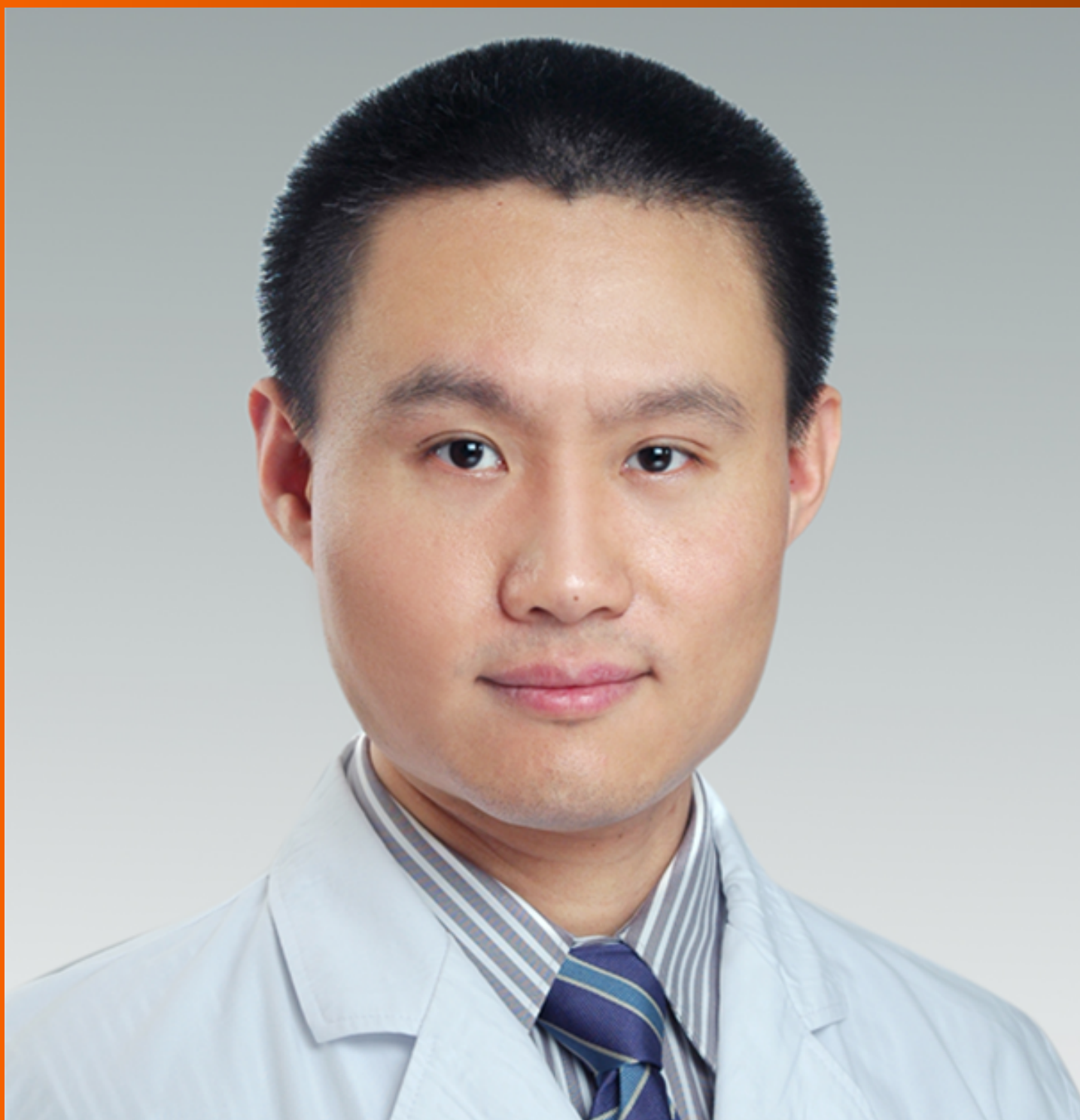


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The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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## Retrospective Study

# Simultaneous transarterial chemoembolization and radiofrequency ablation for large hepatocellular carcinoma

Feng Duan, Yan-Hua Bai, Li Cui, Xiao-Hui Li, Jie-Yu Yan, Mao-Qiang Wang

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**statement:** This study was reviewed and approved by the General Hospital of People's Liberation Army Institutional Review Board.

