Liver Cancer

Liver Cancer 2016;5:8–20
DOI: 10.1159/000367755
Published online: December 15, 2015

2235-1795/16/0051-0008$39.50/0
www.karger.com/lic

Original Paper

The Effectiveness of Multiple Electrode Radiofrequency Ablation in Patients with Hepatocellular Carcinoma with Lesions More than 3 cm in Size and Barcelona Clinic Liver Cancer Stage A to B2

Chen-Chun Lin Ya-Ting Cheng Wei-Ting Chen M Shi-Ming Lin

Division of Hepatology, Liver Research Unit, Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Lin-Kuo, Chang Gung University, Taoyuan, Taiwan

Key Words
Barcelona Clinic Liver Cancer · Hepatocellular carcinoma · Multiple-electrode · Radiofrequency ablation · Survival

Abstract
Outcomes of hepatocellular carcinoma (HCC) lesions >3.0 cm in size including Barcelona Clinic Liver Cancer (BCLC) stage B after radiofrequency ablation (RFA) with a single electrode remain unsatisfactory. This study aimed to investigate the outcomes of RFA with multiple electrodes (ME-RFA) for HCC tumors 3.1–7.0 cm in size and BCLC stage B. This retrospective study included 70 consecutive patients with 58 medium- (3.1–5.0 cm) and 17 large- (5.1–7.0 cm) sized HCCs after ME-RFA using a controller. Outcomes in terms of complete response, primary technique effectiveness, local tumor progression, and overall survival were investigated. After 1–4 applications of ME-RFA, the rates of complete response and PTE in medium-sized tumors were 79.3% and 91.4%, respectively, and in large tumors were 76.5% and 94.1%, respectively. Overall, the major complication rate was 5.7%. After a median 21-month follow-up period, both two- and three-year estimated overall survival rates were above 80%. There were no significant differences in overall survival and local tumor progression rates between medium- and large-size tumors and among BCLC stages A, B1 and B2. A complete response

Shi-Ming Lin, MD

Division of Hepatology, Liver Research Unit, Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Lin-Kuo, Chang Gung University
5, Fu-Hsin St., Kwei-Shan, Taoyuan, Taiwan 333 (ROC)
Tel. 886 3 3281200 Ext. 8107, E-Mail lsmpaicyto@cgmh.org.tw

to ME-RFA was the only significant factor associated with improved survival (p=0.008). In conclusion, ME-RFA can effectively treat 3.1–7.0-cm sized HCCs with a comparable outcome between medium- and large-size tumors and among BCLA stages A to B2.

Study Highlights

What is Current Knowledge

Outcomes of hepatocellular carcinoma (HCC) larger than 3.0 cm in size including Barcelona Clinic Liver Cancer (BCLC) stage B after conventional radiofrequency ablation (RFA) with single electrode and overlapping ablation remain unsatisfactory.

What is New Here

- Multiple electrode radiofrequency ablation (ME-RFA) using a switch controller (SWC) with fewer overlapping applications can achieve high complete response and PTE rates (both >90%) for selected patients with 3.1–7.0 cm sized HCCs and better survival for such patients.
- Patients with large HCCs or multiple HCCs (BCLC stage B1 or B2) do not have inferior outcomes than medium-sized and BCLC stage A HCCs, respectively.
- Complete response to ME-RFA SWC is the only factor associated with overall survival (p=0.008) in patients with HCC of 3.1–7.0 cm in size.

Introduction

RFA has been endorsed as a curative treatment modality by several clinical management guidelines for early-stage, unresectable HCC [1, 2]. The complete response rates for HCCs <3.0 cm in size exceeds 90% [3–5]. However, in prior studies, the complete response rate was reduced to 45%–70% for medium-size HCCs (3.1–5.0 cm), and it was only 23%–45% for large HCCs (>5.0 cm) [6, 7]; in addition, these data implied that RFA was less effective for treating HCC of BCLC stage B.

RFA with ME-RFA connected to a switching radiofrequency controller (SWC) is being developed for the ablation of larger tumors. This system involves simultaneous placement of up to three RFA electrodes into a tumor and alternate activation of all electrodes by switching the RF generator. Until now, only a few preliminary studies have shown that ME-RFA can create a mean coagulation diameter up to 4.2–5.9 cm [8–12]. Recently, ME-RFA achieved a response rate of up to 97% for single medium-sized HCCs [13] and up to 81% for large HCCs of 5.0–8.5 cm in size [14]. However, thus far, only a few studies have been conducted on the survival outcomes for undertaking ME-RFA with HCCs measuring 3.1–7.0 cm in size [14].

Consequently, we retrospectively analyzed a cohort database of 70 consecutive patients with 75 HCCs of 3.1–7.0 cm in size over a median follow-up period of 21 months. The aim of this study was to evaluate the effectiveness and outcomes in patients with tumors of 3.1–7.0 cm in size and BCLC stage B after ME-RFA treatment.

Materials and Methods

Patients and Tumors

This retrospective cohort study was carried out in our department from January 2009 to December 2011, inclusive. The selection criteria for ME-RFA treatment were as follows: 1) age >20 years, 2) all hepatic tumors detectable by ultrasound scan and at least one sized between 3.1–7.0 cm, 3) total number of tumors less than five, 4) well-compensated cirrhosis, 5) correctable platelet count (>50 × 10^3/ml), 6) prothrombin time-international normalized ratio <1.5, and 7) patients were deemed unsuitable for or refused surgical resection. Patients who had major vessel invasion or extrahepatic metastases were excluded. The distance between the tumor margin and the main bile duct had to be more than1.0 cm. All tumors were diagnosed by histopathologically or by the American Association for the Study of Liver Diseases criteria [1]. According to the maximum diameter of the tumor, medium-sized and large-sized HCCs were defined as 3.1–5.0 cm and 5.1–7.0 cm, respectively. BCLC stage B was subclassified according to 'up-to-seven' criteria [15].

