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ORIGINAL ARTICLE

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

Ji-Wei Lin, Chen-Chun Lin, Wei-Ting Chen, Shi-Ming Lin*

Division of Hepatology, Liver Research Unit, Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital and Chang Gung University, Linkou, Taipei, Taiwan

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Abstract Radiofrequency ablation (RFA) is more effective for hepatocellular carcinoma (HCC) < 3 cm. Combining percutaneous ethanol injection and RFA for HCC can increase ablation; however, the long-term outcome remains unknown. The aim of this study was to compare long-term outcomes between patients with HCC of 2–3 cm versus 3.1–4 cm and in high-risk versus non-high-risk locations after combination therapy. The primary endpoint was overall survival and the secondary endpoint was local tumor progression (LTP). Fifty-four consecutive patients with 72 tumors were enrolled. Twenty-two (30.6%) tumors and 60 (83.3%) tumors were of 3.1–4 cm and in high-risk locations, respectively. Primary technique effectiveness was comparable between HCC of 2–3 cm versus 3.1–4 cm (98% vs. 95.5%, $p = 0.521$), and HCC in non-high risk and high-risk locations (100% vs. 96.7%, $p = 1.000$). The cumulative survival rates at 1 year, 3 years, and 5 years were 90.3%, 78.9%, and 60.3%, respectively, in patients with HCC of 2–3 cm; 95.0%, 84.4%, and 69.3% in HCC of 3.1–4.0 cm ($p = 0.397$); 90.0%, 71.1%, and 71.1% in patients with HCC in non-high-risk locations; and 92.7%, 81.6%, and 65.4% in high-risk locations ($p = 0.979$). The cumulative LTP rates at 1 year, 3 years, and 5 years were 10.2%, 32.6%, and 32.6%, respectively, in all HCCs; 12.6%, 33.9%, and 33.9% in HCC of 2–3 cm; 4.8%, 29.5%, and 29.5% in HCC of 3.1–4 cm ($p = 0.616$); 16.7%, 50.0%, and 50.0% in patients with HCC in non-high-risk locations; and 8.8%, 29.9%, and 29.9% in patients with HCC in high-risk locations ($p = 0.283$). The cumulative survival and LTP rates were not significantly different among the various subgroups. Combining RFA and percutaneous ethanol injection achieved comparable long-term outcomes in HCCs of 2–3 cm versus 3.1–4.0 cm and in high-risk versus non-high-

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* Corresponding author. Division of Hepatology, Liver Research Unit, Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital and Chang Gung University, 199 Tunghwa Road, Linkou, Taipei, Taiwan.
E-mail addresses: lsmpaicyto@cgmh.org.tw, lsmpaicyto@gmail.com, 8802027@cgmh.org.tw (S.-M. Lin).

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risk locations. A randomized controlled or cohort studies with larger sample size are warranted.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies and one of the major causes of mortality worldwide [1]. Patients with early-stage HCC are candidates for resection, liver transplantation, or ablation [2]; however, candidacy for resection is determined by tumor location, size, or number of lesions, adequate liver reserve, or comorbid conditions. Orthotopic liver transplantation is considered for patients with poor liver function, but the shortage of donors continues to hinder treatment.

Percutaneous radiofrequency ablation (RFA) has been used to treat patients with HCC since 1990 and has been widely used for $>$ 20 years. A meta-analysis showed that RFA achieved comparable results to liver resection in patients with HCCs $\leq$3 cm [3,4], but inferior outcomes in patients with HCCs $>$ 3 cm [5,6]. In addition to tumor size, the effectiveness of RFA also depends on tumor location. More treatment failures and complications occur after RFA for HCCs in high-risk locations, which are close to the liver capsule, vital organs, vessels, or central bile ducts [7].

