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INTERVENTIONAL

Combined radiofrequency ablation and ethanol injection with a multipronged needle for the treatment of medium and large hepatocellular carcinoma

Guangliang Huang · Manxia Lin · Xiaoyan Xie · Baoxian Liu · Zuofeng Xu · Riccardo Lencioni · Mingde Lu · Ming Kuang

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Abstract
Objective To evaluate the efficacy and safety of combined radiofrequency ablation (RFA) and ethanol injection with a multipronged needle in the treatment of medium (3.1–5.0 cm) and large (5.1–7.0 cm) hepatocellular carcinoma (HCC).
Methods A total of 65 patients with 67 HCC nodules were enrolled in this prospective study. All of them received the treatment of combined RFA and multipronged ethanol injection percutaneously.
Results The average volume of injected ethanol was 14.4± 4.1 ml (range, 9–30 ml). The average number of RFA electrode insertions was 1.7±0.8 (range, 1–4). The rate of initial local complete response (CR) was 94.0 % (63/67). After additional treatment, technical success was achieved in all HCC nodules. There were no treatment-related deaths, and major complications were observed in 3 (4.6 %) patients. After a mean follow-up of 20.0±7.6 months, local tumour progression was observed in 10 (10/67, 14.9 %) tumours, whereas distant recurrence developed in 32 (32/65, 49.2 %) patients. The 1-year and 2-year survival rates were 93.1 % and 88.1 %, respectively.
Conclusion The combination of RFA and multipronged ethanol injection in the treatment of medium and large HCC is safe and effective with a high rate of local tumour control.
Key Points
- *Combined radiofrequency ablation and multipronged ethanol injection is a new therapeutic strategy*
- *Treatment is safe and effective for medium and large hepatocellular carcinoma* (*HCC*)
- *A multipronged needle allows for a homogeneous ethanol distribution*

Keywords Radiofrequency ablation · Multipronged ethanol injection · Hepatocellular carcinoma · Safety · Efficacy

G. Huang · M. Lin · X. Xie · B. Liu · Z. Xu
Department of Medical Ultrasonics, The First Affiliated Hospital of Sun Yat-sen University, Sun Yat-Sen University, 58 Zhong Shan Road 2, Guangzhou 510080, China

M. Lu · M. Kuang
Department of Hepatobiliary Surgery, The First Affiliated Hospital of Sun Yat-sen University, Sun Yat-Sen University, 58 Zhong Shan Road 2, Guangzhou 510080, China

M. Lin · X. Xie (✉) · M. Lu · M. Kuang (✉)
Division of Interventional Ultrasound, Institute of Diagnostic and Interventional Ultrasound, The First Affiliated Hospital of Sun Yat-sen University, Sun Yat-Sen University, 58 Zhong Shan Road 2, Guangzhou 510080, China
e-mail: xxy1992@21cn.com
e-mail: kuangm@mail.sysu.edu.cn

R. Lencioni
Division of Diagnostic and Interventional Radiology, Department of Oncology, Transplant and Advanced Technologies in Medicine, University of Pisa, Pisa, Italy

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most common cause of death from cancer worldwide [1]. Surgical resection still remains the choice of treatment for HCC in patients with cirrhosis. However, only a small number of patients are suitable for curative resection as a result of many factors such as coexisting advanced liver cirrhosis, vascular invasion, extrahepatic metastases and multicentric tumours [2]. A shortage of liver grafts limits the application of liver transplantation. As non-surgical treatment, various local ablation therapies such as ethanol injection and radiofrequency ablation (RFA) have been proposed and encouraging results have been reported [3]. Ethanol injection is a well-established procedure for the treatment of small HCC,

which may bring about long-term results comparable to those of surgical resection [4]. During the past two decades, with the development of medical technology, RFA has been the chief procedure for the treatment of HCC [5–7]. However, because of the limited volume of coagulated necrosis induced by RFA alone, the local complete ablation rates decrease dramatically for HCCs larger than 3 cm in diameter and the local recurrence rate is higher compared with surgical resection [8]. The aim of this study was to prospectively evaluate the efficacy and safety of combined RFA and ethanol injection with a multipronged needle in the treatment of medium (3.1–5.0 cm) and large (5.1–7.0 cm) HCC.

