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Multicenter Study on Transarterial Chemoembolization Combined with Radiofrequency Ablation for Early-Stage Hepatocellular Carcinoma: Primary versus Recurrent HCC

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Purpose: To evaluate the efficacy of transarterial chemoembolization (TACE) combined with radiofrequency ablation (RFA) for both primary and recurrent early-stage hepatocellular carcinoma (HCC) and to analyze the significant prognostic factors.

Patients and Methods: Data from patients with early-stage primary or recurrent HCC who underwent TACE plus RFA between August 2019 and May 2024 were collected from three major general hospitals. 158 patients were divided into a primary group and a recurrent group on the basis of their baseline characteristics. Compared the objective response rate (ORR), 1-, 3-, and 5-year progression-free survival (PFS) rates, 1-, 3-, and 5-year overall survival (OS) rates, and complication rate between the two groups. Multivariate analyses were used to evaluate the factors influencing PFS and OS.

Results: One hundred fifty-eight patients were enrolled. The ORRs of the primary and recurrent groups were 98.2% and 95.1%, respectively, with no statistically significant difference (χ^2= 2.032, P = 0.362). The primary group having a significantly longer PFS time than the recurrent group ($P < 0.001$). However, there was no significant difference in the 1-, 3-, and 5-year OS rates between the two groups (P = 0.218). Multivariate analysis revealed that primary or recurrent HCC and the Child–Pugh score were significant prognostic factors for PFS, whereas the serum albumin level was a significant prognostic factor for OS.

Conclusion: TACE plus RFA has similar clinical efficacy and safety for both primary and recurrent early HCC. Compared with patients with primary HCC, those with recurrent disease had significantly shorter PFS times.

Keywords: hepatocellular carcinoma, radiofrequency ablation, transarterial chemoembolization

Introduction

Liver cancer is the sixth most commonly diagnosed cancer and third most common cause of cancer-related deaths globally, with over 900,000 new cases and more than 830,000 deaths in 2020.[1] Hepatocellular carcinoma (HCC), which accounts for more than 80% of liver cancers, is among the top three causes of cancer-related deaths in 46 countries and among the top five in 90 countries.[2] Surgical resection and liver transplantation, are regarded as curative and can yield median OS of more than 5 and 10 years, respectively, in well-selected patients.[3,4] Local ablation, such as radiofrequency ablation (RFA) or microwave ablation (MWA) is the standard approach for patients with HCC detected at an early-stage

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who are candidates for surgery or transplantation, meanwhile, selective transarterial radioembolization (TARE) or stereotactic body radiotherapy (SBRT) remain alternative.[5] Up to 90% of patients with early-stage HCC exhibit a complete response to RFA,[6] leading to a 5-year survival rate of 66%-86%, even in patients who are unsuitable for surgical resection.[6–11]

However, early-stage HCC lesions often have a small diameter and therefore cannot be clearly visualized during ablation under noncontrast CT or ultrasound guidance, thus pre-ablation TACE, which can be performed to improve lesion visibility and reduce the rate of local tumor progression.[12] Moreover, for HCC lesions larger than 3 cm, RFA alone often fails to achieve a satisfying effect, and TACE before RFA can reduce the "heat sink effect" because arterial blood flow is blocked by the hepatic artery.[13] RFA after TACE can cause coagulative necrosis, and TACE can significantly reduce the size of active lesions, creating conditions for complete RFA. A previous study revealed that micrometastasis is common even in solitary and relatively small HCC lesions and that it is strongly associated with the distance from the original lesion.[14] Expanding the ablation area not only increases the likelihood of complete ablation of micrometastatic lesions but also reduces the risk of recurrence. Moreover, the use of chemotherapeutic agents improve the efficacy of RFA.[15] In summary, the combination of TACE and RFA offers clear visualization of HCC lesions, expands the ablation zone, reduces tumor volume, and thereby enhancing the complete ablation rate. This approach has been widely adopted in clinical practice. Previous studies have demonstrated that TACE plus RFA, as well as RFA alone show equivalent effectiveness for the treatment of small (≤3 cm) HCCs, hence the addition of TACE to RFA under this circumstance may be unnecessary.[16] But the efficacy of TACE combined with RFA is better than that of RFA alone for recurrent HCC.[17] For patients with HCC larger than 3 cm, this combination improves the survival rates compared with RFA monotherapy.[18] In addition, A meta-analysis suggested that TACE plus RFA provides comparable oncologic outcomes in patients with HCC as compared with surgical resection and with added benefit of lower morbidity.[19]

