J Gastroenterol 2003; 38:977–981
DOI 10.1007/s00535-003-1181-0

Journal of Gastroenterology

Risk factors for the local recurrence of hepatocellular carcinoma after a single session of percutaneous radiofrequency ablation

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Background. Radiofrequency ablation (RFA) is a new, minimally invasive treatment for hepatocellular carcinoma (HCC). However, there is little available information regarding local recurrence after a single session of RFA with a single electrode insertion. ***Methods.*** From February 1999 to September 2001, we treated 104 HCC tumors with an expandable needle with four hooks. Ninety-nine of the 104 tumors were successfully treated by single-session RFA with a single electrode insertion. We investigated the relationships between pretreatment factors (tumor size, tumor staining, tumor capsule, and tumor location) and local recurrence in these 99 tumors. ***Results.*** The mean size of the 99 tumors was 21.5 mm in diameter (range, 10 to 33 mm). The overall local recurrence rates were 9.7%, 15.4%, and 20.4%, at 1, 2, and 3 years, respectively. For small tumors (smaller than 25 mm), the local recurrence rates at 1, 2, and 3 years were 4.0%, 8.0%, and 14.6%, respectively. The local recurrence rates were 21.1% and 32.3% at 1 and 2 years, respectively, for large tumors (25 mm or larger), and at 3 years the rate was over 50% for tumors located close to the liver surface. Tumor size and tumor location relative to the liver surface were significantly associated with a higher local recurrence rate. However, other variables tested showed no significant relationship to the local recurrence rate. ***Conclusions.*** This study demonstrated that both tumor size and location relative to the liver surface influence the local efficacy of single-session RFA with a single electrode insertion.

Key words: radiofrequency ablation, hepatocellular carcinoma, local recurrence, risk factor

Received: July 23, 2002 / Accepted: April 4, 2003
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Introduction

Hepatocellular carcinoma (HCC) is the main cause of death in patients with liver cirrhosis. The incidence of HCC has increased in the past decade in Japan. Surgical resection has been found to be a very effective treatment for the prevention of the local recurrence of HCC. However, in most patients with HCC, surgical resection is limited by liver dysfunction caused by liver cirrhosis. Percutaneous ethanol injections (PEI) has been widely used in the treatment of HCC in patients with liver cirrhosis.[1–3] However, five to eight injection sessions and a period of hospitalization of over 1 month are necessary to achieve complete ablation of tumors that are about 3 cm in diameter.[4] Moreover, it has been reported that the local recurrence rate after PEI was 38% for tumors less than 3 cm in diameter.[5] Radiofrequency ablation (RFA) is a thermal treatment technique designed to produce approximately 3-cm-diameter coagulative necrosis of the tissue in a single session.[6] A recent prospective study has demonstrated that RFA requires fewer sessions than PEI in patients with small HCCs.[7] However, there is little information available on the local therapeutic efficacy and risk factors for local recurrence from single-session RFA for small HCCs. The purpose of this study was to report on the local therapeutic efficacy and the risk factors for local recurrence after single-session RFA with a single electrode insertion in the treatment of small HCCs.

Patients and methods

Between February 1999 and September 2001, 104 HCC tumors in 69 consecutive patients (44 men, 25 women; mean age, 66.5 years; age range, 50–84 years) with cirrhosis were treated by percutaneous RFA at the Second Department of Internal Medicine, Miyazaki Medical College. According to the Child-Pugh classification,

40 patients (57.9%) had class A cirrhosis, 20 patients (28.9%) had class B cirrhosis, and 9 (13.0%) had class C cirrhosis. Hepatitis B surface antigen and antibody to hepatitis C virus were positive in 8 (11.6%) and 54 patients (78.3%), respectively. Only one patient (1.4%) was positive for both viral markers. Four patients (5.8%) without evidence of viral hepatitis reported high alcohol consumption, and 2 (2.9%) had cirrhosis of unknown etiology. The mean tumor size was 20.3 mm in diameter (range, 10–33 mm in diameter), based on ultrasonography. All patients were scanned by dynamic-contrast computerized tomography (CT) before RFA. Diagnosis of HCC was based on typical findings demonstrated by enhancement on CT during arteriography (CTA) and by a contrast defect on CT during arterioportography. In tumors without enhancement on dynamic CT, a fine-needle (21-gauge) biopsy was performed in order to diagnose HCC.

