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ORIGINAL RESEARCH

Whether Adjuvant TACE Plus TKI Therapy is More Effective Than TACE Alone in HCC Patients at High Risks of Recurrence Following Radical Hepatectomy

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Purpose: To compare the efficacy and safety of postoperative adjuvant therapy with transarterial chemoembolization (TACE) plus tyrosine kinase inhibitor (TKI) (TPT) versus TACE alone in hepatocellular carcinoma (HCC) patients at high risks of recurrence after radical hepatectomy.

Patients and Methods: We retrospectively analyzed 264 HCC patients who underwent radical hepatectomy (R0 resection) between August 2016 and August 2023. To mitigate selection bias, propensity score matching (PSM) was employed. The primary endpoints were recurrence-free survival (RFS) and overall survival (OS), analyzed using Kaplan–Meier curves and Log rank tests. Treatment-related adverse events (TRAEs) were graded according to CTCAE v4.0. Prognostic factors were evaluated via Cox proportional hazards regression.

Results: Before PSM, the cohort comprised 141 patients receiving TPT and 123 patients treated with TACE alone. After PSM, 81 well-balanced patients were selected per group (all $p > 0.05$). The TPT group exhibited significantly prolonged median recurrence-free survival (mRFS: 37.1 vs 27.7 months; $p < 0.05$) and median overall survival (mOS: 41.3 vs 38.3 months; $p < 0.05$) compared to the TACE alone group. The 1-, 2-, and 3-year RFS rates in the TPT group were 95.1%, 67.9%, and 48.1%, respectively, significantly higher than those in the TACE alone group (76.5%, 55.6%, and 40.7%; all $p < 0.05$). Similarly, the corresponding OS rates were 95.1%, 75.3%, and 54.3% (TPT) versus 81.5%, 66.7%, and 53.1% (TACE alone; all $p < 0.05$). Multivariable Cox regression analyses confirmed TPT as an independent protective factor for both RFS and OS. No significant increase in treatment-related adverse events (TRAEs) was observed with the TPT regimen compared to TACE alone. The overall TRAE rate was 51.8% in the TPT group, with grade ≥3 events occurring in 14.8% of patients, indicating an acceptable safety profile.

Keywords: hepatocellular carcinoma, radical hepatectomy, high risks of recurrence, adjuvant therapy, transarterial chemoembolization, tyrosine kinase inhibitors

Introduction

Hepatocellular carcinoma (HCC) is a malignancy of global importance, ranking as the third highest cause of cancer-related death on a worldwide scale.[1,2] While liver transplantation, ablation, and hepatectomy constitute primary treatment modalities, transplantation is limited by donor scarcity and high costs, and ablation has restrictive eligibility criteria. Consequently, hepatectomy remains a cornerstone of HCC management. Nevertheless, even after radical hepatectomy,

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HCC exhibits a 60–70% 5-year recurrence rate,[3] severely compromising the survival and prognosis of patients. Numerous randomized controlled trials (RCTs) and systematic reviews have identified that maximum tumor diameter ≥5 cm, high preoperative alpha-fetoprotein (AFP) level ≥400 ng/mL, satellite nodules, multiple tumors (number of lesions ≥3), low differentiation of tumor cells and microvascular invasion (MVI) as the independent risk factors associated with high risk of recurrence for HCC following hepatectomy.[4–6] The presence of high-risk recurrence factors is strongly correlated with a significantly elevated risk of postoperative tumor recurrence in HCC patients. Consequently, implementing effective postoperative adjuvant therapy is essential for HCC patients at high risks of recurrence following radical hepatectomy, as it plays a pivotal role in reducing recurrence rates and enhancing long-term survival outcomes.

Over the past three decades, transarterial chemoembolization (TACE) has been extensively validated by medical institutions worldwide as an effective intervention for reducing recurrence rates among HCC patients at high risks of recurrence following hepatectomy.[7–9] However, many patients still experience tumor recurrence, peritoneal carcinomatosis, or distant metastasis.[10,11] Tyrosine kinase inhibitor (TKI) has become a cornerstone of systemic therapy for HCC. Up to now, several oral TKIs, including sorafenib, lenvatinib, and apatinib, have received approval for HCC therapy and have shown notable treatment effectiveness.[12–14] When combined with TACE, these agents may theoretically address both macroscopic and microscopic disease through complementary mechanisms: TACE induces localized tumor ischemia while TKI inhibits angiogenesis and tumor proliferation. Therefore, the objective of this study was to compare the efficacy and safety of postoperative adjuvant TACE plus TKI (TPT) versus TACE alone in HCC patients at high risks of recurrence after radical hepatectomy.

Materials and Methods

Patients

This single-center, retrospective study was conducted in accordance with the ethical principles established by the Declaration of Helsinki (1975). The study protocol received approval from the Ethics Committee of the Affiliated Hospital of Guilin Medical University and all patients received written informed consent during their hospitalization.

The inclusion criteria for this study were established as follows: 1) Individuals between the ages of 18 and 75 years; 2) A histopathologically verified diagnosis of HCC; 3) All patients underwent radical hepatectomy (R0 resection), defined as: (a) Absence of macroscopic tumor thrombi in the hepatic vein, portal vein, bile duct, or inferior vena cava following surgical resection; (b) No evidence of local invasion into adjacent organs, hilar lymph node involvement, or distant metastasis intraoperatively; (c) A liver resection margin of at least 1 cm from the tumor edge. In cases where the resection margin was less than 1 cm, histopathological evaluation of the resected specimen confirmed the absence of residual tumor cells, ensuring a microscopically negative margin; (d) 4–6 weeks post-surgery, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) (at least two imaging technologies) did not reveal any tumor lesions; (e) For patients with elevated blood biochemical markers, including serum AFP and tumor markers, levels should be quantitatively assessed 2 to 3 months after surgery and normalized to the reference range;[15] 4) Eastern Cooperative Oncology Group (ECOG) performance status ≤1; 5) Child-Pugh classification A or B; and 6) Presence of one or more high-risk recurrence factors: maximum tumor diameter ≥5 cm, preoperative AFP ≥400 ng/mL, satellite nodules, multiple tumors (number of lesions ≥3), low differentiation of tumor cells and microvascular invasion (MVI).[5–7] The following conditions were used to determine participant exclusion: 1) History of neoadjuvant therapy or conversion therapy before hepatectomy; 2) History of other postoperative adjuvant therapy, excluding TACE or TKI; 3) History of other malignancies; 4) Extrahepatic metastasis, and 5) Failure to complete the 6-month follow-up assessment.

