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In the April 9, 2008, issue of JAMA, an article entitled “Chemoembolization Combined With Radiofrequency Ablation for Patients With Hepatocellular Carcinoma Larger Than 3 cm: A Randomized Controlled Trial” was published by Dr Cheng and colleagues.1 We subsequently received information that raised concerns about the integrity of the data and the veracity of the report. We conducted an extensive internal investigation into these concerns, contacted the primary author of the study, and also notified Shandong University, the authors’ institution, expressing our concerns about the conduct of the trial and the integrity of the data. Based on the responses we received from the authors, we continued to have concerns about the validity and integrity of the study, and therefore requested a formal investigation by the authors’ institution.

On March 23, 2009, we received a report from Yun Zhang, MD, PhD, Vice President, Shandong University, and Dean, Shandong University School of Medicine. Dean Yun Zhang indicated that “it took a long time to make a complete investigation” because the university “organized a group of experts in the field of hepatology to investigate the article” by Cheng et al and these experts “thoroughly investigated the protocol, ethics, medical records, methods, statistics, results, and conclusions relevant to this article.” In addition, this investigative group carefully studied the comments of the JAMA editors and reviewers and previous versions of the manuscript reporting the results of this study.

The report by the dean indicates the following:

“Based on these investigations, we have drawn the following conclusions:

1. The protocol and ethics of this study were not submitted to the Academic Committee of Shandong University Qilu Hospital for approval. Dr Cheng wrote and submitted this manuscript during his postdoctoral training in Sweden without informing our institution.

2. This study was not a well designed, randomized and controlled clinical trial despite the fact that chemoembolization and radiofrequency ablation for patients with hepatocellular carcinoma have been performed in Shandong University Qilu Hospital for many years. Therefore, conclusions drawn from this study are not valid.

3. Because of these unscientific behaviors, we suggest that the article by Dr Cheng should be withdrawn from JAMA.

We apologize for any negative impacts on JAMA caused by publication of this paper. We have submitted a report on this serious issue to the Academic Committee of Shandong University and will keep you informed of further decisions on Cheng’s mistakes from our university.”

Accordingly, based on this report, we hereby retract this article from JAMA and from the medical literature. We appreciate that readers of JAMA brought their concerns about this article to our attention and their patience in allowing us to investigate, and we are grateful to the dean at Shandong University School of Medicine for the thorough and detailed investigation and professional response to our concerns. The cooperation and professional actions of all involved in this inquiry allowed for a complete investigation. This is an example of how maintaining scientific integrity for published articles requires a team effort by readers, journal editors, and the system of academic oversight.

Financial Disclosures: None reported.

REFERENCE


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Chemoembolization Combined With Radiofrequency Ablation for Patients With Hepatocellular Carcinoma Larger Than 3 cm: A Randomized Controlled Trial

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THE INCIDENCE OF HEPATOCELLULAR carcinoma is increasing worldwide.1 Although surveillance by ultrasonography and α-fetoprotein level can be used for early detection of small hepatocellular carcinoma tumors,2 most hepatocellular carcinomas are diagnosed at intermediate or advanced stages, and only 30% of patients benefit from curative therapies such as resection, liver transplantation, or percutaneous ablation.3,4 Until now, no standard therapy has been established for treatment of hepatocellular carcinoma.3-10

Transcatheter arterial chemoembolization (TACE) slows tumor progression and improves survival by combining the effect of targeted chemotherapy with that of ischemic necrosis induced by arterial embolization.6,7,10 TACE has become the treatment of choice for multinodular hepatocellular carcinoma.8 Radiofrequency thermal ablation (RFA) is an emerging technology that has been proposed as an alternative to conventional percutaneous ethanol injection5,8,9 and as adjuvant therapy during the wait time for liver transplantation.11 Moreover, RFA is an appropriate treatment method for unihodular hepatocellular carcinoma12 and appears to be an effective and safe treatment method for medium and large hepatocellular carcinomas.12

For editorial comment see p 1716.

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However, both TACE and RFA have some well-known limitations. In particular, neither results in adequate control of hepatocellular carcinoma tumors larger than 3 cm. Consequently, multimodal treatment is an appealing alternative, especially for patients with large hepatocellular carcinoma.

