

Postoperative Adjuvant Transarterial Chemoembolization Improves Short-Term Prognosis of Hepatocellular Carcinoma with Bile Duct Tumor Thrombus: A Propensity-Score Matching Study

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Purpose: To evaluate the effect of postoperative adjuvant transarterial chemoembolization (PA-TACE) on the prognosis of hepatocellular carcinoma (HCC) with macroscopic bile duct tumor thrombus (BDTT).

Patients and Methods: This study included 109 patients who underwent R0 resection for HCC with BDTT between January 2008 and December 2017: non-TACE (48) and PA-TACE (61). Propensity-score matching (PSM) was conducted in a 1:1 ratio. Recurrence and overall survival (OS) rates were analyzed using the Kaplan–Meier method. Independent risk factors were identified by univariate and multivariate Cox regression analyses. Subgroup analysis was performed by risk-factor stratification.

Results: The recurrence rates in the non-TACE and PA-TACE groups were different at 6 months (50.9% vs 26.9%, $P=0.03$) before PSM and at 6 months (59.3% vs 26.5%, $P=0.02$) and 12 months (81.4% vs 37.5%, $P=0.022$) after PSM. OS rates of the non-TACE and PA-TACE groups were different at 6 months (74.0% vs 91.6%, $P<0.001$) and 12 months (61.1% vs 77.6%, $P=0.01$) before PSM and at 6 months (73.0% vs 96.8%, $P=0.01$), 12 months (52.1% vs 89.6%, $P=0.001$), and 18 months (33.8% vs 64.4%, $P=0.034$) after PSM. PA-TACE was an independent prognostic factor for both recurrence and OS before and after PSM. Subgroup analysis showed that patients with no HBV infection, tumors >5 cm, macrovascular invasion, alpha-fetoprotein (AFP) >400 ng/mL, or gamma-glutamyl transferase (GGT) >150 U/L benefited significantly from PA-TACE in terms of recurrence rates (all $P<0.05$). Patients with no HBV infection, multiple tumors, tumors >5 cm, macrovascular invasion, or AFP >400 ng/mL benefited significantly from PA-TACE in terms of OS (all $P<0.05$).

Conclusion: PA-TACE could prolong the short-term prognosis of HCC with macroscopic BDTT and should be recommended for patients with no HBV infection, multiple tumors, tumors >5 cm, poor differentiation, macrovascular invasion, AFP >400 ng/mL, or GGT >150 U/L.

Keywords: hepatocellular carcinoma, bile duct tumor thrombus, transarterial chemoembolization, recurrence, survival

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Introduction

Bile duct tumor thrombus (BDTT) involves invasion of hepatocellular carcinoma (HCC) into the biliary tree. The incidence rate of HCC with macroscopic BDTT has

been reported to be 0.45–12.9%.^{1–3} Although the incidence is low, an increasing amount of research has focused on BDTT in recent years. Compared with patients without BDTT, patients with BDTT had a shorter survival time and a higher recurrence rate. This has been proven by different retrospective studies and meta-analyses.^{2,4–10} The median survival of patients with BDTT is 1.6–4.3 months with conservative management.^{11,12}

Surgical resection is the most commonly used management strategy, which allows radical cure of patients with resectable HCC with BDTT. However, the high recurrence rate after resection is a barrier to long-term survival. The 1-year recurrence rate of patients with HCC with BDTT remains between 42.9 and 70.3% even after resection.^{10,13} Therefore, postoperative adjuvant treatment for such patients cannot be ignored.

Postoperative adjuvant transarterial chemoembolization (PA-TACE) has been applied clinically for decades as an anti-recurrence therapy. Some randomized clinical trials have proven that HCC with microvascular invasion or portal vein tumor thrombus can benefit from PA-TACE.^{14–16} However, whether HCC with BDTT after R0 resection could benefit from PA-TACE remains unknown.

Thus, in this study, we aimed to evaluate the short-term effect of PA-TACE on the prognosis of patients after R0 resection.

Patients and Methods

Patient Selection

The study was conducted according to the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies, and was approved by the institutional research ethics committee of Mengchao Hepatobiliary Hospital of Fujian Medical University (Approval Number:2020_077_01). All patients signed an informed consent form before surgery. As some elderly patients cannot read, they sign the informed consent by hand print instead of signature, and their direct relatives sign the informed consent at the same time. Patients who underwent R0 resection for HCC with BDTT between January 2008 and December 2017 at primary liver cancer big data were enrolled for in this study.¹⁷ Data including baseline and clinical characteristics and information on follow-up were extracted and censored on December 31, 2019.

The inclusion criteria for the study were as follows: patients (1) who underwent R0 resection with curative intent for HCC and (2) in whom HCC and macroscopic

BDTT were confirmed by histopathological analysis. The exclusion criteria for the study were as follows: patients (1) aged <18 years; (2) with other accompanying cancers; (3) with recurrent or metastatic HCC; (4) with a diagnosis of combined hepatocellular carcinoma-intrahepatic cholangiocarcinoma (cHCC-ICC); and (5) who received anti-cancer therapy before surgery. R0 resection was defined as removal of all macroscopic tumors with a microscopically negative margin and no recurrence within two months after surgery.

Surgery

The scope of liver resection was determined on the basis of the location and size of the tumor, liver function, and residual liver volume. Hepatectomy includes partial resection, subsegmentectomy, segmentectomy, lobectomy, and extended hepatectomy. The objective of the operation was to completely remove the tumor to achieve R0 resection. When the tumor invaded the extrahepatic bile duct or the contralateral hepatic duct, the extrahepatic bile duct was removed or choledochotomy was performed, and intraoperative choledochoscopy was performed to ensure complete thrombectomy.

