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ORIGINAL RESEARCH

Comparison of the Efficacy and Safety of Transarterial-Chemoembolization versus Radiofrequency-Ablation for Hepatocellular Carcinoma within Milan Criteria: A Propensity Score-Matching Study

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Objective: This study aims to compare the efficacy and safety of transarterial chemoembolization (TACE) and radio-frequency ablation (RFA) in the treatment of hepatocellular carcinoma (HCC) within the Milan criteria.

Materials and Methods: 162 patients with HCC who underwent TACE (n=97) or RFA (n=65) from February 2011 to December 2024. A matched cohort composed of 88 patients was included after propensity score matching (PSM). The primary endpoint was overall survival (OS), and the secondary endpoints were progression-free survival (PFS) and safety.

Results: Baseline characteristics were balanced between the two groups after propensity score matching. Before matching, the 1-, 3-, and 5-year OS rates were 71.0%, 48.7%, 34.1%, respectively, in the TACE group and 87.0%, 69.5%, 63.1%, respectively, in the RFA group (P = 0.006). The 1-, 2-, and 3-year PFS rates were 37.1%, 25.1%, 18.3% in TACE group, and 52.6%, 43.3%, 40.6% in RFA group (P=0.009). After matching, the 1-, 3-, and 5-year OS rates were81.2%, 48.1%, 37.1%, respectively, in the TACE group and 88.6%, 65.6%, and 54.6%, respectively, in the RFA group (p=0.15). The 1-, 2-, and 3-year PFS rates were 33.3%, 20.5%, 17.5% in TACE group, and52.3%, 40.2%, 37.8% in RFA group (P=0.036). Before and after PSM, the incidence of major complications (before PSM P=0.306, after PSM P=0.08) and length of hospital stay (before PSM P=0.25, after PSM P=0.406) were similar between the two groups.

Conclusion: In the treatment of HCC within the Milan criteria, RFA demonstrated a superior median PFS compared to TACE, although there was no significant difference in OS between the two therapies.

Plain Language Summary:

Question: There is a paucity of comparative studies evaluating transarterial chemoembolization (TACE) versus radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC) within Milan criteria.

Findings: Radiofrequency ablation (RFA) and transarterial chemoembolization (TACE) demonstrated comparable overall survival outcomes.

Clinical Relevance: For hepatocellular carcinoma (HCC) patients within Milan criteria who are ineligible for surgical resection or liver transplantation, radiofrequency ablation (RFA) is recommended as the preferred treatment option.

Keywords: carcinoma, hepatocellular, propensity score, chemoembolization, ablation

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Introduction

The standard treatment options for hepatocellular carcinoma within the Milan criteria (defined as a single tumor<5cm in size or three nodules <3cm in size without vascular invasion) are surgical resection or liver transplantation.[1,2] The widespread application of transplantation is constrained by donor organ shortages.[3,4] Hepatic resection remains contraindicated in cases with compromised liver function, marked portal hypertension, or significant concurrent medical conditions.[5]

Radiofrequency ablation (RFA) has been established as the familiar alternative to surgical resection for solitary hepatocellular carcinoma lesions <2 cm in transplantation-ineligible patients.[6,7] Retrospective studies have demonstrated superior long-term survival rates with RFA compared to TACE for small (≤3 cm) hepatocellular carcinomas. These findings provide valuable insights for clinical decision-making in this patient population. However, the therapeutic efficacy of RFA remains controversial for lesions meeting the broader Milan criteria. Transarterial chemoembolization (TACE) is recognized as the first-line therapeutic approach for intermediate-stage HCC (BCLC-B). Notably, clinical data from certain tertiary centers indicate that TACE serves as the initial treatment modality in up to 60% of cases with solitary small HCC.[8] A multicenter European cohort study demonstrated that for transplant-ineligible patients with early-stage multinodular HCC, liver resection (LR) should be prioritized as the primary treatment option. When LR is not feasible, RFA and TACE represent the preferred alternatives, though current evidence remains inconclusive regarding whether RFA or TACE should be preferentially selected.[9] Although several studies with conflicting conclusions have compared the efficacy of radiofrequency ablation versus TACE for hepatocellular carcinoma within the Milan criteria, none have reported on complications.[10–12] In the context of Diagnosis-Related Group (DRG), Chinese clinicians are actively seeking effective and cost-efficient treatment options, with surgical complication rates and length of hospitalization due to complications becoming key focus areas.

Despite some evidence demonstrating the superiority of combined TACE-RFA therapy over either TACE or RFA alone,[13] the pursuit of a single effective treatment modality has gained practical significance under current DRG payment systems and economic constraints. The present study therefore compared the long-term efficacy of TACE and RFA in a propensity score-matched cohort of patients within Milan criteria HCC. We hypothesized that RFA would yield superior survival outcomes compared to TACE in this patient population.

Materials and Methods

Patients

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by our Institutional Review Board, which granted a waiver of informed consent. Inclusion Criteria: (a) Treatment-naïve HCC patients or those with post-surgical recurrence (>6 months disease-free interval); (b) Solitary lesions (≤5 cm) or ≤3 nodules (maximum diameter ≤3 cm); (c) No vascular invasion; (d) Receiving TACE or RFA as first-line therapy; (e) Child-Pugh class A (score 5–6) or early class B (score 7) liver function.