Because blood flow promotes heat loss, and heat loss may reduce the effectiveness of RFA, a possible way to increase the ablation size of RFA thermal lesions would be to reduce or eliminate the heat loss that is mediated by tissue perfusion. Blood flow to hepatocellular carcinoma lesions can be substantially reduced by the arterial embolization effect of TACE treatment. Moreover, TACE has a strong antitumor effect on hepatocellular carcinoma lesions.

Therefore, we hypothesized that if TACE were performed before RFA treatment (TACE-RFA), the ablation volume of coagulation necroses could be increased, possibly enabling effective treatment of patients with larger hepatocellular carcinoma. The effectiveness of this combination treatment has been confirmed by several investigators. However, no randomized controlled trial to compare TACE-RFA with TACE alone and RFA alone in patients with larger hepatocellular carcinoma has, to our knowledge, been reported. We carried out a single-center, prospective, randomized controlled trial to assess the long-term benefits of TACE-RFA for hepatocellular carcinoma larger than 3 cm.

METHODS

Patients

From January 2001 to May 2004, 291 consecutive patients with hepatocellular carcinoma who met the entry criteria and agreed to participate were included in a randomized trial conducted at the departments of gastroenterology and surgery, Qilu Hospital, Shandong University, Jinan, China. The diagnosis of hepatocellular carcinoma was confirmed in all patients either by histopathologic findings (207 patients) or by the finding of a liver tumor with arterial hypervascularization on contrast-enhanced computed tomography or magnetic resonance imaging and a serum alpha-fetoprotein value exceeding 400 ng/mL (84 patients met European Association for the Study of the Liver criteria for the diagnosis of hepatocellular carcinoma).

Eligibility criteria were as follows: (1) no indication for resection; (2) 3 or fewer lesions, each larger than 3 cm but less than or equal to 7.5 cm in greatest diameter; (3) lesions located at least 0.5 cm away from the hepatic hilum or gallbladder and the common bile duct and 1 cm from the bowel; and (4) no previous hepatocellular carcinoma treatment. Exclusion criteria were advanced liver disease (Child-Pugh class C), age older than 75 years, portal vein thrombosis, extrahepatic metastasis, diffuse and infiltrative tumors, gastrointestinal hemorrhage in the past month, refractory ascites, encephalopathy, renal failure, impaired coagulation (e.g., platelet count <60 × 10^9/L; prothrombin activity <60%), contraindications to cisplatin (history of allergic reactions to cisplatin or other platinum-containing compounds or serum creatinine concentration of ≥1.36 mg/dL), or end-stage tumor disease.

Patients who met these criteria and gave written informed consent entered the study, which was approved by the investigation and ethics committee of Qilu Hospital, Shandong University, according to the standards of the Declaration of Helsinki.

Study Design

Before randomization, patients were stratified on the basis of tumor stage (uninodular vs multinodular) and Okuda stage (I vs II) to ensure balanced groups. Randomization was centralized and was performed with a computer-generated allocation list and in sequentially numbered, opaque, sealed envelopes. Patients were assigned to TACE-RFA, RFA alone, and TACE alone in equal proportions. Double-blind and double-dummy techniques were not feasible because of the nature of the treatments and the associated adverse effects.

Patients who met eligibility criteria were randomly assigned to TACE, RFA, or TACE-RFA. Because TACE treatment is administered at different intervals than RFA treatment, we designed similar treatment intervals in this study to allow comparison across the 3 treatment groups. The number of treatments was counted as courses; 1 treatment was defined as 1 course. The initial treatments were performed at baseline, at 2 months, and at 4 months. After 3 courses, treatment was performed on the basis of positive findings such as local recurrence, intrahepatic metastases, or development of new lesions as found on computed tomography and ultrasonography during follow-up. Nonresponders were defined as those with stable or progressive diseases after 3 courses; these patients then received alternative therapies, including crossover treatment among RFA, TACE, and TACE-RFA; percutaneous ethanol injection; symptomatic treatment; or, if treatment was discontinued, best supportive care. Treatment was discontinued if any exclusion criteria developed or per patient request. The interval between random assignment and the first course of treatment was always less than 2 weeks.

Treatment Procedures

All TACE and RFA were performed by the same physicians (B.-Q.C., C.-T.L., W.F., Q.-L.W., and Z.-L.Z.).