In patients underwent surgical resection, recurrence is seen in > 50% of the patients.[20] Furthermore, recurrence after RFA was observed in >80% of patients, either locally or distant at the 5-year follow-up.[20] This poses a significant challenge for HCC treatment, given that patients experiencing recurrent HCC often exhibit poorer liver function reserve and later-stage liver disease. The ideal indications for as well as the efficacy and safety of TACE combined with RFA have been well established in numerous studies,[16,17,21,22] but few studies have compared the efficacy and prognosis of this combined regimen for primary and recurrent early-stage HCC.[23] It remains uncertain whether combination therapy of TACE and RFA yields equivalent efficacy, safety, and prognostic outcomes for patients with recurrent HCC compared to those with primary HCC. To fill this knowledge gap and better inform clinical practice, further investigation is needed. We hypothesize that the prognosis of primary HCC and recurrent HCC after combination therapy may be different. They may require different clinical management and indications for combination therapy. Therefore, in this study, researchers retrospectively analyzed clinical data from patients who underwent TACE plus RFA for early-stage HCC at three major general hospitals to compare the efficacies of combined treatment for primary and recurrent HCC as well as analyze the factors affecting patient prognosis.

Materials and Methods

Patients

A retrospective analysis of clinical data registered in a prospective database was conducted. All procedures were performed in accordance to the tenets of the Declaration of Helsinki, this clinical retrospective analysis was approved by the three participating medical institutes and reported anonymously. All participants signed informed consent documentation. Between August 2019 and May 2024, 158 consecutive patients with HCC who met the criteria were treated with TACE combined with RFA at the three centers. Among these patients, 55 had primary HCC, and 103 had recurrent disease following previous curative treatments. HCC was diagnosed in accordance with the clinical diagnostic criteria of the European Association for the Study of the Liver[12] or on the basis of pathological evidence. The decision to implement this treatment regimen was made by consensus during multidisciplinary meetings and with the patients' consent.

Inclusion and Exclusion Criteria

The inclusion criteria for this study and the indications for HCC treatment were as follows: (1) a single lesion with a maximum tumor diameter ≤ 5 cm or multiple lesions (≤ 3 lesions) with a maximum diameter ≤ 3 cm; (2) no direct invasion of adjacent organs by solid tumors; (3) no portal vein or hepatic vein invasion; (4) Child-Pugh class A or B liver function; (5) no extrahepatic metastasis; and (6) an international normalized ratio (INR) less than 1.6, with a platelet count greater than 50,000/μL (50×10^9/L).

The exclusion criteria were as follows: (1) expected survival time less than 3 months; (2) comorbidity with malignancies elsewhere; (3) refractory ascites or hepatic encephalopathy; (4) serum creatinine levels > 2.0 mg/dL; and (5) incomplete clinical data.

TACE Procedure

The TACE procedure was performed by a team of doctors with at least 5 years of interventional therapy experience. The operation was performed as follows: Following local anesthesia with 2% lidocaine at the right or left femoral artery puncture site, a 5F catheter sheath was inserted using the Seldinger technique. A 5F-RH catheter was introduced, and visceral angiography was performed to assess the arterial blood supplied to the liver and verify the patency of the portal vein. Superselective catheterization of the distal hepatic artery was achieved in all patients using coaxial technology and a microcatheter (Renegade Hi Flo, Boston Scientific Corp., USA). After the microcatheter was in place, 100 mg of oxaliplatin (Hengrui Medical, Suzhou, China) mixed with 50 mL of 5% glucose solution was injected first, and then Lipiodol (Guerbet, Paris, France) emulsion containing 40 mg of epirubicin (Hisun Pfizer Pharmaceuticals, Fuyang, China) was slowly injected under fluoroscopy for embolization. Afterward, absorbable gelatin sponge particles (Alicon Pharmaceutical, Hangzhou, China, 350~560 μm in diameter) or polyvinyl alcohol particles (Alicon Pharmaceutical, Hangzhou, China, 350~560 μm in diameter) were used to retain the embolic agents in the tumor-feeding artery.