PA-TACE

PA-TACE is recommended per the personal experience and judgment of the physician. Initial PA-TACE was performed within 1–2 months after resection. A 5-F catheter or microcatheter was inserted into an appropriate hepatic artery using the Seldinger technique. Hepatic angiography was performed to ascertain the distribution of the arteries. Chemotherapeutic agents, including cisplatin (10–30 mg), doxorubicin hydrochloride (10 mg), and pharmorubicin (20–40 mg) were slowly injected, followed by an emulsion of lipiodol (5–10 mL) (Lipiodol Ultrafluide, Guerbet, AulnaySousBois, France). Individualized dosages of chemotherapeutic agents and lipiodol were determined on the basis of the remaining liver volume and body surface.

Postoperative Follow-Up

All patients were regularly followed up after discharge from the hospital. Follow-up visits were scheduled once every 2–3 months in the first 2 years, once every 6 months from 2 to 5 years, and once every year after 5 years. Routine follow-up tests included a liver function test, a test to determine the serum AFP level, and abdominal ultrasound. Contrast-enhanced computed tomography or magnetic resonance imaging was performed when

recurrence was suspected. Recurrence or metastasis was defined as the appearance of new lesions with radiologic features of HCC, and further treatment was immediately initiated when recurrence was confirmed.

Primary Endpoint

The primary endpoints were the recurrence rate and overall survival (OS) rate. Time to recurrence was defined as the time between the date of resection to the date of recurrence or the date of the latest follow-up, whichever occurred first. OS was calculated from the time of resection to the date of either death or the latest follow-up.

Baseline Characteristics and Clinical Variables of Patients

Baseline characteristics and clinical variables included age, sex, cirrhosis, number of tumors, maximum tumor size, macroscopic and microscopic vascular invasion, presence of satellites and tumor differentiation, preoperative serum HBV DNA, serum hepatitis B surface antigen, gamma-glutamyltransferase (GGT), alkaline phosphatase, total bilirubin, prealbumin, alpha-fetoprotein (AFP), platelet, prothrombin time, Child–Pugh grade, and Fibrosis-4 index. HBV infection was defined as HBV DNA-positive or serum hepatitis B surface antigen positive. Cirrhosis was confirmed histopathologically or via clinical diagnosis. Tumor differentiation was classified according to the Edmonson–Steiner grade.¹⁸ BDTT was classified using Satoh typing¹⁹ as follows: Type I, BDTT is located in the first branch of the hepatic duct and does not reach the confluence of the right and left hepatic ducts; Type II, BDTT extends across the confluence of the right and left hepatic ducts; Type III, BDTT separates from the primary tumor and is located in the common bile ducts.

Propensity-Score Matching

Propensity-score matching (PSM) was adopted to minimize selection bias. Potentially confounding factors either unbalanced in the baseline table or independent in the multivariable Cox model were matched one-to-one using the nearest neighbor method with a caliber of 0.2.

Statistical Analysis

Continuous variables with a normal distribution were expressed as medians with interquartile ranges (IQR) and compared using the Mann–Whitney *U*-test. Fisher's exact

test or the chi-squared test was used for comparison of categorical variables, as appropriate. Comparison of recurrence and OS curves between the non-TACE and PA-TACE groups was performed using the Kaplan–Meier method and tested using the Log rank test. Univariable and multivariable Cox regression analyses were performed to identify the independent risk factors associated with recurrence and OS. Hazard ratios (HRs) and their 95% confidence intervals (95% CI) were estimated using univariable and multivariable Cox regression analyses. Potentially relevant variables (with $P < 0.2$ in the univariable Cox regression analysis) were considered for generating the multivariable Cox model using the stepwise backward method. The forest plot of the subgroup analysis was described with estimated HRs and 95% CIs. Data were analyzed via Rstudio using “Table 1,” “survminer,” “survival,” “forestplot,” “MachIt” packages. Statistical significance was set at $P < 0.05$.

Results

Patients Characteristics

A total of 109 patients were enrolled in this study: 48 in the non-TACE group and 61 in the PA-TACE group. Patients with tumor size > 5 cm and macrovascular invasion were more likely to receive PA-TACE; the difference between the two groups was balanced after 1:1 PSM (Table 1).

Recurrence and OS Rates

The median follow-up period of the whole cohort was 14.0 (7.0–27.0) months. Before PSM, the median recurrence time of the non-TACE and PA-TACE groups was 4.0 (2.0–7.0) and 11 (5.0–17.0) months, respectively ($P=0.09$) (Figure 1A). The recurrence rates in the non-TACE and PA-TACE groups were different at 6 months (50.9% vs 26.9%, $P=0.03$) (Table 2). After PSM, the median recurrence time of the two groups was 3.0 (1.0–6.0) and 12.0 (5.5–18.0) months, respectively ($P=0.0046$) (Figure 1C). The recurrence rates in the two groups were different at 6 months (59.3% vs 26.5%, $P=0.02$) and 12 months (81.4% vs 37.5%, $P=0.022$) (Table 2).