TACE was carried out according to the Seldinger technique of arterial embolization. After the introduction of a 5F pigtail catheter through the femoral artery, hepatic arteriography and superior mesenteric arterial portography were performed to assess portal flow and the size and location of tumor nodules. When portal flow was adequate, the hepatic artery was catheterized. In patients with unilobar tumors, either the right or left hepatic artery was cannulated selectively, then the feeding artery of the tumor was catheterized superselectively.

In patients with bilobar tumors, chemoembolization was usually performed at the common hepatic artery. An emulsion that consisted of 50 mg of cisplatin (Qilu Pharmaceutical Factory, Jinan, China) and 10 mL of lipiodol (Huaihai Pharmaceutical Factory, Shanghai, China) at a volume ratio...
of 1:1 was injected into the blood supply artery of the tumor under fluoroscopic guidance. The injection could be slowed or discontinued if retrograde flow occurred. Embolization was subsequently performed with granules of gelatin sponge particles (Third Pharmaceutical Factory of Nanjing, Nanjing, China). 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 (pentazocine or meperidine) was administered if necessary.

We used a common, commercially available RFA technique and system (RITA 1500X RF generator and RITA StarBurst XL, RITA Medical Systems, Mountain View, California). Grounding was achieved by attaching 2 pads to the patient’s thighs. After administration of analgesia (2.5-5.0 mg of midazolam and 0.05-0.1 mg of fentanyl) as well as local anesthesia (5-15 mL of 1% lidocaine), the electrode needles were introduced into the tumor under ultrasonographic guidance, then a gradual unfolding of the electrodes was obtained, and the generator was activated to achieve RF energy and maintain an average temperature of 100°C. At first, the electrodes were moved by 2 cm, then the electrode needles were pushed forward and unfolded gradually to 3 cm, 4 cm, and 5 cm until they reached or crossed the borders of the tumor according to the ablation range, delivering RF energy for 5 minutes for every intermediate step and for 7 to 10 minutes in the final step of the procedure. The ablation area was intended to cover the tumor as well as at least 0.5 to 1.0 cm of the surrounding tissue. The overlapping mode was used if the ablation range was greater than 5 cm in diameter. During ablation, temperature was measured with a thermocouple in the electrode and tissue impedance was monitored by circuitry incorporated within the generator. To prevent bleeding and tumor seeding, track ablation was performed when withdrawing the RFA electrode in all patients. No antibiotic prophylaxis was given before or after the RFA procedure.

In the TACE-RFA group, because gelatin sponge remains in the tumor for 2 weeks after chemoembolization,21 RFA treatments followed TACE within 2 weeks (median, 8 days; range, 4-12 days).

**Assessment and Follow-up**

Treatment response was assessed by contrast-enhanced spiral computed tomography at 5 months (ie, 1 month after the third treatment course). All computed tomography scans were reviewed by 2 radiologists who were unaware of patient clinical data or treatment assignment. The magnitude of treatment response was defined according to World Health Organization criteria24 as follows: complete response refers to complete disappearance of all known disease and no new lesions, as determined by 2 observations not less than 4 weeks apart; partial response indicates a more than 50% reduction in total tumor load of all measurable lesions, as determined by 2 observations not less than 4 weeks apart; stable disease refers to disease that does not qualify for either complete response/partial response or progressive disease; and progressive disease describes disease with a more than 25% increase in the size of 1 or more measurable lesions or the appearance of new lesions. Objective response includes both complete response and partial response. The cutoff duration of objective response was 6 months after response evaluation.

After 3 courses, patients were assessed every 3 months for 2 years and every 6 months thereafter by spiral computed tomography, ultrasonography, serum biochemistry, and clinical examination. No patient received antiviral treatment during the trial. Patients were followed up until loss to follow-up, death, or December 31, 2006. The median follow-up period was 28.5 months (range, 1-71 months).

**Statistical Analysis**

The primary end point was survival and the secondary end point was treatment response. Overall survival was measured from the date of randomization to death or the date of last follow-up. At the time the study was planned, we estimated on the basis of previous data12,14,18,25 that the 5-year survival rate would be 25% with TACE-RFA and 11% with TACE alone or RFA alone. We calculated that a sample size of at least 92 patients would be required in each group to have 80% power to detect these improvements at a 2-sided level of statistical significance of .05. We also estimated that 5% of patients would be lost during follow-up.