Materials and methods

Patients

From June 2009 to September 2011, a total of 65 patients with 67 HCC nodules (3.1–7.0 cm) were enrolled prospectively in this study. The diagnosis of HCC was based on the non-invasive diagnostic criteria of the European Association for the Study of the Liver or biopsy. The inclusion criteria were as follows: (a) adult patients with HCC or recurrent HCC and refusal to undergo surgery; (b) single or multiple tumour (no more than 3 HCCs), dominant lesion 3.1–7.0 cm in diameter; (c) liver function status at Child–Pugh class A or B; (d) platelet count over 45×10^9/l; (f) prothrombin time ratio greater than 50 %. Exclusion criteria include (a) presence of vascular invasion and extrahepatic metastases at preprocedure imaging study; (b) previous treatment for target HCC; (c) HCC developed in the transplanted liver; (d) ongoing anticoagulant treatment that cannot be stopped.

Baseline evaluation was carried out, including clinical history; full laboratory tests consisting of a complete blood count, platelets, coagulation profile, hepatitis B and C viral serology, electrolytes, albumin (ALB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL) and serum alpha-fetoprotein (AFP); contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen; contrast-enhanced ultrasound; electrocardiogram; and radiograph of the chest. Diagnostic and treatment decisions were made in consensus by a team of hepatobiliary surgeons and interventional radiologists.

This study was approved by the institutional review board and informed consent was obtained from all patients.

Treatment procedure

Treatment was given with the use of conscious sedation and analgesia. Vital signs were continuously monitored during the procedure. All procedures were performed percutaneously by experienced radiologists and under real-time ultrasound guidance with a 3.5-MHz convex probe.

Ethanol injection

A multipronged injection needle (Quadra-Fuse; Rex Medical, Conshohocken, PA) was used for ethanol injection. Under ultrasound guidance, the needle was introduced percutaneously into the centre of the tumour nodule and the needle tip was positioned at the bottom of the target tumour. An injection–rotation–injection manoeuvre was used as described in our previous report [9]. The maximal extent of prong deployment was equal to the largest diameter of the treated tumour. The three prongs were deployed from a 1-cm extent initially to the predetermined maximum extent. The ethanol kept being injected until the whole tumour appeared completely hyperechoic. The amounts of ethanol were determined according to the size of tumours and were always kept between one-third and one-half of the estimated tumour volume. Before 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 ethanol injection, the needle was left in place for 1–2 min before it was removed.

Radiofrequency ablation

Radiofrequency ablation devices in this study were LeVeen electrodes (Boston Scientific, Natick, MA), Starburst XL electrodes (RITA Medical Systems, Mountain View, CA) and Cool-tip electrodes (Valleylab, Boulder, CO). Multi-tined RF system/electrode such as RITA was mostly used in this study, and the Cool-tip system was used when electrode puncture and position was difficult to process because of the location of the tumour. For the treatment of medium tumours, we used a coaxial cannula for insertion of one multipronged ethanol injection needle and one multi-tined RF electrode one by one, and 1–2 RF electrode positions along one access path were used in one session. For the treatment of large tumours, we deployed two RF electrodes in parallel in the low-centre of target tumour at first, then inserted a multipronged ethanol needle in another access path. After completion of ethanol injection, RF ablation was performed with 2–4 electrode positions in the tumour. A grounding pad was placed on each thigh of the patient. For ablation using any type of electrode, multiple overlapping ablations were applied, as described by Chen et al. [10]. RFA was started 3–5 min after ethanol injection following the manufacture's guidelines. The needle track was carefully treated with the electrode being retracted by 1-cm increments to prevent bleeding and tumour seeding. Patients were hospitalized for 1–2 days, unless their complications necessitated longer hospitalization.

Therapeutic efficacy and follow-up

Contrast-enhanced ultrasound (CEUS) was performed the following morning, providing an initial evaluation of treatment effect. An additional treatment would be performed if any tumour residue was found. Local efficacy was assessed by contrast-enhanced CT performed 1 month after the treatment, which was considered the standard evaluation modality. Complete ablation (CA) was defined as non-enhancement in the ablated zone with or without peripheral enhancing rim. In the case of viable residual tumour, additional ablation was given with the aim of complete ablation. If the tumour was still viable after additional ablation, combined ablation was considered a failure and the patient was referred for other therapies. All the ablation-related complications and side effects were defined as described by Goldberg et al. [11]. Patients with tumours that achieved CA entered follow-up. Contrast-enhanced CT and CEUS were performed every 3–6 months. AFP assays were also performed if the value was high before treatment. Local tumour progression (LTP) was assessed on a tumour-by-tumour basis and distant recurrence (DR) on a patient-by-patient basis. This study was censored on 31 May 2012.

