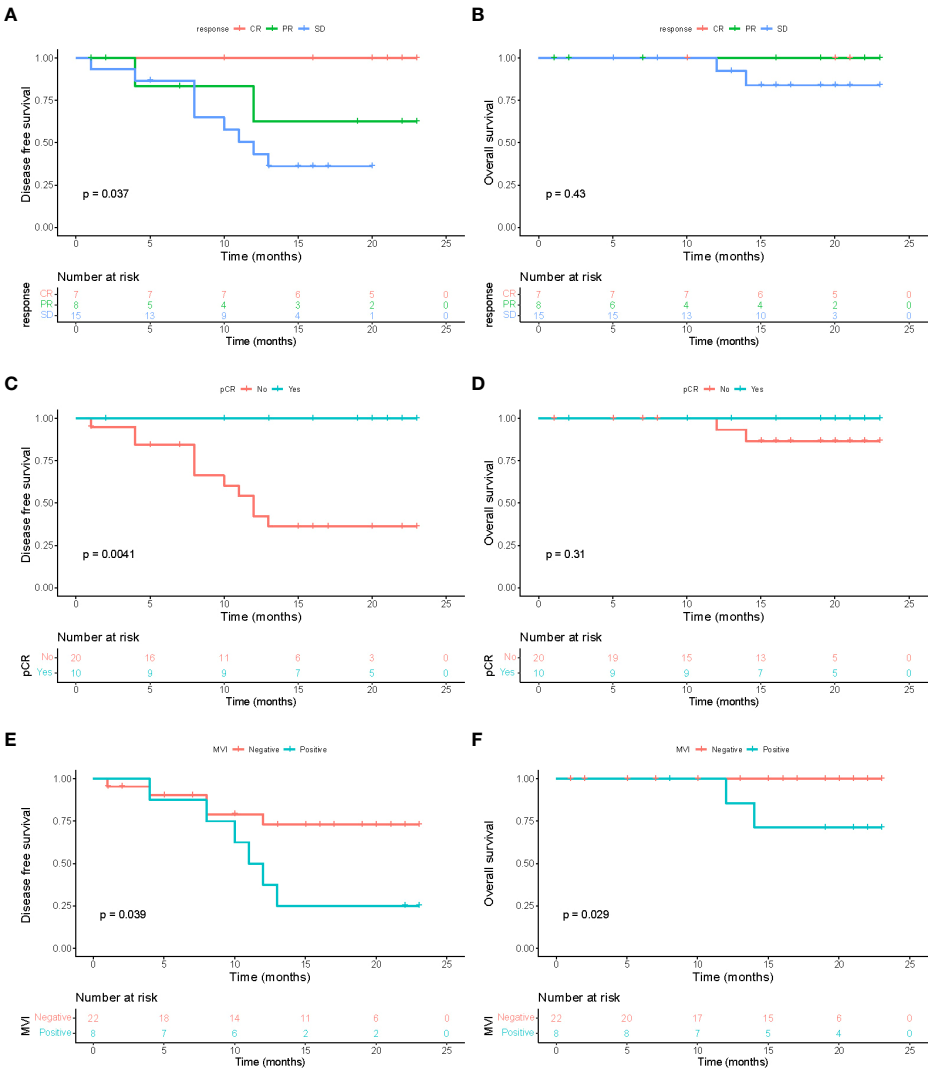

FIGURE 7
Survival analysis. Disease-free survival **(A)** and overall survival **(B)** among patients with different treatment response to combinational therapy evaluated *via* preoperative MR imaging (mRECIST). Disease-free survival **(C)** and overall survival **(D)** between patients who did and did not achieve a pathological complete response (pCR) in all resected specimens. Disease-free survival **(E)** and overall survival **(F)** between patients with and without microvascular invasion (MVI) in resected tumor samples.

surgery so far. The occurrences of adverse events were mainly evaluated according to the blood tests and medical records, thus could be underestimated due to the retrospective nature of our study. Second, the patients in our study were heterogeneous regarding to the regimens of anti-PD-1 monoclonal antibody while no evidence has shown the different effects of these anti-PD-1 antibodies. Thus, this strategy needs prospective validation in a more consistent and large-scale multicenter study in the future.

In conclusion, lenvatinib plus PD-1 inhibitors exhibited promising anti-tumor activity with manageable toxicity. More importantly, this combination treatment strategy results in tumor downsizing and allows patients with unresectable HCC to access surgical resection, with high potential to prolong their long-term survival. Treatment response and MVI status could predict the survival outcomes, especially the tumor-free survival of patients receiving conversion surgery.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by The Ethics Committee of Zhongshan Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Study concept, design, and supervision (S-JQ, NR, JZ, JF), analysis and interpretation of data (YY, B-YS), drafting of the manuscript (B-YS, J-LW, M-HC), acquisition of data (YY, B-YS, CZ), preparation of figures and tables (J-LW, HG), critical revision of the manuscript for important intellectual content (C-HZ, JS), provision of patient tissue samples (CZ, J-YZ). All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Efficacy and safety of transarterial chemoembolization plus antiangiogenic- targeted therapy and immune checkpoint inhibitors for unresectable hepatocellular carcinoma with portal vein tumor thrombus in the real world

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Purpose: This study aimed to assess the efficacy and safety of a triple therapy that comprises transarterial chemoembolization (TACE), antiangiogenic-targeted therapy, and programmed death-1 (PD-1) inhibitors in a real-world cohort of patients with unresectable hepatocellular carcinoma (HCC) with portal vein tumor thrombus (PVTT).

Methods: Consecutive patients treated with TACE combined with antiangiogenic therapy and PD-1 inhibitors at the Eastern Hepatobiliary Surgery Hospital between June 2019 and May 2021 were enrolled. The baseline characteristics and treatment course of the patients were recorded. The tumor response was evaluated based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and HCC-specific modified RECIST (mRECIST). The overall survival (OS) and progression-free survival (PFS) of the patients were analyzed using the Kaplan–Meier method. Adverse events (AEs) were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Results: As of the data cutoff on 30 August 2021, the median follow-up time was 10.0 (3.9–28.4) months. A total of 39 eligible patients were included. The

objective response rate (ORR) and the disease control rate (DCR) were 35.9% and 74.4% according to the RECIST 1.1, and 48.7% and 84.6% according to mRECIST criteria, respectively. The median OS and PFS were 14.0 and 9.2 months, respectively. Moreover, 34 (87.2%) patients experienced at least one treatment-related AE and 8 (20.5%) patients experienced grade 3/4 treatment-related AEs. The most common treatment- and laboratory-related AEs were hypertension (46.2%) and decreased albumin (53.8%), respectively. No treatment-related mortality occurred during the study period.

Conclusions: TACE combined with antiangiogenic-targeted therapy and immune checkpoint inhibitors may have promising anticancer activity in unresectable HCC patients with PVTT. AEs were manageable, with no unexpected overlapping toxicities.

KEYWORDS

hepatocellular carcinoma (HCC), portal vein tumor thrombus (PVTT), transarterial chemoembolization (TACE), anti-angiogenic targeted therapy, PD-1 inhibitor, immune checkpoint inhibitor (ICI), combination therapy

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the fourth-leading cause of cancer-related death worldwide (1). Portal vein tumor thrombus (PVTT) is common in advanced HCC, with a reported incidence of 44%–62.2% (2). If left untreated, the median survival time of these patients is only from 2.7 to 4.0 months (3). PVTT is recognized as an independent prognostic factor for HCC patients (4, 5).

Transarterial chemoembolization (TACE) is the most widely used treatment option for unresectable HCC and has been globally adopted as the standard of care for patients with Barcelona Clinic Liver Cancer (BCLC) stage B HCC (6). Moreover, TACE is proven to be a safe and effective treatment modality for patients with BCLC stage C HCC in the clinical setting (7–9). An established theory holds that TACE stimulates the expression of angiogenic growth factors and promotes the release of an abundance of tumor antigens, which contribute to tumor growth or progression. Since TACE is generally a palliative therapy, it acts as a backbone for the addition of effective systemic therapies aimed at improving survival outcomes.

Recently, increasing studies have investigated the potential clinical role of locoregional–systemic treatments in unresectable HCC patients. Several studies demonstrated that TACE plus sorafenib or lenvatinib significantly improved survival outcomes compared with TACE monotherapy in patients with unresectable HCC (10–12). A single-arm study suggested that the triple therapy approach consisted of PD-1/PD-L1 inhibitors plus radiotherapy, and antiangiogenic therapy appears to be safe with no unexpected adverse events (AEs) (13). A retrospective comparative study found that hepatic arterial infusion chemotherapy (HAIC) combined with PD-1 inhibitors and lenvatinib was associated with a remarkably better treatment response and survival outcomes for patients with advanced HCC compared to patients who received PD-1 inhibitors plus lenvatinib (14). Therefore, the combination of locoregional and systemic therapies is producing exponentially increasing interest in the research field of advanced HCC.

In our study, we focused on a real-world cohort of unresectable HCC patients with PVTT who received a triple therapy approach that comprises TACE plus antiangiogenic-targeted treatment and anti-PD-1 inhibitors (TTP treatment). The therapeutic efficacy and safety of this triple therapy approach were evaluated. We present the following article in accordance with the STROBE reporting checklist.

Materials and methods

Study design and patients

This was a single-arm study to evaluate the efficacy and tolerability of a combination treatment of TACE plus antiangiogenic therapy and anti-PD-1 antibodies in unresectable HCC patients associated with PVTT in the real world. Patients who received TTP treatment to treat HCC with PVTT at the Eastern Hepatobiliary Surgery Hospital of Second Military Medical University between June 2019 and May 2021 were reviewed. The study was conducted in accordance with the

Declaration of Helsinki (as revised in 2013). The study was approved by the institutional ethics committee of Eastern Hepatobiliary Surgery Hospital, and individual consent for this retrospective analysis was waived. All laboratory serum examination data were collected 3 days before the initial treatment. Imaging evaluation comprised contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) examination within 1 week before the initial treatment. All the data were censored on 30 August 2021.

Inclusion and exclusion criteria

The inclusion criteria included the following: (I) unresectable HCC and PVTT confirmed radiologically or histologically according to the AASLD practice guidelines (15); (II) Child–Pugh class A or B liver function; (III) Eastern Cooperative Oncology Group (ECOG) performance status 0–1; (IV) at least one measurable tumor lesion as defined by modified Response Evaluation Criteria in Solid Tumors (mRECIST); (V) at least one follow-up imaging assessment; and (VI) at least one cycle of anti-PD-1 antibody treatment. The exclusion criteria included the following: (I) patients who had the triple therapy as an adjuvant treatment after surgery; (II) patients who had initially unresectable disease were downstaged for surgical resection after TTP treatment; (III) history of other malignancies; and (VI) medical and follow-up data were incomplete or unavailable.

Treatment protocols

TACE was performed according to previously described procedures. Briefly, a 4–5 French catheter was selectively introduced through a femoral artery into the hepatic artery using the Seldinger technique. Arterioportogram was performed to assess tumor staining and vascularity. The tip of the microcatheter was directly advanced into the tumor-feeding arteries depending on the tumor size and location. An emulsion of pirarubicin (30 mg), fluorouracil, oxaliplatin, and lipiodol (10–30 ml; 1–2 ml/cm diameter of the tumor; Lipiodol Ultrafluide, Guerbet, Aulnay-Sous-Bois, France) was infused. Oxaliplatin (100mg or 65 mg/m^2 body surface area) was dissolved in 5 ml of normal saline and infused slowly with a rate of 1 ml/min. Fluorouracil (500 mg or 330 mg/m^2 body surface area) was injected slowly within 10 min. Gelfoam fragments were then injected to embolize the tumor-feeding vessels until stasis of blood flow was achieved. The dosages of lipiodol were determined by the body surface area and underlying liver function. On-demand TACE was conducted repeatedly when the intrahepatic lesion was not fully necrotic and the active area was greater than 50% of the baseline until unTACEable progression occurred. UnTACEable progression was defined as the circumstances in which patients were not capable to benefit from TACE, such as Child–Pugh class C, intrahepatic progression, with new lesions not defined as tumor progression.

Antiangiogenic-targeted agents, including tyrosine kinase inhibitors (sorafenib, lenvatinib, and anlotinib) and vascular endothelial growth factor (VEGF) blockade (apatinib), were administered orally. Sorafenib was given 400 mg/day initially and increased to 800 mg/day in a stepwise manner if tolerated. The dosage of lenvatinib was 8 mg/day (<60 kg) or 12 mg/day (≥60 kg) depending on body weight. Anlotinib was prescribed 12 mg/day during weeks 1–2 of each 3-week cycle. Apatinib was prescribed 500 mg/day initially and increased to 750 mg/day if tolerated.

In this study, four types of PD-1 inhibitors (sintilimab, toripalimab, camrelizumab, and tislelizumab) were used at the standard dose intravenously. The first use of PD-1 inhibitors was within 7 days of the initiation of antiangiogenic-targeted drugs. Patients received targeted drugs and PD-1 inhibitors within 3 days before or after the start of TACE. Dosage reduction or the discontinuation of treatment depended on disease progression, unacceptable toxicity, a patient's withdrawal of consent, or the changes of a treatment plan.

For patients with progressive disease (PD) after TTP therapy, patients could transfer to other recommended combination treatments, such as radiotherapy plus molecular-targeted drugs and PD-1 inhibitor triple therapy, or TACE plus radiotherapy, molecular-targeted drugs and PD-1 inhibitor quadruple therapy, or atezolizumab plus bevacizumab (T+A) first-line therapy. The subsequent therapeutic methods for PD patients were determined after the full discussions of the multidisciplinary treatment meetings, and the final treatment decisions mainly depended on the economic capability of patients.

Treatment efficacy and safety evaluation

The radiological response was evaluated by dynamic CT or magnetic resonance imaging (MRI) at baseline and every 6–12 weeks after the initial treatment. The tumor response including the objective response rate (ORR) and disease control rate (DCR) was assessed in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and HCC-specific modified RECIST (mRECIST). The ORR was calculated as the sum of the complete response (CR) and partial response (PR). DCR was defined as the sum of the CR, PR, and stable disease (SD). Overall survival (OS) was defined as the time interval from the date of treatment initiation to the date of death or the most recent follow-up visit. Progression-free survival (PFS) referred to the time interval from treatment initiation to the first radiologically confirmed PD or death. Treatment safety was continuously evaluated by clinical vital signs and laboratory

tests. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Statistical analysis

Continuous variables were reported as median (interquartile range) or mean ± standard deviation (SD) and compared using Student's t-test or the Mann–Whitney U test according to the normality of data. Categorical variables were presented as frequency (percentage) and compared using Pearson's chi-square test or Fisher's exact test as appropriate. OS and PFS were estimated using the Kaplan–Meier method. Differences in survival curves were analyzed with a log-rank test. Univariate Cox regression analysis was used to evaluate the significance of potential variables associated with OS and PFS. Variables that were significantly related to OS and PFS ($P < 0.05$) were incorporated into multivariate Cox regression analysis. A two-tailed P value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 26.0 software (SPSS Inc., Chicago, IL, USA) and GraphPad Prism, Version 8.2.0 (GraphPad, Inc.).

Results

Identification and characteristics of study patients

From June 2019 to May 2021, 72 advanced HCC patients with PVTT who underwent TTP (TACE + antiangiogenic-targeted therapy + anti-PD-1 antibodies) were identified from the electronic medical system of our hospital. A total of 22 patients received TTP as an adjuvant treatment after surgery. Six patients were treated with TTP as a conversion therapy for subsequent surgical resection. Five patients were lost to follow-up during investigation. Finally, a total of 39 patients who met the eligibility criteria were included in the study. The patients' identification process is shown in Figure 1.

The baseline demographic and clinical characteristics of unresectable HCC patients with PVTT are listed in Table 1. The majority of patients had HBV-associated HCC, and 25.6% of patients had Child–Pugh class B liver function. Liver cirrhosis was observed in 89.7% of patients. All patients were classified as BCLC stage C due to major vascular invasion. The median size of the baseline target lesions was 10.0 cm [interquartile range (IQR), 7.5–12.0 cm]. Two-thirds of patients had multiple tumors. With regard to the extent of PVTT, 66.7% and 25.6% of patients had type II and III PVTT, respectively. A total of 10 patients had combined hepatic vein or inferior vena cava tumor thrombus. Regional or distant lymph node metastasis occurred in nearly half of patients. A total of eight patients had extrahepatic disease spread, including five in the lungs and three in the adrenal gland. The median level of α-fetoprotein (AFP) was 1,509 ng/ml (IQR, 10.1–32,280 ng/ml). The median concentration of protein induced by vitamin K absence or antagonist-II (PIVKAII) was 5,413 mAU/ml (IQR, 617–47,033 mAU/ml). Twenty-two patients had an HBV-DNA level exceeding 1,000 copies/ml.

Number of transarterial chemoembolization procedures and transarterial chemoembolization interval time

A total of 13 patients underwent one session of TACE, and the other 26 patients received two or more sessions of TACE. The median interval between each TACE treatment was 79.8 days (Table 2).

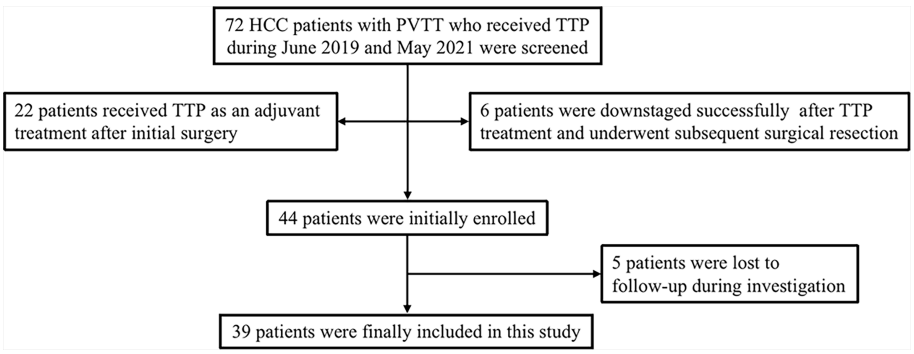

FIGURE 1
Flow diagram of patient enrollment. HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; TTP, TACE plus antiangiogenic-targeted treatment and anti-PD-1 inhibitors.

TABLE 1 Baseline demographic and clinical characteristics of unresectable hepatocellular carcinoma (HCC) patients with portal vein tumor thrombus (PVTT).

Characteristics	All patients (n=39)
Age, median (range), years	56 (31–69)
<60	29 (74.4%)
≥60	10 (25.6%)
Gender	
Male	33 (84.6%)
Female	6 (15.4%)
Hypertension	
Yes	7 (17.9%)
No	32 (82.1%)
Diabetes mellitus	
Yes	4 (10.3%)
No	35 (89.7%)
Antiviral therapy	
Yes	22 (56.4%)
No	17 (43.6%)
Child–Pugh class	
A	29 (74.4%)
B	10 (25.6%)
ALBI score, median (Q1, Q3)	-2.14 (-2.47, -1.94)
ALBI grade	
1	6 (15.4%)
2	31 (79.5%)
3	2 (5.1%)
Etiology	
Hepatitis B	38 (97.4%)
Hepatitis C	1 (2.6%)
Cirrhosis	
Yes	35 (89.7%)
No	4 (10.3%)
Tumor number	
Single	13 (33.3%)
Multiple	26 (66.7%)
Tumor size (cm), median (Q1, Q3)	10.0 (7.5–12.0)
≤5	2 (5.1%)
5–10	19 (48.7%)
>10	18 (46.2%)
Tumor distribution	
Left lobe	5 (12.8%)
Right lobe	25 (64.1%)
Bi-lobe	9 (23.1%)
PVTT type	
I	3 (7.7%)
II	26 (66.7%)
III	10 (25.6%)
Combined HVTT/IVCTT, yes	10 (25.6%)
HVTT	8 (20.5%)
IVCTT	2 (5.1%)
Lymph node metastasis	
Yes	19 (48.7%)
No	20 (51.3%)
Extrahepatic spread, yes	8 (20.5%)
Lung	5 (12.8%)
Adrenal gland	3 (7.7%)
Esophagogastric varices	
Presence	19 (48.7%)
Absence	20 (51.3%)
PT (s), median (Q1, Q3)	12.2 (11.9–13.2)
INR, median (Q1, Q3)	1.02 (0.99–1.10)
WBC (*10^9/L), mean ± SD	5.4 ± 2.2
RBC (*10^12/L), mean ± SD	4.3 ± 0.7
HGB (g/L), mean ± SD	131.1 ± 22.1
PLT (g/L), mean ± SD	146.8 ± 70.4
TBil (μmol/L), median (Q1, Q3)	17.3 (13.1–22.6)
ALB (g/L), mean ± SD	38.2 ± 3.8
ALT (U/L), median (Q1, Q3)	41 (29–59)
AST (U/L), median (Q1, Q3)	59 (46–124)
GGT (U/L), median (Q1, Q3)	192 (116–371)
ALP (U/L), median (Q1, Q3)	144 (109–200)
BUN (mmol/L), median (Q1, Q3)	4.52 (3.77–5.02)
Creatinine (μmol/L), median (Q1, Q3)	67 (57–78)
Glucose (mmol/L), median (Q1, Q3)	4.87 (4.37–5.19)
AFP (ng/ml), median (Q1, Q3)	1,509 (10.1–32,280)
<400	15 (38.5%)
≥400	24 (61.5%)
PIVKAII (mAU/ml), median (Q1, Q3)	5,413 (617–47,033)
< 2,050	14 (35.9%)
≥ 2,050	25 (64.1%)
HBV-DNA, copies/ml	
<50	9 (23.7%)
50–1,000	7 (18.4%)
≥1,000	22 (57.9%)

HCC, hepatocellular carcinoma; PVTT, portal vein tumor thrombus; ALBI, albumin-bilirubin; HVTT, hepatic vein tumor thrombus; IVCTT, inferior vena cava tumor thrombus; PT, prothrombin time; INR, international normalized ratio; WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; PLT, platelet; TBil, total bilirubin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltranspeptidase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; AFP, alpha-fetoprotein; PIVKAII, protein induced by vitamin K absence or antagonist-II.

Types of antiangiogenic-targeted drugs and anti-PD-1 antibodies

For antiangiogenic-targeted drugs, 30 patients initially used lenvatinib, and the remaining 9 patients initially used sorafenib. During the treatment course, because of unacceptable AEs or progressed disease, five patients initially using sorafenib converted to lenvatinib or anlotinib, whereas two patients initially using lenvatinib converted to anlotinib or apatinib. As

TABLE 2 Number of transarterial chemoembolization (TACE) procedures and treatment intervals.

	All patients (n=39)
Number of TACE procedures, n (%)	
1	13 (33.3%)
2	15 (38.5%)
3	8 (20.5%)
4	1 (2.6%)
5	2 (5.1%)
Median interval between TACE (days), mean (SD)	79.8 (53.5)

TACE, transarterial chemoembolization.

for anti-PD-1 antibodies, 16 used sintilimab, 14 had camrelizumab, 6 were treated with toripalimab, and the other 3 patients received tislelizumab. Among them, one patient who was initially treated with sintilimab converted to camrelizumab due to infusion-related reactions (Table 3).

Change of tumor marker expression

The changes of tumor marker levels from the baseline to the first follow-up after the triple treatment approach are shown in Table 4. The median AFP level at the baseline was 1,509 ng/ml, while this level dropped dramatically to 135 ng/ml at the first follow-up (P = 0.126). From a dichotomous point, 15 (38.5%) patients had an AFP level not greater than 400 ng/ml at the baseline, whereas 25 (64.1%) patients had an AFP level within 400 ng/ml at the first follow-up after the triple therapy (P = 0.023). For PIVKAII, the median baseline level was 5,413 mAU/ml, and this level decreased markedly to 950 mAU/ml at the first follow-up (P = 0.003). For HBV-DNA, the median concentration at the baseline was 6,240 copies/ml, which reduced remarkably to 36 copies/ml at the first follow-up (P < 0.001).

