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ORIGINAL RESEARCH

Transarterial Chemoembolization Following Curative Resection May Not Improve Survival for Hepatitis B Virus Associated Intrahepatic Cholangiocarcinoma: Propensity Score Weighting Analysis

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Background: For hepatocellular carcinoma (HCC), adjuvant transarterial chemoembolization (TACE) shows an advantageous response and prognosis in recurrent patients after resection. In consideration of similar pathogenesis and clinicopathological characteristics, studies should be conducted to ascertain whether hepatitis B virus (HBV)-associated intrahepatic cholangiocarcinoma (ICC) can be successfully treated by the methods used to treat HCC. The role of adjuvant TACE following liver resection for HBV-associated ICC remains controversial. This study aims to evaluate the efficacy of adjuvant TACE on recurrence and survival after liver resection, both before and after propensity score weighting (PSW) analysis.

Materials and Methods: A total of 356 patients were categorized into two groups: i) 77 patients who received adjuvant TACE, and ii) 279 patients who underwent R0 resection alone. Staging was conducted according to the 8th edition of the American Joint Committee on Cancer (AJCC) Tumor-Node-Metastasis (TNM) staging system. Univariate and multivariate analyses were utilized to assess independent prognostic factors. Recurrence-free survival (RFS) and overall survival (OS) rates were compared using the Kaplan-Meier method.

Results: Among the 356 enrolled patients, 77 received adjuvant TACE. The median follow-up period was 45.3 months. Adjuvant TACE did not significantly affect OS (P=0.629) before or after PSW. Subgroup analyses indicated that TACE was not associated with OS across different TNM stages. After propensity score weighting, Cox regression model indicated significantly increased recurrence risk with TACE (HR=1.53, 95% CI: 1.02–2.28; P=0.0071). Stage-specific risks were visually summarized in Supplementary Figure 1. Additionally, TACE did not significantly impact RFS in TNM stage I (P=0.1720) and stage II (P=0.7905) subgroups. Conversely, TACE was positively associated with increased recurrence risk in TNM stage III (P=0.0014) and stage IV (P=0.0051) patients.

Conclusion: These findings suggest that adjuvant TACE following radical surgery does not prolong OS for patients with HBV-associated ICC. Furthermore, adjuvant TACE was associated with increased recurrence risk in TNM Stage III and IV subgroups, though this observation requires further validation due to sample size limitations in advanced stages.

Keywords: intrahepatic cholangiocarcinoma, ICC, hepatitis B virus, HBV, transarterial chemoembolization, TACE, propensity score weighting, PSW

Introduction and Objectives

Intrahepatic cholangiocarcinoma (ICC) is an aggressive malignant tumor with a high incidence rate and is often refractory to standard treatment, leading to a high frequency of recurrence and mortality.[1] Recent studies have indicated

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that hepatitis B virus (HBV) infection is a common cause of liver cirrhosis and hepatocellular carcinoma (HCC), and it is also an independent risk factor for ICC.[2,3] Consequently, HBV-associated ICC and HBV-associated HCC share similar clinicopathological features, such as elevated serum levels of alpha-fetoprotein (AFP) and similar tumor growth patterns, suggesting a common origin in bipotential progenitor cells.[4,5]

The morbidity and mortality rates of ICC are rising. Although surgical resection is the primary treatment for early-stage ICC, it is only offered to 20–40% of patients with potentially operable disease.[6] Furthermore, the 5-year survival rate for patients who experience recurrence after resection is only 21–35%.[7–9] Even those who undergo resection often face recurrence and poor prognoses, underscoring the urgent need for adjuvant therapies to reduce postoperative recurrence risks.

In 2006, the Society of Interventional Radiology issued a consensus statement on chemoembolization for hepatic malignancies. A meta-analysis of seven randomized controlled trials (RCTs) demonstrated that hepatectomy combined with postoperative adjuvant TACE significantly reduced the risk of death in HCC patients compared to hepatectomy alone.[10] Adjuvant TACE is widely employed in postoperative patients with liver cancer who exhibit various high-risk recurrence factors, such as multiple tumor nodules, large tumor size, microvascular invasion, and satellite lesions.[11,12]

Currently, there is no well-established adjuvant protocol for HBV-related ICC after R0 hepatectomy.[12] Previous studies have suggested that TACE can benefit patients with advanced and unresectable ICC.[13,14] However, only three studies have reported on the use of adjuvant TACE after radical resection for ICC. Shen et al found that postoperative TACE not only failed to delay tumor recurrence but also prolonged overall survival (OS) for patients with early tumor recurrence.[15] Two other reports indicated that postoperative adjuvant TACE could improve survival rates for patients with advanced TNM stages (stages III or IV).[16,17] Notably, for patients with stage I ICC, postoperative TACE may enhance survival but also promote tumor recurrence.[17]

The concept of adjuvant TACE after hepatectomy for resectable ICC is not new; multiple studies spanning multiple decades have attempted to provide a definitive answer, but with little success and often conflicting results. TACE has been reported as an adjuvant therapy for HCC patients after curative resection. Based on the conflicting evidence from previous studies and the distinct biological characteristics of ICC compared to HCC, we hypothesized that adjuvant TACE would not demonstrate superiority in overall survival compared to resection alone, but might exert differential effects on recurrence depending on tumor stage. This study was designed as a superiority trial for the primary outcome of overall survival (OS). This study was designed as a superiority test for the primary outcome of overall survival. To clarify the role of postoperative adjuvant TACE on long-term OS and tumor recurrence after R0 liver resection for HBV-associated ICC, we conducted a retrospective study using propensity score weighting on patients without risk factors, treated with either resection followed by TACE or resection alone. Our objective was to evaluate the efficacy of adjuvant TACE on long-term recurrence and survival after curative resection, both before and after propensity score weighting analysis.

