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ORIGINAL RESEARCH

Neoadjuvant-Based Triple Therapy for Hepatocellular Carcinoma with Type I/II Portal Vein Tumor Thrombosis

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Purpose: Hepatectomy could provide better survival benefit for hepatocellular carcinoma (HCC) with type I/II portal vein tumor thrombosis (PVTT). However, the postoperative recurrence remains high. We discussed whether neoadjuvant therapy could reduce HCC recurrence for these patients.

Patients and Methods: One hundred and thirty-eight resectable HCC with type I–II PVTT were retrospectively included. The neoadjuvant therapy regimens included tyrosine kinase inhibitor (TKI), programmed death 1(PD-1) antibodies and transarterial chemoembolization (TACE). Short-term and long-term outcomes were compared. Propensity score matching (PSM) was performed to minimize the influence of potential confounders.

Results: Thirty-three patients underwent neoadjuvant therapy and 105 patients underwent surgery alone. In the neoadjuvant group, 7 (21.2%) patients achieved stable disease, 13 (39.4%) achieved partial response and 13 (39.4%) achieved complete response based on the modified Response Evaluation Criteria in Solid Tumors criterion. By PSM, the neoadjuvant therapy resulted in less microvascular invasion (24.1% vs 50.0%, P=0.021), satellite nodule (6.9% vs 24.1%, P=0.036) and less patients with alpha-fetoprotein>20(ng/mL) (37.9% vs 69.0%, P=0.006). The neoadjuvant therapy reduced tumor recurrence and prolonged survival. Multivariate analysis found that neoadjuvant therapy was an independent protective factor for overall survival and recurrence free survival.

Conclusion: Neoadjuvant treatment presents a promising treatment option for HCC patients with type I/II PVTT.

Keywords: hepatocellular carcinoma, neoadjuvant treatment, portal vein tumor thrombosis, TACE, immunotherapy, TKIs

Introduction

Hepatocellular carcinoma (HCC) is the seventh most prevalent cancer and the second causing death cancer worldwide.[1] The overall prognosis of HCC is not satisfactory because most HCCs are diagnosed at an advanced stage due to absence of typical clinical symptoms. HCC often extends into the portal vein branches with an incidence rate of 44%–62.2%. The presence of portal vein tumor thrombosis (PVTT) is classified as advanced stage HCC.[2–4] PVTT is always associated with aggressive tumor biology, high tumor burden, poor liver function, and with a natural median survival time ranging from 2.7 to 4.0 months.[5,6] The Barcelona Clinic for Liver Cancer (BCLC) staging system recommends systemic therapy as the only treatment option for HCC patients with PVTT, but the effect is modest.[7] More aggressive treatment modalities, such as transarterial chemoembolization (TACE), radiotherapy and liver resection, have been proposed in the Asia–Pacific region for selected HCC patients.[8,9] Especially for patients with PVTT limited to the first-order branch, several studies have proved that surgical resection provides more survival benefit than other treatment methods.[3,10,11] However, the short-term 1-year

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recurrence rate is as high as 74.5%–82.1% because of the minimal residual lesions which exist extensively in HCC patients with PVTT and could not be detected by preoperative imageological examination.[12,13] The neoadjuvant therapy strategy, including TACE, radiotherapy, targeted therapy and immunotherapy, has been attempted to reduce postoperative recurrence of these patients and has obtained preliminary results.[14–17] Whether neoadjuvant therapy could reduce HCC recurrence for type I/II PVTT patients is unclear. In this study, we discuss whether neoadjuvant-based triple therapy could reduce HCC recurrence and prolong survival than surgery only, for type I/II PVTT HCC patients.

Materials and Methods

Study Population

One hundred and thirty-eight consecutive resectable HCC patients with type I–II PVTT who underwent radical liver resection at Sichuan Cancer Hospital & Institute Between January 2015 and September 2022 were retrospectively included in this study. The key inclusion criterias for this study were as follows: (1) age 18–75 years with good operative tolerance; (2) liver function Child–Pugh grade A and with the 15-min retention rate of Indocyanine Green less than 20%; (3) the tumor is only located on one hemi-liver of the liver (left or right hemi-liver), without main portal vein trunk involvement and no evidence of extrahepatic metastasis; (4) the future liver remnant volume more than 50% standard liver volume in the cirrhosis patients and at least 35% in non-cirrhosis patients; (5) In line with type I and II in Cheng's classification of PVTT[4]; (6) at least one lesion that can be remeasured according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST);[18] (7) Patients who had not received any previous anti-tumor treatment; (8) good bone marrow and organ function before treatment. The key exclusion criteria were as follows: (1) combined HCC and cholangiocarcinoma; (2) combined with other serious malignant diseases; (3) PVTT involving the bilateral or main trunk of the portal vein. All HCC patients with PVTT were preoperatively clinically diagnosed according to the AASLD guidelines and further confirmed through postoperative histological pathological examination.[19] Based on whether neoadjuvant therapy was performed preoperatively, 105 patients were divided into surgical resection group (SR group) and 33 patients were neoadjuvant therapy combined with surgical resection group (NASR group).

The study protocol was approved by the Clinical Research Ethics Committee of the Sichuan Cancer Hospital conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from all patients according to the policies of the committee. Medical records containing patient demographics, laboratory values, intraoperative parameters and postoperative outcomes were obtained from a prospectively maintained database.

Neoadjuvant Therapy Approach

The neoadjuvant therapy approach included TKIs, anti-PD-1 antibodies and TACE. The TACE procedure has been described in detail previously.[20] Enhanced computerized tomography (CT) or magnetic resonance imaging (MRI) was performed every 4 weeks after TACE and the therapeutic effects were assessed using mRECIST criterion. TACE retreatment was performed only on demand, depending upon the extension of the residual or recurrent viable tumor and patients' clinical conditions.