Exclusion Criteria: (a) History or current diagnosis of non-HCC malignancies; (b) Decompensated cirrhosis (Child-Pugh score 8–12); (c) Lost to follow-up; (d) Postoperative adjuvant TACE administration. HCC diagnosis followed the Chinese Guidelines for Diagnosis and Treatment of Primary Liver Cancer (Figure 1).

The treatment strategy was primarily determined according to established practice guidelines.[5,14,15] TACE was recommended as first-line therapy in the following scenarios: (1) When the target lesion cannot be identified on either ultrasound or non-contrast CT imaging, (2) when no safe ablation pathway was achievable or the access route was severely restricted, or (3) when the tumor was adjacent to critical anatomical structures (hepatic vasculature, major bile ducts, or intestinal loops).

Clinical information including age, sex, date of diagnosis, tumor size, tumor number, pre-TACE: alpha-fetoprotein (AFP), albumin (ALB), total bilirubin (TBIL), Child-Pugh grade, primary or recurrent, liver regenerative nodules, subcapsular location and follow-up results were collected. Subcapsular location was defined the tumor is close (5 mm) to the gastrointestinal tract, diaphragm, and gallbladder.

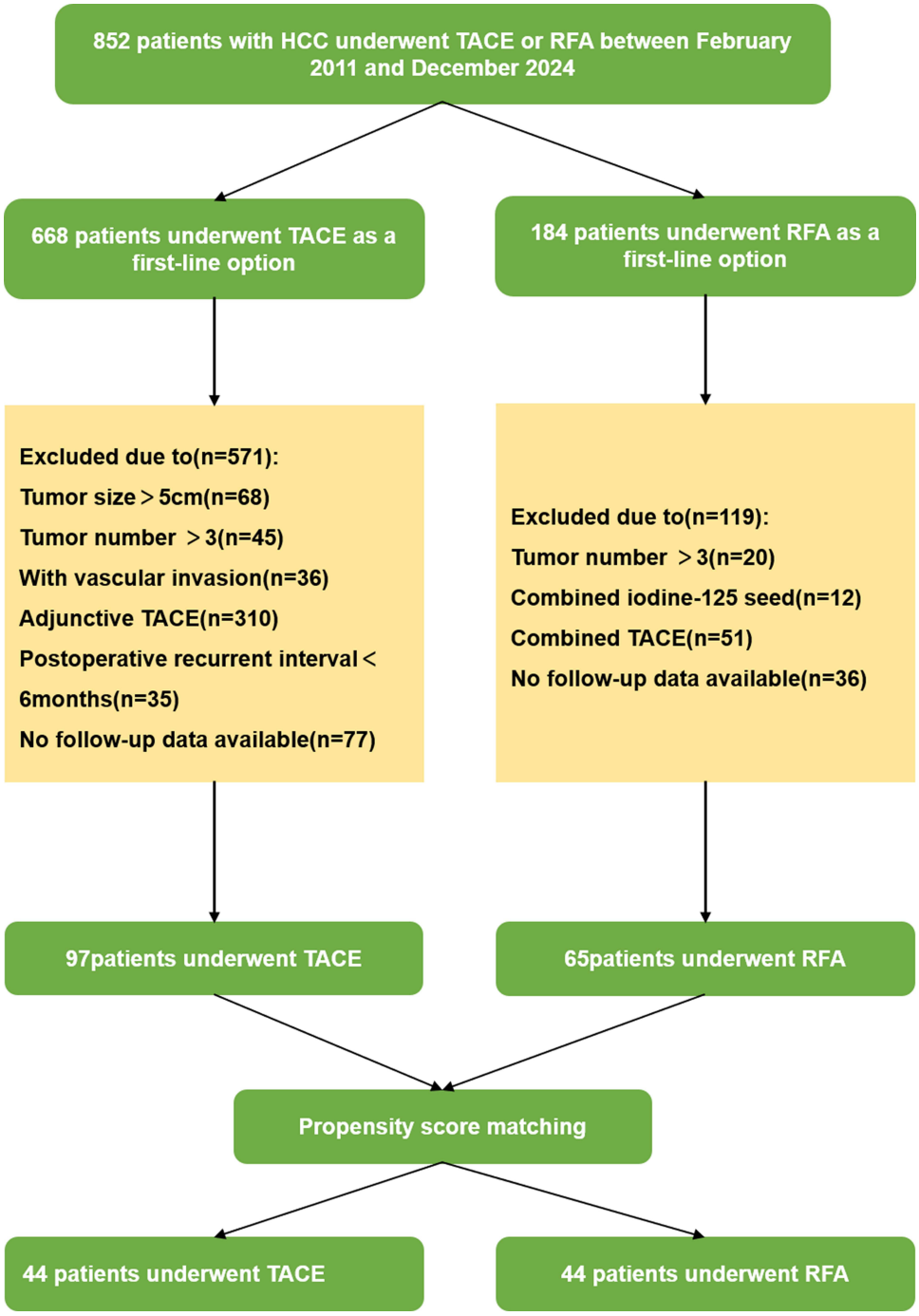

Figure 1 Flow diagram of study treatments.
Abbreviations: HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation.