All analyses were by intention to treat. Pearson χ² tests with Fisher exact probability were performed to compare the frequency distributions of categorical variables between groups. One-way analysis of variance was used to test the differences in means between groups for continuous variables. Survival probabilities were estimated using the life-table method, and differences in survival rates between groups were compared using the log-rank test. Survival curves were estimated using Kaplan-Meier analyses from time of randomization. Cox proportional hazards models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). Sex, age, underlying liver diseases, and Cancer of the Liver Italian Program (CLIP) score26 were adjusted as the potential confounders in the multiple Cox regression models. The proportional hazards assumption in the Cox regression model was tested using Schoenfeld residuals. All statistical analyses were carried out with Stata software, version 9.2 (Stata Corp, College Station, Texas). All reported P values are 2-sided, with P < .05 considered statistically significant. The statistician was unaware of patients’ clinical data or treatment assignment.

**RESULTS**

**Enrollment**

From January 2001 to May 2004, 291 (21.1%) of the 1378 patients diagnosed as having hepatocellular carcinoma at our hospital met the entry criteria and agreed to take part in the study. Of the 1087 patients who did not participate, 210 were excluded because they had poor hepatic function, 205 because they had end-stage cancer, 187 because they had early hepatocellular carcinoma and under-

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This article has been retracted

CHEMOEMBOLIZATION AND RADIOFREQUENCY ABLATION FOR HEPATOCELLULAR CARCINOMA

Figure 1. Flow of Trial Participants

![Flow of Trial Participants Diagram]

TACE indicates transcatheter arterial chemoembolization; RFA, radiofrequency ablation.

went curative therapy (liver transplantation in 23, resection in 109, and percutaneous ethanol injection in 55), 267 because they had contraindications to the study treatments (portal vein thrombosis in 145, including partial thrombosis in 90 and complete thrombosis in 55; and extrahepatic spread in 122), and 104 for other reasons (tumors in 58 patients located near bowel, hepatic hilum, gallbladder, or common bile duct; previous percutaneous ethanol injection treatment in 46) (FIGURE 1). In addition, 114 patients refused to participate (of whom 93 received conservative treatment and 21 received percutaneous ethanol injection).

Of 291 patients who were eligible and consented to be randomly assigned, 95 were assigned to the TACE-alone group, 100 to the RFA-alone group, and 96 to the TACE-RFA group (Figure 1). TABLE 1 lists the baseline characteristics of the patients. There were no significant differences among the 3 groups for any of the variables.

Protocol Violations
Six patients (2 in each group) withdrew from the trial and 2 patients (1 in the TACE group and 1 in the TACE-RFA group) died before treatment could begin. Four patients assigned to RFA alone and 2 assigned to TACE-RFA actually received TACE alone because of the deep location of their tumors. These patients were analyzed as part of their original assigned group according to intention-to-treat principles. Analysis of the data after exclusion of these patients did not change the survival results. Ten patients (3 in the TACE group, 4 in the RFA group, and 3 in the TACE-RFA group) were lost to follow-up, and their data were censored at the time of their last visit.

Survival
At the end of follow-up, 80 patients in the TACE group (84%), 84 in the RFA group (84%), and 66 in the TACE-RFA group (69%) had died. The lower rate of death in the TACE-RFA group was the result of fewer deaths due to tumor progression in this group than in the TACE group (P = .04) or the RFA group (P = .03) (TABLE 2). Median survival times were 24 months (range, 1-63 months) in the TACE group, 22 months (range, 1-63 months) in the RFA group, and 37 months (range, 1-71 months) in the TACE-RFA group. Mean follow-up times were 25.4 months in the TACE group, 24.6 months in the RFA group, and 35.8 months in the TACE-RFA group. The probabilities of survival at 1, 3, and 5 years were 74%, 32%, and 13% in the TACE group; 67%, 32%, and 8% in the RFA group; and 83%, 55%, and 31% in the TACE-RFA group, respectively (TABLE 3). Survival rates were significantly better in the TACE-RFA group than in the TACE group (HR, 1.87; 95% CI, 1.33-2.63; P < .001 by log-rank test) or the RFA group (HR, 1.88; 95% CI, 1.34-2.65; P < .001 by log-rank test) (FIGURE 2).

A subgroup analysis of patients by lesion size identified increased survival in the TACE-RFA group compared with the TACE group (P = .008 by log-rank test) and the RFA group (P = .001 by log-rank test) in patients with lesions ranging from 3.1 to 5 cm; survival was also higher in patients with lesions larger than 5 cm (TACE-RFA vs TACE, P < .001 by log-rank test; TACE-RFA vs RFA, P < .001 by log-rank test) (TABLE 3).

