

Radiofrequency ablation or microwave ablation combined with transcatheter arterial chemoembolization in treatment of hepatocellular carcinoma by comparing with radiofrequency ablation alone

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Objective: To compare radiofrequency ablation (RFA) or microwave ablation (MWA) and transcatheter arterial chemoembolization (TACE) with RFA or MWA monotherapy in hepatocellular carcinoma (HCC).

Methods: A prospective, randomized, controlled trial was conducted on 94 patients with HCC ≤ 7 cm at a single tertiary referral center from June 2008 to June 2010 at the Department of Hepatobiliary Surgery, the Second Affiliated Hospital of Southeast University. The patients were randomly assigned into the TACE-RFA or TACE-MWA (combined treatment group) and the RFA-alone or MWA-alone groups (control group). The primary end point was overall survival. The secondary end point was recurrence-free survival, and the tertiary end point was adverse effects.

Results: Until the time of censor, 17 patients in the TACE-RFA or TACE-MWA group had died. The median follow-up time of the patients who were still alive for the TACE-RFA or TACE-MWA group was 47.5 ± 11.3 months (range, 29 to 62 months). The 1-, 3- and 5-year overall survival for the TACE-RFA or TACE-MWA group was 93.6%, 68.1% and 61.7%, respectively. Twenty-five patients in the RFA or MWA group had died. The median follow-up time of the patients who were still alive for the RFA or MWA group was 47.0 ± 12.9 months (range, 28 to 62 months). The 1-, 3- and 5-year overall survival for the RFA or MWA group was 85.1%, 59.6% and 44.7%, respectively. The patients in the TACE-RFA or TACE-MWA group had better overall survival than the RFA or MWA group [hazard ratio (HR), 0.526; 95% confidence interval (95% CI), 0.334-0.823; $P=0.002$], and showed better recurrence-free survival than the RFA or MWA group (HR, 0.582; 95% CI, 0.368-0.895; $P=0.008$).

Conclusions: RFA or MWA combined with TACE in the treatment of HCC ≤ 7 cm was superior to RFA or MWA alone in improving survival by reducing arterial and portal blood flow due to TACE with iodized oil before RFA.

Keywords: Radiofrequency ablation (RFA); transcatheter arterial chemoembolization (TACE); hepatocellular carcinoma (HCC)



Submitted Sep 25, 2013. Accepted for publication Feb 08, 2014.

doi: 10.3978/j.issn.1000-9604.2014.02.09

Scan to your mobile device or view this article at: <http://www.thecjcr.org/article/view/3350/4183>

Introduction

Hepatocellular carcinoma (HCC, also called malignant hepatoma) is one of the most common and severe malignancies in China. HCC ranks fifth for men and eighth

for women, and accounts for >660,000 new cases annually worldwide (1-3). Most cases of HCC are secondary to either a viral hepatitis infection (hepatitis B or C) or cirrhosis (alcoholism being the most common cause of hepatic cirrhosis). Since radiation and chemotherapy are

not effective for HCC, surgical resection provides the best potentially curative option. Unfortunately, due to poor baseline liver function, over tumor burden, or hepatic vessel invasion of HCC patients, it is barely possible to perform surgical resection. During the past decade, locoregional treatments have been developed rapidly, such as transcatheter arterial chemoembolization (TACE), radiofrequency ablation (RFA), and microwave ablation (MWA). RFA or MWA as a thermal *in situ* destruction technique has been proved to be a safe and effective treatment. It has been accepted as one of the best treatment options for small HCC (4,5). TACE as a palliative therapy has become one of the most widely performed treatments for unresectable HCC (6,7). They all 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. However, the complete necrosis rate of tumors after TACE only reaches 10-20%, and the 1-, 3- and 5-year overall survival rates range from 49.0-71.9%, 23.0-62.5% and 9-17% in most studies (8-13). TACE is the most commonly used therapy for intermediate-stage HCC (5,6). RFA or MWA has emerged as an accepted therapy for small HCC (14). However, it is difficult for RFA or MWA to achieve complete ablation in the treatment of relatively large HCC.

