Safety and Efficacy of Percutaneous Radiofrequency Ablation Combined with Percutaneous Ethanol Injection for Hepatocellular Carcinoma in High-risk Locations

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Objective: The purpose of the study was to evaluate the safety and efficacy of percutaneous ultrasound (US) guided radiofrequency ablation combined with percutaneous ethanol injection to treat hepatocellular carcinoma in presumably high-risk locations.

Methods: Between September 2013 to December 2016, A total of 69 hepatocellular carcinoma patients with 76 nodules in high-risk locations, defined as less than 0.5cm from a large vessel or an extrahepatic organ, who underwent US-guided percutaneous radiofrequency ablation, combined with percutaneous ethanol injection, were retrospectively assessed. One or two radiofrequency electrodes were inserted and placed at designated places in the tumor. One ethanol needle was placed at the tumor periphery near the high-risk location. Absolute ethanol was injected into the tumor before radiofrequency ablation.. The safety and efficacy of the therapy were assessed by clinical data and imaging in follow-up examinations.

Results: All tumors were completely treated with one or two sessions; 61 tumors underwent one session; 15 tumors underwent two sessions. The primary technique was effective in 73 (96.1%) tumors, according to computed tomography (CT) or magnetic resonance imaging (MRI) follow up. No patients had major complications. Two (2.9%) patients died of primary disease progression that was not directly attributable to radiofrequency ablation. Local tumor progression was noted in 3 (3.9%) tumors in the follow-up period. The locally progressing tumors underwent additional therapy (one patient underwent radiofrequency ablation and transcatheter arterial chemoembolization, another patient with 2 nodules underwent transcatheter arterial chemoembolization).

Conclusions: US-guided percutaneous radiofrequency ablation, in combination with percutaneous ethanol injection, is a safe and effective treatment for hepatocellular carcinoma in high-risk locations.

Key words: Ultrasound; Radiofrequency ablation; Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-related death, with increasing annual incidence worldwide [1-2]. Patients with early-stage HCC are candidate for resection, liver transplantation, or ablation [3-5]. However, only a small portion of the patients with early-stage HCC are amenable to resection or liver transplantation because of a shortage of donor, the presence of multiple tumors, unfavorable anatomy, poor hepatic reserve, or other clinical factors such as old age and comorbidities [6-7].

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US-guided percutaneous radiofrequency (RF) ablation is a minimally invasive technique that has been widely used to treat primary and metastatic liver cancer over the past decade, because it is safe, fast, and easily accessible and allows real-time targeting and monitoring of the index tumor during thermal ablation procedure [8-10]. Studies have shown that RF ablation has an ideal primary effectiveness rate in the management of HCC [11-15], and the efficacy varies, however, depending on the proximity of the tumor to various structures. A location close to blood vessels, liver capsule, and vital structures is considered at high-risk of treatment failure and complications [16-18]. Some authors have suggested that tumor location was closely related to the risk of major complications. Tumors adjacent to extrahepatic structures or hepatic hilum were suggested to be unsuitable because of the risk of heat injury, such as bile duct injury and intestinal perforation [19-20]. It was also suggested that RF ablation for tumors adjacent to large vessels may often result in incomplete necrosis because of heat sink effect [21]. As a chemical ablation method, percutaneous ethanol injection (PEI) induces coagulation and obliteration of small intratumoral vessels, cooling the tissue to be ablated. PEI has been reported to be less effective than RF abaltion and has essentially been replaced by RF ablation in recent years [22]. In combination with RF ablation, PEI may have the additional effect of being heated by radiofrequency energy and extending tissue necorsis through the effects of hot ethanol [23-24]. Another advantage of the combined ablation is that the injected ethanol forms the heat isolation to avoid the heat injury of adjacent organs.

Consequently, the purpose of this study was to evaluate the safety and efficacy of US-guided percutaneous RF ablation combined with PEI to treat liver tumors in high-risk locations.