Considering that RFA appears to be the appropriate treatment for patients with uninodular hepatocellular carcinoma and that TACE is the appropriate therapy for multinodular hepatocellular carcinoma,4,6,8,28,29 we preplanned to analyze patients according to nodularity. For patients with uninodular hepatocellular carcinoma, overall survival was statistically significantly better in the TACE-RFA group than in the RFA group (HR, 2.50; 95% CI, 1.33-4.62; P = .001 by log-rank test; FIGURE 3). One-, 3-, and 5-year survival rates were 87%, 50%, and 15%, respectively, in the RFA group and 93%, 79%, and 53%, respectively, in the TACE-RFA group (TABLE 3). In analyses of multinodular hepatocellular carcinomas, the overall survival rate was also statistically sig-
significantly higher in the TACE-RFA group than in the TACE group: 75%, 36%, and 13% at 1, 3, and 5 years, respectively, in the TACE-RFA group and 56%, 13%, and 0%, respectively, in the TACE group (HR, 1.99; 95% CI, 1.31-3.00; \( P < .001 \) by log-rank test; Table 3 and Figure 3).

We further analyzed the factors that were associated with survival using a Cox regression model; the results showed that treatment allocation (TACE-RFA vs TACE, \( P = .009 \) and TACE-RFA vs RFA, \( P = .01 \)). In addition, 56 patients in the TACE group (59%), 69 patients in the RFA group (69%), and 76 patients in the TACE-RFA group (79%) achieved objective response (rate differences: TACE-RFA vs TACE, 0.50 [95% CI, 0.39-0.61; \( P < .001 \)] and TACE-RFA vs RFA, 0.18 [95% CI, 0.05-0.32; \( P = .02 \)]). In addition, 56 patients in the TACE group (59%), 69 patients in the RFA group (69%), and 76 patients in the TACE-RFA group (79%) achieved objective response (rate differences: TACE-RFA vs TACE, 0.20 [95% CI, 0.07-0.33; \( P = .003 \)] and TACE-RFA vs RFA, 0.10 [95% CI, -0.02 to 0.22; \( P = .14 \)]). Thirty-three patients (35%) achieved an objective response that was sustained for at least 6 months in the TACE group, 36 (36%) in the RFA group, and 52 (54%) in the TACE-RFA group (rate differences: TACE-RFA vs TACE, 0.19 [95% CI, 0.06-0.33; \( P = .009 \)] and TACE-RFA vs RFA, 0.18 [95% CI, 0.05-0.32; \( P = .01 \)]).

### Tumor Response

Five patients in the TACE group (5%), 37 patients in the RFA group (37%), and 53 patients in the TACE-RFA group (55%) achieved complete response at the time of response assessment (rate differences: TACE-RFA vs TACE, 0.20 [95% CI, 0.07-0.33; \( P = .003 \)] and TACE-RFA vs RFA, 0.18 [95% CI, 0.05-0.32; \( P = .02 \)]) in the TACE-RFA group. In the RFA group, and 52 patients in the TACE-RFA group (55%) achieved complete response at the time of response assessment (rate differences: TACE-RFA vs TACE, 0.20 [95% CI, 0.07-0.33; \( P = .003 \)] and TACE-RFA vs RFA, 0.18 [95% CI, 0.05-0.32; \( P = .02 \)]).

### Treatment Discontinuation

The mean number of treatments was 3.4 (median, 2 [range, 0-10]) in the TACE group, 3.6 (median, 3 [range, 0-10]) in the RFA group, and 4.4 (median, 4 [range, 0-11]) in the TACE-RFA group. Treatment was discontinued in 83 patients (87%) in the TACE group, 85 patients (85%) in the RFA group, and 68 patients (71%) in the TACE-RFA group.

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Spontaneous bacterial peritonitis: 1 (1) 1 (1) 1 (1) 3 (1)
Treatment-related: 2 (2) 1 (1) 2 (2) 5 (2)
Variceal bleeding: 7 (7) 7 (7) 6 (6) 20 (7)
Liver failure with stable disease: 16 (17) 17 (17) 17 (18) 50 (17)
Multinodular hepatocellular carcinoma
Uninodular hepatocellular carcinoma

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TACE indicates transcatheter arterial chemoembolization; RFA, radiofrequency ablation.