Statistical analysis

Statistical analysis was performed using the SPSS 16.0 software package. *P* values less than 0.05 indicated statistical significance. Continuous data were expressed as the mean ± standard deviation. Data on survival were evaluated by the Kaplan–Meier method. The relationship between each of the variables and LTP/DR was estimated by the log-rank test. The variables included age, gender, presence of hepatitis B or C virus infection, Child–Pugh class for liver function, ALT, TBIL, ALB, PT, PLT, AFP, tumour type (primary or recurrence), tumour number (single or multiple), tumour location, size of the largest tumour, ethanol volume and ablation time. The variables that proved to be significant in univariate analysis were tested by the multivariate Cox proportional hazards model.

Results

Patients and tumour profile

Of 65 patients who met the inclusion criteria, 59 were men and 6 were women, with an average age of 55.6±12.3 years (range, 30–81 years). A total of 58 patients had hepatitis B virus infection and one patient had hepatitis C virus infection. With regard to liver function status, 60 had Child–Pugh classification grade A and five grade B. Fifty patients had a solitary tumour, and 15 had multiple nodules. Of all the nodules, there were 67 nodules measuring 3.1–7.0 cm treated by combined RFA and ethanol injection with a multipronged needle, including 63 with a medium size (3.1–5.0 cm) and four with a large size (5.1–7.0 cm). The mean diameter was 3.8±0.7 cm (range, 3.1–7.0 cm) in the longest dimension and 3.1±0.7 cm (range, 1.7–5.6 cm) in the shortest dimension. Forty-two patients were first diagnosed with HCC and 23 were diagnosed with recurrent HCC after hepatic resection (n=17) or thermal ablation (n=6). A total of 46 tumour nodules were located at unfavourable sites abutting the portal vein (n=12), gallbladder (n=6), bile duct near the porta hepatis (n=3) and liver capsule near intestine or diaphragm or heart (n=25). The demographic data of these patients are shown in Table 1.

The mean volume of injected ethanol per tumour was 14.4 ±4.1 ml (range, 9–30 ml). The average number of RFA electrode insertions was 1.7±0.8 (range, 1–4). The mean size of the ablation zone, as measured on CT or CEUS performed 1 month after treatment, was 5.2±0.9 cm (range, 3.2–7.5 cm)×4.2±0.9 cm (range, 2.7–7.0 cm).

Tumour response to treatment

Complete ablation was obtained in 63 of 67 tumours after initial treatment (Figs. 1 and 2). All the large HCC were ablated completely. CEUS the next day did not show any tumour residue. Four residual tumours were detected by contrast-enhanced CT performed 1 month later, and achieved complete ablation after additional treatment. The mean time interval between the first and second treatments was 47 days. Overall, the technical success rate was 100 % (67/67) in this study.

Table 1 Demographic and tumour characteristic data

Data	Value
Gender (male/female)	59/6
Age (years)	55.6±12.4 (30–81)
Hepatitis virus (B/C/none)	58/1/6
Child–Pugh class (A/B)	60/5
Serum ALT level (U/L)	52.0±59.8 (2.9–434.0)
Serum total bilirubin (mg/dl)	19.5±14.5 (5.6–76.3)
Serum albumin (g/l)	40.7±4.7 (30.3–49.7)
Prothrombin time (s)	12.7±1.4 (10.9–18.3)
Platelet count ($\times 10^9$/l)	148.3±62.1 (47–312)
Serum AFP level (ng/ml)	1,233.9±3,995.4 (0.4–26,822.3)
Tumour type (primary/recurrent)	42/23
Tumour number (single/multiple)	50/15
Tumour size (3.1–5.0 cm/5.1–7.0 cm)	63/4
Tumour location (favorable/unfavorable)	21/46