All patients underwent ME-RFA after being provided with comprehensive details of the process in our HCC multidisciplinary combined meeting. Informed consent was obtained from all patients before treatment. This retrospective study was approved by the Institutional Review Board of Chang Gung Memorial Hospital.

ME-RFA Systems and Treatment Procedures

All treatments were percutaneously performed under real-time ultrasound with a guidance system (Aplio XV®; Toshiba, Tokyo, Japan). During the entire procedure, all patients received intravenous sedation with fentanyl and midazolam, and their vital signs were continuously monitored. A multi-monopolar ME-RFA system (Cool-tip®; Valleylab/Covidien, Boulder, Colorado) was available for the entire study duration. In this system, a switch machine (Valleylab/Covidien) was adjoined to the radiofrequency energy supply machine with a maximum power of 200 watts. A multi-bipolar ME-RFA system (Celon®, Prosurg, Telow, Germany) has been available since January 2010. The switch machine was incorporated into a part of the energy supply machine. Both systems had a cooling pump machine to provide continuous ice or cooled water into the electrodes to avoid char formation during ablation.

In both systems, the electrodes were inserted into the tumors with an equilateral triangular confirmation before initiation of the ablation. The distances between the electrodes were ultrasonographically estimated for the multi-monopolar ME-RFA system and for the multi-bipolar ME-RFA system, and they were about 1.5–2.0 cm [9] and 2.0–3.0 cm [16], respectively. In the multi-monopolar ME-RFA system, the switching machine was set to the auto-mode, and all electrodes worked alternately and switched off automatically after any impendence surge. Continuous ablation lasted for between 12–16 minutes until the impedance shut-off cycle at approximately 15 seconds, and once adequate hyperechoic change of the ablated area was achieved [8]. For the multi-bipolar ME-RFA system, all electrodes worked in pairs and were controlled by the switch machine. The power output was initially set at 90–150 watts; this was automatically decreased by tissue resistance feedback. The endpoint of the multi-bipolar ME-RFA system was decided by the cumulative energy delivery into the tissue, according to the recommendations of the instruction manual provided by the manufacturer [12].

In order to obtain sufficient ablative volume to fully cover the entire tumor, at least a 0.5 cm ablative margin beyond the index tumor was required. In addition, multiple numbers of applications for overlapping ablation were accomplished by repositioning the electrodes. Therefore, the first electrode was inserted along the medial margin of the index tumor, the second electrode was inserted in parallel to the path of first electrode, and the third electrode was inserted in parallel to the path of the two electrodes but in a different plane. The distance between two electrodes ranged from 2.0 to 2.5 cm. Overlapping insertion of electrodes is required for the treatment of HCCs >3.0 cm in size. The overlapping ablation is mandatory to achieve sufficient ablation in different planes of the index tumor.

If the tumors were located near the intestine, gallbladder, or just beneath the diaphragm, adequate artificial ascites was created before the treatment to make an insulation layer between the tumor (s) and these vital organs.

In order to prevent seeding of the HCC in satellite liver or beyond, needle tract ablation under ultrasound-guidance was undertaken for withdrawal of electrodes after ablation by maintaining the multi-monopolar ME-RFA system above 80°C or by the tract ablation mode for the multi-bipolar ME-RFA system. The cooling system was deactivated during the tract ablation.

Evaluation and Follow-Up

Complete response was defined as a tumor without any enhancement during the arterial phase on a four-phase dynamic computed tomography (CT) scan, one month after RFA treatment. Incomplete treatment was considered if the tumor revealed any tissue enhancement. Up to two courses of additional RFA could be performed within three months for patients with an incomplete response to ME-RFA, in order to achieve primary technique effectiveness (PTE). All the patients who achieved PTE for all tumors were followed-up at an interval of every three months by CT scan in the first year and then alternatively with ultrasound examinations. Local tumor progression was defined as enhancing tumors reappearing at the margin of the ablated tumor.

Statistical Analysis

In order to assess the efficacy of treatment of the tumors larger >3.0 cm in size by ME-RFA, we pooled the data of the two systems as a whole cohort for analysis. The primary endpoint was PTE. The secondary endpoints were local tumor progression and overall survival. Differences in categorical variables were compared using the Chi-square test or Fisher's exact probability. Student's *t* test was used for comparing differences in continuous variables. Survival and local tumor progression functions were obtained by Kaplan–Meier analysis. A log-rank test was used to compare the differences between the factors. Prognostic factors for survival and local tumor progression were identified using the Cox Regression Proportional Hazard model. A p value <0.05 was considered significant. All statistical methods were performed using IBM SPSS Statistics version 19 statistical software (SPSS®, Chicago, Illinois, USA).

Results

Patients and Tumors

Seventy patients with 75 index tumors, 58 medium-sized and 17 large-sized, were included in this study. In addition, 37 small-sized (<3.0 cm) tumors were diagnosed in these patients. The pretreatment data are shown in table 1. Among the 40 patients with a single tumor, 30 were medium-sized and classified into stage A. The other patients with a large single tumor and all the patients with multiple tumors were classified into BCLC stage B1 and B2 (table 1). Seventy percent of patients with BCLC stage A were >65 years of age, 90% had cirrhosis, and 83% had thrombocytopenia, respectively.

ME-RFA Treatments

Both ME-RFA systems used similar numbers of electrode placements and applications for treatment of the index tumors (table 2). A large-sized tumor required more electrode placements (9.0±2.2 vs. 5.0±1.7, p<0.001), more application numbers (3.0±0.8 vs. 2.0±0.6, p<0.001), and longer ablation times (45.0±12.3 min vs. 28.5±9.8 min, p<0.001) than a medium-sized tumor for obtaining an adequate ablation volume to fully cover the whole tumor. Thirteen medium-sized tumors could be treated by one application (all tumors ≤4 cm). More than 80% of medium-sized tumors used one or two applications, while 65% of large-sized tumors required three or four applications. Four large-sized tumors and none of the medium-sized tumors required a fourth application for overlapping ablation (fig. 1).