TACE Procedure

Vascular access was obtained via the Seldinger technique with subsequent placement of a selective 5-French catheter (Terumo Corporation). Diagnostic angiography of the abdominal vasculature (including the superior mesenteric artery and common hepatic vessels) was performed to evaluate tumor arterial supply. Superselective distal catheterization of all tumor-feeding arteries was achieved using a microcatheter system (Maestro, Merit Medical Systems). The therapeutic protocol consisted of: (1) hepatic arterial infusion chemotherapy with oxaliplatin (100 mg) and 5-fluorouracil (500 mg), followed by (2) chemoembolization using an emulsion of epirubicin (30 mg) in 2–20 mL of lipiodol (Lipiodol Ultra-

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Fluide, Guerbet), and ultimately (3) embolization with either polyvinyl alcohol particles (Contour SE Microspheres, Cook Medical) or gelatin sponge particles (Gelfoam, Hangzhou Pharmaceutical) until complete angiographic stasis was achieved. Follow-up examinations, including triple-phase contrast-enhanced CT or MRI and liver function tests, should be performed 1–2 months after TACE. If residual tumor is present but liver function remains normal, additional TACE sessions are recommended until disease progression occurs.

RFA Procedure

Percutaneous radiofrequency ablation (RFA) was performed under conscious sedation and local anesthesia with ultrasound guidance, either alone or in combination with CT navigation. Tumor ablation was conducted using a single electrode system (CelonLab POWER, Olympus Surgical Technologies), with radiofrequency current delivered at 250W for 12–15 minutes via an automated impedance-controlled generator to ensure maximum power output. The procedural endpoint was defined as: complete ablation of all visible tumor tissue or creation of a 0.5–1.0 cm ablative margin in surrounding normal hepatic parenchyma. Real-time ultrasound monitoring during RFA included visualization of the developing hyperechoic ablation zone, which progressively obscured the tumor margins, serving as a surrogate marker for adequate thermal coverage.

Follow-Up

Patients were systematically followed with contrast-enhanced four-phase CT or MRI at 1 month after TACE or RFA, followed by serial contrast-enhanced cross-sectional imaging at 3- to 6-month intervals. Indications for retreatment included: (1) detection of new lesions, (2) radiographic evidence of tumor progression, or (3) persistent residual viable tumor showing intralesional enhancement. All patients were followed until either death or study termination per protocol.

Treatment Response

The primary endpoint was overall survival (OS), defined as the time interval between initial treatment and death from any cause or study termination, whichever occurred first. Secondary endpoints included progression-free survival (PFS), calculated from treatment initiation to tumor progression or death, and adverse event rates. Treatment-related complications were recorded and graded according to the Society of Interventional Radiology (SIR) adverse event classification system.[16] Therapeutic efficacy was evaluated using modified RECIST (mRECIST) criteria. Additional outcome measures comprised: (1) single-session complete response (CR) rate, defined as achievement of complete tumor necrosis after a single TACE or RFA procedure, and (2) mean number of treatment sessions required for therapeutic success, calculated as the average number of interventions per patient achieving either CR or partial response (PR) by mRECIST standards. The primary complications were defined as events resulting in prolonged hospitalization, escalated level of care, or readmission for additional treatment.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics 25.0 (IBM Corp.) and R software package (version 4.3.2; R Foundation for Statistical Computing). Baseline characteristics and complication rates were compared using continuity-corrected two-sample t-tests, Pearson's chi-square tests, or Fisher's exact tests, as appropriate. Overall survival (OS) and progression-free survival (PFS) were estimated using Kaplan-Meier analysis, with curve comparisons performed by Log rank test. Univariate analysis was conducted using the Log rank test, while multivariate analysis employed Cox proportional hazards regression models for all variables. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated using Cox proportional hazards models. Prespecified subgroup analyses were performed based on stratification factors (primary vs recurrent lesions and presence of cirrhotic regenerative nodule background). To minimize selection bias from potential confounders, 1:1 propensity score matching (PSM) analysis was implemented. A logistic regression model was applied with treatment group as the independent variable and patient/tumor characteristics as dependent variables. The propensity score model incorporated all relevant covariates including: gender, age, BMI, hepatitis B status, maximal tumor diameter, number of lesions, AFP level, Child-Pugh classification, ALB, TBIL, tumor location, primary/recurrent, background of cirrhotic regenerative nodules, and subcapsular tumor proximity. Matching was performed using the nearest neighbor method with a caliper width of 0.2. All tests were two-sided, and statistical significance was defined as $p < 0.05$.

Results

Study Population

We conducted a retrospective analysis of 97 patients who underwent TACE as first-line treatment and 65 patients who received RFA as initial therapy for hepatocellular carcinoma within Milan criteria at our institution between February 2011 and December 2024. Table 1 summarizes the baseline characteristics of the entire cohort (n=162). The TACE group had significantly higher BMI (p=0.020), elevated AFP levels (p=0.004), lower ALB levels (p=0.046), and more subcapsular tumor locations (p=0.036) compared to the RFA group. After propensity score matching, no significant differences were observed in any covariates between the two treatment groups (Supplementary Table 1 and Supplementary Figure 1).