### Informed consent statement:

Patients were not required to give informed consent to the study because the analysis used anonymous data.

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## Abstract

### BACKGROUND

Hepatocellular carcinoma (HCC) is a common cancer and a leading cause of tumor-related death. Patients with large HCC ( $\geq 8$  cm) are at an advanced stage and have poor prognosis, and hepatic resection may not be suitable, and the incidence of postoperative recurrence is high.

### AIM

To evaluate recurrence and mid-term survival of patients with large HCC treated by transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA).

### METHODS

This was a retrospective study. From 2010 to 2013, 46 consecutive patients with large HCC were treated with simultaneous TACE and RFA. Thirty-five of 46 patients had a single tumor. Progression-free survival (PFS) and overall survival (OS) were analyzed at 2 years and 3 years, respectively.

### RESULTS

Forty-six patients treated by simultaneous TACE and RFA had no significant complications and treatment was successful. After 3 years, median PFS and OS were  $10.21 \pm 1.58$  mo and  $26.44 \pm 2.26$  mo, retrospectively. The survival rate was 67.5% after 2 years and 55.67% after 3 years.

### CONCLUSION

These preliminary data show that simultaneous TACE and RFA are safe and effective for large HCC.

**Key words:** Chemoembolization; Radiofrequency ablation; Hepatocellular carcinoma; Simultaneous treatment; Transcatheter arterial chemoembolization; Radiofrequency ablation

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**Core tip:** Hepatocellular carcinoma (HCC) is a common cancer and a leading cause of tumor-related death. Patients who have large HCC ( $\geq 8$  cm) are at advanced stages and have poor prognosis. Interventional treatment including transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) are commonly used for HCC. However, for patients with large HCC, the use of TACE alone and RFA alone can only lead to partial tumor necrosis with poor local control. Our study showed that simultaneous combination of TACE and RFA may improve therapeutic efficacy and survival for patients with large HCC.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is a common cancer and a leading cause of tumor-related death<sup>[1,2]</sup>. Patients who have large HCC ( $\geq 8$  cm) are generally at advanced stages and have poor prognosis<sup>[3,4]</sup>. Hepatectomy may not be suitable for patients who have large HCC or dysfunction of liver reserve and few patients are suitable for surgery. Besides, the postoperative recurrence is high<sup>[5]</sup>.

Transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) is commonly used for liver cancer. For TACE, the best candidates are patients with no symptoms and well-preserved liver function, as well as multifocal tumors with no vascular invasion or extrahepatic spread. However, TACE alone only leads to partial tumor necrosis. For small liver cancers ( $< 3$  cm), RFA and surgery are comparable when it comes to therapeutic efficacy<sup>[6,7]</sup>, but for tumors  $> 3$  cm, RFA has poor local tumor control<sup>[8,9]</sup>. Therefore, combination of TACE and RFA may improve therapeutic efficacy and extend survival time.

In the present study, we evaluated the efficacy of combined TACE and RFA for large HCC. We retrospectively followed up 46 patients who received the combination treatment from March 2010 to November 2013 and assessed mid-term efficacy of the combination treatment modality as a novel strategy.

## MATERIALS AND METHODS

### Patient data

A total of 46 consecutively identified patients with large HCCs (at least one lesion diameter  $\geq 8$  cm) were enrolled. The baseline characteristics of these patients were as follows: (1) 42 men and four women; (2) Median age: 53.5 years (range 36–70 years); and (3) According to the Barcelona Clinic Liver Cancer (BCLC) staging classification, advanced HCC was classified as B/C (42/4); liver function: Child–Pugh class A ( $n = 45$ ) and class B ( $n = 1$ ). The mean tumor size was 8.17 cm (range 8.0–14.0 cm) (Tables 1 and 2). Sex, age, tumor stage, tumor size, number of tumors, Child–Pugh score, vascular invasion (tumor thrombus in the first branch or trunk of the portal vein) and pseudocapsule were taken into consideration as factors for subgroup analysis. This study was approved by the Ethics Committee of the Chinese People's Liberation Army General Hospital, and patients' informed consent was obtained. The diagnosis of HCC was based on imaging findings and/or  $\alpha$ -fetoprotein (AFP) levels. Tumor stage was classified according to the BCLC classification system. The patients were surgically unsuitable, and without arteriovenous fistula or ascites.