All patients were administered intramuscularly with 15 mg of pentazocine and 15 mg of hydroxyzine for 30 min before treatment. Vital signs were continuously monitored during the procedure, and for 1 h following the procedure. After the skin was cleansed, the most appropriate approach for electrode insertion was selected. Patients were treated using an RF generator (Model 500PA; RITA Medical Systems, Mountain View, CA, USA). The RF energy was delivered using a 25-cm-long, 15-gauge electrode with a 1.0-cm-long tip that was expandable by four hooks to a maximum diameter of 3.0 cm (model 30 electrode; RITA Medical Systems). The electrode was inserted into the center of the tumor, with real-time ultrasonography (US) guidance, using a 3.5-MHz probe (SSD-2200 or SSD-5500; Aloka, Tokyo, Japan), and deployed at the deepest margin of the tumor. The RF generator was activated and the power needed to maintain a temperature of 90°C–120°C at the tip was delivered for 8 min. After the first ablation, the hooks were retracted and the electrode was rotated by 45°. The hooks were then redeployed and the RF generator was reactivated for a further 8 min.

All patients underwent careful follow-up procedures to determine whether they had acute or chronic complications relating to the RFA treatment. Evaluation of the treatment was made using an enhanced CT or magnetic resonance imaging (MRI) scan carried out within 2 weeks of treatment. When the tumor showed a completely avascular area, treatment was finished. In tumors without enhancement on dynamic-contrast CT or MRI, evaluation of RFA treatment was done on the basis of whether the contrast defect in the portal-dominant phase of dynamic CT or MRI was completely covered by the avascular area. When any areas were enhanced by contrast, secondary RFA treatment was performed immediately.

The size of the coagulated necrotic area after a single session of RFA with a single electrode insertion was measured by the portal-dominant phase of dynamic-contrast CT within 2 weeks after treatment. Follow-up US scans, and dynamic CT or dynamic MRI scans, were performed every 3 months thereafter. Local recurrence was defined as any sign of progression in the treated tumor on the follow-up CT or MRI scans, such as the development of tumor staining at the margin of the treated tumor or an enlargement of the treated tumor. No additional treatment was given until evidence of a recurrent tumor was recognized on the imaging studies.

We investigated the local recurrence rate in tumors completely replaced by an avascular area after a single session of RFA with a single electrode insertion. The relationships between pretreatment factors (tumor size, tumor staining, tumor capsule, and tumor location) and local recurrence in the treated tumors were investigated. The status of tumor staining was assessed based on dynamic CT or MRI before the RFA. All tumors were divided into those with positive tumor staining in the early phase on enhancement and those with negative tumor staining. The presence of a tumor capsule was ascertained by imaging techniques (the presence of a halo by US scan and/or ring enhancement in the portal-dominant phase on the dynamic CT or MRI scans). Tumor location was assessed by the location from the liver margin or the intrahepatic vessels, detected by US or CT. The location of the tumors was confirmed by CT, MRI, or US, and those attached to or protruding from the liver surface were confirmed as being located close to the liver surface. The tumors were divided into two groups according to their position relative to the vessel: on the basis of whether part of the tumor was attached to the vessel or not.

All patients were informed of the scientific nature of the investigation and gave their written informed consent. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki revised in 2000.

The local recurrence rate was computed by Kaplan-Meier estimates. For each variable analyzed, differences in the curves were tested with the log-rank test. The parameters assessed before treatment that proved to be significant on univariate analysis were tested by the multivariate Cox's proportional hazards model (Statview 4.5; Abacus Concepts, Overland Park, KS, USA). For statistical analysis, P values were computed by a two-tailed test. A two-tailed P value of less than 0.05 was considered to be statistically significant.