Before PSM, the median OS time of the non-TACE and PA-TACE groups was 10.5 (4.0–24.25) and 15 (11.0–27.0) months, respectively ($P=0.18$) (Figure 1B). The OS rates of the non-TACE and PA-TACE groups were different at 6 months (74.0% vs 91.6%, $P < 0.001$) and 12 months (61.1% vs 77.6%, $P=0.01$) (Table 2). After

Table I Clinicopathological Characteristics of Non-TACE Group Compare with PA-TACE Group Before and After PSM

Parameters	Before PSM			After PSM		
	Non-TACE	TACE	P	Non-TACE	TACE	P
	(n=48)	(n=61)		(n=31)	(n=31)	
Age(years) Mean (IQR)	51.0 [46.0, 56.0]	49.0 [45.0, 55.0]	0.564	54.0 [48.0, 59.0]	51.0 [45.5, 59.0]	0.306
Sex						
Female	6 (12.5%)	11 (18.0%)	0.6	4 (12.9%)	3 (9.7%)	1
Male	42 (87.5%)	50 (82.0%)		27 (87.1%)	28 (90.3%)	
HBV						
No	13 (27.1%)	16 (26.2%)	1	9 (29.0%)	9 (29.0%)	1
Yes	35 (72.9%)	45 (73.8%)		22 (71.0%)	22 (71.0%)	
Cirrhosis						
No	6 (12.5%)	16 (26.2%)	0.125	2 (6.5%)	7 (22.6%)	0.149
Yes	42 (87.5%)	45 (73.8%)		29 (93.5%)	24 (77.4%)	
Tumor Number						
Single	41 (85.4%)	44 (72.1%)	0.153	27 (87.1%)	24 (77.4%)	0.506
Multiple	7 (14.6%)	17 (27.9%)		4 (12.9%)	7 (22.6%)	
Tumor Size(cm)						
≤5cm	30 (62.5%)	16 (26.2%)	<0.001	13 (41.9%)	13 (41.9%)	1
>5cm	18 (37.5%)	45 (73.8%)		18 (58.1%)	18 (58.1%)	
Satellite Nodules						
No	24 (50.0%)	21 (34.4%)	0.149	17 (54.8%)	10 (32.3%)	0.124
Yes	24 (50.0%)	40 (65.6%)		14 (45.2%)	21 (67.7%)	
Differentiation						
I+II	9 (18.8%)	13 (21.3%)	0.928	3 (9.7%)	7 (22.6%)	0.3
III+IV	39 (81.2%)	48 (78.7%)		28 (90.3%)	24 (77.4%)	
Capsule						
No	26 (54.2%)	24 (39.3%)	0.178	14 (45.2%)	10 (32.3%)	0.434
Yes	22 (45.8%)	37 (60.7%)		17 (54.8%)	21 (67.7%)	
MVI						
No	9 (18.8%)	11 (18.0%)	1	5 (16.1%)	5 (16.1%)	1
Yes	39 (81.2%)	50 (82.0%)		26 (83.9%)	26 (83.9%)	
MaVI						
No	41 (85.4%)	41 (67.2%)	0.0498	24 (77.4%)	24 (77.4%)	1
Yes	7 (14.6%)	20 (32.8%)		7 (22.6%)	7 (22.6%)	
Satoh						
I	26 (54.2%)	30 (49.2%)	0.746	16 (51.6%)	15 (48.4%)	1
II+III	22 (45.8%)	31 (50.8%)		15 (48.4%)	16 (51.6%)	
AFP(ng/mL)						
≤400	24 (50.0%)	29 (47.5%)	0.951	10 (32.3%)	17 (54.8%)	0.124
>400	24 (50.0%)	32 (52.5%)		21 (67.7%)	14 (45.2%)	
TBIL(umol/L)						
≤34.2	31 (64.6%)	40 (65.6%)	1	22 (71.0%)	21 (67.7%)	1
>34.2	17 (35.4%)	21 (34.4%)		9 (29.0%)	10 (32.3%)	

(Continued)

Table 1 (Continued).

Parameters	Before PSM			After PSM		
	Non-TACE	TACE	P	Non-TACE	TACE	P
	(n=48)	(n=61)		(n=31)	(n=31)	
ALP(U/L)						
≤150	22 (45.8%)	23 (37.7%)	0.509	14 (45.2%)	14 (45.2%)	I
>150	26 (54.2%)	38 (62.3%)		17 (54.8%)	17 (54.8%)	
GGT(U/L)						
≤150	11 (22.9%)	9 (14.8%)	0.399	8 (25.8%)	4 (12.9%)	0.335
>150	37 (77.1%)	52 (85.2%)		23 (74.2%)	27 (87.1%)	
PALB(mg/L)						
≤170	17 (35.4%)	20 (32.8%)	0.933	11 (35.5%)	11 (35.5%)	I
>170	31 (64.6%)	41 (67.2%)		20 (64.5%)	20 (64.5%)	
PLT(×10⁹/L)						
<100	4 (8.3%)	4 (6.6%)	I	2 (6.5%)	3 (9.7%)	I
≥100	44 (91.7%)	57 (93.4%)		29 (93.5%)	28 (90.3%)	
PT(s)						
≤13	28 (58.3%)	41 (67.2%)	0.45	16 (51.6%)	20 (64.5%)	0.44
>13	20 (41.7%)	20 (32.8%)		15 (48.4%)	11 (35.5%)	
Child-Pugh						
A	43 (89.6%)	55 (90.2%)	I	29 (93.5%)	27 (87.1%)	0.668
B	5 (10.4%)	6 (9.8%)		2 (6.5%)	4 (12.9%)	
FIB-4						
≤3.25	27 (56.2%)	38 (62.3%)	0.659	15 (48.4%)	16 (51.6%)	I
>3.25	21 (43.8%)	23 (37.7%)		16 (51.6%)	15 (48.4%)	

Note: The bold text means $P < 0.05$.

Abbreviations: AFP, alpha-fetoprotein; ALP, alkaline phosphatase; FIB-4, Fibrosis-4 index; GGT, gamma-glutamyltransferase; HBV, hepatitis B virus; IQR, interquartile range; MaVI, macrovascular invasion; MVI, microvascular invasion; PA-TACE, postoperative adjuvant transarterial chemoembolization; PALB, prealbumin; PLT, platelet; PSM, propensity-score matching; PT, prothrombin time; TBIL, total bilirubin.