Preoperative Assessment, Hepatectomy and Follow Up

In patients diagnosed with large HCC, residual liver volume is routinely assessed using 3D reconstruction techniques. R0 resection is performed only in patients whose residual liver volume is adequate to allow radical hepatectomy. The choice of anatomical versus partial hepatectomy was determined by liver function, along with tumor characteristics such as size, location, and extent. Anatomical hepatectomy was preferred for tumors located in a specific segment, sector, or hemisphere of the liver. In contrast, partial hepatectomy was selected as the surgical approach for patients exhibiting compromised liver function or those with tumors situated in peripheral regions of the liver. Following radical hepatectomy, patients underwent a routine follow-up protocol to monitor for potential recurrence. During the initial 2-year period, follow-up assessments were scheduled at 2-month intervals. Following the initial postoperative period, patients were monitored with follow-up appointments every 6 months for a duration of 2 to 5 years. After the 5-year milestone, the frequency of evaluations was reduced to annual visits to assess long-term outcomes and detect any signs of recurrence or complications. This structured follow-up protocol ensured consistent monitoring while adapting to the evolving clinical needs of the patients over time. The standard follow-up regimen included serial measurements of serum AFP levels and abdominal ultrasonography. In cases where clinical suspicion of recurrence arose, CT or MRI was employed to further evaluate suspicious findings. Recurrence was diagnostically confirmed by the identification of new lesions exhibiting radiological features consistent with HCC. If recurrence occurred, the subsequent treatment plan was determined following a multi-disciplinary team (MDT) discussion.

The study endpoints included RFS and OS. RFS was calculated as the period from hepatectomy to tumor progression, death, or the conclusion of follow-up. OS was calculated from the day of hepatectomy until the occurrence of patient death or the conclusion of the follow-up period. The last follow-up date was ascertained using the most recent hospital or outpatient visit records or telephone communication. Vital signs and laboratory findings were documented, and TRAEs were graded based on the CTCAE version 5.0 criteria.

Postoperative TACE Procedure

Postoperative adjuvant TACE has been previously reported.[16] Therapy is generally delivered within 1 to 2 months following liver function recovery, with additional cycles planned by the treating physician according to the individual response to treatment. Prior to receiving postoperative adjuvant TACE, patients undergo comprehensive evaluations, including liver function tests (eg, bilirubin, albumin, and prothrombin time), tumor marker analysis (eg, AFP levels), and imaging studies (CT and/or MRI) to assess for tumor recurrence and ensure suitability for the procedure. Using the Seldinger technique, a hepatic arterial angiographic catheter was introduced via the femoral artery and advanced to the proper hepatic artery. Digital subtraction angiography or CT angiography was utilized intraoperatively to identify any suspicious tumor staining in the remnant liver. If no staining was detected, a chemotherapeutic mixture—comprising lipiodol (5–10 mL), cisplatin (10–30 mg), doxorubicin hydrochloride (10 mg), and pharmorubicin (20–40 mg)—was administered into the remaining liver via the catheter. The administration of drug doses was tailored to each patient based on body surface area (BSA), overall physical condition, and residual liver volume. This approach allowed TACE to be delivered to the entire remnant liver, followed by embolization using various embolic agents chosen by the interventional radiologist based on the procedural circumstances.[17] Lipiodol, cisplatin, and doxorubicin dosages were adjusted based on the patient's body surface area and liver function. The choice of chemotherapeutic agents varied between centers according to local protocols and expertise.

Postoperative TKI Procedure

Liver function tests, AFP and other necessary blood tests were performed prior to initiating TKI therapy. Once the patient's liver function had recovered, all eligible patients began TKI treatment within 2 to 4 weeks after postoperative adjuvant TACE. The decision to administer TKIs, as well as the selection of the specific agent, was made jointly by the patient and their physician. In this study, sorafenib, lenvatinib, and apatinib were the TKIs administered. Sorafenib was prescribed at 400 mg orally twice daily, apatinib at 500 mg orally once daily, and lenvatinib at a weight-adjusted dose of 12 mg once daily for patients ≥60 kg or 8 mg once daily for those <60 kg. TKI treatment was discontinued if grade 3 or 4 TRAEs, as defined by the CTCAE, occurred, if TRAEs were intolerable, or in cases of tumor progression. Dosage adjustments or temporary discontinuation of TKIs were determined by the physician according to the severity of TRAEs experienced by the patient.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation. For data following a normal distribution, comparisons were performed using Student's *t*-test, while non-normally distributed data were analyzed using the Mann–Whitney

U-test. Categorical variables were analyzed using either the chi-square test or Fisher's exact test, depending on the sample size and expected frequencies. PSM analysis was used to reduce selection bias and balance the patient characteristics. The propensity score was estimated to fit the following 22 variables: gender, age, Child-Pugh score, ALBI stage, ECOG performance score, BCLC stage, preoperative AFP, preoperative DCP, preoperative ALT and preoperative AST levels, NLR, PLR, blood loss, MVI, tumor capsule, tumor differentiation, satellite nodules, maximum tumor size, number of lesions, HBsAg status, liver cirrhosis and TKI agent. To create a propensity-matched set of patients treated with TPT or TACE alone (1:1 match), a nearest neighbor matching algorithm with a greedy heuristic was used. The caliper width was defined as 0.02 of the standard deviation of the logit of the propensity score to ensure high-quality matches while avoiding the introduction of excessive bias. Survival outcomes, including RFS and OS, were evaluated through Kaplan–Meier survival analysis, with between-group comparisons performed using the Log rank test. All statistical analyses were conducted using R software (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value threshold of <0.05 was adopted to determine statistical significance throughout the study.

Results

Patient Features

A group of 264 HCC patients who underwent radical hepatectomy were screened for eligibility in our study. Before PSM, the TPT group comprised 141 patients, while the TACE alone group consisted of 123 patients. PSM was applied to perform a 1:1 matching between patients undergoing TPT and those undergoing TACE alone. After PSM, each group consisted of 81 patients (Figure 1). Table 1 summarizes a comprehensive summary of the demographic and baseline clinical characteristics of the study population. Most variables demonstrated no statistically significant differences