Response to ME-RFA

Fifty-two index tumors were treated by the multi-monopolar system and 23 were treated by the multi-bipolar system. Complete response was achieved in 59 (78.8%) index tumors. The two systems had comparable complete response rates (fig. 2). The 37 small-sized non-index tumors were also treated in the same ME-RFA course, and all of them achieved complete ablation. There was no statistical difference for complete response rates between medium- and large-sized tumors and among BCLC stages A, B1 and B2 (table 3).

Liver Cancer 2016;5:8–20
DOI: 10.1159/000367755
Published online: December 15, 2015

Table 1. Pre-treatment data of the 70 patients and the 75 index HCC

	Value
Patients	70
Age (median, years)	71.5 ± 11.0
Age >65 years (N,%)	42 (60.0%)
Male sex (N,%)	42 (60.0%)
HBsAg positive (N,%)	32 (45.7%)
Anti-HCV positive (N,%)	31 (44.3%)
Cirrhosis	64 (91.4%)
Child-Pugh class A/B	60/10
Medium-sized/large-sized	53/17
Single tumor/multiple tumors	40/30
BCLC stage A/B1/B2	30/25/15
Tumor numbers (n=1/2/3/4)	40/21/6/3
AFP >100 ng/ml (N,%)	19 (27.1%)
Albumin (mg/dL)	3.9 ± 0.5
Creatinine (mg/dL)	0.8 ± 1.7
Platelet (x10^3/mm)	105 ± 60
Platelet count <150 x 10^3 /mm	56 (80.0%)
HCC treatment naive	63 (90.0%)
Artificial ascites	41 (58.6%)
Index tumors	
Medium-sized	58
Tumor size (mean ± SD, cm)	3.7 ± 0.4
Subcapsular location (N,%)	36 (62.1%)
Perivascular location (N,%)	17 (29.3%)
Large-sized	17
Tumor size (mean ± SD, cm)	5.7 ± 0.6
Subcapsular location (N,%)	15 (88.2%)
Perivascular location (N,%)	3 (17.6%)

SD=standard deviation; HBsAg=hepatitis B surface antigen; HCV= hepatitis C virus.

A total of 16 residual tumors were found after ME-RFA treatments; nine in the multi-monopolar system and seven in the multi-bipolar system. All the residual tumors were <3.0 cm, and all were found in the tumors having been treated by multiple overlapping ablation. All of these tumors were also found in high-risk locations (11 subcapsular and six perivascular). Of those in the subcapsular locations, seven occurred in the upper segments just beneath the dome of the liver or behind the ribs, and four occurred in the posterior segments abutting the liver capsule.

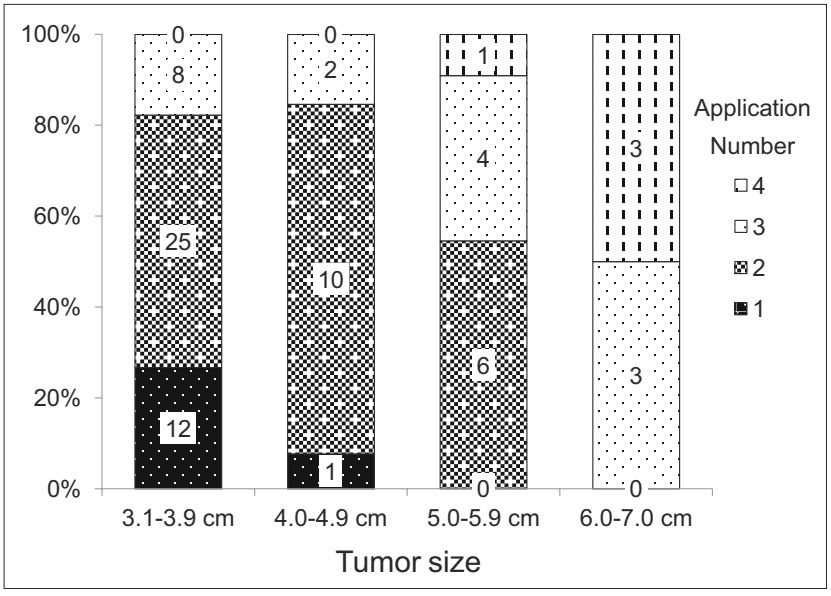

Fig. 1. The graph shows the number of applications used for overlapping ablation of HCCs sized 3.1–7.0 cm by ME-RFA, stratified by 1-cm increments of tumor size.

PTE

Three patients did not receive additional RFA because two patients withdrew consent (one in each system), and one suffered from multiple recurrences (multi-bipolar system). Three patients received two additional courses of RFA. There were a total of 16 additional RFA courses provided. Complete response occurred in six residual tumors in the multi-monopolar system, and in four in the multi-bipolar systems, following the additional RFA treatments. Overall, 69 (92.0%) index tumors achieved PTE. There was no statistical difference in the PTE rates between the two systems (fig. 2). The PTE rates were not statistically different in the subgroups of the tumor size or in the BCLC stages (table 3).