Materials and Methods

Patients

From September 2013 to December 2016, 69 HCC patients with a total of 76 nodules within 0.5cm to the high-risk locations underwent percutaneous US-guided RF ablation combined with PEI for curative intent at the authors' institution. 62 patients had one tumor adjacent to the high-risk locations and 7 patients had two nodules in the high-risk locations. In 14 cases there were coexistent HCC nodules far away from the high-risk location, and these nodules were treated with RF ablation alone. This was done during the same treatment session of the nodules in the high-risk locations. All patients were inpatients and were either not candidates for surgical treatment or had refused surgical treatment. The patients included 55 men and 14 women (age range, 38-75 years; mean age, 57 years). All patients had liver cirrhosis (43 compensated, 26 decompensated) in the study group.

The criteria for RF ablation of HCC at our hospital were the following: (1) tumor accessible via a percutaneous approach; (2) single nodular HCC lesions that was 5.0 cm or smaller; (3) three or fewer multiple nodular hepatic lesions with a maximum dimension of 3.0 cm or smaller for each nodule; (4) the absence of portal vein thrombosis or extrahepatic metastases; (5) a prothrombin time shorter than 25s, prothrombin activity higher than 40%, an INR value between 0.8 to 1.2, and platelet count higher than 30×10^9/L; (6) a Child–Pugh classification A or B liver cirrhosis. We obtained Institutional Review Board approval for the technology used to treat lesions adjacent to the high-risk locations, and written informed consent was obtained from patients prior to RF ablation therapy.

The diagnosis of HCC was based on the National Comprehensive Cancer Network (NCCN) guidelines [25]. A contrast-enhanced (CEUS) examination was performed for all patients before the treatment to accurately measure the size of the lesion.

Among all the 76 nodules, the maximum diameter of the tumors was 4.3 cm, and the average diameter of the tumors was 2.2 cm. There were 61 tumors less than 3.0 cm in diameter and 15 tumors were greater than 3.0 cm. The shortest distance from the lesion margin to the high-risk location was confirmed by contrast-enhanced CT or MRI in the transverse plane and coronal plane. A total of 29 tumors were located less than 0.25cm from the high-risk location and 47 tumors were located between 0.25 cm and 0.5 cm from the high-risk location. One tumor was located in liver segment I, 9 tumors were located in liver segment II, 9 tumors were located in liver segment III, 9 tumors were located in liver segment IV, 11 tumors were located in liver segment V, 11 were located in liver segment VI, 6 tumors were located in liver segment VII, 20 tumors were located in liver segment VIII. Forty tumors were next to the liver capsule, 11 tumors were next to the diaphragmatic dome, 12 tumors were next to the blood vessel, 8 tumors were next to the gallbladder, 2 tumors were next to the kidney, 3 tumors were next to the gastrointestinal tract.

For all 69 patients in the study, 26 patients had a history of previous treatment with transcatheter arterial chemoembolization (TACE), and 16 had undergone previous RF ablation. Three patients had a history of undergoing a liver operation. (Table 1)

Among these patients, 57 had hepatitis B infection, 7 had hepatitis C infection, 2 had alcoholic liver disease, and 3 had autoimmune liver disease. The severity of liver dysfunction was classified by Child-Pugh classification

in all cases. Fifty-one patients were Child-Pugh class A, and 18 patients were Child-Pugh class B, including 2 patients who had been Child-Pugh class C but, following treatment, whose liver function had been restored to Child-Pugh class B.

Table 1 Patient population and tumor characteristics

Variable	Data
Age (years)	57 (range 38-75)
Gender	
Male	55
Female	14
Type of hepatitis	
HBV	57
HCV	7
Alcoholic	2
Autoimmune	3
Tumor diameter (cm)	2.2 (range 0.8-4.3)
< 3 cm	61
3-5 cm	15
Distance to the high-risk location	
< 0.25cm	29
0.25-0.5cm	47
Distribution of high-risk tumors	
Near vessel	12
PV	3
HV	2
IVV	7
Near vital organ	
Subcapsular	40
Diaphragm	11
Gallbladder	8
Kidney	2
Gastrointestinal tract	3
Child-Pugh classification	
A	66
B	10
Previous therapy	
TACE	26
RF ablation	16
Liver operation	3

HBV, hepatitis B virus; HCV, hepatitis C virus; PV, portal vein; HV, hepatic vein; IVV, inferior vena cava; TACE, transcatherter arterial chemoembolisation; RF, radiofrequency.