Some studies have shown that combining RFA and percutaneous ethanol injection (PEI) is effective for larger HCCs, as well as HCCs in high-risk locations [8,9]. Zhang et al. [10] have shown that combination therapy can improve survival compared with RFA monotherapy; however, the long-term outcomes in patients with HCCs 3.1—4 cm in size and in high-risk locations after combination therapy have not been reported. The aim of this study was to compare the long-term survival and local tumor progression (LTP) in patients with HCCs 2—3 cm versus 3.1—4 cm in size, and in high-risk versus non-high-risk locations.

Materials and methods

Patients

This retrospective study reviewed the prospectively collected database of consecutive patients with HCCs $\leq$4 cm in various locations after combination therapy between February 2004 and October 2011 at our institute. Inclusion criteria were patients with larger HCCs (3.1—4 cm) or HCCs in high-risk locations. All of the index HCCs were diagnosed by cytological or pathological evaluation, or according to the criteria of the American Association for the Study of Liver Disease [11]. The number of HCCs was fewer than three. All patients had cirrhosis (Child—Pugh class A or B). None of the patients had extrahepatic metastasis or intrahepatic vascular invasion. Impaired coagulopathy was corrected to a safe level (prothrombin time $<$ 3 seconds and platelet count $>$ 50×10^9/L) prior to treatment. All patients received combination therapy after a comprehensive discussion in our HCC multidisciplinary meeting. Informed consent was obtained from all patients prior to treatment. The decision to perform RFA alone or combine PEI and RFA was left to the discretion of the operator. This study was approved by our Institutional Review Board.

Definition of high-risk locations

Based on our previous description [8], high-risk location was defined as the index tumor located within 10 mm of the liver capsule (subcapsular location), vital organs (stomach, duodenum, colon, gallbladder, common bile duct, or kidneys), the dome of the diaphragm, or directly in contact with a vessel $>$ 3 mm in diameter. If the tumor was located near both structures, we chose the nearest one as the main structure to define high-risk location. The distance between the margin of the tumor and the large vessels or extrahepatic organs was measured on computed tomography (CT) images (Somatom Sensation 16; Siemens, Munich, Germany), reconstructed at 5-mm intervals. Non-high-risk locations referred to index tumors not located in the aforementioned high-risk locations.

Techniques of combining RFA and PEI

RFA and PEI were performed using a percutaneous approach under real-time ultrasound (Aplio XV; Toshiba, Tokyo, Japan). Conscious sedation with pethidine and midazolam was achieved with vital sign monitoring during the entire procedure. RFA and PEI were performed by one of two hepatologists with $>$3 years of experience.

The RF electrode was positioned into the tumor first. The electrode was kept 0.5—1 cm away from the vital organs. PEI was performed by injection of 1—10 mL 99.5% ethanol via a 22-gauge percutaneous needle (15—20 cm in length). The RFA program was activated immediately after PEI. Overlapping ablation was applied to achieve an adequate coagulation volume to cover the entire tumor.

Follow-up protocol

All patients had follow-up for $>$4 months after combination therapy. The follow-up was terminated in August 2012. The post-treatment evaluation mainly included α-fetoprotein and imaging studies. An abdominal echo was routinely performed the day after combination therapy and repeated every 3 months thereafter. At least one dynamic imaging study (CT or magnetic resonance imaging) was performed on all patients at 1 month and every 3 months after RFA for assessment of complete ablation and early diagnosis of HCC recurrence.

Definition of complete ablation, primary technique effectiveness, and LTP

Complete ablation was defined as a low attenuated area on the dynamic liver CT scan or low signal intensity on T2-weighted magnetic resonance imaging after the final ablation therapy, which encompassed the area of the index tumor without nodular peripheral enhancement on dynamic studies [6,8]. Primary technique effectiveness (PTE) was defined as achievement of complete necrosis within three sessions of ablation and within 3 months after the first treatment of the index HCC [8]. LTP was defined as the appearance of any area of high attenuation with peripheral nodular enhancement contiguous with the ablated HCC on dynamic imaging or an enlarged ablated area on follow-up imaging of HCC that had previously been completely ablated [6,8].

