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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Postoperative Adjuvant Transarterial Chemoembolization Improves Outcomes of Hepatocellular Carcinoma Associated with Hepatic Vein Invasion: A Propensity Score Matching Analysis

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ABSTRACT

Background. Vascular invasion is a major determinant of survival outcomes after curative resection for hepatocellular carcinoma (HCC) patients. This study was designed to investigate the efficacy of postoperative adjuvant transarterial chemoembolization (PA-TACE) in patients with HCC with hepatic vein tumor thrombus (HVTT).

Methods. Data from patients who underwent LR for HCC with HVTT at the Eastern Hepatobiliary Surgery Hospital were retrospectively analyzed. The survival outcomes for patients who underwent PA-TACE after LR were compared with those who underwent LR alone. Propensity score matching (PSM) analysis was performed to match patients in a ratio of 1:1.

Results. All included 319 patients who underwent LR for HCC with HVTT, 134 underwent LR alone (the LR group), and 185 patients underwent in adjuvant TACE (the PA-TACE group). PSM matched 107 patients in two groups. The overall survival (OS) and recurrence-free survival (RFS) were significantly better for patients in the PA-TACE group than the LR group (for OS: before PSM, $P < 0.001$; after PSM, $P = 0.004$; for RFS: before PSM, $P < 0.001$; after PSM, $P = 0.013$), respectively. On subgroup analysis, equivalent acceptable results were obtained in patients with peripheral HVTT (pHVTT) and major HVTT (mHVTT). However, PA-TACE resulted in no survival benefits for patients when the HVTT had extended to the inferior vena cava (IVCTT).

Conclusions. PA-TACE was associated with significantly better survival outcomes than LR alone for patients with HCC and HVTT (pHVTT and mHVTT). There was no survival benefits in patients whose HVTT had extended to form IVCTT.

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related death worldwide.[1] HCC often invades into the portal vein or hepatic vein branches to form portal vein tumor thrombus (PVTT) or hepatic vein tumor thrombus (HVTT). Either PVTT or HVTT is a known poor prognostic factor of survival.[2,3] If left untreated, the median survival time (MST) of these patients ranges from 2.7 to 4.0 months.[4,5] The American Association for the Study of Liver Diseases (AASLD) and the Barcelona Clinic for Liver Cancer Staging System (BCLC) and Treatment Guidelines, both classify HCC associated with macroscopic vascular invasion (PVTT or HVTT) to be at an advanced stage of HCC with little hope for a cure.[2,3,6] Recent studies from China

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and Japan, however, showed liver resection (LR) to be associated with better survival outcomes than non-surgical treatment in selected patients with HCC associated with PVTT or HVTT.[7–11] Advances in surgical techniques and perioperative management have also made LR for these patients safe.[4,12–15]

The role of postoperative adjuvant therapy is still controversial for HCC patients after LR.[16,17] A recent retrospective study reported that in selected patients with HCC associated with PVTT, postoperative adjuvant TACE (PA-TACE) was associated with better overall survival, particularly, in patients with PVTT involving the right/left/main portal veins.[18] However, HVTT occurs less frequently than PVTT in patients with HCC. The Japanese Nationwide Survey showed HVTT to occur only in 4.5% of HCC patients.[8] Studies reporting on HVTT alone have been rare.[19,20] To our knowledge, no study has been reported on postoperative adjuvant therapy for patients with HCC associated with HVTT.

This study consists of a large cohort of patients with HCC associated with HVTT. To minimize the potential bias inherent to retrospective studies, propensity score matching (PSM) analysis was used to determine the role of PA-TACE on the long-term survival outcomes in patients with HCC associated with HVTT.

METHODS

Study Population

The demographic, clinical, and pathologic data of consecutive patients with HCC associated with HVTT who underwent LR from January 2002 to December 2015 in the Eastern Hepatobiliary Surgery Hospital (EHBH) was retrospectively reviewed. The study was approved by the Institutional Ethics Committee of the EHBH. Written, informed consent was obtained from all the patients for their data to be used for research purposes.