TABLE 3 Types of antiangiogenic-targeted drugs and anti-PD-1 antibodies.

	All patients (n=39)
Initial treatments	
Antiangiogenic-targeted drugs	
Sorafenib	9 (23.1%)
Lenvatinib	30 (76.9%)
Anti-PD-1 antibodies	
Sintilimab	16 (41.0%)
Toripalimab	6 (15.4%)
Camrelizumab	14 (35.9%)
Tislelizumab	3 (7.7%)
Whole clinical treatment pathway	
Antiangiogenic-targeted drugs	
Sorafenib	9 (23.1%)
Lenvatinib	35 (89.7%)
Anlotinib	2 (5.1%)
Apatinib	1 (2.6%)
Anti-PD-1 antibodies	
Sintilimab	16 (41.0%)
Toripalimab	6 (15.4%)
Camrelizumab	15 (38.5%)
Tislelizumab	3 (7.7%)

Change of liver function

As shown in Table 5, the Child–Pugh class and the ALBI grade were used to assess the hepatic functional reserve in the baseline and the first follow-up after the triple therapy. There was no significant change of liver function between the baseline and the first follow-up after treatment in either the Child–Pugh class or the ALBI grade (P = 0.151 and P = 0.842).

Additional treatments aside from the triple therapy

As shown in Table 6, five (12.8%) patients received additional radiation treatment that was targeted at liver lesions or extrahepatic metastasis. Six (15.4%) patients underwent synchronous percutaneous microwave coagulation therapy. One patient ceased the triple therapy after six cycles of PD-1 treatment and converted to atezolizumab plus bevacizumab (T+A therapy). Four (10.3%) patients received the best supportive care during the treatment course due to liver function deterioration.

Efficacy outcomes

As of the data cutoff on 30 August 2021, the median follow-up time was 10.0 (3.9–28.4) months. Disease progression occurred in 18 (46.2%) patients, and 13 (33.3%) patients died. The median OS was 14.0 months. The 3-, 6-, and 12-month OS was 94.9%, 83.7%, and 57.9%, respectively (Figure 2A). The median PFS was 9.2 months. The 3-, 6-, and 12-month PFS was 74.4%, 58.2%, and 49.6%, respectively (Figure 2B). The best tumor response is summarized in Table 7. The ORR and DCR were 35.9% and 74.4% according to the RECIST 1.1 and 48.7% and 84.6% according to mRECIST criteria, respectively.

Furthermore, as shown in Figure 3, we did subgroup survival analysis according to administered drugs and the number of TACE procedures. No significant differences in OS and PFS were observed for patients initially using sorafenib or lenvatinib (P = 0.92, Figure 3A; P = 0.96, Figure 3B). Similarly, there were no marked OS and PFS differences among patients who were treated with various anti-PD-1 inhibitors (P = 0.22, Figure 3C;

TABLE 4 Change of tumor marker expression.

	Baseline	First follow-up after TTP treatment	*P*-value
AFP (ng/ml), median (Q1, Q3)	1,509 (10.1–32,280)	135 (4.7–9,427)	0.126
PIVKAII (mAU/ml), median (Q1, Q3)	5,413 (617–47,033)	950 (34–11,386)	**0.003**
HBV-DNA (copies/ml)	6,240 (54.7–532,750)	36 (2–191.3)	< **0.001**
HCV-RNA (copies/ml)	55,200	150,000	NA
AFP (ng/ml)			**0.023**
<400	15 (38.5%)	25 (64.1%)	
≥400	24 (61.5%)	14 (35.9%)	
PIVKAII (mAU/ml)			**0.007**
<2,050	14 (35.9%)	26 (66.7%)	
≥2,050	25 (64.1%)	13 (33.3%)	
HBV-DNA (copies/ml)			< **0.001**
<1,000	16 (42.1%)	34 (89.5%)	
≥1,000	22 (57.9%)	4 (10.5%)	

TTP, TACE + antiangiogenic-targeted therapy + anti-PD-1 antibody treatment; AFP, alpha-fetoprotein; PIVKAII, protein induced by vitamin K absence or antagonist-II; HBV-DNA, hepatitis B virus deoxyribonucleic acid; NA, data not available.
P-values in bold denote statistical significance.

TABLE 5 Change of liver function.

	Baseline	First follow-up after TTP treatment	*P*-value
Child–Pugh class			0.151
A	29 (74.4%)	34 (87.2%)	
B	10 (25.6%)	5 (12.8%)	
ALBI grade			0.842
1	6 (15.4%)	7 (17.9%)	
2	31 (79.5%)	29 (74.4%)	
3	2 (5.1%)	3 (7.7%)	

TTP, TACE + antiangiogenic targeted therapy + anti-PD-1 antibody treatment; ALBI, albumin–bilirubin.

TABLE 6 Additional treatments aside from TACE + antiangiogenic targeted therapy + anti-PD-1 antibody treatment.

	All patients (n=39)
Radiotherapy	5 (12.8%)
PMCT	6 (15.4%)
T+A	1 (2.6%)
BSC	4 (10.3%)

TTP, TACE + antiangiogenic targeted therapy + anti-PD-1 antibody treatment; PMCT, percutaneous microwave coagulation therapy; T+A, atezolizumab combined with bevacizumab; BSC, best supportive care.

$P = 0.30$, Figure 3D). Repeated TACE appeared to show survival advantage over a single TACE treatment, but the statistical difference was not significant ($P = 0.08$, Figure 3E; $P = 0.48$, Figure 3F). The results of subgroup survival analysis according to (I) the types of PVTT, (II) the presence or absence of concurrent HVTT/IVCTT, (III) the tumor number, and (IV) tumor size are illustrated in Figure 4. As shown in Figure S1, patients who received additional treatments (radiotherapy, percutaneous microwave coagulation therapy, or T+A) had significantly better OS than those who did not ($P = 0.046$, Figure S1A). The PFS of patients who underwent additional treatments was also better compared with that of patients who did not but without statistical significance ($P = 0.14$, Figure S1B). The results of the univariate analysis of OS and PFS are displayed in Table S1. The association between the different cycles of TTP therapy and liver function and tumor marker expression change can be seen in Figure S2.

Safety outcomes

Treatment- and laboratory-related AEs including frequency and the severity grade were evaluated according to CTCAE, version 5.0. A total of 34 (87.2%) patients experienced at least

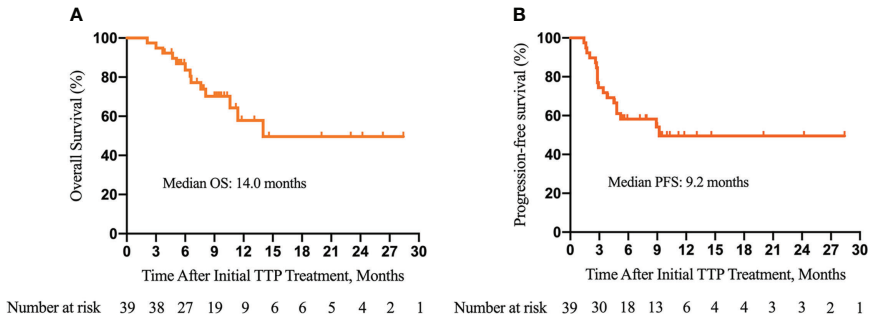

FIGURE 2
Kaplan–Meier survival curves of overall survival (OS) **(A)** and progression-free survival (PFS) **(B)** of patients with unresectable hepatocellular carcinoma and portal vein tumor thrombus (PVTT) who underwent the triple therapy. TTP, transarterial chemoembolization (TACE) plus antiangiogenic-targeted treatment and anti-PD-1 inhibitors.

TABLE 7 Summary of the best tumor response.

	All patients (n=39) mRECIST	All patients (n=39) RECIST 1.1
CR	3 (7.7%)	3 (7.7%)
PR	16 (41.0%)	11 (28.2%)
SD	14 (35.9%)	15 (38.5%)
PD	6 (15.4%)	10 (25.6%)
ORR	19 (48.7%)	14 (35.9%)
DCR	33 (84.6%)	29 (74.4%)

Tumor response was assessed using mRECIST and RECIST 1.1 criteria, respectively. Data are presented as n (%).
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

one treatment-related AE, and 8 (20.5%) patients experienced grade 3/4 treatment-related AEs. The most common treatment-emergent AE of all grade was hypertension (46.2%) followed by diarrhea (35.9%), fatigue (30.8%), PPE (25.6%), weight loss (23.1%), skin pruritis (20.5%), and nausea (20.5%). The most common laboratory-related AE of all grades was decreased albumin (53.8%) followed by thrombocytopenia (41.0%), increased aspartate aminotransferase (30.8%), increased γ-glutamyltranspeptidase (25.6%), increased alanine aminotransferase (23.1%), neutropenia (23.1%), and hyperbilirubinemia (20.5%). In addition, the most common grade 3/4 treatment-emergent AE was hypertension (20.5%), while the most common grade 3/4 laboratory-related AE was thrombocytopenia (10.3%) (Table 8).

Discussion

PVTT remains as the bottleneck in the treatment of HCC, which contributes to high recurrence rates and a poor prognosis. According to the BCLC staging system, HCC with PVTT is graded as the advanced stage, which often precludes the opportunity of surgical resection (6). As a chance for cure, molecular-targeted therapy and PD-1 blockades have revolutionized cancer treatment and drastically changed the treatment landscape for advanced HCC with PVTT.

The gradually evolving role of systemic therapy for advanced HCC has been documented (16, 17). The regulating effect of small molecular-targeted drugs on the tumor microenvironment tends to increase the therapeutic effect of PD-1 inhibitors and vice versa (18). This triggers the combination therapy of immune checkpoint inhibitors (ICIs) with angiogenic targeted drugs for unresectable HCC. A meta-analysis showed that ORR and DCR were 29% (95% CI 0.15–0.43) and 77% (95% CI 0.70–0.84) for patients treated with PD-1/PD-L1 monoclonal antibodies combined with anti-VEGF agents (19). A single-arm retrospective study showed that sintilimab plus tyrosine kinase inhibitors (TKIs) exhibited promising efficacy with tolerable adverse reactions in unresectable HCC (20).

It is notable that locoregional therapies (LRTs) can induce the release of inflammatory and proangiogenic factors and neoantigens and increase the expression of PD-1 and PD-L1; systemic drugs are administered as an adjuvant therapy in combination with LRTs (21–23). Two prospective studies showed that TACE plus lenvatinib is safe, is well tolerated, and has satisfactory efficacy for the treatment of HCC with PVTT (24, 25). Stereotactic body radiotherapy (SBRT) combined with ICIs was reported to have an impressive tumor control capability for patients with unresectable HCC of large tumors (26). In addition, propensity score matching (PSM) analysis suggested that bigeminal therapy with PD-1 blockade plus radiofrequency ablation (RFA) was superior to RFA alone for the long-term survival of recurrent HCC patients (27).

Recently, a triple therapy of TKIs in combination with PD-1 inhibitors and LRTs to treat unresectable HCC patients has

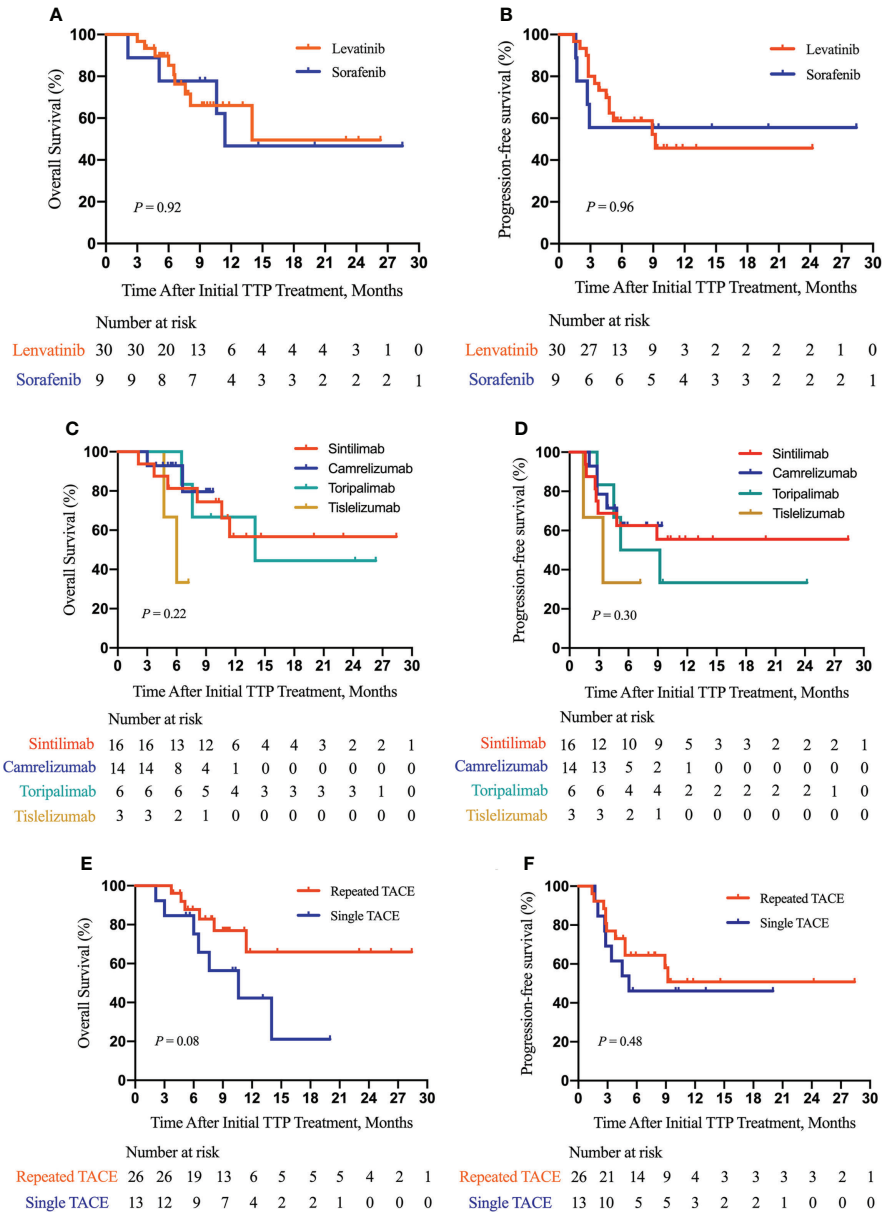

FIGURE 3
Subgroup survival analysis according to the type of molecular targeted drugs, the type of PD-1 inhibitors, and the number of TACE procedures. Subgroup analysis of OS **(A)** and PFS **(B)** according to the type of molecular targeted drugs; a subgroup analysis of OS **(C)** and PFS **(D)** according to the type of PD-1 inhibitors; a subgroup analysis of OS **(E)** and PFS **(F)** according to the number of TACE procedures. TTP, TACE plus antiangiogenic-targeted treatment and anti-PD-1 inhibitors; TACE, transarterial chemoembolization.

gathered much attention and yielded substantial clinical benefits (28, 29). Dai et al. (30) found that the median OS and PFS were 13.0 and 5.0 months, respectively, for inoperable HCC patients who underwent sintilimab combined with sorafenib and TACE. The ORR and DCR were 28.6% and 80.0%, respectively. Teng et al. (31) reported the therapeutic efficacy of TACE plus ICIs and lenvatinib in unresectable HCC. The results showed that the ORR and DCR were 54.9% and 84.3%, respectively, and the median PFS was 8.5 months. Nearly one-third of the patients experienced grade ≥ 3 AEs. Cai et al. (32) showed that the TACE-lenvatinib-PD-1 inhibitor (TACE-L-P) group had a median OS of 16.9 months and a median PFS of 7.3 months. The ORR and DCR of the TACE-L-P group were 56.1% and 85.4%, respectively. A multicenter study recorded that the

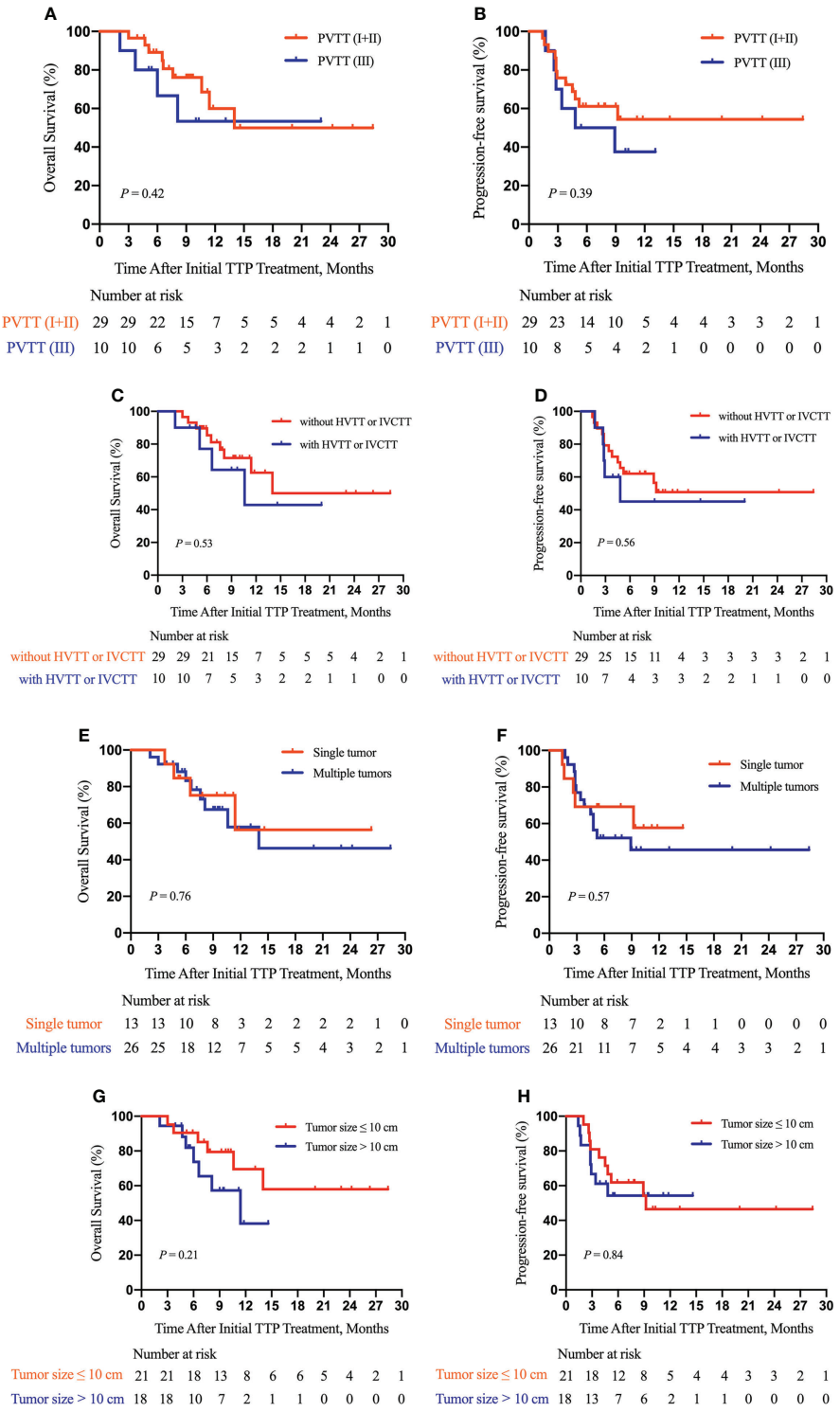

FIGURE 4
Subgroup survival analysis according to the type of PVTT, the presence or absence of hepatic vein tumor thrombus (HVTT)/inferior vena cava tumor thrombus (IVCTT), the tumor number, and tumor size. Subgroup analysis of OS **(A)** and PFS **(B)** according to the type of PVTT; a subgroup analysis of OS **(C)** and PFS **(D)** according to the presence or absence of HVTT/IVCTT; a subgroup analysis of OS **(E)** and PFS **(F)** according to the tumor number; a subgroup analysis of OS **(G)** and PFS **(H)** according to tumor size. TTP, TACE plus anti-angiogenic-targeted treatment and anti-PD-1 inhibitors; PVTT, portal vein tumor thrombus; HVTT, hepatic vein tumor thrombus; IVCTT, inferior vena cava tumor thrombus.

TABLE 8 Summary of adverse events.

Adverse events	Any Gradesn (%)	Grade 3/4n (%)
Treatment-related AEs		
Skin and subcutaneous tissue		
Palmar-plantar erythrodysesthesia	10 (25.6%)	0 (0.0%)
Skin pruritus	8 (20.5%)	1 (2.6%)
Skin rash	6 (15.4%)	1 (2.6%)
Cardiovascular system		
Hypertension	18 (46.2%)	8 (20.5%)
Digestive system		
Diarrhea	14 (35.9%)	1 (2.6%)
Nausea	8 (20.5%)	1 (2.6%)
Gastrointestinal hemorrhage	1 (2.6%)	0 (0.0%)
Kidney and urinary system		
Proteinuria	3 (7.7%)	2 (5.1%)
Nervous system		
Headache	4 (10.3%)	0 (0.0%)
Chest and mediastinum		
Dysphonia	6 (15.4%)	0 (0.0%)
Endocrine system		
Hypothyroidism	4 (10.3%)	0 (0.0%)
Metabolism and nutrition		
Decreased appetite	7 (17.9%)	1 (2.6%)
Weight loss	9 (23.1%)	0 (0.0%)
Systemic symptoms		
Fatigue	12 (30.8%)	0 (0.0%)
Fever	4 (10.3%)	1 (2.6%)
Peripheral edema	2 (5.1%)	0 (0.0%)
Laboratory-related AEs		
Blood biochemistry		
Hyperbilirubinemia	8 (20.5%)	1 (2.6%)
Alanine aminotransferase increased	9 (23.1%)	1 (2.6%)
Aspartate aminotransferase increased	12 (30.8%)	1 (2.6%)
Albumin decreased	21 (53.8%)	0 (0.0%)
γ-Glutamyltranspeptidase increased	10 (25.6%)	1 (2.6%)
Creatinine increased	1 (2.6%)	0 (0.0%)
Blood routine tests		
Anemia	7 (17.9%)	0 (0.0%)
Thrombocytopenia	16 (41.0%)	4 (10.3%)
Neutropenia	9 (23.1%)	0 (0.0%)

The adverse events related with antiangiogenic-targeted drugs and anti-PD-1 antibodies were graded according to Common Terminology Criteria Adverse Events (CTCAE) Version 5.0.

investigator and blinded independent central review–assessed ORR were 80.6% and 77.4%, respectively, for unresectable HCC patients who underwent the triple therapy. Of 62 included cases, 33 (53.2%) patients reached the standard of successful conversion to resectable disease; 16 (25.8%) and 24 (38.7%) patients had complete and major pathological response, respectively (33).

To the best of our knowledge, our study is the first to explore the clinical efficacy and safety of the triple therapeutic approach consisting of TACE, anti-angiogenic therapy, and PD-1 inhibitors in unresectable HCC patients with PVTT. Regarding the safety of the triple therapy, our study showed that 34 (87.2%) patients experienced at least one treatment-related AE, 8 (20.5%) patients experienced grade 3/4 treatment-related AEs, and no treatment-related death occurred. The incidence rates of overall and severe AEs were similar to the previous reports, which proved the acceptable safety profile of the triple therapy in this patient population. With respect to the treatment response and survival outcomes following the triple therapy, the ORR and DCR based on the mRECIST criteria were 48.7% and 84.6%, respectively; and the median OS and PFS were 14.0 and 9.2 months, respectively. The efficacy outcomes were comparable to some previous results (13, 30–32). However, our tumor response rates were lower than those reported by Wu et al. (33). The patient selection difference may be the possible reason as 56.5% patients in their study cohort did not have PVTT. Therefore, based on the above analysis, the triple therapy could result in good efficacy for unresectable HCC with PVTT. TACE, molecular-targeted drugs, and ICIs may have synergistic effects and augment the antitumor activity mutually. However, the mechanisms underlying the triple therapy still need further investigations.

