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Original Article

Predictive factors for the success of "one-off" ablation in single hepatocellular carcinoma patients who underwent percutaneous radiofrequency ablation

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ABSTRACT

Aim: To investigate the technique's effectiveness and evaluate the risk factors affecting the success of "one-off" percutaneous ultrasound-guided radiofrequency ablation (RFA) for single hepatocellular carcinoma (HCC). **Methods:** A total of 462 consecutive patients who received RFA from February 2010 to December 2013 at a single center (Eastern Hepatobiliary Surgery Hospital, Shanghai, China) were enrolled in the study. The patients were followed up for at least 6 months. Herein, this study adopted a new terminology named "one-off" ablation which is defined as achieving complete necrosis and no local residual or recurrent tumor within 6 months after single-session RFA. The incidence of "one-off" RFA was observed and the attributing risk factors were analyzed. A multivariate analysis was conducted to determine the independent predictive factors for the success of "one-off" ablation. **Results:** The technique's effectiveness was 90.0% (416/462). After 6 months, 281 patients achieved "one-off" ablation, while 181 patients failed. On univariate analysis, tumor size ≤ 3 cm and tumor further from organs were found to be significantly correlated with "one-off" complete ablation ($P = 0.003$, and $P = 0.010$, respectively). On multivariate analysis using a logistic regression, tumor size ≤ 3 cm [odds ratio (OR), 0.534; 95% confidence interval (CI): 0.346-0.825, $P = 0.005$] and tumor further from organs (OR, 0.593; 95% CI: 0.387-0.909, $P = 0.017$) remained predictive. **Conclusion:** Tumor size and tumor location are the predictive factors for the success of "one-off" ablation in patients with single HCC.

Key words: Hepatocellular carcinoma; radiofrequency ablation; tumor location; tumor size

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INTRODUCTION

Liver cancer, one of the most fatal cancers, is the second most common cancer in China. Each year, nearly 383,000 people died from liver cancer in China, which accounts for 51% of the deaths from liver cancer worldwide.[1] Hepatocellular carcinoma (HCC) has the highest incidence in all the hepatic malignancies. Liver transplantation (LT) and partial hepatectomy are considered as the main curative treatments for HCC.[2] However, LT for patients who meet the Milan criteria is limited due to the insufficient availability of donors.[2] In addition, anatomic location, multicentric tumor occurrence, and

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poor liver function status also preclude liver resection in majority of patients, with only 9-29% of HCC patients being suitable for partial hepatectomy.[3]

Over the years, local ablation including percutaneous ethanol injection, radiofrequency ablation (RFA), and microwave ablation have gained more interests. Among these techniques, RFA was the most widely applied due to its low mortality, minimal invasiveness, high effectiveness, outpatient-use, and repeatability for recurrence.[3] It was reported that RFA was the most effective treatment for unresectable liver cancer.[4] Some lines of evidence also indicated that RFA can be used as a bridge to LT.[5] The therapeutic goal of RFA is complete necrosis. For patients who had incomplete necrosis, RFA can be repeated.[6] However, a series of studies showed that multiple-session RFA would increase the incidence of complications such as bleeding, hollow organ injury, and tumor diffusion.[7] Meanwhile, the cost-effectiveness of a standardized percutaneous RFA treatment was $20,424.[8] In China, about 75% of the population has no insurance to guarantee their basic health care and nearly 30% of poor families suffered financially due to illness. Therefore, most patients in China cannot afford to take many sessions of RFA.

Herein, we adopted a new terminology named "one-off " ablation, which was proposed by Jiang *et al*.[9-11] and defined as achieving complete necrosis after a single-session of RFA with no local residual or recurrent tumor within 6 months. The present retrospective study tried to investigate the predictive factors related to the success of "one-off " ablation.

METHODS

Patients

The Healthcare Ethics Committee and Institutional Review Board of our hospital have approved that we could use the data of patients for this retrospective study. We reviewed the data of a single center database (Eastern Hepatobiliary Surgery Hospital, Shanghai, China) and screened all patients with single HCC from February 2010 to December 2013. HCC was diagnosed according to the guidelines of American Association for the Study of the Liver Disease (AASLD), that is, a positive result in biopsy or concordant results of at least two imaging techniques or positive finding on one imaging study together with alpha fetal protein (AFP) > 400 ng/mL.[12] Clinical data were collected including demographic characteristics, imaging examinations, intra-RFA parameters, and laboratory tests results.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) single HCC nodule measuring 5.0 cm or less in diameter; (2) liver function of Child-Pugh Class A or B; (3) no macrovascular thrombosis and extra-hepatic metastasis; (4) performance status Eastern Cooperative Oncology Group 0 or 1; and (5) platelet count > 50,000/mL. Exclusion criteria were: (1) poor or absent visualization of nodules on ultrasound (US); (2) any previous treatments aimed at HCC nodules.