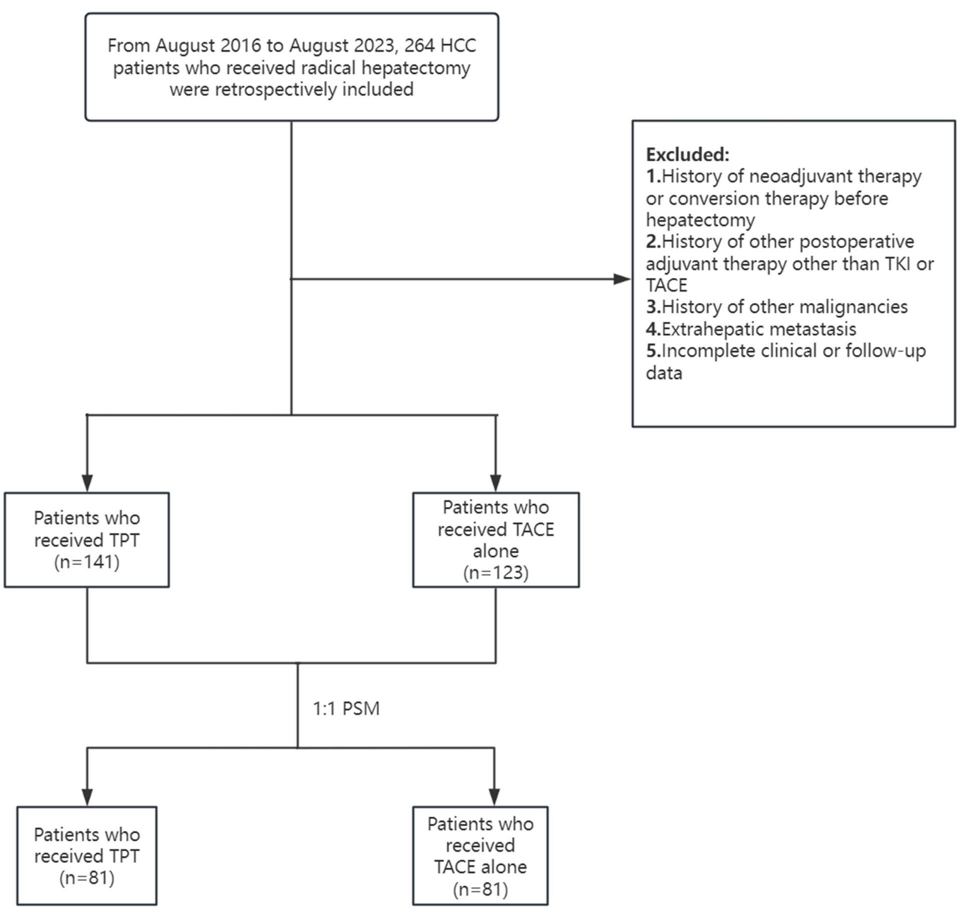

Figure 1 Flow chart of eligible patients enrolled.

Table 1 Baseline Demographic and Clinical Characteristics of Patients

Variables		Before PSM		p	After PSM		p
		TACE Alone (N=123)	**TPT (N=141)**		**TACE Alone (N=81)**	**TPT (N=81)**	
Gender	Female	22 (17.9)	22 (15.6)	0.741	15 (18.5)	15 (18.5)	1
	Male	101 (82.1)	119 (84.4)		66 (81.5)	66 (81.5)	
Age	<65	89 (72.4)	104 (73.8)	0.907	63 (77.8)	59 (72.7)	0.585
	≥65	34 (27.6)	37 (26.2)		18 (23.4)	22 (27.3)	
Child-Pugh score	A	105 (85.4)	125 (88.7)	0.541	73 (90.1)	75 (92.6)	0.78
	B	18 (14.6)	16 (11.3)		8 (9.9)	6 (7.4)	
BCLC stage	A	60 (48.8)	65 (46.1)	0.755	37 (45.7)	41 (50.6)	0.637
	B	63 (51.2)	76 (53.9)		44 (54.3)	40 (49.4)	
Preoperative AFP	<400ng/mL	54 (43.9)	70 (49.6)	0.418	32 (39.5)	33 (40.7)	1
	≥400ng/mL	69 (56.1)	71 (50.4)		49 (60.5)	48 (59.3)	
Preoperative DCP	<400g/mL	41 (33.3)	41 (29.1)	0.541	23 (28.4)	28 (34.6)	0.499
	≥400g/mL	82 (66.7)	100 (70.9)		58 (71.6)	53 (65.4)	
Satellite nodules	Absent	62 (50.4)	98 (69.5)	0.002	46 (56.8)	43 (53.1)	0.752
	Present	61 (49.6)	43 (30.5)		35 (43.2)	38 (46.9)	
Blood loss	<500ml	86 (69.9)	102 (72.3)	0.766	55 (67.9)	54 (66.7)	1
	≥500ml	37 (30.1)	39 (27.7)		26 (32.1)	27 (33.3)	
Maximum tumor size	Mean (SD), cm	8.98 (4.50)	8.55 (4.22)	0.416	8.66 (4.76)	8.13 (4.21)	0.453
NLR	Mean (SD), ratio	3.75 (5.58)	4.92 (9.09)	0.214	4.15 (6.70)	3.73 (6.27)	0.681
PLR	Mean (SD), ratio	147.87 (121.35)	153.44 (99.88)	0.683	163.63 (140.19)	161.06 (117.38)	0.899
ECOG performance score	0	63 (51.2)	71 (50.4)	0.987	43 (53.1)	39 (48.1)	0.637
	1	60 (48.8)	70 (49.6)		38 (46.9)	42 (51.9)	
ALBI stage	1	48 (39.0)	55 (39.0)	0.350	32 (39.5)	36 (44.4)	0.786
	2	67 (54.5)	82 (58.2)		45 (55.6)	42 (51.9)	
	3	8 (6.5)	4 (2.8)		4 (4.9)	3 (3.7)	
Liver cirrhosis	Absent	14 (11.4)	13 (9.2)	0.708	9 (11.1)	9 (11.1)	1
	Present	109 (88.6)	128 (90.8)		72 (88.9)	72 (88.9)	
HBsAg	Negative	15 (12.2)	17 (12.1)	1	11 (13.6)	11 (13.6)	1
	Positive	108 (87.8)	124 (87.9)		70 (86.4)	70 (86.4)	
Number of lesions	<3	49 (39.8)	55 (39.0)	0.991	29 (35.8)	29 (35.8)	1
	≥3	74 (60.2)	86 (61.0)		52 (64.2)	52 (64.2)	
Maximum tumor size	<5cm	19 (15.4)	41 (29.1)	0.013	18 (22.2)	22 (27.2)	0.585
	≥5cm	104 (84.6)	100 (70.9)		63 (77.8)	59 (72.8)	
MVI	No	56 (45.5)	75 (53.2)	0.263	37 (45.7)	38 (46.9)	1
	Yes	67 (54.5)	66 (46.8)		44 (54.3)	43 (53.1)	
Tumor capsule	Complete	82 (66.7)	45 (31.9)	<0.001	42 (51.9)	42 (51.9)	1
	Incomplete	41 (33.3)	96 (68.1)		39 (48.1)	39 (48.1)	
Tumor differentiation	Grade 1-2	52 (42.3)	87 (61.7)	0.002	35 (43.2)	35 (43.2)	1
	Grade 3-4	71 (57.7)	54 (38.3)		46 (56.8)	46 (56.8)	
Preoperative ALT	<40U/L	73 (59.3)	73 (51.8)	0.267	46 (56.8)	40 (49.4)	0.431
	≥40U/L	50 (40.7)	68 (48.2)		35 (43.2)	41 (50.6)	
Preoperative AST	<40U/L	56 (45.5)	56 (39.7)	0.407	34 (42.0)	30 (37.0)	0.63
	≥40U/L	67 (54.5)	85 (60.3)		47 (58.0)	51 (63.0)	
TKI agent	sorafenib		45(31.9)			36 (44.4)	
	apatinib		49(34.8)			27 (33.3)	
	lenvatinib		47(33.3)			18 (22.2)	