ALT alanine aminotransferase, *AFP* alpha-fetoprotein

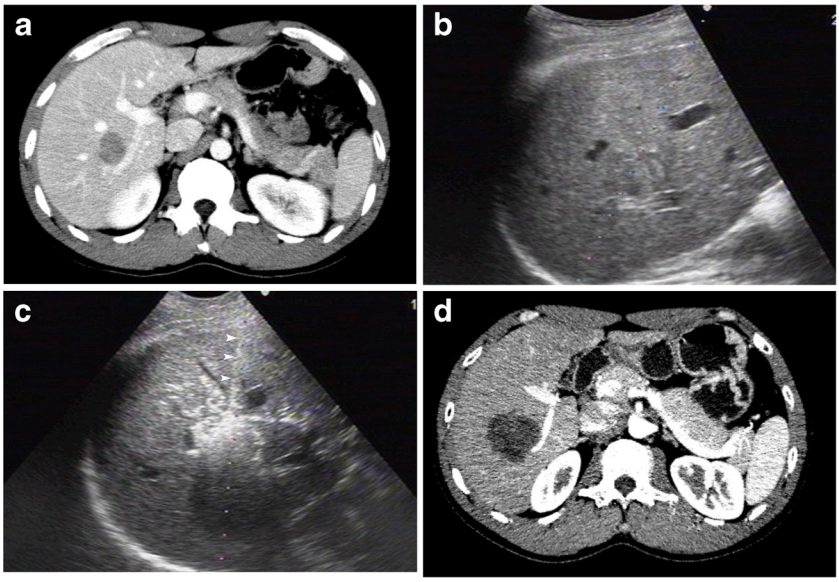

Fig. 1 Images of a 36-year-old male patient with HCC who underwent multipronged ethanol injection and radiofrequency ablation using a multitined expandable electrode (Starburst XL electrode, RITA Medical Systems, Mountain View, CA). Pre-treatment CT (**a**) and ultrasound (**b**) show a 3.3×2.5 cm HCC adjacent to portal vein. **c** Tumour appeared completely hyperechoic after combined treatment (one session, 11 ml of ethanol injected and 15 min of RFA performed). The position of RF electrode was clear (*white arrowheads*). **d** CT scan obtained 1 month after the treatment shows non-enhancing ablation zone completely enveloping the treated tumour

Complications

No ablation-related deaths occurred. The major complication rate was 4.6 % (3/65) in this study, including intra-abdominal haemorrhage in one, liver abscess in one, and massive ascites due to liver function damage in one. All were managed by conservative therapy. Minor complications included asymptomatic intra-abdominal haemorrhage (n=2), pleural effusion (n=2) and biloma secondary to bile duct damage (n=2).

Local tumour progression

All patients with technical success entered follow-up. LTP was observed in 10 (10/67, 14.5 %) during a mean follow-up period of 20.0±7.6 months (range, 6.7–32.6 months), the sustained local CR being 79.1 % (53/67). The local recurrence rate in medium tumours was 15.9 % (10/63), and 0 % (0/4) in large tumours (p>0.05). Among the 16 variables examined, no variable was found to be an independent factor predicting LTP (Table 2).

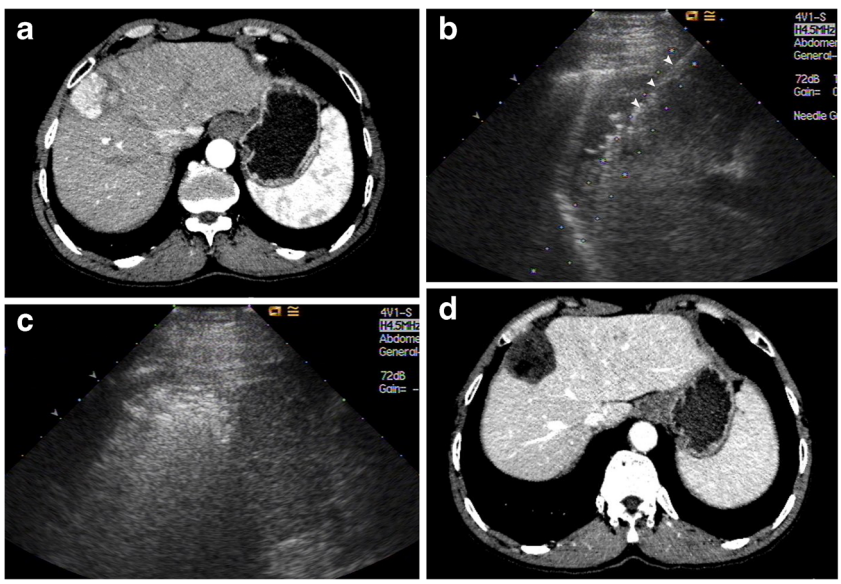

Fig. 2 Images of a 62-year-old male patient with HCC who underwent combined treatment. **a** Pre-treatment CT shows a HCC of 4.6 cm located in segment 8 of the liver. **b** A multipronged needle (*white arrowheads*) was inserted into the tumour and 16 ml of ethanol was being injected. **c** A multitined expandable electrode (Starburst XL electrode, RITA Medical Systems, Mountain View, CA) was inserted and the tumour appeared completely hyperechoic. **d** Image obtained 1 month after the treatment shows no evidence of contrast enhancement in the treated tumour area