RFA Procedure

RFA procedure was performed by doctors with more than 5 years of experience in tumor ablation, utilizing CT guidance within one month (1–30 days) after TACE. The radiofrequency ablation equipment used was from Galvanize Medical Technology Co., Ltd. (model:CR-S2000, Zhejiang, China), and the ablation needle used was cold cycle monopolar RF electrode needle (model: 17–15S20FO or 17–15S30FO, Galvanize Medical Technology Co., Ltd. Zhejiang, China). Each patient underwent nonenhanced CT of the liver prior to RFA to assess the number and location of the intrahepatic tumors as well as to assess the path of the ablation needle. Ablation was performed using single-needle single-point or multi-point techniques. Intravenous access was established before the procedure for conscious sedation using intravenous fentanyl citrate and droperidol. Throughout the entire RFA procedure, the patient's heart rate, blood pressure, respiration, and oxygen saturation were continuously monitored. A 17-G ablation needle was carefully advanced step by step following the pre-planned ablation route. Throughout that procedure, several times of non-enhanced CT scans to confirm the appropriation and safety of ablation needle's position. Adjustments was promptly made if position is incorrect until the needle tip penetrated through the center of lesion. The ablation power and duration were determined on the basis of the size of the lesion. In present study, it was performed at 140–180 W power for 5–12 min. After each ablation procedure, a nonenhanced CT scan was performed to observe the ablation zone and defect area. The ablation zone should cover the entire tumor and at least 5 mm of the surrounding normal liver tissue.[13] Any residual tumors in the ablation zone were subjected to reablation. To prevent bleeding or tumor spread, the intrahepatic needle tract was cauterized during electrode withdrawal after the RFA procedure. After RFA, an immediate follow-up nonenhanced CT scan of liver was examined to observe for any complications.

Postoperative Observation

All the patients were carefully monitored and managed according to practice guidelines. After undergoing TACE operation, patients had no contraindications for RFA, and were well-tolerated of this procedure, which would be prioritized to be initiated. However, patients suffered severe hepatic dysfunction, post-embolization syndrome, or coagulation dysfunction after TACE would first receive conservative medical treatment to facilitate recovery before ablation.

Complications were evaluated in accordance with the guidelines established by the Society of Interventional Radiology.[24] And then routinely discharged the day after RFA if no further treatment for complications was needed.

Efficacy Evaluation and Follow-Up

All patients underwent enhanced liver CT or MRI 1–2 months after combination treatment to evaluate therapeutic efficacy according to the mRECIST criteria.[25] The standard CT/MRI protocol followed practice guidance by the American Association for the Study of Liver Diseases.[26] Enhanced liver CT or MRI were performed every 3–4 months for the first 2 years after treatment, and blood tests were performed at each follow-up visit. In addition, chest radiographs were obtained every 6 months. During the following 2 to 5 years after treatment, patients were followed up every 6 months. During the follow-up visits, tumor progression was assessed and recorded. The primary outcome was progression-free survival (PFS), which was defined as the interval from the start of combined treatment to the date of disease progression or the last follow-up visit. The secondary outcome was overall survival (OS), which was defined as the interval between the start of combined treatment at our center and the date of death or the last follow-up visit.

When residual tumors or recurrence were detected, a new multidisciplinary conference had been organized and subsequent treatment strategies was determined jointly by the advice of conference and patient opinion, patients would undergo TACE, RFA, TACE-RFA, surgical resection, targeted therapy or immunotherapy, depending on the pattern of progression or recurrence as well as the patient's current liver function.

Statistical Analyses

Statistical analyses were performed using SPSS 26.0 software (IBM, Armonk, NY, USA).

Categorical variables are presented as frequencies and percentages and were compared with the χ^2 test or Fisher's exact test. Survival curves were constructed using the Kaplan-Meier method and compared using the Log rank test. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for survival analysis. Univariate analysis was conducted using the Log rank test. Variables with a P value ≤ 0.10 in the univariate analysis were included in the multivariate analysis, which was performed with the Cox proportional hazards regression model. All the statistical tests were two-sided, and a P value < 0.05 indicated statistical significance. Assuming the 1-, 3-year PFS rates of 82.9%, and 65.7% in the primary HCC group and at least 20% lower rates in the recurrent group, the given sample size would have statistical power of 93.5%, and 96.5%, respectively to detect the difference between the two groups.

Results

Study Population

In total, 158 patients were included (55 in the primary HCC group and 103 in the recurrent HCC group). The detailed baseline characteristics of both groups of patients are shown in Table 1. There were no statistically significant differences between the two groups in terms of age, sex, tumor etiology, tumor size, number of tumors, Child-Pugh score, BCLC

Table 1 Baseline Characteristics of Patients with HCC Before TACE+RFA

Variable	Primary HCC (n=55)	Recurrent HCC (n=103)	*P* value
Age (year)			0.516
≤65	34(61.8)	69(67.0)	
>65	21(38.2)	34(33.0)	
Sex			0.211
Male	48(87.3)	96(93.2)	
Female	7(12.7)	7(6.8)	
Child-Pugh score			0.179
A	50(90.9)	99(96.1)	
B	5(9.1)	4(3.9)	

(*Continued*)

Table 1 (Continued).

