OBJECTIVE: To retrospectively evaluate the safety and short-term therapeutic efficacy of radiofrequency ablation (RFA) with a multiple-electrode switching system (MESS) to treat medium-sized (3.1-5.0 cm) hepatocellular carcinomas (HCCs).

SUMMARY OF BACKGROUND DATA: Conventional monopolar RFA is limited in achieving local control for tumors larger than 3 cm. Therefore, MESS-RFA was developed, and can create a sufficiently large ablation volume including the target tumor and a 5−10 mm safety margin in medium-sized tumors.

METHODS: We performed a total of 168 RFAs with a MESS on 166 patients. The patients were treated under ultrasonographic guidance by percutaneous switching system RFA with a multichannel RF generator and two or three internally cooled electrodes. Technical effectiveness, local progression, and remote recurrence of HCC were determined.

RESULTS: For the 166 isolated HCC tumors, the complete ablation rate of MESS-RFA was 98.79% (164/166). Mean ablation time per procedure was 12.33±3.01 min; mean ablation diameter was 5.79±0.61 cm. The complication rate was 2.41%. During follow-up (averaging 16.54 months), local tumor progression occurred in 15/166 patients (9.03%) with technical effectiveness, while new HCCs were detected in 40/166 patients (24.09%). Multivariate analyses revealed that local tumor progression was only associated with serum AFP levels above 100 ng/ml as a risk factor.

CONCLUSION: MESS-RFA for achieving sufficient ablation volume is safe and efficient. This method also showed relatively successful therapeutic effectiveness on short-term follow up in the treatment of medium-sized HCCs.
Percutaneous radiofrequency ablation with Multiple-Electrode Switching System for medium-sized hepatocellular carcinomas

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The study was reviewed and approved Southwest Hospital of Third Military Medical University Institutional Review Board.

All study participants, or their legal guardian, provided informed written consent prior to study enrollment.
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Abstract

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**KEYWORDS:** Minimally invasive, multiple-electrode switching system (MESS), radiofrequency ablation (RFA), medium-sized, hepatocellular carcinoma (HCC)
INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide (1). Surgical resection and liver transplantation are the main treatment for HCC patients. However, only about 20% of HCC patients are candidates for resection (2), and non-surgical therapy is the only option currently available for most patients with HCC.

Radiofrequency ablation (RFA) has been widely utilized as an effective treatment option for hepatocellular carcinoma (HCC) as well as diverse liver metastases (3-5). Compared with surgical resection, RFA shows relatively higher effectiveness. RFA is associated with low complication rates and short hospital stays (6), while providing comparable outcomes (7). Moreover, RFA provides better cost effectiveness than surgical resection, especially in patients with single, small HCCs ≤ 3 cm (8, 9). However, a relatively high local tumor progression rate is regarded as a considerable shortcoming of RFA treatment (10, 11). It is well established that local tumor progression rates increase in larger-sized tumors (12, 13).

Conventional RFA is limited in achieving local control for tumors larger than 3 cm, due to difficulty in creating a sufficiently large ablation volume including the target tumor and a 5–10 mm safety margin (14). With advances in monopolar RFA technology, the multiple-electrode switching RFA system, represented by Covidien Cool-tip®, was developed. MESS-RFA and various strategies have been recently employed to create a sufficient ablation zone, including the use of multi-electrode to increase the ablation area (15), multipolar controllers to provide a synergy of multiple applicators (16), and
clustered internally-cooled electrodes to promote ionic availability (17).

To date, only few preliminary studies have shown that MESS-RFA can create a mean coagulation diameter of up to 4.2-5.9 cm (18-20). Consequently, we retrospectively analyzed a cohort of 166 medium-sized HCC tumors. The aim of this study was to evaluate the effectiveness and outcomes in HCC patients with tumors of 3.1-5.0 cm in size after MESS-RFA treatment.

MATERIALS AND METHODS

Ethics statement

All examinations and treatments performed at our Institution were performed in accordance with the Helsinki declaration. The study was reviewed and approved by the Southwest Hospital of Third Military Medical University Institutional Review Board (approval number 2105042). Written informed consent was provided by the patients for their information to be stored in the hospital’s database and used for research.

Patients

A retrospective analysis of 166 patients undergoing multi-electrode (n≥2) switching RFA from December 2013 to June 2016 was performed. The patients included 130 (78.31%) males and 36 (21.69%) females, with an average age of 53.20 (range, 22-83) years. On 166 primary isolated HCC tumors, a total of 168 MESS-RFA procedures were performed. Average diameter of HCC tumors was 3.94 cm, ranging
from 3.10 to 5.00 cm (Table 1).