The diagnostic criteria of HVTT in patients with HCC were based on the typical preoperative radiological features on imaging studies, which included ultrasound, Doppler ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI), and intraoperative and postoperative histopathology examinations by two senior pathologists from the Pathology Department of our hospital.[2] HVTT was categorized into the following types: (1) tumor thrombosis in hepatic vein (in a peripheral hepatic vein (pHVTT), and tumor thrombosis in a major hepatic vein (mHVTT), which could be the right, middle, or left hepatic vein); (2) tumor thrombosis extending to the inferior vena cava (IVCTT)

Inclusion and Exclusion Criteria

The inclusion criteria were HCC patients with (1) resectable HCC, (2) HVTT diagnosed by the diagnostic criteria as mentioned above, (3) HVTT and IVCTT, (4) HVTT with liver function of Child–Pugh class A or selected B (score ≤ 7), (5) absence of macroscopic PVTT, macroscopic bile duct tumour thrombus, extrahepatic spread, or distant metastases, (6) no other associated malignancies, and (7) no other preoperative anticancer treatment, including TACE, chemotherapy, radiotherapy, or sorafenib. The exclusion criteria were patients with (1) liver function of Child–Pugh class C, (2) coexisting PVTT, and (3) incomplete data.

Surgery and PA-TACE Procedures

The operative procedures for LR have been reported previously.[20,21] Intraoperative ultrasonography was routinely performed to determine the location and extent of the HVTT or IVCTT and to mark the parenchymal transection plane. The tumor thrombus was either resected en bloc with the liver tumor or extracted out of the vascular lumen, depending on its location and extent.[7] After thrombectomy, the vascular lumen was flushed with normal saline. When intraoperative ultrasonography showed no residual tumor thrombus, the vascular incision was sutured.

Four weeks after the operation, all patients underwent a comprehensive evaluation of liver function, serum alpha-fetoprotein (AFP) level, and enhanced MRI or CT scans of the abdomen. After excluding patients who were not suitable for PA-TACE, the remaining patients were recommended PA-TACE due to preoperative HVTT. Whether the patients followed the physician's recommendation mainly depended on their socioeconomic status and compliance with the doctors. A hepatic arterial catheter was placed into the proper hepatic artery through a femoral artery using the Seldinger technique. TACE was performed for the entire liver remnant. Hepatic angiography, CT angiography, or both were performed to detect any obvious tumor stains in the liver remnant. An emulsion of doxorubicin hydrochloride (10 mg), pirarubicin (THP) or pharmorubicin (20–40 mg), and lipiodol (2–10 ml) (Lipiodol Ultrafluide, Guerbet, AulnaySous-Bois, France) was then infused through the catheter.[16,22] The dosages of lipiodol and doxorubicin were determined by the body surface area and the underlying liver function. After follow-up of an additional 1 month, another CT scan was performed.

Follow-Up

The postoperative patient surveillance and managements were performed as reported in our previous study.[23] Follow-up examinations were conducted using laboratory findings (serum AFP, liver function, and complete blood count), abdominal ultrasonography, and contrast-enhanced CT. After surgery, the patients were followed-up once every 3 to 4 months until death or dropout from the follow-up program. A diagnosis of recurrence of HCC was based on CT and/or MRI and elevated serum a-fetoprotein (AFP) levels.

Statistical Analysis

Continuous variables were reported as median with interquartile range (IQR) and were compared by using the Mann–Whitney test. Variables with normal distributions were reported as mean and standard deviation, and they were compared using the Student's *t* tests. Categorical data, presented as frequencies (%), were compared using the Chi square test or the Fisher's exact test. The OS or RFS curves were generated by using the Kaplan-Meier method and compared by using the log-rank test. Univariate and multivariate analyses were assessed using a Cox proportional hazards stepwise model. Factors with a $P < 0.05$ on univariate analysis were incorporated into multivariate analysis. Patients in the PA-TACE group were matched to the LR group using the closest estimated propensity score within 0.1 of the standard deviation of the logit of PS, using a matching ratio of 1:1. $P < 0.05$ was considered statistically significant. After PSM, univariate, multivariate logistic regression, and Kaplan-Meier analyses also were performed. The data analyses were performed by using the SPSS software version 24.0 (Chicago, IL).

RESULTS

Patient Characteristics

The flowchart in Fig. 1 shows how the patients were selected into this study during the study period from 2002 to 2015. Finally, there were 185 patients in the PA-TACE group and 134 patients in the LR group. After PSM with a 1:1 ratio matching, there were 107 patients in each of the PA-TACE and the LR groups.

The baseline characteristics of the patients in the PA-TACE and LR groups are shown in Table 1. After PSM, these clinicopathological features became well-balanced (Supplementary Table 1). The baseline characteristics of the subgroups of patients (HVTT or IVCTT) before PSM are shown in Supplementary Tables 2–3 and after PSM in Supplementary Tables 4–5.