### Treatment protocol

After routine preoperative preparation, TACE was performed first, under sterile conditions and general anesthesia<sup>[10]</sup>. The right femoral artery was cannulated by a 4F vascular sheath (Radifocus Introducer II; Terumo Corp., Japan) and Seldinger's technique. Selective celiac artery and superior mesenteric artery angiography was performed by 4F hepatic artery catheter (HA; Terumo), which was through the



**Table 1** Baseline characteristics of patients before treatment

Characteristics	Before treatment
Sex, M/F	42/4
Age, yr, median (range)	53.5 (36-70)
BCLC stage B/C <sup>1</sup>	42/4
Child-Pugh class A/B/C	45/1/0
ECOG performance status 0/1 <sup>2</sup>	42/4/0
Laboratory values, median (range)	
WBC count, 10 <sup>9</sup> /L	4.98 (2.23-10.09)
Platelet count, 10 <sup>9</sup> /L	158 (49-371)
Hemoglobin, g/dL	135 (76-159)
Serum AST, IU/L	18.85 (16.20-101.60)
Serum ALT, IU/L	28.7 (9.6-178.8)
Serum total bilirubin, mg/dL	13.2 (5.0-41.4)
Serum albumin, g/dL	38.45 (28.8-45.1)
INR	1.10 (0.92-1.33)
Serum creatinine, mg/dL	65.05 (40.30-106.20)
Serum AFP, ng/mL, baseline < 20	7.86 (1.28-24200.00) ( <i>n</i> = 29)
Serum AFP, ng/mL, baseline > 20	170.80 (20.02-24200.00) ( <i>n</i> = 17)
Tumor burden and distribution	
Unifocal/multifocal	35/11
Unilobar/bilobar	44/2
Lesion diameter (cm)	
Largest lesion diameter (mean, range)	14.0 (9.47, 8.2-14.0)

<sup>1</sup>Barcelona Clinic Liver Cancer staging system.

<sup>2</sup>Eastern Cooperative Oncology Group performance status. BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group; WBC: White blood cell; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; INR: International Normalized Ratio; AFP: α-fetoprotein.

vascular sheath. Maximum catheter selectivity of the hepatic artery was achieved using a microcatheter (Progreat; Terumo), with administration of an embolic agent into the tumor feeding arteries. Drug dose varied from 15 to 20 mL lipiodol (Guerbet Corp., France) each procedure, 30–50 mg doxorubicin (Pfizer Pharmaceuticals Ltd., United States), 100–150 mg oxaliplatin (Sanofi Pharmaceuticals Co. Ltd., France), depending on the tumor size, patient's weight and laboratory results. Lipiodol chemotherapeutic agents were injected until stasis to minimize reflux into nontarget vessels. Administration of agents continued until quiescence, and was observed in the arteries that directly fed the tumor (*i.e.*, the control column was fully cleared in five heart beats). After administration of 20 mL lipiodol, gelatin sponge, which served as a supplement, was injected if stasis was not achieved. If the inferior phrenic, internal thoracic artery branches and omental branches fed the tumor, these collateral arteries were embolized accordingly.

Percutaneous RFA was immediately performed after TACE. It was under general anesthesia and with the guidance of digital subtraction angiography (DSA) combined with cone-beam computed tomography (CBCT)<sup>[11]</sup>. One multipolar RF probe (RITA Co., Crystal Lake, IL, USA) with 5–7 cm maximum ablation diameter and 10–15 cm length was used during RFA. Guided by fluoroscopy, the RF probe was inserted into the center of the tumor. During puncture, both the lateral and postural views were obtained. CBCT was then performed to confirm the position of the RF probe (Figure 1). Ablation began when the target position was reached. The operation parameters were power, 150–200 W; and ablation time, 15 min when temperature rose until 105 °C. According to tumor size and maximum ablation diameter, RFA was performed 2–5 times. Puncture tract ablation was carried out to avoid bleeding and tumor seeding.