The primary end point of the study was overall survival; the secondary endpoint was LTP.

Statistical analysis

The outcomes were compared between the tumor size (2.0—3.0 cm vs. 3.1—4.0 cm) and tumor location subgroups (non-high-risk location vs. high-risk location). Baseline characteristics and outcomes between subgroups were analyzed with a χ^2 test or Fisher's exact test for categorical data and the Mann—Whitney *U* test for continuous data. Cumulative survival and LTP were analyzed with the Kaplan—Meier method and the difference was determined by the log-rank test. Univariate analyses were performed using the Cox regression model to identify possible risk factors for death and LTP. A p value <0.05 was considered statistically significant.

Results

The baseline characteristics are shown in Table 1. Initially, 79 patients with 101 HCCs underwent combination therapy during the study period. Twenty-five patients were excluded from the study, including 23 patients with transarterial chemoembolization prior to combination treatment, one foreign patient, and one patient with massive ascites without imaging follow up after RFA. Twelve patients had more than one HCC. Complete ablation and primary technique effectiveness were analyzed according to 72 HCCs with tumor-based data (Table 1), and long-term outcomes were analyzed in 54 patients (Table 2).

Complete ablation and primary technique effectiveness

Complete ablation after one session of treatment was achieved in 66 of 72 HCCs (91.7%). The other six HCCs were all located in high-risk locations. Specifically, two tumors were near vessels (middle and right hepatic veins); two tumors were near the biliary tract; one tumor was near the diaphragm; and one tumor was near a kidney. Four of the six tumors were completely ablated after the second session of treatment. The two tumors located near the middle hepatic vein and kidney did not achieve PTE. The PTE rate was 97.2%.

Table 1 Baseline characteristics of patients and tumors.

Parameters	Values
Patient no.	54
Age (y)	66.3 ± 10.3
Male sex	38 (70.3)
Viral infection	
HBsAg positive	25 (46.3)
HCV antibody positive	22 (40.7)
Cirrhosis	
Child—Pugh A	47 (87.0)
Child—Pugh B	7 (13.0)
Albumin (g/dL)	3.7 ± 0.6
Total bilirubin (mg/dL)	1.2 ± 0.7
Platelet count (10^4/mm^3)	11.1 ± 5.0
Prothrombin time (INR)	1.2 ± 0.2
Tumor no.	72
Tumor size (cm)	2.7 ± 0.6
2.0—3.0 cm	50 (69.4)
3.1—4.0 cm	22 (30.6)
Location	
High-risk	60 (83.4)
Non-high-risk	12 (16.6)
Ablation time (min)	21.7 ± 12.3
Ethanol use (mL)	4.1 ± 1.5

Data are presented as *n* (%) or mean ± SD.
HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; INR = international normalized ratio.

LTP

Eighteen HCCs developed LTP (25%) during follow-up (median, 31.5 ± 23.6 months; range, 1.8—92.0 months), and LTP developed in 13 of 50 (26%) HCCs 2—3 cm in size, and five of 22 (22.7%) HCCs 3.1—4.0 cm in size ($p = 0.768$). In the 2—3-cm tumor group, five of 15 tumors (33.3%) near vessels and four of 26 (15.4%) tumors near vital structures developed LTP ($p = 0.248$). Four of 12 (33.3%) HCCs in non-high-risk locations and 14 of 60 (23.3%) HCCs in high-risk locations developed LTP ($p = 0.479$). Six of 19 (31.6%) tumors near vessels and eight of 41 (22.9%) tumors near vital structures developed LTP ($p = 0.338$; Table 3). Tumors located near vessels received more RFA sessions and higher ethanol volume, but had lower complete ablation and PTE, and higher LTP.