The initial treatment for HCC patients with TKIs and anti-PD-1 antibodies occurs within 1–2 weeks after initial TACE treatment. All patients received TKIs (lenvatinib:8 mg for bodyweight <60 kg or 12 mg for bodyweight ≥60 kg, orally once daily; sorafenib: 400 mg, orally twice daily) and anti-PD-1 antibodies (sintilimab 200 mg or camrelizumab 200 mg) intravenously once every 3 weeks. With dose modifications or interruption according to the presence and severity of toxic side effects according to the drug directions.

Surgical Procedure

All patients underwent liver resection by the same surgery team. The liver resection procedure is the same as previous described.[21] Laparoscopic or open surgery depended on the characteristics and location of the tumor. En bloc resection was performed to remove all portal vein territories involved in PVTT, without exposing the tumor thrombus. If the PVTT grade was type I, sectionectomy or hemi-hepatectomy was performed based on the hepatic functional reserve and the future liver remnant volume. If the PVTT grade was type II, then right or left hemi-hepatectomy was performed. Ligation of the

corresponding hepatic pedicle was performed before mobilization and transection of the liver to eliminate the possibility of tumor scattering. Intraoperative ultrasound was performed to understand the tumor conditions inside the liver, intrahepatic vascular walking and distribution of tumor thrombus, and to determine whether there was extra metastasis. Pringle maneuver was used as previously described.[21] Liver parenchymal transection was performed using Harmonic or an ultrasonic dissector with coagulator. The postoperative therapy for SR group included TKIs for 6 months and once TACE. After surgery, the NASR group continued to receive both PD-1 antibody and TKIs treatment sequentially for 6 months.

Outcome Parameters and Follow-Up

The primary endpoint was recurrence free survival (RFS), and the secondary endpoint was overall survival (OS). The Clavien–Dindo complication classification system was used for postoperative complication grading.[22] More than three Couinaud segments was defined as major resection, or was defined as minor resection. Pathologic complete response (CR) was defined as complete absence of viable tumor cells. Toxicities were evaluated according to the Common Terminology Criteria for Adverse Events version 5.0.

Patients were followed up with CT or MRI, and serum alpha-fetoprotein (AFP) levels at the first month and then every 3 months after surgical treatment. If recurrence was confirmed, patients underwent additional treatment for recurrent HCC according to standard treatment guidelines. The last effective follow-up time was in February 2024.

Statistical Analysis

Continuous variables were reported as mean (SD) or median (range) and were compared using the *Student t* test for continuous variables with parametric distribution, Mann–Whitney *U*-test or Kruskal–Wallis *H*-test for those with nonparametric distribution. Categorical variables were reported as numbers and percentages and compared using Pearson x^2 analysis or Fisher exact test. Survival analysis was calculated by using the Kaplan–Meier survival method and compared using the Log rank test. Meanwhile, prognostic factors were analyzed via univariate and multivariate Cox proportional risk regression analysis. The propensity score matching (PSM) analysis was used to adjust for potential treatment allocation imbalance, and the SR group was 2:1 proportion matched with the NASR group, and the caliper width for the propensity score matching was set to 0.1. All statistical analyses were performed using the SPSS Version 22 statistical software, and statistical significance was set at $P < 0.05$.

Results

Patient Characteristics

Patient characteristics are summarized on Table 1. In all the patients, 73 patients (52.8%) were with type I PVTT and 65 patients (47.2%) were with type II PVTT. Most HCCs were with solitary tumor (81.6%). SR group had significantly more patients with tumor more than 10cm (28.6% vs 6.1%, P=0.024) compared with the NASR group. The Initial AFP levels were similar between the two groups, but the NASR group has more patients with pre-surgery AFP<20 ng/mL (63.6% vs 32.3%, P=0.005). The other characteristics were not significantly different between the two groups.

After neoadjuvant therapy, in the NASR group, 8(24.2%) patients received conventional TACE and 25 (75.8%) patients received drug-bearing TACE. Of these patients, 19 patients underwent one TACE, 7 patients underwent twice TACEs, 4 patients underwent three TACEs and 3 patients underwent four TACEs at intervals of 1–2 months. The median time of neoadjuvant therapy before surgery was 3 (IQR, 2–5) months. All the patients also received TKI therapy and PD-1 antibody at the same time. These treatment options included lenvatinib + camrelizumab (42.4%), lenvatinib + sintilimab (39.4%) and sorafenib + camrelizumab (18.2%). Based on the mRECIST criterion, 7 (21.2%) patients achieved stable disease (SD), 13 (39.4%) patients achieved partial response (PR) and 13 (39.4%) patients achieved complete response (CR). After neoadjuvant therapy, these patients' baseline characteristics had changed (Table 2), including the tendency of more patients with negative HBV-DNA level, lower blood platelet levels, better liver function and less PVTT type II. More importantly, neoadjuvant therapy obviously declined the AFP level and tumor size. After neoadjuvant therapy, the AFP declined from 735 ng/mL to 9.0 ng/mL and ratio of tumor<5cm increased from 30.3% to 63.6%.

