Percutaneous radiofrequency ablation with internally cooled wet electrodes versus cluster electrodes for the treatment of single medium-sized hepatocellular carcinoma

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A B S T R A C T

Background: To compare the effectiveness and complications of radiofrequency ablation (RFA) using cluster electrodes or internally cooled wet (ICW) electrodes in patients with medium-sized hepatocellular carcinomas (HCCs).

Methods: Between February 2008 and September 2013, 40 patients (31 men and 9 women; mean age, 61.2 years) with a single medium-sized HCC (mean size, 3.5 ± 0.5 cm; range, 3.1–5.0 cm) underwent percutaneous RFA with cluster electrodes (n = 19) or ICW electrodes (n = 21). Technical success, technical effectiveness, ablation volume, major complications, and local tumor progression were compared.

Results: After the initial RFA, technical success was achieved in 84% of patients and 90% of patients treated by cluster electrodes and ICW electrodes, respectively (P = 0.654). At 1 month, technical effectiveness was achieved by cluster electrodes and ICW electrodes in 84% and 100% of patients, respectively (P = 0.098). During follow-up period (mean, 17.8 months; range, 0–67 months), the median local tumor progression rates were 21.3 months in the cluster group and 31.0 months in the ICW group. The 6-month, 1-, 2-, and 4-year local tumor progression rates were significantly lower after RFA with ICW electrodes (0%, 7%, 25%, and 57%, respectively) than after RFA with cluster electrodes (26%, 33%, 53%, and 68%, respectively; P = 0.036). Major complications occurred in 15.8% of patients treated with cluster electrodes and in 4.8% of patients treated with ICW electrodes (P = 0.331).

Conclusion: For the treatment of medium-sized HCCs, percutaneous RFA using ICW electrodes results in lower rate of local tumor progression and fewer serious complications, compared to cluster electrodes.

Keywords: Cluster electrode, Hepatocellular carcinoma, Internally cooled wet electrode, Radiofrequency ablation

Introduction

Percutaneous radiofrequency ablation (RFA) is a safe and effective treatment for local tumor control in patients with small (≤3 cm) or medium-sized (3.1–5.0 cm) hepatocellular carcinomas (HCCs).1–3 However, local tumor progression, a common significant prognostic factor of RFA-treated HCC,4 can be as high as 17–35% after mean follow-up periods of 16–25.7 months.7–9 Furthermore, local tumor progression is more common in patients with large tumors.10–11 For medium-sized HCCs, the complete ablation rates ranged from 53% to 74% according to previous studies on RFA.11–13 Thus, a sufficiently large ablation zone is necessary to achieve complete tumor destruction and lower local tumor recurrence rates, especially in patients with medium-sized HCC. To address the many challenges of enlarged ablation zones, several types of electrodes such as internally cooled needles,14 perfused needles,15 and expandable needles13 have been developed; however, the total ablation volume that can be destroyed is limited. For example, to treat HCCs >3 cm in diameter, multiple overlapping ablations are often required to cover the entire tumor volume and the peripheral ablation margins.16,17 However, this procedure is time consuming and technically challenging because gas bubbles that form disturb repositioning the electrode under ultrasound guidance, and thereby leads to incomplete ablation.

To avoid problems related to multiple overlapping ablations such as technical difficulties and a long procedural time, a cluster electrode is typically used to treat medium-sized HCCs.18 A cluster electrode may nevertheless demonstrate a higher incidence of complications because of the greater difficulty of delicately manipulating the cluster electrode to avoid damaging structures such as the hepatic vessels. In addition, the consistently larger ablation zone of a cluster electrode may contribute to collateral thermal injury in adjacent organs.19 Internally cooled wet (ICW) electrodes combine the advantages of cooled and saline-perfused electrodes.20 The ICW electrode
simultaneously provides interstitial infusion of saline and intraelectrode cooling. The original ICW electrode had two coaxial lumina, which thereby enabled the circulation of cooling water and interstitial infusion of saline through side holes. A modified ICW electrode was recently introduced with a simpler design that consists of only one lumen and two microholes on the active tip. However, no comparative studies had assessed the differences between cluster and ICW electrodes in local therapeutic efficacy and safety. Therefore, we compared the effectiveness and complications of RFA using cluster and modified ICW electrodes for treating patients with medium-sized HCCs.

