Effectiveness of Radiofrequency Ablation for Hepatocellular Carcinomas Larger Than 3 cm in Diameter

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Hypothesis: Radiofrequency ablation is a safe and effective treatment for hepatocellular carcinomas 3.1 to 8.0 cm in diameter.

Design: Case series with prospective data collection.

Setting: Tertiary referral center.

Patients: Eighty-six patients with hepatocellular carcinoma treated with radiofrequency ablation from May 1, 2001, to December 31, 2002, were placed into categories of those with tumors 3 cm or smaller (group 1, n=51) and those with tumors 3.1 to 8.0 cm (group 2, n=35) in diameter.

Interventions: Radiofrequency ablation was performed with a single or cluster cool-tip electrode. The choice of treatment route was based on tumor size and position.

Main Outcome Measures: Complication, treatment mortality, and complete ablation rates.

Results: Radiofrequency ablation was performed percutaneously in 26 patients in group 1 and 9 patients in group 2, with laparoscopy in 2 patients in group 1 and 1 patient in group 2, and with open operation in 25 patients in group 1 and 25 patients in group 2. The complication rates were 12% and 17% in group 1 and group 2, respectively (P=.48); treatment mortality rates were 0% and 3%, respectively (P=.41). Complete ablation rates after a single session of ablation assessed by means of computed tomography 1 month after treatment were 94% and 91% in group 1 and group 2, respectively (P=.68).

Conclusion: Radiofrequency ablation is a safe and effective treatment for patients with hepatocellular carcinomas 3.1 to 8.0 cm in diameter.

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Hepatocellular carcinoma (HCC) is the fifth most common malignancy in the world. Although HCC is more prevalent in Asia and Africa, its incidence is increasing in Western countries. Hepatic resection and transplantation are potentially curative treatments for HCC, but only about 20% to 30% of patients are suitable candidates. Various locoregional therapies have been developed for patients with localized HCC who are not amenable to surgical treatment. Such locoregional therapies are particularly important because of the poor response of HCC to systemic therapies.

Radiofrequency ablation (RFA) is one of the most recent modalities of local therapy gaining popularity as a means of treating small inoperable HCCs. Results of several studies have demonstrated a high complete ablation rate of 85% to 95% with use of RFA for HCCs 3 cm or smaller in diameter. In many centers, especially those performing RFA only through the percutaneous route, RFA is used exclusively for HCCs 3 cm or smaller in diameter. Authors of several recent reviews on local ablative therapies for HCC also recommended RFA mainly for tumors 3 cm or smaller in diameter. The effectiveness of RFA for larger HCCs is less well established, although some authors recommended RFA for tumors as large as 5 cm in diameter.

Recent advances in RFA technology such as the development of an internally cooled cluster electrode have enabled ablation of larger hepatic tumors. Furthermore, the use of a laparoscopic or open approach allows repeated placements of RFA electrodes at multiple sites to ablate larger tumors. A few series of RFA for HCCs from groups that used both surgical and percutaneous approaches have included a substantial number of patients with tumors larger than 3 cm in diameter. However, investigators in these studies did not specifically evaluate the effectiveness of RFA for HCCs larger than 3 cm in comparison with HCCs 3 cm or smaller in diameter.

Authors of 1 study examined the effectiveness of percutaneous RFA for medium (3.1-5.0 cm) and large (>5 cm) HCCs. In that study, the overall com-
complete ablation rate for HCCs 3.1 to 9.5 cm in diameter was only 47.6% despite the use of the cool-tip cluster electrode. Even for medium HCCs, the complete ablation rate was only 61.3%. The low complete ablation rate reflected the difficulty of ablating large tumors percutaneously. In that study, the complete ablation rates of medium and large HCCs were not compared with those of HCCs 3 cm or smaller in diameter. However, in another study, the same group reported a 90% complete ablation rate for HCCs 3 cm or smaller in diameter after percutaneous RFA.8 Similar results were reported in a more recent study of percutaneous RFA for HCC in which the same definitions of tumor size were used, with complete ablation after single treatment in 74.4% of medium HCCs and 36.4% of large HCCs, in contrast to 90.9% of small HCCs.23

Although RFA is performed mainly percutaneously by radiologists in some centers, we have advocated active involvement of surgeons in the management of unresectable HCC by using this minimally invasive modality.9 A surgical approach is likely to improve the success of RFA in HCCs larger than 3 cm in diameter.6 In this study, we evaluated the results of RFA for HCCs larger than 3 cm in comparison with results of RFA for HCCs 3 cm or smaller in diameter in a series of patients treated by a joint team of radiologists and surgeons.