The cumulative LTP rate at 1 year, 2 years, and 3 years for all index tumors was 10.2%, 28.2%, and 32.6%, respectively; 12.6%, 30.6%, and 33.9% in tumors 2.0—3.0 cm in size; 4.8%, 23.1%, and 29.5% in tumors 3.1—4.0 cm in size ($p = 0.616$); 16.7%, 33.3%, and 50% in tumors in non-high-risk locations; and 8.8%, 27.3%, and 29.9% in tumors in high-risk locations ($p = 0.283$). Univariate analysis showed that only tumor differentiation was a significant factor related to LTP ($p = 0.02$).

New HCC recurrence

During the follow-up period (48.0 ± 24.6 months; median, 54.3 months), 39 of 54 (73%) patients had new HCC recurrence. There were no apparent risk factors for the new

Table 2 Comparison of baseline characteristics and treatment responses in 72 HCCs with different sizes and locations.

Variables	Size		*p*	Location		*p*
	2.0—3.0 cm	3.1—4.0 cm		Non-high-risk	High-risk	
Baseline characteristics						
Tumor no.	50 (69.4)	22 (30.6)		12 (16.7)	60 (83.3)	
Size (cm)	2.4 ± 0.3	3.5 ± 0.3	<0.001	2.7 ± 0.6	2.8 ± 0.6	0.886
Child—Pugh A	41 (82)	20 (90.9)	0.485	11 (91.7)	50 (83.3)	0.677
Near vessel	15 (30.0)	4 (18.1)	0.390	0	19 (31.7)	
Near vital structure[a]	26 (52.0)	15 (68.2)	0.201	0	41 (68.3)	
Ablation time (min)	19.7 ± 10.9	26.1 ± 14.2	0.035	21.7 ± 9.4	21.7 ± 12.8	0.629
Ethanol use (mL)	4.0 ± 1.3	4.4 ± 1.9	0.376	3.8 ± 1.1	4.2 ± 1.6	0.358
No. of electrode repositions	1.8 ± 0.9	2.1 ± 1.1	0.295	2.0 ± 0.9	1.9 ± 1.0	0.737
Treatment response						
Complete ablation	46 (92.0)	20 (90.9)	1.000	12 (100.0)	54 (90.0)	0.581
Primary technique effectiveness	49 (98.0)	21 (95.5)	0.521	12 (100.0)	58 (96.7)	1.000
Local tumor progression	13 (26.0)	5 (22.7)	0.768	4 (33.3)	14 (23.3)	0.479

Data are presented as *n* (%) or mean ± SD.
HCC = hepatocellular carcinoma.
[a] Vital structure in this table excludes blood vessels.

Table 3 Therapeutic details in 72 HCCs at different locations.

Definite location	No. of tumors	HCC size (cm)	Ethanol used (mL)	No. of directions	RFA time (min)	Complete ablation	PTE	LTP
Non-high-risk location	12	2.71 ± 0.63	3.75 ± 1.14	2 ± 0.85	21.67 ± 9.41	12 (100)	12 (100)	4 (33.3)
Vessel	19	2.71 ± 0.62	4.69 ± 2.08	1.79 ± 0.98	23.84 ± 16.67	17 (89.4)	18 (94.7)	6 (31.6)
Diaphragm	19	2.67 ± 0.59	3.87 ± 1.42	1.74 ± 0.73	18.61 ± 6.87	18 (94.7)	19 (100)	6 (31.6)
Biliary tree	15	2.92 ± 0.53	4.07 ± 1.28	2.13 ± 0.92	23.53 ± 11.99	13 (86.7)	15 (100)	2 (13.3)
GI tract and others	7	2.69 ± 0.38	4.07 ± 1.24	2.14 ± 1.46	20.14 ± 15.75	6 (85.7)	6 (85.7)	0 (0)

Data are presented as *n* (%) or mean ± SD.
HCC = hepatocellular carcinoma; LTP = local tumor progression; PTE = primary technique effectiveness; RFA = radiofrequency ablation.

recurrence versus no new recurrence group; however, patients with liver cirrhosis ($p = 0.084$, odds ratio = 4.36, 95% confidence interval 0.84—22.54) tended to have more new recurrences.