The multiple-electrode switching system RFA procedure

All MESS-RFA procedures were performed by three hepatobiliary surgeons with many years of experience in RFA treatment of HCC tumors. Informed consent was obtained from all patients preoperatively. All operations were performed under monitored anesthesia care. Fentanyl citrate injection (Humanwell Pharmaceutical Co., Ltd., Yichang, China) at a dose of 0.1–0.2 mg was administered for analgesia; dexmedetomidine hydrochloride injection (Hengrui Medicine Co., Ltd., Jiangsu, China) at 50–100 mg was administered for sedation; lidocaine hydrochloride injection (Zhaohui Pharmaceutical Co., Ltd., Shanghai, China) was used for topical anesthesia. All ablations were performed using a multi-target switching system (Cool-tip™ RF Ablation System and Switching Controller; Valley Lab, Boulder, Colorado). The RF electrode (Covidien LLC, Mansfield, MA, U.S.) was placed under ultrasound guidance to the tumor site. The size, shape, and location of a given HCC tumor determined the number of RFA electrodes to be used (Figure 1): two (n = 146) or three (n = 20) electrodes were utilized depending on the location and size of target tumors. 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. Therefore, the first electrode was inserted along the medial margin of the index tumor, the second electrode inserted in parallel to the path of the first one, and the third electrode inserted in parallel to the path of the
above two electrodes but in a different plane. The distance between two electrodes ranged from 2.0 to 2.5 cm to prevent coagulation zones from becoming cleft or irregular (21). In the MESS-RFA procedure, the switching machine was set to auto-mode, and all electrodes worked alternately and switched off automatically after any impedance surge. Continuous ablation lasted for 12-16 minutes, until the impedance shut-off cycle at approximately 15 seconds and achievement of adequate hyperechoic change of the ablated area(22) (Table 2).

**Evaluation and follow-up**

Ultrasonography and contrast-enhanced CT of the liver were performed 24 h after MESS-RFA to assess efficacy and complications. When both imaging methods revealed no enhanced areas in the tumor ablation zone, the technique was considered to be effective, with the case defined as complete ablation. In case of sustained enhancement determined to be residual tumor by the attending physician and radiologist, incomplete ablation was considered, and another RFA procedure was performed. All ablation-related complications and side effects were defined as described by Goldberg et al (23). Ultrasonic contrast and serum alpha-fetoprotein (AFP) assessments were performed every 2 months in the first postoperative year, and every 4 months in subsequent years. Contrast-enhanced CT was performed every 6 months. Local tumor progression was defined as solid tissue with arterial enhancement around the necrotic, treated nodule, in continuity with its border (24) (Figures 2 and 3).
Statistical analysis

Quantitative data are mean±standard deviation (SD) and range (minimum and maximum values). Qualitative data were presented as number of cases and a percentage of total number of cases. The Cox regression model was applied to assess risk factors for tumor progression. All statistical analyses were performed with SAS9.3. P<0.05 was considered statistically significant.

RESULTS

Characteristics of MESS-RFA Procedures

Over the entire study period, a total of 168 RFA procedures were performed on 166 tumors in 166 patients. A total of 355 RFA electrodes were used, with a mean of 2.13 RFA electrodes per procedure. Total ablation time of MESS-RFA was 2047 min, with 12.33±3.01 min per procedure.

Complications

Ablation-related complications and side effects were defined as described by Ahmed et al (25). Over the study period, four complications were observed, i.e. a complication rate of 2.41%. Complication cases included hemothorax (n=1), jejunal perforation (n=1), and minor bleeding at the liver puncture site (n=2). For the latter two cases, clinical observations were performed, with no special treatment administered.
The hemothorax case was treated by thoracoscopic surgery, and the patient with jejunal perforation underwent intestinal repair surgery. Jejunal perforation occurred in a patient with adhesive ileus after open operation. In this case, the jejunum adhered to the liver surface, and heat conduction through the RFA electrodes caused jejunal wall perforation; the symptoms appeared six hours after the RFA procedure. After clinical diagnosis, surgery was performed and the patient was cured.

**Treatment outcomes and follow up**

The mean diameter of HCC tumors was 3.94 cm (range, 3.1–5.0). The 166 enrolled patients (130 men and 36 women) showed a mean age of 53.20 (range, 22–83) years. Of the 166 tumors, complete ablation was achieved in 164 (98.79%). No in-hospital deaths occurred.