Abbreviations: PSM, propensity score matching; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; TPT, transarterial chemoembolization plus tyrosine kinase inhibitor; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; DCP, des-gamma-carboxyprothrombin; ALBI, albumin-bilirubin; HBsAg, Hepatitis B surface antigen; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; ECOG, Eastern Cooperative Oncology Group; MVI, microvascular invasion; ALT, alanine aminotransferase; AST, aspartate transaminase;

between the two groups, except for satellite nodules, maximum tumor size, tumor capsule integrity, and tumor differentiation. The TPT group, relative to the TACE alone group, had a significantly lower proportion of patients with satellite nodules (30.5% vs 49.6%, p=0.002), fewer patients with maximum tumors ≥5 cm (70.9% vs 84.6%,

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p=0.013), a higher proportion of patients with incomplete tumor capsule (68.1% vs 33.3%, p<0.001), and fewer patients with poorly differentiated tumor cells (38.3% vs 57.7%, p=0.002). After PSM, all analyzed variables exhibited no statistically significant differences between the two groups, confirming the effectiveness of the matching process in achieving balanced cohorts (all p>0.05).

Efficacy Assessment

Before PSM, the mRFS was 36.7 months in the TPT group and 28.8 months in the TACE alone group. The 1-, 2-, and 3-year RFS rates were significantly higher in the TPT group (90.8%, 72.3%, and 46.8%) than in the TACE alone group (79.7%, 60.2%, and 39.8%; p<0.0001). Similarly, the mOS was 42.1 months in the TPT group versus 38.1 months in the TACE alone group. The 1-, 2-, and 3-year OS rates were also higher in the TPT group (90.8%, 78.0%, and 55.3%) compared to the TACE alone group (83.7%, 69.9%, and 51.2%; p<0.0001, Figure 2).

After PSM, mRFS was 37.1 months in the TPT group versus 27.7 months in the TACE alone group. The 1-, 2-, and 3-year RFS rates were 95.1%, 67.9%, and 48.1% in the TPT group, compared to 76.5%, 55.6%, and 40.7% in the TACE alone group (p<0.0001). The mOS was 41.3 months in the TPT group and 38.3 months in the TACE alone group. The 1-, 2-, and 3-year OS rates were 95.1%, 75.3%, and 54.3% in the TPT group, compared to 81.5%, 67.9%, and 53.1% in the TACE alone group (p=0.00046, Figure 3). Kaplan–Meier curves revealed significant intergroup differences in both RFS and OS (Figures 2 and 3). The further analysis results of the original cohort suggest that there is no difference in the therapeutic effects of the three different TKIs drugs on the RFS and OS of patients (both p > 0.05, Figures 4 and 5).

Both univariate and multivariate Cox proportional hazards regression analyses revealed multiple statistically significant prognostic determinants demonstrating meaningful associations with RFS and OS. For RFS, the following variables were identified as independent predictors: treatment strategy (HR: 0.41, 95% CI: 0.29–0.58, p<0.01), age (HR: 1.57, 95% CI: 1.08–2.29, p=0.0194), BCLC stage (HR: 0.49, 95% CI: 0.34–0.7, p=0.0001), number of lesions (HR: 1.66, 95% CI: 1.14–2.42, p=0.0085), MVI (HR: 2.4, 95% CI: 1.65–3.49, p<0.01), preoperative AFP level (HR: 1.78, 95% CI: 1.25–2.54, p=0.0016), and maximum tumor size (HR: 1.79, 95% CI: 1.18–2.73, p=0.0062) (Table 2). Independent predictors of OS included the following factors: treatment strategy (HR: 0.54, 95% CI: 0.37–0.79, p=0.0013), BCLC stage (HR: 0.63, 95% CI: 0.44–0.92, p=0.0168), ECOG performance score (HR: 1.74, 95% CI: 1.18–2.59, p=0.0056), number of lesions (HR: 1.73, 95% CI: 1.16–2.59, p=0.0077), MVI (HR: 2.53, 95% CI: 1.66–3.85, p<0.01), preoperative AFP level (HR: 2.26, 95% CI: 1.5–3.4, p=0.0001), and maximum tumor size (HR: 1.76, 95% CI: 1.0–3.07, p=0.0486) (Table 3).

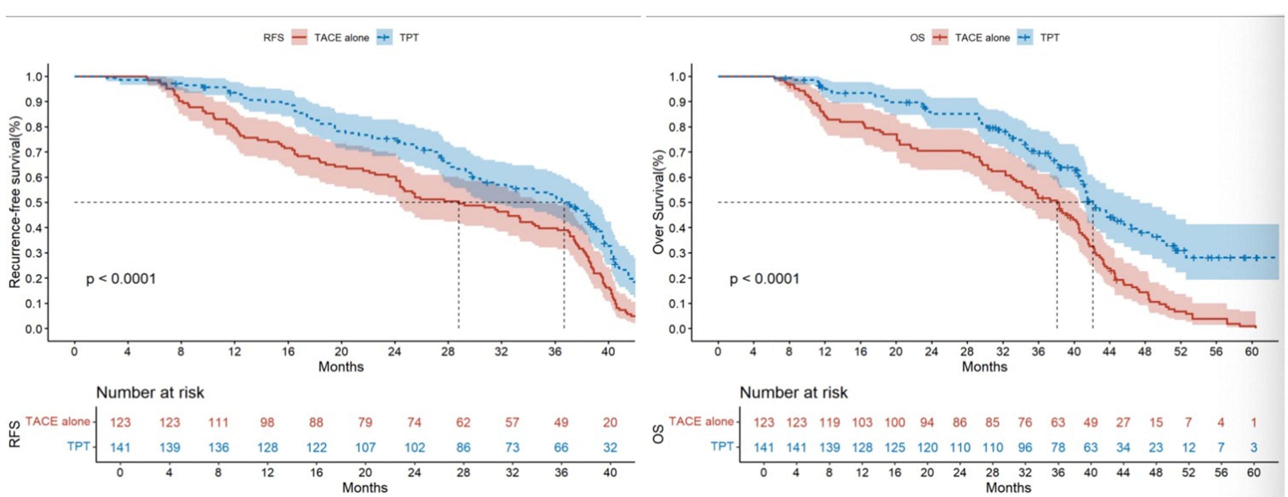

Figure 2 Kapan-Meier curves of RFS and OS before PSM.

