


Radiofrequency Ablation Combined With Transarterial Chemoembolization for Specially Located Small Hepatocellular Carcinoma

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Abstract

Objective: To investigate the safety and efficacy of radiofrequency ablation combined with transarterial chemoembolization in patients with specially located small hepatocellular carcinoma. **Materials and Methods:** Between March 2014 and March 2017, a total of 26 patients with 26 lesions (10 perivascular, 6 subdiaphragmatic, 5 subcapsular, 5 perivascular, and subdiaphragmatic location; mean diameter 2.12 (0.62) cm), who received radiofrequency ablation–transarterial chemoembolization treatment, were retrospectively analyzed. Local tumor response was assessed by computed tomography/magnetic resonance imaging 1 month after the procedure. Tumor-free survival was also assessed according to the modified Response Evaluation Criteria in Solid Tumors. Complications were evaluated according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events (version 4.0). **Results:** Complete response was achieved in all patients 1 month after the procedure. During a median follow-up duration of 16.76 months (95% confidence interval: 7.78–25.73 months), local tumor recurrence occurred in 2 patients and new intrahepatic lesions developed in 7 patients. The 1-, 2-, and 3-year cumulative local tumor progression rates were 3.84%, 7.69%, and 7.69%, respectively. The median tumor-free survival duration was 21.96 months (95% confidence interval: 17.58–26.34 months). The 1-, 2-, and 3-year tumor-free survival rates were 67.4%, 46.1%, and 39.3%, respectively. **Conclusion:** The radiofrequency ablation–transarterial chemoembolization combination therapy appears to be safe and effective and might be a treatment option for specially located small hepatocellular carcinoma lesions that have a risk of incomplete ablation or major complications.

Keywords

radiofrequency ablation, transarterial chemoembolization, hepatocellular carcinoma, specially located, small

Abbreviations

AFP, α -fetoprotein; CI, confidence interval; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IRE, irreversible electroporation; mRECIST, modified Response Evaluation Criteria in Solid Tumors; MWA, microwave ablation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and a major cause of mortality worldwide.¹ For patients with small HCC lesions (<3 cm), resection or transplantation is usually not employed as radical treatment given its poor liver function and comorbidities.² Radiofrequency ablation (RFA) or microwave ablation (MWA) has been the established curative therapeutic option that has resulted in similar clinical benefits in such patients.^{3,4} However, the treatment of specially located lesions, such as perivascular, subdiaphragmatic, and

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subcapsular lesions, remains challenging, as they may be associated with a higher risk of complications, incomplete ablation, and local tumor recurrence and may be difficult to target during RFA due to their dangerous location.^{3,4}

Transarterial chemoembolization (TACE) has been playing an important role in the management of HCC in unresectable candidates. However, given the nature of TACE as a palliative therapy, complete necrosis of the target lesion is difficult to achieve by TACE alone.⁵ Recently, the combination of RFA and TACE has been reported to be effective and to provide additional benefit for local control of large as well as small HCC lesions.⁶⁻¹² However, to the best of our knowledge, few previous studies have assessed the modality of RFA combined with TACE in the treatment of specially located small HCC lesions, and the tumor location was not specified in these randomized controlled studies.¹³

We speculate that TACE performed immediately after RFA is useful for evaluating the efficacy of ablation and for treating residual lesions or vascular-related complications in patients with specially located lesions. The purpose of the study was to investigate RFA-TACE in treating small HCC lesions which is close to vascular, diaphragmatic, and capsular lesions.