During the follow-up period (mean, 16.54 months), local tumor progression occurred in 15/166 patients (9.03%) with technical effectiveness, while new HCCs were detected in 40/166 patients (24.09%). Multivariate analysis revealed that local tumor progression was only associated with serum AFP levels above 100 ng/ml, as a risk factor (Table 3) (Table 4).

**DISCUSSION**

In this study, switching RFA using multiple electrodes in patients with medium-sized HCCs yielded high technical effectiveness (98.79%) and a good local
tumor control rate (90.97%, 151 of 166). These outcomes are significantly improved compared with previous studies assessing percutaneous RFA with a conventional overlapping technique using monopolar electrodes (26, 27). Using the conventional monopolar technique for tumors with diameter >3 cm substantially increases the incidence of residual lesions; meanwhile, incomplete ablation is a risk factor for postoperative relapse (28). Although multiple factors affect tumor relapse, the relatively low complete ablation rate of the conventional monopolar RFA systems is one of the most important (29). With the monopolar RFA system, ablation needs to be conducted sequentially, layer by layer. Single overlapping RFA, 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 constitutes a common reason for treatment failure (18, 30). According to a mathematical estimation, single-electrode RFA needs between 4-6 placements for sequential overlapping to treat tumors of 3.0-5.0 cm(31). In addition, after monopolar RFA, bubbles form in the local tumor tissue (32), affecting local tissue impedance and interfering with the impedance feedback of the RFA system. The improved therapeutic efficiency of MESS-RFA can be attributed to the ability to produce a larger ablation volume compared with conventional RFA using a single electrode.

In the present study, average ablation time was 12.33±3.01 min, which is shorter than 17.2±2.69 min as previously reported (33). Using the same number of samples, MESS-RFA had an operation time 52.83% shorter than the single-sited RFA system. As
shown above, mean ablation time using the switching RF system was also shorter than reported in previous studies using single-electrode RF systems (34). MESS-RFA can simultaneously use several electrodes, and each RFA electrode is independent. When several electrodes are placed close to each other, their thermal effects reinforce each other and the obtained ablation zones overlap, resulting in increased temperature in the core ablation zone. Furthermore, the switching system is not simultaneously powered, but alternately powered to avoid electrical shielding between multiple electrodes. In the switching system, the electrical current flows from the powered electrodes to the non-powered regions following a voltage gradient, leading to higher temperatures within these spaces (35, 36). Finally, MESS-RFA can also block the blood flow in the ablation zone. This accelerates the formation of local vascular thrombosis and reduces heat loss, thereby increasing ablation efficiency. The current findings indicate that MESS-RFA provides a greater ability to achieve a satisfactory ablation zone for medium-size HCCs during a reasonable procedure time compared with the conventional and consecutive overlapping RF systems using single electrodes.

The Cox proportional hazards regression model showed that local tumor progression was only associated with serum AFP levels above 100 ng/ml, and not with incomplete response to MESS-RFA. The main explanations of such apparently contradictory results may be: (1) MESS-RFA can yield a lower local recurrence rate; (2) the majority of local recurrence cases were sufficiently limited to be completely ablated by iterative RFA. As shown above, the rate of major complications after multi-target...
RFA treatment of HCC tumors was 2.41%; there may also be theoretical concerns over the safety of switching monopolar RFA using multiple electrodes. The multiple electrode approach renders more complex the procedure planning, resulting in a relatively higher complication rate compared with that of conventional RFA using a single electrode. However, the complication rate in this study was only marginally higher than or equivalent to those of previous reports regarding the conventional RF system with a single electrode, varying from 1.6% to 2.5% (37-39). The main complications in the current study involved collateral damage of adjacent organs. However, only one case had jejunal perforation requiring surgery; the other complications were minor in that patients were asymptomatic and did not require treatment or extended hospital stay. These findings suggest that increased risk related to the use of multiple electrodes may not be substantial. However, because RF ablation outcomes depend on experience, caution is advised in applying these findings to institutions with limited experience.

This study had some limitations. First, it was retrospectively performed and non-randomized in design. Second, RFA procedures were performed in a single institution. Therefore, randomized, controlled trials are required to confirm these findings. Despite these limitations, this study was adequate as a preliminary report to evaluate the short-term efficacy of MESS-RFA in the treatment of medium-sized HCCs.

