Monopolar Radiofrequency Ablation for Medium-sized Hepatocellular Carcinoma: Preliminary Experience with Single-Electrode Overlapping Ablation and Multiple-Electrode Switching System

Shen-Yung Wang1,5,6*, Tsang-En Wang1,5,8, Ching-Chung Lin1,5,7, Chia-Yuan Liu1,5,8, Horng-Yuan Wang1, Jiunn-Chang Lin3,5, Yu-Chung Hong4, Shu-Jung Tsai1, Chih-Jen Chen1, Wen-Chi Chao2, Jaw-Ching Wu6, Shou-Chuan Shih1,7,8

1 Division of Gastroenterology, Mackay Memorial Hospital, Taipei, Taiwan
2 Division of Chest Medicine, Department of Medicine, Mackay Memorial Hospital, Taipei, Taiwan
3 Department of Surgery, Mackay Memorial Hospital, Taipei, Taiwan
4 Department of Radiology, Mackay Memorial Hospital, Taipei, Taiwan
5 Liver Medical Center, Mackay Memorial Hospital, Taipei, Taiwan
6 Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan
7 Mackay Junior College of Medicine, Nursing, and Management, Taipei, Taiwan
8 Department of Medicine, Mackay Medical College, New Taipei City, Taiwan

Abstract.
Background: Radiofrequency ablation (RFA) has been regarded as an effective treatment for early and small hepatocellular carcinoma (HCC). In vivo porcine studies showed a multiple-electrode switching system could create larger necrotic areas than single-electrode or cluster-electrode ablations. Some recent studies demonstrated a multiple-electrode RFA system could achieve local control of medium-sized HCCs. This study aimed to evaluate the treatment results of monopolar RFA with either single-electrode overlapping ablations or a multiple-electrode switching system in treating medium-sized (3-5 cm) HCC.

Methods: A total of 20 patients with medium-sized hepatocellular carcinomas were included in this study. Nine patients (6 males and 3 females) were treated with single-electrode monopolar RFA. Eleven patients (4 males and 7 females) were treated with multiple-electrode switching monopolar RFA. Twelve patients (60%) included in this study had multi-nodular HCCs at the time of treatment. The tumor size was slightly larger in the multiple-electrode group (4.6 ± 0.3 cm) compared to that in the single-electrode group (3.6 ± 0.6 cm). CT or MR imaging studies were performed at 1 month after RFA to evaluate treatment effectiveness. Thereafter, local tumor progression, treatment effectiveness and survival after RFA were evaluated.

Results: Overall, 18 of 20 patients (90%) showed satisfactory ablation of HCCs 1 month after their RFA procedures. Treatment effectiveness was achieved in 8 patients (88.9%) with single-electrode overlapping ablation and 10 (90.9%) patients with multiple-electrode switching system. The mean follow-up periods were 14.9 (range, 2-26) months in the single-electrode group, and 20.2 (range 4-41) months in the multiple-electrode group. Among the 18 patients who achieved primary tumor control, 2 patients (1 in the single-electrode group and 1 in the multiple-electrode group) had local progression noted during follow-up examinations.

Conclusions: Medium-sized hepatocellular carcinoma can be effectively ablated with monopolar radiofrequency ablation by either single-electrode overlapping ablation or a multiple-
electrode switching system. Regarding mid-term treatment responses, both RFA approaches can achieve similar treatment effectiveness, local tumor progression rate, and survival probabilities. Multiple-electrode switching RFA can treat larger medium-sized HCC with comparable mid-term efficacy as smaller medium-sized HCC treated with single-electrode overlapping RFA.

**Keywords**: monopolar RFA, overlapping ablations, switching system, thermoablation
INTRODUCTION

Radiofrequency ablation (RFA) can effectively treat hepatocellular carcinoma (HCC) smaller than 2 cm [1,2]. Ablation, resection, and transplantation were considered as effective treatments for early-stage HCC [3]. Local ablation was suggested as first-line treatment for HCC less than 3 cm in size [3]. Among local ablation therapies, RFA was one of the most commonly applied treatment because of its low probability of local recurrence and favorable long-term outcomes [4]. RFA was suggested by prospective randomized studies to have comparable outcome to surgical resection treating single small HCC [1]. Therefore, RFA was recommended as one of the curative treatments for early-stage HCC [2].