#### **Patient follow-up and clinical data collection**

Enhanced magnetic resonance imaging was used for follow-up every 1–2 mo during the first year, and every 2–4 months afterwards. Tumor recurrence or metastasis was recognized as disease progression. Comprehensive treatment including TACE, RFA,

**Table 2** Baseline characteristics of patients after treatment

Characteristics	3 d after treatment
Laboratory values, median (range)	
WBC count, 10 <sup>9</sup> /L	4.985 (2.300-9.050)
Platelet count, 10 <sup>9</sup> /L	141 (44-259)
Hemoglobin, g/dL	136.5 (98.0-165.0)
Serum AST, IU/L	28.2 (15.0-103.7)
Serum ALT, IU/L	32.15 (8.40-74.30)
Serum total bilirubin, mg/dL	14.45 (5.40-44.80)
Serum albumin, g/dL	37.75 (24.30-46.30)
INR	1.08 (0.95-1.41)
Serum creatinine, mg/dL	65.7 (45.4-134.6)
Serum AFP, ng/mL, baseline < 20	5.60 (1.12-24200.00) ( <i>n</i> = 29)
Serum AFP, ng/mL, baseline > 20	916.2 (21.1-24200.0) ( <i>n</i> = 17)

WBC: White blood cell; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; INR: International Normalized Ratio; AFP:  $\alpha$ -fetoprotein.

radiotherapy, and sorafenib was performed on patients with disease progression. Two independent authors followed up all the clinical data and follow-up outcomes.

### Statistical analysis

SPSS for Windows (SPSS Inc., Chicago, IL, United States) was used for analyzing data. The estimated local tumor progression and overall survival (OS) rates were compared by the Kaplan-Meier method. Cox proportional hazards model was used to fit survival time for each variable. *P* < 0.05 was considered to be a significant difference.

## RESULTS

### Treatment response

Figure 2 shows a representative condition after TACE and RFA combination treatment. As shown in Tables 1 and 2, there were no significant differences between laboratory results before and 3 d after treatment. After 2 years, OS was  $18.43 \pm 1.34$  mo and progression-free survival (PFS) was  $9.40 \pm 1.31$  mo; however, after 3 years, OS was  $26.44 \pm 2.26$  mo and PFS was  $10.21 \pm 1.58$  mo. Figure 3 shows the OS and PFS results.

Subset analysis showed similar OS and PFS (Table 3). Among these subsets, four groups showed different results, which were the vascular invasion group, non-vascular invasion group, male group, and female group (marked as A, B, C and D, respectively). OS in the A and D groups was shorter than in the B and C groups. The *P* values for B and C were 0.019 and 0.031, respectively.

