Diagn Interv Radiol 2023; DOI: 10.4274/dir.2022.22832

INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Long-term outcomes of combined radiofrequency ablation and multipronged ethanol ablation for the treatment of unfavorable hepatocellular carcinoma

Ming Liu
Xiao-Ju Li
Xiao-Er Zhang
Ming Kuang
Xiao-Yan Xie
Guang-Liang Huang

PURPOSE

To evaluate the local efficacy, safety, and long-term outcomes of combined radiofrequency ablation (RFA) and multipronged ethanol ablation (EA) in the treatment of unfavorable hepatocellular carcinoma (HCC) and to determine the prognostic factors for survival.

METHODS

Between August 2009 and December 2017, 98 patients with 110 unfavorable HCC nodules who underwent combined RFA and multipronged EA were retrospectively enrolled in the study. Unfavorable HCC was defined as a medium (3.1–5.0 cm) or large (5.1–7.0 cm) HCC nodule, a tumor located at a high-risk site, or a perivascular tumor. The treatment response, overall survival (OS), and recurrence-free survival (RFS) were analyzed. The Kaplan–Meier method and Cox proportional hazards regression model were used to evaluate the prognostic factors.

RESULTS

Complete ablation was obtained in 80.9% (89/110) of the tumors after initial treatment. Major complications were observed in 3 (3.1%) patients. The cumulative incidence of local tumor progression (LTP) was 23.5% at five years, and no variable was found to be an independent predictive factor for LTP. The five-year OS and RFS rates were 41.9% and 34.0%, respectively. Multivariate analysis showed that the serum alpha-fetoprotein level, tumor size, presence of residual tumor after ablation, and extrahepatic metastases were significant prognostic factors for OS ($P = 0.023$, $P = 0.030$, $P = 0.001$, and $P = 0.010$, respectively). Tumor type and the number of tumors were predictive factors for RFS ($P = 0.029$ and $P = 0.001$, respectively). A perivascular tumor was not an independent predictive factor for OS or RFS.

CONCLUSION

Combined RFA and multipronged EA is a safe and effective treatment for unfavorable HCC, especially for perivascular tumors.

KEYWORDS

Combine, ethanol, hepatocellular carcinoma, radiofrequency ablation, survival

From the Department of Medical Ultrasonics (M.L., X-J.L., X-E.Z., M.K., X-Y.X., G-L.H. ✉ huanggl9@mail.sysu.edu.cn), The First Affiliated Hospital of Sun Yat-Sen University, Institute for Diagnostic and Interventional Ultrasound, Guangzhou, China; Department of Liver Surgery (M.K.), The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China.

Received 22 August 2021; revision requested 11 October 2021; last revision received 01 February 2022; accepted 16 February 2022.

Epub: 13.02.2023

Publication date: 29.03.2023

DOI: 10.4274/dir.2022.22832

Hepatocellular carcinoma (HCC) is the fifth most common cancer and a major cause of cancer-related death worldwide.[1,2] Patients with early-stage HCC can be cured by therapies such as hepatic resection, liver transplantation, or ablation. Radiofrequency ablation (RFA) has recently become a treatment option for HCC.[3]

Despite the success of RFA treatment for small tumors, the local tumor complete ablation (CA) rates decline markedly for HCC tumors with a diameter >3 cm; meanwhile, the local tumor recurrence rate for RFA is higher than that for resection because RFA alone can only induce a limited volume of coagulated necrosis.[4] A perivascular tumor location has been

You may cite this article as: Liu M, Li XJ, Zhang XE, Kuang M, Xie XY, Huang GL. Long-term outcomes of combined radiofrequency ablation and multipronged ethanol ablation for the treatment of unfavorable hepatocellular carcinoma. *Diagn Interv Radiol.* 2023;29(2):342-349.

reported to be an independent predictive factor for local tumor progression (LTP) after RFA.[5] This finding could be explained to some degree by the "heat-sink" effect, which is a well-known phenomenon that occurs when thermal energy disseminates from the treated lesion because of blood flow in the nearby blood vessels. This has an adverse impact on thermal ablation and induces tumor cells around the major intrahepatic vessels to escape from the thermal energy.

Some studies have shown that combined percutaneous RFA and ethanol ablation (EA) is an effective treatment for HCC in high-risk locations, which is defined as a tumor less than 0.5 cm from the gastrointestinal tract, gallbladder, diaphragm, or large bile duct (including hepatobiliary and bile ducts with a diameter >0.3 cm), a tumor located directly in contact with the liver capsule,[6-8] a tumor near the large vasculature >0.3 cm, or a tumor near to the heart (perivascular tumor).[9,10] A retractable multipronged injection needle was developed to overcome the limitations of the conventional EA technique.[11] The authors' preliminary study confirms that medium (3.1–5.0 cm) and large (5.1–7.0 cm) HCC nodules can be treated effectively and safely with this combined ablation therapy.[12]

The aim of the current study is to evaluate the local efficacy, safety, and long-term outcomes of combined RFA and EA as a treatment for unfavorable HCC, especially perivascular tumors, and determine the prognostic survival factors. A multipronged injection needle (Quadra-Fuse; Rex Medical, Conshohocken, PA, USA) is used for EA. To the authors' knowledge, no previous studies have reported long-term outcomes of combined RFA and EA with a multipronged injection needle.

Methods

An Institutional Review Board of the hospital approved this retrospective study with a waiver of informed consent for participation in the study [ethical review decision/protocol number: 2012 (68)]. Before treatment, the authors obtained written informed consent from each patient.