RFA was less effective against medium and large HCCs [5]. By using a single electrode for HCC between 3 to 4 cm and a triple electrode cluster placed 5 mm apart for HCC larger than 4 cm, RFA can achieve complete ablation in 61% of medium-sized HCC and only 24% in large-sized HCC [5]. A computational analysis suggested that overlapping multiple ablation was required by single-electrode RFA to achieve satisfactory ablation [6]. In vivo porcine studies testing a prototype of multiple-electrode switching system (ValleyLab) could create larger necrotic areas than single-electrode or cluster-electrode ablations [7]. Some recent studies demonstrated a multiple-electrode RFA system could achieve local control of medium-sized HCCs between 3 and 5 cm [8]. However, the effects of monopolar single-electrode system with multiple sequential ablation in managing intermediate sized HCCs have remained unclear.

The effectiveness of RFA in treating medium-sized HCCs remains controversial and has been minimally reported. The purpose of this study was to investigate the technique effectiveness of the monopolar RFA system using single-electrode or a multiple-electrode switching control system in treating intermediate sized HCC. The technique effectiveness and outcome of treatment were compared between the monopolar single-electrode system and the monopolar multiple-electrode switching control system.

MATERIALS AND METHODS

Patients

From Dec. 2009 to Dec. 2013, patients who received RFA procedures for hepatocellular carcinomas were retrospectively evaluated and included into this study using the following criteria: (1) the malignancies were diagnosed by pathological studies, or HCC fulfilled the criteria of the guidelines of the American Association for the Study of Liver Diseases published in 2010 (typical vascular pattern in computed tomography scan or magnetic resonance imaging study) [2], (2) diameter of the largest tumor size between 3 cm to 5 cm, (3) platelet count was more than 40,000/mm3, (4) Child-Pugh class A or B, and (5) no radiographic evidence of HCC invading major vessels including the main portal vein or hepatic veins.

Radiofrequency Ablation

The single electrode RFA procedure was performed as followed: an internally cooled 17-gauge monopolar radiofrequency electrode (Valleylab) with an electrically active tip was placed by percutaneous punctures through the intercostal space or upper ab-
domen to the liver. The electrode was inserted using the freehand technique under real-time sonographic guidance by a 1-5 MHz convex probe (C5-1, Philips) in conjunction with a iU22 ultrasound system (Philips). The radiofrequency energy was delivered to each electrode with a 480-kHz power generator (Series CC-1, Valleylab) with a maximum power of 200 watts. Energy output from the power generator was regulated using a feedback algorithm related to tissue impedance. The electrode was subsequently re-inserted by freehand puncture to pre-procedurally planned positions, 1 to 2 cm distant from each of the ablation tracts. The immediate response was assessed by the presence of a hyperechoic rim beyond the border of target tumors to be ablated the electrode was reinserted and re-ablation was performed at the location around the tumor with incomplete hyperechoic rim.

The multiple-electrode switching control system RFA procedure was performed as followed: Two or three internally cooled 17-gauge monopolar radiofrequency electrodes (Valleylab) with an electrically active tip were placed percutaneously by freehand punctures through the intercostal space or upper abdomen to the target ablation area comprising HCCs. The distances between the electrically active tips of electrodes were 1 to 2 cm. The procedures were performed using the same ultrasound system mentioned in previous sections (the probe was C5-1, Philips, and the ultrasound system used was the iU22, Philips). The switching control system power generator was the same as the one used in the single ablation system. The power generator was capable of delivering a maximum power of 200 watts in 480-kHz (Series CC-1, Valleylab). An additional switching control generator was used to alternate the ablation between either duo or triple electrodes (Valleylab). Only one electrode was utilized to deliver RF energy into the target tissue at the same time. The ablation was performed in the following order: the first phase of ablation was performed using maximum power regulated by a feedback algorithm based on tissue impedance for 3 minutes to each electrode sequentially. The second phase of ablation was performed using the switching system such that radiofrequency energy was delivered to each electrode for 30 seconds unless the tissue impedance had abruptly risen when the energy delivery was switched to the next electrode. We assessed response to ablation based upon the presence of a hyperechoic rim as previously described. Additional ablations were performed at locations with incomplete hyperechoic rim around the tumors.