Table 2. Electrode placement numbers and application sessions for 75 index tumors

	Electrode placement number						
Tumor size	n	MM-SWC RFA		n	MB-SWC RFA		p value
3.0–3.9 cm	33	4.0 ± 1.5	(3, 9)	12	5.0 ± 2.2	(2, 9)	0.309
4.0–4.9 cm	8	5.5 ± 1.2	(4, 7)	5	6.0 ± 2.5	(3, 9)	0.924
5.0–5.9 cm	5	6.0 ± 1.6	(6, 9)	6	7.0 ± 2.1	(4, 9)	0.761
6.0–7.0 cm	6	9.5 ± 1.5	(8, 12)	0	–		–
	Application session						
Tumor size	n	MM-SWC RFA		n	MB-SWC RFA		p value
3.0–3.9 cm	33	2.0 ± 0.6	(1, 3)	12	2.0 ± 0.8	(1, 3)	0.266
4.0–4.9 cm	8	2.0 ± 0.1	(2, 3)	5	2.0 ± 0.7	(1, 3)	0.871
5.0–5.9 cm	5	2.0 ± 0.5	(2, 3)	6	2.5 ± 0.8	(2, 4)	0.550
6.0–7.0 cm	6	3.5 ± 0.5	(3, 4)	0	–		–

Values are expressed with median ± SD (minimum, maximum). MM=multiple-monopolar; MB=multiple-bipolar.

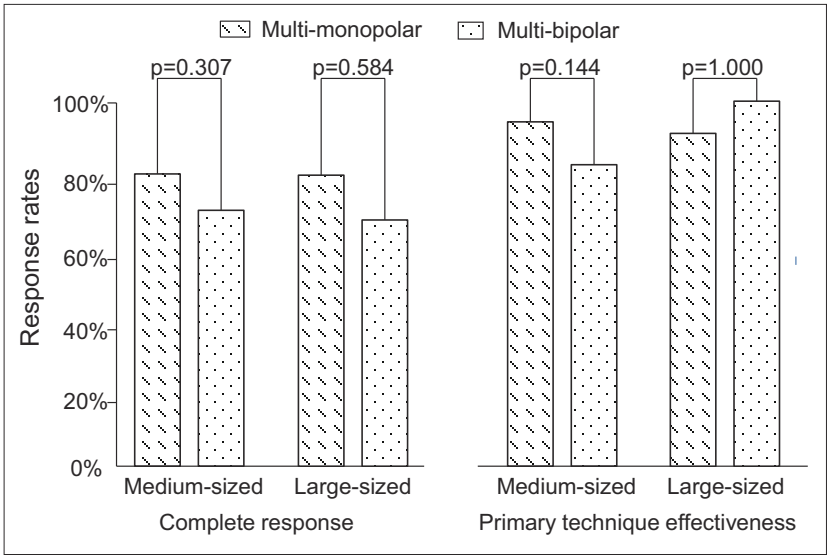

Fig. 2. The graph shows the rates of complete response to ME-RFAs and the rates of primary technique effectiveness of medium-size and large-sized tumors treated by multi-monopolar or multi-bipolar electrodes.

Overall Survival, Local Tumor Progression, and Distal Recurrences

The median follow-up period for all patients was 20.7 ± 10.3 months (1.8–39.2 months). The two systems had different follow-up periods (27.1±9.7 vs. 15.0±6.4 months, p<0.001). Overall, 10 patients died during the follow-up period and half of them had incomplete response to ME-RFA. The causes of death included tumor progression in six patients, liver decompensation in one patient and non-liver causes in three patients.

Survival function is shown in fig. 3. The estimated overall survival rates for all patients at one, two, and three years were 94%, 85%, and 81%, respectively. Patients with large-sized tumors or with BCLC stage B1 or B2 did not appear to have a poorer prognosis than patients with medium-sized tumors or with BCLC stage A (table 3). The tumor size was not associated with survival even when calculated using continuous variables (table 4). Patients with complete responses to ME-RFA had better survival than those with incomplete responses (p=0.008, fig. 3d). This factor alone was significantly associated with survival (table 4).

Sixty-four patients with 69 index tumors achieved PTE. All of them were available for analysis of recurrences. Local tumor progression occurred in 12 (17.4%) tumors. The median time to local recurrence was 12.1 months (4.2–28.0 months). The local tumor progression rate was lower in tumors with a complete response to ME-RFA compared to those with an incomplete response (15.3% vs. 30.0%). However, the difference was not statistically different (p=0.362). Salvage treatments for local tumor progression were applied for six tumors by RFA and for six tumors by transarterial chemoembolization (TACE) due to the association with multiple recurrences. Fig.4 shows local tumor progression functions. The overall estimated local tumor progression rates at one and two years were 10.4% and 17.1%, respectively. Only pretreatment serum alpha-fetoprotein (AFP) >100 ng/ml was associated with local tumor progression (p=0.007, table 4). Distal recurrence occurred in 36 (51.4%) patients. Salvage treatments were given by RFA and by TACE for 26 and eight patients, respectively. In the last follow-up, 41 patients remained tumor-free, 18 had BCLC stage A or B tumors, and 11 progressed to BCLC stage C (including six patients having extrahepatic metastasis to lung, bone,

Table 3. Response, survival and local tumor progression rates for patients with 3.1-7.0 cm HCC after ME-RFA with SWC

	Tumor size			
	Medium	Large	p value	
	n=53	n=17		
Complete response to ME-RFA SWC	79.3%	76.5%	0.749	
PTE	91.4%	94.1%	1.000	
Survival			0.909	
2-year survival rates	84.6%	83.7%		
3-year survival rates	80.8%	83.7%		
Local tumor progression			0.476	
1-year local tumor progression rates	8.6%	18.7%		
2-year local tumor progression rates	16.7%	18.7%		
	BCLC stage			
	Stage A	Stage B1	Stage B2	p value
	n=30	n=25	n=15	
Complete response to ME-RFA SWC	73.3%	80.0%	80.0%	0.806
PTE	90.0%	88.0%	100.0%	0.395
Survival				
2-year survival rates	85.9%	83.1%	83.6%	0.994
3-year survival rates	79.8%	83.1%	83.6%	
Local tumor progression				0.295
1-year local tumor progression rates	7.7%	13.3%	17.0%	
2-year local tumor progression rates	13.5%	21.2%	27.4%	

or adrenal gland). Patients with complete response to ME-RFA had an increased chance to remain tumor-free (66.7% vs. 31.3%, p=0.012).