Table 2 Univariate analysis of risk factors for local tumour progression and distant recurrence of HCC after ablation

Variables	Local tumour progression *P* value	Distant recurrence *P* value
Gender (male)	0.535	0.036
Age (>65 years)	0.558	0.189
Hepatitis B/C virus (+/−)	0.298	0.003
Child–Pugh class (A/B)	0.868	0.569
Serum ALT level (>40 U/l)	0.089	0.990
Serum total bilirubin (>34.2 mg/dl)	0.913	0.395
Serum albumin (>40 g/l)	0.674	0.603
Prothrombin time (>14 s)	0.686	0.600
Platelet count (>100×10^9/l)	0.694	0.436
Serum AFP level (>200 ng/ml)	0.160	0.517
No. of tumours (single/multiple)	0.659	0.933
Tumour size (3.1–5.0 cm/5.1–7.0 cm)	0.204	0.584
Tumour type (primary/recurrent)	0.367	0.033
Tumour location (favorable/unfavorable)	0.725	0.448
Ethanol volume (>14.4 ml)	0.206	0.378
Ablation time (>24 min)	0.712	0.163

+ positive, − negative, *ALT* alanine aminotransferase, *AFP* alpha-fetoprotein

Distant recurrence

Of 65 patients, 32 (49.2 %) developed distant recurrence after ablation, including an intrahepatic new lesion in 30, lung metastases in one and retroperitoneal lymph node metastasis in one. The distant recurrence rate in medium and large tumours was 47.5 % (29/61) and 75 % (3/4), respectively ($p>0.05$). During univariate analysis, three variables were statistically significant, namely gender, presence of hepatitis B/C virus infection and tumour type. The multivariate analysis revealed that presence of hepatitis B or C infection was the significant factor for the recurrence of HCC (Table 3).

Overall survival rates

Of 65 patients, 57 were still alive at the time of study censorship. They survived from 6.7 to 32.6 months after ablation.

Table 3 Multivariate analysis of risk factors for distant recurrence of HCC after ablation

Variables	*P* value	Risk ratio (95 % confidence interval)
Gender (M/F)	0.980	0.000 (0.000–0.000)
Hepatitis B/C (+/−)	0.005	5.205 (1.668–16.664)
Tumour type (primary/recurrent)	0.093	1.842 (0.902–3.758)

Seven of the remaining eight patients died of tumour progression and another one died of liver failure. Overall 1-year and 2-year survival rates were 93.1 % and 88.1 %, respectively.

Discussion

Over the past decade, RFA has evolved into an important therapeutic modality in the management of HCC. More than 90 % initial complete tumour response rate in liver tumour less than 3 cm in diameter and 10–20 % local tumour progression rate have been reported [12–14]. However, as a result of the limited volume of coagulated necrosis induced by RFA alone, the management of medium and large HCC in patients who are not candidates for surgical resection remains a big challenge. It has been declared that the therapeutic efficacy of RFA decreases as the tumour size increases. In 2000, Livraghi et al. reported that RFA therapy resulted in complete necrosis in 71 % of cases and nearly complete necrosis in 24 % in non-infiltrative tumour measuring 3.1–5.0 cm [15]. In 2003, Giorgio et al. reported complete necrosis in 95 % of tumours with diameters equal to or smaller than 3 cm, but dropped to 71 % for tumour measuring 3.1–5.0 cm and only 12 % for tumours larger than 5 cm [16]. To enhance the therapeutic effect of RFA, several treatment modalities have been applied in clinical settings, such as combined use of transarterial chemoembolization (TACE) or saline injection and RFA [17–19]. In the present study, we demonstrated the combined use of RFA and ethanol injection with a multipronged needle was a feasible treatment for medium and large HCC. All tumour nodules were completely ablated after one or two treatment sessions.