A single operator performed all of the RFA procedures in this study. The electrodes used in the single-electrode or multiple-electrode switching control

Table 1. Characteristics of patients and tumors at the baseline of RFA treatment

<table>
<thead>
<tr>
<th></th>
<th>Single-electrode (n=9)</th>
<th>Switching system (n=11)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>60.4 ± 16.5 (42.5-81.7)</td>
<td>70.3 ± 9.4 (59.5-89.8)</td>
<td>0.201</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
<td>4</td>
<td>0.370</td>
</tr>
<tr>
<td>Female</td>
<td>3</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child-Pugh class (A/B)</td>
<td>5/4</td>
<td>8/3</td>
<td>0.642</td>
</tr>
<tr>
<td>Multinodularity</td>
<td>5 (55.6%)</td>
<td>7/11 (63.6%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Size of largest tumor (cm)</td>
<td>3.6 ± 0.6 (3.1-4.5)</td>
<td>4.6 ± 0.3 (3.9-5.0)</td>
<td>0.020</td>
</tr>
<tr>
<td>Follow-up since RFA (mo)</td>
<td>14.9 ± 9.8 (2-26)</td>
<td>20.2 ± 12.0 (4-41)</td>
<td>0.261</td>
</tr>
</tbody>
</table>

Note. Data presented with plus–minus values are means ± SD. HCC: hepatocellular carcinoma; RFA: radiofrequency ablation
system had inflow and outflow connectors for continuous circulation of chilled distilled water maintained by a system pump (model PEPM, Valleylab) to keep the temperature of the active tip of the electrode within 0-10°C. Tract ablation was performed at the end of the procedure to remove the electrodes. Intravenous sedation was induced with meperidine in addition to midazolam, or an anesthesiologist performed intravenous general anesthesia. Neither endotracheal intubation nor mechanical ventilation was required in this study. The subject’s vital signs, electrocardiogram, and oxygen saturation were monitored during the RFA procedure.

**Evaluation of Treatment Response and Follow-up**

One month after the procedure, alpha-fetoprotein and liver biochemistries were evaluated. A multiphase CT or MR imaging (unenhanced, arterial, portal, and venous phases) was performed to evaluate the primary technique effectiveness. Non-enhanced area in portal phase was considered as the necrosis zone. Complete ablation was defined as the necrosis zone incorporating the target tumors. The patients were then regularly followed up every 3 months. Arterial enhancing soft tissue densities or signals around the margin of the necrosis zone related to treatment were defined as local tumor progression. Newly developed intra-hepatic soft tissue densities or signals with radiographic features of HCC but remote to treated nodules were defined as remote recurrence.

**Statistical Analysis**

Patient age, numbers and sizes of tumors, and total ablation time were compared between the treatment sessions with and without recurrence after RFA using the Wilcoxon rank sum test. Gender, multi-nodularity of HCC, and treatment effectiveness at 1 month were evaluated using Fisher’s exact test. The cumulative survival rate and local progression rate were analyzed using the Kaplan-Meier method. The difference of the survival and local progression rate between single-electrode overlapping ablation and multiple-electrode switching system was assessed with the log-rank test. All statistical analyses described were performed using the IBM SPSS Statistics for Windows, Version 20.0. Statistical significance was defined at a two-tailed probability value of less than 0.05 in all analyses.

**RESULTS**

**Patient Characteristics**

There was a total of 20 patients (10 male and 10 female) included in this study. Nine patients (6 males and 3 females) were treated with single-electrode monopolar RFA. Eleven patients (4 males and 7 females) were treated with multiple-electrode switching monopolar RFA. The age of patients at baseline ranged from 42.5 to 89.8 years (mean 65.9). Patients

---

### Table 2. Characteristics and outcomes of RFA treatment

<table>
<thead>
<tr>
<th></th>
<th>Single-electrode (n=9)</th>
<th>Switching system (n=11)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablation time (minutes)</td>
<td>48.6 ± 27.6 (18-87)</td>
<td>59.4 ± 18.5 (27-95)</td>
<td>0.295</td>
</tr>
<tr>
<td>Effectiveness at 1 month</td>
<td>88.9% (8 of 9)</td>
<td>90.9% (10 of 11)</td>
<td>1.000</td>
</tr>
<tr>
<td>Local progression¹</td>
<td>1 of 8</td>
<td>1 of 10</td>
<td>1.000</td>
</tr>
<tr>
<td>Rapid tumor progression²</td>
<td>1³</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. 1. Patients who achieved RFA effectiveness at 1 month were included 2. This patient had local tumor progression and distant metastasis 3. This patient had distant metastasis
in the multiple-electrode group were slightly but not significantly older than those in the single-electrode group (60.4 ± 16.5 vs 70.3 ± 9.4). Five patients in the single-electrode group belonged to Child-Pugh class A and 4 patients belonged to Child-Pugh class B. Within the multiple-electrode group, 7 patients were designated Child-Pugh class A, and 4 patients were designated Child-Pugh class B. Twelve patients had multi-nodular HCCs at the time of RFA treatment (5 in single-electrode, 7 in multiple-electrode). The tumor size was larger in the multiple-electrode group (mean 4.6 cm, standard deviation 0.3 cm) comparing to that in the single-electrode group (mean 3.6 cm, standard deviation 0.6 cm) (Table 1).