Therefore, either TACE or RFA/MWA has its own limitations, in particular, neither can result in adequate control of medium or large HCC (5,15-17). In recent years, the combination of interventional therapies has been widely performed for treatment of HCC. TACE decreases blood flow to the tumor, making subsequent RFA or MWA more effective, as there is less heat loss by convection (18). Several studies have demonstrated the synergistic cytotoxic effects of TACE with RFA for HCC (19). Whether RFA or MWA combined with TACE or RFA monotherapy is the better treatment choice for HCC has long been debated. This is such a study coming from a single tertiary referral center conducted on patients with HCC ≤ 7 cm.

Materials and methods

Patients

The study was a prospective, randomized, controlled trial conducted at the Department of Hepatobiliary Surgery, the Second Affiliated Hospital of Southeast University, Nanjing,

China. From June 2008 to June 2010, patients with HCC who met the entry criteria and agreed to participate were included in the study. HCC was diagnosed, staged, and treated according to a previously reported schedule (20).

The eligibility criteria were as follows: (I) age 18 to 70 years; (II) patient has signed informed consent; (III) a solitary HCC ≤ 7.0 cm in diameter, or multiple HCC ≤ 3 lesions, each ≤ 3.0 cm in diameter; (IV) no evidence of extrahepatic disease; (V) lesions being visible on ultrasound (US) and with an acceptable/safe path between the lesion and the skin as shown on US; (VI) no history of encephalopathy, ascites refractory to diuretics or variceal bleeding; (VII) no previous treatment of HCC except liver resection; (VIII) surgical operation failure and postoperative recurrence; and (VIII) Child-Pugh class A or B cirrhosis.

The exclusion criteria were: (I) patient compliance is poor; (II) severe coagulation disorders [prothrombin activity $< 40\%$ or a platelet count (PLT) of $< 40,000/\mu\text{L}$]; (III) the blood supply of tumor lesions is absolutely poor or arterial-venous shunt so that TACE cannot be performed; (VI) contraindications to carboplatin, epirubicin, mitomycin, or lipiodol; or (V) history of cardiac disease.

Patients who met these criteria and gave written informed consent entered the study, which was approved by the Ethic Committee of the hospital. It conformed to the standards of the Declaration of Helsinki.

Patients were randomly assigned into the TACE-RFA or TACE-MWA group and the RFA-alone or MWA-alone group. Randomization was done using a computer-generated algorithm with numbers by a nurse who was not part of this research team. Double-blind and double-dummy techniques were discarded because the nature of the treatment and their possible adverse effects. The interval between randomization and the treatment was less than two weeks. Treatment was discontinued if any exclusion criteria developed or at the patient's request.

Treatment procedure and follow up

All TACE and RFA/MWA were performed by the same team of doctors. For combined RFA or MWA with TACE (combined treatment group), first TACE was performed according to the following protocol: arterial portography was performed for diagnosis of the patency of the portal vein; 25-30 mL of 65% iopamidol was injected via a 4.0-F preshaped catheter (Selecon-PA Catheter); all patients underwent a distal super-selective catheterization of the hepatic arteries using a coaxial technique and microcatheters