Main points

- Combined radiofrequency ablation (RFA) and multipronged ethanol ablation (EA) is a safe and effective modality for treating unfavorable hepatocellular carcinoma.
- Combined RFA and multipronged EA expand the indication of thermal ablation to tumors of 5 cm in diameter.
- A high serum alpha-fetoprotein level, large tumors, residual tumors after ablation, and extrahepatic metastases have a significant negative effect on overall survival.

Patients

Between August 2009 and December 2017, a total of 98 patients (86 men, 12 women; mean age 55.0 ± 12.7 years) with 110 unfavorable HCC nodules (4.0 ± 1.0 cm) who underwent combined RFA and multipronged EA were retrospectively enrolled in the study. In the current study, unfavorable HCC was defined as medium (3.1–5.0 cm) or large (5.1–7.0 cm) HCC tumors, a tumor located at a high-risk site, or perivascular tumors. The diagnosis of HCC was based on a biopsy or the non-invasive diagnostic criteria of the European Association for the Study of the Liver. The inclusion criteria were as follows: (a) adult patients with HCC or recurrent HCC who refused to undergo surgery; (b) single or multiple tumors (no more than three HCC tumors, with the largest lesion 7.0 cm in diameter) without extrahepatic metastasis or macrovascular invasion; (c) liver function classified as Child–Pugh class A or B; (d) platelet count >50×10^9/L and prothrombin time ratio >50%; and (e) visualization of the HCC nodule at the planning ultrasonography examination for RFA. Patients with liver function classified as Child–Pugh class C, those with uncontrolled coagulopathy, or those with a history of ethanol allergy were excluded from the study.

Tumor diameters were determined as the largest dimension measured using B-mode ultrasound. Tumor numbers were determined from contrast-enhanced ultrasound (CEUS) with SonoVue as a contrast agent and contrast-enhanced computed tomography (CECT) findings. The Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy was used to make treatment decisions for stage 0–A patients. For BCLC stage B patients, treatment decisions were made based on the results of a multidisciplinary team (MDT). Diagnostic and treatment decisions were made in consensus by the MDT consisting of hepatobiliary surgeons and interventional radiologists.

Ethanol ablation

A multipronged injection needle was used to inject ethanol. This device included an 18-gauge 20 cm-long puncture needle consisting of an echogenic tip; three retractable tines, each with two evenly spaced through-holes (four fluid exits); and a connector with extension tubing. With ultrasound guidance, the needle was introduced percutaneously into the tumor center, and the needle tip was positioned at the bottom of the target tumor. An injection–rotation–injection maneuver was used as described in our previous reports.[12,13] The maximal extent of prong deployment was equal to the tumor's largest diameter. Ethanol was injected until the whole tumor appeared completely hyperechoic. The amount of ethanol was calculated according to the tumor size and was kept between one-quarter and one-third of the estimated tumor volume. During any necessary pause of ethanol injection, 0.5–1.0 mL of heparinized saline solution was injected to prevent thrombosis inside the prongs. After the completion of the injection, the needle was left in the tumor for 1–2 min to prevent possible ethanol reflux before it was removed.

Radiofrequency ablation

We used the RITA Medical System (RITA Medical System, Mountain View, CA) and the Cool-tip TM RFA System (Cool-tip System, Covidien, Mansfield, MA). The combined ablation procedure was the same as that described in the authors' previous report for tumors located or not located at high-risk sites.[12,13] For tumors located at high-risk sites, the Cool-tip System was used. For tumors not located at high-risk sites, the RITA Medical System was used. RFA was performed 3–5 min after EA following the manufacturer's guidelines. During the ablation, the authors tried to obtain an adequate coagulation volume with a sufficient safety margin of 0.5 cm. CEUS was performed approximately 30 min after ablation, providing an initial evaluation of the treatment effect. Additional treatment was performed if any tumor residue was found.

Assessment of treatment response and follow-up

All complications related to thermal ablation were categorized according to the grading system of the Society of Interventional Radiology.[14]

The initial CA evaluation performed one month after ablation was assessed using CECT and CEUS simultaneously. All patients were scanned using a 64-slice helical CT scanner (Toshiba, Tokyo, Japan) with the following parameters: 0.5 mm × 64 mm collima-

tion, 120 kV, and 150–200 mA. Follow-up was conducted at regular intervals post-ablation (at three-month intervals for the first year and biannually thereafter). The evaluation included assessing common blood chemistry parameters, serum alpha-fetoprotein (AFP) levels, and performing an abdominal CECT examination.

CA was defined as non-enhancement in the ablated zone one month after ablation. LTP was defined as the appearance of tumor foci at the edge of the ablation zone after a contrast-enhanced examination documented CA according to the imaging criteria.[14] Intrahepatic distant recurrence (IDR) was defined as the appearance of new intrahepatic tumors in locations other than the treated area. Extrahepatic metastases were defined as the appearance of new metastases in other organs.

Statistical analysis

Overall survival (OS) was the time interval between ablation treatment and death, the last follow-up date, or the most recent follow-up date before December 31, 2017. Recurrence-free survival (RFS) was the time interval between ablation treatment and the first date of tumor recurrence (local and/or distant recurrence) or the last follow-up date without recurrence.

According to the normality test for continuous variables, variables conforming to a normal distribution are presented as the means ± standard deviations, and variables not conforming to a normal distribution are presented as the medians (min–max). Categorical variables were compared using the Pearson chi-squared test and Fisher's exact test.

The cumulative incidences of LTP and the survival curves were estimated by using the Kaplan–Meier method. Univariate and multivariate analyses were performed to determine the significant clinical and biological parameters for predicting LTP, OS, and RFS. In addition, a univariate Cox proportional hazards model was fitted to each variable. All variables with a P value < $\alpha = 0.05$ were included in the multiple analysis using a backward stepwise Cox proportional hazards regression model. A P value < $\alpha = 0.05$ indicated a significant difference. All statistical analyses were conducted using SPSS version 18.0.