Table 1 Baseline Characteristics of Patients Before and After PSM

Characteristics	Before PSM			After PSM		
	SR group N=105	NASR group N=33	P value	SR group N=58	NASR group N=29	P value
Male, N (%)	94(89.5%)	30(90.9%)	0.818	52(89.7%)	26(89.7%)	1.000
Age (Years, Mean ± SD)	53.3±10.6	50.7±9.5	0.331	54.1±10.6	49.7±9.6	0.067
HBV, N (%)	99(94.3%)	31(93.9%)	0.941	54(93.1%)	27(93.1%)	1.000
HCV, N (%)	5(4.8%)	1(3.0%)	0.670	2(3.4%)	1(3.4%)	1.000
HBV-DNA>10^3copies/mL, N (%)	30(28.6%)	10(25.0%)	0.848	18(31.0%)	8(27.6%)	0.740
Initial AFP			0.537			0.260
<20(ng/mL), N (%)	34(32.3%)	8(24.2%)		18(31.0%)	5(17.2%)	
20≤AFP≤400(ng/mL), N (%)	25(23.8%)	7(21.2%)		16(27.6%)	7(24.1%)	
>400(ng/mL), N (%)	46(43.8%)	18(54.5%)		24(41.4%)	17(58.6%)	
WBC (10^9/L), Mean ± SD	6.3±3.4	6.2±1.6	0.776	6.4±3.3	6.2±1.7	0.796
PLT (10^9/L), Mean ± SD	148.0±69.4	171.5±61.8	0.084	149.4±76.4	168.6±62.2	0.244
ALT (U/L)>2ULN	25(23.8%)	10(30.3%)	0.455	15(25.9%)	8(27.6%)	0.864
AST(U/L)>2ULN	23(21.9%)	11(33.3%)	0.184	12(20.7%)	9(31.0%)	0.288
CTP Score, N (%)			0.880			0.719
5	84(80.0%)	26(78.8%)		44(75.9%)	23(79.3%)	
6	21(20.0%)	7(21.2%)		14(24.1%)	6(20.7%)	
Tumor Number, N (%)			0.785			0.187
Solitary	85(80.9%)	26(78.7%)		52(89.7%)	23(79.3%)	
Multiple	20(19.1%)	7(21.3%)		6(10.3%)	6(20.7%)	
Type of PVTT, N (%)			0.167			0.649
I	59(56.2%)	14(42.4%)		29(50.0%)	13(44.8%)	
II	46(43.8%)	19(57.6%)		29(50.0%)	16(55.2%)	
Tumor Size, N (%)			0.024			0.194
>10cm	30(28.6%)	2(6.1%)		13(22.4%)	2(6.9%)	
5–10cm	47(44.8%)	21(63.6%)		31(53.4%)	19(65.5%)	
<5cm	28 (26.7%)	10(30.3%)		14(24.2%)	8(27.6%)	
Pre-Surgery AFP			0.005			0.011
<20(ng/mL), N (%)	34(32.3%)	21(63.6%)		18(31.0%)	18(62.1%)	
20≤AFP≤400(ng/mL), N (%)	25(23.8%)	3(9.1%)		16(27.6%)	2(6.9%)	
>400(ng/mL), N (%)	46(43.8%)	9(27.3%)		24(41.4%)	9(31.0%)	

Abbreviations: PSM, propensity score matching; SR, surgical resection; HBV, hepatitis B virus; HCV, hepatitis C virus; HBV-DNA: Hepatitis B virus deoxyribonucleic acid; AFP, alpha-fetoprotein; WBC, white blood cell count; PLT, blood platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTP class: Child-Turcotte-Pugh class; PVTT, portal vein tumor thrombus. N, number. SR: surgical resection; NASR: neoadjuvant therapy and surgical resection. SD: standard deviation. ULN: Upper limit of normal.

Table 2 Baseline Characteristics of Patients Before and After Neoadjuvant Therapy in the NASR Group

Characteristics	Before NA (N=33)	After NA (N=33)	P value
Male, N (%)	30(90.9%)	30(90.9%)	1.000
Age (YEARS, MEAN ± SD)	50.7±9.5	50.7±9.5	1.000
HBV, N (%)	31(93.9%)	31(93.9%)	1.000
HCV, N (%)	1(3.0%)	1(3.0%)	1.000
HBV-DNA>10^3copies/mL, N (%)	10(25.0%)	4(12.1%)	0.071
AFP (ng/mL), (Quartile)	735.0(25.5–9180.0)	9.0(3.0–501.5)	0.002

(*Continued*)

Table 2 (Continued).

Characteristics	Before NA (N=33)	After NA (N=33)	P value
AFP			0.005
<20(ng/mL), N (%)	8(24.2%)	21(63.6%)	
20≤AFP≤400(ng/mL), N (%)	7(21.2%)	3(9.1%)	
>400(ng/mL), N (%)	18(54.5%)	9(27.3%)	
WBC (10^9/L), Mean ± SD	6.2±1.6	5.5±1.6	0.843
PLT (10^9/L), Mean ± SD	171.5±61.8	143.6±53.7	0.055
ALT (U/L)>2ULN	10(30.3%)	4(12.1%)	0.071
AST(U/L)>2ULN	11(33.3%)	4(12.1%)	0.040
CTP Score, N (%)			0.322
5	26(78.8%)	29(87.9%)	
6	7(21.2%)	4(12.1%)	
Tumor Number, N (%)			1.000
Solitary	26(78.7%)	26(78.7%)	
Multiple	7(21.3%)	7(21.3%)	
Type of PVTT, N (%)			0.139
I	14(42.4%)	20(60.6%)	
II	19(57.6%)	13(39.4%)	
Tumor, N (%)			0.001
>10cm	2(6.1%)	2(6.1%)	
5–10cm	21(63.6%)	10(30.3%)	
<5cm	10(30.3%)	21(63.6%)	

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; HBV-DNA: Hepatitis B virus deoxyribonucleic acid; AFP, alpha-fetoprotein; WBC, white blood cell count; PLT, blood platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTP class: Child-Turcotte-Pugh class; PVTT, portal vein tumor thrombus. N, number; NASR: neoadjuvant therapy and surgical resection. SD: standard deviation. ULN: Upper limit of normal.

After PSM (2:1), 58 patients were retained in the SR group and 27 patients in the NASR group. There were no significant differences between the two groups with regards to the baseline characteristics except that NASR patients had more pre-surgery AFP<20 ng/mL (62.1% vs 31.0%, P=0.011). A typical case of HCC patient with portal vein tumor thrombus undergoing neoadjuvant therapy was presented on Figure 1.