The present study had several limitations. First, this was a retrospective study with a limited sample size and a short follow-up time, contributing to potential selection bias and relatively insufficient medical evidence. Second, this study was a single-arm study with no control group, so it was impossible to compare the efficacy and safety of this triple therapy with other combined therapeutic approaches. Third, the substantial heterogeneity of the study population and the inconformity of treatment regimens may influence the interpretation of our findings. Thus, prospective studies with a large sample size are required to determine whether combining TACE, antiangiogenic agents, and PD-1 inhibitors potentiates clinical efficacy.

Conclusion

TACE in combination with antiangiogenic-targeted therapy and PD-1-targeted immunotherapy displayed promising tumor control rates with well-tolerated toxicity in unresectable HCC patients associated with PVTT in the real world. Thus, this triple therapeutic strategy may be an ideal treatment option for these patients. In the future, the identification of molecular biomarkers to select patients who are most likely to benefit from the triple therapy should be highlighted.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by institutional ethics committee of Eastern Hepatobiliary Surgery Hospital. The ethics committee waived the requirement of written informed consent for participation.

Author contributions

Conceptualization and design: S-QC, JZ, J-KF, Z-HL, Z-GF. Administrative support and funding acquisition: S-QC. Provision of study materials or patients: S-QC, JZ, Z-GF, Z-TC, J-XS, KW, Y-QC, L-PZ, JS, W-XG. Collection and assembly of data: J-KF, Z-HL, Z-GF, H-FZ, Y-JX. Data analysis and interpretation: J-KF, Z-HL, Z-GF. Manuscript writing: J-KF. Manuscript review and editing: S-QC, JZ. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.954203/full#supplementary-material

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Prognostic efficacy and prognostic factors of TACE plus TKI with ICIs for the treatment of unresectable hepatocellular carcinoma: A retrospective study

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Hepatocellular carcinoma (HCC) remains a global challenge due to its high morbidity and mortality rates as well as poor response to treatment. Local combined systemic therapy is widely used in the treatment of unresectable hepatocellular cancer (uHCC). This retrospective study was to investigate the prognostic effect and prognostic factors of transcatheter arterial chemoembolization (TACE) plus tyrosine kinase inhibitors (TKI) with immune checkpoint inhibitors (ICIs) in the treatment of uHCC. A retrospective analysis of 171 patients with uHCC was performed in our hospital from April 27, 2015 to October 18, 2021. According to different treatment options, patients were divided into TACE group (n=45), TACE+TKI group (n=76) and TACE+TKI+ICIs group (n=50). In this study, we found that, the median overall survival (mOS) of TACE+TKI+ICIs group was significantly better than TACE+TKI group and TACE group [24.1 (95% CI 15.1-33.1) months vs 14.9 (95% CI 10.7-19.1) months vs 11.4 (95% CI 8.4-14.5) months, hazard ratio (HR) 0.62; 95% CI 0.47-0.81; P=0.002]. A visible difference in the median progression-free survival (mPFS) interval between the groups was discovered [10.6 (95% CI6.5-14.7) months in TACE+TKI+ICIs group vs. 6.7 (95% CI 5.5-7.9) months in the TACE+TKI group vs. 6 (95% CI 2.3-9.7) months in the TACE group (HR 0.66; 95% CI 0.53-0.83; P<0.001)]. The objective response rates (ORR) in the TACE group, TACE+TKI group, and TACE +TKI+ICIs group were 31.1%, 35.5%, and 42%, and the disease control rate (DCR) were 51.1%, 65.8%, and 80%. There were no adverse events (AEs) of arthralgia, diarrhea, rash, and pruritus in the TACE group. The incidence of grade 3 AEs (Hypertension) in the TACE+TKI+ICIs group was significantly higher than that in TACE+TKI and TACE groups (28% vs 17.1% vs 6.7%, P=0.024), and secondly, the morbidity of rash and pruritus in the TACE+TKI+ICIs group was apparently higher than that in the TACE+TKI group (P<0.05). Multivariate analysis showed that ECOG-PS 2 (HR=2.064, 95%CI 1.335-3.191, P=0.001), Hepatitis B virus (HR=2.539, 95%CI 1.291-4.993, P=0.007), AFP≥400 ng/ml (HR= 1.72, 95%CI

1.12-2.643, P=0.013), neutrophil-lymphocyte ratio (NLR) ≥2.195 (HR=1.669, 95% CI 1.073-2.597, P=0.023) were independent risk factors for OS in uHCC patients. So, TACE+TKI+ICIs therapy can prolong the OS and improve the prognosis of patients effectively, with a well-characterized safety profile.

KEYWORDS

hepatocellular carcinoma, tyrosine kinase inhibitor, immune checkpoint inhibitor, transcatheter arterial chemoembolization, prognosis

Introduction

Primary liver cancer is the sixth most common cancer and the third leading cause of cancer deaths worldwide, with hepatocellular carcinoma (HCC) accounting for 75% to 85% (1). Radical therapy (partial hepatectomy, liver transplantation, or percutaneous radiofrequency ablation) provides good prognosis in patients with early-stage HCC (2). However, the pathogenesis of HCC is concealed, and most patients are in an advanced stage when diagnosed, with a low resection probability and bleak prognosis. What's more, patients with large tumor burden, poor liver function, tumor thrombus in the portal vein or inferior vena cava, or extrahepatic metastasis are unable to receive radical treatment and the median overall survival (mOS) was 9 months. The main cause of death was tumor progression (3). With the exploration of the pathogenesis of HCC, the current treatment options for uHCC are transhepatic arterial chemoembolization (TACE), radiotherapy, systemic drug therapy, and so on.

The main blood supply to the normal liver parenchyma is the portal vein, while tumor tissue is supplied by the hepatic artery (4). Embolization after local chemotherapy can prolong the cytotoxic influence and reduce the systemic toxicity of chemotherapy (5). The dual blood supply from the hepatic artery and portal vein to the liver makes general arterial chemoembolization and arterial-directed therapy possible, and avoids normal liver parenchyma ischemia and hypoxia, reducing the damage of liver. So, TACE has a high application value in the treatment of hepatocellular carcinoma (6) (7), and is the most widely used treatment for uHCC (8, 9).

TACE interdicts tumor blood supply and causes tumor tissue ischemia. Residual tumor cells release hypoxia-inducible factor (HIF), leading to increased vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and angiopoietin-2 (Ang-2), promotes tumor angiogenesis and progression, increasing the risk of cancer recurrence and metastasis (10). Tyrosine kinase inhibitors (TKIs), such as sorafenib, lenvatinib, apatinib, regorafenib and bevacizumab, inhibit the phosphorylation of tyrosine kinases. It can not only inhibit the proliferation of tumor cells by blocking the cell signaling pathway directly, but also inhibit the vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) to block the formation of tumor angiogenesis indirectly (11, 12). Therefore, TACE plus TKI therapy has a synergistic effect in theory. Current studies have shown that TACE+TKI inhibits tumor progression and prolongs the survival of patients. For example, in the study of sorafenib with or without TACE, the median progression-free survival (mPFS) of sorafenib+TACE was significantly better than TACE (25.2 vs 13.5 months, P=0.006) (13).

Hepatitis induced by hepatitis B virus (HBV), hepatitis C virus (HCV), nonalcoholic fatty liver disease (NAFLD) or alcohol leads to inflammatory reaction and liver damage, is considered as the main cause of HCC pathogenesis (14). Therefore, HCC is considered an immunogenic tumor (15). T cells play an important role in the body's anti-tumor immune activity, and the up-regulation of Programmed Death-Ligand 1 (PD-L1) in tumor cells contributes to the immune suppressive microenvironment (16). Tumor immune checkpoint inhibitors (ICIs) are the most important aspect of tumor immunotherapy. By inhibiting the immune escape of tumor cells, the autoimmune system is mobilized to eliminate tumors. The research of tumor immune checkpoint inhibitors mainly focuses on three molecules: cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1) and its ligand PD-L1, such as camrelizumab, sintilimab, pembrolizumab, atezolizumab, tislelizumab, nivolumab, ipilimumab. PD-1/PD-L1 immune checkpoint inhibitors have become a research hotspot in immunotherapy, and they have also achieved breakthrough progress in clinical practice.

TACE is targeted for the treatment of local tumors in the liver, and TKI and ICIs are used for systemic treatment through blood circulation to improve the systemic immune system. Combination therapy directly or indirectly inhibits local tumors, slows tumor growth, and even reduces tumor volume, providing the possibility of re-radical therapy for uHCC. However, whether combining ICIs with TKI plus TACE can improve survival in patients with uHCC remains unclear. Hence,

this retrospective study aimed to evaluate the efficacy of TACE+TKI+ICIs on the survival of uHCC patients and the factors that affect their prognosis.

Materials and methods

Study design and patients

This study was approved by the Ethics Committee of the Shandong Provincial Hospital Affiliated to Shandong First Medical University (SWYX: NO.2022-191). The medical records of patients with unresectable HCC who were admitted to our hospital from June 8, 2016 to October 18, 2021 were retrospectively collected. Laboratory measurements within 3 days before TACE were collected from the hospital laboratory enquiry system. Ultimately, 171 patients were included in this study, and all met the following inclusion and exclusion criteria. The inclusion criteria comprised the following: 1. Histologically or cytologically confirmed HCC or clinically confirmed according to the criteria of the American Association for the Study of Liver Diseases; 2. Child-Pugh class A or B; 3. Physical performance status score ECOG-PS ≤ 2; 4. BCLC stages are B to C stages and A stage with contraindications to surgery (such as severe cardiopulmonary insufficiency);5. No prior TACE or systemic antitumor therapy for HCC;6.At least 1 measurable target nodule through the modified new criteria for tumor response evaluation (mRECIST, version 1.1); 7. Complete follow-up data. Exclusion criteria: 1. Past or current presence of other malignant tumors; 2. There are contraindications to TACE; 3. Child-Pugh class C; 4. Previous TACE or systemic therapy;5. Loss of follow-up data or incomplete patient data. The liver function classification standard adopts Child-Pugh classification of liver function. Child-pugh class A: 5-6 points; Child-pugh class B: 7-9; Child-pugh class C: ≥10 points. Tumors were staged according to the Barcelona stage (BCLC). The patient's general condition, disease history, family history, preoperative blood routine, liver and kidney function, tumor markers, imaging and other report materials were collected through the case system.

TACE therapy

The Seldinger method was used to place the 5F hepatic duct through the right femoral artery to the common hepatic artery. After the lesion was visualized by DSA, a microcatheter was inserted into the tumor feeding artery, and oxaliplatin and 5-FU were locally perfused. An appropriate amount of lipiodol mixed with epirubicin was then injected into the tumor lesions, and after the lipiodol was sufficiently deposited, DSA was performed again to evaluate the effect. TACE is performed as needed (patients undergo imaging examinations to evaluate the effect of lipiodol deposition in the lesions. If the deposition effect of lipiodol is good, TACE may not be performed temporarily; if the deposition of lipiodol subsides, TACE is required again.).

TKI combined with ICIs therapy

TKIs are taken for a long time at doses after the first TACE, until the patient cannot tolerate the drug or the disease progresses, and then switch to other TKIs for subsequent treatment. ICIs were administered according to the applied dose on the first day after the first TACE and injected every 21 days thereafter. Medication use included in this article was the medication the patient was on at the end of follow-up. Doses of TKIs and ICIs (Supplementary Table 1).

Follow-up and assessment

Follow-up-related data were obtained from patient follow-up phone calls, outpatient periodic review and readmission case data. The end of follow-up date was March 24, 2022. Overall survival (OS) definition: from the date of onset (or recurrence after liver resection) to the date of death or to the date of termination of follow-up, OS was the primary endpoint of this study. Progression-free survival (PFS) was defined as the period from the date of onset (or recurrence after liver resection) to the date of disease progression or death from any cause, whichever occurred first. Adverse events (AEs) were assessed according to the National Cancer Institute Adverse Events Common Terminology Criteria v 5.0. PFS and frequency of AEs were the secondary endpoints of this study. Efficacy was assessed according to m RECIST criteria: (1) Complete response (CR), the enhancement of intratumoral arteries in all target lesions disappeared or was completely inactivated; (2) Partial response (PR), the tumor survival residual cancer tissue (the sum of the diameters of all target lesions or enhancing lesions) is reduced by at least 30%; (3) Progressive disease (PD): tumor survival and residual cancer tissue increased by at least 20%, or new lesions appeared; (4) stable disease (SD): The tumor changes are between PD and PR.

Statistical analysis

The collected data were systematically analyzed using SPPS version 26.0, and the categorical variables were expressed as percentages and analyzed by $\chi 2$ test. Survival curves were analyzed by Kaplan-Meier, and median overall survival (mOS) and mPFS were calculated, and graphs were drawn. The Receiver Operating Characteristic (ROC) curve was used to obtain the

cutoff value of NLR for predicting OS. Cox regression proportional hazards model was used to perform univariate analysis on the screened clinical indicators, and multivariate analysis was performed on the statistically significant indicators in the univariate analysis to obtain independent risk factors for predicting tumor OS. Hazard ratios (HR) and 95% confidence intervals (CI) for these variables were estimated to quantify the strength of these associations. P<0.05 means there is a difference, which is statistically significant.

Results

Patient characteristics

This study retrospectively analyzed 294 uHCC patients in our hospital. According to the inclusion and exclusion criteria, 171 patients who met the criteria were finally included in this study. The patients were divided into TACE group, TACE+TKI group and TACE+TKI+ICIs group according to different treatment plans. The demographics and baseline characteristics were shown in Table 1. There were no significant differences in general clinical data such as gender, age, Eastern Cooperative Oncology Group performance status (ECOG-PS), Child-Pugh class, BCLC stage, portal vein tumor thrombus, tumor number, tumor size, HBV, AFP, ALT and NLR among the three groups of patients before treatment (P>0.05).

Efficacy and safety

The DCR of TACE group, TACE+TKI group and TACE+TKI+ICIs group were 51.1%, 65.8% and 80%, respectively (P=0.012). The ORR in the TACE+TKI+ICIs group was 42%, while the ORRs in the TACE and TACE+TKI groups were 31.1% and 35.5% (P>0.05) (Table 2). AEs occurred in 166 (97%) patients. Among them, grade 1 and 2 AEs were in the majority, which could be well controlled after symptomatic treatment. Grade 3 AEs occurred in 119 patients, as shown in Table 3. The most frequent grade 3 AEs were elevated AST, elevated ALT, thrombocytopenia, hypertension, fatigue, fever, nausea, arthralgia, decreased appetite, diarrhea, pruritus, and rash. No grade 4 AEs occurred, and no patients experienced treatment-related deaths. Hypertension occurred in 3 patients in the TACE group, 13 patients in the TACE+TKI group, and 14 patients in the TACE+TKI+ICIs group (P=0.024). In addition, there were differences in pruritus (5.3% in the TACE+TKI group and 18% in the TACE+TKI+ICIs group, P=0.021) and rash (6.6% in the TACE+TKI group and 20% in the TACE+TKI+ICIs group, P=0.023), but no significant differences in other grade 3 AEs.

Survival analysis

The patients' survival of the three groups was followed up. The follow-up was from the date of TACE treatment to the date of death or termination of follow-up (March 2022). The total median follow-up time of the three groups was 15.5 (95%CI 11.8-19.2) months, among which the TACE+TKI+ICIs group had the longest mOS, followed by the TACE+TKI group, and the TACE group had the shortest mOS [mOS: 24.1 (95% CI 15.1-33.1) months vs 14.9 (95% CI 10.7-19.1) months vs 11.4 (95% CI 8.4-14.5) months, P=0.002], as shown in Figure 1A. And the TACE +TKI+ICIs group showed longer mOS than the TACE+TKI group (P=0.047, HR=0.585, 95%CI0.342-1.000), as shown in Figure 1B. Compared with the TACE group, mOS in the TACE +TKI+ICIs group and TACE+TKI group was prolonged by 12.7 months (P=0.001, Figure 1C) and 3.5 months (P=0.044, Figure 1D), respectively. So, compared with the TACE group and TACE+TKI group, the TACE+TKI+ICIs group had obvious advantages in prolonging the mOS of patients. Also, the TACE +TKI+ICIs group had the longest mPFS compared with the TACE and TACE+TKI groups, [mPFS: 10.6 (95% CI 6.5-14.7) months vs 6.7 (95% CI 5.5-7.9) months vs 6 (95%CI 2.3-9.7) months, P<0.001] (Figure 2). Also, there were differences among the treatment groups [(TACE vs TACE+TKI, P=0.043), (TACE vs TACE+TKI+ICIs, P<0.001), (TACE+TKI vs TACE+TKI+ICIs, P=0.042)]. Taken together, TACE+TKI+ICIs group significantly prolonged mPFS and mOS in uHCC patients.

Risk factor analysis

The cutoff value of NLR was obtained by the ROC curve, the largest of the NLR area under the curve (AUC) was 0.633, and the NLR cutoff value was 2.195 (P=0.003). Univariate analysis showed that ECOG score, Child-Pugh classification, BCLC stage, portal vein invasion, tumor size, HBV infection, AFP≥400, NLR ≥2.195 and different therapies were associated with OS of uHCC (P<0.05). The results of multivariate analysis showed: ECOG-PS (≤1vs2) (HR=2.064, 95%CI 1.335~3.191, P=0.001), HBV infection (yes vs no) (HR=2.539, 95%CI 1.291~4.993, P=0.007), AFP (<400vs≥400) (HR=1.72, 95%CI 1.12~2.643, P=0.013), NLR (<2.195vs≥2.195) (HR=1.669, 95%CI 1.073~2.597, P=0.023) and different therapies (TACE vs TACE+TKI vs TACE+TKI+ICIs) (HR=0.544, 95%CI 0.402-0.736, P<0.001) were independent risk factors for OS in patients with uHCC, as presented (Table 4). Survival analysis showed that uHCC patients with ECOG-PS 2, Child-Pugh class B, BCLC stage C, portal vein tumor thrombus, tumor size ≥10 cm, HBV positive, AFP ≥ 400, and NLP ≥ 2.195 had a significantly shorter OS, as exhibited in Figures 3A–H.

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TABLE 1 Baseline data of patients included in the study.

Characteristics	TACE	TACE+TKI	TACE+TKI+ICIs	χ^2value	P value
number	**45**	**76**	**50**		
Gender,n (%)				0.285	0.867
Male	38 (84.4)	65 (85.5)	41 (82.0)		
Female	7 (15.6)	11 (14.5)	9 (18.0)		
Age (years),n (%)				0.62	0.733
<60	26 (57.8)	42 (55.3)	25 (50.0)		
≥60	19 (42.2)	34 (44.7)	25 (50.0)		
ECOG-PS,n (%)				2.464	0.292
0-1	28 (62.2)	55 (72.4)	30 (60.0)		
2	17 (37.8)	21 (27.6)	20 (40.0)		
Child-Pugh class,n (%)				4.942	0.085
A	26 (57.8)	55 (72.4)	39 (78.0)		
B	19 (42.2)	21 (27.6)	11 (22.0)		
BCLC,n (%)				0.068	0.967
Stage A+B	30 (66.7)	49 (64.5)	33 (66.0)		
Stage C	15 (33.3)	27 (35.5)	17 (34.0)		
Portal vein tumor thrombus,n (%)				0.304	0.859
Yes	14 (31.1)	27 (35.5)	16 (32.0)		
No	31 (68.9)	49 (64.5)	34 (68.0)		
Tumor number,n (%)				4.99	0.083
Single	20 (44.4)	21 (27.6)	22 (44.0)		
Multiple	25 (55.6)	55 (72.4)	28 (56.0)		
Tumor size (cm),n (%)				0.924	0.63
<10	23 (51.1)	40 (52.6)	30 (60.0)		
≥10	22 (48.9)	36 (47.4)	20 (40.0)		
Hepatitis B virus,n (%)				3.447	0.178
+	35 (77.8)	68 (89.5)	44 (88.0)		
-	10 (22.2)	8 (10.5)	6 (12.0)		
AFP (ng/ml),n (%)				1.913	0.384
<400	22 (48.9)	33 (43.4)	28 (56.0)		
≥400	23 (51.1)	43 (56.6)	22 (44.0)		
ALT (U/L),n (%)				0.103	0.95
<40	22 (48.9)	35 (46.1)	24 (48.0)		
≥40	23 (51.1)	41 (53.9)	26 (52.0)		
NLR,n (%)				5.091	0.078
<2.195	14 (31.1)	32 (42.1)	27 (54.0)		
≥2.195	31 (68.9)	44 (57.9)	23 (46.0)		

TACE, transcatheter arterial chemoembolization; TKI, tyrosine kinase inhibitors; ICIs, immune checkpoint inhibitors; ECOG-PS, Eastern Cooperative Oncology Group performance status; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; ALT, alamine aminotransferase; NLR, neutrophil-lymphocyte ratio

Discussion

TACE treatment inhibites tumor growth through reducing tumor blood supply in uHCC and local infusion of chemotherapeutic drugs reduces systemic adverse reactions in patients. However, patients with uHCC treated with TACE alone suffered high possibility of tumor recurrence and metastasis, which induces short survival. Also, repeated TACE treatment seriously damages liver function and increases the risk of liver failure (17). TACE embolizes the liver blood supply, leading to hypoxis tumor microenvironment, releasing a large number of cytokines that promotes revascularization of the residual tumor tissue (18). Meanwhile, tumor hypoxic microenvironment leads to enhanced tumor cell invasiveness and promotes cancer metastasis (19). In this context, TACE plus TKI and ICIs make it possible. The combination therapy of TACE-TKI-ICIs can play a synergistic effect: 1. Reduce the blood supply of the local tumor, causing tumor ischemic necrosis; 2. Inhibit the

TABLE 2 Theraprutic efcacy of response.

Variable	TACE (n=45)	TACE+TKI (n=76)	TACE+TKI+ICIs (n=50)	P value
Best overall response,*n* (%)				
CR	1 (2.2%)	3 (3.9%)	3 (6%)	
PR	13 (28.9%)	24 (31.6%)	18 (36%)	
SD	9 (20%)	23 (30.3%)	19 (38%)	
PD	22 (48.9%)	26 (34.2%)	10 (20%)	
Objective response rate,*n* (%)	14 (31.1%)	27 (35.5%)	21 (42%)	0.536
Disease control rate,*n* (%)	23 (51.1%)	50 (65.8%)	40 (80%)	0.012

TACE, transcatheter arterial chemoembolization; TKI, tyrosine kinase inhibitors; ICIs, immune checkpoint inhibitors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

TABLE 3 Key treatment-related adverse events of = grade 3.

Variable n %	TACE (n=45)	TACE+TKI (n=76)	TACE+TKI+ICIs (n=50)	P value
Elevated AST	8 (17.8)	15 (19.7)	15 (30)	0.281
Elevated ALT	8 (17.8)	14 (18.4)	11 (22)	0.844
Thrombocytopaenia	0 (0.0)	7 (9.2)	8 (16)	0.250
Hypertension	3 (6.7)	13 (17.1)	14 (28)	0.024
Fatigue	1 (2.2)	4 (5.3)	3 (6)	0.650
Fever	4 (8.9)	7 (9.2)	5 (10)	0.981
Nausea	7 (15.6)	11 (14.5)	7 (14)	0.976
Arthralgia	0 (0.0)	2 (2.6)	1 (2)	0.820
Decreased appetite	8 (17.8)	11 (14.5)	8 (16)	0.889
Diarrhea	0 (0.0)	5 (6.6)	6 (12)	0.464
Rash	0 (0.0)	5 (6.6)	10 (20)	0.023
Pruritus	0 (0.0)	4 (5.3)	9 (18)	0.021

TACE, transcatheter arterial chemoembolization; TKI, tyrosine kinase inhibitors; ICIs, immune checkpoint inhibitors; ALT, alamine aminotransferase; AST, aspartate aminotransferase.

vascular reconstruction of residual tumor tissue and reduce tumor metastasis and invasiveness; 3. Improve the level of autoimmunity and change the immune tolerance state of tumor microenvironment, as well as inhibit tumor immune escape. So, triple therapy can inhibit the progression of HCC and improve the prognosis and survival of patients with uHCC in theory. Also, in this study, we found that no grade 4 AEs occurred and no patients experienced treatment-related deaths. Hypertension, pruritus and rash occurred more frequently in triple therapy group, but no significant differences in other grade 3 AEs. So, triple therapy seems to be an effective and safe choice for patients with uHCC. However, greater sample sizes and a longer follow-up period are required to fully determine the long-term safety of triple therapy.