Results

Patients and tumor profiles

Eighty-six patients (87.8%) infected with hepatitis B or C received antivirus therapy. Forty-nine (50.0%) patients received a first-time diagnosis of HCC, and 49 (50.0%) had recurrence after hepatectomy (n = 34), transcatheter arterial chemoembolization (TACE) (n = 10), RFA (n = 4), or liver transplantation (n = 1). Eighty-two tumors (74.5%) were >3.0 cm in diameter. The other 28 tumors were 3.0 cm; however, of these tumors, 20 were located at high-risk sites, and 8 were perivascular. Eighty (72.7%) tumors were located at high-risk sites. Fifty-eight (52.7%) tumors were perivascular. Forty-three tumors were located at high-risk sites and were perivascular simultaneously. Table 1 shows the demographic and tumor characteristic data.

Tumor response to treatment

After initial treatment, CA was obtained in 80.9% (89/110) of the tumors. The CA rate was 92.9% (26/28) for tumors 3.0 cm in diameter, 82.6% (57/69) for tumors with sizes of 3.1–5.0 cm, and 46.2% (6/13) for tumors with sizes of 5.1–7.0 cm. The CA rate of the tumors with sizes of 3.1–5.0 cm was similar to that of the tumors 3.0 cm in diameter ($P = 0.338$). The CA rates of tumors 3.0 cm in diameter and tumors with sizes of 3.1–5.0 cm were both higher than the CA rate of tumors with sizes of 5.1–7.0 cm ($P = 0.002$ and $P = 0.009$, respectively). Of the 21 residual tumors in 21 patients, 9 residual tumors in 9 patients achieved CA after an additional 1–3 RFA procedures. Overall, the technical success rate was 89.1% (98/110). Regarding the other 12 residual tumors in 12 patients, 3 patients were treated with TACE, 3 patients were treated with repeated RFA that failed, and 2 patients underwent liver transplantation. The remaining 4 patients also had distant multinodular recurrences that were treated with sorafenib.

Table 1. Demographic and tumor characteristic data

Characteristic	Value
Gender (male/female)	86/12
*Age (years)	55.0±12.7
Hepatitis virus (B/C/none)	85/1/12
Child–Pugh class (A/B)	92/6
#Serum alanine aminotransferase level (U/L)	36.0 (2.9–351.0)
#Serum total bilirubin (umol/L)	14.4 (2.8–90.6)
*Serum albumin (g/L)	39.3±4.1 (27.8–49.7)
#Prothrombin time (s)	12.4 (10.2–16.6)
#Platelet count (×10^9/L)	137.0 (47.0–407.0)
Serum alpha-fetoprotein level (ng/mL)	
<20 ng/mL	49
20–200 ng/mL	19
>200 ng/mL	30
Number of patients with primary/recurrent tumor	49/49
Number of patients with single/multiple tumor	67/31
#Tumor size (cm)	3.6 (2.0–7.0)
Number of tumors 3.0 cm/3.1–5.0 cm/5.1–7.0 cm	28/69/13
Number of tumors per location	
Located at high-risk sites (yes/no)	80/30
Perivascular (yes/no)	50/60
#Ethanol volume	15.0 (4.0–30.0)
#Ablation time	24.0 (10.0–60.0)

*Values represent continuous variables conforming to a normal distribution, presented as the means ± standard deviations, #values represent continuous variables not conforming to a normal distribution, presented as the median (min–max).

Complications

No ablation-related deaths occurred in the current study. Three patients (3.1%) experienced major complications. One patient suffered from intra-abdominal hemorrhage and remained hospitalized for 27 days after the ablation procedure. This patient initially presented with abdominal pain, then developed an abdominal infection, and was diagnosed with spontaneous peritonitis, which was successfully treated with ultrasound-guided ascites drainage and antibiotics. Another patient developed acute cholecystitis, which resulted in an eight-day hospital stay after treatment. This patient had a history of gallstones, which were successfully treated. The third patient had a tumor seeding in the abdominal wall at 21.4 months after treatment, and this tumor was successfully treated with RFA.

Ablation-related minor complications occurred in 3 patients (3.1%), including 2 cases of pleural effusion and 1 case of portal venous thrombosis that required no medical intervention.

Local tumor progression

Of the 98 completely ablated tumors, 23 (23.5%) lesions in 23 patients exhibited LTP during the follow-up period of 3.2–98.4 months (median, 31.1 months), and the LTP time was 2.8–64.2 months (median, 12.2 months). The cumulative incidence of LTP was estimated to be 2.3%, 15.9%, and 23.5% at one, three, and five years, respectively. The LTP rate was 29.6% (8/27) for tumors with sizes 3 cm, 23.4% (15/64) for tumors with sizes of 3.1–5.0 cm, and 0% (0/7) for tumors with sizes of 5.1–7.0 cm (P = 0.332). Among the 17 examined variables, including sex (male), age (>65 years), Child–Pugh class (A/B), hepatitis B/C virus status (+/–), serum alanine aminotransferase level (>40 U/L), serum total bilirubin level (>17.1 μmol/L), serum albumin level (>35 g/L), prothrombin time (>14 s), platelet count (>100 × 10^9/L), serum AFP level (<20 ng/mL/20–200 ng/mL >200 ng/mL), tumor type (primary/recurrent), number of tumors (single/multiple), tumor size (3 cm/3.1–5.0 cm/5.1–7.0 cm), tumor location (located at high-risk sites, perivascular), ethanol volume (>14.4 mL), and ablation time (>24 min), no variable was found to be a predictive factor for LTP. Among the 23 patients with LTP, 14 were treated successfully with repeated RFA, 1 was treated with TACE, 1 underwent liver transplantation, and 1 underwent hepatic resection. The remaining 6 patients also had distant multinodular recurrences that were treated with sorafenib.