**Method**

**Patient population**

Our Institutional Review Board (Asan Medical Center, Korea) approved this retrospective review. Patients were included if they had a single HCC measuring 3.1–5.0 cm in diameter, no imaging evidence of vascular invasion, and no evidence of extrahepatic disease. Patients were excluded if they had multiple HCCs, vascular invasion, extrahepatic metastases, or coagulopathy (platelet count <50 × 10^9/L; international normalized ratio >1.5). Forty patients treated between February 2008 and September 2013 met the inclusion criteria. The criteria for the diagnosis of HCC were based on the guidelines of the American Association for the Study of Liver Diseases. Nineteen patients underwent RFA with a cluster electrode and 21 patients underwent RFA with an ICW electrode. The radiologist who performed RFA chose the electrode based on preference or availability. (This study used three radiologists.)

**RFA system**

All RFA procedures were percutaneously performed under ultrasound guidance with the patient under conscious sedation (using midazolam hydrochloride) and local anesthesia (using lidocaine hydrochloride). During the procedure, vital signs and cardiac status were monitored by pulse oximetry and electrocardiography. We used an internally cooled electrode system during all procedures. Two types of electrodes were used with a 200-W radiofrequency generator: (1) a single 17-gauge straight ICW electrode (RF Medical, Seoul, Korea) with a 3-cm active tip used to treat 21 patients and (2) a cluster type electrode (ValleyLab, Burlington, MA, USA) with a 2.5-cm active tip used to treat 19 patients. The internal structure of the exposed tip of the ICW electrode and the conventional internally cooled electrode are identical, except the ICW electrode contains two 0.03-mm side holes. When using ICW electrodes with exposed 3-cm tips, 99% of chilled 0.9% isotonic saline was administered at a rate of 1 mL/min for cooling and 1% isotonic saline was infused at a rate of 1.2 mL/min.

All electrodes were placed via the transhepatic approach. The radiofrequency current was emitted for 12 minutes using a 200-W generator that was set to deliver maximum power using the automatic impedance control method. The overlapping ablation technique was used to treat 13 patients (average, 2.7 times; range, 2–4 times) in the ICW group and treat 10 patients (average, 2.9 times; range, 2–4 times) in the cluster group. Ablation time was subject to the operators’ discretion, and based on tumor size, extent of echogenic clouds, and patient condition (e.g., vital signs, pain). The endpoint of ablation was complete ablation of the visible tumor and its margins, which were 0.5–1.0 cm into the normal liver parenchyma surrounding the tumor. In some patients, artificial ascites or pleural effusion was created to visualize the lesion or avoid thermal injury to the adjacent diaphragm. After ablation, we cauterized the electrode path during retraction of the electrode to minimize bleeding and tract seeding. Patients were discharged from the hospital the day after the procedure if immediate postprocedure computed tomography (CT) images or overnight clinical observation showed no complications.

**Follow-up**

Contrast-enhanced CT examinations were performed <2 hours or 1 day after RFA to evaluate the extent of the treated areas and assess possible complications such as bleeding and fluid collection. Unenhanced CT scans were initially obtained, followed by contrast-enhanced CT scans (contrast medium injection rate: 3.0 mL/s). The contrast-enhanced CT scans were obtained during the hepatic arterial phase (using bolus-tracking methods or 36-second delays), the portal venous phase (72-second delay), and the equilibrium phase (3-minute delay). Additional RFA was performed if residual nodular enhancement was observed near the ablated area. However, transarterial chemoembolization (TACE) was performed if a residual enhanced lesion was difficult to target using RFA. One month after the procedure, RFA efficacy was evaluated using contrast-enhanced CT. The 1-month CT examination consisted of a second CT study, and the imaging technique was identical to the first CT that was performed after RFA.