PSM, the OS time of the two groups was 9.0 (4.0–14.0) and 17.0 (12.0–31.5) months, respectively ($P=0.0068$) (Figure 1D). The OS rate in the two groups was different at 6 months (73.0% vs 96.8%, $P=0.01$), 12 months (52.1% vs 89.6%, $P=0.001$), and 18 months, respectively (33.8% vs 64.4%, $P=0.034$) (Table 2).

Risk Factors Associated with Recurrence and OS

Multivariate analysis showed that $GGT > 150$ U/L and PA-TACE were independent prognostic factors for recurrence both before and after PSM; $GGT > 150$ U/L (HR=3.233, 95% CI=1.353–7.723, $P=0.008$ before PSM and HR=2.908, 95% CI=1.071–7.9, $P=0.036$ after PSM) and PA-TACE (HR=0.537, 95% CI=0.313–0.921, $P=0.024$ before PSM and HR=0.319, 95% CI=0.156–0.655, $P=0.002$) (Tables 3 and 4).

For OS, multivariate analysis showed that multiple tumors (HR=3.409, 95% CI=1.609–7.223, $P=0.001$), macrovascular invasion (HR=4.947, 95% CI=2.321–10.542, $P < 0.001$), AFP > 400 ng/mL (HR=2.376, 95% CI=1.289–4.382, $P=0.006$), and PA-TACE (HR=0.266, 95% CI=0.133–0.529, $P < 0.001$) were independent risk factors before PSM (Table 3), whereas satellite nodules (HR=2.976, 95% CI=1.124–7.884, $P=0.028$), macrovascular invasion (HR=2.917, 95% CI=1.138–7.48, $P=0.026$), AFP > 400 ng/mL (HR=2.688, 95% CI=1.13–6.394, $P=0.025$), and PA-TACE (HR=0.177, 95% CI=0.068–0.46, $P < 0.001$) were independent risk factors after PSM (Table 4).

Subgroup Analysis

Subgroup analysis showed that patients who were not infected with HBV (HR=0.312, 95% CI=0.103–0.948, $P=0.04$), had tumor size > 5 cm (HR=0.351, 95%