Distant recurrence

Distant recurrence included IDR and extrahepatic metastases. Seventy (71.4%) of the 98 patients had IDR, which was identified 3.0–65.1 months after ablation (median, 8.0 months), during the follow-up period, including 19 patients with IDR in the left lobe of the liver, 34 patients with IDR in the right lobe of the liver, and 17 patients with IDR in the whole liver. In addition, 2 patients developed a portal vein tumor thrombus, which occurred after 2.2 months in one patient and after 3 months in the other patient. During the follow-up period, extrahepatic metastases, which were identified 3.0–55.5 months after ablation (median, 7.2 months), developed in 20 (20.4%) of the 98 patients, and the locations of the initial extrahepatic metastases were as follows: the lungs (n = 9), lymph nodes (n = 6), abdominal wall (n = 2), bone (n = 1), adrenal gland (n = 1), and spleen (n = 1).

Survival analysis

Overall survival

During the follow-up period, 53 (54.1%) patients died after ablation. The median survival time of patients who died after the procedure was 21.2 months, and the minimum and maximum survival times were 5.1 and 81.3 months, respectively. The interquartile range was 22.2 months. Among the patients who died, 37 (69.8%) deaths were related to HCC progression; 14 (26.4%) were attributed to cirrhosis-related complications, such as variceal bleeding and liver failure; and 2 (3.8%) involved causes unrelated to liver disease (e.g., one patient had pneumonia, and the other had a stroke). Six (6.1%) patients underwent liver transplantation 4.2–77.5 months after ablation (median, 6.3 months). The reasons for liver transplantation were HCC recurrence in 5 patients and liver failure in 1 patient.

The estimated one-, three-, and five-year OS rates after RFA were 87.3%, 54.3%, and 41.9%, respectively (Figure 1). In the multivariate analysis, the serum AFP level (P = 0.023), tumor size (P = 0.030), residual tumor (P = 0.001), and extrahepatic metastases (P = 0.010) were significant independent predictive factors for OS (Table 2).

Recurrence-free survival

The estimated one-, three-, and five-year RFS rates were 63.1%, 46.9%, and 34.0%, respectively. Estimates of the mean and median RFS were 42.8 months [95% confidence interval (CI): 33.0–52.6] and 31.9 months (95% CI: 11.8-52.0), respectively. In the multivariate analysis, tumor type (P = 0.029) and the number of tumors (P = 0.001) were significant independent predictive factors for RFS (Table 3).

Table 4 shows the local efficacy and long-term outcome of different tumor and patient types.

Discussion

One procedure of one radiofrequency electrode produces a necrotic zone of 3.0–5.0 cm in diameter. The form and size of the ablation area may be errant because of the heat-

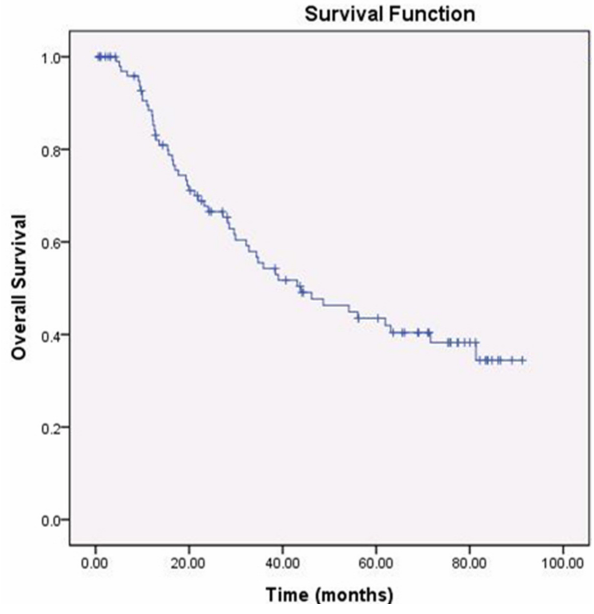

Figure 1. A graph showing Kaplan–Meier overall survival estimation for 98 patients who underwent combined radiofrequency ablation and multipronged ethanol ablation for hepatocellular carcinoma.

Table 2. Cox survival analysis of predictors for OS in 98 patients with 110 HCCs after combined RFA and multipronged EA