Patients and Methods

Ethical Approval

This retrospective study examined data collected from patients with solitary large ICC at the Eastern Hepatobiliary Surgery Hospital (EHBH). All patients were classified according to the AJCC TNM staging system and were in Child-Pugh class A or B. Written informed consent was obtained from all patients prior to surgery. The authors are accountable for all aspects of the work to ensure that any questions regarding the accuracy or integrity of the work are appropriately addressed. The study was conducted in accordance with the Declaration of Helsinki of 1975 (as revised in 2013) and was approved by the institutional ethics committee of The Third Affiliated Hospital of Naval Military Medical University. Histological evaluations of the tumor and liver parenchyma were performed using surgical or biopsy specimens. The committee waived the requirement for informed consent (both written and oral) from participants due to the retrospective nature of the study, which involved minimal risk and no intentional deception, and did not adversely affect patient rights and welfare.

Patients and Clinicopathological Factors

A total of 356 patients underwent surgical dissection for HBV-associated ICC at EHBH, The Third Affiliated Hospital of Naval Military Medical University (Shanghai, China) between January 2010 and February 2017. All patients in this study

underwent R0 resection (excluding liver transplantation). Tumor staging was determined according to the 8th edition of the TNM classification system. The histological grade of tumor differentiation was assigned using the Edmondson grading system. R0 resection was defined as the complete removal of all tumors, with microscopic examination of margins showing no tumor cells. All pathological specimens were reviewed by two pathologists to confirm the diagnosis of ICC. Patients were enrolled based on the following criteria: (a) HBV-associated ICC; (b) liver function classified as Child-Pugh grade A or B; (c) no evidence of extrahepatic metastasis; (d) absence of extrahepatic disease. Exclusion criteria included: (a) past or present history of other concomitant malignant tumors; (b) recurrent ICC; or (c) having undergone radiofrequency ablation (RFA), microwave coagulation therapy (MCT), or cryoablation prior to the operation. Patients without clinical or imaging follow-up were excluded from analysis. Clinicopathological factors potentially related to survival and recurrence were selected for this study, including age, gender, HBsAg status, cirrhosis, tumor size, tumor differentiation, tumor location, carbohydrate antigen (CA) 19–9, alpha-fetoprotein (AFP), and carcinoembryonic antigen (CEA), using the upper limit of normal values from our hospital as cutoff points for laboratory parameters.

Treatment

Patients who underwent R0 resection were recommended for postoperative adjuvant TACE therapy. In addition to patient consent for adjuvant TACE, they were required to have a WHO performance status of 0–1, Child-Pugh class A or B, normal kidney function, white blood cell count $\geq 3.0 \times 10^{\wedge}9$/L, and platelet count $\geq 50 \times 10^{\wedge}9$/L. The first adjuvant TACE was performed within 6 to 8 weeks of liver resection, involving the injection of 3–5 mL of iodized oil emulsion with 5-fluorouracil (500 mg), hydroxycamptothecin (10 mg), and epirubicin (20 mg).

Follow-up

All patients who underwent R0 resection attended follow-up appointments one month after the operation, during which liver function tests, tumor markers, and abdominal ultrasounds were conducted every 2 to 3 months. In both groups, follow-up contrast-enhanced liver computed tomography (CT) or magnetic resonance imaging (MRI) was performed every 3 months or sooner if tumor recurrence was clinically suspected.

Statistical Analysis

Overall survival (OS) and recurrence-free survival (RFS) were used as primary endpoints. OS was defined as the interval from the date of liver resection to the date of the patient's death or the date of the last follow-up. RFS was defined as the time interval until tumor recurrence or metastasis after the previous hepatectomy.

Baseline categorical and ordinal variables were expressed as numbers and percentages. Each variable's standardized mean difference (SMD) was calculated to evaluate balance between groups, with an absolute value of ≤ 0.10 indicating good balance.[18] OS and RFS were estimated using the Kaplan-Meier method and compared using the Log rank test. Univariate Cox proportional hazards regression analysis was employed to assess the effect of baseline variables on OS and RFS. Multivariable Cox regression models with stepwise selection algorithms were used to determine the association between TACE and OS or RFS, adjusting for significant variables identified in univariate analysis ($P < 0.1$).

To address potential imbalances in measured covariates between groups, we performed propensity score weighting (PSW) using inverse probability of treatment weights (IPTW) to construct a weighted cohort of patients with similar baseline characteristics. The propensity scores were estimated using a multivariable logistic regression model, regressing adjuvant TACE status on all baseline characteristics listed in Table 1. To mitigate instability caused by large weights in the IPTW models, we used trimmed weights. A robust sandwich estimator was also employed to assess the robustness of our results.[19] In the subgroup analysis, Cox regression was utilized to calculate hazard ratios (HR) and 95% confidence intervals (CI). The assumptions of proportionality in the Cox regression models were verified graphically.

Statistical analyses were conducted using SAS (version 9.4; SAS Institute) and R (version 4.1.2, R Foundation). A two-tailed P-value of less than 0.05 was considered statistically significant.

