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Radiofrequency Ablation With or Without Transcatheter Arterial Chemoembolization in the Treatment of Hepatocellular Carcinoma: A Prospective Randomized Trial

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ABSTRACT

Purpose
To compare radiofrequency ablation (RFA) with or without transcatheter arterial chemoembolization (TACE) in the treatment of hepatocellular carcinoma (HCC).

Patients and Methods
A randomized controlled trial was conducted on 189 patients with HCC less than 7 cm at a single tertiary referral center between October 2006 and June 2009. Patients were randomly asssigned to receive TACE combined with RFA (TACE-RFA; n = 94) or RFA alone (n = 95). The primary end point was overall survival. The secondary end point was recurrence-free survival, and the tertiary end point was adverse effects.

Results
At a follow-up of 7 to 62 months, 34 patients in the TACE-RFA group and 48 patients in the RFA group had died. Thirty-three patients and 52 patients had developed recurrence in the TACE-RFA group and RFA group, respectively. The 1-, 3-, and 4-year overall survivals for the TACE-RFA group and the RFA group were 92.6%, 66.6%, and 61.8% and 85.3%, 59%, and 45.0%, respectively. The corresponding recurrence-free survivals were 79.4%, 60.6%, and 54.8% and 66.7%, 44.2%, and 38.9%, respectively. Patients in the TACE-RFA group had better overall survival and recurrence-free survival than patients in the RFA group (hazard ratio, 0.525; 95% CI, 0.335 to 0.822; $P = .002$; hazard ratio, 0.575; 95% CI, 0.374 to 0.897; $P = .009$, respectively). There were no treatment-related deaths. On logistic regression analyses, treatment allocation, tumor size, and tumor number were significant prognostic factors for overall survival, whereas treatment allocation and tumor number were significant prognostic factors for recurrence-free survival.

Conclusion
TACE-RFA was superior to RFA alone in improving survival for patients with HCC less than 7 cm.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most frequent cause of cancer death.[1] Although more patients with HCC are diagnosed at an earlier stage,[2-4] most HCCs are still diagnosed late, and only approximately 30% of patients can benefit from curative therapies such as resection, liver transplantation, or percutaneous ablation.[5,6] Until now, there has been no universally accepted protocol for treatment of HCC.[5-10] Locoregional treatments such as transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) are minimally invasive options that may individually or in combination achieve the pertinent balance in successful tumor eradication and maximal preservation of liver function. TACE slows tumor progression and improves survival by combining the effect of targeted chemotherapy with ischemic necrosis by arterial embolization.[8,10] TACE is the most commonly used therapy for intermediate-stage HCC.[11] RFA has emerged as an accepted therapy for early HCC because of its effectiveness and safety. Nowadays, RFA is generally considered as an alternative treatment to partial hepatectomy for early HCC, especially for patients with impaired liver function and when liver transplantation is not indicated, although some authors believe RFA can be used as a first-line treatment for early HCC.[10,12-14] Either TACE or RFA has its own

limitations; in particular, neither can result in adequate control of medium or large HCC.[7-9] The combined use of TACE with RFA is appealing.[15] TACE decreases blood flow to the tumor, making subsequent RFA more effective, as there is less heat loss by convection.[16] Several studies have demonstrated the synergistic cytotoxic effects of TACE with RFA for HCC.[17-20] To the best of our knowledge, there have not been any prospective randomized controlled studies to compare the long-term survivals of patients with HCC treated with TACE-RFA or RFA alone. This is such a study coming from a single tertiary referral center conducted on patients with HCC $\leq$ 7 cm.

PATIENTS AND METHODS

Patients

This prospective randomized controlled trial was conducted at the Department of Hepatobiliary Surgery, Cancer Center of the Sun Yat-sen University, Guangzhou, China. From October 2006 to June 2009, patients with HCC who met the entry criteria and who agreed to participate were included. The diagnosis of HCC was based on the diagnostic criteria used by the European Association for the Study of the Liver[21]: two imaging techniques showing typical features of HCC or positive findings on one imaging study together with an α-fetoprotein level of more than 400 ng/mL (n = 137), or cytologic/histologic diagnosis of HCC (n = 52).