METHODS

Between May 1, 2001, and December 31, 2002, 86 patients with HCC underwent elective RFA for 111 tumor nodules at University of Hong Kong Medical Centre, Queen Mary Hospital, Hong Kong, People’s Republic of China. Two patients who underwent RFA for hemostasis of ruptured HCC diagnosed during emergency laparotomy for hemoperitoneum in that period were excluded from the present study. Sixty-eight patients underwent ablation of 1 tumor, 13 patients underwent ablation of 2 tumors, 3 patients underwent ablation of 3 tumors, and 2 patients underwent ablation of 4 tumors in a single session of RFA. Diagnosis of HCC was confirmed by means of fine-needle aspiration cytologic examination or core biopsy. Tumor size, defined as the maximum diameter of the tumor at a helical contrast material–enhanced computed tomography (CT), ranged from 0.8 cm to 8.0 cm.

The 86 patients were placed into 1 of 2 groups according to the size of the largest tumor: group 1 with HCCs 3 cm or smaller in diameter (n=51) and group 2 with at least 1 HCC larger than 3 cm in diameter (n=35). Group 2 consisted of 29 patients with HCCs of medium size (3.1-5.0 cm) and 6 patients with large HCCs (5.1-8.0 cm) as defined in previous studies.24,25 Group 1 and group 2 included 10 and 5 patients, respectively, who had resectable HCC but were treated with RFA in a prospective randomized trial begun January 1, 2002, in which resection and RFA for HCC 3 cm or smaller in diameter is being compared. The other patients were not candidates for resection because of poor hepatic function reserve (n=58), bilobar multiple tumors (n=9), or high surgical risk (n=4). Criteria for exclusion from RFA in our center were extrahepatic disease, more than 4 tumor nodules, tumor larger than 8.0 cm, Child class C cirrhosis, and severe ascites refractory to diuretics.

A team of hepatobiliary surgeons (R.T.P.P., K.K.C.N., C.M.I., S.T.F.) and interventional radiologists (J.Y., V.A.) performed RFA. All RFA treatments were performed with a standard protocol by using a cool-tip RFA system (Radionics Inc, Burlington, Mass). A single electrode with a 2-cm or 3-cm exposed tip was used for tumors 3 cm or smaller in diameter, and a cluster electrode consisting of 3 parallel electrodes was used for tumors greater than 3 cm in diameter. Each ablation cycle lasted 6 to 12 minutes. Multiple overlapping ablations were performed for large tumors. We aimed at ablation of all tumors with a curative intent, with a margin of 1 cm, in a single session of RFA.

Patients with small tumors located in a position amenable to percutaneous RFA were treated with this approach. Open approach was offered in the following circumstances: large tumors that required multiple ablations even with the cluster electrode; tumors located near the dome of the liver, for which percutaneous ablation might cause pneumothorax or damage to the diaphragm; or tumors that were located near visceral organs such as the gallbladder, colon, or stomach. Figure 1 illustrates a large HCC in a patient with poor hepatic function treated with open RFA. In selected patients who had not undergone a previous upper abdominal operation, a laparoscopic approach was used instead of an open approach if the tumor position was favorable. All patients were examined by the team before the appropriate approach for RFA was decided.

Percutaneous RFA was performed in the radiology suite by an interventional radiologist with ultrasonographic guidance after the patient had received local anesthesia and intravenous sedation. The patient was kept in the hospital overnight and was discharged the next day if well. Surgeons performed all open or laparoscopic RFA with use of intraoperative or laparoscopic ultrasonographic guidance. The Pringle maneuver was not used in any patient.