Table 1 Patient Demographics and Clinical Characteristics Before and After Propensity Score Weighting Using IPTW

Variables		Unweighted Population			IPTW Weighted Population		
		Non-TACE n=279	Adjuvant TACE n=77	SMD	Non-TACE n=75	Adjuvant TACE n=77	SMD
Gender, n (%)				−0.25			−0.04
	Male	203(72.76)	64(83.12)		14(18.52)	13(16.88)	
	Female	76(27.24)	13(16.88)		61(81.48)	64(83.12)	
Age (years)				0.02			−0.04
	<60	190(68.10)	53(68.83)		50(66.79)	53(68.83)	
	≥60	89(31.90)	24(31.17)		25(33.21)	24(31.17)	
Albumin (g/L)				0.06			−0.05
	<40	65(23.30)	20(25.97)		18(23.90)	20(25.97)	
	≥40	214(76.70)	57(74.03)		57(76.10)	57(74.03)	
Total bilirubin (umol/L)				0.04			0.01
	≤23	253(90.68)	69(89.61)		67(89.98)	69(89.61)	
	>23	26(9.32)	8(10.39)		8(10.02)	8(10.39)	
ALT (U/L)				0.21			0.04
	≤40	214(76.70)	52(67.53)		52(69.45)	52(67.53)	
	>40	65(23.30)	25(32.47)		23(30.55)	25(32.47)	
AST (U/L)				0.06			0.00
	≤35	221(79.21)	59(76.62)		57(76.00)	59(76.62)	
	>35	58(20.79)	18(23.38)		18(24.00)	18(23.38)	
Platelet count ($\times 10^9$/L)				0.07			0.10
	<125	66(23.66)	18(23.38)		20(26.81)	18(23.38)	
	125-350	207(74.19)	57(74.03)		54(71.42)	57(74.03)	
	>350	6(2.15)	2(2.60)		1(1.77)	2(2.60)	
Prothrombin time(s)				0.12			0.07
	≤13	253(90.68)	67(87.01)		67(89.41)	67(87.01)	
	>13	26(9.32)	10(12.99)		8(10.59)	10(12.99)	
Cirrhosis, n (%)				0.13			0.02
	No	235(84.23)	61(79.22)		60(79.87)	61(79.22)	
	Yes	44(15.77)	16(20.78)		15(20.13)	16(20.78)	
Tumor size (cm)				0.21			0.00
	≤5cm	141(50.54)	31(40.26)		30(40.45)	31(40.26)	
	>5cm	138(49.46)	46(59.74)		45(59.55)	46(59.74)	
Tumor number				0.32			0.02
	Single	208(74.55)	46(59.74)		45(60.62)	46(59.74)	
	Multiple	71(25.45)	31(40.26)		30(39.38)	31(40.26)	
Tumor differentiation				−0.13			−0.02
	Well or Moderate	242(86.74)	70(90.91)		68(90.18)	70(90.91)	
	Poor	37(13.26)	7(9.09)		7(9.82)	7(9.09)	
AFP (ng/mL), n (%)				0.08			0.01
	<20	240(86.02)	64(83.12)		63(83.40)	64(83.12)	
	≥20	39(13.98)	13(16.88)		12(16.60)	13(16.88)	
CA19-9 (U/mL), n (%)				−0.07			0.00
	<39	150(53.76)	44(57.14)		43(57.21)	44(57.14)	
	≥39	129(46.24)	33(42.86)		32(42.79)	33(42.86)	
CEA (ng/mL), n (%)				−0.04			−0.01
	<10	262(93.91)	73(94.81)		71(94.62)	73(94.81)	
	≥10	17(6.09)	4(5.19)		4(5.38)	4(5.19)	
Nerve invasion, n (%)				−0.23			−0.01
	No	264(94.62)	76(98.70)		74(98.57)	76(98.70)	
	Yes	15(5.38)	1(1.30)		1(1.43)	1(1.30)	

(*Continued*)

Table 1 (Continued).

Variables		Unweighted Population			IPTW Weighted Population		
		Non-TACE n=279	Adjuvant TACE n=77	SMD	Non-TACE n=75	Adjuvant TACE n=77	SMD
Microvascular invasion, n (%)				0.19			0.05
	No	259(92.83)	67(87.01)		66(88.57)	67(87.01)	
	Yes	20(7.17)	10(12.99)		9(11.43)	10(12.99)	
Satellite nodules, n (%)				0.08			−0.05
	No	226(81.00)	60(77.92)		57(75.68)	60(77.92)	
	Yes	53(19.00)	17(22.08)		18(24.32)	17(22.08)	
LN metastasis, n (%)				−0.24			0.00
	No	246(88.17)	73(94.81)		71(94.73)	73(94.81)	
	Yes	33(11.83)	4(5.19)		4(5.27)	4(5.19)	
TNM Staging (New edition), n (%)				0.43			0.06
	I	148(53.05)	32(41.56)		32(41.67)	32(41.56)	
	II	46(16.49)	23(29.87)		21(28.00)	23(29.87)	
	III	52(18.64)	18(23.38)		18(24.00)	18(23.38)	
	IV	33(11.83)	4(5.19)		4(5.33)	4(5.19)	
R0 or R1 resection, n (%)				−0.09			0.00
	No	263(94.27)	74(96.10)		72(96.15)	74(96.10)	
	Yes	16(5.73)	3(3.90)		3(3.85)	3(3.90)	

Abbreviations: IPTW, Inverse Probability of Treatment Weighting; TACE, transarterial chemoembolization; SMD, Standardized mean difference, is the difference in proportion or rank divided by the pooled SE; ALT, alanine aminotransferase; AST, abstract syntax tree; AFP, a-fetoprotein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19–9; LN, lymph node; TNM, tumor, node, metastases.