Characteristic	Univariate			Multivariate		
	HR	95%CI	*P*	HR	95% CI	*P*
Gender (male)	0.698	0.277–1.750	0.441	-	-	-
Age (>65 years)	0.835	0.452–1.541	0.563	-	-	-
Hepatitis B/C virus (+/–)	0.866	0.344–2.178	0.760	-	-	-
Child–Pugh class (A/B)	0.789	0.244–2.556	0.693	-	-	-
Serum alanine aminotransferase level (>40 U/L)	1.192	0.678–2.093	0.542	-	-	-
Serum total bilirubin (>17.1 umol/L)	1.230	0.683–2.215	0.491	-	-	-
Serum albumin (>35 g/L)	0.912	0.457–1.819	0.793	-	-	-
Prothrombin time (>14 s)	0.972	0.351–2.696	0.957	-	-	-
Platelet count (>100×10^9/L)	1.152	0.616–2.155	0.657	-	-	-
Serum alpha-fetoprotein level (ng/mL)	-	-	0.011	-	-	0.023
20 vs. 20–200	1.551	0.731–3.289	0.252	0.396	0.205–0.766	0.006
20 vs. >200	2.513	1.375–4.594	0.003	0.576	0.233–1.423	0.232
Tumor type (primary/recurrent)	0.408	0.232–0.718	0.002	0.592	0.320–1.093	0.094
Number of tumors (single/multiple)	0.384	0.223–0.662	0.001	0.539	0.283–1.028	0.061
Tumor size (cm)			<0.001			0.030
3.0 vs. 3.1–5.0	1.067	0.524–2.171	0.859	0.343	0.134–0.877	0.025
3.0 vs. 5.1–7.0	5.174	2.168–12.349	<0.001	0.349	0.154–0.789	0.011
Tumor location						
Located at high-risk sites (yes/no)	0.948	0.540–1.664	0.853	-	-	-
Perivascular (yes/no)	0.892	0.520–1.529	0.677	-	-	-
Ethanol volume (>14.4 mL)	1.038	0.604–1.781	0.894	-	-	-
Ablation time (>24 min)	1.012	0.575–1.783	0.967	-	-	-
Complication (yes/no)	1.504	0.468–4.883	0.493	-	-	-
Residual tumor (yes/no)	0.201	0.098–0.412	<0.001	0.237	0.103-0.545	0.001
LTP (yes/no)	1.697	0.828–3.477	0.149	-	-	-
IDR	0.305	1.138–1.677	0.004	0.452	0.197-1.041	0.062
Extrahepatic metastases	0.386	0.218–0.685	0.001	0.385	0.186-0.795	0.010

P values of the Cox proportional hazards regression model <0.001. CI, confidence interval; EA, ethanol ablation; HCC, hepatocellular carcinoma; HR, hazard ratio; IDR, intrahepatic distant recurrence; LTP, local tumor progression; OS, overall survival; RFA, radiofrequency ablation.

sink effect, which can lead to an inadequate ablation area and a higher rate of LTP in patients treated with RFA than in those treated with resection. Therefore, the use of RFA for HCC close to large intrahepatic vessels poses a great challenge in clinical practice. Moreover, the use of RFA is still limited for some tumors in other high-risk locations.[15] Several strategies, such as the combined use of RFA and EA or TACE, ablation with artificial hydrothorax and ascites, a no-touch ablation procedure, and irreversible electroporation, have been developed to solve these problems.[16-18]

RFA combined with EA can produce a larger ablation area; with this technique, tumors with diameters of less than 5 cm can be completely ablated with an appropriate safety margin.[19] Factors that contribute to the favorable efficacy of this technique include the following: first, the reduction in the heat-sink effect produced by the ethanol-induced destruction of the vessels within or around the HCC tumors; and second, the diffusion of hot ethanol into the area not covered by radiofrequency power and the improved thermal conduction associated with the decreased extent of tissue carbonization.[10,20] With this increased safety margin, the likelihood of clearing micrometastases increases, and the risk of LTP decreases.

In this study, the CA rate of tumors with sizes of 3.1–5.0 cm was similar to that of tumors with sizes 3.0 cm. Among the tumors with sizes of 3.1–5.0 cm, 74.3% (52/70) were located at high-risk sites, and 44.3% (31/70) were located at perivascular sites. Among the 31 perivascular tumors, only 2 exhibited residual tumors after treatment, while 3 non-perivascular tumors were residual after treatment. These findings indicate that the use of RFA combined with EA improves the initial complete necrosis rate of tumors with sizes of 3.1–5.0 cm but not that of tumors 3.0 cm in diameter or larger tumors with sizes of 5.1–7.0 cm. A growing body of literature suggests that RFA is very effective for tumors <3.0 cm, as studies have shown a complete tumor necrosis rate of 90% or more and survival rates comparable to those of patients who underwent surgery for these tumors.[21-25] Our study indicates that adding multipronged EA to RFA significantly improves the local efficacy (CA rate) of ablation for HCC tumors with a size of 3.1–5.0 cm, but this method is not suitable for tumors >5.0 cm in diameter due to the high residual rate.

The current study's 3.1% major complication rate was close to the rates in the previous studies of thermal ablation for HCC (0%–6.1%)[21,25,26] or RFA combined with EA for HCC (0%–4.6%).[12,27] No deaths or serious procedure-related complications resulted from

Table 3. Cox survival analysis of predictors for RFS in 86 patients with 98 HCCs after combined RFA and multipronged EA

Characteristic	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Gender (male)	0.532	0.164–1.723	0.293	-	-	-
Age (>65 years)	0.719	0.365–1.419	0.342	-	-	-
Hepatitis B/C virus (+/–)	0.938	0.332–2.649	0.903	-	-	-
Child–Pugh class (A/B)	0.650	0.198–2.132	0.478	-	-	-
Serum alanine aminotransferase level (>40 U/L)	0.910	0.490–1.691	0.767	-	-	-
Serum total bilirubin (>17.1 umol/L)	1.325	0.666–2.634	0.423	-	-	-
Serum albumin (>35 g/L)	0.960	0.445–2.072	0.917	-	-	-
Prothrombin time (>14 s)	1.187	0.423–3.335	0.745	-	-	-
Platelet count (>100×10^9/L)	1.199	0.589–2.440	0.617	-	-	-
Serum alpha-fetoprotein level (ng/mL)			0.053	-	-	0.117
20 vs. 20–200	1.359	0.594–3.107	0.468	1.437	0.607–3.403	0.410
20 vs. >200	2.282	1.170–4.453	0.016	2.098	1.038–4.240	0.039
Tumor type (primary/recurrent)	0.442	0.238–0.823	0.010	0.488	0.257–0.928	0.029
Number of tumors (single/multiple)	0.264	0.143–0.489	<0.001	0.338	0.177–0.646	0.001
Tumor size (cm)			0.001	-	-	0.053
3.0 vs. 3.1–5.0	1.191	0.563–2.519	0.648	1.498	0.698–3.217	0.300
3.0 vs. 5.1–7.0	7.217	2.292–22.724	0.001	4.809	1.482–15.600	0.009
Tumor location						
Located at high-risk sites (yes/no)	1.044	0.765–1.423	0.787	-	-	-
Perivascular (yes/no)	0.930	0.690–1.255	0.637	-	-	-
Ethanol volume (>14.4 mL)	0.942	0.698–1.271	0.695	-	-	-
Ablation time (>24 min)	0.990	0.522–1.879	0.975	-	-	-
LTP (yes/no)	1.074	0.741–1.556	0.707	-	-	-