Although the HCC was medium and large in size, the technique success was 100 % in the present study. A previous in vivo experiment [20] and a clinical randomized controlled trial [21] both have shown that ethanol injection prior to RFA could achieve larger coagulated necrosis compared to RFA alone. Several possible explanations are as follows: first, the destruction of peri- or intra-tumour vessels by ethanol injected reduces the "heat-sink" effect that diminishes the efficacy of RFA and induces larger coagulated necrosis. Second, the ethanol injected can make the tissue around the electrode less prone to carbonization and further the thermal conduction. Therefore, we chose to inject the ethanol before placing the RFA electrode, although the hyperechogenicity caused by ethanol injection may obscure the tumour and make repositioning the electrode difficult [2]. In such circumstances, we counted the scale mark both from the electrode and the puncture line and ensured a uniform depth. On the other hand, the ethanol was injected with a multipronged needle in the current study, which allowed for a homogeneous ethanol distribution [9]. In the past, ethanol injection was often performed with a 21-gauge percutaneous transhepatic cholangiography needle

and the ethanol distribution was uneven and limited. These factors contribute to the favourable therapeutic efficacy, as well as overall survival.

With the improvements in devices and techniques, microwave ablation (MWA) has displayed the potential capability for treating HCC larger than 3 cm [22–24]. Theoretically, MWA is more efficient than RFA and less influenced by the heat-sink phenomenon. Simultaneous MWA did show an advantage in producing a large coagulation area, but the relatively high complication rate caused by increased energy application and tissue destruction limit its use for tumours close to critical structures. Combination of RFA and TACE increases volume of coagulated necrosis [25, 26]. In theory, TACE is superior to ethanol injection in destruction of peritumour blood vessels, owing to the larger effective area of the former. However, the size of the ablation zone will decrease with time interval between TACE and RFA increases. It is believed that the shorter time interval provides better therapeutic efficacy with a larger ablation zone [26]. Although Morimoto et al. [27] performed TACE and RFA on the same day, technical difficulties can not be ignored. Ethanol injection was improved in this study with the use of a multipronged needle, which allowed more ethanol to be delivered into the tumour and the peritumour area in multiple directions. Moreover, RFA combined with ethanol injection can be performed in the same session, with low cost, less effort and less side effects. Further study is required to compare the therapeutic efficacy of these treatments for medium and large HCC.

The major complication rate of 4.6 % found in this study was similar to what we had reported previously with thermal ablation alone (4–9.2 %) [24, 28]. All were cured by conservative therapy. Hence, this study demonstrated that combined RFA and ethanol injection with a multipronged needle in the treatment of medium and large HCC is relatively safe with a low incidence of serious complications. It is noteworthy that tumours near the hepatic capsule, gallbladder and major blood vessels were successfully treated without complications.

Previous studies have reported LTP incidence to be as high as 26.4 % in patients with HCC smaller than 4 cm [29]. In a report by Mulier et al., the local recurrence was 14 % in tumours less than 3 cm but increased to 25 % in tumours of 3–5 cm and was 45 % for tumours larger than 5 cm [8]. LTP was observed in 14.9 % of patients in the present study, which is lower than the previously reported rate. Our ablative margins all exceeded 0.5 cm, which were measured with the use of dedicated three-dimension volumetry software, and a clear safety margin of 0.5–1.0 cm is important not only for liver resection but also for RFA [30–32]. Patients with HCC may have many micrometastases which can appear up to 1.0 cm away from the main tumour, even with an encapsulated tumour of 3.0 cm or smaller [33]. An ablative margin of 0.5–1.0 cm should be produced around the tumour to ensure the eradication of satellite lesions or microscopic invasion around the periphery of a tumour. Therefore, the treatment of combined RFA and ethanol injection with a multiple multipronged needle inducing larger necrosis can yield a safety margin which facilitates a decrease in local recurrence. Tumour size [29, 34], tumour location [34] and patient age [34, 35] have been reported as the predisposing factors for LTP of HCC. However, no such factors were found in our study.

As a result of the multicentric occurrence of HCC and metastasis to other sites via portal vein, distant recurrence is very common after ablation. In this study, the multivariate analysis revealed that presence of hepatitis B or C infection was a significant factor for the distant recurrence of HCC. Therefore, patients with hepatitis virus infection should be monitored more frequently and carefully.

It is indubitable that there were some limitations in our study. First and foremost, it was a single arm of HCC treatment and there was no direct comparison. Randomized controlled clinical trials are needed to provide a complete evaluation of this combined technique for the treatment of HCC. Second, only four patients with large HCC were included in this study. Further group analyses between medium and large HCC are ineligible. Third, the follow-up period ranged from 6.7 to 32.6 months. The long-term results of the treatment are still unclear.

In summary, medium and large HCC can be treated safely and effectively with the combination of RFA and ethanol injection with a multipronged needle, although more data and long-term results are needed for further validation.

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