With the in-depth study of the tumor microenvironment (TME) and immune mechanism of liver cancer, the TME is involved in the occurrence, development, and metastasis of HCC. The TME plays a role in evading immune surveillance and promoting drug resistance tumor invasion, metastasis, resulting in poor efficacy (20). Therefore, combinatorial therapies will be the choice for uHCC (21). The main basis for the application of TKIs and ICIs is to adjust the TME from immune resistance to immune stimulation environment by anti-VEGF (22). Under such conditions, ICIs could promote anti-tumor immunity of T-cell (23). Recent study shows that low-dose apatinib modulates the tumor immunosuppressive microenvironment and enhances the anti-tumor effect of anti-PD-L1 medicine, which delays tumor growth, reduces the number of metastases, and prolonged survival in mouse models (24). In a phase Ib trial of lenvatinib combined with pembrolizumab in patients with uHCC, the mPFS and mOS of lenvatinib+pembrolizumab were 9.3 months and 22 months, respectively, reflecting the advantages of TKI+ICIs therapy for stable disease status (25). Another retrospective study showed the effect of lenvatinib+TACE and pembrolizumab+lenvatinib +TACE in the treatment of uHCC with PD–L1 expression.

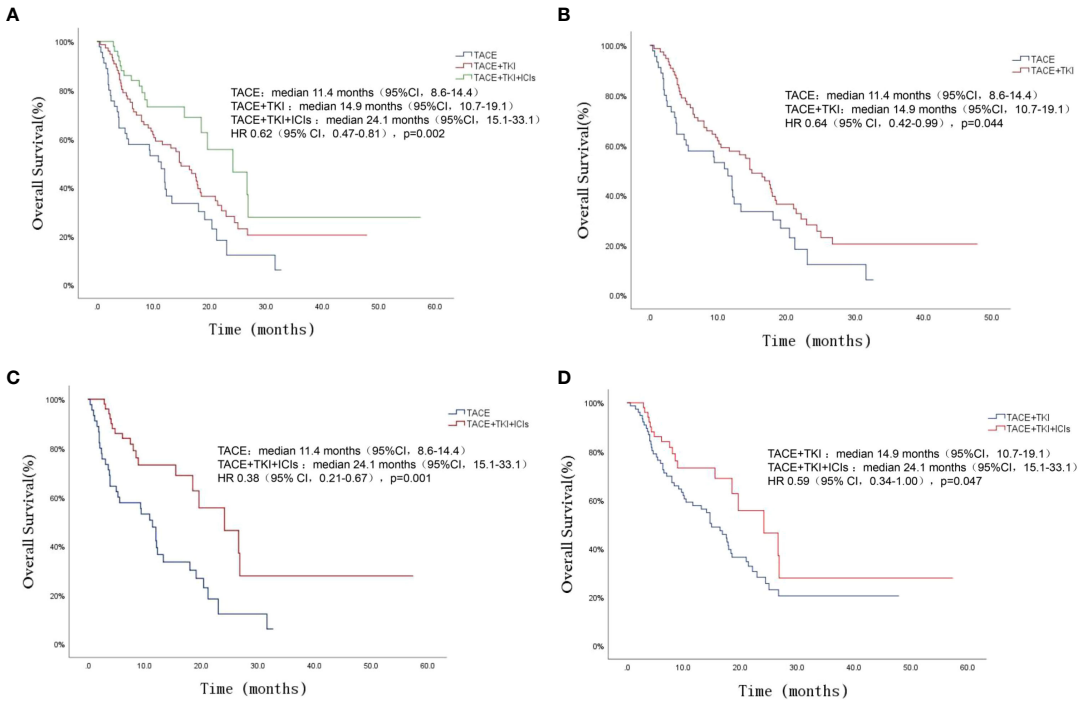

FIGURE 1
Kaplan-Meier survival curves showing OS stratified by treatment options in patients of uHCC. Comparison of OS among the three groups of patients **(A)**. OS comparison between TACE group and TACE+TKI group **(B)**. OS comparison between TACE group and TACE+TKI+ICIs group **(C)**. OS comparison between TACE+TKI group and TACE+TKI+ICIs group **(D)**.

Pembrolizumab+lenvatinib+TACE treatment was more advantageous than lenvatinib+TACE in mOS and conversion rate [(18.1vs14.1, P=0.004), (25.7%vs11.1%, P=0.025)] (26). Also, TKI+ICIs treatment added the opportunity to for downstaging and resection of uHCC, (15.9% underwent R0 resection) (27); and another study showed the conversion rate was 60% after TACE+TKI+ICIs therapy (28). All the studies demonstrated that the combination of TKIs and ICIs was a feasible means of conversion therapy. A clinical study compared effect of first- and second-line treatment in advanced HCC with camrelizumab+ apatinib. In the first- and second-line groups, the ORR was 34.3% and 22.5%, the mPFS was 5.7 months and 5.5 months, and the one-year survival rates were 74.7% and 68.2%. So, the combination therapy strategy of TKI+ICIs can be used as a new choice for the first- and second-line treatment of HCC (29). A study of atezolizumab combined with bevacizumab versus sorafenib in the treatment of advanced uHCC (IMbrave150) showed that atezolizumab+bevacizumab significantly improved the patients' mOS and mPFS compared with sorafenib [(19.2vs13.4, P<0.001), (6.9vs4.3, P<0.001)] (30). Also, the mPFS of sintilimab+bevacizumab was significantly longer than that of sorafenib (4.6vs2.8, P<0.0001), and the overall survival of the combination therapy was significantly better than that of sorafenib in the first overall survival analysis (ORIENT-32) (31). Except uHCC, TKI+ICIs treatment as preoperative neoadjuvant therapy for resectable HCC were also in development. Recent study showed that after preoperative neoadjuvant therapy with apatinib

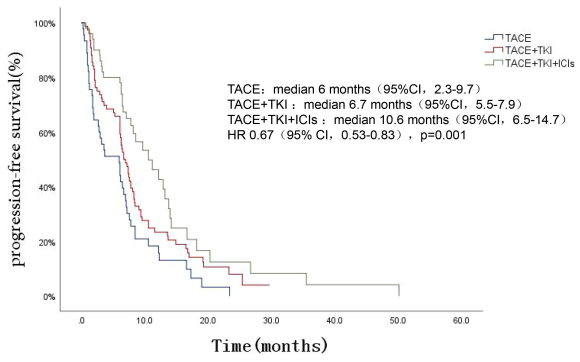

FIGURE 2
Kaplan-Meier survival curves showing PFS stratified by treatment options in patients of uHCC.

TABLE 4 Analysis of OS prognostic factors in unresectable HCC patients.

Variable	N	mOS(month)	Univariate analysis			Multivariate analysis		
			P value	HR	95% CI	P value	HR	95% CI
Age(<60/≥60)	93/78	14.9/15.5	0.831	1.043	0.711~1.529			
Gender(Male/Female)	144/27	15.5/14	0.394	1.249	0.749~2.084			
ECOG-PS(≤1/2)	113/58	18/8.9	0.005	1.752	1.184~2.594	0.001	2.064	1.335~3.191
Child-Pugh class(A/B)	120/51	18.3/8.3	0.001	1.924	1.296~2.856			
BCLC(A+B/C)	112/59	17.8/10.9	0.033	1.527	1.034~2.257			
Portal vein tumor thrombus(Yes/No)	57/114	10.9/17.8	0.042	1.501	1.014~2.222			
Tumor number(Single/Multiple)	63/108	17.6/15.5	0.942	1.016	0.671~1.538			
Tumor size(<10/≥10)	93/78	17.6/12.1	0.027	1.546	1.052~2.271			
Hepatitis B virus(+/-)	147/24	14.6/22.9	0.03	2.062	1.074~3.958	0.007	2.539	1.291~4.993
AFP(<400/≥400)	83/88	12.0/18.0	0.03	1.535	1.042~2.259	0.013	1.72	1.12~2.643
ALT(<40/≥40)	81/90	17.6/14.6	0.337	0.91	0.751~1.103			
NLR(<2.195/≥2.195)	73/98	20.4/11.6	0.001	2.024	1.345~3.044	0.023	1.669	1.073~2.597
Treatment options(TACE/TACE+TKI/TACE+TKI+ICIs)	45/76/50	11.4/14.9/24.1	0.001	0.615	0.466~0.81	<0.001	0.544	0.402~0.736

TACE, transcatheter arterial chemoembolization; TKI, tyrosine kinase inhibitors; ICIs, immune checkpoint inhibitors; ECOG-PS, Eastern Cooperative Oncology Group performance status; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; ALT, alamine aminotransferase; NLR, neutrophil-lymphocyte ratio; mOS, overall survival.

+camrelizumab, the pathological results of patients with HCC resection showed that 90% of the tumor resection tissue was necrotic and had no residual cancer cells, and the one-year recurrence-free survival (RFS) rate after HCC resection was 53.85% (32). A randomized phase 3 LEAP-012 study is ongoing: TACE with or without lenvatinib+pembrolizumab treatment of incurable intermediate-stage HCC was sesigned to verify the efficacy of triple therapy in prolonging OS and PFS (33). In this retrospective study, we found that TACE+TKI+ICIs treatment had obvious advantages in prolonging the survival time of uHCC compared with TACE and TACE+TKI. The mOS in the TACE+TKI+ICIs group was 24.1 months, and the mOS was prolonged by 12.7 months and 9.2 months compared with the TACE group and the TACE+TKI group. Compared with the TACE and TACE+TKI groups, the TACE+TKI+ICIs group had the longest mPFS [10.6 months vs 6.7 months vs 6 months, P<0.001]. So, for uHCC, TACE-TKI-ICIs triple therapy can effectively control the tumor progression, prolong the survival time of patients and improve the prognosis of patients.

Hepatocellular carcinoma is an inflammation-related cancer, mainly as a result of chronic liver damage or chronic inflammation (34). Long-term inflammatory stimulation causes liver fibrosis, which is an important component of the HCC TME. There are also a large number of vascular endothelial cells, immune cells (T cells, macrophages, neutrophils, dendritic cells) and cytokines in the TME (35). Virchow had already discovered a close relationship between inflammation and cancer in 1863 (36).Among them, serum NLR was considered as an index reflecting the inflammatory state. In this study, the high NLR suggested the worse the prognosis of patients., And the level of NLR may be closely related to the prognosis of advanced HCC. Accumulating evidence indicates that tumor-associated inflammatory response is closely related to the TME and plays an important role in cancer development, invasion and metastasis (37). Recent studies found that NLR above the threshold was closely related to shorter OS in head and neck squamous cell carcinoma, which was consistent with our data (38). Also, in other solid tumors, studies on the pre-correlation of NLR with its prognosis have also been carried out, and the results are consistent with the above study (39–41).

However, several limitations should be acknowledged. First, the types of TKIs and ICIs are not the same, there may be a selection bias, and it is impossible to accurately assess a certain triple therapy. Second, the causes of death in patients are less detailed, which has implications for overall survival analysis. Third, some imaging data of patients are from other hospitals, and the assessment of tumor status is biased. Fourth, this was a single-center study and the sample is small. So, multi-center and large-scale samples for further validation are needed. Fifth, the follow-up period is relatively short. Also, in this study, endpoint of follow-up was patient cannot tolerate the drug or the disease progresses followed with subsequent treatment. So, we didn't refer patients received subsequent lines of therapy after the combination therapy of TACE+TKI+checkpoint inhibitors or OS between the cohorts - one with concurrent combination therapy versus sequential therapy. So, further research was need to explore whether there was a survival advantage for sequential therapy versus combination therapy. Finally, because kinds of TKIs or ICIs are not covered by medical insurance, the patients cannot afford multiple treatment costs, and there is a bias in the choice of drugs.

In conclusion, the results of this retrospective study show that compared with TACE alone and TACE+TKI, TACE+TKI+ICIs therapy has a better prognostic effect for uHCC.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Shandong Provincial Hospital Affiliated to Shandong First Medical University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

HG and JL. designed experiments. ZY, JW, QN and HZ. collected the data. ZH, FY and XZ analyzed and interpreted the data. ZH and FY wrote the manuscript. HG and JL made critical revisions to the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Efficacy and safety of lenvatinib versus sorafenib in first-line treatment of advanced hepatocellular carcinoma: A meta-analysis

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Objective: Lenvatinib and sorafenib are first-line oral multikinase inhibitors approved for the treatment of advanced hepatocellular carcinoma (HCC). However, the choice of the primary therapeutic agent among these two remains controversial. This meta-analysis aimed to estimate the efficacy and safety of lenvatinib and sorafenib in patients with advanced HCC.

Methods: PubMed, Cochrane Library, Web of Science, and Embase databases were searched for relevant research published up to June 30, 2022. After quality assessment and data extraction of the included studies, RevMan 5.3 software was used for analysis. Odds ratio (OR) and hazard ratio (HR) with a 95% confidence interval (CI) were calculated using a fixed-effects or random-effects model.

Results: Fifteen studies containing 3908 patients were included after final scrutiny. Our meta-analysis showed that there was no significant difference in overall survival (OS) between the lenvatinib and sorafenib groups (HR = 0.86; 95% CI: 0.72–1.02; p = 0.09); however, the progression-free survival (PFS) (HR = 0.63; 95% CI: 0.53–0.74; $p < 0.00001$), complete response (CR) (OR = 5.61; 95% CI: 2.71–11.64; $p < 0.00001$), partial response (PR) (OR = 4.62; 95% CI: 3.06–6.98; $p < 0.00001$), objective response rate (ORR) (OR = 5.61; 95% CI: 3.90–8.09; $p < 0.00001$), and disease control rate (DCR) (OR = 2.42; 95% CI: 1.79–3.28; $p < 0.00001$) in the lenvatinib group were significantly better than those in the sorafenib group. In terms of treatment safety, lenvatinib had similar incidences of any grade adverse events (AEs) (OR = 0.99; 95% CI: 0.47–2.09; p = 0.98) and grade ≥ 3 AEs (OR = 1.17, 95% CI; 1.00–1.37; p = 0.05) compared to sorafenib. Besides, lenvatinib was significantly associated with a higher incidence of hypertension, proteinuria, fatigue, decreased appetite, and weight loss, whereas sorafenib was associated with a higher incidence of diarrhea and hand-foot skin reaction ($p < 0.05$).

Conclusion: Given its potential survival benefit and good tolerability, lenvatinib is an appropriate and promising alternative to sorafenib as first-line systemic therapy in patients with advanced HCC.

Systematic review registration: https://www.crd.york.ac.uk/prospero/, identifier: CRD 42022327398.

KEYWORDS

hepatocellular carcinoma, lenvatinib, sorafenib, systemic therapy, meta-analysis

1 Introduction

Hepatocellular carcinoma (HCC), the most common type of primary liver cancer, ranks as the fourth leading cause of cancer-associated deaths worldwide (1). For patients with early-stage HCC, curative treatments such as surgical resection, transplantation, and ablation, have been shown to improve survival (2, 3). However, HCC is generally diagnosed at an advanced stage and usually occurs in people with chronic liver disease, limiting the feasibility of such curative therapies. For patients with advanced HCC, systemic therapy is the primary treatment option which is shown to significantly improve the overall survival (OS) and quality of life of HCC patients (4).

Sorafenib is an oral multikinase inhibitor that modulates multiple tumor-signaling pathways by inhibiting several receptor tyrosine kinases, such as vascular endothelial growth factor receptor (VEGFR) 1-3, platelet-derived growth factor receptor (PDGFR), KIT, and RET; and downstream Raf signaling molecules (5–7). A phase 3 randomized controlled trial (RCT) which enrolled 601 patients with advanced HCC revealed that the median OS was significantly improved with sorafenib treatment compared to the placebo group (10.7 months vs. 7.9 months, hazard ratio [HR]: 0.69; 95% confidence interval [CI]: 0.55–0.87, $p < 0.001$) (8). Further, the outcome of another phase 3 RCT involving patients from the Asia-Pacific region indicated a similar observation that sorafenib treatment improved the OS (6.5 months in sorafenib vs. 4.2 months in placebo, HR: 0.68; 95% CI: 0.50–0.93, $p < 0.014$) (9). Since then, several multikinase inhibitors have been developed, but none of them have shown non-inferiority or superiority to sorafenib as a first-line therapy for advanced HCC (10–12).

In 2018, the REFLECT trial demonstrated that lenvatinib, an oral multikinase inhibitor, was non-inferior to sorafenib in terms of OS for the treatment of advanced HCC (median OS: 13.6 months for lenvatinib vs. 12.3 months for sorafenib, HR: 0.92; 95% CI: 0.79–1.06) (13, 14). In addition, lenvatinib showed a significant improvement in progression-free survival (PFS) and objective response rate (ORR). Owing to these encouraging results, lenvatinib became the second therapeutic agent approved for first-line systemic treatment for advanced HCC. Although several subsequent studies have been conducted to compare the efficacy of lenvatinib and sorafenib, they have yielded inconsistent results. Hence, for the treatment of patients with advanced HCC, the choice of the primary systemic therapeutic agent remains controversial. In this meta-analysis, we comprehensively evaluated the clinical efficacy and safety of lenvatinib, thereby providing a more reliable basis for clinical decision-making.

2 Materials and methods

2.1 Protocol and registration

This review was performed in compliance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (15). Besides, the prospective protocol for this study was registered with the PROSPERO (Registration number: CRD 42022327398).

2.2 Search strategy

All studies evaluating the efficacy of lenvatinib and sorafenib on advanced HCC were identified by searching PubMed, Cochrane Library, Web of Science, and Embase databases from inception until June 30, 2022. The search keywords or the medical subject headings (MeSH) terms were as follows: “hepatocellular carcinoma”, “liver cell carcinoma”, “liver cancer”, “hepatoma”, “lenvatinib”, and “sorafenib”. The search strategy used in PubMed was as follows: ((((hepatocellular OR hepato-cellular OR hepatic OR liver) and (carcinom* OR cancer OR neoplasm* OR malign* OR tumor)) OR hepatocellular carcinoma OR HCC) OR “Carcinoma, Hepatocellular”[MeSH] OR Liver Neoplasms[MeSH]) AND (((((((sorafenib) OR (Nexavar)) OR (BAY 43-9006)) OR (Sorafenib N-Oxide)) OR (BAY-673472)) OR (BAY 545-9085)) OR (Sorafenib Tosylate)) OR (“Sorafenib”[Mesh]) AND (((((((((lenvatinib) OR

(Lenvima)) OR (E 7080)) OR (ER-203492-00)) OR (E-7080 mesylate)) OR (lenvatinib metabolite M2)) OR (lenvatinib mesylate)) OR (lenvatinib methanesulfonate)) OR (lenvatinib mesilate)) OR ("lenvatinib" [Supplementary Concept]). Furthermore, the reference lists of the included studies or the relevant reviews were checked manually to identify other potentially eligible studies. The literature search was limited to articles written in English language.

2.3 Inclusion and exclusion criteria

Two authors independently screened the results of initial searches, and any disagreement was resolved *via* discussion with a third author. The inclusion criteria were as follows (1): all prospective or retrospective studies comparing the efficacy of lenvatinib with sorafenib in the treatment of advanced HCC; (2) all trial participants with histologically or radiologically diagnosed advanced HCC, who were not previously treated with systemic therapies; (3) experimental intervention: lenvatinib; (4) control intervention: sorafenib; and (5) studies reporting at least one of the following outcomes: OS, PFS, ORR, disease control rate (DCR), complete response (CR), partial response (PR), and adverse events (AEs). The exclusion criteria were as follows: (1) studies without a control group; (2) case reports, abstracts, letters, reviews, conference reports, or expert opinions; and (3) studies without the full text. In the case of replication studies based on the same study patients, we included the most comprehensive and up-to-date data.

2.4 Data extraction

Three authors reviewed the full text of the eligible studies and extracted data independently. Any discrepancies or disagreements in the extracted data were solved through consensus in a plenum. Data extraction was performed using a single form that included the following items: the first author, date of publication, region, study type, sample size, drug dose, the main condition of patients, and outcome indicators. The hazard ratios of time-to-event variables (OS and PFS) were extracted directly from the original studies or estimated indirectly through the reported number of events and the relevant p value for the log-rank statistics.

2.5 Quality assessment

The Cochrane risk of bias assessment tool (16) was used to evaluate the quality of the selected RCTs based on the following seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome and assessment, incomplete outcome data, selective reporting, and other bias. Each item was graded as high, low, or unclear risk of bias. In addition, the quality of the included non-randomized comparative studies was assessed using the Newcastle-Ottawa scale (NOS) (17). This scale measures quality based on three parameters: selection, comparability, and outcome assessment, with a maximum of 9 points. Studies with a score of more than 6 were determined to be of high quality.

2.6 Statistical analysis

Statistical analyses were performed using the Cochrane Review Manager software (RevMan, version 5.3). The primary endpoints in this meta-analysis were OS and DFS, and the effect sizes were determined by HR with 95% CI. Dichotomous variables were assessed by OR with 95% CI. Besides, between-study heterogeneity was evaluated using the χ^2 test and expressed by the I^2 index. Heterogeneity was regarded as significant when the $p < 0.1$ or $I^2 > 50\%$. The random-effects model was used to calculate the pooled data if heterogeneity was significant; otherwise, the fixed-effects model was adopted. Potential publication bias was assessed by visually inspecting the funnel plots. Sensitivity analysis was conducted by removing each study in turn. A $p < 0.05$ was considered statistically significant.

3 Results

3.1 Literature search

A total of 1328 records were identified through the initial search; of which, 176 articles were removed for duplication, and 1124 studies were discarded after scanning the titles and abstracts. After a detailed reading and full text assessment, 13 articles were further excluded as they did not meet the inclusion criteria as 3 of them were reviews, 4 were not case-control studies, 2 lacked the related data, and 4 were sub-studies of previous trials. Finally, 15 articles were included in this analysis, including 1 RCT (13) and 14 retrospective cohort studies (RCS) (18–31). The literature selection process is shown in Figure 1.

3.2 Study characteristics and quality assessment

All eligible studies included a total of 3908 participants: 1722 in the lenvatinib group and 2186 in the sorafenib group. The published year ranged from 2018 to 2022, and the regions studied included Asia, Europe, and North America. The dosage of the drugs was consistent in the majority of the studies (13, 18, 19, 21–24, 26–28, 31). For instance, the initial dose of sorafenib was 400 mg twice daily, while lenvatinib was administered at a dose of 12 mg once daily for patients with body weights ≥ 60 kg or 8 mg once daily for those with body weights <

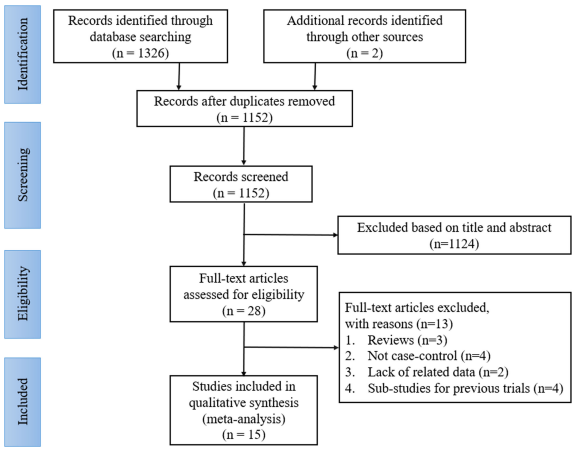

FIGURE 1
Flowchart of the study selection process.