Figure 2. Overall Survival Curves

Table 3. Comparison of Overall Survival Rates Among 3 Treatment Methods

<table>
<thead>
<tr>
<th>Treatment Methods by Tumor Type</th>
<th>Overall No. of Patients</th>
<th>Survival Rate, % (95% Confidence Interval)</th>
<th>P Value</th>
<th>Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>All hepatocellular carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACE alone</td>
<td>95</td>
<td>74 (64-81) 32 (23-41) 13 (7-21)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>RFA alone</td>
<td>100</td>
<td>67 (57-75) 32 (23-42) 8 (3-16)</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>TACE-RFA</td>
<td>96</td>
<td>83 (74-89) 55 (45-66) 31 (21-41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor size ≤5 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACE alone</td>
<td>45</td>
<td>93 (81-98) 62 (46-74) 26 (13-40)</td>
<td>.008</td>
<td></td>
</tr>
<tr>
<td>RFA alone</td>
<td>47</td>
<td>89 (76-95) 62 (46-74) 15 (6-30)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>TACE-RFA</td>
<td>45</td>
<td>96 (83-99) 77 (62-87) 56 (39-69)</td>
<td></td>
<td></td>
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<tr>
<td>Tumor size &gt;5 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACE alone</td>
<td>50</td>
<td>56 (41-66) 6 (2-15) 0</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>RFA alone</td>
<td>53</td>
<td>47 (33-59) 5 (1-14) 0</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>TACE-RFA</td>
<td>51</td>
<td>72 (57-82) 35 (22-48) 5 (1-17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uninodular hepatocellular carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACE alone</td>
<td>43</td>
<td>95 (83-99) 56 (40-69) 27 (15-42)</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>RFA alone</td>
<td>45</td>
<td>87 (72-94) 50 (34-63) 15 (6-30)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>TACE-RFA</td>
<td>43</td>
<td>93 (80-98) 79 (63-88) 53 (36-68)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multinodular hepatocellular carcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TACE alone</td>
<td>52</td>
<td>56 (41-66) 13 (6-24) 0</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>RFA alone</td>
<td>55</td>
<td>51 (37-63) 18 (9-29) 2 (0-11)</td>
<td>.004</td>
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</tr>
<tr>
<td>TACE-RFA</td>
<td>53</td>
<td>75 (61-85) 36 (23-49) 13 (5-24)</td>
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Abbreviations: RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization.

aComparison vs TACE-RFA treatment, determined using a 2-way log-rank test.

The difference in rates of treatment discontinuation in the 3 groups reflects the different rates of tumor progression in the 3 groups (TABLE 4).

Recurrence

During follow-up, recurrences were detected in 76 patients (80%) in the TACE group, 81 patients (81%) in the RFA group, and 57 patients (59%) in the TACE-RFA group (TACE-RFA vs TACE, HR, 1.82; 95% CI, 1.28-2.58; P=.001 and TACE-RFA vs RFA, HR, 1.90; 95% CI, 1.35-2.68; P<.001). These included 62 patients with new lesions distant from the initial tumor (12 with extrahepatic tumors) and 14 patients with local tumor recurrence in the TACE group; 65 patients with new lesions distant from the initial tumor (11 extrahepatic tumors) and 16 local recurrences in the RFA group; and 53 patients with new lesions distant from the initial tumor (7 extrahepatic tumors) and 4 local tumor recurrences in the TACE-RFA group. Excluding patients with extrahepatic tumors (n = 30) and treatment discontinuation (n = 78), of the remaining 106 patients, 72 patients (68%) were treated with the same treatment, whereas the remaining 34 patients (32%) received a different treatment, including 9 patients from the TACE group treated with RFA and 5 with TACE-RFA; 10 patients from the RFA group treated with TACE and 6 with TACE-RFA; and 4 patients in the TACE-RFA group treated with percutaneous ethanol injection.