RFA procedures and techniques

All RFA sessions were performed by the same team who had more than 30 years of experience in interventional radiology. The Cool-Tip Radiofrequency System (Radionics, Burlington, Massachusetts, USA) contains a generator, a monopolar-array needle electrode (LeVeen, RadioTherapeutics), which has a 2 or 3 cm exposed tip and a dispersive electrode pad. The radiofrequency electrode is 17-gauge which contains internal channels and the five hook-shaped expandable electrode tines with a diameter of 2.0-, 3.0- or 3.5-expansion. For nodules < 1.5 cm in diameter, an electrode with 2.0-cm expanded tines; for nodules 1.5-2.5 cm in diameter, an electrode with 3.0-cm expanded tines; and for nodules larger than 2.5 cm in diameter, and an electrode with 3.5-cm expanded tines were used.

Prior to the operation, pethidine 100 mg and anisodamine hydrochloride (654-2) 10 mg were given through intra-muscular injection as a basal anesthesia. Tumor localization detection was under real-time US. Patient's posture would be changed according to the tumor location. The insertion site of the skin depends on the biggest cross-section of tumors in US. Local anesthesia with 1% lidocaine was given from the insertion site down to the peritoneum along the planned puncture track, and conscious analgesia-sedation was induced by intravenous administration of 0.1 mg of Tramadol (SanJiu Pharmaceutical Ltd., Zhejiang, China). During the puncture procedure, damage to the visceral organs, such as gallbladder, bowels, and stomach, was avoided by keeping 1 cm away from adjacent organ so that we can place the needle into nodules easily. After the electrode was placed into the center of the nodule under the guidance of US, the hooks then expanded. The initial output was 30-50 W with an increase of 10 W every 60 s till the power of about 60-90 W, which was maintained for 5 min, and then, increasing the power again to the maximum level (90-130 W) step by step. The selection of the power level depended on the size of tumor. Ablation was maintained for at least 15 min.[8] During ablation, water was administered at a base rate of 20 mL/10 min by the syringe pump to cool the electrode tip to reduce injury to the surrounding tissue. For larger tumors (≥ 3.0 cm), the RF probe with 3.5-cm expanded tines was introduced into a 0.5-1.0 cm deep position from the center of the nodule to create overlapping coagulation zones with adequate ablation margin of 0.5-2.0 cm. At the end of the procedure, the needle track was cauterized for 15 s to prevent possible tumor seeding or bleeding.

Follow-up and endpoint

Two days af ter RFA, contrast-enhanced computer tomography (CT) or magnetic resonance imaging (MRI) was performed. If any irregular contrast enhancement was found inside or beside the ablation zone, additional RFA would be performed in 1 week. Thirty days after the first RFA, contrast-enhanced CT or MRI was carried out again. If the enhancing tissue at the tumor site disappeared, it was classified as "complete necrosis".[6] Laboratory test of AFP was also used to evaluate the efficiency of RFA in patients with high pre-operative AFP levels. Then, patients were regularly followed up in the outpatient clinic every 3 months for the first 2 years. In our study, the endpoint was "one-off" ablation, which was assessed at the 6th month after RFA.

Statistical analysis

Data were analyzed with the SPSS statistical software (SPSS version 20.0, Chicago, IL, USA). Homogeneity of continuous data was performed by the Gaussianity test, and described as means ± standard deviations or median (range) and compared using the unpaired *t*-test. Categorical variables were compared using Chi-square test or the Fisher's exact test, where appropriate. Variables with a $P < 0.05$ in the univariate analysis would be added to the multivariate model. In the multivariate analysis, a multiple logistic regression was used to determine the predictors of the success of "one-off " ablation.