Complications

There were no deaths within 30 days of treatment. Most patients suffered from side effects such as pain requiring medication (48.5%) or fever (30.6%). Two major complications occurred with the multi-monopolar system: 1) a subcutaneous burn injury in a subcapsular tumor and 2) abscess formation in an ablated tumor. Two major events were noted using the multi-bipolar system: 1) biliary tree infection and 2) severe hemothorax. All four major events subsided with the proper medical treatments and without associated mortality. The major complication rate was 5.7%. Minor complications occurred with comparable frequency in both systems (21% in multi-monopolar system and 17% in multi-bipolar system), mostly being transient elevations of serum transaminases or total bilirubin levels and transient asymptomatic right pleural effusion. All minor complications subsided within one month of follow-up. The post-procedure hospital stay was 3.0±2.1 days. No cases of tumor seeding were observed during follow-up.

Liver Cancer 2016;5:8–20
DOI: 10.1159/000367755
Published online: December 15, 2015

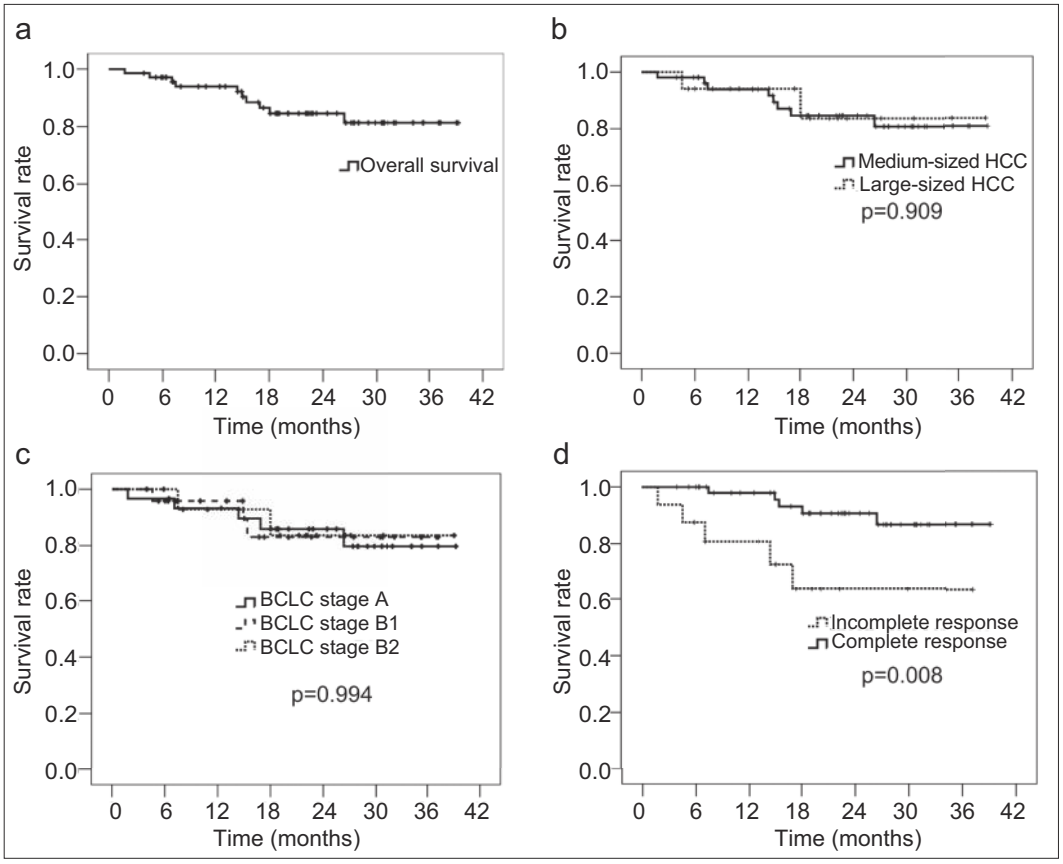

Fig. 3. The graph shows survival functions estimated by (**a**) Kaplan–Meier method for all patients, (**b**) subgroups of tumor sizes, (**c**) BCLC stages, and (**d**) complete response to ME-RFA for patients with HCCs sized 3.1–7.0 cm.

Discussion

Today, treating HCCs >3.0 cm in size by nonsurgical methods remains a challenge. According to current guidelines, surgical resection may be effective in selected patients with a single HCC >3.0 cm; however fewer than 20% of patients are candidates for surgery [1, 17]. TACE is recommended for patients in the intermediate stage, but suboptimal response rates have resulted in TACE also being used as a palliative measure [18–20]. In this study, we demonstrate that ME-RFA can effectively treat HCCs of 3.1–7.0 cm in size and those of BCLC stage B1 and B2. Moreover, patients tend to have better survival if there is a complete response to ME-RFA treatment.

ME-RFA is an emerging modality of RFA for larger liver tumors [8–14, 21, 22]. In this study, we used two ME-RFA systems, and the results showed a comparable response rate. However, we did not further analyze the differences in survival and local recurrence rates between the two systems because the multi-monopolar system commenced about one year before the multi-bipolar system. As there are different follow-up periods and sample sizes, this may influence the survival and local recurrence rates.