60 kg. The characteristics of the included studies are summarized in Table 1. The bias risk of one RCT (13) was assessed using the Cochrane Collaboration tool and determined to be low (Figure 2). Besides, the 14 retrospective studies (18–31) had NOS scores ranging from 7 to 9, indicating a high quality of data in all included studies (Table 1).

3.3 Efficacy analysis

3.3.1 OS

Eleven studies (13, 18–20, 22–24, 27–29, 31) involving 3347 patients reported OS. The meta-analysis indicated that there was no significant difference in the OS between the two groups (HR = 0.86; 95% CI: 0.72–1.02; $p = 0.09$). A random-effects model was used, as statistical heterogeneity was identified among the included studies ($p = 0.006$, $I^2 = 60\%$; Figure 3). On the contrary, the pooled analysis showed that OS was significantly higher in the lenvatinib group as compared to the sorafenib group (HR = 0.90; 95% CI: 0.82–1.00; $p = 0.04$) when the heterogeneity was reduced ($p = 0.12$, $I^2 = 38\%$) by excluding two trials (18, 22).

3.3.2 PFS

Thirteen studies (13, 19–29, 31) enrolling 3760 patients provided data concerning PFS. The pooled analysis showed that compared with sorafenib, lenvatinib was associated with significantly improved PFS (HR = 0.63; 95% CI: 0.53–0.74; $p < 0.00001$). A random-effects model was used, due to statistical heterogeneity ($p = 0.0002$, $I^2 = 68\%$; Figure 4). To reduce the heterogeneity, two studies (20, 23) were removed ($p = 0.10$, $I^2 = 38\%$). The recalculated results consistently showed that the treatment with lenvatinib was associated with greater improvement in PFS compared with sorafenib (HR = 0.60; 95% CI: 0.55–0.67; $p < 0.00001$).

TABLE 1 Characteristics of the included studies.

Author (year)	Region	Study type	Intervention	Sample size	Age (Years)	Gender (M/F)	BCLC stage: B/C	Child-Pugh class: A/B	ECOG score: 0/1	NOS
Kudo (13) (2018)	Asia, European, North American	RCT	Lenv	478	63.0 (20–88)	405/73	104/374	475/3	304/174	–
			Sora	476	62.0 (22–88)	401/75	92/384	471/5	301/175	
Kuzuya (18) (2020)	Japan	RCS	Lenv	13	70.0 (53–92)	11/2	0/13	13/0	12/1	7
			Sora	28	67.0 (35–82)	21/7	0/28	28/0	18/10	
Lee (19) (2020)	Korea	RCS	Lenv	43	60 (32–85)	35/8	8/35	37/6	16/27	7
			Sora	55	63 (43–86)	42/13	8/47	52/3	22/33	
Nakano (20) (2020)	Japan	RCS	Lenv	146	72.8 ± 9.6	125/21	79/67	134/12	NA	9
			Sora	146	72.8 ± 8.5	121/25	81/65	137/9		
Terashima (21) (2020)	Japan	RCS	Lenv	45	Median:70	33/12	NA	39/6	36/8	7
			Sora	135	Median:69	96/39	NA	114/21	106/22	
Burgio (22) (2020)	Italy	RCS	Lenv	144	< 70: 52.8%	111/33	36/108	137/7	114/30	7

(Continued)

TABLE 1 Continued

Author (year)	Region	Study type	Intervention	Sample size	Age (Years)	Gender (M/F)	BCLC stage: B/C	Child-Pugh class: A/B	ECOG score: 0/1	NOS
			Sora	144	< 70: 52.7%	119/25	36/108	134/10	114/30	
Casadei (23) (2020)	Italy, Japan and Korea	RCS	Lenv	385	72.1 ± 10.0	303/82	NA/175	339/46	NA	8
			Sora	555	62.6 ± 11.5	485/70	NA/483	512/43	NA	
Fukushima (24) (2021)	Japan	RCS	Lenv	110	73.0 (67.3–78.0)	91/19	59/49	86/24	NA	7
			Sora	110	72.0 (67.0–78.0)	94/16	47/62	85/25	NA	
Kim (25) (2021)	Korea	RCS	Lenv	44	56.0 (51.0–66.3)	39/5	NA	36/8	41/3	8
			Sora	61	64.0 (58.0–70.5)	51/10	NA	56/5	59/2	
Kuo (26) (2021)	China	RCS	Lenv	70	65.0 ± 12.3	50/20	14/56	68/2	NA	8
			Sora	140	65.7 ± 11.6	100/40	25/115	138/2	NA	
Rimini (27) (2021)	Italy and Japan	RCS	Lenv	92	< 65: 25%	75/17	36/56	87/5	70/22	8
			Sora	92	< 65: 35.87%	81/11	36/56	85/7	65/27	
Tomonari (28) (2021)	Japan	RCS	Lenv	52	70 (53–88)	36/16	27/25	52/0	38/14	8
			Sora	52	71 (43–85)	35/17	29/23	52/0	37/15	
Choi (29) (2022)	Korea	RCS	Lenv	44	58 (51.5–64.8)	40/4	4/39	29/13	32/12	7
			Sora	88	58 (52.3–64.8)	80/8	8/77	63/19	55/33	
Lee (30) (2022)	China	RCS	Lenv	22	63.95 ± 11.38	18/4	0/22	22/0	NA	8
			Sora	44	63.77 ± 10.53	36/8	0/44	44/0	NA	
Park (31) (2022)	Korea	RCS	Lenv	34	62 (55–67)	29/5	1/29	0/30	NA	7
			Sora	60	65 (56–72)	52/8	4/52	0/56	NA	

NA, not available; RCT, randomized controlled trial; RCS, retrospective cohort study; Lenv, lenvatinib; Sora, sorafenib; M, male; F, female; BCLC, Barcelona clinic liver cancer; NOS, Newcastle-Ottawa scale.

3.3.3 Treatment response

In this study, CR, PR, ORR, and DCR were used to evaluate tumor treatment response. Eleven studies (13, 18–21, 24, 26, 28–31) which included 2391 patients reported CR and PR, fourteen studies (13, 18–24, 26–31) which enrolled 3803 patients investigated ORR, and thirteen studies (13, 18–22, 24, 26–31) which recruited 2863 patients documented DCR. The pooled analysis showed that CR (3.22% vs. 0.60%; OR = 5.61; 95% CI:

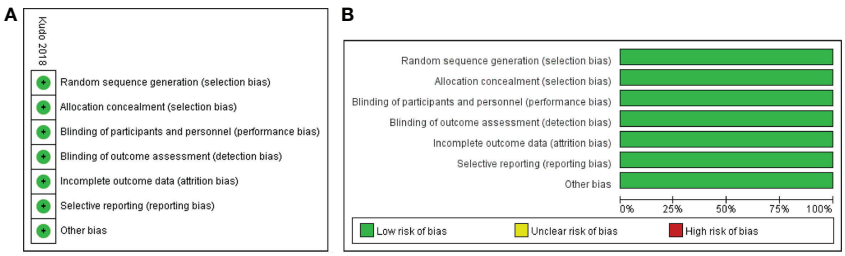

FIGURE 2
Assessment of risk of bias for RCT. Risk of bias summary **(A)**; risk of bias graph **(B)**.

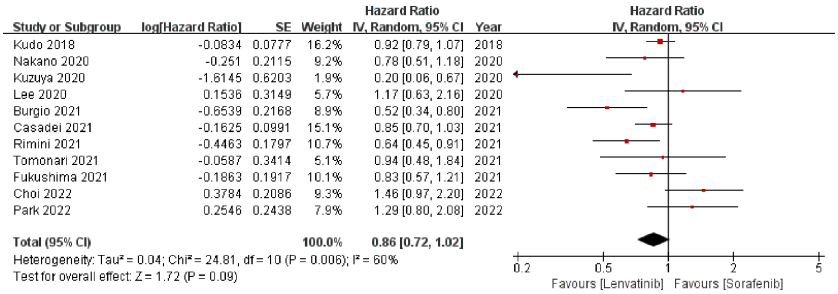

FIGURE 3
Forest plot on OS. OS, overall survival.

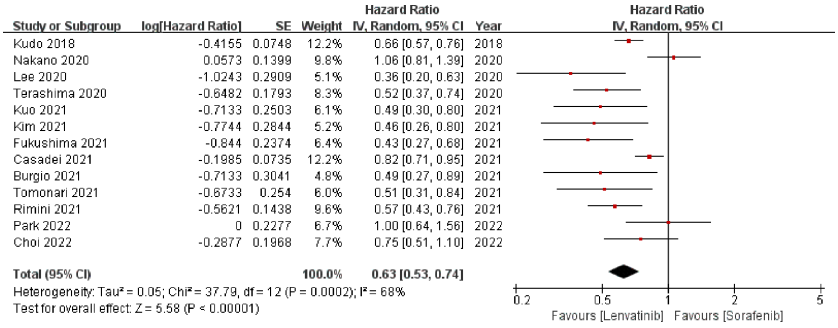

FIGURE 4
Forest plot on PFS. PFS, progression-free survival.

2.71–11.64; $p < 0.00001$; Figure 5A), PR (23.94% vs. 6.97%; OR = 4.62; 95% CI: 3.06–6.98; $p < 0.00001$; Figure 5B), ORR (25.74% vs. 6.4%; OR = 5.61; 95% CI: 3.90–8.09; $p < 0.00001$; Figure 5C), and DCR (71.54% vs. 51.59%; OR = 2.42; 95% CI: 1.79–3.28; $p < 0.00001$; Figure 5D) of the lenvatinib group were better than those of the sorafenib group.

3.4 Safety analysis

The incidence of any grade AEs was reported in 8 studies (13, 19, 20, 22, 23, 26, 27, 31), which included a total of 3019 patients. The pooled analysis showed no significant difference in the incidence of any grade AEs between the lenvatinib group

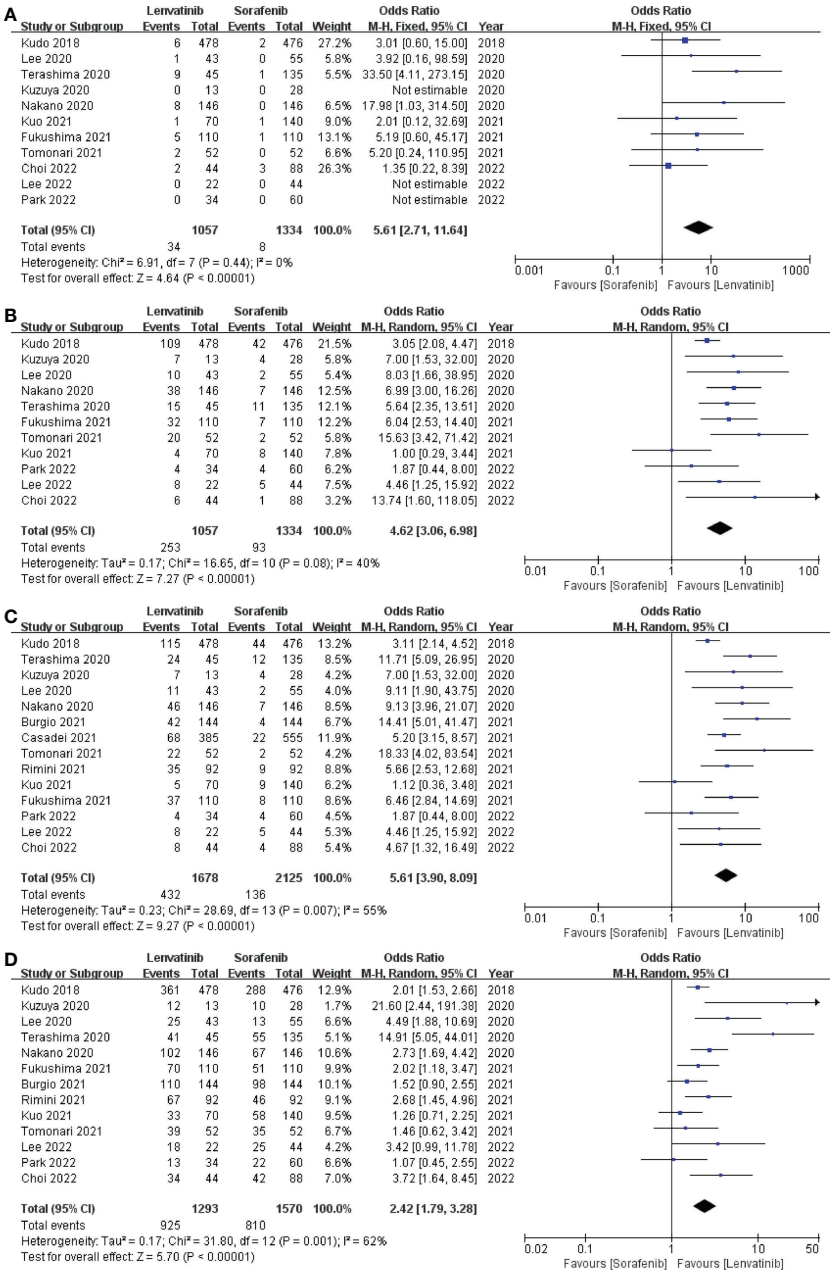

FIGURE 5
Forest plot on CR **(A)**, PR **(B)**, ORR **(C)**, and DCR **(D)**. CR, complete response; PR, partial response; ORR, objective response rate; DCR, disease control rate.

(92.34%) and the sorafenib group (93.09%) (OR = 0.99; 95% CI: 0.47–2.09; $p = 0.98$; Figure 6A). The incidence of grade ≥ 3 AEs was reported in 11 studies (13, 18, 19, 22, 23, 25–28, 30, 31), which involved a total of 3043 patients. Similarly, the pooled data indicated no significant difference in the incidence of grade ≥ 3 AEs between the two groups, with lenvatinib and sorafenib groups exhibiting 38.89% and 33.25%, respectively (OR = 1.17; 95% CI: 1.00–1.37; $p = 0.05$; Figure 6B).

Treatment of HCC with tyrosine kinase inhibitors (TKIs) could lead to some common AEs, including hand-foot skin reaction, diarrhea, hypertension, decreased appetite, decreased weight, fatigue, and proteinuria. The pooled analysis showed that the incidence of hand-foot skin reaction and diarrhea was significantly lower in the lenvatinib group compared to the sorafenib group. Whereas, the incidence of hypertension, decreased appetite, weight loss, fatigue, and proteinuria in the

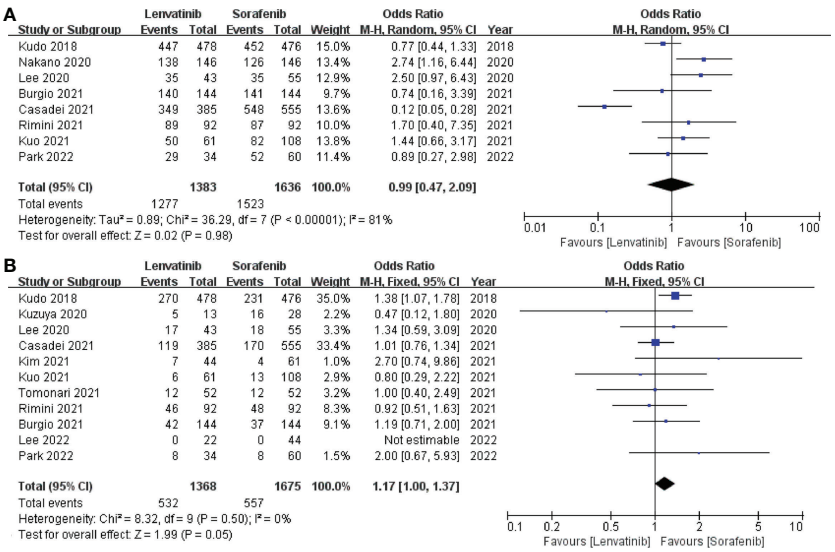

FIGURE 6
Forest plot on any grade AEs **(A)** and grade ≥ 3 AEs **(B)**. AEs, adverse events.

lenvatinib group was significantly higher than in the sorafenib group (Table 2).

3.5 Subgroup analysis

Subgroup analyses were further performed based on the study design and region, yielded similar results to the primary analysis except for the incidence of any grade AEs; the subgroup of Asian region showed the incidence of any grade AEs was significantly lower in the sorafenib group compared to the lenvatinib group (OR = 1.86; 95% CI: 1.18–2.92; p = 0.008). The results are summarized in Table 3.

3.6 Publication bias

To understand whether there is any publication bias influencing our study, funnel plots were drawn for OS, PFS, CR, and grade ≥3 AEs. The funnel plots of the studies were not asymmetrical and were evenly vertically distributed, demonstrating no or limited publication bias (Figure 7).

4 Discussion

Being one of the most prevalent malignant tumors, HCC poses a major threat to human health. Due to its insidious onset,

TABLE 2 Comparison of the incidence of common AEs between the two groups.

Outcomes	No. of studies	Incidence rate (%)		Heterogeneity		The pooled analysis		
		Lenvatinib	Sorafenib	I^2	p	OR	95% CI	p
Hand-foot skin reaction	12 (13, 18–20, 22, 23, 25–28, 30, 31)	23.58	43.68	38%	0.09	0.39	0.33–0.45	< 0.00001
Diarrhea	11 (13, 18, 19, 22, 23, 25–28, 30, 31)	27.56	35.04	47%	0.04	0.67	0.50–0.90	0.007
Decreased appetite	9 (13, 18–20, 25–28, 31)	33.02	21.61	71%	0.0006	1.87	1.13–3.11	0.02
Weight loss	2 (13, 25)	29.12	20.11	4%	0.31	1.59	1.20–2.12	0.01
Hypertension	12 (13, 18–20, 22, 23, 25–28, 30, 31)	36.21	24.22	71%	< 0.0001	2.65	1.78–3.93	< 0.00001
Fatigue	9 (13, 20, 22, 25–28, 30, 31)	33.55	22.15	75%	< 0.0001	1.78	1.12–2.83	0.02
Proteinuria	8 (13, 18–20, 25, 26, 28, 31)	18.94	7.00	0	0.46	3.07	2.27–4.15	< 0.00001

AEs, adverse events; OR, odds ratio; CI, confidence interval.

TABLE 3 Results of subgroup analyses.

Outcomes	No. of studies	No. of Patients	Heterogeneity		The pooled analysis		
			I^2	*p*	HR/OR	95% CI	*p*
RCS							
OS	10 (18–20, 22–24, 27–29, 31)	2393	63%	0.004	0.84	0.67–1.05	0.13
PFS	12 (19–29, 31)	2806	70%	0.0001	0.62	0.51–0.75	< 0.00001
CR	10 (18–21, 24, 26, 28–31)	1437	8%	0.37	6.59	2.89–15.00	< 0.00001
PR	10 (18–21, 24, 26, 28–31)	1437	29%	0.18	5.18	3.27–8.19	< 0.00001
ORR	13 (18–24, 26–31)	2849	41%	0.06	6.15	4.27–8.87	< 0.00001
DCR	12 (18–22, 24, 26–31)	1909	65%	0.0009	2.54	1.76–3.67	< 0.00001
Any grade AEs	7 (19, 20, 22, 23, 26, 27, 31)	2065	83%	< 0.00001	1.04	0.41–2.67	0.93
Grade ≥ 3 AEs	10 (18, 19, 22, 23, 25–28, 30, 31)	2089	0	0.66	1.06	0.87–1.30	0.55
Asian region							
OS	7 (18–20, 24, 28, 29, 31)	981	51%	0.03	0.96	0.71–1.30	0.80
PFS	9 (19–21, 24–26, 28, 29, 31)	1394	72%	0.0004	0.60	0.46–0.78	0.0002
CR	10 (18–21, 24, 26, 28–31)	1437	8%	0.37	6.59	2.89–15.00	< 0.00001
PR	10 (18–21, 24, 26, 28–31)	1437	29%	0.18	5.18	3.27–8.19	< 0.00001
ORR	10 (18–21, 24, 26, 28–31)	1437	48%	0.05	5.80	3.50–9.61	< 0.00001
DCR	10 (18–21, 24, 26, 28–31)	1437	69%	0.0007	2.77	1.76–4.37	< 0.0001
Any grade AEs	4 (19, 20, 26, 31)	653	0	0.39	1.86	1.18–2.92	0.008
Grade ≥ 3 AEs	7 (18, 19, 25, 26, 28, 30, 31)	677	1%	0.41	1.18	0.78–1.79	0.43

HR, hazard ratio; OR, odds ratio; CI, confidence interval; RCS, retrospective cohort study; OS, overall survival; PFS, progression-free survival; CR, complete response; PR, partial response; ORR, objective response rate; DCR, disease control rate; AEs, adverse events.

most patients are diagnosed at an advanced stage and are not eligible for curative treatments. Therefore, systemic therapy plays a crucial role in the treatment of advanced HCC, and the TKIs sorafenib and lenvatinib are currently the most effective first-line monotherapies (32).

Lenvatinib is a selective, multi-targeted TKI of VEGFR1-3 and other receptor tyrosine kinases associated with proangiogenic and oncogenic pathways, including FGFR1-4, PDGFRα, cKIT, and RET (33, 34). Compared to sorafenib, the distinguishing features of lenvatinib is its potent activity against FGFR1-4 (35). Besides, recent studies have revealed that lenvatinib has immunomodulatory activity (36–38). Preliminary data from a clinical trial have also shown that the therapeutic combination of lenvatinib with pembrolizumab resulted in an ORR of 46%, exhibiting promising efficacy in advanced HCC (39). Furthermore, the cost-utility analysis showed that lenvatinib offered similar clinical effectiveness at a lower cost than sorafenib, indicating that lenvatinib may be a cost-saving alternative in patients with advanced HCC (40). However, recent studies that compared the efficacy of lenvatinib and sorafenib in HCC found conflicting results (18–31, 41), and hence the optimal choice for the patient between these two drugs remains controversial. Therefore, our primary aim to perform this systematic review is to evaluate the feasibility and safety of lenvatinib as a first-line treatment for advanced HCC.