Variable	Primary HCC (n=55)	Recurrent HCC (n=103)	*P* value
BCLC Stage			0.089
0	28(50.9)	38(36.9)	
A	27(49.1)	65(63.1)	
No. of tumors			0.175
1	43(78.2)	70(68.0)	
2~3	12(21.8)	33(32.0)	
Tumor size (cm)			0.604
≤3	50(90.9)	96(93.2)	
>3	5(9.1)	7(6.8)	
Hepatitis B			0.773
YES	50(90.9)	95(92.2)	
NO	5(9.1)	8(7.8)	
Serum AFP level (ng/mL)			0.728
≤20	24(43.6)	42(40.8)	
>20	31(56.4)	61(59.2)	
Serum AST or ALT (IU/L)			0.255
≤40	37(67.3)	78(75.7)	
>40	18(32.7)	25(24.3)	
Serum albumin (g/dL)			0.221
≥35	46(83.6)	93(90.3)	
<35	9(16.4)	10(9.7)	
Serum total bilirubin (mg/dL)			0.255
≤17.1	37(67.3)	78(75.7)	
>17.1	18(32.7)	25(24.3)	
Serum ALP (IU/L)			0.611
≤125	43(78.2)	84(81.6)	
>125	12(21.8)	19(18.4)	

Note: Data are No. (%) unless otherwise specified.
Abbreviations: HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

stage, preoperative serum laboratory tests, or proportion of patients with elevated serum alpha-fetoprotein levels. The follow-up periods for the primary and recurrent groups were 3–62 months (median 31 months) and 4–62 months (median 31 months), respectively. By the end of the follow-up period, disease progression was observed in 84 patients, including 17 in the primary group (30.9%) and 67 in the recurrent group (65.0%); 33 patients had died, 7 of whom were from the primary group (12.7%) and 26 were from the recurrent group (25.2%). In the primary group, 2 patients died of gastrointestinal bleeding, while 5 died of liver failure; in the recurrent group, 4, 7, and 15 patients died from gastrointestinal bleeding, tumor progression, and liver failure, respectively.

Efficacy Evaluation After TACE Combined with RFA

All 158 patients underwent enhanced CT or MRI 1–2 months after one session of TACE combined with RFA. The results based on the mRECIST criteria are shown in Table 2. In the primary group, 54 patients (98.2%) exhibited a complete response (CR), whereas only 1 patient (1.8%) experienced disease progression and underwent additional RFA, resulting in an objective response rate (ORR) of 98.2%. In the recurrent group, 96 patients (93.2%) experienced a CR, 2 exhibited a partial response (PR), and 5 experienced disease progression (PD), resulting in an ORR of 95.1%. There were no significant differences in the best response rate (χ^2= 2.032, P = 0.362) or ORR (χ^2= 0.905, P = 0.342) between the two groups.

Table 2 Tumor Response at 1–2 Months After Combination Treatment

Variable	mRECIST		*P* value
	Primary HCC (n=55)	Recurrent HCC (n=103)	
Best response			0.362
Complete response	54(98.2)	96(93.2)	
Partial response	0	2(1.9)	
Stable disease	0	0	
Progressive disease	1(1.8)	5(4.9)	
Objective response	54(98.2)	98(95.1)	0.342
Disease control	54(98.2)	98(95.1)	0.342

Note: Unless otherwise indicated, data are numbers of patients, and data in parentheses are percentages. mRECIST, modified response evaluation criteria in solid tumors.

PFS and Influencing Factors

After TACE combined with RFA, the 1-, 3-, and 5-year PFS rates of the primary group were 82.9%, 65.7%, and 40.3%, respectively, with the median PFS duration of 60 months (95% CI, 30.33–89.67). For the recurrent group, the 1-, 3-, and 5-year PFS rates were 56.7%, 35.0%, and 27.5%, respectively, with a median PFS duration of 18 months (95% CI, 9.79–26.20). The comparison between the two groups (Figure 1) revealed that the PFS duration was significantly longer in the primary group (χ^2 = 13.837, P < 0.001). Multivariate Cox proportional hazards regression analysis revealed that