RESULTS

Baseline data

A total of 983 patients were screened while 735 patients were included in the study, 273 patients were excluded based on our study exclusion criteria and failure to follow -up. Therefore, a total of 462 patients were enrolled for the analysis. Clinical and demographic characteristics were summarized in Table 1. There were 373 male patients and 89 females, with a mean age of 56.6 ± 11.0 years. Most patients (85.7%) had a background of viral hepatitis (hepatitis B and/or hepatitis C). Tumor diameter ≤ 3.0 cm and > 3 cm diameter were present in 362 (70.6%) and 136 (29.4%) patients, respectively. Tumor location included deep-parenchyma (307 patients, 66.5%) and sub-capsular (155 patients, 43.5%). Among them, 109 (23.6%) tumors were close to organs (space between tumor and organ < 1 cm)[13] (22 nodules close to stomach, 48 close to gallbladder, 23 close to jejunum, 8 close to pericardium, and 17 close to kidney), and 40 tumors (3.9%) were close to the main blood vessels (between tumor and vessels < 5 mm)[11] such as post-hepatic vena cava, hepatic vein, and the portal vein.

Complications of RFA

Most patients experienced mild pain or discomfort during ablation. Twenty patients (4.3%) had one or more complications. One patient died in the hospital due to liver failure. Other complications were listed on Table 2. Further analyses showed that there was no significant difference between the "one-off" group and other treatment groups.

"One-off" ablation and predictive factors for its success

During the CT evaluation 2 days after RFA, there were 416 (90.0%) patients who had achieved "complete necrosis", while 46 (10.0%) patients had not. When evaluated at 6 months after the treatment, 281 (60.8%) patients achieved "one-off" ablation, while 181 (39.2%) patients failed. Clinical data were compared between patients who achieved "one- off" ablation and those who failed

Table 1: Baseline characteristics of all 462 patients

Variables	*n* = 462
Gender (male/female) (%)	373 (80.7)/89 (19.3)
Age (years)	56.6 ± 11.0
PLT (×10^9/L)	131.1 ± 57.1
PT (s)	12.3 ± 0.95
Total bilirubin (μmol/L)	17.2 ± 10.9
ALT (IU/L)	86.5 (9.4, 546.8)
Albumin (g/L)	41.3 ± 4.0
Prealbumin (mg/dL)	186.6 ± 52.1
AFP (ng/mL)	26.5 (0.6, 584.0)
Child-Pugh classification	
Class A	442
Class B	20
Hepatitis background	
HBV	333
HCV	7
HBV-HCV[#]	4
HBsAg	
Present	333
Absent	129
HBeAg	
Present	117
Absent	345
Tumor size (cm)	2.6 ± 1.1
Tumor location	
Parenchyma	307
Sub-capsular	155
Close to organs	
Gallbladder	48
Stomach	22
Jejunum	23
Pericardium	8
Kidney	17
Close to main blood vessels	
Yes	40
No	422

[#]Co-occurrence of HBV and HCV. PLT: platelet; PT: prothrombin time; ALT: alanine aminotransferase; AFP: alpha fetal protein; HBV: hepatitis B virus; HCV: hepatitis C virus; HBsAg: hepatitis B surface antigen; HBeAg: hepatitis B e antigen

Table 2: Complications of radiofrequency ablation

Complications	Number
Severe pain	3
Cholecystitis	6
Bile leakage	2
Intestinal leakage	1
Abdominal bleeding	2
Liver abscess	2
Pleural effusion	3

[Table 3]. On univariate analysis, patients with tumor size ≤ 3 cm had a higher rate of achieving "one-off" ablation than those with tumor size > 3 cm (92.0% *vs.* 85.3%, $P = 0.003$), while tumor close to the organs had a lower rate of achieving "one-off" ablation than those further from organs (50.8% *vs.* 64.2%, $P = 0.010$). On multivariate analysis using a logistic regression, tumor size ≤ 3 cm [odds ratio (OR), 0.534; 95% confidence interval (CI): 0.346-0.825, $P = 0.005$] and tumor further from organs (OR, 0.593; 95% CI: 0.387-0.909, $P = 0.017$) remained predictive for the success of "one-off" RFA [Table 4].

DISCUSSION

RFA, a newly developed local ablative technique,[14] is suggested by AASLD and the European Association for the Study of the Liver (EASL) as the first-line treatment for HCC due to its safety, lower mortality and morbidity, and shorter hospitalization.[15] "One-off" ablation, first proposed by Jiang *et al.*,[9-11] defined as (1) the diameter of post-RFA zone demonstrated by contrast-enhanced CT is more than the maximal length of the tumor, and (2) no tumor recurrence within 6 months after RFA. However, not all tumors can achieve "one-off" ablation after a single-session RFA. So far, numerous investigators have described prognostic factors for survival after RFA. However, no large study has illustrated the predictive factors for the success of "one-off" ablation after a single-session RFA. In the study, we focused on the analyses of the effectiveness of single-session RFA in single HCC, and investigated the risk factors influencing the success of "one-off" ablation to provide clinicians a guideline for their routine medical treatments.