Clinical data for all patients were collected prospectively in a computerized database. The treatment protocol and data collection were approved by the institutional review board of our institution. We compared the clinical data and treatment outcomes in the 2 groups of patients categorized according to tumor size. The main outcome measures were post-RFA complication, treatment mortality, and complete ablation rates. Recurrence and survival rates during short-term follow-up in the 2 groups were also compared. A complication was defined as any adverse event after RFA, excluding pain or transient febrile response after the procedure. Treatment mortality was defined as any death within 30 days after RFA. Response to RFA was assessed by means of helical CT 1 month after RFA. Complete ablation was defined as the absence of any peripheral enhancement indicating residual tumor in the arterial phase at the ablation site on the 1-month CT scans.

All patients underwent serial monitoring of serum α-fetoprotein level and chest radiography and CT every 3 months for detection of intrahepatic recurrence or distant metastasis. Local recurrence was defined as tumor recurrence within or at the periphery of ablated lesion on the subsequent CT scans after complete ablation was documented on the first post-RFA CT scan. Distant intrahepatic recurrence was defined as a new tumor that appeared in the liver separate from the ablated area. Extrahepatic metastasis refers to any tumor recurrence outside the liver.

Continuous data were expressed as the median and range. Groups were compared by using the χ² test with Yates correction, or the Fisher exact test where appropriate, for nominal variables. The Mann-Whitney U test was used for continuous variables. Survival rates were estimated by means of the Kaplan-Meier method and compared by using the log-rank test. All statistical analyses were performed by using the SPSS 10.0 for Windows statistical package (SPSS Inc, Chicago, Ill). A P value less than .05 was considered to indicate statistical significance.
RESULTS

PATIENT CHARACTERISTICS

Table 1 shows the baseline characteristics of the 2 groups of patients. There were more male patients in group 2, and comorbid illnesses were significantly more frequent in group 2. Otherwise, there were no significant differences between the 2 groups. Cirrhosis was evident in the imaging or operative findings in all except 2 patients in group 1, and most cases of HCC were related to hepatitis B viral infection in both groups.

Similar proportions of patients in each group (20% and 14%) had potentially resectable disease but were treated with RFA in a randomized trial. All patients with tumor size larger than 5 cm had unresectable disease. More patients in group 1 underwent RFA for recurrent HCC after previous hepatic resection, as compared with the number in group 2, but the difference was not significant (33% vs 17%; \( P = .10 \)). Fourteen patients in group 1 and 10 patients in group 2 were initially treated with transarterial chemoembolization and were then treated with RFA because of progressive disease or vascular contraindications (hepatic arterial thrombosis and arteriovenous shunting) for continuing chemoembolization. In addition, 2 patients in group 1 had previously undergone ethanol injection, and RFA was performed for failed tumor control. The 2 groups were comparable in hepatic function, with no significant differences in serum albumin and bilirubin levels and indocyanine green retention rate at 15 minutes.

TREATMENT DATA, MORBIDITY, AND MORTALITY

Table 2 depicts RFA treatment data. Significantly more patients in group 2 underwent open RFA, as compared with those in group 1 (71% vs 45%). All patients with HCCs larger than 5 cm in diameter in group 2 underwent open RFA. More patients in group 2 had more than 1 nodule ablated (29% vs 16%), but the difference with group 1 was not significant. The total ablation time was significantly longer in group 2.

Hepatic function after RFA was significantly worse in group 2, as compared with that in group 1 in terms of day-7 serum bilirubin level and indocyanine green retention rate at 15 minutes (Table 2). Group 2 had a longer...
hospital stay and a higher complication rate than did group 1, but the differences were not statistically significant.

In group 1, 6 patients developed complications, which included persistent fever (>38°C) for more than 48 hours (n=2), cardiac arrhythmia (n=2), pneumonia (n=1), and wound infection (n=1). In group 2, 6 patients developed complications, which included pneumonia (n=1), pleural effusion (n=1), ascites (n=1), transient wound infection (n=1), cardiac arrhythmia (n=2), pneumonia (n=1), and multiorgan failure (n=1). Four of the 6 complications in group 1 and all 6 complications in group 2 occurred after open RFA. No adjacent organs were injured during RFA.