Overall survival

During follow-up, 16 of 54 (29.6%) patients died, 18 (16 lost to follow-up and 2 received liver transplantation) of 54 (33.3%) patients withdrew, and 20 of 54 (37.0%) patients were alive. The deaths were largely due to liver failure (75%) related to rapid liver decompensation with sepsis caused by pneumonia ($n = 3$), biliary tract infection ($n = 2$), spontaneous bacterial infection ($n = 4$), postoperative duodenal ulcer with bacteremia and fungemia ($n = 1$), and post-chemotherapy for HCC with neutropenia and septic shock ($n = 1$). One patient died of a hepatitis B flare with liver failure. Another cause of death was variceal bleeding ($n = 2$), HCC rupture ($n = 1$), and tumor progression and transfer to hospice care ($n = 1$). The mean survival was 33.7 ± 23.5 months (median, 31.6 months; range, 4.4—94.6 months). Twenty-one of 32 (65.6%) patients with tumors 2—3 cm in size and 17 of 22 (77.2%) patients with tumors 3.1—4 cm in size remained alive at analysis. The cumulative survival rate at 1 year, 3 years, and 5 years for all patients was 92.2%, 81.0%%, and 67.6%, respectively; 90.3%, 78.9%, and 60.3% in the 2.0—3.0-cm group; 95.0%, 84.4%, and 69.3% in the 3.1—4.0-cm group ($p = 0.397$); 90.0%, 71.1%, and 71.1% in non-high-risk locations; and 92.7%, 81.6%, and 65.4% in high-risk locations ($p = 0.979$). Univariate analysis, including tumor size and tumor location, were not significant risk factors. Due to disease progression after initial combination therapy, 22 patients received transarterial chemoembolization during follow-up.

Adverse effects

The definitions of ablation-related complications and side effects were according to the Standardization of Terminology and Reporting Criteria [12]. One patient with an index HCC under the diaphragm had an asymptomatic pleural effusion. Among all of the patients, there were 26 (36%) episodes of grade 1 or 2 abdominal pain and eight (11.1%) episodes of low-grade fever after treatment; the pain and fever were both controlled after medication.

Discussion

Previous studies have shown RFA alone can achieve a better outcome in small HCCs (≤3 cm) [5]. Moreover, combining PEI and RFA can achieve a better outcome in HCCs 3.1—5.0 cm in size and difficult-to-treat HCCs; especially tumors close to large vessels or vital organs [10]. The mechanisms favoring combination therapy probably include the expansion of the ablation area by diffusion of hot ethanol into the areas not reached by RF power and reduction in the heat-sink effect [8,10,13]. The current results confirm that combining RFA and PEI can achieve comparable long-term outcomes in patients with larger HCCs measuring 2—3 cm versus 3.1—4 cm and in high-risk locations versus non-high-risk locations.

Previous studies [14], including meta-analyses [15,16], have shown that 85—100% of HCCs ≤ 3—4 cm and 96—100% of small HCCs (<3 cm) in size are completely ablated after RFA. The current study showed a comparable complete ablation rate compared with previous studies.

Previous studies have also shown that the LTP rate of small HCCs after RFA was 1.3—14% at 1 year, 1.7—24% at 2 years, and 1.7—30% at 3 years [7,14,17—19], whereas the corresponding rates were higher in our study. The suboptimal results of LTP in our study may be related to the limited sensitivity of detecting residual viable tumors after RFA with dynamic CT scan [20] and the higher recurrence rates after RFA for HCCs > 3 cm and located near intrahepatic blood vessels and in subcapsular locations [21]. In addition, because 83.3% of patients with HCC in this series were in high-risk locations, the LTP might be higher than that reported elsewhere [7,17—19].

To determine the impact of tumor size on treatment effects, no significant relationship was found between subgroups. This finding implies that combining PEI and RFA can induce a synergistic necrotizing effect and expand coagulation volumes, which are larger than those obtained with PEI or RFA alone. Indeed, Vallone et al. [9] reported that combining PEI and RFA is effective in HCCs > 4.0 cm in size.