The eligibility criteria were as follows: (1) age 18 to 75 years; (2) a solitary HCC $\leq$ 7.0 cm in diameter, or multiple (three or fewer) HCC lesions, each $\leq$ 3.0 cm in diameter; (3) no radiologic evidence of invasion into major portal/hepatic venous branches and no extrahepatic metastases; (4) lesions visible on ultrasound with an acceptable and safe path between the lesion and skin as shown on ultrasound; (5) an Eastern Cooperative Oncology Group performance status of 0; (6) no previous treatment; and (7) Child-Pugh class A or B cirrhosis. The exclusion criteria were (1) severe coagulation disorders (prothrombin activity $<$ 40% or a platelet count of $<$ 40,000/μL); (2) evidence of hepatic decompensation including ascites refractory to diuretics, esophageal or gastric variceal bleeding, or hepatic encephalopathy; and (3) contraindications to carboplatin, epirubicin, mitomycin, or lipiodol.

This study was approved by the ethics committee of the Cancer Center of the Sun Yat-sen University, and it conformed to the standards of the Declaration of Helsinki. All patients gave written inform consent to this study.

Study Design

Patients were stratified using tumor size ($\leq$ 3 v $>$ 3 cm) and tumor number (single v multiple) before they were randomly assigned into the TACE-RFA and the RFA-alone groups. The randomization was done at a central registry using computer-generated numbers by a nurse who was not part of this research team. Double-blind and double dummy techniques were not used because of the nature of the treatments and their possible adverse effects. The interval between randomization and the treatment was less than 2 weeks. Treatment was allowed to be discontinued if any exclusion criteria developed in the patient or per patient's request.

Treatment Protocols

All TACE and RFA were performed by the same team of doctors. TACE was performed according to the following protocol[22]: A selective 5-F catheter was introduced, and visceral angiography was carried out to assess the arterial blood supply to the liver and to confirm patency of the portal vein. All patients underwent a distal super-selective catheterization of the hepatic arteries using a coaxial technique and microcatheters (2.9 F; Terumo Corporation, Tokyo, Japan). Then, the same three chemotherapeutic agents at the same dosages were used throughout this study, regardless of tumor number and size. Hepatic artery infusion chemotherapy was performed using carboplatin 300 mg (Bristol-Myers Squibb, New York, NY). Next, chemolipiodolization was performed using epirubicin 50 mg (Pharmorubicin; Pfizer, Wuxi, China), and mitomycin 8 mg (Zhejiang Hisun Pharmaceutical, Taizhou, China) mixed with 5 mL of lipiodol (Lipiodol Ultra-Fluide; André Guerbet Laboratories, Aulnay-Sous-Bois, France). If the territory of the chemolipiodolized artery did not show stagnant flow, pure lipiodol was then injected. For all cases, embolization was finally performed with absorbable gelatin sponge particles (Gelfoam; Hanzhou Alc, Hangzhou, China; 1 to 2 mm in diameter) or polyvinyl alcohol particles (Alicon Pharm SCT&TEC, Hangzhou, China; 350 to 560 μm