Materials and Methods

Patient Selection

This retrospective study was conducted with Zhongshan Hospital's institutional review board approval (No: B2014-102). Written informed consent was obtained from each patient before treatment. Between March 2014 and March 2017, a total of 358 consecutive patients with malignant liver tumors (178 with tumors adjoining a large vessel, the liver capsule, or the diaphragm), who were unable or unwilling to receive surgery, underwent RFA-TACE combination therapy at our institution. A perivascular tumor was defined as a tumor located within 5 mm from a vessel such as the portal vein/hepatic vein (≥ 3 mm) or the inferior vena cava. Lesions <1.0 cm from the hepatic capsule or diaphragm were defined as subcapsular or subdiaphragmatic lesions. Tumor size and location were assessed and determined by 2 radiologists, each with more than 5 years of experience. The exclusion criteria included the following: (1) more than 3 lesions or any lesion >3 cm in diameter, (2) tumor invasion into major intrahepatic blood vessels and extrahepatic metastases, and (3) metastasis or primary liver cancer other than HCC. Hepatocellular carcinoma was diagnosed based on pathology or the following typical clinical features: nodules >2 cm for patients with cirrhosis and coincidental findings by 2 imaging techniques that were considered diagnostic or, alternatively, by one imaging technique along with α -fetoprotein (AFP) levels over 400 ng/mL according to the guidelines of the American Association for the Study of Liver Diseases.

A total of 26 lesions (10 perivascular, 6 subdiaphragmatic, 5 subcapsular, 5 perivascular and subdiaphragmatic) in 26 patients (20 males and 6 females) were included in this

Table 1. Clinical Characteristic of the Patients.^a

Characteristics	Values
Age (years)	57.73 (10.98)
Sex	
Male	20
Female	6
Tumor location	
Perivascular	10
Subdiaphragmatic	6
Subcapsular	5
Perivascular and subdiaphragmatic	5
Maximum tumor diameter (cm)	2.12 (0.62)
AFP	
>400 ng/mL	3
≤ 400 ng/mL	23
ECOG (0/1)	23/3
Previous treatment history	12
Surgery	3
Ablation (RFA or MWA)	1
TACE	2
Surgery and TACE	4
Ablation and TACE	1
Transplantation, ablation, and TACE	1

Abbreviations: AFP, α -fetoprotein; ECOG, eastern cooperative oncology group; MWA, microwave ablation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

^aN = 26.

study. All patients had a history of hepatitis B virus (HBV) infection and a mean age of 57.73 (10.98) years (range: 35-78 years). The mean tumor diameter was 2.12 (0.62) cm (range: 1.3-2.9 cm). The clinical characteristics of the patients are summarized in Table 1.

Combination Treatment Procedures

All RFA-TACE procedures were performed by 3 interventional radiologists, each with more than 15 years of experience in performing interventional radiological procedures. The procedures were performed under conscious sedation and local anesthesia. Fentanyl (Yichang Humanwell Pharmaceutical Co, Ltd, Hubei, China) at a dose of 0.1 to 0.2 mg was used for analgesia, and 0.1% lidocaine hydrochloride was used for local anesthesia. To evaluate tumor location and tumor-feeding arteries, celiac and superior mesenteric arteriography was performed through a 5F catheter (RH; Terumo Corp, Tokyo, Japan; Figure 1B). A 2.7F microcatheter (Progreat; Terumo Corp) was then used for superselective catheterization. Ultrasound (ACUSON X300; Siemens, Seoul, Korea) was used to detect the index tumor immediately after arteriography (Figure 2). Radiofrequency ablation was performed under both ultrasound and fluoroscopy guidance and immediately followed by TACE (Figure 1). Blood pressure, respiration, pulse, oxygen saturation, and electrocardiograms were monitored throughout the procedures.