Complications

Common complications in all 3 groups were fever (temperature ≥ 38°C), pain, vomiting, decrease in leukocyte count, increased serum alanine aminotransferase or aspartate aminotransferase levels, increased serum bilirubin level, ascites, gastrointestinal hemorrhage, encephalopathy, pleural effusion, liver abscess, and spontaneous bacterial peritonitis. Other complications included cholecystitis and inguinal hematoma in the TACE and TACE-RFA groups and seeding of tumor cells and skin burn in the RFA and TACE-RFA groups (TABLE 5).
Five deaths were considered treatment-related. These included 3 patients with Child-Pugh class A disease who died of liver failure 2 weeks after the second course of treatment in the TACE group (1 patient) and 2 weeks after the third course of treatment in the TACE-RFA group (2 patients). 1 patient who died of rupture of esophagogastric varices 3 days after the fourth course of treatment in the TACE group, and 1 patient who died of gastrointestinal bleeding 2 days after the sixth course of treatment in the TACE group. The deaths of 7 other patients who died within 2 months after randomization were not as clearly related to treatment.

**COMMENT**
The present study shows that performing TACE prior to RFA is beneficial in that it achieves better ablation than either TACE alone or RFA alone in selected candidates with hepatocellular carcinoma greater than 3 cm. This result could be explained by the modification in hepatocellular carcinoma tissue conductance that occurs after the sudden hemodynamic changes caused by occlusion of the hepatocellular carcinoma–feeding artery using gelatin sponge. During the RFA procedure, because heat loss is reduced after the occlusion of arterial flow, the mean impedance values in the hepatocellular carcinoma are lower than those in the hepatocellular carcinoma tissue without occlusion of hepatic blood flow, and tissue with lower impedance tends to produce larger lesions. However, the persistent ischemia induced by the gelatin sponge particle occlusion during TACE contributes to tumor necrosis. Moreover, disruption of intratumoral septa may facilitate heat distribution within the tumor. Intratumoral septa and fibrosis are considered to influence heat diffusion within the tumor, but they are usually disrupted after TACE.

The rationale of the present study design is as follows: (1) the ideal candidates for both TACE and RFA are pa...
patients with well-preserved liver function (Child-Pugh classes A and B) and without portal vein thrombosis, (2) patients with 3 or fewer nodules are the best candidates for percutaneous RFA under ultrasonographic imaging guidance, and (3) compared with conventional electrodes, the RFA system used in this study has higher power output and multitined expandable electrodes, which can create ablation zones up to 5 cm, thus extending the limit of ablation volume for tumors. Moreover, multiple RFA processes with overlapping modes were used if the tumor was greater than 5 cm in diameter, and RFA ablation is an efficacious, safe, and relatively simple procedure for the treatment of medium and large hepatocellular carcinoma lesions. To ensure that comparisons across the 3 methods would be appropriate, we selected 7.5 cm as the upper limit of tumor size as an eligibility criterion.

Overall survival of patients treated with TACE-RFA was higher than that of patients treated with TACE (HR, 1.87; 95% CI, 1.33–2.63) or RFA (HR, 1.88; 95% CI, 1.34–2.65) alone. Moreover, a survival benefit with combined treatment was seen not only for patients with uninnodular tumors compared with RFA treatment (HR, 2.50; 95% CI, 1.42–4.42), but also for patients with multinodular tumors compared with TACE treatment (HR, 1.99; 95% CI, 1.31–3.00). The benefits of this combined therapy in survival can be ascribed to both the complete response to treatment and maintenance of objective response. The cause of death was progression of hepatocellular carcinoma in most patients in our study. Therefore, treatment responses and objective sustained response are important factors in achieving a low hepatocellular carcinoma recurrence. Although there was no difference in objective response rates between TACE-RFA and RFA, rates of both complete response and objective sustained response for at least 6 months were higher in the TACE-RFA group than TACE or RFA alone; as a result, the survival was also significantly improved in the TACE-RFA group because complete response and objective sustained response are the most essential factors to obtain lower hepatocellular carcinoma recurrence and better survival rate.

In multivariate analyses, treatment and CLIP score were the most important factors associated with survival. CLIP score accounts for both liver function and tumor characteristics relevant to prognostic assessment for patients with hepatocellular carcinoma and has the highest stratification ability regarding prognosis in patients with hepatocellular carcinoma. Takayasu et al found that both the degree of liver damage and the TNM staging system could stratify patients with statistically significantly different survival rates, such that the lower the degree of liver damage and TNM stage, the better the survival rates of patients. In general, tumor burden and hepatic functional reserve have been regarded as prognostic factors.