If the 1-month CT showed a completely ablated tumor and no new tumors were noted at other liver sites, subsequent follow-up contrast-enhanced CT scans were obtained every 2–3 months. All new tumors—whether in the ablated lesion or at other liver sites—present during the follow-up period were treated with RFA if the patient still met the criteria for such treatment; if not, the lesions were treated by TACE.

**Evaluation of ablation volume**

To assess the ablation volume, CT analysis was performed immediately after RFA or 1 day after RFA. Volumetric data were obtained from the portal phase images, and the margins of the ablated area were manually drawn slice-by-slice from top to bottom. We calculated the volume using the summation-of-area method.

**Definition and evaluation of data**

Data were analyzed on an intention-to-treat basis. Technical success was defined as treatment completion, based on the protocol, with complete coverage and adequate safety margins evident at the time of the procedure. One month after RFA, technical effectiveness was defined as the complete ablation of the tumor on imaging. At 1 month after RFA, local tumor progression was defined as nodular or irregular enhancement at any follow-up assessment. Major complications were defined as any event that required additional treatment such as increased level of care, hospital stay beyond the observation status (including readmission after initial discharge), or permanent adverse sequelae such as substantial morbidity, disability, or death. Tumors were categorized as nonsubcapsular or subcapsular, and subcapsular tumors were defined as lesions with margins located <1 cm from the liver surface. The rates of technical success, technical effectiveness, ablation volume, major complications, and local tumor progression were compared between the two groups.

**Statistical analysis**

The Mann–Whitney U test was used to compare pairs of independent continuous variables. Fisher’s exact test was used to compare categorical variables. Local tumor progression rates were
calculated using the Kaplan–Meier method and compared using Gehan’s generalized Wilcoxon test (Breslow test). Patients who underwent surgery or liver transplantation during the follow-up period were censored. All statistical analyses were performed using SPSS (version 21.0; SPSS Inc., Chicago, IL, USA). Two-sided $P < 0.05$ were considered statistically significant.

**Results**

**Patient characteristics**

Table 1 summarizes the characteristics of the patients in this study. Of the 40 patients, 29 patients tested positive for hepatitis B virus, six patients tested positive for hepatitis C virus, and five patients tested negative for either virus. At the time of RFA, 39 of 40 patients had cirrhosis. The mean tumor size was $3.6 \pm 0.6$ cm (median size, 3.3 cm; range, 3.1–5.0 cm) in the cluster group and $3.4 \pm 0.3$ cm (median size, 3.3 cm; range, 3.1–4.0 cm) in the ICW group. There were no significant between-group differences in patient age, sex, positivity for hepatitis B or C virus, increase in serum alpha-fetoprotein, Child-Pugh score, median tumor size, or tumor location (i.e., subcapsular or nonsubcapsular).

**Technical success and effectiveness**

During the initial treatment, the 19 patients in the cluster group underwent 20 ablations and the 21 patients in the ICW group underwent 23 ablations. To visualize the lesion and avoid thermal injury to the adjacent diaphragm, artificial ascites or pleural effusion was required in four cluster group patients and in four ICW group patients. Technical success after the first RFA session was achieved in 16 (84%) of 19 patients in the cluster group and in 19 (90%) of 21 patients in the ICW group ($P = 0.654$; Fig. 1, 2) One of three patients in the cluster group who had initial technical failure received additional RFA for a residual enhanced lesion. One patient in the cluster group underwent TACE because of a residual enhanced lesion that was difficult for RFA targeting. One patient in the cluster group had technical failure because of developing cardiac tamponade during the procedure. Two patients with initial technical failure in the ICW group underwent additional RFA: one of these patients had a residual enhanced lesion and the second patient had an insufficient ablation margin after the initial RFA. The interval between the first and second RFA was within 1 day.