Overall Survival and Progressive-Free Survival Before Propensity Score Analysis

During a median follow-up of 49 months (range: 2–142 months), 54 patients (55.7%) in the TACE group and 16 patients (24.6%) in the RFA group died. The cumulative 1-, 3-, and 5-year OS rates were 71.0%, 48.7%, and 34.1% in the TACE

Table 1 Baseline Characteristics of Patients Before and After Propensity Score Matching

	Before Matching			After Matching		
	TACE (n=97)	**RFA (n=65)**	***P* value**	**TACE (n=44)**	**RFA (n=44)**	***P* value**
Sex (M/F)	83(86%)/14(14%)	56(86%)/9(14%)	0.916	39(88.6%)/5(11.4%)	38(86.4%)/6(13.6%)	0.747
Age (years)*	63.8±9.2	63.3±10.2	0.769	63.6±7.8	62.4±10.9	
BMI**	22.7 (20.7–24.5)	24.0(22.1–25.8)	0.020	22.9(20.8–25.7)	23.1(21.1–25.7)	0.955
TBIL (μmol/L)**	17.0 (13.2–23.1)	15.4(12.2–20.1)	0.235	14.5(11.5–18.0)	15.2(10.4–18.9)	0.744
ALB (g/L)**	38.0 (35.0–41.7)	40.0(37.0–42.9)	0.046	40.9(37–42.5)	40.3(37.3–32.9)	0.978
AFP (ng/mL)			0.002			0.676
≤200	71(73%)	60(92%)		42(95.5%)	40(90.9%)	
>200	26(27%)	5(7.7%)		2(4.5%)	4(9.1%)	
HBsAg			0.209			0.803
Negative	26(26.8%)	11(17%)		11(25%)	10(22.7%)	
Positive	71(73.2%)	54(83%)		33(75%)	34(77.3%)	
Child-Pugh score			0.092			0.694
5	74(76%)	57 (88%)		40(90.9%)	38(86.4%)	
6	8 (8.2%)	5 (7.7%)		1(2.3%)	3(6.8%)	
7	15 (15%)	3 (4.6%)		3(6.8%)	3(6.8%)	
Primary or recurrent			0.289			0.067
Primary	47(48%)	26(40%)		10(22.7%)	18(40.9%)	
Recurrent	50(52%)	39(60%)		34(77.3%)	26(59.1%)	
Regenerative nodule			0.086			0.806
Yes	38(39%)	17(26%)		10(22.7%)	12(27.3%)	
No	59(61%)	48(74%)		34(77.3%)	32(72.7%)	
Tumor size (cm)			0.197			1.000
≤3	74(76%)	55(85%)		36(81.8%)	36(81.8%)	
>3	23(24%)	10(15%)		8(18.2%)	8(18.2%)	
Tumor number			0.156			1.000
1	70(72%)	55(85%)		34(77.3%)	34(77.3%)	
2	11(11%)	3(4%)		4(9.1%)	3(6.8%)	
3	16(17%)	7(11%)		6(13.6%)	7(15.9%)	
Tumour location			0.341			0.713
Uni-lobar	85(88%)	60(92%)		41(93.2%)	39(88.6%)	
Bi-lobar	12(12%)	5(7.7%)		3(6.8%)	5(11.4%)	
Subcapsular locations[†]			0.036			0.507
Yes	41(42%)	17(26%)		18(40.9%)	14(31.8%)	
No	56(58%)	48(74%)		26(59.1%)	30(68.2%)	

Notes: Except where indicated, data values represent the number of patients. *mean ± standard deviation. ** median (25th percentile—75th percentile). [†]Subcapsular location; the tumor is close (<5 mm) to the gastrointestinal tract, diaphragm, and gallbladder.

Abbreviations: TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; HbsAg, hepatitis B surface antigen; BMI, body mass index; ALB, albumin; TBIL, total bilirubin; AFP, alpha fetoprotein.