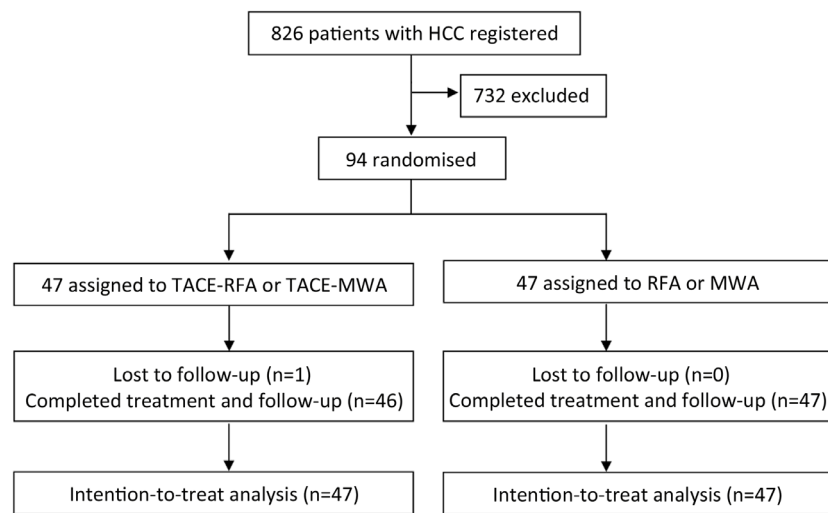


Figure 1 Trial profile. HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; MWA, microwave ablation; TACE, transcatheter arterial chemoembolization.

(2.9 F; Terumo Corporation, Tokyo, Japan). Then the same three chemotherapeutic agents were administered, carboplatin 300 mg (Bristol-Myers Squibb, New York, NY, USA), epirubicin hydrochloride 50 mg (Pharmorubicin; Pfizer, Wuxi, China), and mitomycin 8 mg (Zhejiang Hisun Pharmaceutical, Taizhou, China).

RFA or MWA was performed a week after TACE by using a commercially available system (RF 2000; Radio-Therapeutics, Mountain View, CA, USA). RFA was applied until either there was a marked increase in impedance or 15 min had elapsed. If the marked increases in impedance were not obtained, the second treatment was carried out within 15 min. No more than three applications of RFA or MWA were given in a treatment session. Tumors less than 3 cm in their greatest diameter can be ablated with single ablation. Tumors more than 3 cm in their greatest diameter should be treated with multiple overlapping ablations (21). In the TACE-RFA group, because gelatin sponge remains in the tumor for 2 weeks after chemoembolization, 24 RFA or MWA treatments followed TACE within 2 weeks (median, 7 d; range, 3 to 14 d).

Treatment response was assessed by contrast-enhanced spiral computed tomography (CT). Thereafter, the patients were followed up once every 3 months for the first 2 years, once every 6 months from 2 to 5 years after treatment and then to once every 12 months after 5 years. All CT scans were reviewed by two radiologists who were unaware of patient clinical data or treatment assignment. At each follow-up visit, US and blood tests including serum liver

function tests and α -fetoprotein (AFP) were carried out. No patient received antiviral treatment during the trial. Chest radiography, ultrasonography, serum biochemistry, and clinical examination were performed once every 6 months. The treatment course and follow-up are shown in *Figure 1*.

Statistical analysis

The statistical analyses were performed using the SPSS 13.0 software (SPSS, Chicago, IL, USA). Differences in $\bar{x} \pm s$ were analyzed by student's paired *t*-test. Differences in the median were analyzed by χ^2 test. The survival curves according to the Kaplan-Meier method were compared by the Mantel-Cox test, stratified by tumor size and tumor number. Multivariate Cox's proportional hazard regression model was used to analyze the relative prognostic significance of the variables in predicting overall survival rates. $P < 0.05$ was considered statistically significant.

Results

Enrollment

From June 2008 to June 2010, 94 (11.4%) of 826 patients diagnosed as HCC met the entry criteria and agreed to take part in the study, 622 patients did not participate, and 110 patients did not meet the inclusion criteria of the study.

Of 94 patients who were eligible and consented to be randomly assigned, 47 patients were assigned to the RFA-alone or MWA-alone group, and 47 to the TACE-RFA group