In the present study, our findings suggested that there was no significant difference in the OS between the lenvatinib and sorafenib groups. However, the lenvatinib group demonstrated a significantly better outcome in terms of OS than the sorafenib group after the heterogeneity was reduced by excluding outlier trials. Besides, we also found that the PFS, CR, PR, ORR, and DCR values in the lenvatinib group were significantly superior to those in the sorafenib group, indicating the therapeutic advantage of lenvatinib. These results were generally consistent with the results of most of the included studies, in which lenvatinib was non-inferior to sorafenib in terms of OS. A multicentric analysis of 184 patients with advanced HCC in Italy and Japan reported the median OS being 15.2 and 10.5 months for lenvatinib and sorafenib arms, first demonstrating the superiority of lenvatinib over sorafenib regarding the OS in a real-world setting (27). Similarly, recent real-world data from 466 patients in Italy showed a significant advantage in the OS for lenvatinib compared to sorafenib as first-line therapy for advanced HCC (22). Notably, the subgroup analyses showed

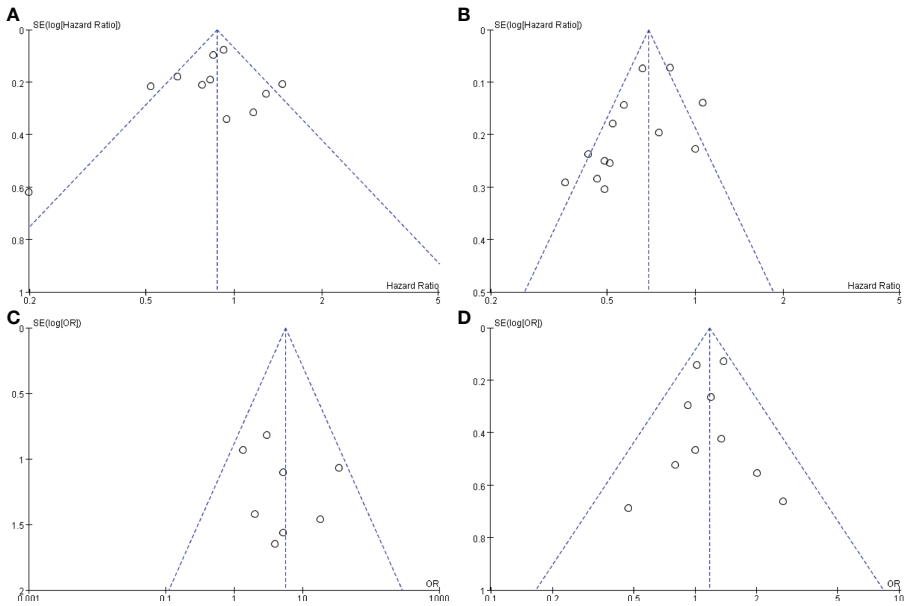

FIGURE 7
Funnel plots based on OS **(A)**, PFS **(B)**, CR **(C)**, and grade ≥3 AEs **(D)**. OS, overall survival; PFS, progression-free survival; CR, complete response; AEs, adverse events.

that patients with objective response had significantly better median OS than those with progressive disease in both sorafenib and lenvatinib groups (18, 20, 30). Although OS is an unbiased primary endpoint for evaluating novel agents in oncology investigations, it has been suggested that PFS and ORR might be better surrogate endpoints. Both PFS and ORR reliably reflect survival benefits and could be assessed before the administration of additional efficacious drugs (42). Besides, Llovet et al. (43) confirmed that PFS had a significant correlation with OS at the trial level and that PFS with a threshold of HR ≤0.6 was highly predictive of a significant improvement in OS. This could explain the significant difference in PFS between the two groups in our study, with HR reaching 0.63 (95% CI: 0.53–0.74), while there was no significant difference in OS.

Regarding treatment safety, this meta-analysis found that lenvatinib had similar incidences of any grade AEs (92.34% vs. 93.09%) and grade ≥ 3 AEs (38.89% vs. 33.25%) compared to sorafenib. Even though the incidence was comparable, lenvatinib and sorafenib showed significant differences in the type of AEs. For instance, lenvatinib was associated with a higher incidence of hypertension, proteinuria, fatigue, decreased appetite, and weight loss, whereas sorafenib was associated with a higher incidence of diarrhea and hand-foot skin reaction. Considering the balance between safety and efficacy and to minimize early dose reduction or interruption, the recommended starting dose of lenvatinib was 8 mg per day for patients weighing < 60 and 12 mg per day for patients weighing ≥ 60 kg (44, 45). The safety profiles of lenvatinib and sorafenib in this study were consistent with those observed in previous studies, which further confirmed that lenvatinib was well tolerated as first-line therapy for advanced HCC.

Similar results were reported in a previous meta-analysis conducted by Facciorusso et al. (41) which included 5 studies involving a total of 1481 patients. The authors compared the efficacy of lenvatinib and sorafenib as first-line therapy for advanced HCC. Their study showed that there was no significant difference in the outcome of OS between the two groups (HR = 0.81; 95% CI: 0.58–1.11); however, lenvatinib significantly improved PFS (HR = 0.67; 95% CI: 0.48–0.94), ORR (OR = 7.70; 95% CI: 2.99–19.82), and DCR (OR = 2.41; 95% CI: 1.55–3.77) compared to sorafenib. Besides, the incidence of severe AEs in the lenvatinib group was 64.9%, which was comparable to that in the sorafenib group (56.4%; OR = 1.31; 95% CI: 0.82–2.09). These results indicated that lenvatinib is associated with a longer PFS and higher response rates as compared to sorafenib, revealing a significantly better therapeutic effect. However, in contrast to our study, the analysis of Facciorusso et al. (41) included only 5 studies with relatively small sample sizes, which might affect the reliability of the results. In addition, our study also conducted a comprehensive comparative analysis of common AEs to confirm the good tolerability of lenvatinib.

Nonetheless, our study has several limitations. First, significant heterogeneity among studies in some outcomes was observed, which could be attributed to parameters such as different study designs, population demographics, follow-up times, and interventions. Second, our analysis was limited by studies published in English language, and therefore omission of relevant

articles published in other languages is a possibility. Finally, most of the included studies (n=14) were retrospective and nonrandomized, suggesting that unmeasured confounders and selection or recall bias may have influenced the results of these studies.

5 Conclusion

This systematic review and meta-analysis showed that lenvatinib potentially has a survival advantage over sorafenib in terms of OS, in addition to having significant gains in PFS, CR, PR, ORR, and DCR. Moreover, the safety profiles of lenvatinib and sorafenib were found to be similar and well-tolerated. In conclusion, our study shows that lenvatinib is an appropriate and promising first-line systemic therapy for advanced HCC. However, given the limitations of this analysis, further large-sample and high-quality RCTs are required to conclusively establish this finding in the future.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Author contributions

JL, BG, and BL conceived and designed the study. ZL and HF screened electronic databases. WM, DY, and QY extracted data from the selected articles. JT and XY evaluated eligible study quality and potential bias risk. Statistical analyses were performed by BG. JL and BG wrote the manuscript. JL and BL supervised the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Identify optimal HAP series scores for unresectable HCC patients undergoing TACE plus sorafenib: A Chinese multicenter observational study

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Background: Hepatoma arterial-embolization prognostic (HAP) series scores have been proposed for prognostic prediction in patients with unresectable hepatocellular carcinoma (uHCC) undergoing transarterial chemoembolization (TACE). However, their prognostic value in TACE plus sorafenib (TACE-S) remains unknown. Here, we aim to evaluate their prognostic performance in such conditions and identify the best model for this combination therapy.

Methods: Between January 2012 and December 2018, consecutive patients with uHCC receiving TACE-S were recruited from 15 tertiary hospitals in China. Cox regression analyses were used to investigate the prognostic values of baseline factors and every scoring system. Their prognostic performance and discriminatory performance were evaluated and confirmed in subgroup analyses.

Results: A total of 404 patients were enrolled. In the whole cohort, the median follow-up period was 44.2 (interquartile range (IQR), 33.2–60.7) months, the median overall survival (OS) time was 13.2 months, and 336 (83.2%) patients died at the end of the follow-up period. According to multivariate analyses, HAP series scores were independent prognostic indicators of OS. In addition, the C-index, Akaike information criterion (AIC) values, and time-dependent area under the receiver operating characteristic (ROC) curve (AUC) indicated that modified HAP (mHAP)-III had the best predictive performance. Furthermore, the results remained consistent in most subsets of patients.

Conclusion: HAP series scores exhibited good predictive ability in uHCC patients accepting TACE-S, and the mHAP-III score was found to be superior to the other HAP series scores in predicting OS. Future prospective high-quality studies should be conducted to confirm our results and help with treatment decision-making.

KEYWORDS

hepatocellular carcinoma, transarterial chemoembolization, sorafenib, HAP series scores, predictive value

Introduction

Transarterial chemoembolization (TACE) is the mainstay of therapy modalities for unresectable hepatocellular carcinoma (uHCC) patients in real-world clinical practice, while upregulation of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptor after TACE is closely associated with poor prognosis (1, 2). As a commonly used systematic treatment, sorafenib could suppress the factors mentioned above; thus, the treatment strategy of TACE plus sorafenib (TACE-S) is theoretically proposed to be a "good marriage" (3–5). Nevertheless, previous randomized controlled trials (RCTs) and observational studies have failed to reach a consensus on whether the combined use of sorafenib could bring survival benefits for uHCC patients as compared with TACE alone (6–12). Moreover, the median overall survival (OS) of uHCC patients undergoing TACE-S varies widely from 15.1 to 29.7 months (6–13). Therefore, we might infer that there was high heterogeneity among uHCC patients treated with TACE-S, and a well-performing prognostic model would be helpful for accurate survival prediction, as well as individual patient selection.

Unlike other solid tumors, liver function also plays an important role in decision-making and prognostic evaluation in addition to the tumor itself (14, 15). Child–Pugh classification, albumin–bilirubin (ALBI) grade, and platelet–albumin–bilirubin (PALBI) grade were used to assess liver function in clinical practice and were verified to be predictive for survival in uHCC patients treated with TACE-S (13, 16). Considering both tumor- and liver function-related factors, the hepatoma arterial-embolization prognostic (HAP) score (including tumor size, bilirubin, albumin, and α-fetoprotein (AFP)) has exhibited a promising prediction performance in uHCC patients following TACE (17–20). Subsequently, modified HAP (mHAP), mHAP-II, and mHAP-III scores were developed to enhance the prognostic ability of the HAP score originally proposed by L. Kadalayil. Nevertheless, the prognostic value of HAP series scores remained unknown in uHCC patients undergoing TACE-S.

In summary, this large multicenter exploratory study aims to investigate the prognostic factors in uHCC patients undergoing TACE-S, evaluate the predictive values of HAP series scores, and identify the most reliable one for survival prediction and patient selection.

Materials and methods

Study population and eligibility

Between January 2012 and December 2018, study data on consecutive uHCC patients receiving TACE-S were retrospectively extracted from a multicenter database of 15 Chinese tertiary hospitals. HCC was diagnosed according to the American Association for the Study of Liver Diseases/ European Association for the Study of the Liver guidelines (21, 22). Patients needed to meet the following inclusion criteria: I) Child–Pugh grade A or B, II) Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0 or 1, III) time interval between the first TACE and sorafenib initiation at no more than 30 days, and IV) treatment-naïve uHCC patients. Patients were excluded based on the following criteria: I) missing variables included in calculating HAP, modified HAP (mHAP, mHAP-II, and mHAP-III) scores; II) combined with other tumors or severe cardiac, cerebral, and renal insufficiency; III) diffused tumor; IV) moderate or severe ascites. Finally, a total of 404 eligible HCC patients undergoing TACE-S were included (Figure 1). Written informed consent was obtained from all patients before treatment initiation, which consisted of consent to treatment and the potential use of clinical data in future investigations. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institute's committee on human research of each participating center.

Treatment and follow-up

According to the study protocol, treatment decisions were made at the discretion of the institutional multidisciplinary liver tumor boards of each enrolled center. Before TACE, hepatic arteriography was carried out to evaluate the vascular anatomy and tumor vascularity. During the TACE procedure, a vascular catheter was inserted selectively into the tumor-feeding artery with an injection containing a mixture of doxorubicin (10–50 mg) and lipiodol (2–20 ml), cisplatin (10–110 mg), epirubicin (10–50 mg), and oxaliplatin (100–200 mg), which were selected according to the practice of each center, followed by embolization using gelatin sponge particles. When residual viable tumors were confirmed or new lesions developed in patients with adequate liver function, repeated TACE was permitted. At an initial dose of 400 mg twice daily, sorafenib was initiated before/at/after the day of the first TACE and continuously used with no breaks thereafter. Moreover, the dose of sorafenib could be modified on the basis of the presence of toxicity and individuals' drug tolerance. In general, patients were encouraged to continue sorafenib therapy unless unmanageable or life-threatening adverse events occurred. The patients who were concomitantly treated by sorafenib within 30 days before or after initial TACE were considered to be receiving TACE-S therapy. All patients were followed up at 1 month after TACE therapy and then at 3-month intervals in the first year and every 6–12 months thereafter. In clinical practice, the intensity of follow-up depends on individuals' baseline characteristics and responses to the last treatment, as appropriate. Routine examinations were conducted at each follow-up, which included physical examinations, blood tests (tumor markers, blood and urine routine, and liver and renal function), and imaging examinations (chest X-ray, abdominal ultrasonography, abdominal contrast-enhanced CT, or MRI). The follow-up of the last patient was completed in September 2021.

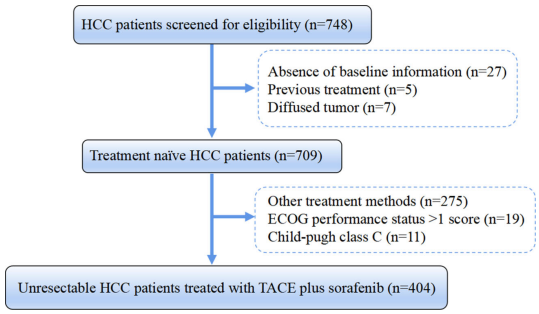

FIGURE 1
Flowchart of the patient selection process. HCC, hepatocellular carcinoma; HBV, hepatitis B virus; ECOG, Eastern Cooperative Oncology Group; TACE, transarterial chemoembolization.

HAP serial score calculation

The detailed scoring method of each HAP series score is shown in Table 1. All HAP scores and their modified versions included the most significant indicators of OS: albumin, AFP, and tumor size. However, not exactly the same as the HAP score, mHAP removed the variable bilirubin; mHAP-II added tumor number based on the HAP score; and with the same factors of mHAP-II, the mHAP-III components were continuous instead of dichotomized (17–20).

Statistical analysis

Continuous variables were described by the mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables were expressed as frequencies and percentages. OS was defined as the time from the first session of TACE until death or last follow-up, and patients who were still alive were censored at the date of the last contact. Median OS was estimated using the Kaplan–Meier curves and compared with the log-rank test. Univariate and multivariate Cox

TABLE 1 HAP serial score calculation.

Prognostic model	HAP (17)	mHAP (18)	mHAP-II (19)	mHAP-III (20)
Author (year)	L. Kadalayil et al. (2013)	David J. Pinato et al. (2015)	Yehyun Park et al. (2016)	Alberta Cappelli et al. (2016)
Sample size (n)	114	723	280	361
Prognostic factors	a. Albumin (<36 g/dl: 1 point; ≥36 g/dl: 0 points) b. Bilirubin (>17 μmol/L: 1 point; ≤17 μmol/L: 0 points) c. AFP (>400 ng/ml: 1 point; ≤400 ng/ml: 0 points) d. Tumor size (>7 cm: 1 point; ≤7 cm: 0 points)	a. Albumin (<36 g/dl: 1 point; ≥36 g/dl: 0 points) b. AFP (>400 ng/ml: 1 point; ≤400 ng/ml: 0 points) c. Tumor size (>7 cm: 1 point; ≤7 cm: 0 points)	a. Albumin (<36 g/dl: 1 point; ≥36 g/dl: 0 points) b. Bilirubin (>17 μmol/L: 1 point; ≤17 μmol/L: 0 points) c. AFP (>400 ng/ml: 1 point; ≤400 ng/ml: 0 points) d. Tumor size (>7 cm: 1 point; ≤7 cm: 0 points) e. Tumor number (≥2 nodules: 1 points; <2 nodules: 0 points)	(0.104 * size in cm) + (0.3089 * number (single nodule = 1; 2–3 nodules = 2; more than three nodules = 3)) + (0.2185 * Log10AFP in ng/ml) − (0.4049 * Albumin in g/dl) + (0.1506 * Bilirubin in mg/dl)
Classification	HAP A: 0; HAP B: 1; HAP C: 2; HAP D: >2	mHAP A: 0; mHAP B: 1; mHAP C: 2; mHAP D: >2	mHAP-II A: 0; mHAP-II B: 1; mHAP-II C: 2; mHAP-II D: >2	–

HAP, hepatoma arterial-embolization prognostic; mHAP, modified HAP; AFP, α-fetoprotein.

proportional hazards regression models were used to analyze independent prognostic factors. Notably, five multivariate models with stepwise methods were separately conducted to avoid collinearity: model 1 included the baseline characteristics; model 2 included the baseline characteristics and HAP score but excluded albumin, AFP, tumor size, and bilirubin; model 3 included the baseline characteristics and mHAP score but excluded albumin, AFP, and tumor size; model 4 included the baseline characteristics and mHAP-II score but excluded albumin, AFP, bilirubin, tumor number, and tumor size; model 5 included the baseline characteristics and mHAP-III score but excluded albumin, AFP, bilirubin, tumor number, and tumor size. The discriminatory abilities of different prognostic score methods were compared using the C-index and time-dependent area under the receiver operating characteristic curve (AUC). Correlation analysis was performed by Kendall's rank correlation coefficient tau-b. The Akaike information criterion (AIC) was also calculated to compare the loss of information for different models. The net reclassification improvement (NRI) statistic and the integrated discrimination improvement (IDI) statistic were used to evaluate the overall improvement in predictive value among HAP series scores. Subgroup analyses for the above evaluation indicators were conducted among different baseline backgrounds in order to avoid the potential influence of confounders. An additional benefit was also evaluated using decision curve analysis (DCA). Briefly, DCA was used to calculate the net benefit of new markers across various risk thresholds by taking into account weighted risks and benefits. Two-tailed p-values <0.05 for all analyses were identified as statistically significant. Statistical analyses were performed using R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS software version 26.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Among the 404 enrolled patients, the mean age was 52.2 years, 336 (83.2%) patients were male, and the most common etiology was hepatitis B virus infection (337, 83.4%). The median tumor size (maximum diameter of the largest tumor) was 8.4 (IQR, 6.0–11.5) cm, and the median tumor number was 1 (IQR, 1.0–2.8). Additionally, 194 (48.0%) patients were classified as ECOG-PS of 0. Extrahepatic spread (EHS) was present in 12.9% (52), and portal vein tumor thrombosis (PVTT) was noted in 17.1% (69) of the whole population. According to the HAP, mHAP, and mHAP-II scoring systems, patients were divided into four distinct groups (A, B, C, and D). In addition, the median mHAP-III score of all patients was 0.50 (IQR, 0.03–1.07). For consistency with the scoring systems mentioned above, patients were classified into four groups (A, B, C, and D) based on the median and IQR of the mHAP-III score. The detailed baseline characteristics are described in Table 2.

Survival analysis of the whole cohort

In the whole cohort, the median follow-up period was 44.2 (IQR, 33.2–60.7) months, 68 (16.8%) patients were alive at the end of the follow-up period, and 336 (83.2%) patients had died. The median OS of the entire cohort reached 13.2 [95% confidence interval (CI) 11.6–14.8] months with 1-, 2-, and 3-year survival rates of 53.9%, 29.1%, and 17.0%, respectively (Figure 2). In univariate and multivariate analyses (Tables 2, 3), tumor size (adjusted HR 1.047, 95% CI 1.012–1.085), tumor number (adjusted HR 1.040, 95% CI 1.091–1.191), AFP

TABLE 2 Baseline characteristics for the study patients (n = 404).

Characteristics	Values
Gender, male/female, n (%)	336 (83.2)/68 (6.8)
Age at start, year, mean ± SD	52.2 ± 12.6
Etiology, HBV/non-HBV, n (%)	337 (83.4)/67 (16.6)
Tumor size, cm, median (IQR)	8.4 (6.0–11.5)
Tumor number, cm, median (IQR)	1.0 (1.0–2.8)
PVTT, positive/negative, n (%)	69 (17.1)/335 (82.9)
EHS, positive/negative, n (%)	52 (12.9)/352 (87.1)
AFP, ≤400/>400 ng/ml, n (%)	212 (52.5)/192 (47.5)
HGB, g/L, mean ± SD	134.4 ± 21.7
PLT, 10^9/L, median (IQR)	141.0 (89.0–188.5)
INR, median (IQR)	1.09 (1.02–1.19)
ALT, U/L, median (IQR)	37.5 (25.0–56.0)
AST, U/L, median (IQR)	48.5 (31.0–74.0)
ALB, g/L, mean ± SD	39.1 ± 50.2
TBIL, μmol/L, median (IQR)	15.4 (11.3–20.9)
BUN, mmol/L, median (IQR)	4.7 (3.9–5.7)
SCr, μmol/L, median (IQR)	81.0 (69.0–94.0)
Child–Pugh class, A/B, n (%)	368 (91.1)/36 (8.9)
Ascites, positive/negative, n (%)	50 (12.4)/354 (87.6)
ECOG score, 0/1, n (%)	194 (48.0)/210 (52.0)
BCLC stage, A/B/C/D, n (%)	88 (21.8)/65 (16.1)/201 (49.8)/50 (12.4)
TNM classification, I_B/II/III_A/IV_A/IV_B	149 (36.9)/65 (16.1)/138 (34.2)/7 (1.7)/45 (11.1)
HAP, A/B/C/D, n (%)	35 (8.7)/129 (31.9)/148 (36.6)/92 (22.8)
mHAP, A/B/C/D, n (%)	59 (14.6)/170 (42.1)/145 (35.9)/30 (7.4)
mHAP-II, A/B/C/D, n (%)	16 (4.0)/85 (21.0)/126 (31.2)/177 (43.8)
mHAP-III score, median (IQR)	0.5 (0.0–1.1)

SD, standard deviation; HBV, hepatitis B virus; IQR, interquartile range; AFP, α-fetoprotein; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; PVTT, portal vein tumor thrombosis; EHS, extrahepatic spread; HAP, hepatoma arterial-embolization prognostic; mHAP, modified HAP; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; SCr, serum creatinine; INR, international normalized ratio; HGB, hemoglobin; TBIL, total bilirubin; ALB, albumin; PLT, platelet.

(adjusted HR 1.271, 95% CI 1.010–1.600), total bilirubin (TBIL) (adjusted HR 1.021, 95% CI 1.005–1.037), ALB (adjusted HR 0.952, 95% CI 0.927–0.977), PVTT (adjusted HR 3.020, 95% CI 2.202–4.142), and EHS (adjusted HR 2.082, 95% CI 1.503–2.886) were independent significant predictors of OS (all $p < 0.05$).

Prognostic values of HAP series scores in TACE-S

According to the Kaplan–Meier analyses, the HAP, mHAP, and mHAP-III scores had obvious discriminatory abilities among the A, B, C, and D groups ($p < 0.05$), whose OS showed a gradient downward trend (Figures 3A, B, D). However, although mHAP-II had a gradient downward trend in median survival through classes, it could not distinguish patients between Groups A and B ($p = 0.935$) or between Groups A and C ($p = 0.183$) (Figure 3C). According to multivariate models 2 to 5, the HAP (adjusted HR 1.274, 95% CI 1.107–1.466), mHAP (adjusted HR 1.266, 95% CI 1.084–1.478), mHAP-II (adjusted HR 1.422, 95% CI 1.230–1.644), and mHAP-III (adjusted HR 1.772, 95% CI 1.455–2.158) score systems remained independent predictors of OS in patients treated with TACE-S (all $p < 0.05$, Table 4).

By comparing high-grade HAP series scores (grade C/D) with low-grade HAP series scores (grade A/B), there were significant differences in age, etiology, PVTT, and liver and renal function (platelet (PLT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), and serum creatinine (SCr)) in addition to the components of HAP series scores (Tables S1–4). Furthermore, Kendall's tau-b analysis showed that there were certain correlations among HAP series scores (Figure S1).

Comparing the performance of HAP series scores

On the basis of time-dependent AUC analysis and AIC value, mHAP-III had the lowest AIC value (C-index, 0.684; AIC, 3398.64), which indicated a more favorable prognostic performance and

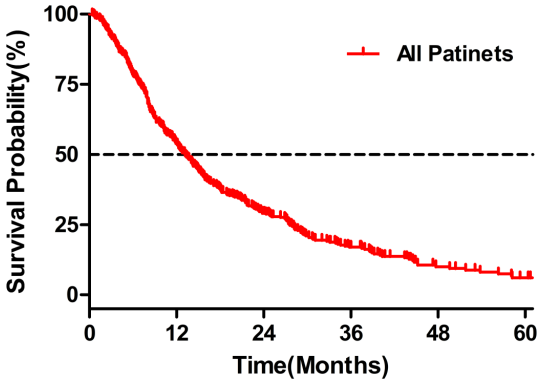

FIGURE 2
Survival analyses in the whole cohort.

TABLE 3 Univariate analyses for OS in the whole cohort.