Liver failure after TACE is a substantial limitation to survival benefit; it occurred in more than 50% of patients in a previous study. But in our study, there were no significant differences among the 3 groups or between 2 groups in serum bilirubin, leukocyte count, prothrombin activity, albumin, or alanine aminotransferase or aspartate aminotransferase concentrations before and after treatment. One week after treatment, liver function returned to almost the same level that was observed before treatment. Thus, the benefit of combined treatment was not offset by any adverse effect on the function of the normal liver. Although there were 2 deaths attributed to liver failure in patients who received TACE-RFA, this might partly reflect the natural course of the underlying liver disease when death caused by tumor progression has been effectively delayed with TACE-RFA treatment.

Table 5. Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>TACE Alone (n = 96)</th>
<th>RFA Alone (n = 100)</th>
<th>TACE-RFA (n = 96)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (temperature ≥38°C)</td>
<td>73 (77)</td>
<td>76 (78)</td>
<td>75 (78)</td>
<td>.94</td>
</tr>
<tr>
<td>Pain</td>
<td>74 (78)</td>
<td>80 (80)</td>
<td>72 (75)</td>
<td>.70</td>
</tr>
<tr>
<td>Grade 1</td>
<td>56</td>
<td>67</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>16</td>
<td>12</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Serum AST or ALT increased to ≥2 × baseline value</td>
<td>47 (49)</td>
<td>50 (50)</td>
<td>52 (54)</td>
<td>.78</td>
</tr>
<tr>
<td>Serum bilirubin increased by ≥0.5 mg/dL</td>
<td>48 (51)</td>
<td>11 (11)</td>
<td>50 (52)</td>
<td>.85</td>
</tr>
<tr>
<td>Vomiting</td>
<td>45 (47)</td>
<td>28 (28)</td>
<td>47 (49)</td>
<td>.85</td>
</tr>
<tr>
<td>Grade 2</td>
<td>44</td>
<td>28</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>White blood cell count decreased by &gt;500/µL</td>
<td>44 (46)</td>
<td>12 (12)</td>
<td>50 (52)</td>
<td>.47</td>
</tr>
<tr>
<td>Ascites</td>
<td>7 (7)</td>
<td>7 (7)</td>
<td>8 (8)</td>
<td>.96</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>6 (6)</td>
<td>3 (3)</td>
<td>5 (5)</td>
<td>.52</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>4 (4)</td>
<td>.37</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>3 (3)</td>
<td>0</td>
<td>3 (3)</td>
<td>.20</td>
</tr>
<tr>
<td>Death</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>.75</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Seeding of tumor cells</td>
<td>0</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>.78</td>
</tr>
<tr>
<td>Liver abscess</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Inguinal hernioma</td>
<td>1 (1)</td>
<td>0</td>
<td>1 (1)</td>
<td>.55</td>
</tr>
<tr>
<td>Skin burn</td>
<td>0</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

aDifference in measured value between baseline and 3 days after first round of treatment.

bFor comparison of TACE alone vs TACE-RFA.
Before the trial, we estimated that the 5-year survival rate would be 25% with TACE-RFA and 11% with TACE or RFA alone and calculated that a sample size of at least 92 patients would be required in each group. Based on our present results, the survival rate was 31% in the TACE-RFA group, 13% in the TACE group, and 8% in the RFA group. The 2-sided α was .05 and the staggered entry of the participants was also taken into account. We recalculated the power after trial completion, and the results showed that the total sample size of 291 patients provides 94% power to re-examine the nature of treatment and the association of treatment and the underlying cause of adverse effects of these treatments. However, blinding was maintained in analyzing the data by diagnosticians and in analyzing the data by statisticians. Second, this is a single-center study and the results may not be generalizable. It is possible that our results may not apply to patients with hepatocellular carcinoma in other countries because of differences in demographics and underlying cause of liver disease. For example, hepatitis B virus is the main cause of hepatocellular carcinoma in China, whereas hepatitis C virus, alcohol abuse, and other diseases are prevalent causes of hepatocellular carcinoma in Japan and Western countries.5,6,8,10 However, the strengths of our study are the complete data in a large number of patients and uniformity with regard to the diagnosis and treatment. The prospective, randomized design and long-term survival data are also major strengths of this study.

The current study demonstrates that combination therapy with TACE and RFA was an effective and safe treatment that may improve long-term survival for patients with hepatocellular carcinoma larger than 3 cm.

Author Contributions: Dr Cheng had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.