The current results showed a high PTE rate after ME-RFA; 91% for medium-sized tumors and 94% for large-sized tumors. These results are superior to that by single-electrode RFA [3–5] and they are also comparable to the 97% response rate of single medium-sized HCCs [13] and to the 81% response rate of large-sized HCCs using the multi-biopolar ME-RFA sys-

Table 4. Prognostic factors associated with overall survival and local tumor progression

	Overall survival		Local tumor progression	
	HR (95% CI)	p value	HR (95% CI)	p value
Liver characteristics				
Child-Pugh class A (vs. class B)	0.34 (0.09, 1.33)	0.105	1.88 (0.24, 14.6)	0.546
Tumor characteristics				
Medium-sized (vs. large-sized)	1.09 (0.23, 5.17)	0.909	0.62 (0.17, 2.31)	0.480
Maximum diameter (per 1.0 cm)	0.73 (0.34, 1.59)	0.432	1.13 (0.63, 2.05)	0.680
Subcapsular (Yes vs. No)	0.45 (0.13, 1.57)	0.199	0.46 (0.15, 1.43)	0.180
Perivascular (Yes vs. No)	1.75 (0.49, 6.20)	0.380	0.24 (0.03, 1.85)	0.170
Serum AFP >100 ng/ml (Yes vs. No)	1.30 (0.33, 5.03)	0.706	5.18 (1.56, 17.21)	0.007
BCLC stage A (vs. BCLC stage B)	1.07 (0.31, 3.70)	0.918	0.65 (0.18, 2.33)	0.510
Treatment characteristics				
Complete response to ME-RFA (Yes vs. No)	0.22 (0.06, 0.76)	0.008	0.37 (0.10, 1.39)	0.141
Local tumor progression (Yes vs. No)	1.70 (0.41, 7.13)	0.463		

HR=hazard ratio; CI=confidence interval.

tem [14]. To the best of our knowledge, this is the first study to use ME-RFA with successful ablation of medium- and large-sized HCCs. The current study also had a larger sample size and longer follow-up period compared with previous studies [10, 14]. In addition, in the current study, ME-RFA also resulted in a better survival rate in these patients. We demonstrate that both the estimated two- and three-year overall survival rates were more than 80%, and these compare better than 40%–71% for patients with HCCs >3.0 cm in size reported in previous studies [7, 23, 24]. However, a survival analysis using the Kaplan-Meier method is influenced by the short study period and also by a proportion of censored cases in the current results. From this point, a three-year survival analysis might be not enough to indicate a better survival than with other similar studies. Further direct comparisons with longer study periods may be required to verify the current results.

Attempting to enlarge the coagulation volume is believed to be an important reason leading to a high complete response rate for treating large tumors. ME-RFA, cluster RFA, or internally cooled wet electrode RFA have the ability to increase ablation zones [25, 26]. ME-RFA can create a larger and nearly spherical confluent ablated zone compared to simultaneous cluster RFA or single overlapping RFA [8, 10, 11]. Once a larger ablated zone is created, a reduced number of applications for overlapping RFA is required [11]. An increase in the number of sequential overlapping ablations usually results in an irregular shape of coagulation. Incomplete ablation may occur with irregular ablated zones and it is a common reason for treatment failure [10, 11]. According to a mathematical estimation, a single-electrode RFA needs between 4–6 and 7–12 placements for sequential overlapping to treat tumors of 3.0–5.0 cm and 5.0–7.0 cm, respectively [27]. In this study, we also used an overlapping method with multiple application numbers of ME-RFA to treat tumors between 3.1cm and 7.0 cm in size. The electrode placement numbers were comparable to sequential single-electrode RFA. However, the overlapping application numbers were reduced to less than four for treating the tumors between 3.1 cm and 7.0 cm in size by ME-RFA. Reduced overlapping numbers by ME-RFA not only saves time for ablation but it also contributed to better efficacy in treating larger tumors.

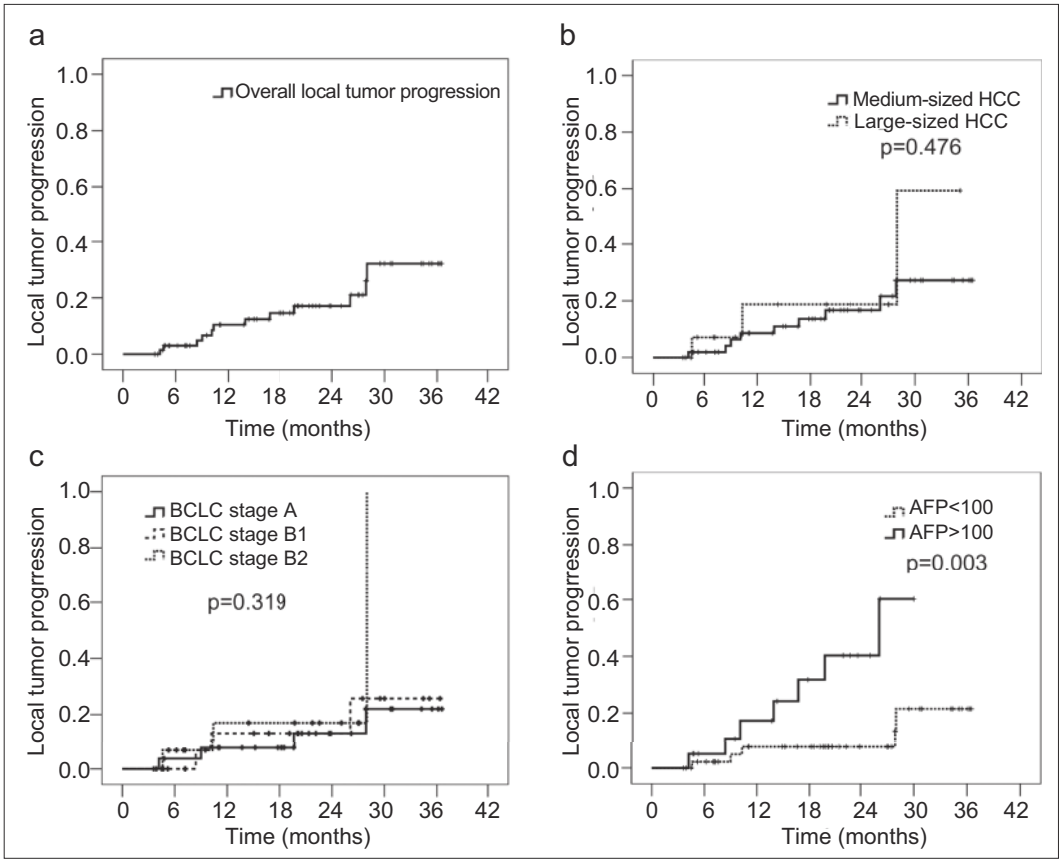

Fig. 4. The graph shows local tumor progression functions estimated by (**a**) Kaplan–Meier method for all patients, (**b**) subgroups of tumor sizes, (**c**) BCLC stages, and (**d**) pre-treatment serum AFP levels for patients with HCCs sized 3.1–7.0 cm.