There was 1 patient with treatment mortality in the whole series. This patient in group 2 had cirrhosis and multifocal recurrent HCCs after previous hepatectomy. He developed acute respiratory failure, renal failure, hepatic failure, and shock the first day after open RFA of 4 recurrent HCCs 4.9, 2.5, 1.0, and 0.6 cm in diameter, and he died of multiorgan failure on the fourth day after RFA.

At further subgroup analysis within group 2, the complication rate for the 29 patients with medium HCCs was 17% (n=5), and the corresponding rate for the 6 patients with large HCCs was 17% (n=1; P > .99). Treatment mortality in patients with medium HCCs was 3% and for those with large HCCs was 0% (P > .99).

**COMPLETE ABLATION RATE AND SHORT-TERM FOLLOW-UP RESULTS**

Completeness of tumor ablation could not be assessed in the patient with 4 tumor nodules who died of multiorgan failure after RFA. Completeness of tumor ablation and follow-up data were evaluated in the remaining 85 patients. Overall, complete ablation was achieved after a single session of RFA in 79 patients (93%). Three patients in group 1 and 3 patients in group 2 had residual tumors, and they were treated with repeated RFA (n=3) or transarterial chemoembolization (n=3). The complete ablation rates in group 1 (94%) and in group 2 (91%) were comparable (P = .68). Within group 2, 2 patients with medium HCCs (3.5 and 4.5 cm in diameter) and 1 patient with a large HCC (6.5 cm in diameter) had residual tumors. Hence, the complete ablation rates of patients with medium HCCs and those with large HCCs were 93% and 83%, respectively (P = .44). Within group 2, there was no significant difference in the complete ablation rate between the open approach (21 [88%] of 24) and the percutaneous approach (9 [100%] of 9; P = .55). One patient in group 2 underwent laparoscopic RFA, and the ablation was complete.

When tumor nodules instead of patients were considered, the overall ablation rate of the 107 tumor nodules assessed was 94%. The complete ablation rates of small, medium, and large HCCs were 96% (69 of 72), 93% (27 of 29), and 83% (5 of 6), respectively. There were no significant differences in the complete ablation rates between small and medium HCCs (P = .62), medium and large HCCs (P = .44), or small and large HCCs (P = .28).

Group 1 was observed for a median of 11.5 months (range, 5.0-24.0 months), and group 2 was observed for a median of 11.0 months (range, 5.0-24.0 months).

**Table 3** shows the incidences of recurrence at different locations in the 2 groups. None of the patients developed needle tract seeding. The incidences of local and distant intrahepatic recurrences were not significantly different between the 2 groups. Local or distant intrahepatic recurrences were treated mainly by means of repeated RFA sessions (n=13) or transarterial chemoembolization (n=9). Two patients (+) in group 1 and 2 patients in group 2 (6%) developed extrahepatic metastasis. Extrahepatic metastasis occurred in the lung in 3 patients and in the brain in 1 patient. In the subgroup of patients with HCCs larger than 5 cm in group 2, none developed local recurrence after follow-up of 5.0 to 22.0 months, 2 (33%) developed distant intrahepatic recurrences, and 1 (17%) developed extrahepatic metastasis.

By the time of data analysis, 29 patients (57%) in group 1 and 22 patients (65%) in group 2 were alive and disease free, 17 patients (33%) in group 1 and 6 patients (18%) in group 2 were alive with recurrence, and 5 pa-
A growing body of literature in recent years suggests that RFA is a safe and effective modality for small unresectable HCCs. As a result, RFA is now widely accepted as a treatment for small HCCs. However, the exact indication for RFA in terms of tumor size remains unclear. Currently, some authors recommend using RFA mainly for HCCs 3 cm or smaller in diameter, and some recommend RFA for HCCs as large as 5 cm in diameter. Although tumors larger than 3 cm or larger than 5 cm in diameter are considered contraindications for RFA by some authors, other clinicians have used RFA for HCCs as large as 8 or 9 cm in diameter. From recent reports, there is an apparent trend of using RFA for larger HCCs in many centers after initial favorable experiences with small HCCs. However, there are few data on the effectiveness of RFA for HCCs larger than 3 cm in diameter.