Surgical Outcomes and Pathological Findings

All the 138 HCC achieved radical resection (Table 3). The satellite nodule was found in 19.0% in the SR group, which was higher than in the NASR group (6.1%), but the difference was not statistically significant. The SR group had more microvascular invasion (MVI) (48.6% vs 24.2%, P=0.014), more poor differentiation HCC (25.7% vs 6.1%, P=0.015) and more wide margin (margin>1cm) (46.7% vs 24.2%, P=0.022). The two groups had similar intraoperative blood loss and postoperative complications. After PSM, SR group still had more patients with MVI (50.0% vs 24.1%, P=0.021), more wide margin (margin>1cm) (51.7% vs 27.6%, P=0.032) and more satellite nodule (24.1% vs 6.9%, P=0.036). According to pathological examination, in the NASR group, only 9 (27.2%) patients achieved pathological CR. The other 4 patients with clinical CR were ultimately identified as pathological PR.

Survival Analysis

The median follow time was 26 months (IQR, 18–40) months in all patients. The corresponding 1-year, 3-year and 5-year RFS rate were 49.9%, 23.5% and 14.4% in the SR group vs 75.0%, 65.6% and 65.6% in the NASR group (P=0.001) (Figure 2A). The 1-year, 3-year and 5-year survival rate were 84.7%, 38.6% and 25.4% in the SR group, which was shorter than the NASR group (P=0.007) with the 1-year, 3-year and 5-year survival rate of 93.9%, 75.4% and 67.0%

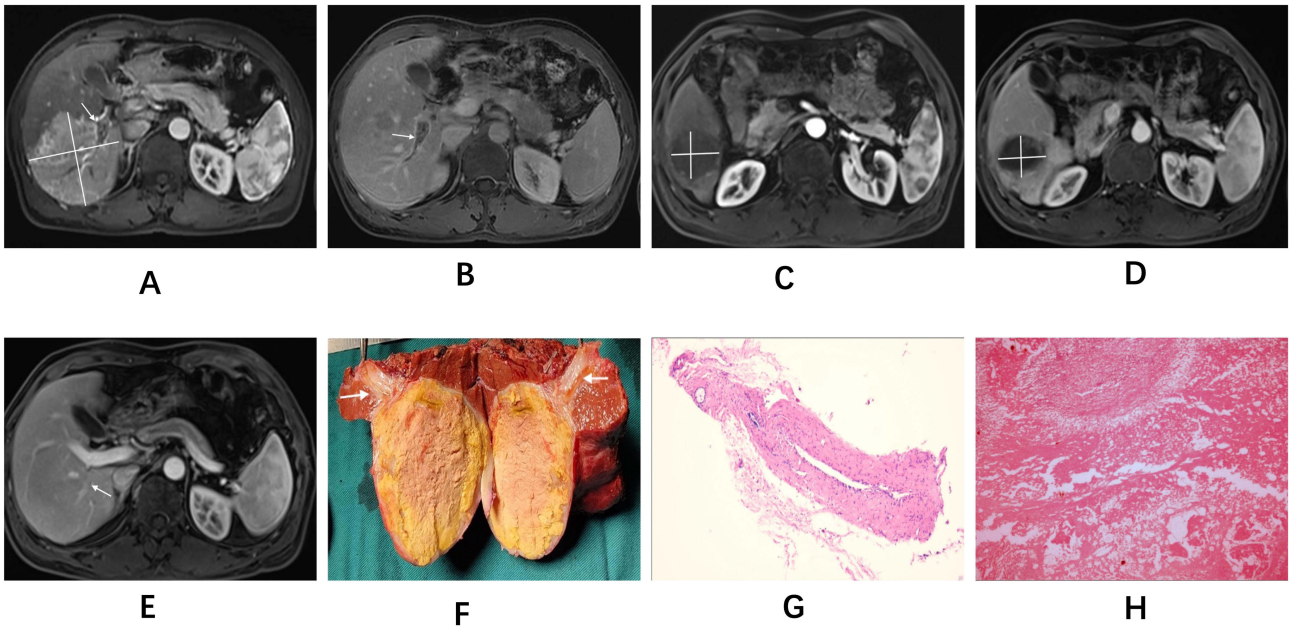

Figure 1 A case of HCC with neoadjuvant therapy and subsequent liver resection.
Notes: A case of HCC patients (**A**) with the right posterior of portal vein tumor thrombus (**B**, white arrow). The patient received TACE every 6 weeks, sorafenib 400 mg twice daily and sintilimab 200 mg every 3 weeks for 9 weeks. After neoadjuvant therapy, the tumors showed shrinkage (**D**) with no arterial enhancement(**C**) on contrast-enhanced MRI, and the portal vein tumor thrombosis regressed (**E**, white arrow). Curative liver resection was performed (**F**, white arrow showing the margin of portal vein). H&E staining of the surgically incisal margin of portal vein (**G**) and resected specimen (**H**) showed a pathological CR.

(Figure 2B). After PSM, the 1-year, 3-year and 5-year RFS rate were 55.0%, 22.7% and 19.9% in the SR group, which was obviously shorter than the NASR group (P=0.002) with the 1-year, 3-year and 5-year RFS of 75.0%, 61.3% and 61.3% (Figure 2C). Similarly, the NASR group also had longer 1-year, 3-year and 5-year survival rate of 96.6%, 77.0% and 67.9% than the SR group, which had a 1-year, 3-year and 5-year survival rate of 93.1%, 34.7% and 28.5% (P=0.038) (Figure 2D). The overall median RFS and OS time were 13.0 month and 34.0 months, but they were not reached in the NASR group.