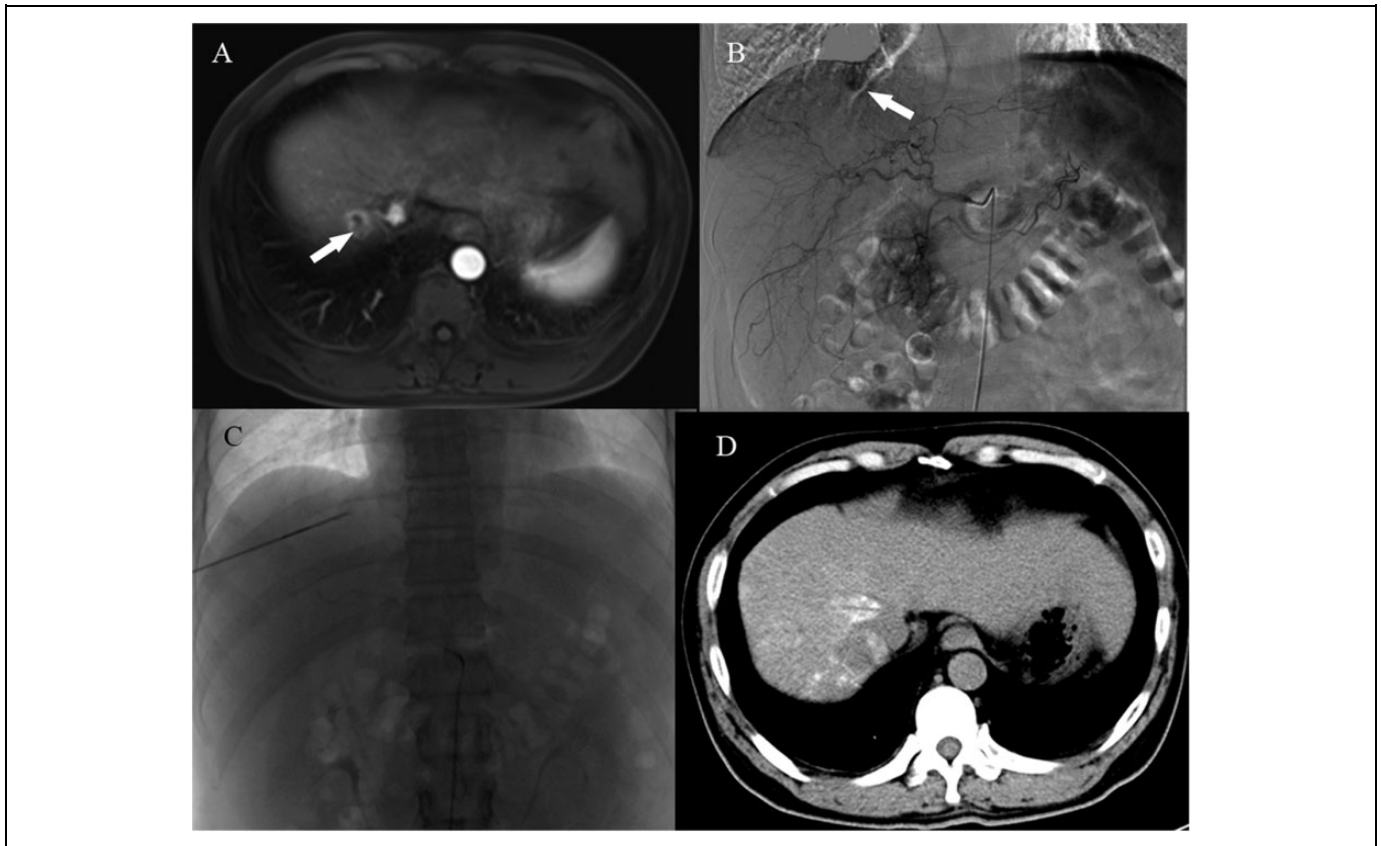


Figure 1. A, A preprocedure abdominal contrast-enhanced MRI (venous phase) shows a subdiaphragmatic tumor (white arrow). B, Tumor staining is clearly demonstrated by angiography (white arrow). C, An electrode and a microcatheter are in position during the RFA-TACE procedure. D, A noncontrast-enhanced CT scan 3 days after the procedure. CT indicates computed tomography; MRI, magnetic resonance imaging; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.



Figure 2. Ultrasound and fluoroscopy intergraded guidance for tumor targeting. A, A single small HCC lesion is inconspicuous (white arrow) under conventional ultrasonography. B, The index tumor became conspicuous after hepatic angiography with iopromide injection (white arrow). C, The RFA electrode (white arrow) within the index tumor. HCC indicates hepatocellular carcinoma; RFA, radiofrequency ablation.