Table 1 Baseline characteristics of the patients

Characteristics	TACE-RFA or TACE-MWA (n=47)	RFA or MWA (n=47)	P
Age ($\bar{x}\pm s$), year	56.8±5.6	55.9±5.4	0.357
Male/female	37/10	34/13	0.728
HbsAg			0.685
Positive	42	41	
Negative	5	6	
HCV-Ab			0.822
Positive	4	5	
Negative	43	42	
AFP, ng/mL			0.725
<200	32	32	
200-400	5	6	
>400	10	9	
No. of tumors			0.784
1	36	37	
2	7	6	
3	4	4	
Size of main tumor ($\bar{x}\pm s$), cm	3.45±1.45	3.38±1.33	0.654
Size range of tumor, cm			0.511
≤3	22	20	
>3	25	27	
γ-glutamyltransferase ($\bar{x}\pm s$), μ/L	64.8±30.2	67.2±31.1	0.485
AST ($\bar{x}\pm s$), μ/L	44.3±27.7	43.2±25.4	0.596
ALT ($\bar{x}\pm s$), μ/L	34.9±11.2	33.4±9.9	0.412
TBIL ($\bar{x}\pm s$), μmol/L	13.6±3.1	14.0±3.2	0.552
PLT ($\bar{x}\pm s$), 10 ⁹ /L	122±64	116±65	0.358
Prothrombin activity ($\bar{x}\pm s$), %	77.7±10.2	76.9±10.2	0.758
ALB, g/L			0.965
<35	7	8	
≥35	40	39	
ICGR15, %			0.859
<10	39	40	
10-19.9	6	5	
≥20	2	2	
Child-Pugh class			0.922
A	45	44	
B	2	3	

Table 1 (continued)

Table 1 (continued)

Characteristics	TACE-RFA or TACE-MWA (n=47)	RFA or MWA (n=47)	P
Ascites			0.958
Yes	3	4	
No	44	43	

HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; AFP, α-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin; PLT, platelet count; ALB, albumin; ICGR15, indocyanine green retention rate in 15 min.

Table 2 Causes of death during follow-up

Cause of death	TACE-RFA or TACE-MWA (n=47)	RFA or MWA (n=47)	P
Tumor progression	10	21	0.022
Liver failure with stable tumor	5	2	0.231
Variceal bleeding	1	1	0.999
Other	1	1	0.999

TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; MWA, microwave ablation.

or TACE-MWA group (Figure 1). Table 1 lists the baseline characteristics of the patients. There were no significant differences among the two groups for any of the variables.

Survivals

Until the time of censor, 17 patients in the TACE-RFA and TACE-MWA group had died. The median follow-up time of the patients who were still alive for the TACE-RFA or TACE-MWA group was 47.5±11.3 months (range, 29 to 62 months) (Table 2). The 1-, 3- and 5-year overall survival for the TACE-RFA or TACE-MWA group was 93.6%, 68.1% and 61.7%, respectively (Table 3). Twenty-five patients in the RFA or MWA group had died. The median follow-up time of the patients who were still alive for the RFA or MWA group was 47.0±12.9 months (range, 28 to 62 months) (Table 2). The 1-, 3-, and 5-year overall survival for the RFA or MWA group were 85.1%, 59.6% and 44.7%, respectively (Table 3).

Using the Cox proportional hazards regression model, analysis was performed for each group. The patients in

Table 3 Overall survival of patients

Survival outcomes	Overall survival				
	TACE-RFA or TACE-MWA	RFA or MWA	P	HR	95% CI
No. of patients	47	47	0.002	0.526	0.334-0.823
1-year survival (95% CI), %	93.6 (88.3-96.9)	85.1 (80.1-90.1)			
3-year survival (95% CI), %	68.1 (59.5-74.0)	59.6 (51.5-66.5)			
5-year survival (95% CI), %	61.7 (54.8-68.8)	44.7 (37.8-52.2)			

TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; MWA, microwave ablation; HR, hazard ratio; 95% CI, 95% confidence interval.

Table 4 Recurrence-free survival for patients

Survival outcomes	Recurrence-free survival				
	TACE-RFA or TACE-MWA	RFA or MWA	P	HR	95% CI
No. of patients	47	47	0.008	0.582	0.368-0.895
1-year survival (95% CI), %	80.9 (74.5-85.5)	66.0 (60.0-73.8)			
3-year survival (95% CI), %	66.0 (60.0-73.8)	44.7 (37.0-52.0)			
5-year survival (95% CI), %	55.3 (47.2-62.2)	38.3 (32.0-46.0)			

TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; MWA, microwave ablation; HR, hazard ratio; 95% CI, 95% confidence interval.

the TACE-RFA or TACE-MWA group had better overall survival than the RFA or MWA group [hazard ratio (HR), 0.526; 95% confidence interval (95% CI), 0.334-0.823; P=0.002] (Table 3), and showed better recurrence-free survival than the RFA or MWA group (HR, 0.582; 95% CI, 0.368-0.895; P=0.008) (Table 4).