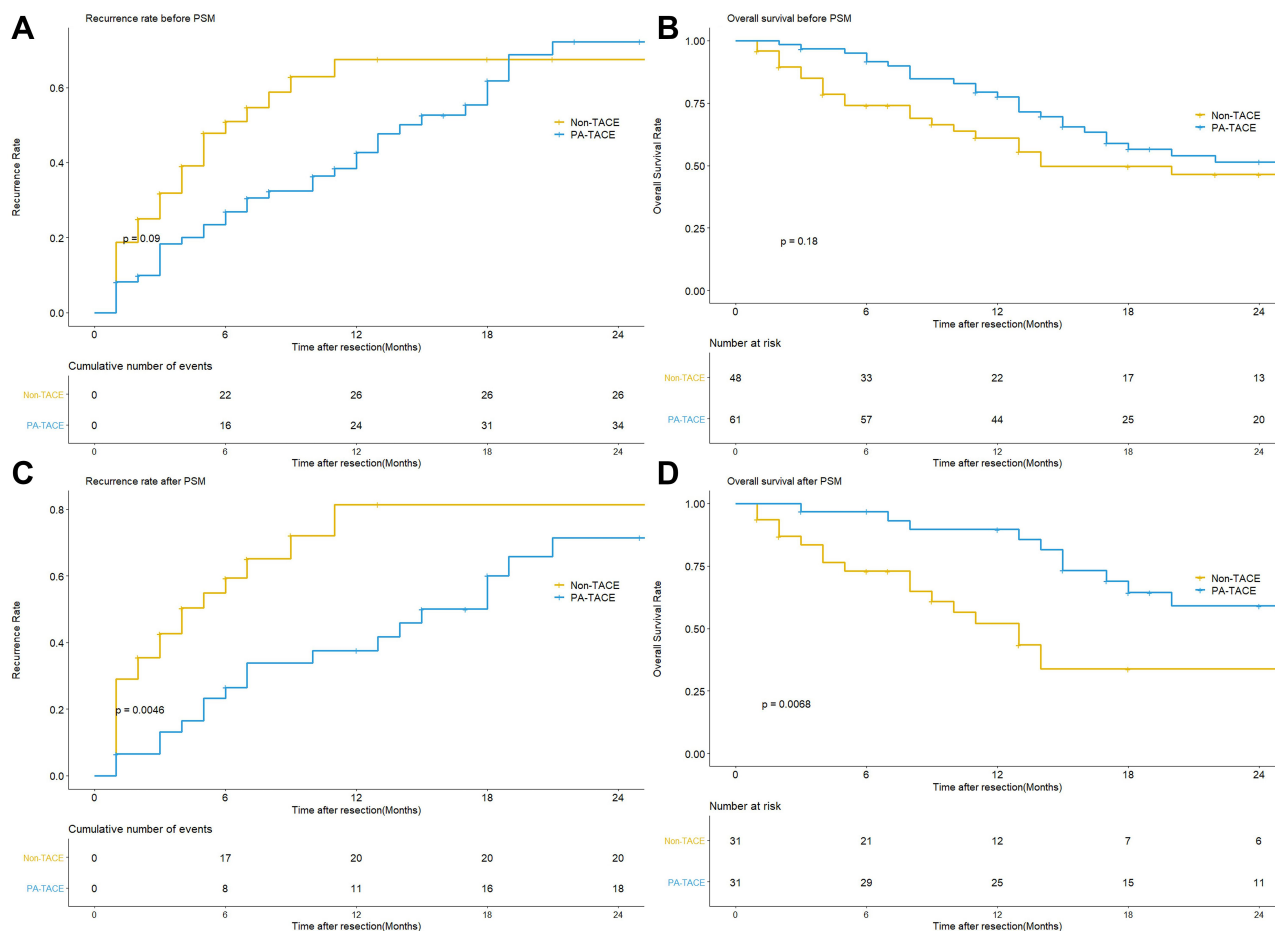


Figure 1 (A) Comparison of recurrence rate between the PA-TACE and non-TACE groups before PSM. (B) Comparison of overall survival rate between the PA-TACE and non-TACE groups before PSM. (C) Comparison of recurrence rate between the PA-TACE and non-TACE groups after PSM. (D) Comparison of overall survival rate between the PA-TACE and non-TACE groups after PSM.

CI=0.157–0.784, P=0.011), macrovascular invasion (HR=0.175, 95% CI=0.041–0.746, P=0.018), AFP > 400 ng/mL (HR=0.345, 95% CI=0.156–0.765, P=0.009), or GGT > 150 U/L (HR=0.556, 95% CI=0.316–0.977, P=0.041) benefited from PA-TACE on recurrence significantly (Figure 2), whereas patients who were not infected with HBV (HR=0.029, 95%

CI=0.003–0.347, P=0.001), had multiple tumors (HR=0.189, 95% CI=0.044–0.807, P=0.025), tumor size > 5 cm (HR=0.315, 95% CI=0.143–0.692, P=0.004), macrovascular invasion (HR=0.212, 95% CI=0.063–0.708, P=0.012), or AFP > 400 ng/mL (HR=0.351, 95% CI=0.169–0.728, P=0.005) benefited from PA-TACE on OS significantly (Figure 3).

Table 2 Recurrence Rate and Overall Survival of Non-TACE Group Compare with PA-TACE Groups Before and After PSM

Time	Before PSM						After PSM					
	Recurrence Rate			Overall Survival Rate			Recurrence Rate			Overall Survival Rate		
	Non-TACE	PA-TACE	P	Non-TACE	PA-TACE	P	Non-TACE	PA-TACE	P	Non-TACE	PA-TACE	P
6 mo	50.9%	26.9%	0.03	74.0%	91.6%	<0.001	59.3%	26.5%	0.02	73.0%	96.8%	0.01
12 mo	67.5%	42.7%	0.12	61.1%	77.6%	0.01	81.4%	37.5%	0.022	52.1%	89.6%	0.001
18 mo	67.5%	61.8%	0.73	49.7%	56.6%	0.55	81.4%	60.0%	0.303	33.8%	64.4%	0.034
24 mo	67.5%	72.2%	0.87	46.4%	51.5%	0.52	81.4%	71.4%	0.602	33.8%	59.0%	0.155

Note: The bold text means P<0.05.

Table 3 Univariate and Multivariate Analysis of Recurrence and Overall Survival for HCC with BDTT Before PSM

Parameters	Recurrence						Overall Survival					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	CI95%	P	HR	CI95%	P	HR	CI95%	P	HR	CI95%	P
Age, >50 years	1.238	0.745–2.057	0.41				1.504	0.847–2.67	0.164			
Sex, male	1.698	0.804–3.584	0.165				1.424	0.637–3.186	0.389			
HBV, yes	1.09	0.614–1.935	0.769				1.453	0.721–2.926	0.296			
Cirrhosis, yes	2.301	1.125–4.704	0.022				1.662	0.744–3.713	0.215			
Tumor Number, multiple	0.986	0.512–1.898	0.966				1.922	0.995–3.711	0.052	3.319	1.54–7.156	0.002
Tumor Size, >5cm	0.777	0.467–1.29	0.329				1.035	0.58–1.846	0.907			
Satellite Nodules, yes	1.201	0.717–2.012	0.487				1.372	0.761–2.472	0.293			
Differentiation, III+IV	2.122	1.04–4.329	0.039				1.49	0.695–3.192	0.306			
Capsule, yes	1.303	0.778–2.182	0.315				0.692	0.389–1.231	0.21			
MVI, yes	1.418	0.718–2.802	0.314				1.424	0.638–3.181	0.388			
MaVI, yes	1.485	0.824–2.676	0.189				2.489	1.337–4.636	0.004	4.318	2.099–8.885	<0.001
BDTT type, II+III	1.053	0.634–1.749	0.842				1.582	0.886–2.823	0.121			
AFP, >400ug/L	0.925	0.557–1.537	0.764				2.221	1.223–4.035	0.009	2.389	1.297–4.4	0.005
ALP, >150U/L	1.065	0.636–1.783	0.812				1.763	0.954–3.257	0.07			
GGT, >150U/L	2.985	1.269–7.023	0.012	3.233	1.353–7.723	0.008	2.848	1.02–7.951	0.046			
TBIL, >34.2umol/L	0.813	0.463–1.429	0.473				1.516	0.839–2.738	0.168			
PALB, >170mg/L	1.195	0.681–2.098	0.534				0.745	0.407–1.365	0.341			
PLT, ≥100×10 ⁹ /L	0.959	0.383–2.397	0.928				0.533	0.226–1.255	0.15			
PT, >13s	0.94	0.552–1.599	0.819				0.938	0.513–1.715	0.835			
Child-Pugh, B	0.957	0.345–2.657	0.932				2.89	1.282–6.512	0.01			
FIB-4, >3.25	1.017	0.606–1.705	0.95				1.003	0.56–1.796	0.993			
PA-TACE, yes	0.649	0.385–1.092	0.103	0.537	0.313–0.921	0.024	0.683	0.385–1.212	0.193	0.291	0.147–0.577	<0.001