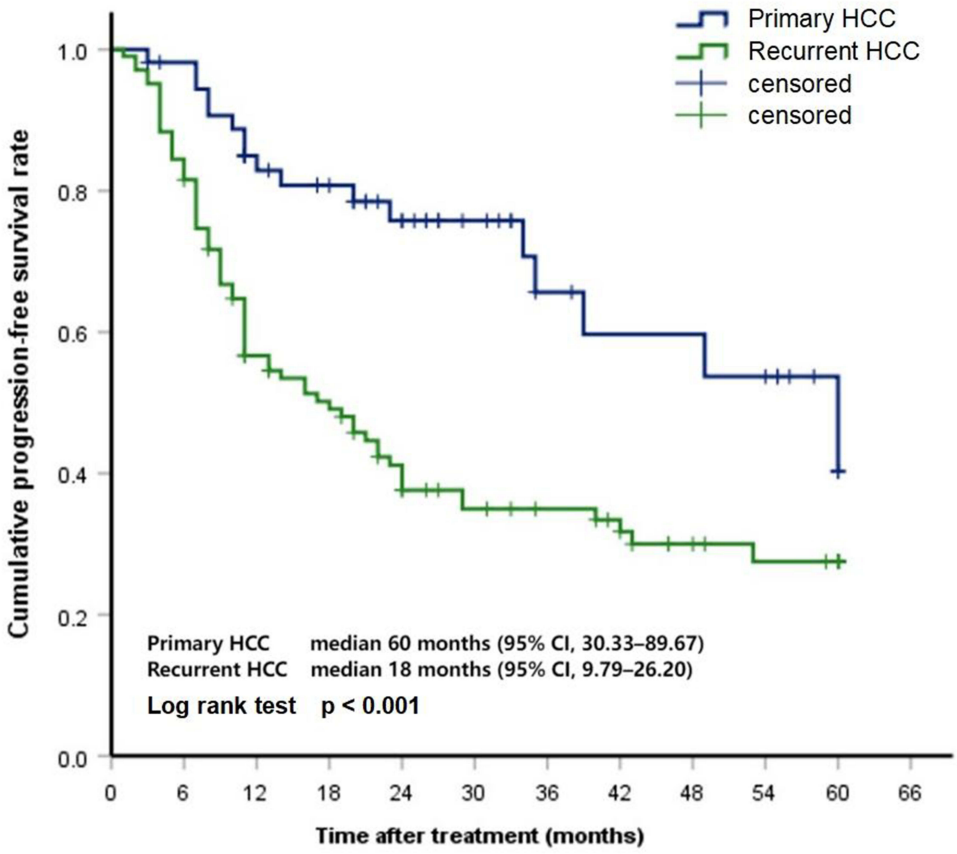

Figure 1 Kaplan-Meier curves for progression-free survival in primary and recurrent hepatocellular carcinoma (HCC) after combination therapy of transarterial chemoembolization (TACE) and radiofrequency ablation (RFA).

Child-Pugh score (HR = 0.351; 95% CI, 0.153–0.804; P = 0.013) and primary or recurrent HCC (HR = 0.361; 95% CI, 0.206–0.631; P < 0.001) were significant prognostic factors for PFS (Table 3).

OS and Influencing Factors

After combination treatment, the 1-, 3-, and 5-year OS rates of the primary group were 100%, 86%, and 72.2%, respectively. In contrast, in the recurrent group, the 1-, 3-, and 5-year OS rates were 96%, 76.9%, and 63.5%, respectively. Comparisons between the cumulative survival curves of both groups did not reveal any statistically significant differences (χ^2 = 1.518, P = 0.218) (Figure 2).

Multivariate Cox proportional hazards regression analysis indicated that the serum albumin level (HR = 0.311; 95% CI, 0.109–0.892; P = 0.030) was a significant prognostic factor for OS (Table 4).

Complications

There were no treatment-related deaths in this study. A total of 13 patients experienced complications, with an overall incidence rate of 8.2%. Post-embolization syndrome (nausea, vomiting, low-grade fever) was excluded from the complications of combined treatment. The major complications observed included liver failure (5 cases, accounting for 3.2%), bone marrow suppression (3 cases, accounting for 1.9%), subcapsular hepatic hemorrhage (2 cases, accounting for 1.3%), and liver abscess (3 cases, accounting for 1.9%). There was no significant difference in the incidence of major complications between the primary and recurrent groups (Table 5). All patients who developed complications recovered with conservative treatment during hospitalization.