### Adverse effects and complications

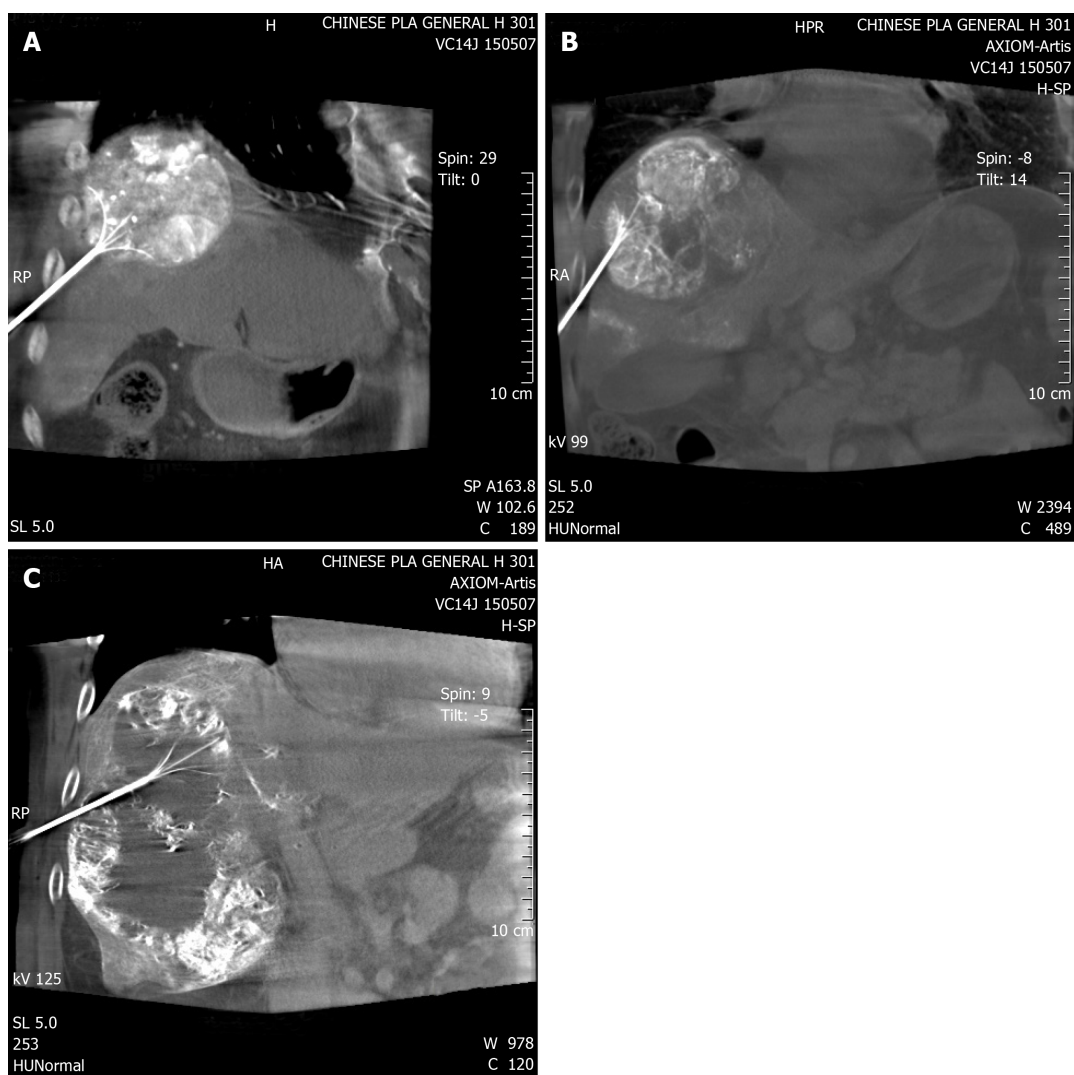
Clinical adverse events included fever, pain, nausea, fatigue, transient reduction in blood counts and transient elevations of aspartate aminotransferase and alanine aminotransferase levels, but were mostly limited to grade 1 and 2 (Table 2). No severe complications associated with our treatment protocol were noted.

## DISCUSSION

HCC is a leading cause of liver-disease-related mortality. Although rapid progress in treatment for large liver cancer has been made in the past few years, neither the prognosis nor postoperative outcomes are satisfactory.

According to a previous report, the combination of TACE and RFA has a synergistic effect on HCC inactivation<sup>[12]</sup>. The combination improves treatment efficacy, prolongs survival, and reduces recurrence rate. Thus, the combined treatment is superior to TACE or RFA alone<sup>[5,13]</sup>. So far, treatments are generally launched separately in practice. The time interval between the two modalities was 1 d to 4 wk. Because of the possible collateral formation and elimination of lipiodol chemotherapeutic agents after embolism, the effects of TACE or RFA alone are not





**Figure 1** Cone-beam computed tomography image confirmed the position of the radiofrequency probe. A-C: Radiofrequency probe inserted at an angle to avoid lung damage.

synergistic<sup>[6,14,15]</sup>. Therefore, evaluating the effect of the combined treatment is necessary.