Notes: The bold text means P<0.2 in univariable Cox regression analysis and P<0.05 in multivariable Cox regression analysis.
 Abbreviations: AFP, alpha-fetoprotein; ALP, alkaline phosphatase; FIB-4, Fibrosis-4 index; GGT, gamma-glutamyltransferase; HBV, hepatitis B virus; IQR, interquartile range; MaVI, macrovascular invasion; MVI, microvascular invasion; PA-TACE, postoperative adjuvant transarterial chemoembolization; PALB, prealbumin; PLT, platelet; PSM, propensity score matching; PT, prothrombin time; TBIL, total bilirubin.

Table 4 Univariate and Multivariate Analysis of Recurrence and Overall Survival for HCC with BDTT After PSM

Parameters	Recurrence						Overall Survival					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	CI95%	P	HR	CI95%	P	HR	CI95%	P	HR	CI95%	P
Age, >50 years	1.159	0.609–2.206	0.654				1.724	0.774–3.841	0.183			
Sex, male	0.935	0.361–2.423	0.89				5.032	0.681–37.18	0.113			
HBV, yes	0.995	0.414–2.391	0.991				1.667	0.629–4.419	0.304			
Cirrhosis, yes	0.691	0.364–1.31	0.257				0.751	0.353–1.6	0.458			
Tumor Number, multiple	1.026	0.516–2.039	0.942				1.473	0.621–3.496	0.379			
Tumor Size, >5cm	2.787	0.85–9.136	0.091				1.311	0.394–4.364	0.659			
Satellite Nodules, yes	1.492	0.777–2.867	0.229				1.757	0.802–3.849	0.159			0.028
Differentiation, III+IV	1.471	0.611–3.541	0.39				2.062	0.619–6.867	0.238			
Capsule, yes	1.773	0.688–4.569	0.236				2.672	0.632–11.302	0.182			
MVI, yes	1.067	0.55–2.068	0.848				0.644	0.302–1.371	0.253			
MaVI, yes	1.165	0.508–2.675	0.718				2.542	1.061–6.088	0.036			0.026
BDTT type, II+III	1.427	0.751–2.712	0.278				1.407	0.658–3.01	0.379			
AFP, >400ug/L	1.442	0.754–2.758	0.269				2.099	0.955–4.613	0.065			0.025
ALP, >150U/L	0.981	0.519–1.857	0.954				1.219	0.57–2.608	0.61			
GGT, >150U/L	1.972	0.757–5.138	0.165				1.948	0.584–6.494	0.278			
TBIL, >34.2umol/L	1.218	0.61–2.434	0.576				1.328	0.577–3.058	0.505			
PALB, >170mg/L	1.686	0.818–3.475	0.157				1.009	0.44–2.313	0.983			
PLT, ≥100×10 ⁹ /L	1.417	0.433–4.639	0.565				0.825	0.248–2.744	0.753			
PT, >13s	0.977	0.299–3.193	0.969				1.971	0.583–6.657	0.275			
Child-Pugh, B	0.831	0.438–1.578	0.572				0.652	0.302–1.406	0.276			
FIB-4, >3.25	1.085	0.566–2.08	0.806				0.678	0.304–1.513	0.343			
PA-TACE, yes	0.398	0.201–0.79	0.008				0.356	0.162–0.785	0.01			<0.001
							2.908	1.071–7.9	0.036			
							0.319	0.156–0.655	0.002			

Notes: The bold text means P<0.2 in univariable Cox regression analysis and P<0.05 in multivariable Cox regression analysis.
 Abbreviations: AFP, alpha-fetoprotein; ALP, alkaline phosphatase; FIB-4, Fibrosis-4 index; GGT, gamma-glutamyltransferase; HBV, hepatitis B virus; IQR, interquartile range; MVI, macrovascular invasion; MaVI, macrovascular invasion; MVI, macrovascular invasion; PA-TACE, postoperative adjuvant transarterial chemoembolization; PALB, prealbumin; PLT, platelet; PSM, propensity score matching; PT, prothrombin time; TBIL, total bilirubin.