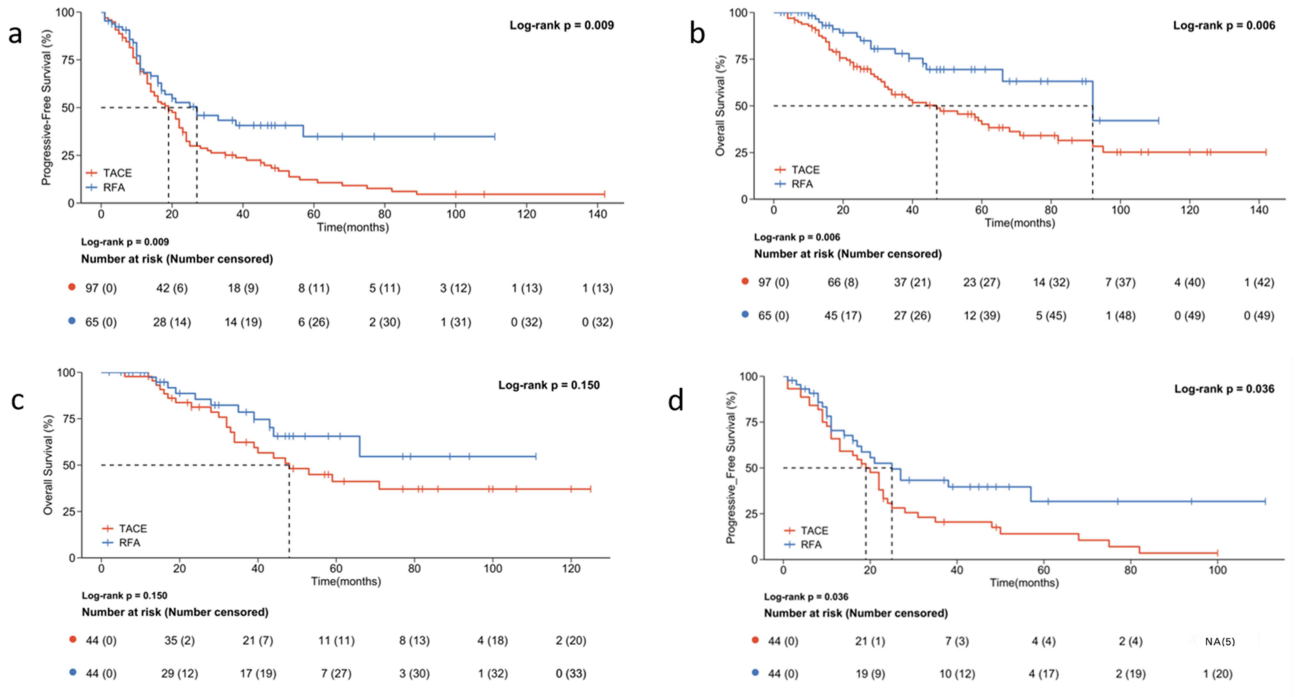

Figure 2 Cumulative survival curves of hepatocellular carcinoma (HCC) patients within Milan criteria undergoing transarterial chemoembolization (TACE) and radiofrequency ablation (RFA). (**a**) Pre-propensity score matching (PSM) overall survival (OS) curve; (**b**) Pre-PSM progression-free survival (PFS) curve; (**c**) Post-PSM OS curve; (**d**) Post-PSM PFS curve.

group versus 87.0%, 69.5%, and 63.1% in the RFA group, with significantly better OS observed in the RFA group (p=0.006, Figure 2a). Disease progression occurred in 83 patients (85.6%) in the TACE group and 33 patients (50.8%) in the RFA group during follow-up. The cumulative 1-, 2-, and 3-year PFS rates were 37.1%, 25.1%, and 18.3% in the TACE group compared with 52.6%, 43.3%, and 40.6% in the RFA group, demonstrating significantly superior PFS in the RFA group (p=0.009, Figure 2b). Multivariate analysis identified AFP level [hazard ratio (HR)=0.54; 95% confidence interval (CI), 0.31–0.93; p=0.027] as the only independent prognostic factor for OS. Tumor location and treatment modality (TACE vs RFA) were significant determinants of PFS outcomes (Table 2).

Table 2 Univariate and Multivariate Analyses of Predictors for Progressive-Free Survival and Overall Survival

Factors	Progressive-Free Survival			*P* value	Overall Survival			*P* value
	Univariate	Multivariate			Univariate	Multivariate		
	P value	HR	95% CI		*P* value	HR	95% CI	
Gender (F/M)	0.096	0.67	0.37–1.23	0.195	0.74			
Age (years, ≤60/>60)1	0.024	0.85	0.71–1.08	0.203	0.305			
BMI	0.942				0.484			
HBV (±)	0.559				0.258			
Albumin (g/L,<35/≥35)	0.844				0.586			
TBIL (μmol/L)	0.077	0.983	0.963–1.004	0.103	0.805			
Tumor number (1/2/3)	0.003	1.08	0.49–2.37	0.849	<0.001	0.6	0.29–1.26	0.175
Child-Pugh score (5/6/7)	0.767				0.537			
AFP level (ng/mL, ≤200/>200)	0.067	0.73	0.46–1.16	0.18	0.003	0.54	0.31–0.93	0.027
Tumor size (cm, 3/3.1–5.0)	0.415				0.677			
Uni-lobar/bi-lobar	0.004	0.44	0.25–0.79	0.005	0.003	0.55	0.24–1.24	0.15

(*Continued*)

Table 2 (Continued).

Factors	Progressive-Free Survival			*P* value	Overall Survival			*P* value
	Univariate	Multivariate			Univariate	Multivariate		
	P value	HR	95% CI		*P* value	HR	95% CI	
Primary or recurrent	0.049	0.73	0.49–1.09	0.122	0.470			
Regenerative nodule (yes/no)	0.844				0.261			
Subcapsular location (yes/no)	0.10				0.805			
Treatment type (TACE/RFA)	0.011	1.57	1.03–2.39	0.035	0.008	1.61	0.89–2.91	0.117

Abbreviations: HR, hazard ratio; HBV, hepatitis B virus; BMI, body mass index; TBIL, total bilirubin; AFP, alpha fetoprotein; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation.