Characteristics	Univariate analyses	
	HR (95% CI)	p-Value
Gender, male (ref: female)	1.112 (0.831–1.489)	0.475
Age, per year increase	0.995 (0.987–1.004)	0.273
Etiology, others (ref: HBV)	0.834 (0.624–1.114)	0.218
Tumor size, per 1 cm increase	1.094 (1.064–1.125)	<0.001
Tumor number, per 1 lesion increase	1.180 (1.130–1.231)	<0.001
AFP > 400 ng/ml (ref: ≤400 ng/ml)	1.461 (1.178–1.810)	0.001
ALB, per 1 g/dl increase	0.938 (0.918–0.959)	<0.001
TBIL, per 1 μmol/L increase	1.030 (1.016–1.045)	<0.001
AST, per 1 U/L increase	1.007 (1.005–1.009)	<0.001
ALT, per 1 U/L increase	1.001 (0.998–1.004)	0.368
PLT, per 1 × 10^9/L increase	1.001 (0.999–1.002)	0.376
INR, per 1% increase	2.357 (1.487–3.737)	<0.001
BUN, per 1 mmol/L increase	1.005 (0.932–1.083)	0.904
SCr, per 1 μmol/L increase	0.998 (0.982–0.995)	<0.001
Ascites, positive (ref: negative)	1.720 (1.263–2.343)	0.001
PVTT, positive (ref: negative)	3.593 (2.708–4.768)	<0.001
EHS, positive (ref: negative)	1.759 (1.302–2.378)	<0.001
ECOG, per 1 grade increase	2.245 (1.802–2.798)	<0.001
HAP score, per 1 grade increase	1.604 (1.414–1.819)	<0.001
mHAP score, per 1 grade increase	1.682 (1.466–1.930)	<0.001
mHAP-II score, per 1 grade increase	1.706 (1.488–1.956)	<0.001
mHAP-III score, per 1 score increase	2.319 (1.972–2.726)	<0.001

OS, overall survival; HR, hazard ratio; HBV, hepatitis B virus; AFP, α-fetoprotein; ECOG, Eastern Cooperative Oncology Group; PVTT, portal vein tumor thrombosis; EHS, extrahepatic spread; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; SCr, serum creatinine; INR, international normalized ratio; TBIL, total bilirubin; ALB, albumin; PLT, platelet.

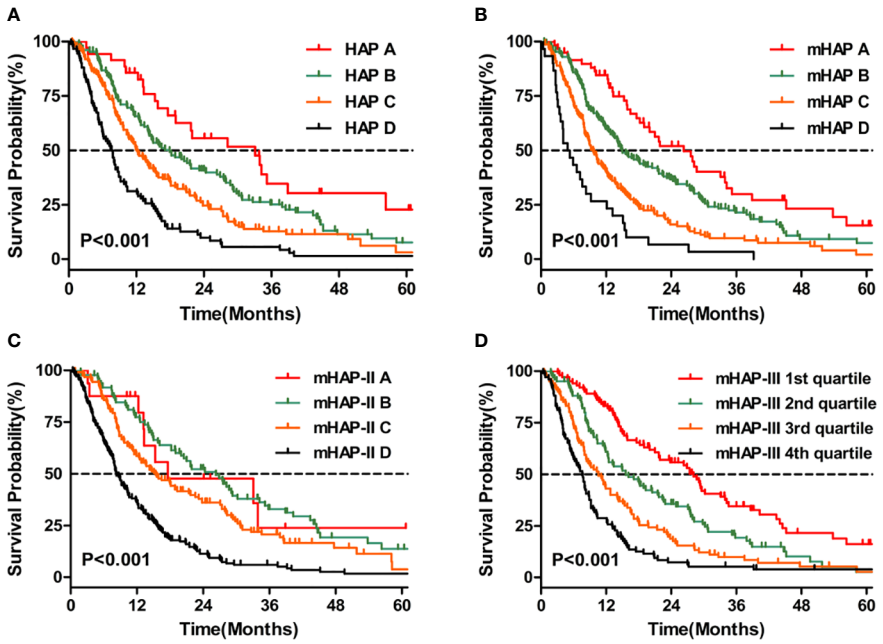

FIGURE 3
Kaplan–Meier curves for OS. **(A)** Comparison of survival between patients with HAP A, HAP B, HAP C, and HAP D **(B)** Comparison of survival between patients with mHAP A, mHAP B, mHAP C, and mHAP D **(C)** Comparison of survival between patients with mHAP-II A, mHAP-II B, mHAP-II C, and mHAP-II D **(D)** Comparison of survival between patients with mHAP-III (1st quartile, 2nd quartile, 3rd quartile, and 4th quartile). HAP, hepatoma arterial-embolization prognostic; mHAP, modified hepatoma arterial-embolization prognostic; OS, overall survival.

model-fitting ability as compared with the HAP (C-index, 0.628; AIC, 3447.08), mHAP (C-index, 0.628; AIC, 3447.82) and mHAP-II score (C-index, 0.637; AIC, 3438.40) in the whole cohort ($p < 0.05$) (Figure 4). As was shown in the forest plots, mHAP-III still showed an obvious and stable predictive performance among the majority of subsets (Figure 5). The detailed p-value of mHAP-III compared with HAP, mHAP, and mHAP-II scores in the whole cohort and each subset has been clarified in Table S5. Notably, according to the NRI and IDI statistics, the predictive ability of the mHAP-III was improved as compared with that of other scoring systems at the time point of 1, 2, and 3 years in the whole cohort. Similarly, the superiority of mHAP-III in predicting survival was subsequently confirmed in subset analyses (Figure 6). Moreover, the performance of the BCLC stage (C-index, 0.662; AIC, 3426.11) and TNM classification (C-index, 0.634; AIC, 3455.08) significantly lowered the mHAP-III, especially in the hepatitis B virus (HBV) subsets (Table S5). The DCA curve showed that the HAP series models achieved great clinical benefits (Figure 7).

Discussion

TACE-S is usually used for the treatment of uHCC in clinical practice, but there are no suitable methods available for individual survival prediction. By comparing the predictive abilities of HAP series scores in uHCC patients treated by TACE-S, this nationwide multicenter retrospective observational study found that HAP series scores could predict survival in TACE-S and that mHAP-III had the best discriminatory performance. The advantages of our study lie in the multicenter nature and large sample size, as well as the first time to explore the prognostic values of HAP series scores in TACE-S.

It has been demonstrated that the TACE procedure might upregulate the expression of hypoxia-inducible factor-1α (HIF-1α) and then activate the proangiogenic factors VEGF and PDGF, which are associated with early tumor recurrence and poor prognosis of HCC (1, 2). Acting through selectively targeting VEGF and PDGF receptors, sorafenib plays a vital role in suppressing angiogenesis and exerts direct antitumor effects (4, 5). Therefore, combining TACE and sorafenib may be a good strategy for improving clinical outcomes (3). Previous studies have reported a median OS of 15.1–29.7 months in uHCC patients treated with TACE-S (6–13). However, the median OS of 13.2 months in our study was shorter, which was probably attributed to a higher proportion of patients with ECOG 1, PVTT, and/or EHS. The large variation in OS indicated substantial heterogeneity among uHCC patients undergoing TACE-S. Therefore, using effective baseline clinical features to identify optimal candidates who tend to benefit most from

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TABLE 4 Multivariate analyses for OS in the whole cohort.

Characteristics	Model 1		Model 2		Model 3		Model 4		Model 5	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Tumor size, per 1 cm increase	1.047 (1.012–1.085)	0.009								
Tumor number, per 1 lesion increase	1.140 (1.091–1.191)	<0.001	1.140 (1.092–1.191)	<0.001	1.141 (1.093–1.192)	<0.001				
AFP > 400 ng/ml (ref: ≤400 ng/ml)	1.271 (1.010–1.600)	0.041								
ALB, per 1 g/dl increase	0.952 (0.927–0.977)	<0.001								
TBIL, per 1 μmol/L increase	1.021 (1.005–1.037)	0.008			1.017 (1.002–1.691)	0.029				
AST, per 1 U/L increase	1.002 (0.999–1.005)	0.119	1.004 (1.001–1.006)	0.004	1.003 (1.001–1.006)	0.010	1.004 (1.002–1.006)	0.001	1.002 (1.000–1.005)	0.106
INR, per 1% increase	1.202 (0.621–2.326)	0.585	1.428 (0.832–2.452)	0.196	1.381 (0.783–2.438)	0.265	1.558 (0.943–2.575)	0.083	1.726 (1.069–2.787)	0.025
SCr, per 1 μmol/L increase	0.999 (0.993–1.005)	0.742	0.996 (0.990–1.002)	0.178	0.997 (0.991–1.002)	0.251	0.995 (0.989–1.001)	0.098	0.998 (0.992–1.004)	0.457
Ascites, positive (ref: negative)	1.035 (0.731–1.463)	0.848	1.052 (0.747–1.482)	0.770	1.021 (0.722–1.443)	0.907	1.145 (0.819–1.602)	0.428	1.230 (0.879–1.720)	0.226
PVTT, positive (ref: negative)	3.020 (2.202–4.142)	<0.001	2.908 (2.134–3.962)	<0.001	2.923 (2.143–3.986)	<0.001	2.661 (1.952–3.626)	<0.001	2.539 (1.857–3.470)	<0.001
EHS, positive (ref: negative)	2.082 (1.503–2.886)	<0.001	2.007 (1.462–2.756)	<0.001	1.983 (1.445–2.722)	<0.001	2.045 (1.490–2.807)	<0.001	1.929 (1.403–2.650)	<0.001
ECOG, per 1 grade increase	1.201 (0.925–1.559)	0.170	1.340 (1.040–1.727)	0.023	1.306 (1.009–1.691)	0.042	1.426 (1.115–1.824)	0.005	1.290 (1.005–1.657)	0.046
HAP score, per 1 grade increase			1.274 (1.107–1.466)	0.001						
mHAP score, per 1 grade increase					1.266 (1.084–1.478)	0.003				
mHAP-II score, per 1 grade increase							1.422 (1.230–1.644)	<0.001		
mHAP-III score, per 1 score increase									1.772 (1.455–2.158)	<0.001

AFP, α-fetoprotein; ECOG, Eastern Cooperative Oncology Group; PVTT, portal vein tumor thrombosis; EHS, extrahepatic spread; HAP, hepatoma arterial-embolization prognostic; mHAP, modified HAP; AST, aspartate aminotransferase; SCr, serum creatinine; INR, international normalized ratio; TBIL, total bilirubin; ALB, albumin.

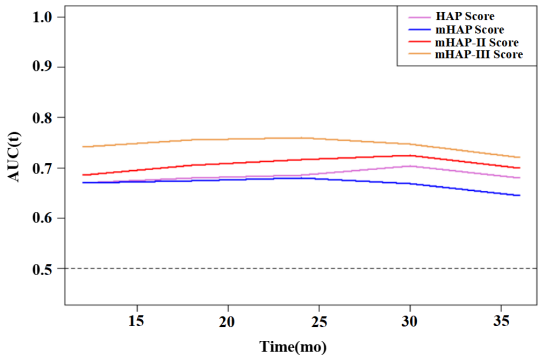

FIGURE 4
Time-dependent AUC for HAP series scores for predicting OS. HAP, hepatoma arterial-embolization prognostic; mHAP, modified hepatoma arterial-embolization prognostic; OS, overall survival; mo, months; AUC, area under the receiving operating curve.

TACE-S is needed. Tumor burden is closely related to the prognosis of HCC patients. According to a previous study, tumor size and number increased, and the death risk was significantly increased for HCC patients treated by TACE-S (13). Similarly, our analyses suggested that tumor size and tumor number were independent prognostic risk factors among those patients. In addition, high serum AFP level has been identified as a biomarker for HCC associated with a more aggressive tumor phenotype and inferior outcomes after different treatment modalities in accordance with our statistical analyses (23). However, except for the indicators of tumor aggressiveness, it should be noted that the prognosis of HCC is more complicated than that of other solid malignant tumors, as most HCC patients have underlying liver diseases, such as liver cirrhosis, which is a major hurdle in prognosis assessment and patient management. As expected, a number of studies have identified indicators of liver function (ALBI, PALBI, and Child–Pugh grade) associated with the prognosis of patients undergoing TACE-S (13, 16). In the current study, albumin and total bilirubin were also deemed as independent prognostic factors. Given the aforementioned reasons, we should take both tumor characteristics and indicators of liver function into consideration when evaluating the prognosis of HCC patients.

The HAP score integrated tumor size, AFP, bilirubin, and albumin together, and the three modified HAP series scores (mHAP, mHAP-II, and mHAP-III) were subsequently developed through various adjustments subsequently (17). All of these scores, which were originally used to predict the outcomes of HCC patients after TACE, were also proven to have predictive abilities in TACE-S in this study (18–20). Furthermore, mHAP-III still had the best prognostic performance consistently at each time point, as displayed in the time-dependent AUC, which might be because of the following: i) mHAP-III included more indicators than the HAP and mHAP scores, ii) the use of continuous variables in the mHAP-III provided detailed information and individual

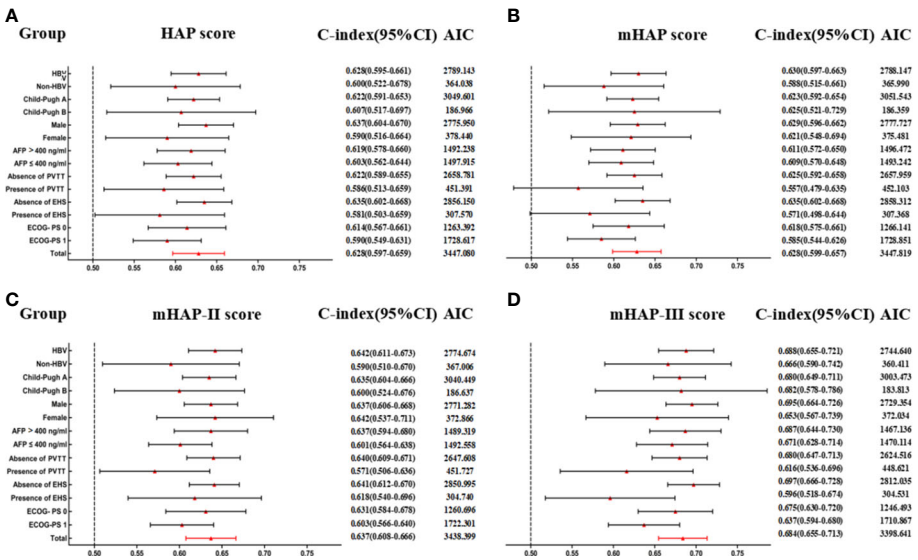

FIGURE 5
Subgroup analyses for HAP series scores to predict OS. **(A)** Predictive ability of HAP score in different subgroups. **(B)** Predictive ability of mHAP score in different subgroups. **(C)** Predictive ability of mHAP-II score in different subgroups. **(D)** Predictive ability of mHAP-III score in different subgroups. AIC, Akaike information criterion; HBV, hepatitis B virus; AFP, α-fetoprotein; ECOG, Eastern Cooperative Oncology Group; PS, performance status; HAP, hepatoma arterial-embolization prognostic; mHAP, modified HAP.

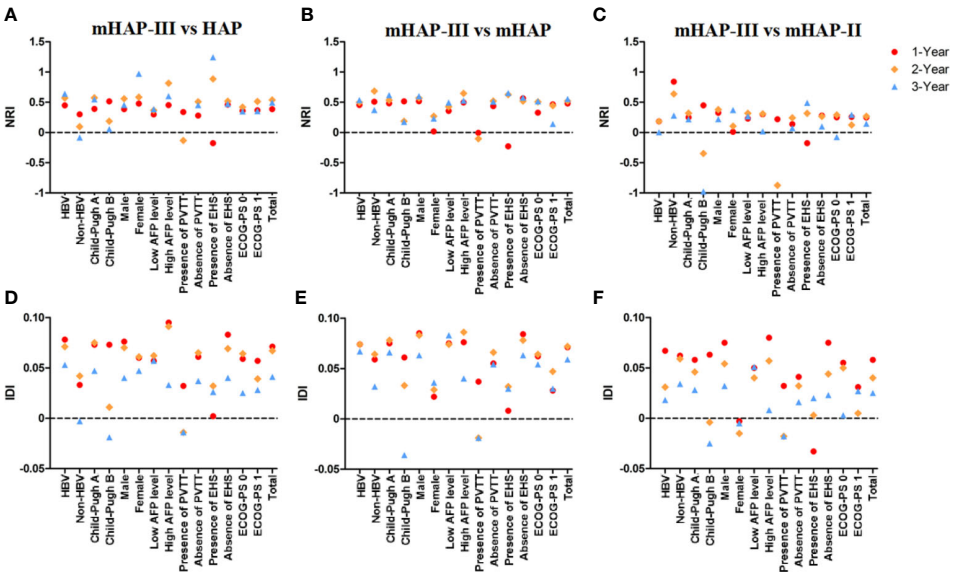

FIGURE 6
Net reclassification index (NRI) and integrated discrimination improvement (IDI) statistics. **(A–C)** NRI for mHAP-III *vs.* HAP, mHAP-III *vs.* mHAP, and mHAP-III *vs.* mHAP-II. **(D–F)** IDI for mHAP-III *vs.* HAP, mHAP-III *vs.* mHAP, and mHAP-III *vs.* mHAP-II. HAP, hepatoma arterial-embolization prognostic; mHAP, modified HAP.

predictions, and iii) mHAP-III applied different weights for each independent prognostic factor. Subgroup analyses were also conducted to verify the stability of our results, and mHAP-III showed the highest C-index and the lowest AIC value, particularly in patients with good baseline characteristics. The reason might be that HAP series scores were initially established in well-performing HCC patients treated with TACE alone. It was also suggested that the HAP series scores might be more suitable for the uHCC patients treated with TACE-S in the early and intermediate stages. Moreover, although mHAP-II and mHAP-III had the same variables, mHAP-II was less discriminative than mHAP-III, which may be due to

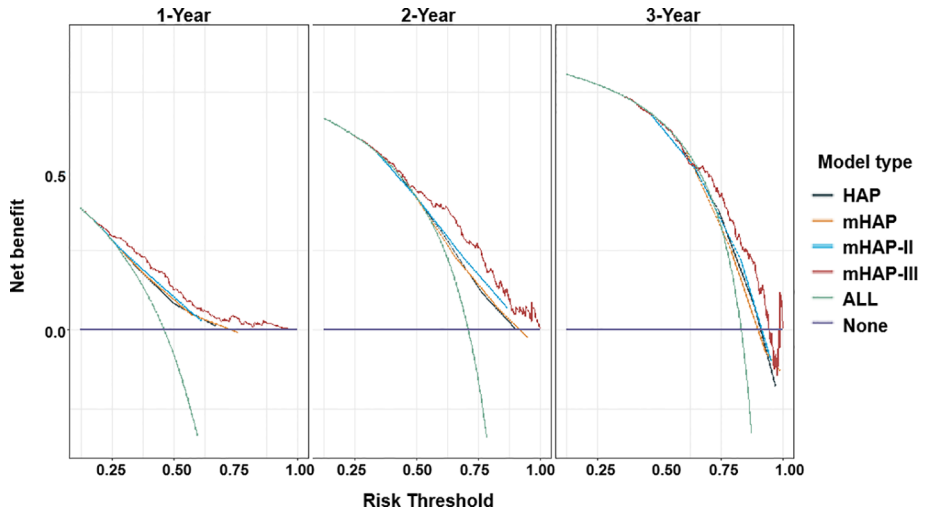

FIGURE 7
Decision curve analysis (DCA) for HAP series scores. Net benefit of using a model to predict 1-, 2-, and 3-year events of death as compared with strategies of "assume high risk to all" or "assume low risk to all" for different thresholds. HAP, hepatoma arterial-embolization prognostic.

categorical variables on arbitrary or optimal cutoffs being used in mHAP-II, and appropriate weights were not designated in each enrolled variable. In aggregate, mHAP-III showed superior predictive accuracy and discriminatory abilities in patients treated with not only TACE but also TACE-S. In fact, the factors included in the HAP series are closely related to the prognosis of HCC patients, and they can also be used to predict the prognosis of HCC patients treated with other therapies.

To the best of our knowledge, PVTT and EHS reflect the aggressiveness of HCC and have been deemed as negative prognostic predictors in different staging systems (24–27). Beyond the guideline recommendation, TACE-S has been widely used to manage uHCC patients with PVTT and EHS in real-world clinical practice. In the present study, patients with PVTT (adjusted HR 3.020, 95% CI 2.202–4.142) and EHS (adjusted HR 2.082, 95% CI 1.503–2.886) were involved, increasing mortality risk by approximately two- to threefold in uHCC patients undergoing TACE-S. Therefore, considering that sorafenib is a systematic treatment for advanced HCC, a possible way would be to include factors such as both of them to further refine the prognostic model. Additionally, NRI was closely related to the set time point, and the survival time of patients with PVTT in this study was less than 3 years. Thus, there was no point in the presence of PVTT at 3 years (Figures 6A–C). Furthermore, ECOG-PS has also been identified as being associated with survival, which plays an important role in risk stratification for HCC patients (28). However, the influence of ECOG-PS did not reach significant statistical significance in model 1, which might be because ECOG-PS was affected by tumor burden and liver function, while the effect was offset by these cofounders. This finding emphasized from another perspective that huge heterogeneity exists in uHCC patients and individual patient-level prognostication should be conducted. Moreover, future studies could explore and consider multiple risk factors, such as age, etiology, and renal function, and integrate various evaluation indicators to find the optimal prediction model.

The results of this study should nevertheless be interpreted in light of several limitations. On the one hand, the existence of information bias in this article is inevitable due to its retrospective nature. To minimize potential bias, uHCC patients treated with TACE-S from a national multicenter were included, and multiple follow-up visits were attempted for each unreachable patient. Due to the decrease in sample size in each risk stratification, the statistical power was weakened during subgroup analysis. Consequently, a larger sample size and prospective research are needed to further verify the results of our study. Moreover, the retrospective study cannot explore the causal relationship between survival and the scoring system. We also will further explore this issue in subsequent prospective studies. On the other hand, most of the patients in our study had HBV-related HCC. In addition, hepatitis C virus infection and alcoholic liver disease are also important pathogenic factors of HCC (29, 30). It is worth noting that there has been a marked increase in non-viral hepatitis mostly caused by metabolic-associated fatty liver disease (MAFLD), gradually becoming one of the most critical medical issues in the field of hepatology (31). The generalization and application of our findings should be done with caution, and future prospective studies are needed. Last but not least, it is notable that macoscopic vascular invasion (MVI), EHS, and ECOG were independent risk factors associated with poor prognosis, and future studies should take these factors into consideration and assign weights appropriately to achieve individualized and accurate prediction for patients receiving TACE-S.