Table 3 Operative Outcomes of Patients Before and After PSM

Characteristics	Before PSM			After PSM		
	SR group N=105	NASR group N=33	P value	SR group N=58	NASR group N=29	P value
Major Resection, N (%)	45(42.9%)	15(45.5%)	0.793	28(48.3%)	15(51.7%)	0.762
Anatomic resection, N (%)	66(62.9%)	23(69.7%)	0.474	43(74.1%)	21(72.4%)	0.864
Satellite nodule, N (%)	20(19.0%)	2(6.1%)	0.102	14(24.1%)	2(6.9%)	0.036
MVI, N (%)	51(48.6%)	8(24.2%)	0.014	29(50.0%)	7(24.1%)	0.021
Blood Loss(mL), mean ± SD	411.9±273.8	378.8±273.5	0.868	411.2±280.8	382.7±281.6	0.657
Poor differentiation, N (%)	27(25.7%)	2(6.1%)	0.015	10(17.2%)	1 (3.4%)	0.045
Transfusion, N (%)	24(22.9%)	3(11.1%)	0.129	13(22.4%)	3(10.3%)	0.171
Margin(cm), (mean ± SD)	0.90±0.77	0.65±0.82	0.112	1.01±0.89	0.67±0.86	0.102
Margin>1cm, N (%)	49(46.7%)	8(24.2%)	0.022	30(51.7%)	8(27.6%)	0.032
Complication, N (%)	33(31.4%)	8(24.2%)	0.431	16(27.6%)	8(27.6%)	1.000
Complication I–II, N (%)	21(20.0%)	7(21.2%)	0.880	11(19.0%)	7(24.1%)	0.574
Complication III–IV, N (%)	12(11.4%)	2(6.1%)	0.518	5(8.6%)	2(6.9%)	0.778

Abbreviations: PSM, propensity score matching; SR, surgical resection; MVI: microvascular invasion. NASR: neoadjuvant therapy and surgical resection. N, number. SD: standard deviation.

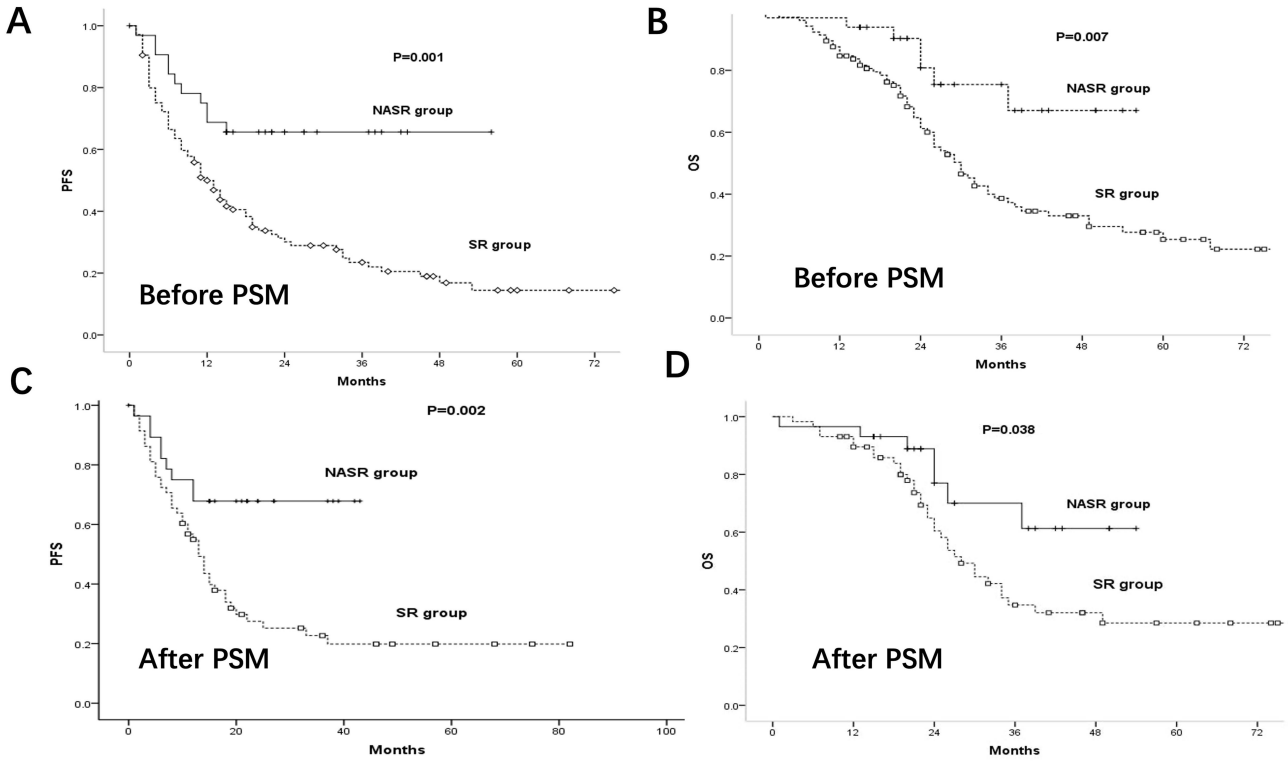

Figure 2 Kaplan–Meier analysis for the PFS (**A**) and OS (**B**) before PSM and after PSM (**C** and **D**).

On univariate analysis, factors which were associated with RFS included tumor size, type of PVTT, pre-surgery, satellite nodule, MVI and neoadjuvant therapy (Table 4). By multivariate analysis, only tumor size, pre-surgery AFP, satellite nodule and neoadjuvant therapy were independent risk factors for RFS. The associated risk factors for OS included pre-surgery AFP, anatomic resection, complication III–IV and neoadjuvant therapy. By multivariate analysis, only pre-surgery AFP, complication III–IV and neoadjuvant therapy were independent risk factors for OS. After PSM, by univariate analysis, tumor size, type of PVTT, pre-surgery AFP, satellite nodule, MVI and neoadjuvant therapy were associated with RFS. But only tumor size, pre-surgery AFP>20 and neoadjuvant therapy were independent risk factors for RFS. For OS, tumor size, pre-surgery AFP and neoadjuvant therapy were independent risk factors for both univariate and multivariate analysis (Table 5).