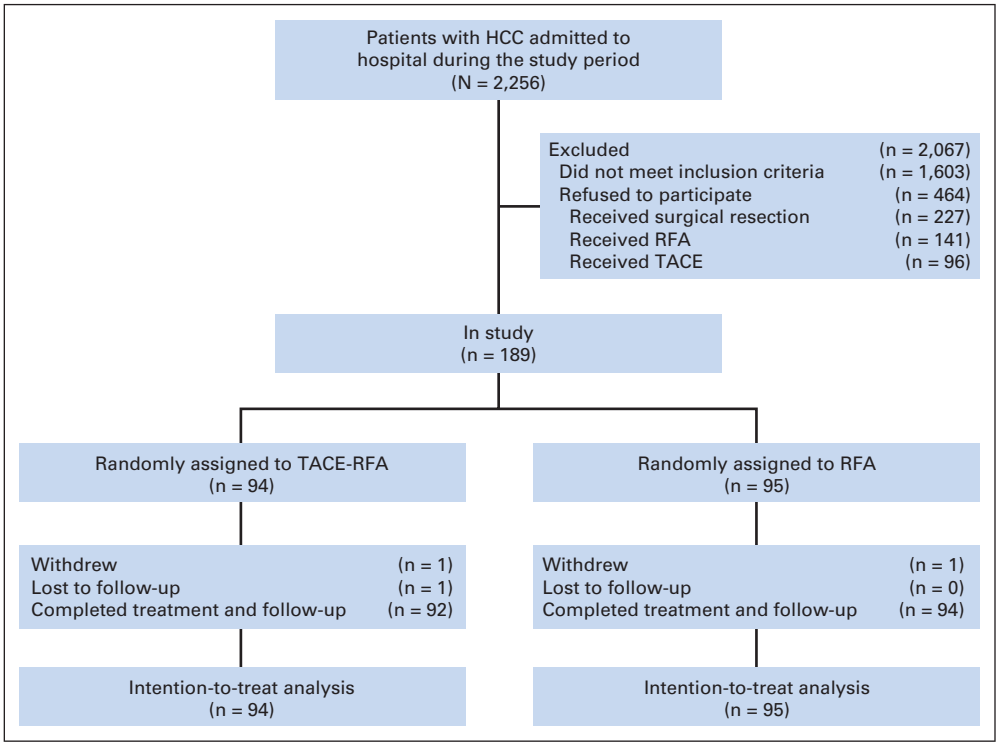

Fig 1. CONSORT diagram of the trial. HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization.

in diameter) through the microcatheter to achieve stasis in the tumor-feeding artery. After embolization, angiography was performed to determine the extent of vascular occlusion and to assess blood flow in other arterial vessels. Patients were observed carefully, and analgesia (morphine or meperidine) was administered if necessary.

RFA was performed by using a commercially available system (RF 2000; Radio-Therapeutics, Mountain View, CA) under real-time ultrasound guidance (EUB-2000; Hitachi Medical Systems, Tokyo, Japan) and a needle electrode with a 15-Ga insulated cannula with 10 hook-shaped expandable electrode tines with a diameter of 3.5 cm at expansion (LeVeen; RadioTherapeutics). Grounding was achieved by attaching two pads to the patient's back. After administration of analgesia (50 to 60 mg of propofol and 0.05 to 0.1 mg of fentanyl) as well as local anesthesia (5 to 15 mL of 1% lidocaine) by an anesthesiologist, a 15-Ga RFA needle was first inserted into the tumor. After the 10 tines of the needle were deployed, the RF generator was activated and initiated with 10 W of power. The power was increased 10 W per minute to 90 W. RFA was applied until either there was a marked increase in impedance or 15 minutes had elapsed. If a marked increase in impedance was not achieved, a second application of RF was given. No more than three applications of RFA were given in a treatment session. For tumors $\leq$ 3.0 cm in greatest dimension, a single ablation was performed. For tumors more than 3.0 cm in greatest dimension, multiple overlapping ablations as described by Chen et al[23] were performed.

For patients with multiple tumors, all lesions were treated in one single session. In the TACE-RFA group, as gelatin sponge remains in the tumor for 2 weeks after chemoembolization,[24] RFA followed TACE within 2 weeks (median, 7 days; range, 3 to 14 days).

Follow-Up and Further Treatment

Four weeks after the first treatment of RFA, a dynamic enhanced computed tomography (CT) was performed to assess the extent of the treated areas. In the TACE-RFA group, the post-treatment CT showed iodized oil accumulated in the treated nodule with a surrounding nonenhancing area treated with RFA. When the nonenhancing area had a diameter greater than the area of accumulated iodized oil, the treatment was considered complete and technically successful.[25] Residual viable tumor tissue was considered to be present if enhancement areas were seen near to the area of accumulated iodized oil on post-treatment CT. An additional session of RFA was given. In the RFA group, when the nonenhancing area had a diameter greater than that of the treated nodule, the treatment was considered complete and technically successful. If enhancement areas were observed, an additional session of RFA was given. When nodule enhancement was still present on CT after the additional session of RFA in the two groups, the treatment was defined as incomplete.[25] For these patients, TACE was recommended.

Thereafter, the patients were followed up once every 3 months for the first 2 years. At each follow-up visit, ultrasound and blood tests including serum liver function tests and α-fetoprotein were carried out. Chest radiography was performed once every 6 months. CT, magnetic resonance imaging, and bone scintigraphy were performed when clinically indicated. The follow-up visits were extended to once every 6 months from 2 to 5 years after treatment and then to once every 12 months after 5 years.

When recurrence was detected, the patients were treated with RFA, TACE, systemic chemotherapy, or conservative treatment, depending on the site of the tumor, the liver function, and the general condition of the patient. For patients who received systemic chemotherapy, cisplatin, interferon, doxorubicin, and fluorouracil in combination, as described by Yeo et al,[26] was used. Complications were reported using the National Cancer Institute Common Toxicity Criteria grading version 4.0.[27] This study was censored on December 31, 2011.