Univariate and Multivariable Analysis for RFS and OS

Univariate analyses before PSM demonstrated that different treatments ($P < 0.001$), different types of tumor thrombus ($P < 0.001$), Child Pugh score ($P = 0.003$), number of tumor ($P = 0.013$), AFP level ($P = 0.047$), tumor diameter ($P < 0.001$), ALT level ($P = 0.029$), and AST level ($P = 0.017$) were independently related to OS. On multivariable analysis, different treatments ($P < 0.001$), different types of tumor thrombus ($P < 0.001$), Child Pugh score ($P = 0.003$), AFP level ($P = 0.045$), and AST level ($P = 0.020$) were independent risk factors of OS (Supplementary Table 11). Supplementary Table 6 showed univariate and multivariable analysis of poor RFS. After PSM, Supplementary Tables 7–8 showed univariate multivariable analyses of OS and RFS.

Survival Analysis in All Patients between the LR and the PA-TACE Groups

Before PSM, the median OS times (MOST 95% CI) after resection were 17.2 (14.3–19.2) months for the LR group and 27.8 (25.1–34.0) months for the PA-TACE group (Supplementary Table 9). The OS was significantly better for the PA-TACE group than the LR group (1 year, 78.8 vs. 62.9%; 3 years, 38.7 vs. 18.7%; 5 years, 11.7 vs. 5.4%; $P < 0.001$; Fig. 2a). The median RFS times (MRFST 95% CI) after resection were 12.6 (range 10.4–15.9) months for the LR group and 19.3 (range 13.3–23.1) months for the PA-TACE group (Supplementary Table 9; Fig. 2b).

After PSM, the MOST (95% CI) after liver resection were 18.0 (14.3–21.2) months for the LR group and 28.7 (24.4–35.0) months for the PA-TACE group (Supplementary Table 10). The OS was significantly better for the PA-TACE group than the LR group (1 year, 79.3 vs. 66.1%; 3 years, 38.2 vs. 21.1%; 5 years, 10.6 vs. 7.1%; $P = 0.004$; Fig. 2C). The MRFST (95% CI) after resection were 12.4 (range 8.9–15.6) months for the LR group and 16.1 (range 13.1–24.0) months for the PA-TACE group (Supplementary Table 10; Fig. 2D).

Subgroup Analysis on Survival for Patients with HVTT (pHVTT and mHVTT) and IVCTT

For HCC patients with HVTT (pHVTT and mHVTT), the OS was significantly better for the PA-TACE group than the LR group before PSM (1 year, 81.3 vs. 68.0%; 3 years, 46.4 vs. 20.5%; 5 years, 17.1 vs. 7.1%; $P < 0.001$; Fig. 3a; Supplementary Table 9). The RFS in the PA-TACE group was significantly longer than the LR group (1 year, 72.5 vs. 59.0%; 3 years, 36.3 vs. 10.3%; 5 years, 7.1 vs. 3.7%; $P < 0.001$; Fig. 3b; Supplementary Table 9).