Our study showed that tumors measuring 3 cm in greatest dimension and which are further to organs were most suitable for a single-session, single application of percutaneous RFA [Table 3]. As reported, when RFA was performed on small HCC nodules (≤ 3 cm), complete necrosis can be achieved in more than 90% patients.[16] As the tumor size increased, the therapeutic effect of RFA decreased. For tumors 3.0-5.0 cm and tumors larger than 5.0 cm, complete tumor necrosis rates was 71% and 45%, respectively.[17] In this study, the mean tumor size is 2.6 ± 1.1 cm. The primary effectiveness was 90.0% and the rate of "one-off " ablation in our study was 60.8%. Patients with tumor size ≤ 3 cm had a higher rate to achieve "one-off" ablation than those with tumor size > 3 cm, similar to observations by Komorizono *et al*.[18] Komorizono's study showed that tumors measuring ≤ 2 cm in greatest dimension were indicated for an optimal ablation.[18] Tumor size may influence the success of "one-off " RFA due to three possible reasons: first, RFA induced tumor coagulative necrosis by putting high-frequency alternating electrodes within the tumor tissue. The temperature inside the ablated tissue must be > 60 °C to achieve coagulation necrosis. Some authors suggested that the cirrhotic tissue around small HCC behaved like a thermal insulator, increasing the heat retention within the tumor and preventing heating outside the tumor. However, when the tumor is > 3 cm, heat may be lost in the periphery. Meanwhile, Ahmed *et al*.[19] used an established computer simulation model of RFA to characterize the combined effects of varying perfusion, electrical, and thermal conductivity on radiofrequency (RF) heating. They observed that electrical and thermal

Table 3: Univariate analysis of factors related to "one-off" radiofrequency ablation

Variables	Achieved (n = 281) (%)	Failed (n = 181) (%)	P
Sex			
Male	221 (59.2)	152 (40.8)	0.156
Female	60 (67.4)	29 (32.6)	
Age			
≤ 60	180 (59.2)	125 (40.8)	0.268
> 60	101 (64.3)	56 (35.7)	
PLT (×10⁹/L)	143.0 ± 57.9	119.2 ± 54.6	0.119
PT (s)	12.2 ± 0.98	12.4 ± 0.93	0.533
Bilirubin (μmol/L)	17.8 ± 14.3	16.7 ± 6.1	0.713
Albumin (g/L)	41.2 ± 4.2	41.4 ± 4.0	0.857
Prealbumin (mg/dL)	189.5 ± 54.9	183.8 ± 50.1	0.687
ALT (IU/L)	94.8 (9.40, 546.80)	70.2 (18.10, 154.80)	0.710
AFP (ng/dL)			
≤ 400	225 (60.3)	148 (39.7)	0.652
> 400	56 (62.9)	33 (37.1)	
Child-Pugh classification			
Class A	267 (60.4)	175 (39.6)	0.390
Class B	14 (70.0)	6 (30.0)	
Hepatitis background			
HBV and/or HCV	204 (59.3)	140 (40.7)	0.253
None	77 (65.3)	41 (34.7)	
HBsAg			
Present	197 (59.2)	136 (40.8)	0.239
Absent	84 (65.1)	45 (34.9)	
HBeAg			
Present	67 (57.2)	50 (42.7)	0.362
Absent	214 (62.0)	131 (38.0)	
Tumor size (cm)			
≤ 3.0	184 (92.0)	142 (8.0)	0.003
> 3.0	97 (85.3)	39 (14.7)	
Tumor location			
Parenchyma	181 (59.0)	126 (41.0)	0.248
Sub-capsular	100 (64.5)	55 (35.5)	
Close to organs			
Yes	60 (50.8)	58 (49.2)	0.010
No	221 (64.2)	123 (37.8)	
Close to blood vessels			
Yes	25 (62.5)	15 (37.5)	0.820
No	256 (60.1)	166 (39.3)	

PLT: platelet; PT: prothrombin time; ALT: alanine aminotransferase; AFP: alpha fetal protein; HBV: hepatitis B virus; HCV: hepatitis C virus; HBsAg: hepatitis B surface antigen; HBeAg: hepatitis B e antigen