The present study involved 3-year follow-up of the efficacy of simultaneous TACE and RFA in patients with large HCC. This combination treatment may have the following advantages. First, DSA or CBCT can clearly show blood vessels. Both imaging modalities allow successful puncture of the liver and can verify treatment efficacy during the treatment in real time<sup>[16,17]</sup>. Second, during combination treatment, iodine oil precipitates around the lesions. Thus, it can be used as a heat-transmitting medium to improve ablation efficiency and make the surrounding HCC microenvironment inactive<sup>[18]</sup>. This can reduce tumor recurrence by improving ablation efficacy. Third, TACE can block blood flow into the tumor, thereby reducing heat loss during RFA<sup>[19]</sup>. Fourth, after TACE, ablation can be performed immediately, which may also localize damage such as liquefaction necrosis as well as coagulation sclerosis. Moreover, the immediate combination procedure is considered to reduce the side effects of TACE<sup>[20]</sup>. Finally, in one session of treatment, combination of TACE and RFA can be performed, which may reduce financial burden for the patient. In general, TACE with simultaneous RFA leads to synergistic effects of thermal ablation and chemotherapy. No significant adverse effects were observed in our study. In short, for the efficacy and survival of patients with large HCCs, TACE with simultaneous RFA may be a useful and novel tactic.

During our follow-up, the incidence of intrahepatic and extrahepatic metastases was higher in patients with vascular invasion than in those without vascular invasion. This indicates that tumor thrombus exhibits poor response to treatment. Multivariate Cox proportional hazard analysis also demonstrated that vascular invasion was an important prognostic factor. In addition, the male and female patients showed



**Figure 2** A 41-year-old male patient re-examined 2 and 4 years after combination therapy. A: Magnetic resonance imaging (MRI) at 2 years; B: MRI at 4 years. Hepatocellular carcinoma lesions showed pyknosis and necrosis.

significant differences in OS and PFS. The cause of the false-positive result may be the small size of the female group. The pseudocapsule group showed better treatment efficacy mainly because the pseudocapsule may enhance the thermal aggregation effect of ablation, resulting in greater tumor inactivation. However, it was not significant, possibly because of the small sample size. The other subgroups did not show significant differences.

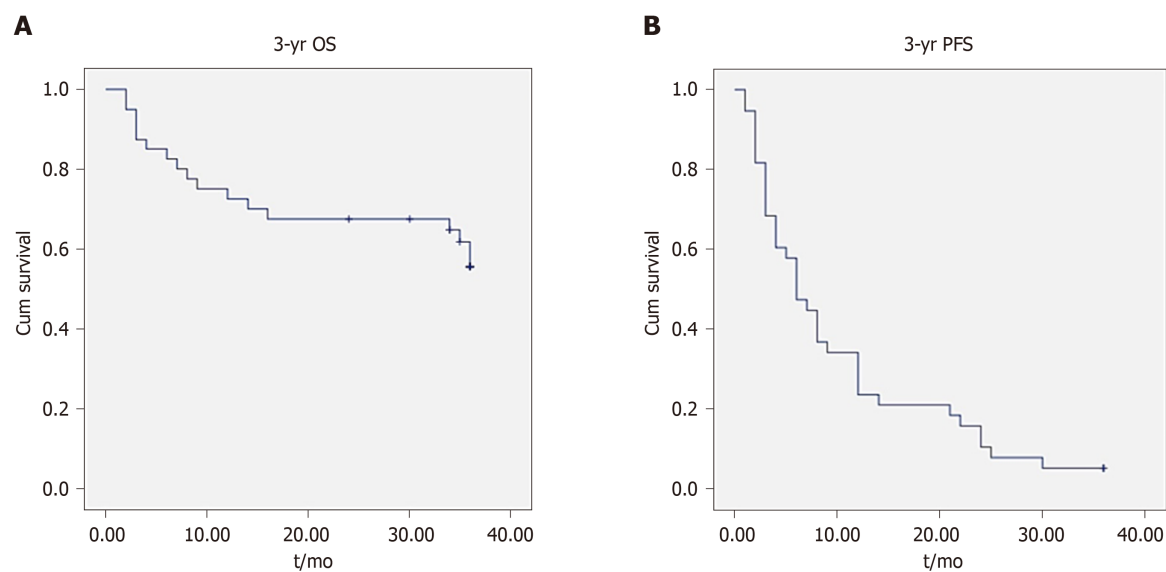
The main limitation of our study was that it was retrospective. Thus, a multicenter prospective study, with a large sample size should be conducted to evaluate further the outcome of TACE and RFA combination treatment in patients with large HCCs.

In conclusion, these preliminary data show that the simultaneous TACE and RFA is a safe, effective and valuable strategy for large HCC, as it improves efficacy and prognosis.