**RFA Treatment and Effectiveness of Treatment**

CT or MR imaging studies were performed 1 month after RFA to evaluate treatment effectiveness, which was defined as complete necrosis of target ablation tumor. Among the 20 patients, treatment effectiveness was achieved in 18 patients (90%) at 1 month. For patients where different approaches were used, 8 patients (88.9%) in single-electrode group and 10 (90.9%) patients had effective treatment.

One patient that belonged to the multiple-electrode group in this study had a bile duct injury with biloma and required drainage. One patient with local progression in the single-electrode group received 2 follow-up RFA interventions to treat locally progressed HCC. However, the deterioration of liver reserve including intractable ascites and aggravated coagulopathy limited the effectiveness of the follow-up RFA procedures and caused intraperitoneal hemorrhage and regional peritoneal tumor seeding. No immediate or periprocedural mortality was associated with RFA in this study.

Rapid tumor progression was observed in 2 patients. These patients were found to have HCC systemic metastases within 1 month after the procedure. One patient’s outcome in the single-electrode group who did not achieve treatment effectiveness suggested that 1 of 3 target tumors had rapid local progression, portal vein thrombosis, and metastasis to bone and brain within one month after treatment. One patient in the multiple-electrode group showed metastasis to the lymph nodes within 3 weeks after treatment and subsequent brain and spinal metastasis despite complete
necrosis of the 4 targeted HCCs. This patient received RFA for recurrent HCCs, which occurred only 3 months after primary resection of HCC. Pathological studies for the initial HCC specimen revealed microscopic vascular invasion that is reported to be associated with early recurrence and poor prognosis [9].

Local Tumor Progression and Survival

The mean follow-up period after ablation for HCC was 17.8 (range from 2 to 41) months. The mean follow-up periods were 14.9 (range, 2-26) months in the single-electrode group, and 20.2 (range 4-41) months in the multiple-electrode group. Among the 18 patients who achieved primary local tumor control, one patient in the single-electrode group had local progression 6 months after the first treatment and one patient in the multiple-electrode group had local progression 10 months from the initial RFA treatment. Figure 1 showed the cumulative incidence of local tumor progression after initial RFA treatment in all patients and corresponding RFA treatment groups.

Overall, a total of 6 patients died during follow-up. The cause of death in all of these patients was related to liver cancer. Two patients died of rapid tumor progression, one patient died of local tumor progression, one patient had local progression controlled but died of intrahepatic remote recurrence, and two patients died of intrahepatic remote recurrence. The overall cumulative probabilities of survival at 1-year and 2-year were 77% and 63%, respectively. The probabilities of survival in the single-electrode and multiple-electrode group at 1-year were 73% and 81%, respectively. Figure 2 showed the overall survival after initial RFA treatment.

DISCUSSION

Medium-sized HCC can be effectively ablated using either the single-electrode overlapping ablation or the multiple-electrode switching system. Monopolar single-electrode RFA overlapping ablation achieved 88.9% (8 of 9) complete ablation of the target HCC, whereas the multiple-electrode switching system achieved 90.9 % (10 of 11) complete ablation. Overall, monopolar RFA achieved 90% effectiveness in treating medium-sized HCC. The local progression rates in the single-electrode and multiple-electrode groups at 1-year were 17% and 12%, respectively. The probabilities of survival in the single-electrode and multiple-
electrode groups at 1-year was 73% and 81%, respectively.

A single radiofrequency ablation with a single internally cooled electrode was not satisfactory for treating medium-sized HCC. Livraghi et al. reported that RFA induced 61% complete necrosis rate for 3 to 4 cm HCC with a single electrode in one ablation, 4 to 5 cm HCC with a triple electrode cluster in one ablation or a single electrode in 2 to 4 ablations [5]. Regarding the expandable electrode RFA system, complete necrosis was observed in 93.0 to 97.8% in ablating HCC less than 3 cm [10,11]. RFA with an expandable electrode was less effective against medium-sized HCC, in which the complete necrosis rate was 64.7% [11]. Overlapping RFA alone with a single internally cooled electrode was reported to reach 94% technique effectiveness in ablating medium-sized HCC [12]. Insertion of a single electrode was generally not unduly demanding even in patients with a small window allowed for needle pass. However, single-electrode overlapping ablation would be difficult to perform due to the presence of microbubbles from preceding ablations which obscured the path for placing the electrode in subsequent target positions.