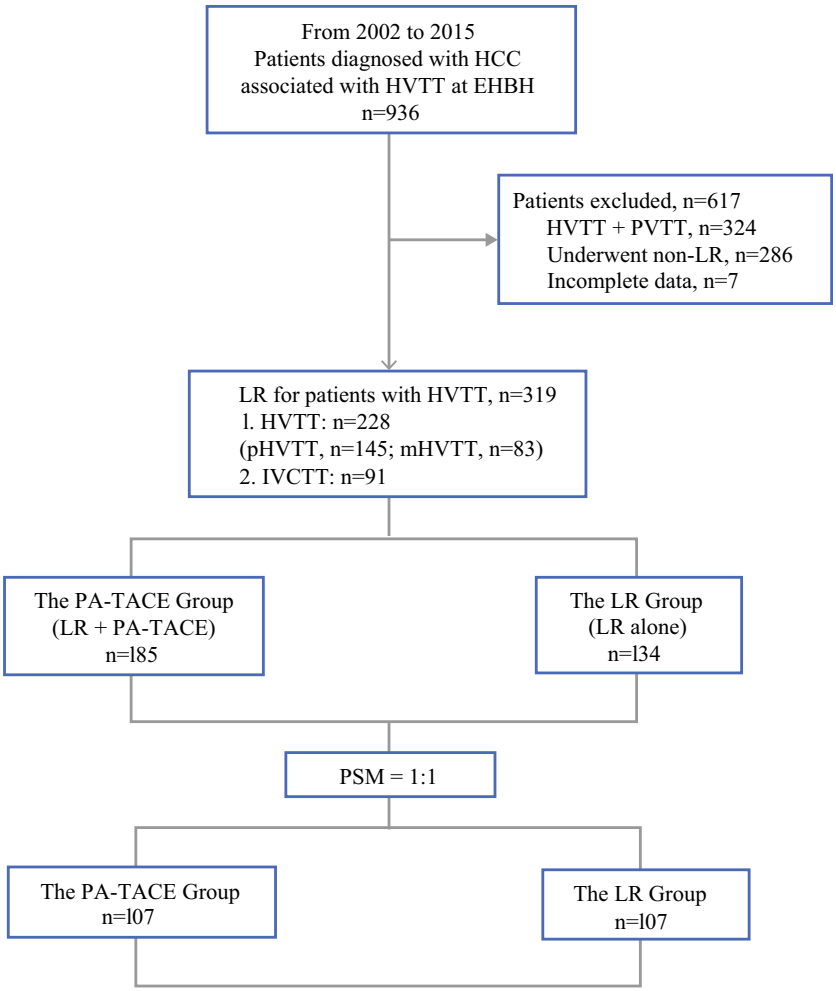

FIG. 1 Flow chart to select HCC patients with HVTT for the study. *HCC* hepatocellular carcinoma, *EHBH* Eastern Hepatobiliary Surgery Hospital, *HVTT* hepatic vein tumor thrombus, *pHVTT* hepatic vein tumor thrombus affecting peripheral branches, *mHVTT* hepatic vein tumor thrombus affecting major branches, *IVCTT* inferior vena cava tumor thrombus, *PVTT* portal vein tumor thrombus, *LR* liver resection, *PA-TACE* postoperative adjuvant transcatheter arterial chemoembolization, *PSM* propensity score matching

After PSM, the OS and RFS also were significantly better for the PA-TACE group (OS: 1 year, 88.0 vs. 74.3%; 3 years, 55.0 vs. 22.5%; 5 years, 17.4 vs. 9.2%; $P = 0.002$, Fig. 3c; and RFS: 1 year, 81.1 vs. 62.9%; 3 years, 44.5 vs. 12.6%; 5 years, 8.9 vs. 4.5%; $P < 0.001$, Fig. 3d; Supplementary Table 10). For HCC patients with pHVTT and mHVTT, PA-TACE prolonged OS and RFS of these patients as shown in Supplementary Figure 1 ($P = 0.001$ and $P = 0.001$).

For HCC patients with IVCTT, there were no significant differences in OS and RFS between the two groups of patients before PSM ($P = 0.072$, Fig. 4a; $P = 0.207$, Fig. 4b; Supplementary Table 9). After PSM, there were similar results in OS and RFS for the two groups (Fig. 4c, d; Supplementary Table 10).

DISCUSSION

Vascular invasion is one of the most important poor prognostic factors of long-term survival in HCC patients.[20,24,25] The previously reported incidences of HVTT in HCC patients ranged from 1.4 to 4.9%.[26–28] HVTT and PVTT usually coexist, and only approximately 50% of HCC patients had HVTT only.[7,8] Although many therapeutic modalities have been proposed to treat HCC patients with associated HVTT, the optimal treatment remains controversial. A Japanese Nationwide Survey with a large sample size concluded that LR is associated with good prognosis in HCC patients with HVTT, especially in patients without PVTT.[8] With advances in perioperative management and surgical techniques, LR for patients with HCC and associated HVTT has become relatively safe with some risks. Furthermore, postoperative adjuvant therapy using PA-TACE has been shown to improve prognosis of HCC patients with microvascular invasion or with PVTT.[5,17,18,22,29] It remains unclear whether patients with HCC associated with HVTT or IVCTT would truly benefit from PA-TACE.

To our knowledge, our large-scale study is the first to report on the beneficial effects of PA-TACE on survival outcomes in HCC patients with HVTT (pHVTT and mHVTT), but not with IVCTT, after LR.

TABLE 1 Clinicopathological features of all patients with HVTT before PSM (n = 319)