**Table 3** Multivariate analysis using Cox proportional hazard model, *n* (%)

Characteristics	<i>n</i>	Median OS (mo)	1-yr survival	2-yr survival	3-yr survival	<i>P</i> value
Sex						0.031
Female	4	10.5	2 (50.0)	1 (25.0)	0	
Male	42	34.5	31 (73.8)	27 (64.3)	23 (54.5)	
Age (yr)						0.264
≤ 60	37	34	26 (70.3)	22 (59.5)	20 (54.1)	
> 60	9	35	7 (77.8)	6 (66.7)	4 (44.4)	
BCLC staging						0.657
B	10	37.5	8 (80.0)	8 (80.0)	7 (70.0)	
C	36	30	25 (69.4)	20 (55.6)	17 (47.2)	
Size of tumor (cm)						0.300
8-10	23	34	18 (78.3)	14 (60.9)	12 (51.4)	
> 10	23	26	15 (65.2)	14 (60.9)	12 (52.2)	
No. of tumors						0.087
Single	35	34	26 (74.3)	23 (65.7)	20 (56.7)	
Multiple	11	19	7 (63.6)	5 (54.5)	4 (36.4)	
Child-Pugh class						0.640
A	45	34	32 (77.8)	28 (62.2)	24 (53.3)	
B	1	19	1 (100)	0	0	
Pseudocapsule						0.289
Yes	11	44	10 (90.9)	9 (81.8)	7 (63.6)	
No	35	30	23 (65.7)	19 (54.3)	17 (48.2)	
Vascular invasion						0.019
Yes	4	8	1 (25.0)	1 (25.0)	0	
No	42	34.5	32 (76.2)	27 (64.3)	24 (56.8)	
AFP positive <sup>1</sup>						0.051
Yes	17	14.5	9 (52.9)	6 (35.3)	6 (35.3)	
No	29	35	24 (79.3)	22 (75.9)	18 (61.4)	

<sup>1</sup> AFP ≥ 200 ng/mL. BCLC: Barcelona Clinic Liver Cancer; OS: Overall survival; AFP: α-fetoprotein.



**Figure 3** Kaplan-Meier analysis of overall survival and progression-free survival. Kaplan-Meier survival curves shown for patients with large hepatocellular carcinomas treated with combination therapy. A: 3-year overall survival; B: 3-year progression-free survival. OS: Overall survival; PFS: Progression-free survival.

## ARTICLE HIGHLIGHTS

**Research background**

Hepatocellular carcinoma (HCC) is a common cancer and a leading cause of tumor-related death. Patients who have large HCC ( $\geq 8$  cm) are at advanced stages and have poor prognosis. Transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) is commonly used for patients with large HCC, however, both treatments has their own limitation. Recently study showed that combination of TACE and RFA may improve therapeutic efficacy, but how to combine these two treatment modalities is still a controversial topic.

**Research motivation**

The combination of TACE and RFA has a synergistic effect on HCC inactivation; however, most treatments are generally launched separately in practice, the effects of TACE or RFA alone are not synergistic very well. Therefore, evaluating the effect of the simultaneous combined treatment is necessary.

**Research objectives**

In the present study, we evaluated the efficacy and safety of simultaneous combined TACE and RFA for large HCC, to figure out how to combine these two treatment modalities.

**Research methods**

A retrospective study was conducted. From 2010 to 2013, 46 consecutive patients with large HCC were treated with simultaneous TACE and RFA. Thirty-five of 46 patients had a single tumor. Progression-free survival (PFS) and overall survival (OS) were analyzed at 2 years and 3 years, respectively.

**Research results**

Forty-six patients treated by simultaneous TACE and RFA had no significant complications and treatment was successful. After 3 years, median PFS and OS were  $10.21 \pm 1.58$  and  $26.44 \pm 2.26$  mo, retrospectively. The survival rate was 67.5% after 2 years and 55.67% after 3 years.

**Research conclusions**

These preliminary data show that simultaneous TACE and RFA are safe and effective for large HCC.

**Research perspectives**

With the simultaneous combination of TACE and RFA, it is expected to bring us a better treatment for large HCC.

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