At the 1-month follow-up CT scan, 16 tumors in the cluster group and 21 tumors in the ICW group were completely ablated, which demonstrated technical effectiveness rates of 84% (16 of 19 patients) and 100% (21 of 21 patients; $P = 0.098$), respectively. Nodular enhancement near the ablated area was observed in two patients in the cluster group. All lesions were successfully treated using an additional RFA session ($n = 1$) or TACE ($n = 1$).

**Ablation volume**

The mean ablation volume was not statistically significant, although it tended to be larger in the ICW group (46.0 ± 21.8 cm$^3$; range, 18.5–107.5 cm$^3$) than in the cluster group (40.7 ± 21.4 cm$^3$; range, 17.8–91.2 cm$^3$; $P = 0.335$).

**Major complications**

Major complications developed in three (15.8%) of 19 patients in the cluster group and in one (4.8%) of 21 patients in the ICW group ($P = 0.331$). In the cluster group, one of the three patients developed hepatic parenchymal bleeding in the ablated area and required conservative treatment, and one patient developed hepatic surface bleeding and iatrogenic arteriopetal shunting. The latter patient was successfully treated by transarterial embolization. Twelve minutes after initiating RFA to treat a segment II tumor (i.e., subcapsular area) of the liver, one patient developed sudden hemodynamic collapse. Cardiac tamponade was diagnosed on ultrasonography. Despite aggressive resuscitation, including evacuation of the hemopericardium, the patient did not recover and subsequently underwent exploratory thoracotomy. Injury to the right coronary artery and significant hemopericardium were confirmed during thoracotomy.

The patient died 1 day later. In two of the three patients with bleeding complications in the cluster group, the tumors were located in the subcapsular portion. In the ICW group, pleural effusion requiring chest tube insertion or prolonged hospital stay developed in one patient.

**Local tumor progression rate**

During the follow-up period (mean period, 17.8 ± 17.3 months; range, 0–67 months), local tumor progression in the treated lesions occurred in 8 (42.1%) of 19 patients in the cluster group and in 6 (28.6%) of 21 patients in the ICW group. The median local tumor progression rates were 21.3 ± 11.3 months in the cluster type group and 31.0 ± 2.7 months in the ICW group. Cumulative local tumor progression rates at 6 months, 1-, 2-, and 4-years were 26%, 33%, 53%, and 68%, respectively, in the cluster group, and 0%, 7%, 25%, and 57%, respectively, in the ICW group. The rates were significantly lower in the ICW group ($P = 0.036$; Fig. 3).

**Discussion**

Sufficient safety margins around the ablated areas surrounding target tumors can decrease local tumor progression. However, RFA on medium-sized HCCs remains an important therapeutic challenge because of the difficulty of creating sufficient safety margins. The methods used to increase ablation volume include applying multiple overlapping treatments in a contiguous fashion and using expandable electrodes. Multiple overlapping ablations are technically challenging and placement errors are likely to occur because the electrode requires multiple positions. This technical difficulty may be
particularly acute during RFA treatment of subcapsular tumors or tumors adjacent to major hepatic vessels. Large ablation volumes have been achieved using cluster electrodes; however, this may result in a higher incidence of complications because of the greater difficulty in delicately manipulating cluster electrodes to avoid damaging structures such as the hepatic vessels.

Kim et al. recently reported that percutaneous RFA using ICW electrodes is safe and provides successful local HCC tumor control. The authors suggest that using the ICW electrode results in consistent and large ablation volumes because it successfully combines cooling and perfusion. The two microholes maintain a controlled, reduced rate of saline infusion (1–1.2 mL/min) despite the fast circulation rate (110 mL/min) delivered by the peristaltic pump. Furthermore, these authors compared ablation volumes between conventional internally cooled electrodes and ICW electrodes. The ablation volumes, which were confirmed using CT immediately after RFA or 1 day after RFA, were significantly larger in the ICW group than in the conventional internally cooled group using 2 cm exposed tips [14.5 cm³ (ICW group) vs. 6.2 cm³ (conventional group); \( P < 0.001 \)] and 3 cm exposed tips [32.7 cm³ (ICW group) vs. 15.2 cm³ (conventional group); \( P < 0.001 \)]. These results are similar to results obtained in ex vivo bovine and in vivo porcine livers.