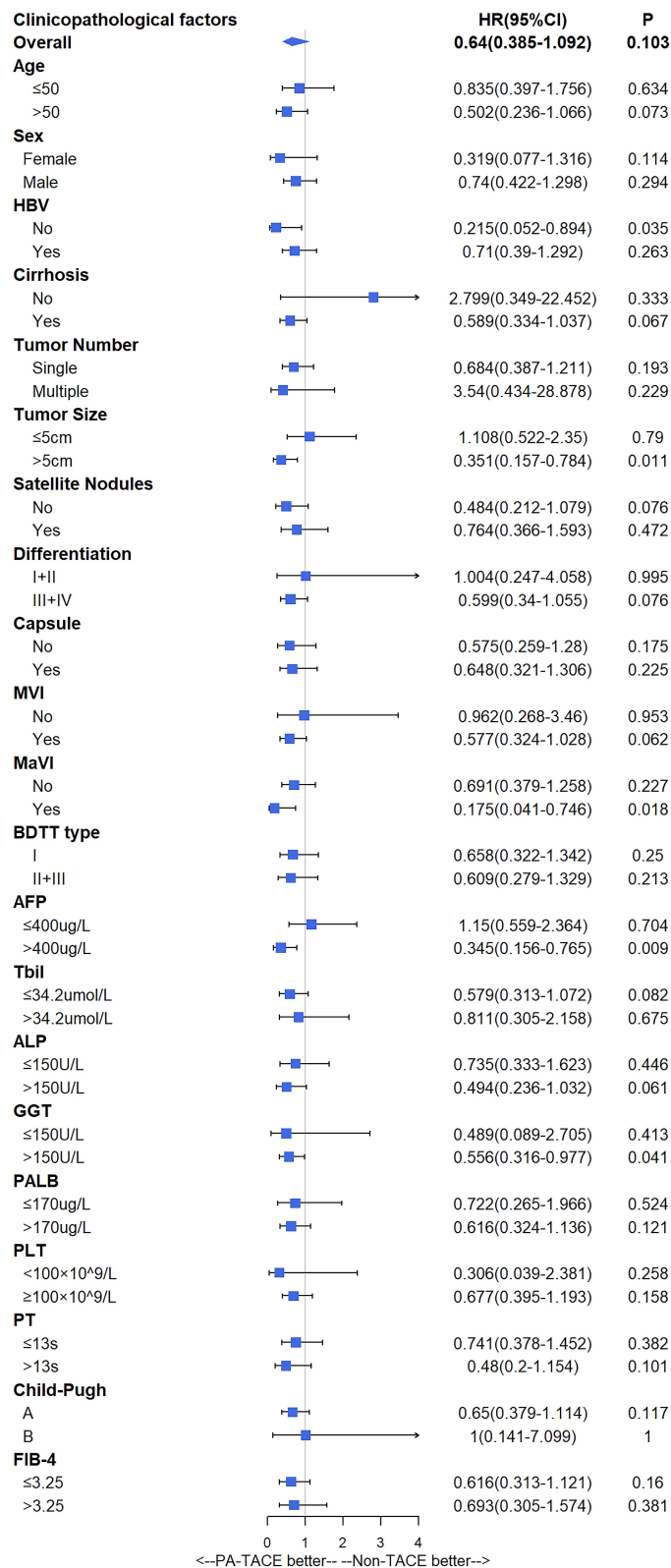


Figure 2 Subgroup analysis of recurrence.

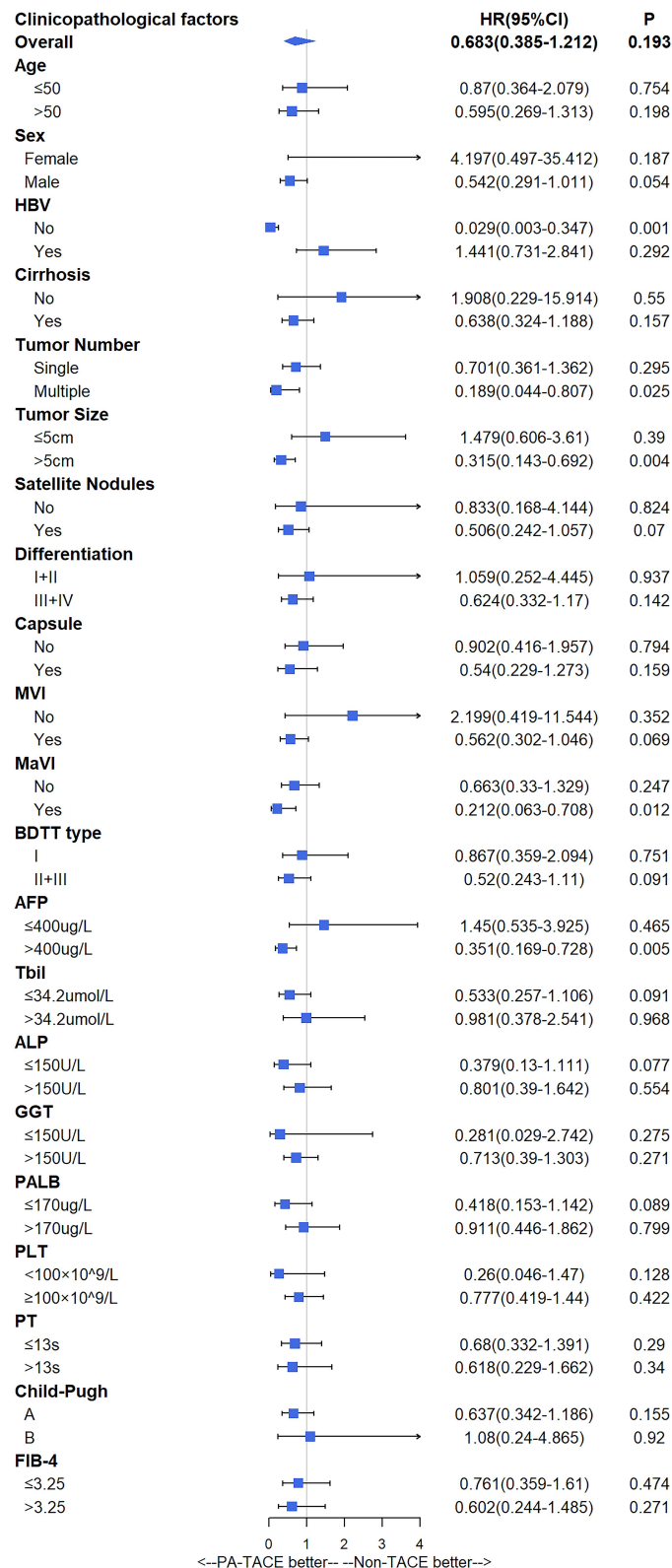


Figure 3 Subgroup analysis of overall survival.