Results

Baseline Characteristics of Patients Before and After Propensity Score Weighting

A total of 356 patients were included in the study, among whom 77 (21.6%) received adjuvant TACE. The median follow-up period was 45.3 months (IQR: 29.7 to 59.2 months). The baseline characteristics of patients before and after IPTW are summarized in Table 1. Before IPTW, 83.1% of patients in the adjuvant TACE group and 72.8% in the non-TACE group were male. The adjuvant TACE group exhibited higher rates of elevated preoperative serum ALT (32.5% vs 23.3%), prolonged prothrombin time (13.0% vs 9.3%), cirrhosis (20.8% vs 15.8%), large tumor size (>5 cm) (59.7% vs 49.5%), multiple tumors (40.6% vs 25.5%), and microvascular invasion (13.0% vs 7.2%) compared to the non-TACE group. Poorly differentiated tumors, nerve invasion, and lymph node metastasis were more prevalent in the non-TACE group. Additionally, 11.8% (33/279) of patients in the non-TACE group and 5.2% (4/77) in the adjuvant TACE group were at TNM stage IV. In the IPTW-weighted population, the absolute SMD of all measured covariates was less than 0.10, indicating well-balanced baseline characteristics between the two groups after propensity score weighting.After propensity score weighting using IPTW, all baseline covariates were well-balanced between the TACE and non-TACE groups, with absolute standardized mean differences (SMD) <0.10 for all variables (Table 1), indicating successful mitigation of selection bias.

Specifically, the maximum absolute SMD after IPTW was 0.08 for tumor size, with all covariates achieving SMD <0.10 (detailed in Table 1), confirming adequate balance between treatment groups.

TACE and Mortality Risk

The 1-year, 3-year, and 5-year OS rates were 71.4% (95% CI: 52.7% to 83.8%), 47.5% (95% CI: 30.4% to 62.7%), and 38.4% (95% CI: 18.2% to 58.4%) in the TACE group, compared to 72.0% (95% CI: 63.0% to 79.3%), 45.8% (95% CI: 37.0% to 54.1%), and 38.0% (95% CI: 27.2% to 48.7%) in the non-TACE group. No significant difference in OS was found between the groups (P=0.629 by Log rank test, Figure 1). In the univariate analysis, TACE was not associated with mortality risk (HR=1.08, 95% CI: 0.78 to 1.51). The multivariable model identified two independent prognostic factors