Results

In the present study, 104 tumors were treated by percutaneous RFA. In 99 of the 104 tumors, complete

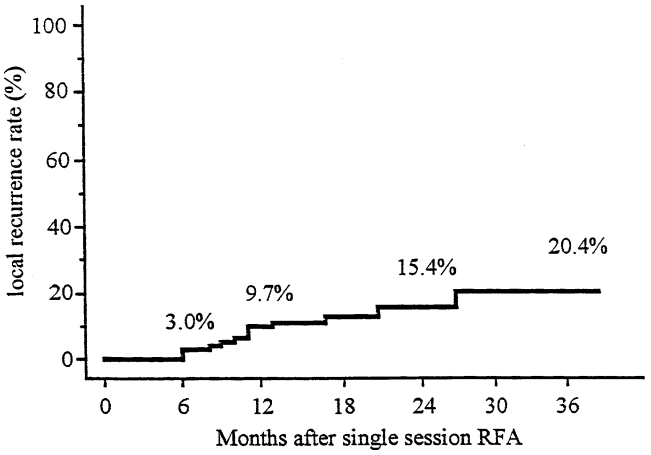

Fig. 1. Overall local recurrence curve for 99 nodules treated with single-session radiofrequency ablation (*RFA*)

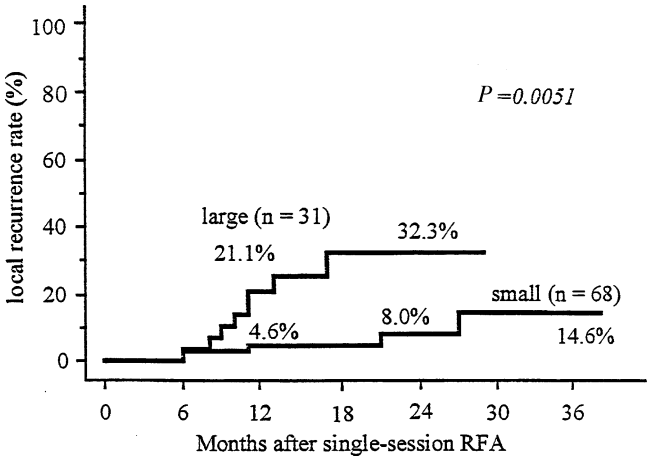

Fig. 2. Local recurrence curves by subsets of tumor size. The *large* (25 mm or more in diameter) tumors were significantly associated with a higher local recurrence rate, compared with the *small* (less than 25 mm in diameter) tumors

coagulation of the necrotic area was achieved by single-session RFA with a single electrode insertion. Dynamic CT and MRI scans after single-session RFA with a single electrode insertion revealed that the coagulated necrotic area was 30.5 × 25.5 mm.

The local recurrence rate in the 99 tumors treated successfully by single-session RFA with a single electrode insertion was calculated. The mean follow-up period after single-session RFA was 18.1 months (range, 6–38 months). The overall local recurrence rates at 1, 2, and 3 years were 9.7%, 15.4%, and 20.4%, respectively (Fig. 1).

Because the greatest short-axis dimension of the area coagulated by single-session RFA was 25.5 mm, all tumors were divided into two subsets based on size: "small," less than 25 mm in diameter, and "large", 25 mm or more in diameter. Large tumors were significantly associated with a higher local recurrence rate compared with the small tumors ($P = 0.0051$; log-rank test). There was local recurrence in more than 30% of the large tumors, whereas the 2-year local recurrence rate in the tumors smaller than 25 mm was 8.0% (Fig. 2). However, local recurrence had no significant correlation with two other tumor variables (tumor staining and tumor capsule; Table 1).

In this study, 15 of the 99 tumors were attached to or protruding from the liver surface; thus, these 15 were confirmed as being located close to the liver surface. The remaining 84 were situated deep within the liver. Four of the 31 large tumors (12.9 %) and 11 of the 68 small tumors (16.2%) were located on the liver surface. There was no significant difference in the distribution of tumor locations between these two groups ($P = 0.647$). The recurrence rates at 1, 2, and 3 years were 20.0%, 34.5%, and 50.9%, respectively, in the tumors located close to the surface and 7.8%, 11.0%, and 11.0%, respectively, in the tumors located deep within the liver. Tumors located close to the surface were significantly ($P = 0.0034$) associated with a higher local recurrence rate compared with the tumors located deep within the liver (Fig. 3). However, the local recurrence rate was not affected by the position in relation to the vessel, as detected by abdominal imaging (US, CT, or MRI).