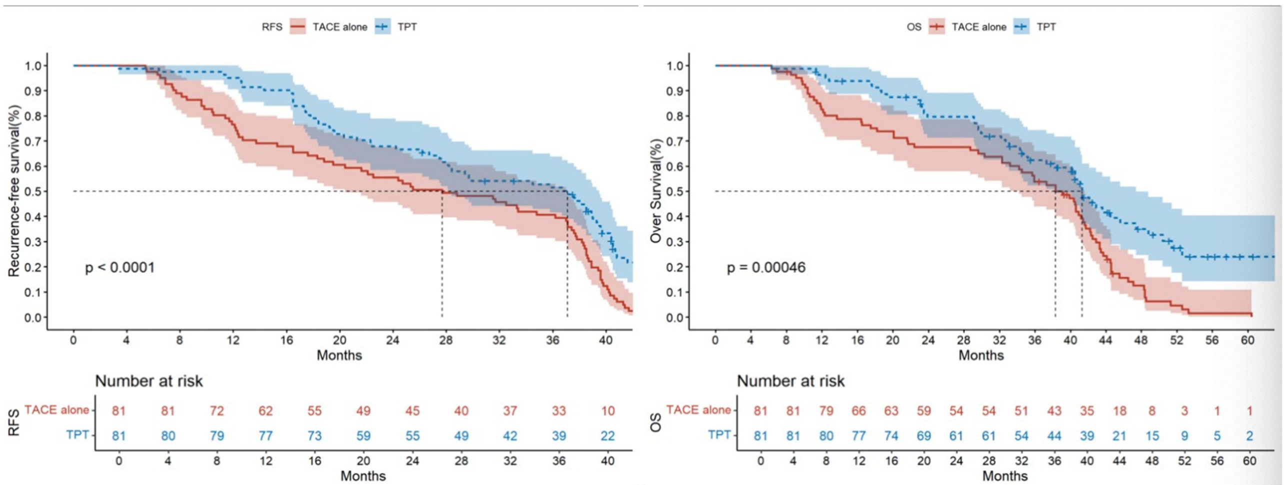

Figure 3 Kapan-Meier curves of RFS and OS after PSM.

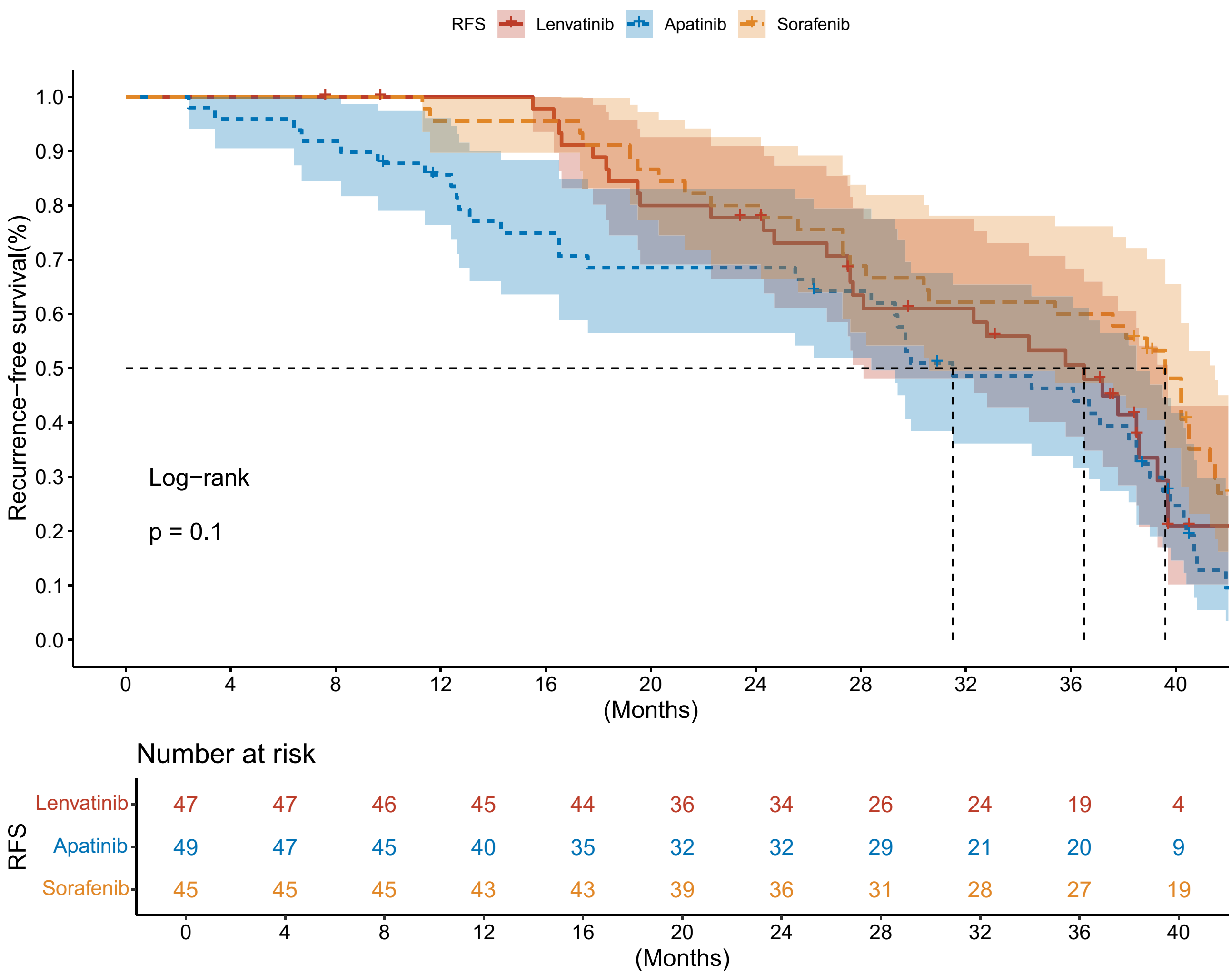

Figure 4 The RFS curves of three TKIs drugs.