Recurrence Pattern

In all the patients, 80(76.2%) patients in the SR group and 11(10.5%) patients in the NASR group had tumor recurrence. The most common recurrence site was intrahepatic recurrence (43.8%), followed by extrahepatic and intrahepatic recurrence (28.6%), and only extrahepatic recurrence (3.8%). But less intrahepatic only recurrence (15.2%) and both extrahepatic and intrahepatic recurrence (6.1%) occurred in the NASR group. The other recurrence pattern included only extrahepatic recurrence (12.1%). Similarly, the NASR group also had less intrahepatic recurrence after PSM. The treatment after recurrence included surgical resection, radiofrequency ablation, TACE and systematic treatment. The treatment pattern after recurrence was similar between the two groups (Table S1).

Adverse Events and Postoperative Complications

The summary of treatment-related adverse events in the NASR therapy group was present on Table S2. Treatment-related adverse events of any grade occurred in 30/33 patients (90.9%) and grade 3 and 4 treatment-related adverse events occurred in 8/33 patients (24.2%). The most common treatment-related adverse events were aspartate aminotransferase increase (81.8%), alanine aminotransferase increase (78.7%), nausea and vomiting (48.5%) and hypertension (39.3%).

Table 4 Univariate and Multivariate Analyses of the Effects of Clinical Characteristics on PFS and OS Before PSM

Variable	RFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Male, N (%)	1.005(0.503–2.004)	0.990			0.941(0.450–1.967)	0.872		
Age (years, Mean ± SD)	0.990(0.969–1.011)	0.342			0.999(0.977–1.022)	0.941		
HBV, N (%)	1.079(0.395–2.945)	0.882			0.822(0.274–2.796)	0.822		
HCV, N (%)	0.514(0.162–1.635)	0.260			0.260(0.036–1.878)	0.182		
HBV DNA>1000 copies/mL, N (%)	1.183(0.763–1.834)	0.453			1.077(0.658–1.763)	0.768		
Initial AFP		0.172				0.174		
<20(ng/mL), N (%)	0.643(0.401–1.030)	0.066			0.619(0.362–1.303)	0.079		
20≤AFP≤400(ng/mL), N (%)	0.775(0.443–1.355)	0.371			0.691(0.362–1.058)	0.253		
>400(ng/mL), N (%)	1(Reference)	0.176			1(Reference)	0.175		
WBC (10^9/L), mean ± SD	0.996(0.936–1.059)	0.897			1.011(0.947–1.080)	0.738		
PLT(≤100×10^9/L)	0.998(0.995–1.001)	0.250			0.999(0.995–1.002)	0.443		
ALT (U/L)>2UNL, N (%)	1.090(0.687–1.730)	0.714			0.756(0.442–1.292)	0.306		
AST (U/L)>2UNL, N (%)	1.278(0.806–2.026)	0.298			0.805(0.466–1.389)	0.435		
CTP class score	1.357(0.827–2.226)	0.227			1.309(0.721–2.376)	0.377		
Tumor number, N (%)		0.425				0.435		
Solitary	1(Reference)				1(Reference)			
multiple	1.229(0.741–2.040)				1.249(0.715–2.184)	0.435		
Tumor size, N (%)		0.093				0.104		
≥10cm	1.816(1.010–3.265)	0.046	1.985(1.079–3.649)	0.027	1.702(0.897–3.227)	0.104		
5cm-10cm	1.202(0.690–2.093)	0.516	1.064(0.591–1.915)	0.835	1.008(0.541–1.880)	0.979		
<5cm	1(Reference)		1(Reference)	0.020	1(Reference)			
Type of PVTT		0.020				0.317		
I type	1(Reference)				1(Reference)			
II type	0.613(0.405–0.927)				0.787(0.492–1.259)			
Pre-surgery AFP		0.002				0.005		
<20(ng/mL), N (%)	0.461(0.284–0.749)	0.002	0.549(0.329–0.918)	0.022	0.405(0.230–0.714)	0.002	0.468(0.264–0.832)	0.010
20≤AFP≤400(ng/mL), N (%)	1.016(0.604–1.709)	0.952	0.977(0.580–1.647)	0.930	0.780(0.437–1.391)	0.002	0.778(0.435–1.349)	0.399
>400(ng/mL), N (%)	1(Reference)	0.003	1(Reference)	0.056	1(Reference)	0.007	1(Reference)	0.035
Major Resection, N (%)	1.383(0.915–2.089)	0.124			1.259(0.787–2.012)	0.336		
Anatomic resection, N (%)	1.269(0.819–1.965)	0.287			1.694(1.011–2.838)	0.045		
Satellite nodule, N (%)	2.279(1.392–3.730)	0.001	2.170(1.290–3.651)	0.004	1.625(0.940–2.811)	0.082		
MVI, N (%)	1.555(1.029–2.351)	0.036			1.450(0.907–2.316)	0.121		
Blood Loss>800mL, N (%)	1.225(0.592–2.535)	0.584			1.323(0.632–2.771)	0.458		

Transfusion, N (%)	1.317(0.801–2.164)	0.278			1.566(0.915–2.680)	0.102		
Poor differentiation, N (%)	1.425(0.880–2.305)	0.149			1.653(0.983–2.780)	0.058		
Margin(cm), (mean ± SD)	1.199(0.947–1.519)	0.132			1.205(0.923–1.573)	0.171		
Complication, N (%)	1.082(0.686–1.708)	0.733			1.552(0.933–2.582)	0.090		
Complication I–II, N (%)	0.949(0.560–1.610)	0.847			1.021(0.546–1.908)	0.949		
Complication III–IV, N (%)	1.692(0.720–2.691)	0.325			2.059(1.052–4.028)	0.035	2.153(1.094–4.237)	0.026
Neoadjuvant therapy (%)	0.364(0.193–0.684)	0.002	0.458(0.233–0.897)	0.023	0.358(0.164–0.783)	0.010	0.433(0.195–0.964)	0.040

Abbreviations: PSM, propensity score matching; RFS, recurrence free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; SR, surgical resection; HBV, hepatitis B virus; HCV, hepatitis C virus; HBV-DNA: Hepatitis B virus deoxyribonucleic acid; AFP, alpha-fetoprotein; WBC, white blood cell count; PLT, blood platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTP class: Child-Turcotte-Pugh class; PVTT, type of portal vein tumor thrombus. N, number. SR: surgical resection; NASR: neoadjuvant therapy and surgical resection. MVI: microvascular invasion. ULN: Upper limit of normal.