To our knowledge, this is the first study in which the effectiveness of RFA of HCCs 3.1 to 8.0 cm in diameter by means of a predominantly surgical approach was evaluated specifically. Authors of 2 studies evaluating the effectiveness of RFA for HCCs of similar size demonstrated complete ablation rates of 47.6% and 66.6% after a single ablation with a percutaneous approach alone. These results were substantially inferior to the 90% complete ablation rate for HCCs smaller than 3 cm in diameter reported by the same groups. One group used cool-tip electrodes similar to those we used, but the other group used an expandable electrode consisting of 4 curved prongs.

In the current study, we demonstrated that with a predominantly surgical approach of RFA with a cool-tip cluster electrode, an overall complete ablation rate of 91% was achieved for HCCs 3.1 to 8.0 cm in diameter. For HCCs 3.1 to 5 cm in diameter, the complete ablation rate of 93% was remarkably better than those of 61.3% and 74.4% in the 2 previous studies in which percutaneous RFA was used. For HCCs larger than 5 cm in diameter, the complete ablation rate of 83% was also superior to those of 23.9% and 36.4% in the previous studies.

Radical ablation of large tumors is difficult to achieve percutaneously, even with repeated sessions. Moreover, planning a complete map of needle electrode insertions to cover the whole tumor is difficult with the percutaneous route. There are several advantages of open RFA over percutaneous RFA that probably have accounted for the superior results in medium and large HCCs in our study. First, the open approach allows placement of a cluster electrode without any restriction. In the study by Livraghi et al, a cluster electrode could not be used in some cases owing to a narrow intercostal space or because an oblique subcostal approach was required. Second, intraoperative ultrasonography provides better resolution of the tumor, as compared with that of transabdominal ultrasonography for percutaneous treatment, which helps to ensure complete ablation of the tumor margin. Third, the open approach allows free insertion of the electrode at different angles, with mobilization of the liver if necessary; the open approach allows complete circumferential ablation of the margin of a large tumor by means of multiple punctures of the needle electrode at different angles. Fourth, accurate positioning of the tip of the needle in the deep margin of a large tumor can sometimes be aided by palpation in superficial tumors. Finally, intraoperative ultrasonography allows detection and ablation of satellite nodules that may be missed at CT. Livraghi et al attributed their limited success with percutaneous RFA for medium and large HCCs partly to the inability to ablate these satellite nodules that are common in large HCCs. More patients had multiple tumor nodules ablated in group 2 than in group 1 in our study.

Total ablation time was significantly longer in group 2 than in group 1 because multiple overlapping ablations were needed for larger tumors. The hospital stay was also longer because of more open RFAs in group 2. Post-RFA hepatic function was significantly worse in group 2. This finding was related to the larger volume of tissue ablation, including nontumorous liver in the ablation margin, because of the larger tumor size and also a higher frequency of RFA of multiple nodules in group 2. The complication rate was higher in group 2 than in group 1. However, the difference was not statistically significant. The higher complication rate may be related to a higher frequency of comorbid illness in group 2 in addition to the larger volume of tissue ablation.

Authors of a recent literature review reported a complication rate of 8.9% after RFA for hepatic tumors, but...
the study included both patients with HCC and those with secondary hepatic metastasis. The complication rate is likely to be higher in patients with HCC because of underlying cirrhosis. The review’s authors also pointed out that complications after RFA might have been underreported in early retrospective studies. The complication rate in patients in group 2 in the current study was 17%, which was within the range of 13% to 20% reported in series of RFA for HCCs. In our experience, this complication rate was lower than that of about 40% after hepatic resection for HCCs smaller than 5 cm in diameter in patients with cirrhosis.