To our knowledge, this is the first study to compare the safety and efficacy of RFA using cluster and ICW electrodes in patients with medium-sized HCCs. The ICW electrodes, compared to the cluster electrodes, tended to yield higher initial technical success (90% vs. 84%, respectively) and technical effectiveness rates (100% vs. 84%, respectively). During a mean follow-up period of 17.8 months (range, 0–67 months), the local tumor progression rate was significantly lower in ICW-treated patients than cluster electrode-treated patients (26%, 33%, 53%, and 68% in the cluster group vs. 0%, 7%, 25%, and 57% in the ICW group at 6 months, 1-, 2-, and 4-years, respectively; \( P = 0.036 \)). These findings indicate that RFA using ICW electrodes provides better local tumor control and results in lower rates of local tumor progression, compared to cluster electrodes, for treating medium-sized HCCs.

The major complication rate was higher using cluster electrodes (15.8%) in comparison to ICW electrodes (4.8%; \( P = 0.331 \)), although this difference was not statistically significant. To avoid incomplete ablation, the tip of the cluster electrode would have to extend to the end of the tumor. When tumors are located in the subcapsular area or close to other organs such as the diaphragm, gallbladder, and gastrointestinal tract, extension of the cluster electrode may increase the likelihood of injury to the liver capsule or adjacent organs. In our study, 31 of 40 HCCs were located in the subcapsular portion. Two of three patients who developed hemorrhagic complications after RFA using cluster electrodes also had subcapsular HCCs.

Furthermore, hemorrhagic cardiac tamponade resulted in the death of one patient after RFA in which the cluster electrode was...
to treat a lesion in hepatic segment II. Several articles report potentially fatal complications during RFA using expandable electrode needles. In 2005, Moumouth et al. reported the first case of cardiac tamponade during RFA of a lesion in hepatic segment II. These authors proposed two possible explanations for the cardiac tamponade. First, it may be difficult to ascertain the exact location of the expandable RFA electrodes and ensure that none of the expandable electrodes are in the diaphragm or pericardium, although the position of the electrodes was checked prior to starting the procedure. Second, the in vivo distribution of heat may be unpredictable, and the pericardium may be thermally damaged by heat conduction, which has been demonstrated in other visceral organs. Silverman et al. recently presented two cases of hepatocellular carcinoma in segment II of the liver in which the tumors were a major risk factor for cardiac tamponade during RFA.

By contrast, the ICW electrode may not have to be close to the liver capsule or adjacent organs, and thereby reduce the potential risks of unintended injury. In addition, the ICW needle, which can be more confidently positioned and monitored, may be a good alternative and prevent fatal complications such as cardiac tamponade during ablation of a subcapsular lesion in segment II of the liver.

The principal limitation of this study is its retrospective and nonrandomized design and the use of electrodes in patients with medium-sized HCCs was individually determined based on the attending physician’s preference or electrode availability. This likely led to selection bias in our study population. In addition, the number of patients enrolled in our study was relatively small. Therefore, a prospective, large-series, randomized, controlled trial is required that compares the clinical efficacy and complication rate of cluster and ICW electrodes for clinically treating medium-sized HCCs. In conclusion, percutaneous RFA using ICW electrodes results in lower rates of local tumor progression and less serious complications, compared to RFA using cluster electrodes, for the treatment of medium-sized HCCs.

Conflicts of interest

All contributing authors declare no conflicts of interest.

References


Fig. 3. The Kaplan-Meier curves show the rates of local tumor progression in the cluster electrode group and ICW electrode group. ICW, internally cooled wet.