Combining PEI and RFA can also achieve a better effect for HCCs in high-risk locations by reducing the heat-sink effect [22]. However, RFA for HCCs in high-risk locations may result in more complications or inadequate safety margins due to concern about complications. In our study there was no difference in the complete ablation rate between HCCs in high-risk locations and non-high risk locations.

Univariate analysis showed that tumor differentiation influenced LTP after combination treatment. Tumors with poor differentiation have a higher incidence of satellite nodules and microvascular invasion, which may contribute to higher LTP [23]. Our study also showed that combination treatment might reduce the LTP in larger HCCs and HCCs in high-risk locations. The benefit might be due to the expansion of the ablation area, including the area containing satellite nodules.

After RFA, the intrahepatic new recurrence rate of HCCs was 13—36% at 1 year, 24—38% at 2 years, 30—49% at 3 years, and up to 81% at 4 years [14,17—19,24]. New recurrences in this study were slightly fewer than in a previous study [3].

In our study no significant complications were noted. Livraghi et al. [6] reported a 1.8% complication rate in HCCs < 2.0 cm in size after RFA, which was comparable to our results. This finding was due to the safety of combination treatment in the prevention of thermal injuries to adjuvant vital structures.

Shiina et al. [25] reported 1-, 3-, and 5-year survival rates of 96.6%, 80.5%, and 65.1% in a 10-year follow-up study. Moreover, the study also showed that HCC ≤3 cm in size was a favorable factor for survival. Compared to the previous report, the 1-, 3-, and 5-year survival rates in our series were slightly better at 3 years and 5 years, even in our patients with relatively larger HCCs (median, 2.63 cm; mean, 2.74 ± 0.57 cm), and more patients had HCCs in high-risk locations. Previous studies have shown that significant factors for longer survival were as follows: smaller tumors (≤2 or 3 cm); Barcelona Clinic Liver Cancer (BCLC) stage A; higher albumin level (≥3.5 gm/dL); higher platelet count (≥100,000/mm^3); lower serum lectin-reactive α-fetoprotein level (≤10%); [26] and complete ablation at 1 month [19]. Our study showed that the addition of PEI was the only important factor related to better survival, which might have been due to the effects of combination therapy or smaller sample size.

The satisfactory survival rate in our study may be attributed to better local control after combination therapy. Therefore, with the exception of the two patients who died (HCC rupture and chemotherapy with neutropenia and sepsis), the major cause of death in our study was not related to tumor progression, but due to underlying liver disease or nonhepatic causes [HCC progression vs. non—HCC—related causes (12.5% vs. 87.5%)]. Univariate analysis, including tumor size and location, revealed no significant risk factors, which implies combination therapy may overcome large size and high-risk location.

Some limitations were encountered in this study. First, the sample size was small. Our study did show that combination treatment could achieve a comparable effect between patients with larger HCCs and high-risk locations. Second, long-term follow-up analysis was begun in 2004. The novel RFA with multiple electrodes and switching the RF controller have emerged in recent years, thus, the benefit of combing PEI and RFA may not be clearly demarcated.

In conclusion, our study showed that combining RFA and PEI could achieve comparable long-term outcomes in subgroups of HCCs (2—3 cm vs. 3.1—4.0 cm or high-risk vs. non-high-risk locations). We may conclude that combining radiofrequency ablation and ethanol injection may achieve comparable long-term outcomes in the larger HCC of 3.1—4 cm compared with HCC <3.1 cm and in high-risk locations. However, due to the absence of patients who received RFA alone for comparison, our findings do not definitely prove that combination therapy is superior to RFA alone or other curative treatment. Further randomized controlled trials or comparative studies with a larger sample size might be required to further confirm the benefit of combination treatment for larger HCCs or HCCs in high-risk locations.

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