Discussion

According to several practice guidelines, RFA is recommended for HCC,[27–29] especially for early-stage HCC. Pre-ablation TACE can enhance lesion visibility during the ablation procedure, reduces tumor volume, as well as reduces the "heat sink effect", thereby improving the rate of complete tumor ablation.[12,13] Thus, for select patients for whom RFA alone is technically not feasible, TACE combined with RFA is an important therapeutic option.[22] In our study, we compared the efficacy, prognosis (PFS and OS), and safety of TACE combined with RFA in patients with early-stage primary HCC versus recurrent HCC. The results demonstrated that patients with primary HCC exhibited higher 1-, 3-, and 5-year PFS rates and longer PFS durations compared to those with recurrent HCC. However, there were no significant differences in the 1-, 3-, and 5-year OS rates between the two groups.

Table 3 Univariate and Multivariate Analyses of Factors That Affect the Progression-Free Survival

Variable	Univariate Analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (≤65/>65 y)	1.193(0.725–1.962)	0.567		
Tumor size (≤3/>3 cm)	0.631(0.316–1.260)	0.192		
Number of lesions (single/multiple)	0.545(0.348–0.854)	0.008	0.675(0.397–1.149)	0.147
Child-Pugh score (A/B)	0.482(0.222–1.048)	0.066	0.351(0.153–0.804)	0.013
BCLC Stage (0/A)	0.507(0.319–0.806)	0.004	0.744(0.422–1.313)	0.308
Hepatitis B (yes/no)	0.685(0.277–1.693)	0.413		
Total bilirubin (≤17.1/>17.1umol/L)	0.839(0.526–1.340)	0.463		
Serum albumin (≥35/<35 g/dl)	0.682(0.361–1.288)	0.238		
Serum ALP (≤125/>125IU/L)	0.596(0.366–0.973)	0.038	0.726(0.434–1.215)	0.657
Serum AFP (≤20/>20 ng/mL)	0.691(0.450–1.062)	0.092	0.668(0.432–1.004)	0.054
Primary or recurrent HCC	0.409(0.243–0.689)	0.001	0.361(0.206–0.631)	<0.001
Serum AST or ALT (≤40/>40) (IU/L)	0.661(0.350–1.246)	0.200		

Abbreviations: HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

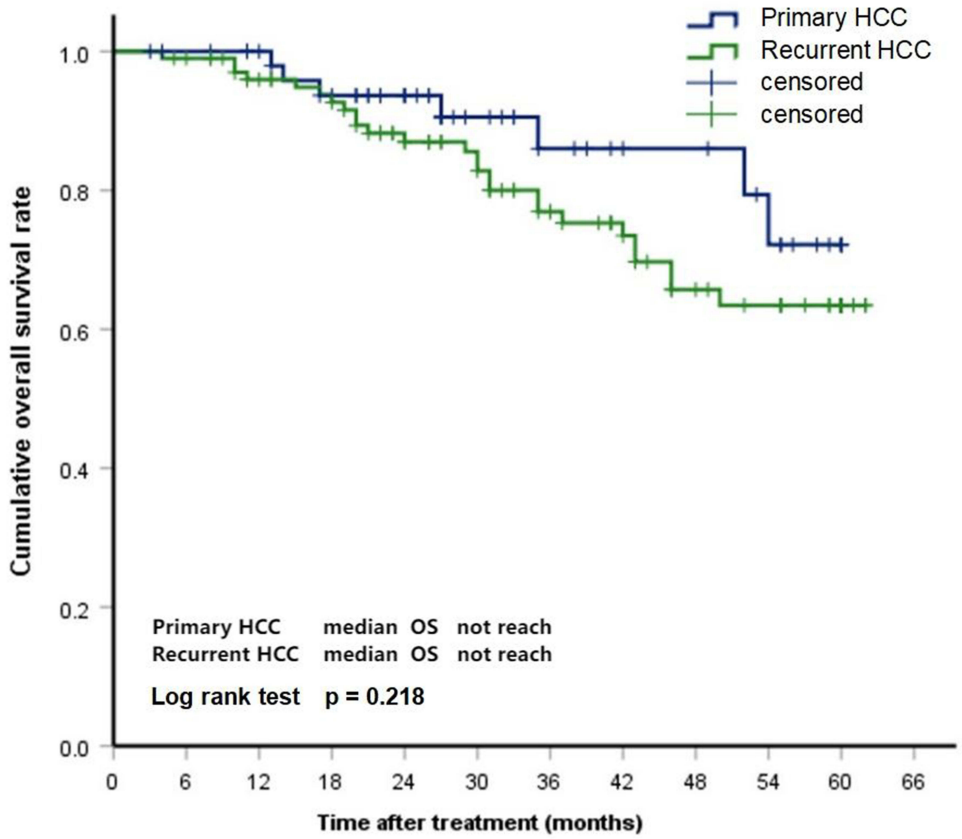

Figure 2 Kaplan-Meier curves for overall survival in primary and recurrent hepatocellular carcinoma (HCC) after combination therapy of transarterial chemoembolization (TACE) and radiofrequency ablation (RFA).