P value of the Cox proportional hazards regression model <0.001. CA, complete ablation; CI, confidence interval; EA, ethanol ablation; HCC, hepatocellular carcinoma; HR, hazard ratio; RFA, radiofrequency ablation; RFS, recurrence-free survival; LTP, local tumor progression.

Table 4. Local efficacy and long-term outcome of different tumor and patient type

Tumor type	CA	LTP	Patient type	3-year OS	5-year OS	3-year RFS	5-year RFS
Medium tumor	57/69	15/64	Patients with medium tumor	0.564	0.634	0.464	-
Large tumor	6/13	0/7	Patients with large tumor	0.091	0	0	0
Tumor in high-risk locations	70/80	11/70	Patients with tumor in high-risk locations	0.335	0.531	0.429	-
Perivascular tumor	45/50	14/45	Patients with perivascular tumor	0.516	0.570	0.490	-

CA, complete ablation; LTP, local tumor progression; OS, overall survival; RFS, recurrence-free survival.

the combined ablation procedure used in the current study or were reported by other literature.[9,12] Tumors located at high-risk sites or perivascularly were generally successfully treated without complications in the current study (Figures 2, 3), which indicates the minimal invasiveness of this combined therapy. The complication rates of patients with and without perivascular tumors were similar (3/58 vs. 3/52, respectively, $P = 1.000$).

The LTP rate was 23.5% in the current study. This rate is similar to the rates observed in other studies of combined RFA and EA treatment for HCC, which have been reported to be approximately 12.5%–32.6%.[9,10,12,20] Some studies have reported that factors such as tumor size and perivascular tumor location were predisposing factors for LTP.[23,28] However, no such factor was found in the current study. The LTP rates of the patients with and without perivascular tumors were similar (14/58 vs. 9/52, respectively, $P = 0.379$). Because HCC has a relatively high tendency to exhibit intrahepatic vascular invasion, the current study implies that RFA and EA combination therapy is useful for preventing LTP in patients with perivascular tumors. The LTP rate is highest for small tumors and decreases with increasing tumor diameter, which occurs because many large tumors are not completely ablated during the initial treatment.

In recent years, TACE, followed by RFA, has been more widely applied in clinical settings because TACE can reduce the heat-sink effect of blood flow by lessening hepatic arterial flow. The five-year OS of TACE and RFA has been reported to be approximately 31.0%–46.0%,[29] which was similar to the current data of our study (41.9%). Our results showed that the significant predictive factors for poor OS were a high serum AFP level, tumor size, residual tumor after ablation, and extrahepatic metastases. Tumor size as a predictive factor for OS has been reported in many previous studies.[22,30-32] A high serum AFP level is usually related to tumors with a higher degree of malignancy and is predictive of a high rate of HCC recurrence and poor prognosis after percutaneous ablation. Residual tumor after ablation indicates treatment failure; there-

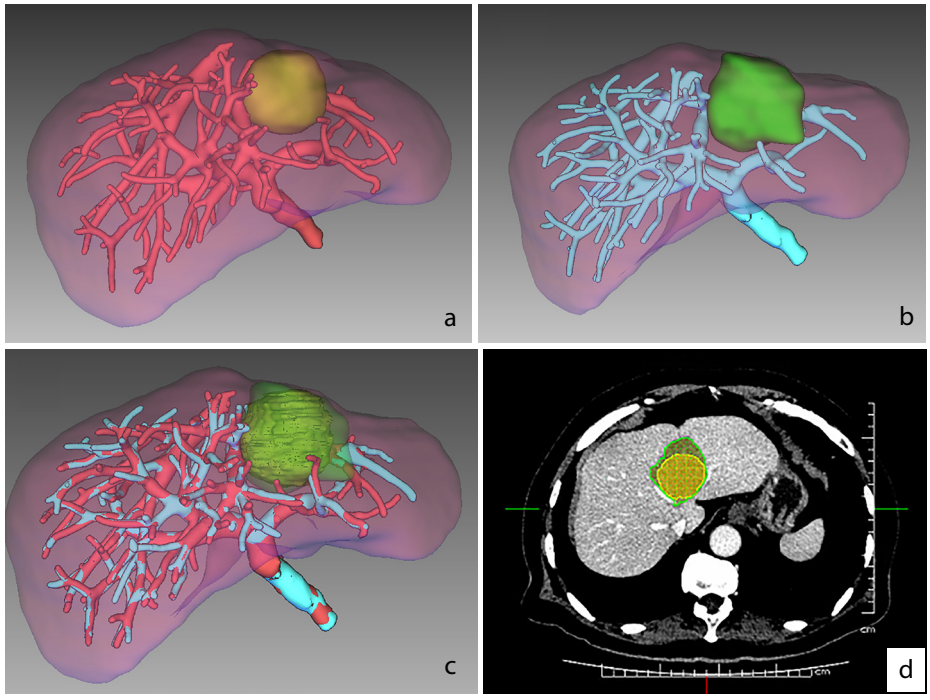

Figure 2. A hepatocellular carcinoma tumor located in contact with large vessels (the left and middle hepatic veins) in an 87-year-old man was treated by radiofrequency ablation (RFA) combined with multipronged ethanol ablation: **(a)** a computed tomography (CT) fusion obtained before performing combined ablation showed a lesion with a diameter of 4.2 cm in segment IV (marked in orange); **(b)** a CT fusion obtained one month after combined ablation showed the ablation zone (marked in green), which confirmed the complete ablation of the tumor; **(c)** a CT fusion showed that the tumor was successfully covered by the translucence ablation zone (green); **(d)** the pre-RFA tumor was overlaid on the post-RFA images. The ablation zone (marked in green line) covered the tumor (marked in yellow line). The minimal ablative margin was 0 cm at the side of the ablation zone in contact with the left and middle hepatic veins.