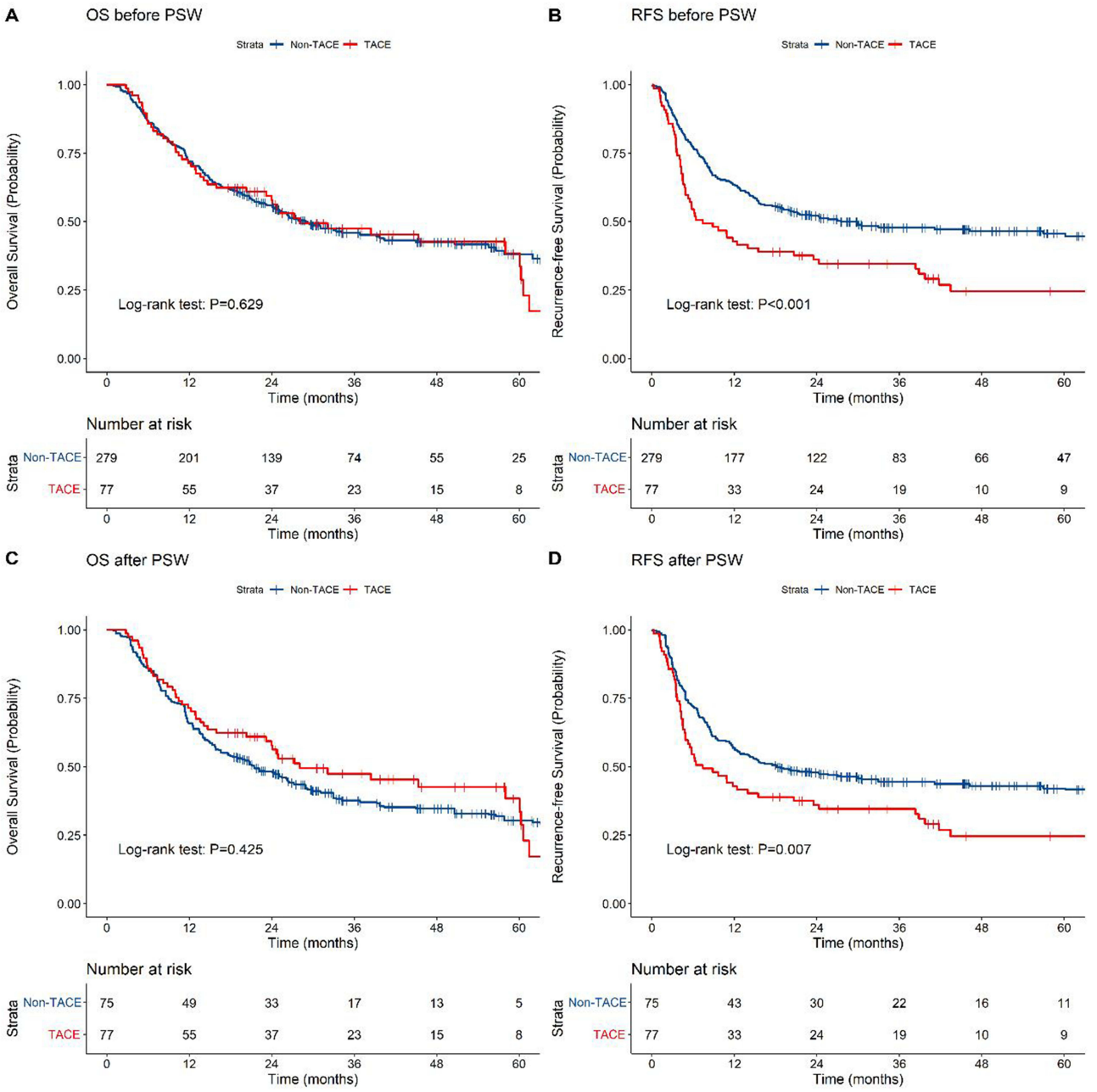

Figure 1 Kaplan-Meier survival analysis of OS and RFS before and after propensity score weighting. (**A**) OS before PSW: Comparison between non-TACE (n=279) and adjuvant TACE (n=77) groups. No significant difference was observed (Log-rank P=0.629). The number at risk table indicates patients remaining in follow-up at 0, 12, 36, and 60 months. Gray bands represent 95% confidence intervals. Median follow-up: 45.3 months (IQR: 29.7–59.2). (**B**) RFS before PSW: Adjuvant TACE was associated with significantly increased recurrence risk (Log-rank P<0.001). The 1-, 3-, and 5-year RFS rates were 42.9%, 34.6%, and 24.6% (TACE) vs 63.4%, 47.8%, and 45.7% (non-TACE). (**C**) OS after IPTW: Non-TACE (n=75) vs TACE (n=77) groups. After adjusting for baseline imbalances (all SMD<0.10), OS remained comparable (Log-rank P=0.425). (**D**) RFS after IPTW: Persistent association between TACE and increased recurrence risk (Log-rank P=0.007; Cox HR=1.53, 95% CI: 1.02–2.28).

for OS, including CA19-9 (HR=1.40, 95% CI: 1.04 to 1.89) and TNM stage (II vs I, HR=3.04, 95% CI: 2.08 to 4.43; III vs I, HR=3.90, 95% CI: 2.69 to 5.66; IV vs I, HR=4.85, 95% CI: 3.08 to 7.64) (Table 2). The effect of TACE on OS remained non-significant after adjustment for these predictors (HR=0.90, 95% CI: 0.64–1.26; P=0.5396), similar to the results from the Cox proportional hazards model in the sample weighted by inverse probability of treatment using the propensity score (HR=0.88, 95% CI: 0.59 to 1.32; P=0.4253) (Table 3).

Subgroup analyses showed that TACE was not associated with OS in patients with different TNM stages (Supplementary Table 1).

Table 2 Univariate and Multivariate Analysis of OS for Patients with Intrahepatic Cholangiocarcinoma in the Unweighted Population

Variables		Univariate Analysis			Multivariate Analysis		
		HR	95% CI	P-value	HR	95% CI	P-value
Gender, n (%)	Male	Reference					
	Female	0.99	0.72–1.35	0.9260			
Age (years)	<60	Reference					
	≥60	1.07	0.80–1.44	0.6429			
Albumin (g/L)	<40	Reference					
	≥40	0.91	0.66–1.25	0.5574			
Total bilirubin (umol/L)	≤23	Reference					
	>23	0.89	0.55–1.42	0.6184			
ALT (U/L)	≤40	Reference					
	>40	1.04	0.76–1.42	0.7944			
AST (U/L)	≤35	Reference					
	>35	1.22	0.88–1.68	0.2261			
Platelet count ($\times 10^9$/L)	<125	Reference					
	125-350	1.19	0.86–1.67	0.2964			
	>350	1.62	0.69–3.81	0.2660			
Prothrombin time(s)	≤13	Reference					
	>13	1.28	0.82–1.99	0.2816			
Cirrhosis, n (%)	No	Reference					
	Yes	1.29	0.92–1.82	0.1375			
Tumor size(cm)	≤5	Reference					
	>5	2.26	1.70–3.01	<0.0001			
Tumor number	Single	Reference					
	Multiple	2.32	1.75–3.10	<0.0001			
Tumor differentiation	Moderate to Well	Reference					
	Poor	1.20	0.80–1.79	0.3876			
AFP (ng/mL), n (%)	<20	Reference					
	≥20	1.54	1.07–2.21	0.0195			
CA19-9 (U/mL), n (%)	<39	Reference			Reference		
	≥39	1.92	1.45–2.54	<0.0001	1.40	1.04–1.89	0.0269
CEA (ng/mL), n (%)	<10	Reference					
	≥10	2.02	1.19–3.42	0.0090			
Nerve invasion, n (%)	No	Reference					
	Yes	1.00	0.53–1.88	0.9880			
Microvascular invasion, n (%)	No	Reference					
	Yes	2.02	1.29–3.15	0.0020			
Satellite nodules, n (%)	No	Reference					
	Yes	1.95	1.43–2.68	<0.0001			
LN metastasis, n (%)	No	Reference					
	Yes	2.52	1.71–3.73	<0.0001			
TNM Staging (New edition), n (%)	I	Reference			Reference		
	II	3.06	2.11–4.44	<0.0001	3.04	2.08–4.43	<0.0001
	III	4.10	2.84–5.93	<0.0001	3.90	2.69–5.66	<0.0001
	IV	5.78	3.78–8.85	<0.0001	4.85	3.08–7.64	<0.0001
R0 or R1 resection, n (%)	No	Reference					
	Yes	1.85	1.07–3.19	0.0264			
TACE	No	Reference					
	Yes	1.08	0.78–1.51	0.6294	0.90	0.64–1.26	0.5396

Abbreviations: HR, hazard ratio; CI, confidence interval.