Pre-ablation work-up and histological diagnosis

Pretreatment investigation included US, contrast-enhanced US (CEUS), contrast-enhanced CT and/or contrast-enhanced MRI, and tumor marker assay in all patients. The maximum diameter of the index tumors was measured on CEUS. US and CEUS were performed using the LOGIQ E9 system (GE Healthcare, Milwaukee, USA) with 3.5-5.0 MHz curved-array multifrequency transducers. The system was equipped with the software for CEUS imaging. SonoVue (Bracco, Milan, Italy), a sulphur hexafluoride-filled microbubble contrast agent encapsulated by a flexible phospholipid shell, was injected as the contrast agent for CEUS. The shortest distance from the edge of the lesion to the vital structures such as larger vessels or extrahepatic organs was confirmed by contrast enhanced CT or MRI in the transverse plane and coronal plane.

Histological diagnosis was obtained by US-guided tumor biopsy using an 18-gauge needle (Bard Medical, Covington, GA, USA) in all patients. For patients with multiple nodules, at least one biopsy was performed. If new tumors emerged after ablation, biopsies of the new nodules were performed.

Laboratory data

Since an increase in serum alpha-fetoprotein (AFP) levels may indicate recurrence or new nodules, AFP assay was performed in all patients before and after RF ablation. The AFP level was abnormal (range 22-9100 µg/L) in 32 patients (46.4%). Serum AFP assay was performed at 1 month after treatment, and follow-up was performed at an interval of 3 months.

Radiofrequency ablation

All treatments were performed in the operating room under intravenous anesthesia. The RF system (Celon Lab Power, Olympus, Hamburg, Germany) provides a maximum power output of 250 W (rated frequency, 470±10 kHz) and is capable of connecting one to three electrodes with an exposed tip of 20-40 mm. Each electrode has a 20 cm shaft (diameter of 1.8 mm) which could be easily visualized on sonographic image. The system consists of three water-pumping machines, which can drive three cool-tip needle electrodes. A detailed protocol was worked out for each patient on an individual basis before treatment, which included the placement of the electrodes, power output setting, emission time, and appropriate approach. In general, for tumors less than 1.5 cm in diameter, a single electrode was used; for tumors 1.5cm or larger, multiple electrodes were required. An output setting between 40 W and 60 W was used during ablations. The tip of the electrode was at least 3 mm away from the high-risk location (perpendicular approach,

the electrode aiming at the high-risk location), and the body of the electrode was at least 5 mm away from the high-risk location (parallel approach, the electrode was placed parallel to the high-risk location) according to the thermal field effect of RF electrode. During the therapy, we monitored the hyperechoic area of ablation using real-time US to decide the end point of treatment. If the hyperechoic region on grayscale US covered the entire target region, we completed the treatment session. After ablation the electrodes were slowly withdrawn, and RF emission was continued until the electrodes were pulled just under the skin entrance site. This method allowed needle track cauterization to prevent tumor seeding and to minimize bleeding after ablation.

All therapy was performed by two experienced radiologists with more than 10 years of experience with interventional procedures. During the procedure, the patient's symptoms and vital signs were monitored continually. Immediately after ablation, CEUS was carried out to evaluate whether the ablation area had covered the whole tumor. If residual tumor was detected, additional treatment was performed.

Percutaneous ethanol injection

For all 76 tumors in the study, PEI as the adjuvant therapy was adopted before RF ablation. All ethanol injections were planned beforehand, and to ensure that patients with no history of alcohol allergies. The standard total dose of injected ethanol is calculated according to the tumor's size. The diffusion of ethanol in the tumor was monitored with real-time US guidance, when a hyperechoic zone from injection had completely covered the tumor margin adjacent to the vital structures, then withdrew the needle. In particular, the injection should be stopped all at once when significant ethanol leaking into surrounding veins or surrounding structures was founded. With US guidance, one to two 21-gauge percutaneous ethanol injection needles (Hakko, Tokyo, Japan) were placed into marginal tissue of tumor proximal to the gastrointestinal tract for 5 tumors in the study group. There are three side holes at the point of the needle, which allows for uniform distribution of the injected ethanol. Dehydrated, sterile, 99.5% ethanol was slowly injected into marginal tissue of tumor under US guidance before RF ablation.