Variables	LR+PA-TACE (N = 185)	LR (N = 134)	Statistics	P value
Tumor thrombus			0.66	0.418
HVTT	129 (69.7%)	99 (73.9%)		
IVCTT	56 (30.3%)	35 (26.1%)		
Age	52.00 (47.0–59.0)	53.00 (47.0–64.0)	1.43	0.153
Sex			0.00	0.946
Male	162 (87.6%)	117 (87.3%)		
Female	23 (12.4%)	17 (12.7%)		
Child Pugh			12.00	<0.001
A	182 (98.4%)	120 (89.6%)		
B	3 (1.6%)	14 (10.4%)		
HBsAg			0.23	0.632
Yes	161 (87.0%)	119 (88.8%)		
No	24 (13.0%)	15 (11.2%)		
Ascites			2.48	0.115
Yes	24 (13.0%)	10 (7.5%)		
No	161 (87.0%)	124 (92.5%)		
No. of tumor			9.57	0.002
Single	144 (77.8%)	83 (61.9%)		
Multiple	41 (22.2%)	51 (38.1%)		
Satellite nodules			2.57	0.109
Yes	52 (28.1%)	49 (36.6%)		
No	133 (71.9%)	85 (63.4%)		
AFP			0.45	0.503
< 400	94 (50.8%)	63 (47.0%)		
≥ 400	91 (49.2%)	71 (53.0%)		
Lymph node invasion			4.51	0.034
Yes	17 (9.2%)	23 (17.2%)		
No	168 (90.8%)	111 (82.8%)		
Tumor diameter	8.7 (5.6–11.4)	10.8 (9.0–13.2)	4.89	<0.001
TBIL	15.8 (12.8–20.5)	15.8 (11.9–20.5)	− 0.44	0.658
DBIL	8.8 (6.6–11.8)	9.3 (6.3–12.0)	0.22	0.829
TBA	68.1 ± 6.76	68.5 ± 5.87	− 0.45	0.655
ALB	39.1 (36.7–42.5)	38.1 (33.8–41.3)	− 2.93	0.003
ALT	38.0 (26.0–62.0)	39.6 (24.0–71.0)	0.27	0.788
AST	46.0 (33.0–69.0)	50.0 (35.0–81.0)	1.26	0.209
GGT	165.78 ± 148.13	172.8 ± 144.05	− 0.42	0.671
ALP	106.0 (88.0–145.0)	105.0 (84.0–156.0)	0.24	0.812
PT	12.4 ± 1.32	12.3 ± 1.56	0.86	0.393
PLT	158.00 (91.0–203.0)	159.0 (110.0–205.0)	0.62	0.536
CEA	2.5 (1.7–3.7)	2.7 (1.6–3.6)	− 0.04	0.966
CA199	29.7 (12.8–50.0)	27.9 (14.4–47.6)	0.22	0.829

HBsAg hepatitis B surface antigen, *AFP* α-fetoprotein, *TBIL* total bilirubin, *DBIL* direct bilirubin, *TBA* total bile acid, *ALB* albumin, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* γ-Glutamyltransferase, *ALP* alkaline phosphatase, *PT* prothrombin time, *PLT* platelet, *CEA* carcinoembryonic antigen, *CA199* carbohydrate antigen 19-9

The BCLC staging classifies HCC with extrahepatic metastasis and macrovascular invasion as advanced HCC.[3] However, management of HCC associated with macroscopic vascular invasion is still controversial. LR has been reported to produce good results in patients with PVTT in Eastern and Western countries.[4,7,10,15,30]