Large tumor size and multiple liver tumors are commonly associated with reduced survival after RFA [5, 23, 24]. This current study has showed that complete response to ME-RFA is the only significant factor involved in survival after ME-RFA. It may be that ME-RFA overcomes the limitation of tumor size and contributes to better survival for patients after successful ablation. Moreover, our study was one of the first to show comparable survival rates between BCLC stage A, B1 and B2. Most of the patients were elderly, and had cirrhosis and thrombocytopenia. Thrombocytopenia in cirrhosis is one of the clinical presentations of portal hypertension [18] and it has been reported as a poor prognostic factor after surgical resection [28]. The three-year survival rate for patients with HCC and portal hypertension after resection is about 60% [29, 30]. In our study, the estimated 3-year survival rates were nearly 80% or more for patients in BCLC stage A to B2, even though most of the patients had cirrhosis and thrombocytopenia. Although patients in BCLC stage B had multiple tumors, their complete response, local tumor progression, and survival rates were comparable to BCLC stage A. Furthermore, the current results also show that the survival of patients with BCLC stage B after ME-RFA for HCC are superior to those who have been treated with TACE in previous reports [20].

The risk of local tumor progression was only associated with serum AFP level above 100 ng/ml, but not associated with incomplete response to ME-RFA. It might be due to the exclusion of the tumors which did not achieve PTE. The tumors without achieving PTE might contribute to a poor overall survival, but this could not be calculated in the analysis of local tumor progression. The safety of ME-RFA was acceptable, but the major complication rate was

5.7%. Most of the complications occurred in tumors located in subcapsular areas resulting in abscess, burn injury, and hemorrhage. Creation of artificial ascites, artificial pleural effusions, and real-time virtual sonography might help to conquer this limitation by precisely placing the electrodes in such high-risk locations [31, 32]. Avoiding the selection of tumors in the location nearby to the major biliary tree is an important measure for preventing major complications. Higher recurrence rate is another limitation. This might be due to non-early stage HCCs in some of the current study patients. The combination with TACE might help to decrease the risk of recurrence [33]. Finally, the survival benefit of ME-RFA for HCCs sized between 3.1 cm and 7.0 cm could not be measured by this single arm retrospective study without control groups for comparison.

In conclusion, ME-RFA could effectively treat tumors sized of 3.1–7.0 cm in patients with HCC with a fewer number of applications, obtain a higher rate of complete response, and may lead to a better overall survival. The treatment efficacy is comparable between medium- and large-sized tumors, and among BCLC stages A, B1 and B2. Furthermore, the safety profile is acceptable. Patients with a complete response to ME-RFA appear to have a better survival. Therefore, in selected patients with HCC >3.0 cm in size or BCLC stage up to B2, ME-RFA is a useful therapeutic option.

Acknowledgements

Funding supportNone

Conflict of Interest

None.

References

1 Bruix J, Sherman, M Practice Guidelines Committee, American Association for the Study of Liver Diseases: Management of hepatocellular carcinoma. Hepatology 2005;42:1208–1236.
2 Kudo M, Izumi N, Kokudo N, Matsui O, Sakamoto M, Nakashima O, Kojiro M, Makuuchi M, HCC Expert Panel of Japan Society of Hepatology: Management of hepatocellular carcinoma in Japan: Consensus-Based Clinical Practice Guidelines proposed by the Japan Society of Hepatology (JSH) 2010 updated version. Dig Dis 2011;29:339–364.
3 Shiina S, Teratani T, Obi S, Sato S, Tateishi R, Fujishima T, Ishikawa T, Koike Y, Yoshida H, Kawabe T, Omata M: A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. Gastroenterology 2005;129:122–130.
4 Lencioni RA, Allgaier HP, Cioni D, Olschewski M, Deibert P, Crocetti L, Frings H, Laubenberger J, Zuber I, Blum HE, Bartolozzi C: Small hepatocellular carcinoma in cirrhosis: randomized comparison of radiofrequency thermal ablation versus percutaneous ethanol injection. Radiology 2003;228:235–240.
5 Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC: Randomised controlled trial comparing percutaneous radiofrequency thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less. Gut 2005;54:1151–1156.
6 Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Ierace T, Solbiati L, Gazelle GS: Hepatocellular carcinoma: radio-frequency ablation of medium and large lesions. Radiology 2000;214:761–768.
7 Sala M, Llovet JM, Vilana R, Bianchi L, Solé M, Ayuso C, Brú C, Bruix J, Barcelona Clínic Liver Cancer Group: Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. Hepatology 2004;40:1352–1360.
8 Laeseke PF, Sampson LA, Haemmerich D, Brace CL, Fine JP, Frey TM, Winter TC 3rd, Lee FT Jr: Multiple-electrode radiofrequency ablation creates confluent areas of necrosis: in vivo porcine liver results. Radiology 2006;241:116–124.