Discussion

Generally, tumor recurrence is classified into early and late recurrence according to a cutoff interval of 2 years. More than 70% of tumor recurrences occur within 2 years of surgical resection.²⁰ One of the main reasons for the high early recurrence rate is the presence of invisible intrahepatic metastases before surgery, which are difficult to remove completely through surgical resection. For this reason, many radical surgeries do not achieve “radical cure;” hence, postoperative adjuvant therapy has great clinical significance in these patients.

PA-TACE is a widely used anti-recurrence therapy in the clinic setting. In terms of local treatment, the concentration of chemotherapeutic drugs in the liver is 100–400-fold higher than that in the whole body; this is because hepatic artery perfusion results in considerably higher concentrations than those achieved via oral administration or intravenous injection. The accumulation of drugs in HCC lesions due to TACE resulted in 5–10-times higher drug concentrations in tumor areas than in normal liver tissue.²¹ There have been many previous studies on PA-TACE. Xie et al²¹ suggested that PA-TACE significantly improves the prognosis of low-risk patients. Gao’s study²² showed that PA-TACE was beneficial for patients with high-risk factors. Tong’s research²³ indicated that single, postoperative, adjuvant TACE was beneficial for selected patients, such as patients with stage I with tumors sized <5 cm (low-risk) or those with high preoperative serum alpha-fetoprotein levels or positivity for alpha-fetoprotein on pathological analysis (high-risk). In contrast, Jiang et al²⁴ reported that postoperative adjuvant TACE does not improve OS or reduce recurrence in HCC patients. However, whether patients with HCC with macroscopic BDTT can benefit from PA-TACE after R0 resection remains unknown. To our knowledge, this was the first study to investigate the clinical value of PA-TACE for HCC accompanied by macroscopic BDTT.

Our study showed that there were significant differences in recurrence rates and OS between the non-TACE and PA-TACE groups within 6 months after resection, and after PSM, these differences were observed for a duration of 12 months, although the differences faded gradually thereafter. Multivariate analyses confirmed that PA-TACE was an independent prognostic factor for recurrence and OS. Hence, we believe that PA-TACE could confer short-term survival benefits in HCC patients with macroscopic BDTT. This

phenomenon was also observed in a previous study.^{25,26} The following may be the reasons for this phenomenon: (1) the different cycles of PA-TACE had diverse clinical benefits, and (2) the long-term survival after recurrence was affected by the treatment after recurrence also.

In this study, a high GGT level was another independent risk factor for recurrence. The relationship between high GGT levels and early recurrence has been reported, and this relationship may be based on the following mechanisms: (1) high GGT levels may induce DNA instability, leading to tumor formation; and (2) GGT may be associated with the degree of malignancy of HCC (in terms of vascular invasion, tumor metastasis, or poor tumor differentiation).²⁷ Most patients in our cohort had elevated GGT levels, poor differentiation, and a high microvascular invasion incidence, consistent with the results of previous study.²⁷ However, the correlation between GGT levels and BDTT needs to be explored further.

The subgroup analysis in our study showed that patients could significantly benefit from PA-TACE in prolonging the time to recurrence if they had no HBV infection, cirrhosis, a tumor size >5 cm, poor differentiation, macrovascular invasion, AFP levels > 400 ng/mL, or GGT levels >150 U/L. Patients without an HBV infection, multiple tumors, a tumor size >5 cm, macrovascular invasion, or AFP levels >400 ng/mL benefited from PA-TACE in terms of OS. HBV infection has been commonly regarded as a low-risk factor, while cirrhosis, tumor size >5 cm, poor differentiation, macrovascular invasion, high AFP levels, and high GGT levels have been regarded as high-risk factors. In the PA-TACE group of this study, both the time to recurrence and OS were significantly prolonged in patients with no HBV infection compared with those in patients with HBV infection. The reason for this difference is that TACE might induce HBV re-activation,²⁸ which increases the risk of HCC recurrence and counteracts the partial anti-recurrence effect of PA-TACE. Consequently, there was no obvious survival benefit in patients with HBV infection. Regarding high-risk factors, different studies^{29–32} have reported that patients with a tumor size >5 cm, multiple tumors, high AFP levels, high GGT levels, or macrovascular invasion could benefit from PA-TACE, consistent with our results. Based on the abovementioned information, we thought it might be inappropriate to judge whether patients could benefit from PA-TACE by classifying patients into high- and low-risk groups.

It is difficult to conduct a randomized controlled trial due to the low incidence of BDTT. This retrospective study had several limitations. First, it was difficult to avoid selection bias, although propensity-score matching was conducted. Second, due to the lack of imaging data for some patients, it was impossible to judge whether the BDTT was separated from the primary lesion; therefore, we were unable to distinguish between type II and type III BDTT. Third, the lack of data on PA-TACE cycles and antiviral therapy precluded further subgroup analysis.

Conclusion

In summary, PA-TACE could improve the short-term prognosis of patients with HCC with macroscopic BDTT after R0 resection. PA-TACE should be recommended for selected patients with no HBV infection, multiple tumors, tumor size >5 cm, macrovascular invasion, AFP levels >400 ng/mL, or GGT levels >150 U/L.

Abbreviations

AFP, alpha-fetoprotein; ALP, alkaline phosphatase; BDTT, bile duct tumor thrombus; cHCC-ICC, combined hepatocellular carcinoma-intrahepatic cholangiocarcinoma; FIB-4, Fibrosis-4 index, GGT, gamma-glutamyltransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IQR, interquartile range; MaVI, macrovascular invasion; MVI, microvascular invasion; OS, overall survival; PA-TACE, postoperative adjuvant transarterial chemoembolization; PALB, prealbumin; PLT, platelet; PSM, propensity-score matching; PT, prothrombin time; TBIL, total bilirubin.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest.

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