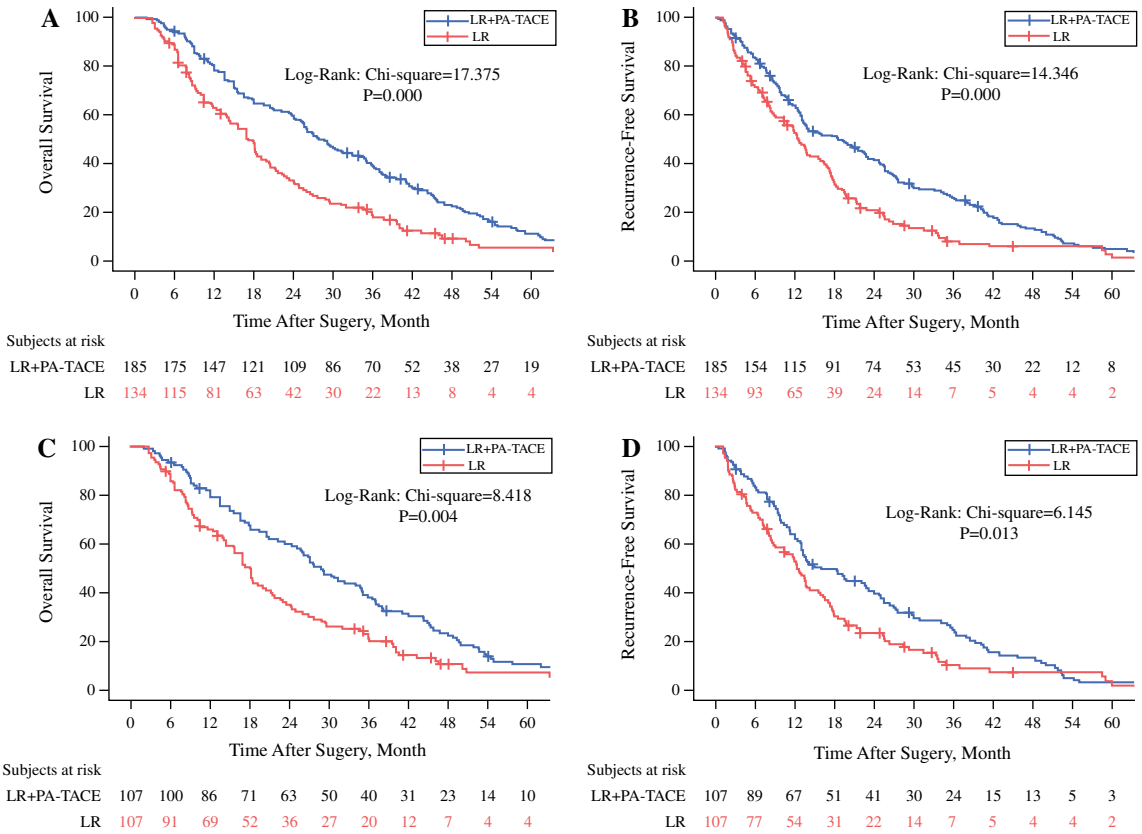

FIG. 2 Kaplan-Meier analysis for the OS and RFS in all HCC patients with HVTT. OS for HCC patients with or without PA-TACE (185 vs. 134 patients) after LR before PSM (**a**) ($P < 0.001$); RFS for HCC patients with or without PA-TACE (185 vs. 134 patients) after LR before PSM (**b**) ($P < 0.001$); OS for HCC patients with or without PA-TACE (107 vs. 107 patients) after LR following PSM (**c**) ($P = 0.004$); RFS for HCC patients with or without PA-TACE (107 vs. 107 patients) after LR following PSM (**d**) ($P = 0.007$)

However, little is known about HVTT. This lack of knowledge is because HVTT is relatively rarer than PVTT in patients with HCC.[8] Thus, most studies reported HVTT together with PVTT, and studies focusing on HVTT alone are uncommon. The impression that HCC patients with macroscopic vascular invasion have a poor prognosis mainly comes from the results in treating patients with PVTT. The Japanese Nationwide Survey showed the MST after LR was more than 5 years in HCC patients with HVTT but without PVTT.[8] Thus, the clinical prognosis of HCC patients with HVTT is much better than those with PVTT. Because HVTT is still a known independent risk factor of poor prognosis after LR, it is important to study whether postoperative adjuvant therapy can reduce postoperative recurrence and prolong long-term survival after LR.

TACE has been used to treat unresectable HCC.[31–34] The BCLC recommends TACE to treat stage B HCC patients, with acceptable safety and effectiveness.[3,35] A network meta-analysis reported that TACE combined with anticancer agents showed significantly better clinical effectiveness in HCC patients.[36] Even for unresectable HCC with a dismal prognosis, TACE is still safe and effective. It has been used in downstaging HCC and as a bridge to liver transplantation.[37] A retrospective study showed TACE to be an effective therapy in selected HCC patients with extrahepatic disease compared with sorafenib.[38] TACE has been reported to result in a better OS and RFS in HCC patients with macrovascular invasion.[39–41]

A randomized, controlled trial (RCT) showed adjuvant TACE significantly reduced tumor recurrence, improved RFS, and OS for patients with HBV-related HCC who had an intermediate or high risk of recurrence after curative hepatectomy, and the procedure was well tolerated.[17] In a study reported by us, PA-TACE beneficial to HCC patients with MVI. The 1-, 2-, 3-, and 5-year overall survival (OS) rates were 94.2, 78.8, 71.5, and 54.0% for the PA-TACE group and 78.9, 62.2, 54.1, and 43.2% for the LR group respectively ($P = 0.006$).[22] Another study demonstrated that in 540 patients with HCC with associated PVTT, PA-TACE resulted in a lower risk of death, particularly in