Overall Survival and Progressive-Free Survival After Propensity Score Analysis

After propensity score matching (PSM), 44 matched pairs were included in the analysis. The cumulative 1-, 3-, and 5-year OS rates were 81.2%, 48.1%, and 37.1% in the TACE group versus 88.6%, 65.6%, and 54.6% in the RFA group, although this difference did not reach statistical significance (p=0.15, Figure 2c). Following PSM, the cumulative 1-, 2-, and 3-year PFS rates were 33.3%, 20.5%, and 17.5% in the TACE group compared with 52.3%, 40.2%, and 37.8% in the RFA group, demonstrating that RFA maintained a significantly superior PFS benefit even after matching (p=0.036, Figure 2d).

Subgroup Analyses

Subgroup analyses were performed based on whether HCC originated from malignant transformation of cirrhotic regenerative nodules. The study included 38 solitary HCC lesions arising from non-cirrhotic regenerative nodules and 17 from cirrhotic nodules. After propensity score matching (PSM), 10 and 12 cases were allocated to the TACE and RFA groups, respectively, in the cirrhotic nodule subgroup.

In non-cirrhotic nodule-derived HCCs, the cumulative 1-, 2-, and 3-year PFS rates were 32.4%, 19.4%, and 16.2% for TACE versus 59.2%, 46.5%, and 41.3% for RFA, demonstrating significantly superior PFS with RFA (P=0.01, Figure 3a). However, no significant PFS difference was observed between treatments for HCCs arising from cirrhotic nodules (P=0.52, Figure 3b).

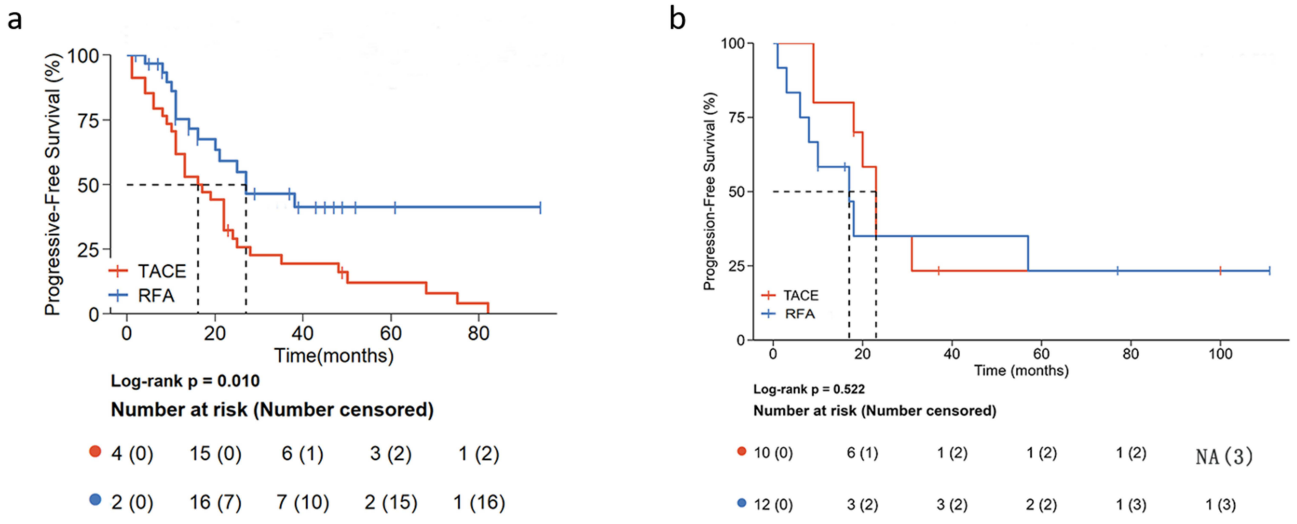

Figure 3 Subgroup analysis of progression-free survival (PFS) in hepatocellular carcinoma (HCC) patients stratified by tumor origin from cirrhotic regenerative nodules. (**a**) Patients without background cirrhotic regenerative nodules: The radiofrequency ablation (RFA) group showed significantly better treatment efficacy (P = 0.01). (**b**) Patients with cirrhotic regenerative nodules: No statistically significant difference in PFS was found between the RFA and transarterial chemoembolization (TACE) groups (P = 0.522).

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Additional subgroup analysis stratified by treatment-naïve versus recurrent lesions showed no significant PFS differences between TACE and RFA across these subgroups (all P>0.05, Supplementary Figure 2) on Kaplan-Meier analysis.

Complications

The TACE group experienced one treatment-related mortality case (due to hepatic failure), while no deaths occurred in the RFA group (Table 3). Prior to propensity score matching (PSM), the incidence of major complications was comparable between groups (16/97 [16.5%] in TACE vs 7/65 [10.8%] in RFA; P=0.306), though the pre-matched cohorts showed significant baseline differences (P=0.009). After PSM, no statistically significant difference in major complication rates persisted (P=0.08). Regarding hospitalization duration, both pre- and post-PSM analyses revealed comparable postoperative hospital stays between groups (pre-PSM: 5.3±2.9 days for TACE vs 4.6±2.4 days for RFA, P=0.25; post-PSM: 5.5±3.1 days vs 5.0±2.6 days, P=0.406).