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Table 5 Univariate and Multivariate Analyses of the Effects of Clinical Characteristics on PFS and OS After PSM

Variable	RFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Male, N (%)	0.736(0.265–2.046)	0.557			0.759(0.269–2.140)	0.602		
Age (years, Mean ± SD)	0.990(0.964–1.017)	0.454			1.002(0.973–1.031)	0.910		
HBV, N (%)	1.237(0.385–3.975)	0.721			2.500(0.343–18.250)	0.366		
HCV, N (%)	0.394(0.054–2.862)	0.358			0.046(0.000–25.191)	0.338		
HBV-DNA>1000 copies/mL, N (%)	1.579(0.911–2.798)	0.102			1.342(0.712–2.529)	0.364		
Initial AFP		0.162			0.192	0.188		
<20(ng/mL), N (%)	0.554(0.281–1.092)	0.088			0.596(0.281–1.261)	0.176		
20≤AFP≤400(ng/mL), N (%)	0.636(0.323–1.253)	0.191			0.525(0.233–1.184)	0.121		
>400(ng/mL), N (%)	1(Reference)	0.165			1(Reference)	0.192		
WBC (10^9/L), Mean ± SD	1.048(0.948–1.157)	0.360			1.066(0.954–1.191)	0.261		
PLT(>100×10^9/L), N (%)	0.998(0.994–1.002)	0.390			0.999(0.994–1.003)	0.587		
ALT (U/L)>2UNL, N (%)	0.988(0.534–1.828)	0.970			0.574(0.278–1.185)	0.133		
AST (U/L)>2UNL, N (%)	1.213(0.646–2.278)	0.547			0.574(0.264–1.250)	0.162		
CTP class score	1.324(0.713–2.456)	0.374			1.422(0.689–2.936)	0.341		
Tumor Number, N (%)		0.608				0.435		
Solitary	1(Reference)				1(Reference)			
Multiple	1.218(0.573–2.590)				1.243(0.549–2.815)			
Tumor size, N (%)		0.093				0.036		
≥10cm	1.816(1.010–3.265)	0.046	2.851(1.102–7.376)	0.031	2.494(0.960–6.482)	0.061	3.503(1.275–9.625)	0.015
5cm-10cm	1.202(0.690–2.093)	0.516	0.867(0.321–2.342)	0.779	1.092(0.435–2.738)	0.852	0.800(0.306–2.090)	0.649
<5cm	1(Reference)		1(Reference)	0.005	1(Reference)			0.002
Type of PVTT		0.006				0.223		
I type	1(Reference)				1(Reference)			
II type	0.453(0.257–0.799)	0.315			0.661(0.340–1.286)			
Pre-Surgery AFP		0.001				0.010		
<20(ng/mL), N (%)	0.328(0.169–0.636)	0.001	0.436(0.203–0.938)	0.034	0.327(0.154–0.697)	0.004	0.310(0.138–0.695)	0.004
20≤AFP≤400(ng/mL), N (%)	0.876(0.448–1.715)	0.700	0.897(0.443–1.816)	0.763	0.607(0.277–1.330)	0.212	0.647(0.296–1.534)	0.347
>400(ng/mL), N (%)	1(Reference)	0.003	1(Reference)	0.101	1(Reference)	0.014	1(Reference)	0.017
Major Resection, N (%)	1.612(0.929–2.796)	0.090			1.335(0.712–2.504)	0.368		
Anatomic Resection, N (%)	1.273(0.667–2.430)	0.464			1.940(0.886–4.248)	0.098		
Satellite Nodule, N (%)	2.838(1.561–5.158)	0.001			1.939(0.984–3.820)	0.056		
MVI, N (%)	2.244(1.295–3.886)	0.004			1.864(0.998–3.482)	0.051		
Blood Loss>800mL, N (%)	1.281(0.508–3.228)	0.600			1.816(0.761–4.331)	0.179		

Transfusion, N (%)	1.261(0.648–2.454)	0.495			1.449(0.687–3.056)	0.329		
Poor Differentiation, N (%)	1.609(0.783–3.305)	0.195			1.643(0.722–3.737)	0.237		
Margin(cm), Mean ± SD)	1.177(0.895–1.546)	0.243			1.212(0.897–1.638)	0.212		
Complication, N (%)	1.117(0.611–2.039)	0.720			1.405(0.694–2.841)	0.345		
Complication I–II, N (%)	1.076(0.551–2.098)	0.831			1.107(0.486–2.525)	0.808		
Complication III–IV, N (%)	1.283(0.509–3.234)	0.597			1.316(0.467–3.710)	0.603		
Neoadjuvant therapy, N (%)	0.364(0.193–0.684)	0.002	0.395(0.176–0.889)	0.025	0.358(0.164–0.783)	0.010	0.374(0.155–0.901)	0.028

Abbreviations: PSM, propensity score matching; RFS, recurrence free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; SR, surgical resection; HBV, hepatitis B virus; HCV, hepatitis C virus; HBV-DNA: Hepatitis B virus deoxyribonucleic acid; AFP, alpha-fetoprotein; WBC, white blood cell count; PLT, blood platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTP class: Child-Turcotte-Pugh class; PVTT, portal vein tumor thrombus. N, number. SR: surgical resection; NASR: neoadjuvant therapy and surgical resection. MVI: microvascular invasion. ULN: Upper limit of normal.

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No grade 5 adverse events occurred. The postoperative complications were similar in the two groups before and after PSM. There were no perioperative deaths in both groups.