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Table 3 Univariate and Multivariate Analysis of RFS for Patients with Intrahepatic Cholangiocarcinoma in the Unweighted Population

Variables		Univariate Analysis			Multivariate Analysis		
		HR	95% CI	P-value	HR	95% CI	P-value
Gender, n (%)	Male	Reference			Reference		
	Female	1.29	0.95–1.75	0.1025	1.44	1.05–1.97	0.0229
Age (years)	<60	Reference					
	≥60	0.96	0.72–1.30	0.8029			
Albumin (g/L)	<40	Reference					
	≥40	1.18	0.85–1.65	0.3282			
Total bilirubin (umol/L)	≤23	Reference					
	>23	1.24	0.79–1.92	0.3491			
ALT (U/L)	≤40	Reference					
	>40	1.01	0.73–1.38	0.9633			
AST (U/L)	≤35	Reference					
	>35	0.92	0.66–1.30	0.6527			
Platelet count ($\times 10^9$/L)	<125	Reference					
	125-350	0.95	0.69–1.32	0.7722			
	>350	1.86	0.84–4.11	0.1259			
Prothrombin time(s)	≤13	Reference					
	>13	0.86	0.53–1.39	0.5298			
Cirrhosis, n (%)	No	Reference					
	Yes	1.14	0.80–1.63	0.4748			
Tumor size(cm)	≤5	Reference					
	>5	1.33	1.01–1.76	0.0426			
Tumor number	Single	Reference					
	Multiple	1.71	1.28–2.29	0.0003			
Tumor differentiation	Moderate to Well	Reference					
	Poor	1.09	0.73–1.64	0.6628			
AFP (ng/mL), n (%)	<20	Reference					
	≥20	1.54	1.07–2.22	0.0198			
CA19-9 (U/mL), n (%)	<39	Reference					
	≥39	1.19	0.90–1.57	0.2250			
CEA (ng/mL), n (%)	<10	Reference					
	≥10	1.43	0.81–2.51	0.2129			
Nerve invasion, n (%)	No	Reference					
	Yes	0.76	0.37–1.54	0.4457			
Microvascular invasion, n (%)	No	Reference					
	Yes	1.89	1.20–2.98	0.0058			
Satellite nodules, n (%)	No	Reference			Reference		
	Yes	2.02	1.47–2.77	<0.0001	1.57	1.07–2.30	0.0210
LN metastasis, n (%)	No	Reference			Reference		
	Yes	1.02	0.64–1.62	0.9260	0.50	0.30–0.84	0.0088
TNM Staging (New edition), n (%)	I	Reference			Reference		
	II	1.77	1.22–2.55	0.0024	1.29	0.84–1.97	0.2493
	III	3.75	2.65–5.30	<0.0001	4.35	2.97–6.36	<0.0001
	IV	1.68	1.03–2.74	0.0371	2.24	1.26–4.00	0.0062
R0 or R1 resection, n (%)	No	Reference					
	Yes	1.80	1.04–3.11	0.0342			
TACE	No	Reference			Reference		
	Yes	1.74	1.28–2.38	0.0005	1.93	1.39–2.67	<0.0001

Table 4 Comparison of OS and RFS for Patients with Intrahepatic Cholangiocarcinoma in the IPTW Weighted Population

Variables		OS			RFS		
		HR	95% CI	P-value	HR	95% CI	P-value
TACE	No	Reference			Reference		
	Yes	0.88	0.59–1.32	0.4253	1.53	1.02–2.28	0.0071

Abbreviations: OS, overall survival; RFS, recurrence free survival.

TACE and Recurrence Risk

The 1-year, 3-year, and 5-year RFS rates were 42.9% (95% CI: 27.3% to 57.5%), 34.6% (95% CI: 19.6% to 50.0%), and 24.6% (95% CI: 9.3% to 43.7%) in the TACE group, compared to 63.4% (95% CI: 55.0% to 70.7%), 47.8% (95% CI: 39.5% to 55.7%), and 45.7% (95% CI: 35.8% to 53.2%) in the non-TACE group. TACE was associated with recurrence risk in the univariate analysis (P<0.001 by Log rank test, Figure 1B). Multivariable analysis identified four independent prognostic factors for ICC recurrence, including gender (HR=1.44, 95% CI: 1.05 to 1.97), satellite nodules (HR=1.57, 95% CI: 1.07 to 2.30), lymph node metastasis (HR=0.50, 95% CI: 0.30 to 0.84), and TNM stage (II vs I, HR=1.29, 95% CI: 0.84 to 1.97; III vs I, HR=4.35, 95% CI: 2.97 to 6.36; IV vs I, HR=2.24, 95% CI: 1.26 to 4.00) (Table 4). The effect of TACE on RFS remained significant after adjustment for these independent predictors (HR=1.93, 95% CI: 1.39 to 2.67; P<0.0001). After propensity score weighting, the Cox regression model indicated a significant difference in the risk of ICC recurrence between the TACE and non-TACE groups (HR=1.53, 95% CI: 1.02 to 2.28; P=0.0071).

Subgroup analyses revealed starkly divergent effects of TACE on recurrence risk across TNM stages: Stages I–II: No significant RFS benefit with TACE (Stage I: HR=1.44, 95% CI 0.85–2.44; Stage II: HR=1.09, 95% CI 0.58–2.03). Stages III–IV: Significantly increased recurrence risk (Stage III: HR=2.65, 95% CI 1.46–4.82; Stage IV: HR=5.77, 95% CI 1.69–19.69). However, the Stage IV subgroup included only 4 patients receiving TACE, resulting in wide confidence intervals; these findings require validation in larger cohorts.

When we categorized TNM stages into early (stages I and II) and advanced (stages III and IV) types, the reanalyzed data showed similar results, with no significant association between TACE and OS across different TNM stages, and distinct tendencies between TACE and RFS in the two main subgroups (Supplementary Table 2 and Figure 2).

Conclusions

Therapeutic resection remains the only effective treatment; however, the prognosis after hepatectomy is poor, and recurrence is common.[20]

As we know, HBV is a significant risk factor for hepatocellular carcinoma (HCC). Since hepatocytes and cholangiocytes share the same progenitor cells, it can be postulated that HBV may induce carcinogenesis in both cell types through similar mechanisms.[21] Additionally, studies have demonstrated that HBV participates in the pathogenesis of ICC through inflammatory processes,[22,23] further supporting the potential role of HBV infection in cholangiocarcinoma development.