Table 4: Multivariate analysis of factors related to "one-off" radiofrequency ablation

Variables	OR	95% CI	P
Tumor size (≤ 3 cm *vs.* > 3 cm)	0.534	0.346-0.825	0.005
Tumor close to organs (no *vs.* yes)	0.593	0.387-0.909	0.017

OR: odds ratio; CI: confidence interval

conductivity had greatest differences in effect seen in tumor range. Therefore, some researchers suggested that when tumor size > 2 cm, repeated RFA or combination treatment may be beneficial. Second, as reported by Kim *et al.*,[20] a margin of 3 mm or more is associated with a lower rate of local tumor recurrence after percutaneous RFA of HCC. Some clinicians have reported difficulty in obtaining adequate circumferential ablative margin for large tumors after a single-session of RFA. Overlapping treatment or combining with transcatheter arterial chemoembolization were needed.[21] Third, the effectiveness of RFA may be related with the perfusion of the tumor, although it is still debated. Some researchers found that RFA with occlusion of tumor blood supply in tumors measuring 3.5 cm was beneficial.[22] Documented pathology showed that blood supplies changed as tumors grow larger. As the perfusion of tumors aggravated, the "heat-sink effect" (HSE) may be induced which will influence the effectiveness of the RFA.[23]

In addition to tumor size, proximity of the tumor to organs is also one of the most important factors influencing the success of "one-off" ablation. In the clinic, tumors adjacent to gallbladder, kidney, diaphragm, and so on were thought to be high-risk.[24] Local ablation for tumors in "high-risk" location is technically challenging because of the poor visibility of the tumor and for fear of collateral thermal injury to the adjacent organs and causing serious post-operative complications.[25,26] The complication rate of our study is 4.3%, similar to the report of Lau and Lai,[15] which indicated a complication rate of RFA ranging from 3% to 7%. Most patients experienced mild pain or discomfort during the ablation. Six patients had bile leakage on the 3rd or 4th post-operative day. One patient died from liver failure. These tumors were all located in "high-risk" areas. To achieve better ablation effects, some clinicians suggest departing the vulnerable structures from the area of ablation[27] or using laparoscopic ablation (LA).[28] L A was proved to be a safe and effective technique for high-risk lesions not manageable by percutaneous approach and not suitable for surgical resection.[28]

Surprisingly, our study indicated that tumor close to vascular and capsular sites did not influence the success of "one-off" RFA. Tumor located near the capsular has no influence on the success of "one-off" ablation, which is contrary to Komorizono's retrospective study that showed patients who had sub-capsular tumors had significantly shorter recurrence free intervals compared with patients who had non-sub-capsular tumors.[18] Further prospective study is needed to clarify this inconsistency. In addition, whether tumor close to vascular will influence the effectiveness of ablation is also unclear. Our result is similar to the study of Komorizono *et al.*[18] which also showed that proximity of a tumor to vessel did not influence the local effect of ablation, which was contrary to previous reports.[29,30] In the current study, one patient whose tumor was seen adjacent to the portal vein, hepatic artery, and bile duct by enhanced CT died due to liver failure. Using a pig model, Lu *et al.*[31] found that when vessel size was > 3 cm, HSE and river-flow effect occurred. Heat could be carried away by the blood flow, infusing into regional hepatic segments or lobes along the blood flow, causing thermal lesion to liver cells and finally impairing liver function with sustained high heat.[9] Hence, to achieve "one-off" ablation and decrease these complications, laparoscopic approaches or pringle maneuver seem to be appropriate for tumors close to vasculature.[31,32]

This study has several limitations. First, most patients did not have pathological examination. The diagnosis of HCC relied on their hepatitis history and imaging examination. Therefore, it is possible that benign liver diseases were included, which may influence the judgment of "one-off" ablation. Second, all RFA procedures were performed by the same team, which may introduce bias to our results. Third, our study was a retrospective study, and limited to single-center (Eastern Hepatobiliary Surgery Hospital). Further analyses including randomized controlled trials in multi-center sites are needed.

In conclusion, for single HCC with diameters smaller than 3 cm and which are further from organs, "one-off" percutaneous RFA was beneficial. Our study also elucidated the scientific rationale of RFA treatment criteria (AASLD and EASL) for HCC regarding tumor size. For tumors located at specific sites of the liver, open or laparoscopic RFA or combination with other techniques may be a better choice.

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Conflicts of interest

There are no conflicts of interest.

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