In conclusion, MESS-RFA is safe and time-efficient, and can achieve an adequate ablation volume, showing short-term therapeutic effectiveness for medium-sized HCCs.
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Figure legends

Figure 1 The multiple-electrode switching system RFA procedure.

Figure 2 Axial CT image acquired prior to RFA, showing a 3.5 cm sized, hypervascular lesion in the right lobe of the liver.

Figure 3 Axial CT image acquired immediately after RFA, showing the ablation zone sufficiently covering the index tumor, measured as 5.0 cm in long diameter, including the safety margin.
# Table 1 Baseline Characteristics

| Characteristics          | Value          |
|--------------------------|----------------|
| Age (yr)                 |                |
| **Mean ± SD**            | 53.20±12.06    |
| **Range**                | 22-83          |
| Sex: male/female         | 130/36         |
| Serum AFP (ng/ml)        |                |
| **Mean ± SD**            | 200.81±684.92  |
| **Range**                | 0.38-6040      |
| ≤100/>100                | 131/35         |
| Platelet count (× 10^9/l)|                |
| **Mean ± SD**            | 105.33±60.66   |
| **Range**                | 28-364         |
| ≤100/>100                | 108/58         |
| Serum albumin (g/l)      |                |
| **Mean ± SD**            | 41.41±4.12     |
| **Range**                | 30.6-49.9      |
| ≤40/>40                  | 76/90          |
| Liver cirrhosis          |                |
| Yes                      | 151            |
| No                       | 15             |
| Cause                    |                |
| Data | Description | Value |
|------|-------------|-------|
| Hepatitis B surface antigen | 155 |
| Hepatitis C virus | 11 |

**Child-pugh class**

| Class | Value |
|-------|-------|
| A     | 111   |
| B     | 55    |

**Tumor size (cm)**

| Description | Value |
|-------------|-------|
| Mean ± SD   | 3.94 ± 0.58 |
| Range       | 3.1-5.0  |

**Follow-up (mo)**

| Description | Value |
|-------------|-------|
| Mean ± SD   | 16.54 ± 4.61 |
| Range       | 5-23   |

Note.—Data are number of patients, unless otherwise indicated.

* Data are the mean ± standard deviation

AFP = α-fetoprotein
Table 2 Characteristics of Radiofrequency Ablation Procedures and Ablation Zone

| Characteristics                  | Value                      |
|----------------------------------|----------------------------|
| No. of inserted needles          |                            |
| 2°                               | 145                        |
| 3°                               | 21                         |
| Ablation time (minutes)          | 12.33±3.01(9-16) *         |
| Energy (kj)                      | 164.47±23.02(67-202)       |
| Ablation area (cm)               | 5.79±0.61(4.6-8.4)         |
| Technical effectiveness rates    | 98.79% (164/166)           |

Note. * Data are expressed as mean value ± standard deviation, with ranges in parentheses.

° Data are expressed as frequency.
### Table 3 Univariate Analysis for Factors Associated with Local Tumor Progression

| Characteristics          | HR   | 95% CI for HR | PValue |
|--------------------------|------|---------------|--------|
| Age (y) >60              | 1.621| 0.586         | 4.487  | 0.866* |
| Sex Male                 | 0.866| 0.185         | 4.058  | 0.855  |
| Serum AFP (ng/ml) >100   | 17.497| 4.605         | 66.439 | 0.000  |
| Platelet count (× 10^9/l) ≤100 | 1.538| 0.489         | 4.838  | 0.462  |
| Serum albumin ≤40        | 0.549| 0.187         | 1.608  | 0.274  |
| Tumor size (cm) >4       | 1.080| 0.627         | 1.860  | 0.781  |
| Liver cirrhosis Yes      | 6.643| 2.855         | 15.454 | 0.000  |
| Hepatitis B surface antigen Yes | 2.317| 0.291         | 18.447 | 0.427  |
| Hepatitis C virus Yes    | 0.574| 0.072         | 4.561  | 0.600  |
| Child-pugh class A YES   | 2.892| 0.906         | 9.233  | 0.073  |
| completely ablation No   | 4.998| 0.631         | 39.574 | 0.128  |

Note. * Cox regression model was applied to analyze the risk factors for tumor progression.

AFP = α-fetoprotein
| Characteristics       | HR   | 95% CI for HR | P Value |
|-----------------------|------|--------------|---------|
| Serum AFP (ng/ml) > 100 | 20.884 | 11.000 | 39.650 | 0.000* |

Note. * Stepwise regression analysis was performed on variables that were significant for univariate analysis.

AFP = α-fetoprotein