Sample Size Estimation

At the beginning of the study, the 5-year overall survival rate after treatment was used as the outcome measure to estimate the sample size. This was based on the published data[16,28-31] that the 5-year survival rate was 50% with TACE-RFA and 25% with RFA alone. A sample size of at least 60 patients was required in each of the groups to give a 80% power for a two-sided significant difference reaching a *P* value of .05. In accordance with the trial policy, the

Table 1. Baseline Patient Characteristics

Characteristic	TACE-RFA (n = 94)	RFA (n = 95)	*P*
Age, years			.247
Mean	53.3	55.3	
SD	11.0	13.3	
Sex			.488
Male	75	71	
Female	19	24	
HBsAg			.644
Positive	85	83	
Negative	9	12	
HCV-Ab			.999
Positive	6	6	
Negative	88	89	
AFP, ng/mL			.730
< 200	61	64	
200-400	9	11	
> 400	24	20	
No. of tumors			.792
1	62	67	
2	21	18	
3	11	10	
Size of main tumor, cm			.531
Mean	3.47	3.39	
SD	1.44	1.35	
Size range of tumor, cm			.771
$\leq$ 3	43	46	
> 3	51	49	
GGT, μ/L			.504
Mean	65.7	68.4	
SD	30.3	28.9	
AST, μ/L			.424
Mean	44.0	42.0	
SD	29.3	24.1	
ALT, μ/L			.620
Mean	35.0	33.6	
SD	10.3	9.7	
TBIL, μmol/L			.524
Mean	13.5	13.8	
SD	2.9	3.3	
PLT, $10E^9$/L			.346
Mean	121	118	
SD	65	64	
Prothrombin activity, %			.826
Mean	77.6	76.8	
SD	9.4	10.1	
ALB, g/L			.838
< 35	13	15	
$\geq$ 35	81	80	
ICGR15, %			.975
< 10	72	74	
10-19.9	18	17	
$\geq$ 20	4	4	
Child-Pugh class			.999
A	90	90	
B	4	5	
Ascites			.999
Yes	6	7	
No	88	88	

Abbreviations: AFP, α-fetoprotein; ALB, albumin; GGT, γ-glutamyltransferase; HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; ICGR15, indocyanine green retention rate in 15 minutes; PLT, platelet count; RFA, radiofrequency ablation; SD, standard deviation; TACE, transcatheter arterial chemoembolization; TBIL, total bilirubin.

Table 2. Causes of Death

Cause of Death	TACE-RFA (n = 94)	RFA (n = 95)	*P*
Tumor progression	21	42	.024
Liver failure with stable tumor	9	4	.252
Variceal bleeding	2	1	.999
Other	1	1	.999

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

study was reviewed annually. In the interim analysis in October 2007, the efficacy of RFA was better than our original estimation. Thus the 5-year survival rate of 50% with TACE-RFA and 30% with RFA alone were used for sample size estimation. Then, a sample size of at least 92 patients was required in each group. We also estimated and added 5% of patients who might be lost to follow-up.

Statistical Analysis

The statistical analyses were performed using the SPSS 10.0 statistical software (SPSS, Chicago, IL). Comparisons between the two groups were done using *t* test for continuous data and the χ^2 test for categorical data. The survival curves were constructed by the Kaplan-Meier method and compared by Cox proportional hazards models, stratified by tumor size and tumor number. The relative prognostic significance of the variables in predicting overall survival rates was assessed using multivariate Cox proportional hazards regression analysis. Results were given as mean ± standard deviation. All statistical tests were two-sided, and a significant difference was considered when $P < .05$.

RESULTS

Enrollment

From October 2006 to June 2009, of 2,256 patients with HCC who were treated in our hospital, 1,603 did not meet the inclusion criteria of this study. The reasons for exclusion were portal vein thrombosis (n = 256), extrahepatic metastasis (n = 156), tumor size ≥ 7 cm or number more than three (n = 891), severe liver dysfunction (n = 138), and significant coagulopathy (n = 162). Of the remaining patients, 464 patients refused to participate in this study, and they received surgical resection (n = 227), RFA (n = 141), and TACE (n = 96). Finally, 189 eligible patients consented to be randomly assigned to the TACE-RFA group (n = 94) and the RFA group (n = 95; Fig 1). Two patients (one in each group) withdrew from the trial after randomization. These two patients received partial hepatectomy and were analyzed together in their originally assigned groups using the intention-to-treat principle. One patient in the TACE-RFA group was lost to follow-up. Table 1 lists the baseline characteristics of the patients. There were no significant differences between the two groups of patients for any of the variables.