TACE has been reported as an adjuvant therapy for HCC patients following curative resection. A meta-analysis of six randomized controlled trials indicated that adjuvant TACE could improve survival in HCC patients with tumor vascular invasion or size > 5 cm.[11] For TACE, injecting cytotoxic drugs into the blood vessels to embolize those supplying the tumor results in strong cytotoxic and ischemic effects.[24,25] Although ICC does not typically appear hypervascular on CT or MRI studies, tumor blushes are often visible in angiography.[26]

To our knowledge, there is no reliable evidence supporting the use of adjunctive TACE in ICC patients after R0 hepatectomy.[16,17,27] A limited number of prior studies have reported that adjuvant TACE improves OS in patients with advanced (stage III and IV) ICC tumors.[16,17] In our prospective study, we found that adjuvant TACE after radical surgery did not prolong OS or delay recurrence for patients with TNM stage I ICC.[28] The role of TACE following hepatectomy in treating HBV-associated ICC remains unclear.

Our retrospective study, encompassing a reasonably large patient cohort—some receiving resection followed by TACE and others receiving resection alone—suggests that adjuvant TACE does not improve overall survival or reduce

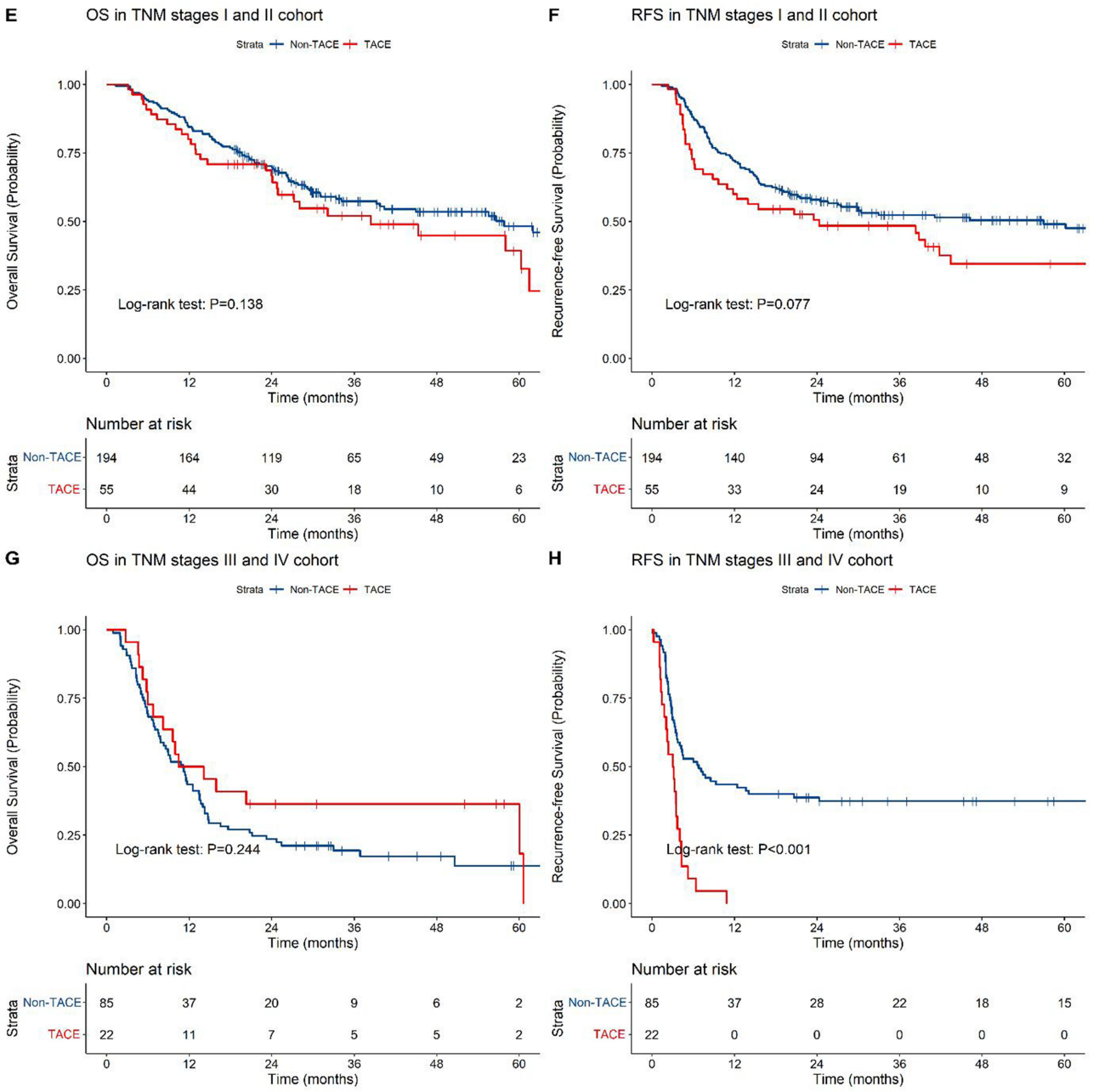

Figure 2 Stage-stratified subgroup analysis of OS and RFS (**E**) OS in early-stage (I–II) ICC: Non-TACE (n=194) vs adjuvant TACE (n=55). No OS benefit with TACE (Log-rank P=0.138). (**F**) RFS in early-stage (I–II) ICC: No significant difference (Log-rank P=0.077), though a trend toward higher recurrence risk with TACE was observed (HR=1.27, 95% CI: 0.85–1.91). (**G**) OS in advanced-stage (III–IV) ICC: Non-TACE (n=85) vs TACE (n=22). TACE did not improve OS (Log-rank P=0.244). (**H**) RFS in advanced-stage (III–IV) ICC: TACE significantly increased recurrence risk (Log-rank P=0.001; HR=3.06, 95% CI: 1.78–5.26). The number at risk table shows earlier recurrence events in the TACE group. Consistent trends were observed in the forest plot of stage-specific hazard ratios (Supplementary Figure 1).