Multiple-electrode switching RFA showed favorable short-term and mid-term outcomes in treating medium-sized HCC [4,8,13]. The major advantage of this system was reported to be the creation of a larger necrosis volume than either the single-electrode or multiple-electrode cluster RFA [7]. Thus, a wider tumor-free margin can be theoretically achieved. Previous RFA studies of small HCC suggested that tumor-free margin was related to local tumor progression [14]. In fact, the local tumor progression rate of medium-sized HCC treated by multiple-electrode switching RFA was lower than that rate reported in previous studies with single-electrode multiple ablations [13]. Without ultrasound artifacts related to preceding ablations, the placement of electrodes in the switching system can be placed in more desirable locations. However, the insertion of multiple needles can be challenging especially in patients with narrow intercostal spaces. The treatment time required by switching RFA system was reported to be shorter than that of single-electrode overlapping ablation [15]. Time savings can be significant as a dozen ablations may be required for a single-electrode system to ablate substantially larger tumors [6].

Rapid growth of residual HCCs or early diffuse recurrence after RFA was uncommon [16,17]. Ill-defined tumor margin and large-size HCC were suggested as risk factors for early diffuse HCC recurrence [16]. This intrahepatic recurrence pattern was associated with poor prognosis [17]. Rapid tumor progression observed in our study was defined as multiple intrahepatic or systemic metastases within 1 month after RFA. The 2 patients with rapid tumor progression after RFA had more ominous courses and had survived only 2 and 4 months after RFA, respectively. In vitro studies mimicking suboptimal RFA with heat treatment found that the residual tumors had enhanced tumor growth and angiogenesis through HIF-1α/VEGFA pathway [18]. Epithelial-mesenchymal transition (EMT), a process related to cancer invasion or metastasis, was promoted in HCC cell lines after sublethal heat treatment [19]. These in vitro studies suggested that heat treatment might promote the growth and metastasis of HCC. These studies may imply potential mechanisms for the rapid tumor progression observed in our study. One hypothesis is that those recurrent or metastatic HCCs may have earlier existed as microscopic metastasis undetectable by preprocedural studies and RFA promotes the growth of those microscopic metastasis despite complete ablation of the target tumors. Another hypothesis is that RFA ablated the tumor incompletely and the residual tumor cells may exert elevated malignant potential and metastasis.

The current study was limited by several factors. First, the patient number was small and the study design was retrospective. The selection of RFA treatment with either single-electrode overlapping ablation
or multiple-electrode switching system was not randomized. Second, the patient population was heterogeneous. Half of the patients (10 of 20, 50%) had prior HCC treatments in diversified modalities. One patient of the single-electrode group received intravenous sedation due to patient preference, whereas the others in this study received intravenous general anesthesia. Finally, the lack of ultrasound contrast limited the immediate real-time evaluation of ablation zones after RFA procedures. We used the development of a hyperechoic rim around the HCC under conventional ultrasound to guide our ablations. In vivo porcine studies using an expandable electrode suggested that the presence of hyperechoic rim was related to complete necrosis of liver tissue [20]. RFA in HCC patients with an internally cooled electrode (Cool-Tip) or expandable electrode showed that the hyperechoic rim correlated well with perfusion defects detected on contrast-enhanced ultrasound and on fused images from contrast-enhanced CT and ultrasound performed 3-4 days after RFA [20].

In summary, medium-sized hepatocellular carcinoma can be effectively ablated with monopolar radiofrequency ablation by using either the single-electrode overlapping ablation or a multiple-electrode switching system. Regarding mid-term treatment responses, both RFA approaches can achieve similar treatment effectiveness, local tumor progression rate, and survival probabilities. Multiple-electrode switching RFA can treat larger medium-sized HCC with comparable mid-term efficacy as smaller medium-sized HCC treated with single-electrode overlapping RFA.

REFERENCES
(3.1-5.0 cm) hepatocellular carcinoma: transarterial chemoembolization plus radiofrequency ablation versus radiofrequency ablation alone. **Ann Surg Oncol** 18: 1624-9, 2011.