Patients with a single HCC lesion with a maximum diameter ≤5 cm or ≤3 HCC lesions (maximum diameter ≤3 cm) were included in our study. The results revealed that after one session of TACE combined with RFA, the objective response rates (ORRs) of the primary and recurrent groups were 98.2% and 95.1%, respectively, similar to the ORR of 96.5% reported in a previous study.[30] We compared the best response rates ($\chi^2 = 2.032$, P = 0.362) and ORRs ($\chi^2 = 0.905$,

Table 4 Univariate and Multivariate Analyses of Factors That Affect the Overall Survival

Variable	Univariate Analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (≤65/>65 y)	1.207(0.574–2.537)	0.619		
Tumor size (≤3/>3 cm)	0.714(0.251–2.036)	0.529		
Number of lesions (single/multiple)	0.537(0.262–1.098)	0.088	0.482(0.226–1.027)	0.058
Child-Pugh score (A/B)	0.325(0.125–0.842)	0.021	0.961(0.255–3.621)	0.953
BCLC Stage (0/A)	0.650(0.319–1.324)	0.235		
Hepatitis B (yes/no)	1.122(0.267–4.704)	0.875		
Total bilirubin (≤17.1/>17.1 umol/L)	0.573(0.282–1.166)	0.124		
Serum albumin (≥35/<35 g/dl)	0.284(0.131–0.613)	0.001	0.311(0.109–0.892)	0.030
Serum ALP (≤125/>125IU/L)	0.401(0.197–0.816)	0.012	0.503(0.241–1.050)	0.067
Serum AFP (≤20/>20 ng/mL)	1.373(0.693–2.716)	0.365		
Primary or recurrent HCC	1.678(0.727–3.872)	0.225		
Serum AST or ALT (≤40/>40) (IU/L)	5.385(0.735–39.442)	0.097	4.446(0.595–33.213)	0.146

Abbreviations: HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

Table 5 Complications After Combination Treatment

Complication	Primary HCC (n=55)	Recurrent HCC (n=103)	*P* value
Death	0	0	
Liver failure	2	3	0.804
Myelosuppression	1	2	0.957
Subcapsular hematoma	1	1	0.650
Liver abscess	1	2	0.957

Note: Data are numbers of patients.

P = 0.342) between the two groups but found no significant differences. These findings suggest that combined treatment leads to favorable short-term outcomes for patients with early primary and recurrent HCC.

The 1-, 3-, and 5-year PFS rates were 82.9%, 65.7%, and 40.3%, respectively, in the primary group and 56.7%, 35.0%, and 27.5%, respectively, in the recurrent group. The duration of PFS in the primary group was significantly longer than that in the recurrent group (χ^2 = 13.837, P < 0.001). Moreover, multivariate analysis indicated that primary or recurrent HCC (HR = 0.361; 95% CI, 0.206–0.631; P < 0.001) was a significant prognostic factor for PFS, which is consistent with the study by Sun Yu et al.[23] This may be because patients with recurrent HCC have relatively poor post-treatment liver function reserve, which promotes tumor progression. Moreover, the existence of undetectable intrahepatic micrometastases during the last curative treatment for primary lesions cannot be ruled out.[17] Recent studies exploring the differences in tumor microenvironment between primary and recurrent HCC, have found that recurrent HCC exhibits a more aggressive and immunosuppressive phenotype compared to primary HCC.[31] These combined factors contribute to a shorter PFS for recurrent HCC compared to primary HCC. Multivariate analysis revealed that the Child–Pugh score (HR = 0.351; 95% CI, 0.153–0.804; P = 0.013) was another significant prognostic factor for PFS. The Child-Pugh score reflects the patient's liver function, and higher scores indicate a higher risk of HCC progression and recurrence, highlighting the role of liver function in the development of HCC.[32] These findings suggest that for patients with recurrent HCC, especially those with higher Child-Pugh scores, close follow-up after combined treatment are necessary to detect tumor recurrence and progression in a timely manner.