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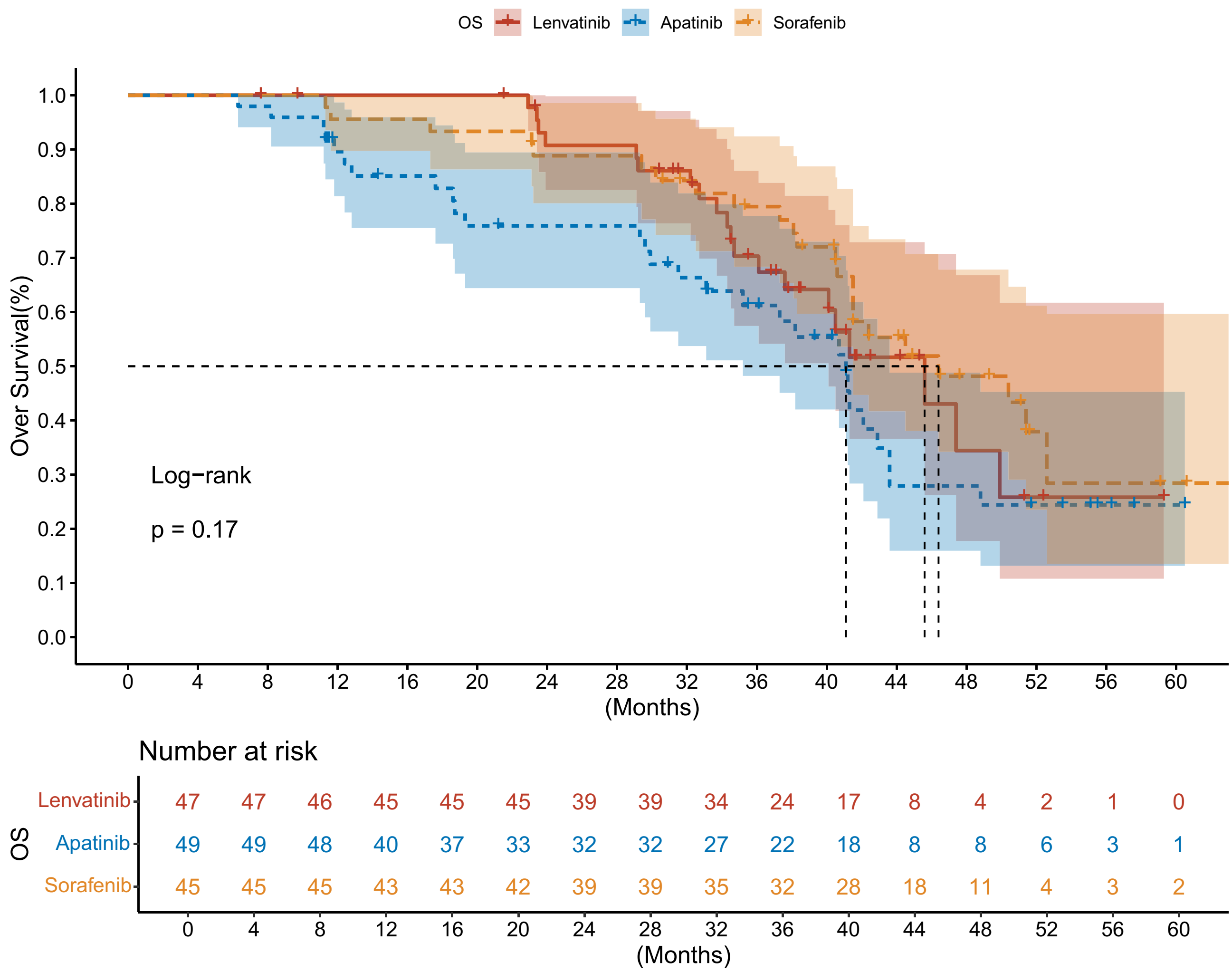

Figure 5 The OS curves of three TKIs drugs.

Adverse Events

Table 4 lists the TRAEs in both groups. The incidence of TRAEs was comparable between the TPT group and the TACE alone group, with no statistically significant differences. The most common TRAEs included pruritus, hand-foot

Table 2 Univariate and Multivariate Analysis of the Prognostic Factors for RFS in All Patients

Variable	Univariate		Multivariate	
	HR (95% CI)	**P Value**	**HR (95% CI)**	**P Value**
Gender (Male vs Female)	0.88(0.58–1.32)	0.537		
Age (≥65 vs <65)	1.69(1.2–2.37)	0.002	1.57(1.08–2.29)	0.0194
BCLC stage (B vs A)	0.64(0.46–0.88)	0.007	0.49(0.34–0.7)	0.0001
ECOG performance score (1 vs 0)	1.48(1.06–2.07)	0.021	1.31(0.93–1.85)	0.1284
Liver cirrhosis (Present vs Absent)	0.82(0.49–1.39)	0.459		
HBsAg (Positive vs Negative)	0.79(0.48–1.28)	0.331		
Number of lesions (≥3 vs <3)	1.46(1.04–2.05)	0.029	1.66(1.14–2.42)	0.0085
MVI (Yes vs No)	2.04(1.46–2.85)	<0.01	2.4(1.65–3.49)	<0.01

(*Continued*)

Table 2 (Continued).

Variable	**Univariate**		**Multivariate**	
	HR (95% CI)	**P Value**	**HR (95% CI)**	**P Value**
Tumor capsule (Incomplete vs Complete)	1.16(0.83–1.6)	0.383		
Tumor differentiation (Grade 3-4 vs Grade 1-2)	1.07(0.77–1.48)	0.699		
Child-Pugh score (B7 vs A5/6)	1.79(1–3.19)	0.048	1.42(0.78–2.58)	0.2503
Preoperative AFP (≥400 vs <400g/mL)	1.92(1.37–2.69)	<0.01	1.78(1.25–2.54)	0.0016
Preoperative DCP (≥400 vs <400g/mL)	1.2(0.85–1.71)	0.299		
Satellite nodules (Present vs Absent)	0.84(0.61–1.17)	0.311		
Maximum tumor size (≥5 vs <5cm)	2.09(1.42–3.09)	<0.01	1.79(1.18–2.73)	0.0062
Blood loss (≥500ml vs <500ml)	0.77(0.55–1.09)	0.146		
ALBI stage	1.28(0.95–1.73)	0.106		
Preoperative ALT (≥40 vs <40U/L)	1.01(0.73–1.39)	0.967		
Preoperative AST (≥40 vs <40U/L)	0.99(0.71–1.38)	0.956		
Treat (TPT vs TACE alone)	0.51(0.36–0.72)	<0.01	0.41(0.29–0.58)	<0.01

Abbreviations: RFS, recurrence-free survival; TKI, tyrosine kinase inhibitor; TPT, transarterial chemoembolization plus tyrosine kinase inhibitor; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; AFP, alpha-fetoprotein; DCP, Des-gamma-carboxyprothrombin; MVI, microvascular invasion; HBsAg, Hepatitis B surface antigen; ALT, alanine aminotransferase; AST, aspartate transaminase; HR, hazard ratio; CI, confidence interval.

Table 3 Univariate and Multivariate Analysis of the Prognostic Factors for OS in All Patients

Variable	**Univariate**		**Multivariate**	
	HR (95% CI)	**P Value**	**HR (95% CI)**	**P Value**
Gender (Male vs Female)	1.12(0.7–1.78)	0.638		
Age (≥65 vs <65)	1.88(1.29–2.75)	0.001	1.5(0.98–2.3)	0.0626
BCLC stage (B vs A)	0.68(0.47–0.96)	0.03	0.63(0.44–0.92)	0.0168
ECOG performance score (1 vs 0)	1.46(1.02–2.09)	0.041	1.74(1.18–2.59)	0.0056
Liver cirrhosis (Present vs Absent)	0.84(0.47–1.49)	0.544		
HBsAg (Positive vs Negative)	0.73(0.45–1.2)	0.218		
Number of lesions (≥3 vs <3)	1.77(1.21–2.59)	0.003	1.73(1.16–2.59)	0.0077
MVI (Yes vs No)	2.53(1.75–3.66)	<0.01	2.53(1.66–3.85)	<0.01
Tumor capsule (Incomplete vs Complete)	1.3(0.91–1.86)	0.146		
Tumor differentiation (Grade 3-4 vs Grade 1-2)	1.08(0.76–1.55)	0.658		
Child-Pugh score (B7 vs A5/6)	1.26(0.64–2.49)	0.511		
Preoperative AFP (≥400 vs <400g/mL)	2.65(1.79–3.92)	<0.01	2.26(1.5–3.4)	0.0001
Preoperative DCP (≥400 vs <400g/mL)	1.34(0.9–1.99)	0.152		
Satellite nodules (Present vs Absent)	0.82(0.58–1.18)	0.284		
Maximum tumor size (≥5 vs <5cm)	2.63(1.65–4.18)	<0.01	1.76(1–3.07)	0.0486
Blood loss (≥500ml vs <500ml)	0.91(0.62–1.32)	0.608		
ALBI stage	0.054(0.99–1.9)	1.38		
Preoperative ALT (≥40 vs <40U/L)	1.15(0.81–1.64)	0.446		
Preoperative AST (≥40 vs <40U/L)	0.94(0.65–1.35)	0.728		
Treat (TPT vs TACE alone)	0.52(0.36–0.76)	0.001	0.54(0.37–0.79)	0.0013