Treatment Cost-Effectiveness Analysis

In the pre-PSM cohort, the single-session treatment success rates were comparable between groups, with 56 of 63 patients (88.9%) achieving therapeutic efficacy after one TACE procedure versus 58 of 63 (92.1%) for RFA (P=0.763). This equivalence persisted post-PSM (P=0.425). However, the mean number of treatment sessions required for therapeutic success differed significantly: pre-PSM, TACE required 1.44±0.66 sessions compared to RFA's 1.03±0.18 (P<0.001); post-PSM, RFA achieved therapeutic success in a single session in all matched patients, whereas TACE required a mean of 1.47±0.76 sessions (P<0.001). RFA demonstrated superior cost-effectiveness through significantly fewer treatment sessions per responder (Table 4).

Table 3 Complications After Treatment

Variable	Before Matching			After Matching		
	TACE (n=97)	RFA (n=65)	*p* value	TACE (n=44)	RFA (n=44)	*p* value
Major complication	16(16.45%)	7(10.8%)	0.306	10(22.7%)	4(9.1%)	0.08
Mortality	1(1%)	0	0.999	0	0	0.999
Liver failure	1(1%)	0	0.999	0	0	0.999
Gastrointestinal	1(1%)	0	0.999	1(2.3%)	0	0.999
Haemorrhage	0	4(6.2%)	0.024	0	2(4.5%)	0.494
Pain						
Grade3	9(9.3%)	2(3.1%)	0.202	6(13.6%)	1(2.3%)	0.110
Vomiting						
Grade3	1(1%)	0	0.999	1(2.3%)	0	0.999
Ascites						
Grade1	0	1(1.5%)	0.401	0	1(2.3%)	0.999
Grade2	3(3.1%)	0	0.275	2(4.5%)	0	0.494
Minor complication						
Fever	33(34%)	12(18.5%)	0.033	12(27.3%)	11(25%)	0.808
Pain						
Grade1	18(18.6%)	20(30.8%)	0.089	9(20.5%)	15(34.1%)	0.231
Grade2	7(7.2%)	4(6.2%)	0.792	4(9.1%)	3(6.8%)	0.999
Vomiting						
Grade1	10(10.3%)	0	0.006	5(11.4%)	0	0.055
Grade2	1(1%)	0	0.999	1(2.3%)	0	0.999
Hospital stay (days)*	5.3±2.9	4.6±2.4	0.250	5.5±3.1	5.0±2.6	0.406

Notes: Except where indicated, data values represent the number of patients with percentages in parentheses. *Data are the days of hospital stay. mean ± standard deviation.

Abbreviations: TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation.

Table 4 Treatment Cost-Effectiveness Analysis

	Before Matching			After Matching		
Number of people receiving only one treatment	TACE (n=63)	RFA (n=63)	*P* value	TACE (n=29)	RFA (n=44)	*P* value
Efficacy rate in patients receiving only one treatment*	56(88.9%)	58(92.1%)	0.763	25(86.1%)	41(93.2%)	0.425
Number of effectively treated patients	TACE (n=87)	RFA (n=60)	*P* value	TACE (n=38)	RFA (n=41)	*P* value
Number of treatments required to achieve effectiveness**	1.44±0.66	1.03±0.18	<0.001	1.47±0.76	1±0	<0.001

Notes: *Data values represent the number of patients (percentage). **Mean ± standard deviation.

Discussion

Our study demonstrates that for hepatocellular carcinoma (HCC) within the Milan criteria, radiofrequency ablation (RFA) achieves superior local control rates and survival outcomes compared to transarterial chemoembolization (TACE). Specifically, a trend toward longer progression-free survival (PFS) and overall survival (OS) was observed in the RFA group. However, after propensity score matching (PSM), while PFS remained significantly different between the two groups, the difference in OS disappeared. This can be explained by adjustments for baseline characteristic disparities between the groups. PSM is a statistical method used to reduce bias caused by confounding variables. The improvement in progression-free survival (PFS) without a corresponding overall survival (OS) benefit may be attributed to potential factors such as the administration of effective salvage therapies following disease progression (eg, crossover to the alternative treatment).