There were 2 major complications: 1 segmental bile duct injury and 1 multiorgan failure. The latter resulted in the only treatment mortality of the series. Multiorgan failure is a well-known complication of cryotherapy and is attributed to a systemic cytokine response after cryoablation of a large volume of hepatic tissue, but it was rarely reported after RFA. In our patient who developed multiorgan failure, the total volume of ablated tissue was substantial after RFA of 4 tumor nodules, the largest 1 with a diameter of 4.9 cm. This volume of ablation might have triggered a systemic cytokine response similar to that seen with cryotherapy. We are now conducting an animal study to elucidate the systemic cytokine response to large-volume hepatic RFA. This death suggests the need for more careful patient selection among those with large and multiple tumors requiring RFA. However, in our experience, ablation of a solitary tumor as large as 8.0 cm in selected patients appeared to be safe.

The short-term follow-up results in terms of tumor recurrences after RFA of HCCs 3.1 to 8.0 cm in diameter were comparable with those of smaller HCCs. Only 1 patient (3%) in group 2 developed local recurrence after a median follow-up of 11.0 months, and the incidence was even lower than that in group 1 (8%). This finding again reflected the effectiveness of open RFA for medium and large HCCs. Curley et al reported a local recurrence rate of 3.6% after RFA in 110 patients with HCC, and they found that the open approach resulted in a lower local recurrence rate, as compared with recurrence with percutaneous RFA. Authors of another recent study in patients with predominantly hepatic metastasis also reported superior local control with use of open RFA, as compared with that with percutaneous RFA. Laparoscopic RFA could theoretically provide similar advantages to those of open RFA.

For HCCs 3.1 to 8.0 cm in diameter, the exact role of RFA relative to other treatment modalities such as hepatic resection and transarterial chemoembolization needs to be judged ultimately in terms of long-term survival. Currently, data are limited on long-term survival after RFA because follow-up was short in most series. Some authors suggested that long-term survival after RFA for HCCs 3 cm or smaller or 5 cm or smaller in diameter may be comparable with that for resection. This is the rationale for the randomized trials ongoing in our center. However, before results of randomized trials comparing RFA and hepatic resection for HCCs are available, RFA should still be considered a treatment for unresectable HCCs outside the setting of randomized trials.

Our results showed comparable cumulative 1-year survival rates of 86% and 81% in group 1 and group 2, respectively. These 1-year survival rates were similar to that of 86.8% after hepatic resection for HCCs 5 cm or smaller in diameter in patients with cirrhosis with preserved hepatic function in our previous study, even though most patients in the current study had unresectable disease because of poor hepatic function. However, most patients in group 2 had medium HCCs, and the number of patients with HCCs larger than 5 cm in diameter in our current series was small. Furthermore, follow-up in this study was relatively short. Long-term survival after RFA for large HCCs is likely to be worse than that for small and medium HCCs because of a higher frequency of microscopic venous invasion and intrahepatic metastasis associated with large HCCs, which leads to recurrence with longer follow-up.

For unresectable HCCs larger than 5 cm in diameter, transarterial chemoembolization used to be considered the only treatment. However, chemoembolization is associated with a high morbidity rate of 23% to 33%—in particular, a high hepatic failure rate—and a complete tumor necrosis rate of only 26% to 36%. Recently, some authors suggested the combined use of transarterial embolization followed by percutaneous RFA for large HCCs to achieve better tumor ablation, but repeated sessions of RFA are still frequently required. On the basis of our preliminary favorable results, we offer RFA with a surgical approach to more patients with unresectable HCCs 5 to 8.0 cm in diameter.

In conclusion, on the basis of immediate and short-term follow-up, the results of this study show that RFA is a safe and effective treatment for HCCs 3.1 to 8.0 cm in diameter, even for patients with cirrhosis with suboptimal hepatic function. However, studies with long-term follow-up data are awaited to further clarify the role of RFA in the treatment of this group of patients, and prospective randomized trials are needed to compare its effectiveness with that of other currently available treatments for HCC.

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