Follow-up

CEUS was performed one or two days after ablation to assess the completeness of ablation and detect the presence of immediate complications. If residual tumor was detected, an additional session was performed to achieve complete ablation. The follow-up period was calculated from the beginning of radiofrequency ablation

for all patients. All patients underwent contrast-enhanced CT or MRI examination at one month after RF ablation and then at 3- to 6-month intervals. If the patients were not suitable for contrast agent CT or MRI, a contrast-enhanced US was performed.

The therapeutic effectiveness was based on the results of contrast-enhanced imaging and the serum tumor marker levels.

Residual tumor that was not completely ablated was defined as the presence of any remaining enhancing foci in the ablation zone as depicted by either contrast-enhanced US or other early follow-up contrast-enhanced imaging. Complications were identified with clinical symptoms and imaging techniques. The complications including pneumothorax, tumor seeding, perforation, bile duct stricture and skin burn, and side effects such as fever, pleural effusion and pain, were also documented [26]. The median follow-up time was 20.3 months (range 4 to 38 months)

Statistical analysis

Data analysis was done using SPSS for windows (Version 17.0) and the data was expressed as means ± standard deviation (SD). Independent-samples t test was used to compare the means between the groups, and Chi-square test was undertaken to compare the proportions. $P < 0.05$ was considered statistically significant.

Results

All cases in this study were inpatients. They were admitted for additional examination and treatment before the operation and discharged 1-3 days after ablation if they lacked residual tumor and complications. The average time that patients had spent in the hospital was 10.9 days, which was similar to the time for other patients with HCC treated with RF ablation because they did not undergo any special measurements after the treatment.

Outcome of ablation

Seventy-three (96.1%) of 76 tumors achieved complete ablation as confirmed at 1-month follow-up by contrast-enhanced imaging. Among the tumors with more than 6 months follow-up after treatment, 37 (94.9%) of 49 tumors were completely ablated (Fig. 1). All patients were followed up regularly according to the follow-up protocol. During the follow-up period, 2 patients (2.63%) died of progression of primary disease that was not directly attributable to the RF ablation.