Percutaneous RFA

An RFA system (S-1500; MedSphere International, Shanghai, China) was used to generate up to 150 W of energy to achieve adequate coagulation necrosis of the target tumor. Expandable electrodes (range: 14-19 gauge; 15 or 20 cm in length; 2, 3, and 4 cm in diameter) with an outer insulated sheath and a core

needle with multiple umbrella-shaped electrodes were inserted into the tumors under ultrasound guidance. The electrode diameter was selected according to the size of the target tumor. Power output was set at 60 W and slowly increased by 10 W every 2 minutes until tissue impedance reached 100%. Puncture track ablation at 60 W was conducted during electrode withdrawal in all patients.

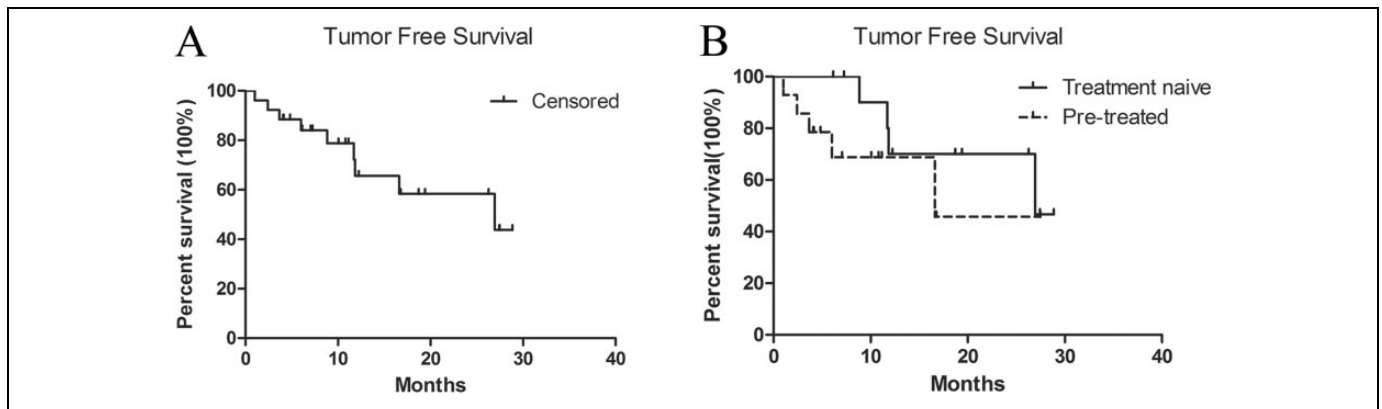


Figure 3. Kaplan-Meier curves for tumor-free survival.

Chemoembolization Procedure

Arteriography was performed immediately after RFA to evaluate the coagulated zone, residual tumor vascularity, and postablative complications such as intrahepatic hemorrhage or arteriovenous fistula. An emulsion consisting of 20 mg of epirubicin (Farmorubicin; Pfizer, Wuxi, China) and 2 to 5 mL of iodized oil (Lipiodol; Guerbet, Roissy, France) was slowly injected through the microcatheter. Subsequently, 350 to 510 μm of gelatin sponge particles (Ailikang Medicine, Hangzhou, China) mixed with contrast medium were injected to reduce residual blood flow. If hemorrhage or arteriovenous fistula was observed, the involved artery was embolized using gelatin sponge particles.

Follow-Up

Laboratory tests, including routine blood tests, AFP, liver functions, renal functions, coagulation functions, and noncontrast computed tomography (CT) were performed 3 to 7 days after the RFA-TACE procedure. Patients were examined using triphasic contrast-enhanced CT or magnetic resonance imaging, and routine laboratory tests were conducted at 1 month and then every 3 months after the procedure. Local tumor response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST).¹⁴ Tumor-free survival was determined from the time between treatment administration and intrahepatic lesion detection. Complications were evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events Toxicity Criteria (NCI-CTCAE 4.0).

Statistical Analyses

Continuous variables were expressed as the mean (standard deviation) and category data as frequencies and percentages. A *P* (2-tailed) value less than .05 was considered statistically significant. Tumor-free survival duration was calculated using the Kaplan-Meier method. Data analysis was performed using SPSS (version 20.0; IBM, Armonk, New York).