Technical Success of RFA, Recurrence, and Treatment

Technical success of RFA was achieved in 91 of 94 patients in the TACE-RFA group. For the three patients with residual viable tumor after RFA, technical success was achieved after an additional session of RFA. For the RFA group, a single RFA session was required in 88 patients, and two RFA sessions were required in seven patients. Technical success was achieved in 92 patients. In three patients, even after two sessions of RFA, viable tumor was still present, and these patients were defined as failure for the RFA treatment. These three patients underwent TACE.

At a median follow-up of 36 months, 35.1% of patients (33 of 94, two local recurrences and 31 distant recurrences) and 54.7% (52 of 95, three local recurrences and 49 distant recurrences) had developed intrahepatic recurrence in the TACE-RFA group and RFA group, respectively ($P = .116$). In the TACE-RFA group, 22 recurrences were treated with RFA. Except for one patient with recurrence who received systemic chemotherapy, the remaining patients received TACE. In the RFA group, 20 patients with recurrences received RFA, 24 received TACE, five received systemic chemotherapy, and three received conservative treatment (Appendix Table A1, online only).The median number of TACE sessions was two (range, one to eight sessions) for the TACE-RFA group and two (range, one to eight sessions) for the RFA group.

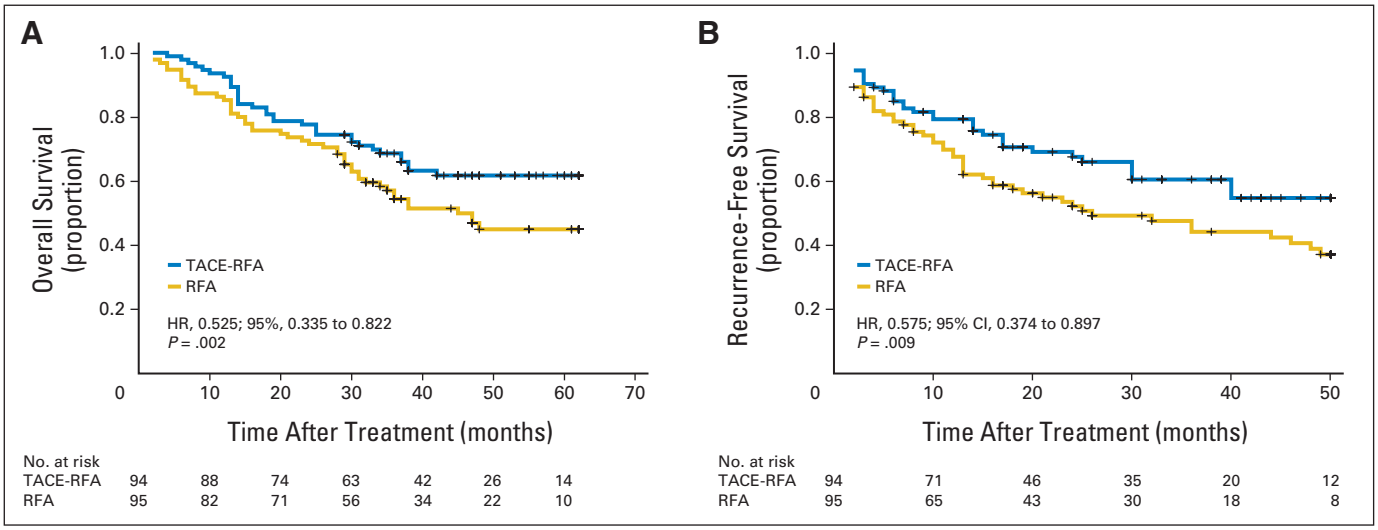

Fig 2. Overall (A) and recurrence-free (B) survival curves for the transcatheter arterial chemoembolization (TACE) plus radiofrequency ablation (RFA) and RFA groups. HR, hazard ratio.