Abbreviations: OS, overall survival; TKI, tyrosine kinase inhibitor; TPT, transarterial chemoembolization plus tyrosine kinase inhibitor; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; AFP, alpha-fetoprotein; DCP, Des-gamma-carboxyprothrombin; MVI, microvascular invasion; HBsAg, Hepatitis B surface antigen; ALT, alanine aminotransferase; AST, aspartate transaminase; HR, hazard ratio; CI, confidence interval;

syndrome, decreased appetite, and fever. Most of these adverse events were reversible with symptomatic treatment. Grade 3 or higher TRAEs were observed in 21 patients (14.9%) in the TPT group and 18 patients (14.6%) in the TACE alone group. In the TPT group, TRAEs required TKI dose reduction in 19 patients (13.5%) and TACE discontinuation in

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Table 4 Treatment-Related Adverse Events

Adverse Events	Any Grade		P Value	≥ Grade 3		P Value
	TACE Alone n=123,%	TPT n=141,%		TACE Alone n=123,%	TPT n=141,%	
Pruritus	44 (35.8)	41 (29.1)	0.303	5 (4.1)	5 (3.5)	1
Hand-foot syndrome	29 (23.6)	23 (16.3)	0.185	4 (3.3)	5 (3.5)	1
Decreased appetite	21 (17.1)	23 (16.3)	1	4 (3.3)	3 (2.1)	0.855
Fever	20 (16.3)	24 (17.0)	1	2 (1.6)	3 (2.1)	1
Abnormal liver function	17 (13.8)	22 (15.6)	0.816	2 (1.6)	5 (3.5)	0.559
Fatigue	17 (13.8)	18 (12.8)	0.944	2 (1.6)	1 (0.7)	0.905
Hypertension	16 (13.0)	19 (13.5)	1	4 (3.3)	5 (3.5)	1
Lymphopenia	13 (10.6)	17 (12.1)	0.853	0 (0.0)	2 (1.4)	0.539
Rash	11 (8.9)	12 (8.5)	1	2 (1.6)	3 (2.1)	1
Abdominal pain	10 (8.1)	19 (13.5)	0.235	3 (2.4)	5 (3.5)	0.87
Diarrhea	9 (7.3)	19 (13.5)	0.155	2 (1.6)	2 (1.4)	1
Neutropenia	9 (7.3)	19 (13.5)	0.155	2 (1.6)	2 (1.4)	1
Hypoalbuminemia	8 (6.6)	13 (9.2)	0.571	0 (0.0)	1 (0.7)	1
Hypothyroidism	8 (6.5)	10 (7.1)	1	2 (1.6)	1(0.7)	0.905
Leukocytopenia	7 (5.7)	15 (10.6)	0.22	4 (3.3)	1 (0.7)	0.289
Hyperthyroidism	4 (3.3)	8 (5.7)	0.518	2 (1.6)	2 (1.4)	1
Thrombocytopenia	3 (2.4)	7 (5.0)	0.454	0 (0.0)	1 (0.7)	1
Hepatic failure	2 (1.6)	4 (2.8)	0.807	2 (1.6)	1(0.7)	0.905
Hematencephalon	2 (1.6)	2 (1.4)	1	0(0.0)	0(0.0)	-
Alimentary tract hemorrhage	2 (1.6)	2 (1.4)	1	2 (1.6)	0 (0.0)	0.419
Joint pain lower extremity	0 (0.0)	2 (1.4)	0.539	0(0.0)	0(0.0)	-

Abbreviations: TKI, tyrosine kinase inhibitor; TPT, transarterial chemoembolization plus tyrosine kinase inhibitor;

9 patients (6.4%). In contrast, in the TACE alone group, TRAEs necessitated TKI dose reduction in 8 patients (6.5%). The TPT regimen exhibited an acceptable safety profile, with TRAEs occurring in 51.8% of patients, of which 14.8% were grade 3 or higher. No treatment-related deaths were recorded in either group (Table 4).

Discussion

However, despite radical hepatectomy, the probability of recurrence of HCC within 5 years remains high, ranging from 60% to 70%.[3,4] The high recurrence rate continues to pose a significant clinical challenge, negatively impacting the efficacy of hepatectomy. Therefore, reducing the postoperative recurrence rate in high-risk HCC patients is crucial for improving overall patient prognosis.