Results

Tumor Response

The RFA-TACE procedure was successfully performed in all the patients. Angiography after RFA showed the surrounding hyperemia edema ring and the avascular area of the central ablation zone. According to mRECIST, complete response was achieved in all patients 1 month after treatment. The median follow-up duration was 16.76 months (95% confidence interval [CI]: 7.78-25.73 months). There were 2 cases of local tumor recurrence during the follow-up period. New intrahepatic lesions occurred in 7 patients. The 1-, 2-, and 3-year cumulative local tumor progression rates were 3.84%, 7.69%, and 7.69%, respectively. The median tumor-free survival duration was 21.96 months (95% CI: 17.58-26.34 months; Figure 3A). The mean tumor-free survival duration was 22.99 months (95% CI: 17.97-28.01 months) in 14 (53.85%) patients without previous treatment and 17.49 months (95% CI: 10.91-24.08 months) in 12 (46.15%) patients with previous treatment ($P = .272$, Figure 3B). The 1-, 2-, and 3-year tumor-free survival rates were 67.4%, 46.1%, and 39.3%, respectively (Table 2). Recurrent or new tumors were treated with repeated RFA-TACE ($n = 2$), serial TACE ($n = 6$), or RFA ($n = 1$). One patient died of liver failure 2 years after the procedure. One month after the procedure, AFP dropped to normal levels (≤ 20 ng/mL) in all patients, including in 8 of 9 patients who had previously elevated AFP level ($n = 9$), except in 1 patient whose AFP level decreased from 228.2 to 24 ng/mL.

Complications

No major complications were observed, and the combination therapy was well tolerated in all patients. Postembolization syndromes such as fever, abdominal pain, and vomiting were managed with analgesics, antiemetics, and other symptomatic treatments. Arteriovenous fistulas after RFA were identified by angiography in 3 patients and were promptly treated by embolization. Asymptomatic pleural effusion (CTCAE 4.0 grade 1) was observed in 8 patients and spontaneously resolved within 1 month. A transient impairment of liver function (grade 3) was

Table 2. The Outcome of Patients.

Status	Percentage
Overall complete ablation	26/26 (100%)
Local recurrence at ablated site	2/26 (7.69%)
New intrahepatic recurrence	7/26 (26.9%)
Death	1/26 (3.85%)
1-year tumor-free survival	17/26 (67.4%)
2-year tumor-free survival	12/26 (46.1%)
3-year tumor-free survival	9/26 (39.3%)

Table 3. Preprocedure and Postprocedure Laboratory Test Changes.^a

Laboratory Test	Preprocedure, mean (SD)	Postprocedure, mean (SD)	P Value ^b	CTCAE
				Grade, No. of grade: 1/2/3/4
ALT (U/L)	28.54 (12.15)	116.81 (73.29)	.000	10/5/3/0
AST (U/L)	30.76 (11.21)	123.00 (98.52)	.000	12/5/4/0
TB (μmol/L)	13.17 (7.26)	24.45 (14.54)	.000	6/4/1/0
CB (μmol/L)	5.85 (3.93)	12.2 (10.01)	.000	5/3/1/0
ALB (g/L)	40.65 (4.74)	38.42 (5.577)	.022	3/0/0/0
WBC (10 ⁹)	4.66 (1.71)	7.20 (3.51)	.000	3/1/0/0
Hb (g/L)	136.15 (16.36)	129.88 (16.54)	.005	10/4/0/0
PLT (10 ⁹)	127.27 (63.60)	119.77 (66.14)	.265	9/4/7/0
Cr (μmol/L)	73.81 (22.86)	72.54 (24.80)	.650	1/0/0/0

Abbreviations: ALT, alanine aminotransferase; ALB, albumin; AST, aspartate aminotransferase; CB, conjugated bilirubin; Cr, creatinine; CTCAE, Common Terminology Criteria for Adverse Events; Hb, hemoglobin; PLT, platelet; TB, total bilirubin; WBC, white blood cell.

^aN = 26.

^bPaired samples *t* test (2-sided).

recorded in 4 of 26 patients (Table 3) and was addressed by supportive treatment within 7 days.