Table 3. Overall Survival and Recurrence-Free Survival for Patients

Survival Outcomes	Survival Analysis									
	Overall Survival					Recurrence-Free Survival				
	TACE-RFA	RFA	*P*	HR	95% CI	TACE-RFA	RFA	*P*	HR	95% CI
No. of patients	94	95	.002	0.525	0.335 to 0.822	94	95	.009	0.575	0.374 to 0.897
1-year survival										
%	92.6	85.3				79.4	66.7			
95% CI	88.9 to 96.4	80.3 to 90.3				73.6 to 85.2	60.0 to 73.4			
3-year survival										
%	66.6	59.0				60.6	44.2			
95% CI	60.0 to 73.4	52.0 to 66.0				53.6 to 67.6	37.1 to 51.3			
4-year survival										
%	61.8	45.0				54.8	38.9			
95% CI	54.9 to 68.7	37.9 to 52.1				47.7 to 61.9	32.0 to 45.8			

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

Survivals

At the time of censor, 34 patients in the TACE-RFA group and 48 patients in the RFA group had died. The median follow-up times for the patients who were still alive for the TACE-RFA group and the RFA group were 47.5 ± 11.3 months (range, 29 to 62 months) and 47.0 ± 12.9 months (range, 28 to 62 months), respectively. The causes of death are shown in Table 2.

Overall survival. The 1-, 3-, and 4-year overall survivals for the TACE-RFA group and the RFA group were 92.6%, 66.6%, and 61.8% and 85.3%, 59%, and 45.0%, respectively (Fig 2A, Table 3). Using the Cox proportional hazards models and stratified by tumor size and tumor number, the TACE-RFA group showed better overall survival than the RFA group (hazard ratio [HR], 0.525; 95% CI, 0.335 to 0.822; $P = .002$; Appendix Table A2, online only).

Recurrence-free survival. The 1-, 3-, and 4-year recurrence-free survivals for the TACE-RFA group and the RFA group were 79.4%, 60.6%, and 54.8% and 66.7%, 44.2%, and 38.9%, respectively (Fig 2B, Table 3). Using the Cox proportional hazards models and stratified by tumor size and tumor number, the TACE-RFA group showed better recurrence-free survival than the RFA group (HR, 0.575; 95% CI, 0.374 to 0.897; $P = .009$; Appendix Table A2).

Multivariate Cox regression analyses showed treatment allocation (HR = 1.876; 95% CI, 1.194 to 2.948; $P = .006$), tumor size (HR = 1.738; 95% CI, 1.100 to 2.746; $P = .018$), and tumor number (HR = 2.492; 95% CI, 1.594 to 3.897; $P < .001$) to be significant prognostic factors of overall survival. Tumor number (HR = 1.973; 95% CI, 1.268 to 3.070; $P = .003$) and treatment allocation (HR = 1.674; 95% CI, 1.083 to 2.568; $P = .020$) were significant prognostic factors of recurrence-free survival.

Complications

There were no treatment-related deaths. Common complications in the two groups of patients were fever, pain, vomiting, ascites, pleural effusion, and skin burn. Other more significant complications included bile duct stenosis and gastric hemorrhage in the TACE-RFA group and abdominal infection and small intestinal obstruction in the RFA group (Table 4).

DISCUSSION

RFA has been widely used for the treatment of small HCCs (≤ 3 cm) with encouraging results. However, the limited volume of coagulative necrosis obtained with RF systems and the occasionally irregular burn shape caused by the heat-sink effect of large vessels in the proximity of

Table 4. Complications After Treatment

Complication	TACE-RFA (n = 94)		RFA (n = 95)		*P*
	No.	%	No.	%	
Pain	57	60.6	51	53.7	.639
Grade 1	44	46.8	42	44.2	
Grade 2	11	11.7	8	8.4	
Grade 3	2	2.1	1	1.1	
Fever (temperature > 38.5°C)	33	35.1	26	27.4	.457
Grade 1	30	31.9	25	26.3	
Grade 2	3	3.2	1	1.1	
Vomiting	40	42.6	29	30.5	.260
Grade 1	36	38.3	28	29.4	
Grade 2	4	4.3	1	1.1	
Ascites	5	5.3	4	4.2	.999
Grade 1	4	4.2	4	4.2	
Grade 2	1	1.1	0	0	
Pleural effusion	3	3.2	2	2.2	.999
Grade 1	2	2.1	1	1.1	
Grade 2	1	1.1	1	1.1	
Skin burn	1	1.1	1	1.1	.999
Grade 1	1	1.1	1	1.1	
Bile duct stenosis	1	1.1	0	0	.999
Grade 2	1	1.1	0	0	
Gastric hemorrhage	1	1.1	0	0	.999
Grade 1	1	1.1	0	0	
Abdominal infection	0	0	1	1.1	.999
Grade 3	0	0	1	1.1	
Small intestinal obstruction	0	0	1	1.1	.999
Grade 2	0	0	1	1.1	