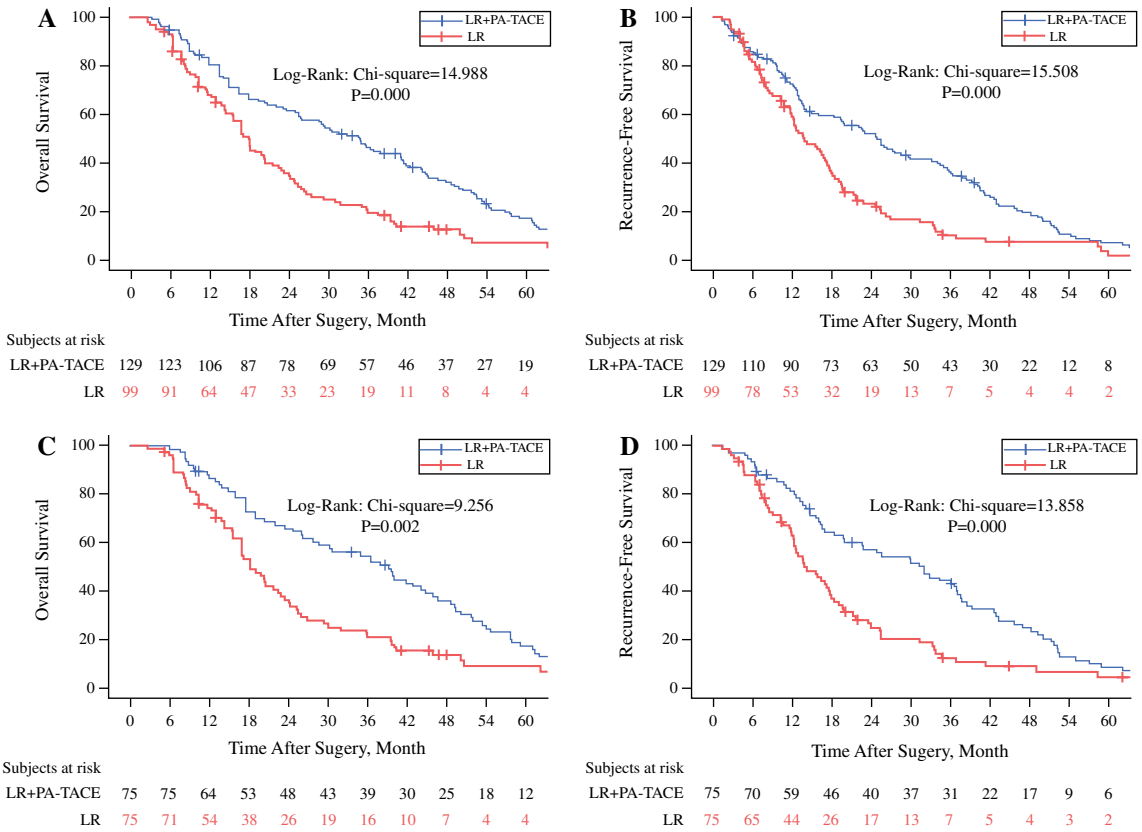

FIG. 3 Kaplan–Meier analysis of OS and RFS for HCC patients with HVTT (pHVTT and mHVTT) on subgroup analysis. OS for HCC patients with or without PA-TACE (129 vs. 99 patients) after LR before PSM (**a**) ($P < 0.001$); RFS for HCC patients with or without PA-TACE (129 vs. 99 patients) after LR before PSM (**b**) ($P < 0.001$); OS for HCC patients with or without PA-TACE (75 vs. 75 patients) after LR following PSM (**c**) ($P = 0.002$); RFS for HCC patients with or without PA-TACE (75 vs. 75 patients) after LR following PSM (**d**) ($P < 0.001$)

HCC with PVTT involving the right/left or main portal vein. In our study, PA-TACE prolonged RFS and OS in HCC patients with HVTT after LR.

Data on the treatment strategies for IVCTT are extremely limited because of the rarity of the disease. Tumor thrombus extending from the hepatic vein(s) to the inferior vena cava (IVCTT) is rarely resectable. However, surgical resection for IVCTT patients has been reported to result in an MST similar to that reported in the present report.[21] In these IVCTT patients, the MSTs were shorter than that of the patients with pHVTT and mHVTT.[7,8] Neoadjuvant and/or adjuvant treatments using sorafenib and/or TACE should be considered for patients undergoing LR, because HCC associated with IVCTT is at an advanced stage.[42] However, there was little evidence to demonstrate the effectiveness of TACE for IVCTT. In the subgroup analysis of this study, PA-TACE was shown to be a promising treatment for HCC patients with pHVTT and mHVTT but not for patients with IVCTT. PA-TACE failed to provide survival benefits in HCC patients with IVCTT.

This study has some limitations. First, the data that came from a single study center were acquired retrospectively. Better designed prospective studies should be conducted to evaluate further the impact of PA-TACE on these patients. Second, the vast majority of our patients had a background of HBV infection. Whether the results obtained in this study can be extrapolated to HCV-related or alcohol-related HCC is not certain.

CONCLUSIONS

This study showed that PA-TACE was associated with improved survival outcomes of HCC patients with hepatic vein invasion (pHVTT and mHVTT) after surgical resection but not for patients when the tumor thrombosis extended into the inferior vena cava. PA-TACE is a potential therapeutic strategy for HCC patients with HVTT.