However, a standardized approach for adjuvant therapy following radical hepatectomy in HCC patients remains lacking.[18] Recently, though, Liang et al reported the results of a randomized, open-label Phase 3 clinical trial showing that adjuvant TACE therapy after radical hepatectomy did not prolong RFS and OS in AJCC TNM stage I or II HCC patients.[9] In contrast, a recent systematic review and meta-analysis showed that postoperative adjuvant TACE treatment significantly prolonged long-term survival in patients with HCC accompanied by hepatic vein tumor thrombus (HVTT), inferior vena cava tumor thrombus (IVCTT) and/or right atrium tumor thrombus (RATT), with good safety.[19] Several RCTs and systematic reviews have demonstrated the efficacy of postoperative adjuvant TACE in preventing recurrence after hepatectomy, particularly in patients with high risk for recurrence.[16,20,21] Wei et al assessed the benefits of adjuvant TACE in HCC patients with maximum tumor size ≥5 cm and MVI after hepatectomy. The results showed that, compared to hepatectomy alone, postoperative adjuvant TACE significantly prolonged median disease-free survival (mDFS) (17.45 vs 9.27 months) and mOS (44.29 vs 22.37 months).[16] Similarly, Huo et al found that postoperative adjuvant TACE significantly improved OS (HR: 2.53, 95%CI: 1.70–3.76, $p<0.001$) and disease-free survival (DFS) (HR: 1.91, 95%CI: 1.60–2.28, $p<0.001$) in HCC patients with MVI and satellite nodules.[20] A meta-analysis of 40 studies, including 10 RCTs and 30 non-RCTs, highlighted the benefits of postoperative adjuvant TACE for HCC patients with high risk of recurrence (maximum tumor size ≥5 cm, multinodular tumors, and MVI-positive), demonstrating that postoperative TACE improved both OS (HR: 0.71, 95%CI: 0.65–0.77, p<0.001) and DFS (HR: 0.73, 95%CI: 0.66–0.80, p<0.001) compared to hepatectomy alone.[21] However, the effectiveness of TKI in reducing recurrence rates remains uncertain. The STORM trial, an international Phase III clinical study, demonstrated that HCC patients treated with sorafenib after hepatectomy did not experience prolonged RFS or OS. Instead, the treatment led to an increase in side effects such as skin reactions, diarrhea, and fatigue. The negative results observed in the STORM trial might be due to the inadequate representation of patients with intermediate or high-risk factors for recurrence.[22] A meta-analysis of 296 HCC patients reached a similar conclusion as that of the STORM trial.[23] Conversely, Zhang et al observed that postoperative adjuvant sorafenib significantly improved OS (p=0.007) and RFS (p=0.029) in HCC patients with MVI.[24] Furthermore, lenvatinib and apatinib have shown encouraging outcomes, although the limited research on their efficacy in preventing recurrence following hepatectomy warrants further investigation.[25,26] A multicenter prospective cohort study, the LANCE trial, involving 90 HCC patients with high risk for postoperative recurrence, demonstrated that postoperative lenvatinib combined with TACE significantly prolonged mDFS (12.0 months vs 8.0 months) compared to TACE alone (HR: 0.5, 95%CI: 6.0–12.0, p=0.0359).[27] Compared to the LANCE trial, we observed a significant extension of mRFS (37.1 months vs 27.7 months) and mOS (41.3 months vs 38.3 months). Several factors may contribute to these differences: 1) The study cohort included a substantial proportion of individuals with a documented background of hepatitis B virus infection (87.8% vs 73.3%), which may influence the efficacy of oral TKI agents;[28] 2) To minimize bias, PSM was performed before staging in our study, whereas PSM was not applied in the LANCE trial; 3) In comparison to the LANCE trial, the postoperative TACE procedures in this single-center study were performed by highly experienced physicians, which may have impacted outcomes, potentially introducing some variability. This study demonstrated that TPT is superior to TACE alone as a postoperative adjuvant therapy following radical hepatectomy in HCC patients with high risk for recurrence. These findings are of clinical significance for guiding anti-recurrence treatment in HCC following radical hepatectomy, offering a new approach to postoperative adjuvant therapy for HCC.

Our single-center retrospective study demonstrated that TPT significantly extended patients' RFS and OS compared to TACE alone and reduced the incidence of recurrence or metastasis in high-risk HCC patients after radical hepatectomy. The favorable results in our study may be attributed to the synergistic anti-tumor effects of the two treatment regimens. First, hepatic angiography can help detect early signs of tumor proliferation or recurrence during TACE therapy, allowing for timely detection and chemoembolization, which improves postoperative survival. Second, TACE therapy, following radical hepatectomy, embolizes the blood vessels supplying recurrent tumors, cutting off the nutrients necessary for tumor growth and inhibiting the recurrence of tumor cells. Third, chemotherapy drugs are delivered directly to the tumor through its supplying arteries, achieving a local drug concentration roughly 200 times greater than that of intravenous chemotherapy, thereby ensuring therapeutic efficacy. Topical chemotherapy rarely enters the systemic circulation, minimizing damage to normal tissues and reducing side effects, which has a smaller impact on the patients' quality of life and improves survival.[29] Furthermore, TKIs exert anti-angiogenic effects by inhibiting VEGF-mediated cell proliferation and tumor microvessel density, thus enhancing the anti-tumor treatment effect and ultimately improving patient survival.[30] In this study, the safety of TPT was deemed acceptable, and no serious TRAEs or deaths occurred in either group during treatment. Consistent with previous studies,[31] common TRAEs included pruritus, hand-foot syndrome, and fever. Univariate and multivariate analyses revealed that the combination of TACE and TKI served an independent prognostic factor for RFS and OS, suggesting that it may serve as a beneficial postoperative adjuvant option for high-risk HCC patients following radical hepatectomy. It is notable that the results of a recent meta-analysis suggest that tumor-associated lymphatic vessel density is significantly associated with OS and RFS after radical resection of hepatobiliary malignancies.[32]

Although the findings of this study indicate that postoperative adjuvant TACE plus TKI is superior to TACE alone, certain limitations should be considered. First, the follow-up time was relatively short, which may have impacted the observation period and the long-term outcomes. Second, univariate and multivariate analyses indicated that patients with specific pathological characteristics may particularly benefit from the combination therapy. Consequently, the development of advanced predictive models, such as image-omics, dynamic models, or machine learning models, could enhance patient selection. Finally, this study was retrospective, and although PSM was applied to minimize bias, treatment was determined according to the preferences of attending physicians and patients, which may have introduced selection bias. As a result, to establish the clinical validity and generalizability of these findings, rigorously designed, multicenter, prospective cohort studies with adequate statistical power are warranted. Such studies should aim to include diverse patient populations and standardized treatment protocols to ensure the generalizability and reliability of the results. This will help establish evidence-based guidelines for clinical practice.

Conclusion

Postoperative adjuvant TACE plus TKI significantly improved survival outcomes with an acceptable safety profiles in HCC patients at high risks for recurrence after radical hepatectomy. This study indicates that the TPT regimen may serve as a feasible postoperative adjuvant option for HCC patients at high risks of recurrence.

Abbreviations

HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; TPT, transarterial chemoembolization plus tyrosine kinase inhibitor; PSM, propensity score matching; OS, overall survival; RFS, recurrence-free survival; TRAEs, treatment-related adverse events; CTCAE, Common Terminology Criteria; PFS, progression-free survival; ICIs, immune checkpoint inhibitors; RCT, randomized controlled trial; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; DCP, des-gamma-carboxyprothrombin; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; HBs, HBsAg, Hepatitis B surface antigen; ALT, alanine aminotransferase; AST, aspartate transaminase; MVI, microvascular invasion; mRFS, median RFS; mOS, median OS; HR, hazard ratio; CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging; mRECIST, modified RECIST; MDT, multi-disciplinary treatment; CTCAE, Common Terminology Criteria for Adverse Events; HVTT, hepatic vein tumor thrombus; IVCTT, inferior vena cava tumor thrombus; RATT, right atrium tumor thrombus; TME, the tumor microenvironment.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The research protocol received formal approval from the Institutional Review Board of Guilin Medical University (Ethics Approval Number: 2023YJSLL-92), ensuring compliance with both the ethical principles outlined in the Declaration of Helsinki (1975) and its subsequent amendments. Written informed consent was obtained from all participating subjects following a comprehensive explanation of the study objectives, potential risks, and benefits. The consent process included specific authorization for the collection and analysis of clinical data, with particular attention to maintaining patient confidentiality and data security throughout the research process.

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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

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