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

the ablated area prevented the widespread use of RFA in the treatment of hepatic tumors. To obtain a large coagulation area, various techniques have been advocated,[16,20,30-35] and TACE-RFA has been reported to be effective and safe in the treatment of HCC.[20,30-32]

This study showed TACE-RFA to give better efficacy than RFA for HCCs ≤ 7 cm. To perform TACE before RFA is beneficial for several reasons. First, occlusion of hepatic arterial flow by embolization reduces the cooling effect of hepatic blood flow on thermal coagulation. Furthermore, iodized oil and gelatin sponge particles used in TACE fill the peripheral portal vein around the tumor by going through multiple arterioportal communications,[36,37] thus reducing the portal venous flow. As a consequence, RFA can induce a bigger area of necrosis. Morimoto et al[20] reported that TACE before RFA expanded the short axis of the ablated area and resulted in a more spherical ablated area. They postulated that a spherical ablated area was more effective than a nonspherical ablated area in ensuring local tumor control because a spherical ablated area was more likely to completely cover the target tumor. Furthermore, to enlarge the ablation zone improves the prognosis for HCC after RFA. The authors' previous study showed that even at an early T stage when HCC was solitary and small, micrometastases were common and were closely related to the distance from the primary tumor.[38] Several studies also showed that recurrent tumors commonly occurred in the liver remnant near the RFA ablated region.[39,40] Therefore, an enlarged ablation zone improves the chance of total ablation of micrometastasis, and reduces the chance of recurrence. Second, the effect of chemotherapeutic anticancer agents on cancer cells enhances the effect of hyperthermia.[41] Third, TACE before RFA controls micro-lesions, which contribute to recurrence after treatment. Moreover, disruption of intratumoral septa, which usually happens after TACE,[42] facilitates heat distribution within the tumor, and intratumoral septa and fibrosis are considered to hamper heat diffusion within the tumor.

There are some limitations of this study. First, the number of patients in this study is relatively small. The majority of patients had one or two lesions, and almost half of the patients had a tumor ≤ 3 cm. Second, this is a single-center experience, and the results may not be generalizable to patients with HCC in other countries. Third, this is not a double-blind study. However, the radiologists who evaluated the tumor response and the statistician who analyzed the data were blinded to the treatment the patients received.

The future standard of care for HCC treatable with RFA should shift toward the combination treatment. The study also provides evidence that altering the tumor microenvironment and supporting vasculature may help improve the efficacy of locoregional therapy in HCC. Logical further studies will be to investigate the potential benefit offered by complementary treatment modalities, such as targeted agents in combination with TACE-RFA.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Zhen-Wei Peng, Min-Shan Chen, Wan Yee Lau
Financial support: Min-Shan Chen
Administrative support: Min-Shan Chen
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Data analysis and interpretation: Zhen-Wei Peng, Yao-Jun Zhang, Min-Shan Chen
Manuscript writing: All authors
Final approval of manuscript: All authors

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Appendix

Table A1. Recurrence and Treatment

Variable	TACE-RFA (n = 33)	RFA (n = 52)	*P*
RFA	22	20	.183
TACE	10	24	.401
Systemic chemotherapy	1	5	.405
Conservative treatment	0	3	.289

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

Table A2. Comparisons of Overall Survival and Recurrence-Free Survival Between TACE-RFA Group and RFA Group by Using Cox Proportional Hazards Models, Stratified by Tumor Size (≤ 3 *v* > 3 cm) and Tumor Number (single *v* multiple)

	Overall Survival			Recurrence-Free Survival		
Variable	*P*	HR	95% CI	*P*	HR	95% CI
Treatment allocation, TACE-RFA *v* RFA	.002	0.525	0.335 to 0.822	.009	0.579	0.374 to 0.897
Tumor size, ≤ 3 *v* > 3 cm	.019	0.580	0.368 to 0.914	.226	0.761	0.489 to 1.184
Tumor number, single *v* multiple	< .001	0.403	0.258 to 0.629	.008	0.542	0.344 to 0.853

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