In this study, TACE patients exhibited lower plasma albumin levels, higher alpha-fetoprotein (AFP) levels, and a greater proportion of lesions located near the liver capsule. Elevated AFP has been reported to indicate higher tumor burden and worse liver function, both of which shorten survival in HCC patients.[16] The application of PSM indeed helped mitigate the bias in baseline characteristics between the two groups. After PSM, although the RFA group did not show an OS benefit, the prolonged PFS suggests that patients lived longer without disease progression—typically associated with fewer symptoms and better quality of life. This is crucial for patient well-being. Jonathan et al compared the therapeutic efficacy of TACE and RFA for solitary HCC ≤3 cm.[17] This multicenter study included 348 patients before PSM and 230 after PSM with single HCC (≤3 cm) and found no significant difference in OS rates between the TACE and RFA groups before or after PSM (P=0.652). Post-PSM, the 1-year OS rates for TACE and RFA were 95.5% and 92%, respectively, while the 3-year OS rates were 62.2% and 60.8% (p=0.021), consistent with our findings. A significant difference in PFS was observed between the two groups. After PSM, the 1-year and 3-year cumulative progression-free survival rates were 33.3% and 17.5% in the TACE group, compared to 52.3% and 37.8% in the RFA group. These findings are consistent with the results reported by Changyou Jing et al.[18]

Further subgroup analysis revealed that RFA achieved longer PFS in the absence of cirrhotic regenerative nodules. Conversely, in patients with cirrhotic regenerative nodules, TACE and RFA exhibited similar survival outcomes. A possible explanation is that TACE has a broader therapeutic scope than RFA, as intraoperative chemotherapy and embolization materials may also exert a therapeutic effect on potentially malignant regenerative nodules—an advantage not seen with RFA, which only targets specific localized lesions. In the recurrent HCC subgroup analysis, TACE and RFA showed comparable results. Given that recurrent HCC often presents with multiple lesions and possible occult foci, TACE appears to have a biological advantage in treating recurrent HCC.[19] Therefore, for lesions in special locations (eg, adjacent to the gallbladder, intestines, or stomach), considering TACE as an alternative treatment for recurrent HCC patients may be reasonable.

Multiple studies have suggested that combining TACE with ablation techniques may reduce progression rates and improve patient outcomes. However, the efficacy of this combined therapy remains a topic of ongoing debate.[20] Liu et al found no significant difference in prognosis between 43 patients treated with TACE alone and 45 patients with advanced HCC treated with TACE-RFA combination therapy.[21] In contrast, Zhang et al reported that patients receiving combined TACE and RFA treatment achieved a higher five-year survival rate (52.0%) compared to those treated with RFA alone (43.2%).[22] Meanwhile, Chen et al conducted a retrospective analysis of 244 HCC cases with tumor diameters <5 cm and found no difference in overall survival (OS) between TACE-MWA and TACE alone.[23] Under the DRG (Diagnosis-Related Group) payment system, actively exploring more cost-effective treatment approaches holds significant practical value. Our study reveals a notable difference ($P < 0.001$) in the average number of treatments required for therapeutic success between RFA and TACE. By significantly reducing the number of treatments per responder, RFA demonstrates superior cost-effectiveness.

In this study, AFP was significantly correlated with OS rates. A separate study evaluating the relationship between AFP levels and prognosis in 1447 HCC patients found that those with elevated AFP levels had poorer outcomes due to more severe cirrhosis, more frequent vascular invasion, higher tumor burden, and worse performance status (all $p<0.001$), which aligns with our findings.[24] Tumor location and treatment modality were significantly associated with PFS, with multilobar tumor involvement negatively affecting PFS rates—likely attributable to early intrahepatic micrometastases and multicentric occurrence of HCC.[25]

In this study, there was no significant difference in the incidence of major complications between the two groups. However, one treatment-related death occurred in the TACE group due to liver failure. Our results were slightly higher than those reported in previous studies,[13,26,27] which may be attributed to the fact that 35% of patients in the TACE group underwent multiple treatments, and this study included the cumulative complications after each treatment session. No severe adverse sequelae were observed in patients with major complications, and all recovered after symptomatic treatment. Additionally, there was no significant difference in postoperative hospital stay between the two groups. Therefore, both TACE and RFA are safe treatment options for hepatocellular carcinoma.

Our study has several limitations. First, due to the inherent nature of the retrospective single-center study design, some selection biases could not be completely avoided. For instance, the extended follow-up period in this study may introduce potential biases due to technological differences across various stages and variations in operator skill levels. Second, because of the sample size, we did not perform further subgroup analyses by categorizing the included studies into single tumors and multiple tumors. The sample sizes in these subgroups (especially the cirrhotic nodule subgroup with 10 vs 12 patients) are very small. However, comparative studies on TACE versus RFA for single tumors have already been reported in previous research.[17,28] Third, these findings represent the experience of a single center. Although the results obtained by balancing the demographics, tumor characteristics, and liver function reserves of the two patient groups through PSM provide a management strategy for hepatocellular carcinoma within the Milan criteria, larger-sample multicenter studies are needed to validate these findings. Also, mention that despite PSM, unmeasured confounding factors (eg, exact tumor location specifics, patient fitness) could still influence the results, which is an inherent limitation of retrospective studies.

Conclusion

In conclusion, RFA demonstrated superior local efficacy and survival outcomes compared to TACE in HCC patients within Milan criteria, with its advantages manifested in prolonged progression-free survival and higher cost-effectiveness.

Ethical Considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki. All data were anonymized and handled in strict confidence, accessible only to the principal investigators. Formal ethical approval was obtained from the Shaoxing people's hospital Ethics Committee (2020-K-Y-063-01).

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Disclosure

The authors report no conflicts of interest in this work.

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