9 Laeseke PF, Sampson LA, Frey TM, Mukherjee R, Winter TC 3rd, Lee FT Jr, Brace CL: Multiple-electrode radiofrequency ablation: comparison with a conventional cluster electrode in an in vivo porcine kidney model. J Vasc Interv Radiol 2007;18:1005–1010.
10 Lee JM, Han JK, Kim HC, Kim SH, Kim KW, Joo SM, Choi BI: Multiple-electrode radiofrequency ablation of in vivo porcine liver: comparative studies of consecutive monopolar, switching monopolar versus multipolar modes. Invest Radiol 2007;42:676–683.
11 Brace CL, Sampson LA, Hinshaw JL, Sandhu N, Lee FT Jr: Radiofrequency ablation: simultaneous application of multiple electrodes via switching creates larger, more confluent ablations than sequential application in a large animal model. J Vasc Interv Radiol 2009;20:118–124.
12 Frericks BB, Ritz JP, Roggan A, Wolf KJ, Albrecht T: Multipolar radiofrequency ablation of hepatic tumors: initial experience. Radiology 2005;237:1056–1062.
13 Lee J, Lee JM, Yoon JH, Lee JY, Kim SH, Lee JE, Han JK, Choi BI: Percutaneous radiofrequency ablation with multiple electrodes for medium-sized hepatocellular carcinomas. Korean J Radiol 2012;13:34–43.
14 Seror O, N'Kontchou G, Ibraheem M, Ajavon Y, Barrucand C, Ganne N, Coderc E, Trinchet JC, Beaugrand M, Sellier N: Large (>or=5.0-cm) HCCs: multipolar RF ablation with three internally cooled bipolar electrodes—initial experience in 26 patients. Radiology 2008;248:288–296.
15 Bolondi L, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, Raoul JL, Sangro B: Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis 2012;32:348–359.
16 Ritz JP, Lehmann KS, Reissfelder C, Albrecht T, Frericks B, Zurbuchen U, Buhr HJ: Bipolar radiofrequency ablation of liver metastases during laparotomy. First clinical experiences with a new multipolar ablation concept. Int J Colorectal Dis 2006;21:25–32.
17 Lencioni R, Crocetti L: Local-regional treatment of hepatocellular carcinoma. Radiology 2012;262:43–58.
18 European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer: EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908–943.
19 Omata M, Lesmana LA, Tateishi R, Chen PJ, Lin SM, Yoshida H, Kudo M, Lee JM, Choi BI, Poon RT, Shiina S, Cheng AL, Jia JD, Obi S, Han KH, Jafri W, Chow P, Lim SG, Chawla YK, Budihusodo U, Gani RA, Lesmana CR, Putranto TA, Liaw YF, Sarin SK: Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. Hepatol Int 2010;4:439–474.
20 Tsurusaki M, Murakami T: Surgical and Locoregional Therapy of HCC: TACE. Liver Cancer 2015;4:165–175.
21 Lin SM: Local ablation for hepatocellular carcinoma in taiwan. Liver Cancer 2013;2:73–83.
22 Kang TW, Rhim H: Recent advances in tumor ablation for hepatocellular carcinoma. Liver Cancer 2015;4:176–187.
23 Peng ZW, Zhang YJ, Chen MS, Liang HH, Li JQ, Zhang YQ, Lau WY: Risk factors of survival after percutaneous radiofrequency ablation of hepatocellular carcinoma. Surg Oncol 2008;17:23–31.
24 Shiina S, Tateishi R, Arano T, Uchino K, Enooku K, Nakagawa H, Asaoka Y, Sato T, Masuzaki R, Kondo Y, Goto T, Yoshida H, Omata M, Koike K: Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. Am J Gastroenterol 2012;107:569–577, quiz 578.
25 Kim JH, Kim PN, Won HJ, Shin YM: Percutaneous radiofrequency ablation using internally cooled wet electrodes for the treatment of hepatocellular carcinoma. Am J Roentgenol 2012;198:471–476.
26 Park MJ, Kim YS, Rhim H, Lim HK, Lee MW, Choi D: A comparison of US-guided percutaneous radiofrequency ablation of medium-sized hepatocellular carcinoma with a cluster electrode or a single electrode with a multiple overlapping ablation technique. J Vasc Interv Radiol 2011;22:771–779.
27 Chen MH, Yang W, Yan K, Zou MW, Solbiati L, Liu JB, Dai Y: Large liver tumors: protocol for radiofrequency ablation and its clinical application in 110 patients—mathematic model, overlapping mode, and electrode placement process. Radiology 2004;232:260–271.
28 Pang Q, Zhang JY, Song SD, Qu K, Xu XS, Liu SS, Tai MH, Liu HC, Liu C: Thrombocytopenia as an inexpensive, valuable predictor for survival in patients with hepatocellular carcinoma. Scand J Gastroenterol 2014;49:1507–1508.
29 Santambrogio R, Opocher E, Costa M, Barabino M, Zuin M, Bertolini E, De Filippi F, Bruno S: Hepatic resection for "BCLC stage A" hepatocellular carcinoma. The prognostic role of alpha-fetoprotein. Ann Surg Oncol 2012;19:426–434.
30 Llovet JM, Fuster J, Bruix J: Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999;30:1434–1440.
31 Song I, Rhim H, Lim HK, Kim YS, Choi D: Percutaneous radiofrequency ablation of hepatocellular carcinoma abutting the diaphragm and gastrointestinal tracts with the use of artificial ascites: safety and technical efficacy in 143 patients. Eur Radiol 2009;19:2630–2640.
32 Nakai M, Sato M, Sahara S, Takasaka I, Kawai N, Minamiguchi H, Tanihata H, Kimura M, Takeuchi N: Radiofrequency ablation assisted by real-time virtual sonography and CT for hepatocellular carcinoma undetectable by conventional sonography. Cardiovasc Intervent Radiol 2009;32:62–69.
33 Peng ZW, Zhang YJ, Chen MS, Xu L, Liang HH, Lin XJ, Guo RP, Zhang YQ, Lau WY: Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial. J Clin Oncol 2013;31:426–432.