Discussion

Radiofrequency ablation is a curative therapeutic modality for patients with early-stage HCC according to Barcelona Clinic Liver Cancer strategy.⁵ Compared to surgical resection, percutaneous RFA may provide similar therapeutic effects with fewer major complications, shorter hospital stays, and lower cost.¹⁵⁻¹⁷

Furthermore, RFA is a preferred choice for centrally located tumors that are smaller than 2 cm in diameter.^{16,18} However, the incidence of local tumor recurrence after RFA for small HCC lesions (<3 cm) ranges from 1.7% to 26%.^{13,17,19,20} Specially located tumors, such as perivascular, subdiaphragmatic, and subcapsular lesions, pose a challenge for the operators of RFA and confer a high risk of complications, incomplete ablation, and local tumor recurrence.²¹⁻²³ In an animal study, heat sink effect was identified in 50% of veins greater than 3 mm, and this increased to 100% of veins greater than 5 mm.²⁴ Recently, in a retrospective study of patients with HCC treated using RFA prior to transplantation, histologic examination of explanted human liver tissues revealed that 8 (53%) of 15 perivascular lesions were unsuccessfully treated.²⁵ Furthermore, RFA for subcapsular and subdiaphragmatic lesions can increase

complications such as peritoneal seeding, peritoneal bleeding, and pleural effusion.^{21,23,26} Special attention should be paid to such dangerously located small HCC lesions.

There currently is little evidence in the treatment of these specially located small HCC lesions. It is a great challenge in resection to locate the lesions adjacent to vascular or diaphragm. For RFA of these HCC locations, it is difficult to place an electrode and not being able to obtain enough ablative margin. Therefore, the optimal treatment strategies of these lesions remain controversial. Various combination treatment modalities have been reported for the treatment of high-risk HCC lesions in particular locations. Radiofrequency ablation combined with percutaneous ethanol injection (PEI) was reported for the treatment of high-risk lesions. The local tumor progression rates at 18 months were 21% for RFA-PEI versus 24% for RFA alone for high-risk lesions.²⁷ In another study, the 1- and 3-year disease-free survival rates were 79% and 41% for patients with perivascular lesions treated by RFA alone, respectively.²⁸ A combination therapy modality including TACE was demonstrated to have greater benefits than RFA/MWA alone.^{6,7} The TACE-RFA combination therapy has been reported to be safe and effective for HCC with tumors located in the caudate lobe or in the subcapsular region.^{29,30} However, in a recent randomized control study, Toshiya *et al* reported that combination treatment may not be necessary for small HCC lesions (<3 cm).¹³ In the study, the actual local tumor progression rate at 15 months was much lower than expected; hence, the results should be interpreted with caution. Furthermore, tumor locations were not clarified in the study. We herein reported a new treatment modality of RFA-TACE for specially located small HCCs. All HCC lesions included in our study were dangerously located. And the main study end point was local tumor response. A good local tumor response was obtained, and no major complication was observed. During the follow-up period, 2 patients experienced local tumor recurrence, and the 1-, 2-, and 3-year cumulative local tumor progression rates were 3.84%, 7.69%, and 7.69%, respectively, which are higher than those reported in previous studies (3-year cumulative local tumor progression rates: 13.2%-18.8%).³¹ The 1- and 3-year tumor-free survival rates in our study (67.4% and 39.3%, respectively) were similar to those of previous reports that included both centrally and dangerously located small HCC lesions (66%-81% and 31%-54%, respectively).^{9,13} However, all patients had HBV-related HCC in the present study, and half of them had a history of previous treatment.

Conventionally, RFA is performed after TACE. One of the advantages of this combination modality is that intratumoral lipiodol deposition after TACE can facilitate tumor targeting during subsequent RFA. Meanwhile, embolization reduces the cooling effect of hepatic blood flow and portal veins around the tumor so that RFA can induce a greater extent of necrosis.³²⁻³⁴ In this study, TACE performed immediately after RFA was adopted to treat these specially located small HCC lesions. With regard to tumor location, an increased risk of major complications is often associated with the RFA procedure, and