Discussion

In this retrospective study, we discussed the role of neoadjuvant therapy for HCC patients with type I/II PVTT and found that neoadjuvant therapy could reduce MVI and satellite nodule. The triple therapy model with TACE, TKI and PD-1 antibody reduced HCC recurrence and offered better survival benefits with adequate security in patients with type I/II PVTT patients.

Liver resection is the main option of radical therapy for HCC, but it is controversial and have not been recommended for patients with PVTT by BCLC staging system.[23] However, many high-volume surgical centers proactively performed liver resection for selective patients, especially for HCC patients with PVTT within the ipsilateral first/second portal branch (type I/II).[24,25] Because these PVTTs can be easily resected together with the primary tumors at the time of hemihepatectomy or segmentectomy.[26] Series studies with large samples have identified that surgical resection was associated with improved survival compared to systemic therapy,[11] TACE[3] and other treatment.[27] The median survival time in the surgical group varied from 21.4 months to 75 months and the 5-year survival rates ranged from 39.1% to 55.9%.[3,25] Especially, hepatectomy offered better survival benefits in patients with type I/II PVTT patients.[12,24]

However, the tumor recurrence rates were as high as 74.5% one year after hepatectomy.[12] MVI, satellite nodules, tumor burden and AFP have been identified as important risk factors for HCC recurrence by many studies.[4,28–31] The MVI was found as high as 91.5% in the HCCs with PVTT and the satellite nodules incidence was as high as 73.2%,[29] and these risk factors caused the tumor to recur easily. In addition, minimal residual diseases, such as circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA), existed extensively and could be the source of the relapse. Due to the greater accessibility of tumor cells in the thrombus to the blood stream, HCC patients with PVTT had higher preoperative CTCs counts than those without, with the positive rate ranging from 66.7% to 89.9%.[32,33] The ctDNA positive rate could be as high as 80%.[34] As the origin of cancer metastasis, the preoperative minimal residual diseases were substantially existed and eventually led to tumor metastasis and recurrence. Hence, additional perioperative treatments are urgently needed to reduce minimal residual diseases, decrease tumor recurrence and improve overall survival.

Neoadjuvant treatment utilizing TACE or systemic treatment has demonstrated encouraging results in the setting of studies.[17,28,34–40] In a randomized, multicenter controlled study, neoadjuvant radiotherapy promoted MVI to reduce by 9.3% and resulted in 20.7% of PR.[29] A study applied D-TACE and tislelizumab therapy as neoadjuvant treatment and the pathological CR was as high as 31.7% and the incidence of MVI was only 4.9%, which was much less than that 60.9% in the surgery only group.[36] Wu[28] combined TACE, TKI and PD-1 antibodies as neoadjuvant treatment, and the results showed that 33.3% of these HCCs had CR and the MVI declined by 61% compared with surgery alone group. The application of PD-1 antibodies in neoadjuvant settings could have a substantial impact, by both driving immediate induction of tumour-cell killing and potentially inducing durable immune responses capable of eliminating residual micro-metastatic disease. In a Phase II clinical trial, neoadjuvant therapy with camrelizumab plus apatinib was applied on 18 patients with resectable HCC. The positive rate of ctDNA were 80% before neoadjuvant therapy. For all the positive patients, ctDNA decreased to 73.3% after neoadjuvant therapy and decreased to 28.6% after surgery. Survival analysis showed that patients with ctDNA negative presented a trend of longer RFS than those with positive ctDNA.[34] These neoadjuvant treatment significantly reduced HCC-related mortality and HCC recurrence rates compared with surgery alone.[28,29,36]

In our study, we selected HCC patients with PVTT within the ipsilateral first/second portal branch because en-bloc removal of all tumors and macroscopic PVTT was deemed possible, without thrombectomy and vascular remodeling. By our triple neoadjuvant strategy, the incidence rate of MVI decreased by 25.9% (50.0% vs 24.1%, P=0.021) and the satellite nodule decreased by 17.2% (24.1% vs 6.9%, P=0.021). The neoadjuvant treatment achieved 27.2% of pathological CR and made AFP decreased from 735.0 ng/mL to 9.0 ng/mL. The AFP level is an important characteristic of HCC biology and preoperative AFP has demonstrated the important prognostic value after HCC.[30,41] Tumor size was another prognostic factor for tumor recurrence.[4,12,42] Hence, by reducing tumor burden, decreasing MVI and satellite nodule, eliminating residual micro-metastatic disease through immunotherapy, our neoadjuvant treatment offered better

survival benefits in patients with type I/II PVTT patients. Both before and after PSM, multivariate analysis found that neoadjuvant therapy was an independent protective factor for OS and PFS.

Preoperative locoregional therapies and systemic treatment might adversely impair liver function and would inevitably increase risks of postoperative complications, increasing with more preoperative treatment cycles.[43,44] But in our study, these patients with neoadjuvant therapy remained with Child Pugh A grade liver function after neoadjuvant therapy and had similar post-hepatectomy complication. So, careful selection of patients for neoadjuvant therapy and limited therapy cycles would not make liver function deterioration and provided acceptable security.

Some limitations existed in the study. Firstly, the patients in the NASR group were highly selective HCC patients. Secondly, this study was a retrospective study with small sample size. Thirdly, the neoadjuvant therapy scheme and the treatment selection after recurrence is inconsistent. Nevertheless, despite the significant heterogeneity, our findings might have substantial implications for selecting neoadjuvant therapy before hepatectomy for HCC patients with type I/II PVTT.

Conclusion

In conclusion, TACE combined with TKI and PD-1 antibody treatment strategies before surgery presents a promising treatment option for HCC patients with type I/II PVTT. Prospective randomized controlled study should be performed to further prove the role of neoadjuvant treatment.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Informed consent was obtained from the patients for their data to be used for research purposes. The study protocol was approved by the Clinical Research Ethics Committee of the Sichuan Cancer Hospital conformed to the ethical guidelines of the 1975 Declaration of Helsinki (as revised in 2013).

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Disclosure

The authors report no conflicts of interest in this work.

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