Complications

There were no treatment-related deaths, and no serious complications were observed after TACE and RFA/MWA treatment. Common complications of TACE and RFA/MWA were fever, pain, vomiting, ascites, pleural effusion, and skin burn. Other complications included bile duct stenosis and gastric hemorrhage in the TACE-RFA or TACE-MWA group, and abdominal infection and small intestinal obstruction in the RFA or MWA group (Table 5).

Discussion

RFA is usually performed to treat small (≤ 3 cm) HCC nodules (22). However, the limited coagulative necrosis induced by RFA or MWA alone and the occasionally irregular burn shape caused by the heat-sink effect of large

vessels in the proximity of the ablated area prevented the widespread use of RFA for the treatment of intermediate-to large-sized hepatic tumors. To obtain a large coagulation area, various techniques have been advocated (22-27). We conducted a randomized controlled trial to evaluate the advantages of combining RFA or MWA with TACE for treating patients with HCC. This study showed that TACE-RFA or TACE-MWA gives better efficacy than RFA or MWA alone for HCC ≤ 7 cm. TACE before RFA/MWA is beneficial because it enables better ablation than that achieved with RFA or MWA alone and possibly facilitates the effective treatment of patients with HCC. TACE can block hepatic arterial blood flow and attenuate the cooling effect of tumoral arterial blood flow (8,19). Furthermore, iodized oil and gelatin sponge particles used in TACE can increase RFA or MWA-induced coagulation necrosis by going through multiple arteriportal communications and effects are added in terms of ablation time, maximum output, and portal angiography by TACE with iodized oil. Several studies also revealed that recurrent tumors commonly occurred in the liver remnant at a segment distant from the resection margin or at multiple liver segments (28,29). Therefore, an enlarged ablation zone improves the chance of total ablation of micrometastasis,

Table 5 Complications after treatment

Complication	TACE-RFA or TACE-MWA (n=47)	RFA or MWA (n=47)	P
Pain	28	26	0.642
Grade 1	22	21	
Grade 2	5	4	
Grade 3	1	1	
Fever (>38.5 °C)	16	13	0.445
Grade 1	15	12	
Grade 2	1	1	
Vomiting	20	15	0.225
Grade 1	18	14	
Grade 2	2	1	
Ascites	3	2	0.587
Grade 1	2	1	
Grade 2	1	0	
Pleural effusion	2	2	0.999
Grade 1	1	1	
Grade 2	1	1	
Skin burn	1	1	0.999
Grade 1	1	1	
Bile duct stenosis	1	0	0.999
Grade 2	1	0	
Gastric hemorrhage	1	0	0.999
Grade 1	1	0	
Abdominal infection	1	0	0.999
Grade 3	1	0	
Small intestinal obstruction	1	0	0.999
Grade 2	1	0	

TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; MWA, microwave ablation.

reduces the risk of tumor recurrence for patients with HCC, enhances the effect of hyperthermia and controls microlesions (30).

In conclusion, RFA or MWA combined with TACE in the treatment of HCC ≤ 7 cm was superior to RFA or MWA alone in improving survival by reducing arterial and portal blood flow due to TACE with iodized oil before RFA.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Yi Y, Zhang Y, Wei Q, Zhao L, Han J, Song Y, Ding Y, Lu G, Liu J, Ding H, Dai F, Tang X. Radiofrequency ablation or microwave ablation combined with transcatheter arterial chemoembolization in treatment of hepatocellular carcinoma by comparing with radiofrequency ablation alone. *Chin J Cancer Res* 2014;26(1):112-118. doi: 10.3978/j.issn.1000-9604.2014.02.09