Ethanol (range 0.4-4.0 ml, mean 1.79 ml) was injected into the tumors in 69 patients with 76 nodules. With 1-3 injection sessions (mean 1.4 ± 0.5 sessions) and total dose of 2.5 - 8.0 ml (mean 4.2 ± 2.1 ml) by the end of the treatment.
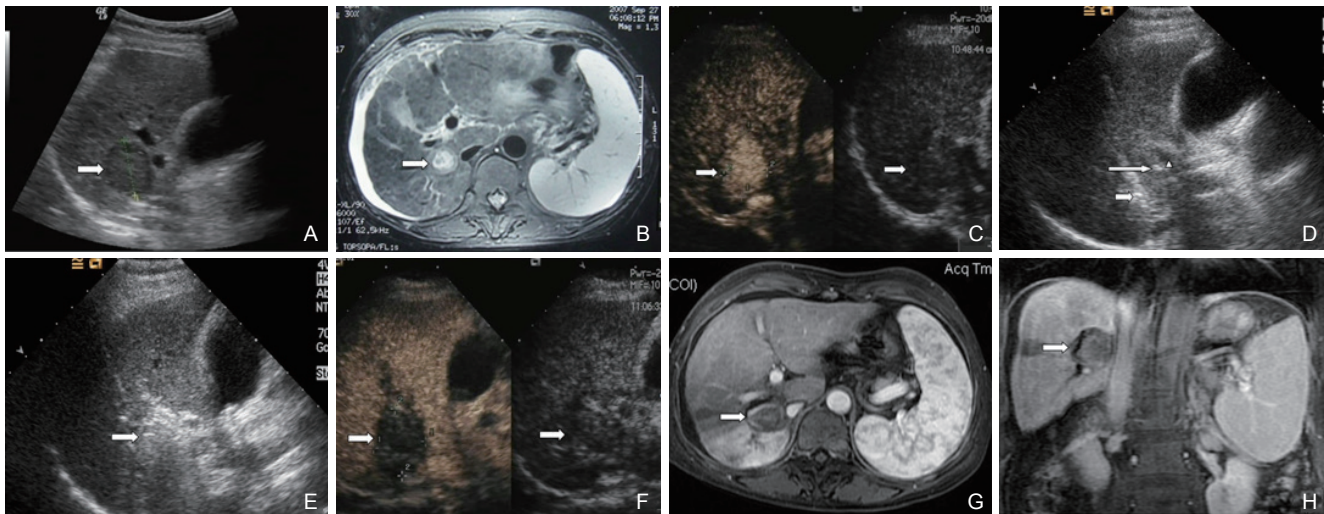
Figure 1 A 55-year-old woman with hepatitis B virus-related cirrhosis and HCC in the right lobe of the liver treated with RF ablation combined with PEI, and the tumor is adjacent to the hepatic hilum. (A) Gray-scale ultrasound shows the tumor (arrow) was hypoechoic and adjacent to the hepatic hilum;(B) CEUS shows the tumor hyper-enhanced (arrow) in the arterial phase;(C) MRI shows the tumor (arrow) located adjacent to the hepatic hilum;(D) The RF ablation electrode (short arrowhead) is placed into the tumor and the PEI needle (long arrowhead) is placed into the margin of the tumor proximal to the right hepatic duct (△);(E) During the therapy, the hyperechoic area of ablation (arrow) is monitored by real-time US;(F) One day after ablation, the ablated zone (arrowhead) is evaluated by CEUS and the tumor is completely destroyed;(G) Six months after ablation, MRI shows the tumor is completely destroyed (arrow);(H) Twelve months after therapy, MRI coronal plane scan shows the ablation zone (arrow).

Complications

There were no treatment-related deaths, pneumothorax, perforation, bile duct stricture, skin burn or other major complications.

After treatment, according to the common toxicity criteria for reporting pain published by the National Cancer Institute [27], 3 patients (4.3%) had suffered grade 3 pain, which is a major complication that required the administration of analgesics. Eighteen patients (26.1%) had suffered grade 1-2 pain lasting for one day or more. Twenty-two patients (31.9%) had a fever of 37.5-38.8 ℃ that persisted for 1-2 days. All patients were given antibiotics on the operation day. Seven patients (10.1%) reported right upper quadrant discomfort. Two patients (2.9%) reported nausea. One patient (1.4%) had right side pleural effusion according to CT, and he did not undergo additional therapy, and the effusion disappeared by the 1-month follow-up US examination. One patient (1.4%) had infection with leukocytosis, and last for three days after added antibiotics. The ablation zone was well defined on contrast-enhanced CT/MRI and CEUS, and it shrank gradually after ablation. (Table 2)

Changes of AFP level

Among the 32 patients with abnormal AFP level before treatment in the study, 24 (75.0%) showed a completely negative result post treatment, and 7 (21.8%) had the level decrease by more than 50% one month after the ablation. There was one patient whose tumor had not been ablated completely and the AFP level did not decrease.

Table 2 Ablation complications

Complications	Data
Pain (grade 3)	3
Pain (grade 1-2)	18
Fever	21
Right upper quadrant discomfort	7
Nausea	2
Right side pleural effusion	1
Infection	1

Local tumor progression

Local tumor progression was noted in 3 tumors (3.9%) by contrast-enhanced imaging during the follow-up period, and the incidence of local tumor progression in the study: 1 year: 2.6%, 2 years: 3.9%, 3 years: 3.9%. These patients underwent additional therapy to treat the locally progressed tumors (one patient underwent RF ablation and TACE, another patient with two nodules underwent TACE). (Table 3)

In the study, 21 patients (30.4%) had one to three new HCCs at the follow-up period. There were 12, 4, 2 and 3 patients underwent RF ablation, TACE, cryoablation, radiation therapy or liver resection as the additional treatments respectively.