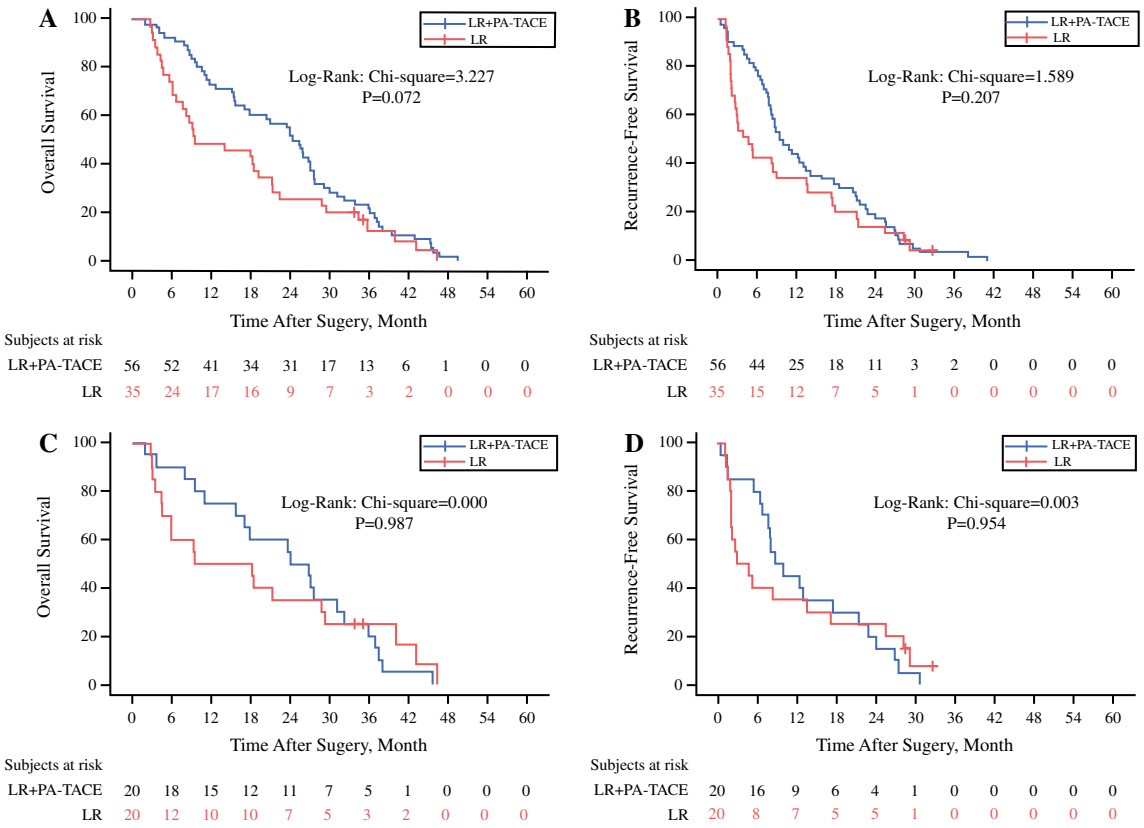

FIG. 4 Kaplan–Meier analysis of the OS and RFS of HCC patients with IVCTT on subgroup analysis. OS for HCC patients with or without PA-TACE (56 vs. 35 patients) after LR before PSM (**a**) (P = 0.072); RFS for HCC patients with or without PA-TACE (56 vs. 35 patients) after LR before PSM (**b**) (P = 0.207); OS for HCC patients with or without PA-TACE (20 vs. 20 patients) after LR following PSM (**c**) (P = 0.987); RFS for HCC patients with or without PA-TACE (20 vs. 20 patients) after LR following PSM (**d**) (P = 0.954)

AUTHORS CONTRIBUTIONS Conception and design: Shu-Qun Cheng, Wan Yee Lau, Xiu-Ping Zhang; Financial support: Shu-Qun Cheng; Provision of study materials or patients: Ju-Xian Sun, Kang Wang, Zong-Tao Chai, Jie Shi, Wei-Xing Guo, Meng-Chao Wu; Collection and assembly of data: Xiu-Ping Zhang, Yan-Chen Liu, Zhen-Hua Chen; Data analysis and interpretation: Xiu-Ping Zhang, Yan-Chen Liu, Zhen-Hua Chen; Manuscript writing: Xiu-Ping Zhang, Wan Yee Lau; Final approval of manuscript: All authors.

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