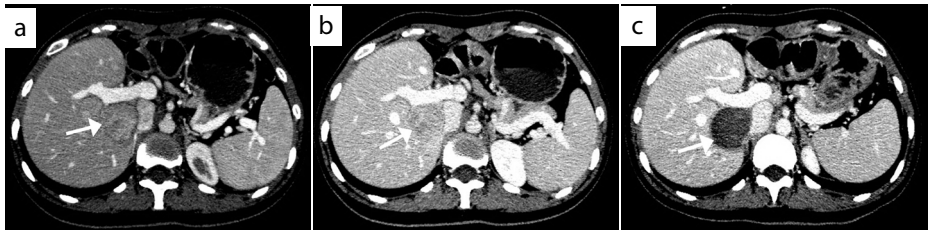

Figure 3. A hepatocellular carcinoma tumor located in contact with large vessels (main portal vein and postcava) in a 32-year-old female was treated with radiofrequency ablation combined with multipronged ethanol ablation: **(a)** the late arterial phase of pre-treatment computed tomography (CT) showed a lesion with a diameter of 4.1 cm in segment VIII (arrow); **(b)** the portal venous phase of pre-treatment CT showed that the tumor (arrow) was close to the main portal vein and postcava; and **(c)** a CT obtained one month after combined ablation showed the ablation zone (arrow), which confirmed the complete ablation of the tumor.

fore, patients undergo other treatments, which may have a poor effect on OS.[32] Multiple tumors were another significant predictor of poor RFS. The possible reasons include the following: first, as the number of tumors increases, the possibility of incomplete tumor removal increases; second, patients with multiple tumors might have a higher incidence of satellite nodules and micro-invasion, resulting in a higher rate of recurrence and worse survival; and, finally, after patients with multiple tumors undergo the combined ablation, when tumors recur, additional treatments are less likely to be performed. It is noteworthy that the presence of perivascular tumors did not predict worse OS or RFS, which implies that combination therapy may overcome some obstacles observed with RFA alone in HCC.

The current study has some limitations. First, a potential risk exists of selection bias because this was a retrospective study. Second, this study included only a single HCC treatment without direct comparisons.

In conclusion, combined RFA and multipronged EA is a safe and effective modality with a five-year OS rate of 41.9% for unfavorable HCC, and this approach was especially effective in patients with perivascular tumors. The presence of recurrent and multiple tumors had a significant negative effect on OS and RFS. Using this combined method, the authors have expanded the indications for thermal ablation to tumors with a diameter of 5 cm and those in high-risk locations.

Funding

This study has received funding by the National Natural Science Foundation of China (no: 81530055).

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global Cancer Statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87-108. [CrossRef]
2. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):359-386. [CrossRef]
3. Kawamura R, Seki T, Umehara H, et al. Combined treatment of large hepatocellular carcinoma with transcatheter arterial chemoembolization and percutaneous ethanol injection with a multipronged needle: experimental and clinical investigation. *Cardiovasc Intervent Radiol*. 2012;35(2):325-333. [CrossRef]
4. Lupo L, Panzera P, Giannelli G, Memeo M, Gentile A, Memeo V. Single hepatocellular carcinoma ranging from 3 to 5 cm: radiofrequency ablation or resection? *HPB (Oxford)*. 2007;9(6):429-434. [CrossRef]
5. Lu DS, Raman SS, Limanond P, et al. Influence of large peritumoral vessels on outcome of radiofrequency ablation of liver tumors. *J Vasc Interv Radiol*. 2003;14(10):1267-1274. [CrossRef]
6. Chen J, Peng K, Hu D, et al. Tumor location influences oncologic outcomes of hepatocellular carcinoma patients undergoing radiofrequency Ablation. *Cancers (Basel)*. 2018;10(10):378. [CrossRef]
7. Hsieh YC, Limquiaco JL, Lin CC, Chen WT, Lin SM. Radiofrequency ablation following artificial ascites and pleural effusion creation may improve outcomes for hepatocellular carcinoma in high-risk locations. *Abdom Radiol (NY)*. 2019;44(3):1141-1151. [CrossRef]
8. Lin SM. Local ablation for hepatocellular carcinoma in taiwan. *Liver Cancer*. 2013;2(2):73-83. [CrossRef]
9. Lin JW, Lin CC, Chen WT, Lin SM. Combining radiofrequency ablation and ethanol injection

may achieve comparable long-term outcomes in larger hepatocellular carcinoma (3.1-4 cm) and in high-risk locations. *Kaohsiung J Med Sci*. 2014;30(8):396-401. [CrossRef]