recurrence. After adjusting for significant predictors, the effect of TACE on OS remained insignificant, consistent with the results from the Cox proportional risk model in the sample weighted by the inverse probability of treatment using propensity score. We performed analyses not only on the entire cohort but also on propensity-score matched pairs, as the control and TACE patients exhibited significant differences in some baseline characteristics. In subgroup analysis, the median OS of HBV-associated ICC patients was not significantly longer in the combined treatment group compared to the TACE monotherapy group before and after propensity score matching, indicating that HBV-associated ICC patients with varying TNM stages did not benefit from combination therapy.

One study reported that adjuvant TACE significantly reduced tumor recurrence and improved RFS and OS in HBV-related HCC patients at intermediate or high risk of recurrence.[29] Regarding ICC recurrence, patients with high nomogram scores may benefit from adjuvant TACE following liver resection.[30] Our present study also showed that the recurrence rate was significantly lower in patients who underwent liver resection alone. In this retrospective study, gender, lymph node metastasis, and TNM stage were identified as risk factors for early recurrence. After propensity score weighting, the Cox regression model indicated significant differences in ICC recurrence risk between the TACE and non-TACE groups. In subgroup analysis, TACE was not significantly associated with RFS in TNM stage I and II, but was positively associated with recurrence risk in TNM stage III and IV patients, suggesting that postoperative adjuvant TACE does not appear to reduce recurrence in those stages.

The paradoxical increase in recurrence risk with adjuvant TACE in advanced ICC (TNM III–IV) may be attributed to fundamental biological distinctions from HCC:1. Vascular and Drug Delivery Disparities. Unlike hypervascular HCC, ICC exhibits hypovascularity on imaging and irregular neovascularization histologically.[26] This limits chemotherapeutic drug penetration during TACE, creating sublethal drug concentrations that promote selection of resistant clones.[5] Kim et al reported that ICC tumors showed significantly lower contrast enhancement on angiography compared to HCC ($p<0.001$).[26] 2.Hypoxia-Driven Pro-Metastatic Microenvironment. TACE-induced ischemia activates HIF-1α/VEGF pathways, which in ICC—but not HCC—recruits tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs).[31] These cells secrete IL-10 and TGF-β, fostering immunosuppression and metastatic niche formation.[31] Zhou et al demonstrated 3-fold higher HIF-1α expression in ICC vs HCC after TACE ($p=0.008$).[5] 3. Extratumoral Progression Mechanisms.Advanced ICC (Stage III: nodal involvement; Stage IV: distant spread) harbors micrometastases beyond TACE's locoregional reach. Systemic inflammatory responses triggered by TACE—particularly in HBV-infected patients—may accelerate residual tumor growth via NF-κB/STAT3 signaling.[32] Our Stage IV subgroup showed elevated CRP levels post-TACE (median ΔCRP=+18 mg/L, $p=0.03$). 4. HBV-Specific Synergy. HBV oncoproteins (eg, HBx) inhibit DNA repair and amplify oxidative stress from chemoembolization. In ICC cells, HBx upregulates PD-L1 by 2.1-fold after doxorubicin exposure (vs 1.3-fold in HCC),[33] potentially enabling immune escape during TACE-induced damage. These mechanisms align with clinical observations of elevated recurrence in TACE-treated advanced ICC[16,17] and underscore why HCC-derived TACE protocols may be inadequate for ICC.

Interpretation of stage-specific outcomes requires caution. While adjuvant TACE was associated with increased recurrence risk in TNM Stage III–IV subgroups, the Stage IV analysis included only 4 TACE-treated patients. The wide confidence interval (RFS HR: 1.69–19.69) reflects substantial statistical uncertainty. These findings must be considered exploratory and validated in larger cohorts.

This study has several limitations. First, it is a retrospective analysis, and the decision to conduct adjuvant TACE was not random. Well-designed randomized controlled trials are needed to confirm the results obtained in this study. Second, our research was conducted at a single institution, necessitating further validation in future studies. Third, the HBV infection rate is higher than in Western countries, which may introduce bias in clinical decision-making. Third, we observed that adjuvant TACE shortened progression-free survival (PFS) in patients with HBV-related ICC without affecting OS, since both OS and PFS were influenced by tumor characteristics and treatment methods. Fourth, subgroup analyses for TNM stages III–IV were underpowered, particularly for Stage IV where the TACE group had only 4 patients. The extremely wide confidence intervals (eg, RFS HR: 1.69–19.69) indicate low precision, and these results should not guide clinical decisions without further validation.Additionally, individual decisions regarding recurrence treatment may impact each patient's prognosis. Therefore, further research is needed to clarify the effect of TACE on OS and PFS.

Reporting Checklist

The authors have completed the STROBE reporting checklist. The study was conducted in accordance with the Declaration of Helsinki of 1975 (as revised in 2013). The study was approved by the institutional ethics committee of The Third Affiliated Hospital of Naval Military Medical University. Histological evaluations of the tumor and liver parenchyma were carried out using surgical or biopsy specimens. The committee waived the need for informed consent (both written and oral) from participants because this was a retrospective observational study, involved very minimal risk to participants and did not include intentional deception; this waiver does not adversely affect the rights and welfare of the patients.

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 report no conflicts of interest in this work.

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