Table 3 Characteristics of local tumor progression

NO.	Location	Diameter (cm)	Distances: proximity to the high-risk structure (cm)	Additional Treatment
1	S8	2.8	0.3	RF ablation and TACE
2	S3	1.6	0.3	TACE
3	S8	1.2	0.4	TACE

Discussion

Treatment for patients with tumors in the high-risk locations is difficult. Image-guided thermal ablation has been considered a safe technique; however, a broad spectrum of complications has been reported in several large series [28-29]. Some investigators have suggested that tumor location was closely related to the risk of major complications. Central tumors close to the hepatic hilum were reported to be unsuitable for percutaneous RF ablation because of the risk of injuring adjacent bile ducts [30]. It was also suggested that RF ablation for nodules adjacent to large vessels may often result in incomplete necrosis because of a heat sink effect. In addition, peripheral tumors adjacent to extrahepatic organs were also suggested to be unsuitable because of the risk of heat injury, such as intestinal perforation and pleural effusion. Thus, there may be a difficulty with RF ablation of nodules in such high-risk locations, possibly resulting in complications or not allowing sufficient treatment [31]. Some authors reported that for treating such tumors, special interventional techniques such as introducing artificial ascites and hyaluronic acid gel injection are necessary to separate the gastrointestinal tract from the liver [32-33]. However, the occurrence of complications such as intraperitoneal bleeding, intestinal perforation and peritoneal seeding increased [34]. Therefore, special precautions and strategies are required to treat tumors in these dangerous locations.

Combinations of chemical and thermal ablation have been reported. The combination of RF ablation and PEI in the management of HCC in high-risk locations was more effective than RF ablation alone [35]. In a study by Zhou [36], combining PEI and MW ablation achieved a significantly wider maximum diameter of coagulation and more complete necrosis of the treated tumors. This was thought to be due to increased thermal conduction and diffusivity through previously coagulated tissue. In our study, percutaneous RF ablation therapy combined with ethanol injection were performed for hepatocellular carcinoma in the high-risk locations to achieve complete necrosis of the marginal tissue of tumor and avoid thermal injury. PEI has two effects: procuring chemical ablation for the marginal cells of the tumor and achieving a synergistic effect with combined use of ethanol and

thermal ablation. This is probably due to the effect of hot ethanol in extending tissue necrosis, diffusion of ethanol into areas not reached by radiofrequency energy, and reduction of the heat-sink effect. Experimental and clinical reports have shown that combined use of ethanol and radio-frequency or microwave ablation causes a synergistic necrotizing effect, with coagulation volumes clearly larger than those usually obtained with RF ablation, MW ablation or PEI alone [37-38]. Meanwhile, the relatively high rate of complete ablation (73/76, 96.1%) and low rate of complication achieved may be attributable to the following reasons: 1) Our accumulated experience in percutaneous microwave ablation procedures amounting to a total of 1136 cases; 2) In our study, PEI was performed before RF ablation to augment the effect of RF ablation. The risk of thermal injury to the high-risk locations may preclude complete RF ablation of the tumor periphery close to the large vessel, but the tumor periphery could be coagulated by the chemical ablation effect of the absolute ethanol injected.

In this study we found that percutaneous RF ablation therapy combined with ethanol injection for hepatocellular carcinoma in the high-risk locations is a safe and effective treatment option with low occurrence of complications and local tumor progression.

This study has some limitations. First, these data were obtained from a single center with extensive experience in microwave ablation for liver tumors. A multicenter study is required to confirm these findings. Second, the amount of ethanol injected was not standardized. The volume of coagulation necrosis and possibly the risk of complications may be proportionally increased with the volume of ethanol injected. Last, because of the relatively short follow-up period, some late complications, such as seeding and biliary tract injury, might have been underreported.

Conclusions

In a conclusion, US-guided percutaneous RF ablation combined with ethanol injection is a safe and effective treatment option for HCC in high-risk locations.

Conflicts of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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