complete ablation of these lesions can be difficult to achieve. Therefore, TACE after RFA could not only evaluate the efficacy of ablation but also treat residual lesions or other microlesions, which are related to long-term recurrence. The anticancer effect of TACE can be enhanced by the administration of a high concentration of chemotherapeutic drugs into a relatively small volume of residual viable neoplastic tissue and a reduction in cellular resistance to the drug due to the exposure to sublethal heating.³⁵ Recently, Hyun D *et al* reported cone-beam CT-guided percutaneous RFA performed immediately after TACE for caudate lobe HCC. The 1- and 3-year progression-free survival rates were 81.8% and 51.9%.³⁶ This one-step TACE-RFA combination therapy was similar to our treatment modality. The treatment outcomes were better than ours. Notably, the targeted lesions were <2 cm in diameter and thus were smaller than the lesions treated in our study. Masashi *et al* reported TACE-RFA for caudate HCC lesions <5 cm in diameter. Radiofrequency ablation was performed with a mean interval of 10.5 days after TACE. Local tumor recurrence was observed in 1 (5%) of 20 patients, and new intrahepatic tumor in 8 (40%) of 20 patients. The recurrence-free survival rates were 70.8% at 1 year and 36.9% at 3 years. Hepatocellular carcinoma lesions larger than 3 cm were included in the study, and this may have contributed to the relatively lower tumor control rate than ours.²⁹

Furthermore, angiography after RFA facilitates the prompt management of RFA-related complications. Embolization may reduce bleeding complications associated with RFA.^{6,37} Dongho *et al* reported self-limiting capsular bleeding in 1 patient that was noted on an angiogram after RFA.³⁶ Fujimori *et al* reported embolization of intercostal artery bleeding in one patient and self-limiting subcapsular liver hematoma in another.²⁹ Although abdominal hemorrhage after RFA was not recorded in our study, arteriovenous fistulas were revealed by subsequent angiography in 3 patients. This complication could theoretically lead to intrahepatic or lung metastasis. Technique-related complications can be promptly managed by performing TACE immediately after RFA.

Technically, small HCC lesions are not always visualized on ultrasonography because of their unfavorable locations or isoechogenicity with the surrounding cirrhotic liver parenchyma.³⁸ A laparoscopic ablation technique can provide better visualization of superficial lesions.³⁹⁻⁴¹ However, the difficulty in access caused by adhesion of the postoperative mass may limit the application of laparoscopic ablation in patients with previous treatment history. An integrated guiding method that consists of ultrasonography and fluoroscopy was employed for tumor targeting in our study. Interestingly, tumor visualization under ultrasound guidance was improved, and the tumor boundary was clearly delineated after contrast media injection. Furthermore, some previous invisible lesions were detected after contrast media injection. In these cases, the use of CT guidance can be avoided, as it is both time-consuming and expensive.

This study has some unavoidable limitations. First, it was a retrospective and noncontrolled study at a single institution.

Second, the sample size was small, and the follow-up period was relatively short. In addition, complicated clinical factors inevitably influenced the long-term efficacy and overall survival. Therefore, we focused on local tumor control and safety of the combination treatment. Although current evidence seems to favor combination therapy, the potentially curative effect of RFA immediately followed by TACE in the management of patients with specially located small HCC lesions should be further studied. Finally, the study included perivascular, subdiaphragmatic, and subcapsular lesions, and these locations may contribute to different prognosis. In addition, about half of the included patients were not treatment naive. These patients might have poor prognoses. As other alternative methods, MWA creates a larger ablation area within a shorter time, and irreversible electroporation (IRE) is a nonthermal technique that does not produce the heat sink effect. Both MWA and IRE may be better choices for perivascular lesions, but this notion needs further investigation.

In conclusion, US-guided percutaneous RFA immediately followed by TACE appears to be safe and effective and might be a treatment option for specially located small HCC lesions that have a risk of incomplete ablation or major complications. Therefore, a prospective randomized controlled trial with a longer follow-up duration is needed in the future.

Authors' Note

W.Y., M.-J.Y., and J.X. contributed equally to this work and should be considered as co-first authors. All authors read and approved the final manuscript. J.-H.W. and S.Q. took equally responsibility for this work and should be identified as co-corresponding authors.

Declaration of Conflicting Interests

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