Conclusion

In summary, we demonstrated that the HAP series scores exhibited good predictive ability in uHCC patients accepting TACE-S, and the mHAP-III score was found to be superior to the other HAP series scores in predicting OS. Future prospective high-quality studies should be conducted to confirm our results and help with treatment decision-making.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual (s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JL, XLD, DFC and LL conceived and supervised the project. YJZ, EXW, SJZ and DDH retrieved patients' clinical information and conducted the telephone follow-up. YJZ performed data curation and analysis and prepared data visualization. YJZ, ENW, SJZ and DDH drafted the manuscript. JL, XLD, DFC and LL reviewed and revised the manuscript. YZ, HC, JZ, THH, YB, YJL, YCZ, MY, LZ, JHF, XC, JJ, WBW, WRR, TTB, SZM, FHX, YXT, YH, JLZ and XSQ provided patient care and performed the clinical assessments. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.983554/full#supplementary-material

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Glossary

AFP	α-fetoprotein
AIC	Akaike information criterion
ALBI	albumin–bilirusbin
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under ROC curve
BCLC	Barcelona Clinic Liver Cancer
BUN	blood urea nitrogen
CI	confidence interval
CT	computed tomography
ECOG	Eastern Cooperative Oncology Group
EHS	extrahepatic spread
HCC	hepatocellular carcinoma
HAP	hepatoma arterial-embolization prognostic
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio
IDI	integrated discrimination improvement
INR	international normalized ratio
IQR	interquartile range
MAFLD	metabolic-associated fatty liver disease
mHAP	modified HAP
MRI	magnetic resonance imaging
NRI	net reclassification improvement
OS	overall survival
pALBI	platelet–albumin–bilirubin
PDGF	platelet-derived growth factor
PS	performance status
PVTT	portal vein tumor thrombosis
RCT	randomized controlled trial
ROC	receiver operating characteristic
SD	standard deviation
TACE	transarterial chemoembolization
TBIL	total bilirubin
TKIs	multikinase inhibitor tyrosine kinase inhibitors
VEGF	vascular endothelial growth factor

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Analysis of risk factors of hepatocellular carcinoma and establishment of a clinical prognosis model

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Liver cancer is a common malignancy of the digestive system. Hepatocellular carcinoma (HCC) accounts for the most majority of these tumors and it has brought a heavy medical burden to underdeveloped countries and regions. Many factors affect the prognosis of HCC patients, however, there is no specific statistical model to predict the survival time of clinical patients. This study derived a risk factor signature of HCC and reliable clinical prediction model by statistically analyzing The Surveillance, Epidemiology, and End Results (SEER) database patient information using an open source package in the python environment.

KEYWORDS

HCC (hepatic cellular carcinoma), SEER (Surveillance Epidemiology and End Results) database, machine learning - ML, risk factors, random survival forest model

1 Background

Liver cancer is a common malignancy of the digestive system (1, 2). Primary liver cancer mainly includes hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) (3). HCC accounts for most of these tumors and is the fifth leading cause of cancer and the fourth leading cause of cancer-related deaths worldwide (4, 5).Men have a higher risk of HCC than women, comprising the second leading cause of cancer death in men. Besides, HCC morbidity and mortality are still rising (6, 7). The main risk factors for HCC development are cirrhosis and chronic liver disease (8). Cirrhosis is an important process for HCC viral carcinogenesis (9). Additionally, chronic hepatitis, caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, is an important risk factor for liver cancer (10). Most new liver cancer cases occur in developing countries with a high rate of hepatitis B virus infections. Meanwhile, non-alcoholic fatty liver disease (NAFLD) is the leading cause of HCC in developed countries (11, 12).

Liver Doppler ultrasound and AFP are simple and easy methods to screen liver cancer (13). Elevated AFP and DCP levels are typical features of liver cancer (14). Additionally,

CT, enhanced CT, MRI, enhanced MRI, and other imaging methods are helpful for precise HCC diagnosis (15). Since liver biopsy is related to tumor implantation and bleeding risks, and false negative results might occur, it is generally not recommended for HCC (16).

At present, the most commonly used staging systems for liver cancer include the TNM (tumor node metastasis), China liver cancer (CNLC), and Barcelona clinical liver cancer (BCLC) staging systems (17). The TNM staging was jointly proposed by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) and has been widely used in clinical practice. TNM is a tumor staging system based on tumor morphology (T), regional lymph node metastasis (N), and distant metastasis (M). The TNM staging of liver cancer is very detailed, especially the T staging, including the invasion of microvessels around the tumor that can better help evaluate the prognosis.

Radical surgical resection is the primary treatment for early HCC. However, whether advanced HCC patients can benefit from surgery is controversial. Recently, breakthroughs have been made in non-surgical treatments. For example, drug therapy, immunotherapy, and targeted therapy have been successfully applied to treat advanced liver cancer (18). Transcatheter arterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), and radiotherapy can improve patient prognosis (19). Some experts believe that conventional chemotherapy can also benefit HCC patients (20). Nevertheless, most experts believe that conventional chemotherapy has little effect on liver cancer (21–23).

The SEER database is a publicly available cancer reporting system funded by the US federal government (24). This representative and reliable data come from 18 US states. Users can retrieve the patient's sex, age, surgical method, chemotherapy, radiotherapy, other clinical information, survival time, and status. This study obtained permission to use the SEER PLUS database. Thus, to further explore HCC risk factors and treatment plans and establish a machine learning model to guide clinical treatment, we retrieved HCC patient data from the SEER database and analyzed them after the screening.

2 Methods

2.1 Data acquisition

Herein, we retrieved data from 107148 HCC patients from the SEER database. Clinical information included gender, age, race, histological type, histological grading, surgical method, regional lymph node dissection, radiotherapy, chemotherapy, diagnosis to treatment time, AFP, TNM staging, survival time, and survival status.

2.2 Excluding factors

To ensure the accuracy of the machine learning model, we did not use automatic imputation of missing information. Data were filtered according to the clinical characteristics of each group, and the information gaps and unknown groups were excluded from a total of 102680 patients. Finally, 4468 patients were selected for subsequent analysis.

2.3 Statistical methods

The algorithm applied here was based on python 3.10.6 (Python Software Foundation, https://www.python.org/). Clinical feature analysis was conducted with TableOne. The COX regression analysis was performed using Lifelines. The random survival forest (RSF) analysis was carried out using Scikit-Survival. The survival curves of clinical patients were predicted using the random forest model. The accuracy of the model was evaluated using the C-index.

3 Results

3.1 Clinical characteristics

After the screening, 4468 patients were selected for further analysis (Table 1) . The clinical characteristics were analyzed in Table 1. A total of 2324 patients received chemotherapy, and 2144 patients did not. Most clinical features significantly differed between the two groups, including gender, race, histological type, surgery, regional lymph node dissection, diagnosis to treatment time, survival time, AFP, survival status, and T, N, M stages (χ^2 test, $p < 0.05$).

3.2 Overall risk factors

Furthermore, we used COX regression analysis to evaluate the impact of various clinical features on the survival of HCC patients (Table 2). Distant organ metastasis, lymph node metastasis, chemotherapy, AFP positive, histological grade, sex, race, tumor size, and age were risk factors for HCC. On the other hand, surgical treatment and early diagnosis and treatment were remission factors for HCC ($p < 0.05$). No significant differences were detected for radiotherapy and regional lymph node dissection ($p > 0.05$). The C-index of the COX regression model was 0.76 (Figure 1).

3.3 Risk factors at different stages

To explore the differences in treatment plans for HCC patients at different TNM stages, we divided patients into I, II, IIIa, IIIb, IVa, and IVb groups according to the 7th edition of the AJCC staging system. Then, we applied COX regression analysis to evaluate the risk for each group (Table 3). We found that early diagnosis and treatment, and timely surgery were mitigating factors for HCC patients at stages I, II, and IIIa. In contrast, chemotherapy, radiotherapy, and positive AFP were risk factors for HCC patients, unfavorable for prognoses. Surgical treatment and early

TABLE 1 Clinical characteristics.

		Grouped by Chemotherapy					
		Overall	0	1	P-Value	Test	SMD (0,1)
n		4468	2144	2324			
Sex, n (%)	**Female**	1031 (23.1)	568 (26.5)	463 (19.9)	<0.001	Chi-squared	0.156
	Male	3437 (76.9)	1576 (73.5)	1861 (80.1)			
Race, n (%)	**American Indian/Alaska**	60 (1.3)	28 (1.3)	32 (1.4)	<0.001	Chi-squared	0.214
	Asian/Pacific	906 (20.3)	530 (24.7)	376 (16.2)			
	Black	543 (12.2)	252 (11.8)	291 (12.5)			
	White	2959 (66.2)	1334 (62.2)	1625 (69.9)			
Histological grade, n (%)	**I**	1311 (29.3)	596 (27.8)	715 (30.8)	<0.001	Chi-squared	0.132
	II	2164 (48.4)	1111 (51.8)	1053 (45.3)			
	III	932 (20.9)	410 (19.1)	522 (22.5)			
	IV	61 (1.4)	27 (1.3)	34 (1.5)			
Surgery, n (%)	**None**	1816 (40.6)	214 (10.0)	1602 (68.9)	<0.001	Chi-squared (warning: expected count < 5)	nan
	Local tumor destruction	613 (13.7)	401 (18.7)	212 (9.1)			
	Wedge or segmental resection	813 (18.2)	702 (32.7)	111 (4.8)			
	Lobectomy	457 (10.2)	376 (17.5)	81 (3.5)			
	Extended lobectomy	122 (2.7)	89 (4.2)	33 (1.4)			
	Hepatectomy	633 (14.2)	352 (16.4)	281 (12.1)			
	Excision of a bile duct	1 (0.0)	1 (0.0)				
	Excision of a bile duct & partial hepatectomy	5 (0.1)	4 (0.2)	1 (0.0)			
	Bile duct and hepatectomy WITH transplant	8 (0.2)	5 (0.2)	3 (0.1)			
Regional lymph node dissection, n (%)	**None**	4055 (90.8)	1880 (87.7)	2175 (93.6)	<0.001	Chi-squared	0.204
	1-3	364 (8.1)	231 (10.8)	133 (5.7)			
	≥4	49 (1.1)	33 (1.5)	16 (0.7)			
Radiation, n (%)	**None**	3994 (89.4)	1924 (89.7)	2070 (89.1)	0.499	Chi-squared	0.022
	Yes	474 (10.6)	220 (10.3)	254 (10.9)			
Time from diagnosis to treatment (months), median [Q1,Q3]		2.0 [1.0,3.0]	1.0 [0.0,3.0]	2.0 [1.0,3.0]	<0.001	Kruskal-Wallis	0.033
Survival time(months), median [Q1, Q3]		33.0 [10.0,66.0]	54.0 [21.0,76.2]	18.0 [7.0,50.2]	<0.001	Kruskal-Wallis	-0.645
AFP, n (%)	**Negative**	1462 (32.7)	848 (39.6)	614 (26.4)	<0.001	Chi-squared	0.282
	Positive						

(Continued)

TABLE 1 Continued

		Grouped by Chemotherapy					
		Overall	0	1	P-Value	Test	SMD (0,1)
		3006 (67.3)	1296 (60.4)	1710 (73.6)			
Survival status,n (%)	**Alive**	1712 (38.3)	1168 (54.5)	544 (23.4)	<0.001	Chi-squared	0.672
	Dead	2756 (61.7)	976 (45.5)	1780 (76.6)			
TNM-T, n (%)	**T1**	2107 (47.2)	1260 (58.8)	847 (36.4)	<0.001	Chi-squared (warning: expected count < 5)	nan
	T2	1159 (25.9)	564 (26.3)	595 (25.6)			
	T3a	647 (14.5)	176 (8.2)	471 (20.3)			
	T3b	374 (8.4)	81 (3.8)	293 (12.6)			
	T3NOS	8 (0.2)	3 (0.1)	5 (0.2)			
	T4	171 (3.8)	60 (2.8)	111 (4.8)			
	T0	2 (0.0)		2 (0.1)			
TNM-N, n (%)	**N0**	4205 (94.1)	2118 (98.8)	2087 (89.8)	<0.001	Chi-squared	0.395
	N1	263 (5.9)	26 (1.2)	237 (10.2)			
TNM-M, n (%)	**M0**	4090 (91.5)	2084 (97.2)	2006 (86.3)	<0.001	Chi-squared	0.404
	M1	378 (8.5)	60 (2.8)	318 (13.7)			
Age, median [Q1,Q3]		62.0 [56.0,69.0]	62.0 [56.0,69.0]	62.0 [56.0,69.0]	0.479	Kruskal-Wallis	0.043

TABLE 2 Risk factors for survival.

	coef	exp (coef)	se (coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%	p	-log2 (p)
Sex	0.19	1.21	0.05	0.09	0.28	1.1	1.33	<0.005	13.31
Race	0.08	1.09	0.02	0.04	0.13	1.04	1.14	<0.005	11.74
Histological grade	0.25	1.28	0.03	0.2	0.3	1.22	1.35	<0.005	68.75
Surgery	-0.03	0.97	0	-0.03	-0.03	0.97	0.97	<0.005	296.84
Regional lymph node dissection	0.07	1.07	0.08	-0.08	0.21	0.92	1.24	0.38	1.39
Radiation	0.04	1.04	0.06	-0.08	0.15	0.93	1.16	0.54	0.89
Chemotherapy	0.35	1.41	0.05	0.26	0.44	1.29	1.55	<0.005	43.84
Time from diagnosis to treatment(months)	-0.09	0.92	0.01	-0.11	-0.07	0.9	0.94	<0.005	48.23
AFP	0.3	1.34	0.04	0.21	0.38	1.23	1.47	<0.005	35.68
TNM-T	0.02	1.02	0	0.02	0.02	1.02	1.02	<0.005	150.79
TNM-N	0.39	1.48	0.07	0.24	0.53	1.28	1.71	<0.005	22.56

(Continued)

TABLE 2 Continued

	coef	exp (coef)	se (coef)	coef lower 95%	coef upper 95%	exp(coef) lower 95%	exp(coef) upper 95%	p	-log2 (p)
TNM-M	0.64	1.89	0.07	0.51	0.77	1.66	2.15	<0.005	72.38
Age	0.01	1.01	0	0.01	0.01	1.01	1.01	<0.005	22.23
Concordance	0.76								
Partial AIC	41495.47								
log-likelihood ratio test	2229.19 on 13 df								
-log2(p) of ll-ratio test	inf								

diagnosis and treatment were also remission factors for stage IV HCC patients. Nevertheless, the prognosis risk was reduced in patients at stage IVa receiving radiotherapy, comprehending a mitigating factor. The survival of patients receiving chemotherapy did not differ. However, radiotherapy and chemotherapy were mitigating factors in the IVb group.

3.4 Clinical feature importance and survival prediction

We randomly selected 25% of the included test group data, and the remaining 75% was used as the training group data. To obtain the best model, the survival analysis of the post-screening data was performed using the RSF model based on hyperparameter optimization with manual parameter adjustment, leading to a C-index of 0.80 for the training set and 0.77 for the testing set. Thus, the RSF model had slightly better reliability than the Cox regression model.

The clinical feature importance ranking indicated that surgical treatment was the most important feature among clinical factors in the RSF model (Table 4). Then, three patients in surgery and non-surgery groups were separately retrieved from the test group to draw predictive survival curves. Patients in the surgery group had a significantly better prognosis than those in the non-surgery group (Figure 2).

Subsequently, we used Streamlit to establish a clinical patient survival prediction platform based on the RSF model. In this framework, clinicians can enter the corresponding clinical information, which is used to generate survival and cumulative risk curves of predicted patients and real-time survival curve changes by dynamically adjusting treatment parameters. Therefore, this platform can be used to guide clinical treatment selection (Video 1).

4 Discussion

The incidence and mortality of liver cancer continue to rise, and its treatment remains a global challenge (25). Surgery is the primary treatment of liver cancer (26). Nevertheless, liver cancer treatment has entered a new era with the development of immunotherapy and targeted therapeutic drugs. Since early liver cancer has no specific manifestation, few patients are diagnosed at early stages during

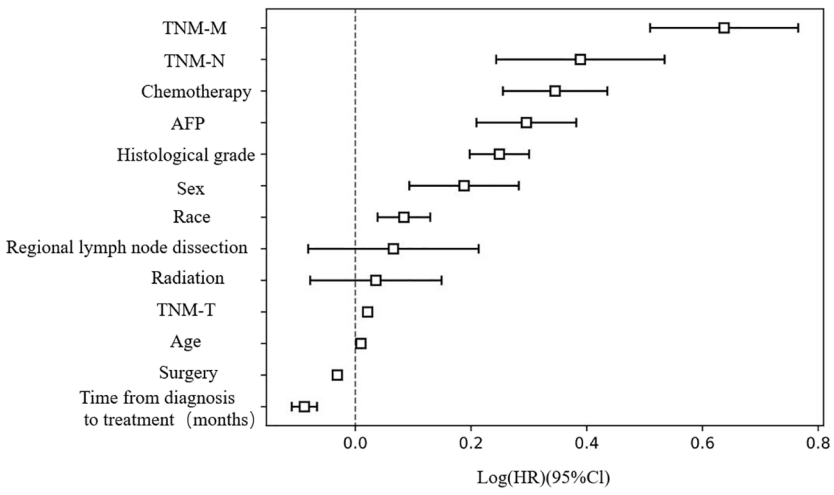

FIGURE 1
Risk factors assessment for HCC patients..

TABLE 3 Risk factors at different stages.

	I		II		IIIa		IIIb		IVa		IVb	
	exp (coef)	p	exp (coef)	p	exp (coef)	p	exp (coef)	p	exp (coef)	p	exp (coef)	p
Sex		1.31	1.09	0.41	1.23	0.02	1.32	0.3	1.67	0.12	0.93	0.61
Race	1.15	<0.005	1.13	0.02	1.03	0.43	0.98	0.84	0.97	0.81	1.01	0.83
Histological grade	1.17	<0.005	1.34	<0.005	1.33	<0.005	1.17	0.25	1.3	0.02	1.18	0.02
Surgery	0.97	<0.005	0.97	<0.005	0.97	<0.005	0.99	0.1	0.97	<0.005	0.97	<0.005
Regional lymph node dissection	1.09	0.54	0.87	0.39	0.95	0.7	1.04	0.87	1.69	0.11	0.73	0.19
Radiation	1.32	0.02	1.38	0.02	0.87	0.11	1.41	0.29	0.59	0.04	0.67	<0.005
Chemotherapy	1.6	<0.005	1.35	<0.005	1.17	0.09	1.3	0.3	1.13	0.68	0.67	0.01
Time from diagnosis to treatment(months)	0.93	<0.005	0.92	<0.005	0.87	<0.005	0.88	0.21	0.73	<0.005	0.8	<0.005
AFP	1.23	<0.005	1.47	<0.005	1.39	<0.005	1.33	0.31	1.42	0.11	1.26	0.1
Age	1.02	<0.005	1.01	0.01	1	0.55	1	0.94	1.01	0.37	1	0.87

regular physical examinations. Hence, most liver cancer patients are diagnosed at advanced stages when they present abdominal pain, jaundice, and other discomfort symptoms, missing the best time for treatment.

Moreover, HCC has brought a heavy medical burden to underdeveloped countries and regions (18).Chronic HBV infection, chronic HCV infection, NAFLD, aflatoxin, and alcohol intake are important causes of HCC. For example, Hepatitis B virus vaccination can reduce HCC incidence. Herein, the COX regression analysis showed that the time from diagnosis to treatment was a remission factor for HCC patients. Thus, early detection and timely treatment might improve the prognosis of HCC patients (HR: 0.92, $p < 0.005$). Thus, government departments and relevant medical security institutions should strengthen the health testing of high-risk HCC groups to achieve early detection and treatment, which can prolong the survival time of patients and reduce the economic burden on families and medical security institutions.

We found that positive AFP was also a risk factor for HCC patients at stages I, II, and IIIA. Hence, AFP can be used as an indicator of the prognosis of HCC patients, and similar conclusions have been reached in other studies (27).The Cox regression and RSF models indicated that surgery could reduce HCC risk and improve patient outcomes. Surgical treatment was the most important clinical feature affecting the survival of HCC patients in the RSF model, comprising a key factor for HCC management. For patients who can tolerate surgery, appropriate surgical treatment should be implemented as early as possible to avoid missing the optimal timing of treatment. Meanwhile, for patients not temporarily

TABLE 4 Clinical feature importance.

	Importances_mean	Importances_std
Surgery	0.109762	0.005483
TNM-T	0.036965	0.003964
TNM-M	0.011606	0.002241
Histological grade	0.007685	0.002583
Time from diagnosis to treatment(months)	0.006859	0.001441
Age	0.00568	0.001741
TNM-N	0.003543	0.000769
AFP	0.002642	0.001283
Radiation	0.001912	0.000937
Race	0.00102	0.001027
Chemotherapy	0.000678	0.001564
Sex	0.000492	0.00097
Regional lymph node dissection	0.000161	0.000466

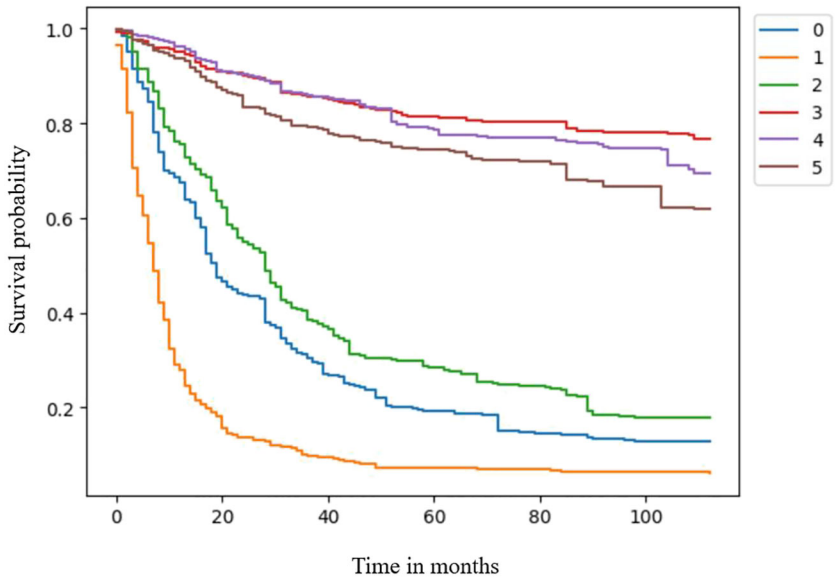

FIGURE 2
Survival curves for the surgery and non-surgery groups.

suitable for surgery, neoadjuvant treatments such as targeted therapy, immunotherapy, and TACE can be immediately implemented when the condition permits further operation.

We found that chemotherapy and radiotherapy were unsuitable for early liver cancer patients. Unnecessary radiotherapy and chemotherapy can increase the risk of these patients. However, chemotherapy can be used for advanced liver cancer patients, who might benefit from systemic chemotherapy (HR: 0.67, $p < 0.005$). Sun et al. showed that chemotherapy was a common treatment for advanced HCC, but the effects were not ideal. Adding all-trans-retinoic acid (ATRA) to fluorouracil, leuprorelin, and oxaliplatin (FOLFOX4) to treat advanced HCC can improve the overall survival and disease progression time of patients.

However, our study also has some limitations. First, the SEER database does not contain specific information on targeted therapy and immunotherapy regimens, which can extend the survival time of patients with recurrent or advanced liver malignancies. Second, we did not evaluate various objective factors affecting tumor patients' survival time, such as economic conditions, medical insurance systems, and the level of medical development in the region. Finally, different machine learning models exhibit varying degrees of prognostic evaluation of patients. Therefore, this study should only be considered a machine-learning reference for treating tumor patients. With the continuous refinement of local databases and the optimization of artificial intelligence algorithms, machine learning models will be increasingly close to the reality of clinical practice.

Herein, we obtained a relatively reliable machine learning model by RSF. Then, we used this model to establish a survival prediction platform for HCC patients. This platform can generate a predicted survival curve by inputting clinical patient information. Survival curves can also be compared to get the best clinical treatment plan. Since the SEER database does not contain immunotherapy, targeted therapy, TACE, and other information, this platform only tests the feasibility of methods based on existing data to guide further research.

5 Conclusion

In the present study, we found that distant organ metastasis, lymph node metastasis, histological grade, sex, race, tumor size, and age were risk factors for HCC patients. Additionally, early detection and timely treatment might improve the prognosis of HCC patients, and positive AFP might be used as a risk indicator. Moreover, surgical treatment is crucial for HCC patient survival. Chemotherapy and radiotherapy are inappropriate for early liver cancer patients since these treatments can increase their risk. Nevertheless, advanced liver cancer patients might benefit from systemic chemotherapy. Finally, the RSF model can be used for clinical survival prediction.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

X-YG is responsible for writing manuscripts and program codes; M-CS and T-YW are responsible for literature retrieval; X-MW, GL, Y-ML and TY are responsible for the program code; WW is responsible for proofreading and reviewing. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1067353/full#supplementary-material

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