The 1-, 3-, and 5-year OS rates were 100%, 86%, and 72.2%, respectively, in the primary group and 96%, 76.9%, and 63.5%, respectively, in the recurrent group, and the differences were not significant (χ^2 = 1.518, P = 0.218). The PFS in recurrent group is shorter than that in primary HCC, however, it did not affect OS, fully indicating the importance of early detection of recurrent HCC patients and the necessity of close follow-up for recurrent HCC patients, as the prognosis of HCC patients depends on tumor burden and liver reserve function (the basis of BCLC HCC staging). Early-stage recurrent HCC can still achieve comparable survival outcomes as primary HCC through combination therapy. Combination therapy is more likely to achieve a pathological complete response in patients with early-stage recurrent HCC, thereby improving the prognosis of such patients.[33] Multivariate analysis revealed that the serum albumin level (HR = 0.311; 95% CI, 0.109–0.892; P = 0.030) was a significant prognostic factor for OS. The serum albumin level is a crucial indicator reflecting the nutritional status and liver synthesis function of the body. For HCC patients, a low serum albumin level may indicate malnutrition or compromised liver function, which can impact their ability to combat tumors and postoperative recovery, and ultimately affect the patient's survival time.[34] Moreover, the serum albumin level is not only utilized to determine the Child-Pugh score, but also serves as an important objective indicator of the underlying liver function, which is significantly associated with the survival and prognosis of HCC patients.[35] This implies that we need to enhance the protection of patients' liver function and offer rational nutritional support during combined therapy.

During the perioperative period, 13 patients (8.2%) experienced major complications. The overall incidence of major complications in previous studies revealing the same therapy ranged from 2% to 32%,[16,22,36,37] but the methods used to detect post-treatment complications differed across studies, especially in those involving patients without clinical manifestations. The occurrence of these complications prolonged the hospitalization time of patients and impacted their quality of life, especially prolonged management of complications may affect the patient's subsequent anti-tumor

treatment. Superselective embolization during TACE can reduce the incidence of liver failure,[38] especially in recurrent HCC patients with unreserved liver function. The lipiodol deposition of HCC lesions after TACE may make the lesions more visible and may also improve the accuracy of puncture during RFA procedure. In our study, however, bone marrow suppression occurred, which is clearly only related to TACE.[39] Therefore, it is necessary to strictly screen the best candidates for combination therapy. For example, RFA alone is sufficient for small diameter (<3cm) HCC that can be clearly displayed under CT or US. It may not benefit from combination therapy and instead increase the risk of complications.[40] Overall, our study revealed that the complications caused by this combination treatment are relatively manageable and that the incidence of major complications was not significantly different between the primary and recurrent groups. A previous randomized controlled trial revealed that, compared with RFA alone, TACE plus RFA significantly improved OS and recurrence-free survival (RFS), indicating that TACE combined with RFA might be more effective than RFA alone in treating recurrent HCC.[21] Additionally, complication rate of combination therapy for recurrent HCC is not higher than that for primary HCC, proving the safety convincingly. From this perspective, it seems that recurrent HCC is more likely to benefit from combination therapy.

This study has several limitations. First, as a retrospective cohort study, selection bias in patient enrollment is possible. More than 90% of the patients in this study are hepatitis B virus related HCC. Whether the results of this study can be applied to non-hepatitis B virus related HCC is still unknown. Secondly, the follow-up period in this study was relatively short, which affected the persuasiveness of the OS results for both groups. Thus, future prospective studies are essential for assessing the long-term prognostic outcomes.

Conclusion

In summary, the clinical efficacy and safety of TACE combined with RFA are similar in the treatment of either primary or recurrent early-stage HCC. Compared with patients with primary HCC, patients with recurrent disease, especially those with relatively poor liver function, had significantly shorter PFS times after the combination treatment. Close follow-up is necessary to detect tumor progression in a timely manner and improve patient prognosis. For patients with recurrent HCC, close follow-up manifested that diagnosis of recurrent HCC in early stage and timely curative treatment can still lead to favorable efficacy and OS extension. Our research showed no significant difference in the OS time between patients with primary HCC and those with recurrent HCC who underwent combination therapy, but the serum albumin level was a significant factor affecting OS. For this reason, attention ought to be paid to protect the patient's liver function and provide rational nutritional support, especially in recurrent patients. Due to the limitations of retrospective studies and limited follow-up time, it is still required to conduct more prospective studies in the future to evaluate long-term prognosis outcomes.

Ethics Approval and Consent to Participate

All procedures were performed in accordance to the tenets of the Declaration of Helsinki and this clinical retrospective analysis was approved by the Ethics Committee of Fujian Provincial Hospital, Fujian Cancer Hospital, Zhangzhou Affiliated Hospital of Fujian Medical University and reported anonymously. All participants signed informed consent documentation.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, 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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