10. Wong SN, Lin CJ, Lin CC, Chen WT, Cua IH, Lin SM. Combined percutaneous radiofrequency ablation and ethanol injection for hepatocellular carcinoma in high-risk locations. *AJR Am J Roentgenol*. 2008;190(3):187-195. [CrossRef]
11. Hines-Peralta A, Liu ZJ, Horkan C, Solazzo S, Goldberg SN. Chemical tumor ablation with use of a novel multiple-tine infusion system in a canine sarcoma model. *J Vasc Interv Radiol*. 2006;17(2 Pt 1):351-358. [CrossRef]
12. Huang G, Lin M, Xie X, et al. Combined radiofrequency ablation and ethanol injection with a multipronged needle for the treatment of medium and large hepatocellular carcinoma. *Eur Radiol*. 2014;24(7):1565-1571. [CrossRef]
13. Kuang M, Lu MD, Xie XY, et al. Ethanol ablation of hepatocellular carcinoma Up to 5.0 cm by using a multipronged injection needle with high-dose strategy. *Radiology*. 2009;253(2):552-561. [CrossRef]
14. Ahmed M, Solbiati L, Brace CL, et al. Image-guided tumor ablation: standardization of terminology and reporting criteria--a 10-year update. *J Vasc Interv Radiol*. 2014;25(11):1691-1705. [CrossRef]
15. Karaman B, Battal B, Sari S, Verim S. Hepatocellular carcinoma review: current treatment, and evidence-based medicine. *World J Gastroenterol*. 2014;20(47):18059-18060. [CrossRef]
16. Lucchina N, Tsetis D, Ierardi AM, et al. Current role of microwave ablation in the treatment of small hepatocellular carcinomas. *Ann Gastroenterol*. 2016;29(4):460-465. [CrossRef]
17. Seror O, N'Kontchou G, Nault JC, et al. Hepatocellular carcinoma within milan criteria: no-touch multibipolar radiofrequency ablation for treatment-long-term results. *Radiology*. 2016;280(2):611-621. [CrossRef]
18. Sutter O, Calvo J, N'Kontchou G, et al. Safety and efficacy of irreversible electroporation for the treatment of hepatocellular carcinoma not amenable to thermal ablation techniques: a retrospective single-center case series. *Radiology*. 2017;284(3):877-886. [CrossRef]
19. Chen S, Peng Z, Lin M, et al. Combined percutaneous radiofrequency ablation and ethanol injection versus hepatic resection for 2.1-5.0 cm solitary hepatocellular carcinoma: a retrospective comparative multicentre study. *Eur Radiol*. 2018;28(9):3651-3660. [CrossRef]
20. Cha DI, Lee MW, Rhim H, Choi D, Kim YS, Lim HK. Therapeutic efficacy and safety of percutaneous ethanol injection with or without combined radiofrequency ablation for hepatocellular carcinomas in high risk locations. *Korean J Radiol*. 2013;14(2):240-247. [CrossRef]
21. Lee DH, Lee JM, Lee JY, et al. Radiofrequency ablation of hepatocellular carcinoma as first-line treatment: long-term results and prognostic factors in 162 patients with cirrhosis. *Radiology*. 2014;270(3):900-909. [CrossRef]
22. Lee DH, Lee JM, Lee JY, Kim SH, Han JK, Choi BI. Radiofrequency ablation for intrahepatic recurrent hepatocellular carcinoma: long-term results and prognostic factors in 168 patients with cirrhosis. *Cardiovasc Intervent Radiol*. 2014;37(3):705-715. [CrossRef]
23. Kim YS, Lim HK, Rhim H, et al. Ten-year outcomes of percutaneous radiofrequency ablation as first-line therapy of early hepatocellular carcinoma: analysis of prognostic factors. *J Hepatol*. 2013;58(1):89-97. [CrossRef]
24. Shiina S, Tateishi R, Arano T, et al. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. *Am J Gastroenterol*. 2012;107(4):569-577. [CrossRef]
25. Ng KKC, Chok KSH, Chan ACY, et al. Randomized clinical trial of hepatic resection versus radiofrequency ablation for early-stage hepatocellular carcinoma. *Br J Surg*. 2017;104(13):1775-1784. [CrossRef]
26. Facciorusso A, Serviddio G, Muscatiello N. Local ablative treatments for hepatocellular carcinoma: An updated review. *World J Gastrointest Pharmacol Ther*. 2016;7(4):477-489. [CrossRef]
27. Chen S, Peng Z, Xiao H, et al. Combined radiofrequency ablation and ethanol injection versus repeat hepatectomy for elderly patients with recurrent hepatocellular carcinoma after initial hepatic surgery. *Int J Hyperthermia*. 2018;34(7):1029-1037. [CrossRef]
28. Waki K, Aikata H, Katamura Y, et al. Percutaneous radiofrequency ablation as first-line treatment for small hepatocellular carcinoma: results and prognostic factors on long-term follow up. *J Gastroenterol Hepatol*. 2010;25(3):597-604. [CrossRef]
29. Xu Z, Xie H, Zhou L, Chen X, Zheng S. The combination strategy of transarterial chemoembolization and radiofrequency ablation or microwave ablation against hepatocellular carcinoma. *Anal Cell Pathol (Amst)*. 2019;2019:8619096. [CrossRef]
30. Tsukamoto M, Yamashita YI, Imai K, et al. Long-term favorable outcomes of radiofrequency ablation for hepatocellular carcinoma as an initial treatment: a single-center experience over a 10-year period. *Anticancer Res*. 2018;38(2):1047-1052. [CrossRef]
31. Shiina S, Tateishi R, Imamura M, et al. Percutaneous ethanol injection for hepatocellular carcinoma: 20-year outcome and prognostic factors. *Liver Int*. 2012;32(9):1434-1442. [CrossRef]
32. Ng KK, Poon RT, Lo CM, Yuen J, Tso WK, Fan ST. Analysis of recurrence pattern and its influence on survival outcome after radiofrequency ablation of hepatocellular carcinoma. *J Gastrointest Surg*. 2008;12(1):183-191. [CrossRef]