Table 1. Pathological risk factors for local recurrence of HCC after single-session RFA (log-rank test)

Variables	Values	*P* value
Tumor size in mm; median (range)	Small 68 (10–23) Large 31 (25–33)	$P = 0.0051$
Capsule	Yes: 51 No: 48	NS
Tumor staining	Yes: 74 No: 25	NS
Location	Surface: 15 Deep: 84	$P = 0.0034$
Vessel	Close: 11 Apart: 88	NS

HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; NS, not significant

The Cox's proportional hazards model was used for the variables that were proven to be significant based on the univariate analysis (tumor size and tumor location relative to the liver surface; Table 2). The model showed that both variables were significant independent risk factors for local recurrence after single-session RFA (tumor size, Student's *t*-statistic value, 7.396; $P = 0.0062$; location relative to the liver surface, Student's *t*-statistic value, 5.909; $P = 0.0158$).

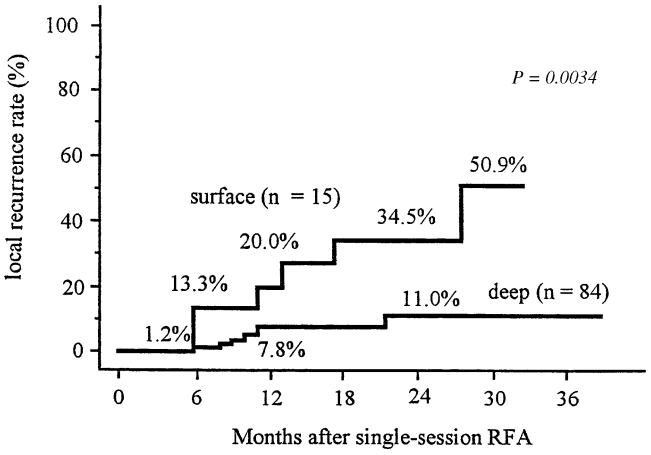

Fig. 3. Local recurrence curves by subsets of tumor location (*surface*, tumors located close to the liver surface; *deep*, tumors situated deep within the liver)

Table 2. Significant risk factors based on univariate analysis tested by Cox's proportional hazards model

Variables	*t* value	*P* value
HCC size	7.396	$P = 0.0062$
Location (surface)	5.909	$P = 0.0158$

Discussion

Recently, percutaneous local therapies (PEI and microwave coagulation therapy [MCT]) for HCC have been used extensively around the world.[8,9] However, both PEI and MCT have needed multiple needle insertions to obtain complete necrosis of the tumor.[4,10] On the other hand, RF needle electrodes have been developed with multiple-array hook electrodes that are deployed from the needle tip into the tumor.[11,12] Multiple-array electrodes can produce larger areas of coagulated necrosis than PEI and MCT. A multiple-array electrode (model 30; Rita Medical Systems) was designed to create a 3-cm zone of coagulated necrosis. However, the present study has shown that the greatest short-axis dimension of the area coagulated by single-session RFA with a single insertion was only 25.5 mm. Rossi et al.[11] and Goldberg et al.[13] also reported that the maximum diameter of the coagulated necrosis was 25 mm. In the present study, the mean tumor size was 21.5 mm and the multiple-array hook electrodes were extended beyond the tumor and deployed in the surrounding cirrhotic tissue. It was reported that the coagulated necrotic area produced by RFA conformed to the size of the tumor and was smaller than expected in the surrounding cirrhotic tissue.[14] Therefore, the greatest short-axis dimension of the coagulated area was less than 3.0 cm in diameter.

The local recurrence rate in tumors larger than 25 mm in diameter was higher than that in the small tumors (Fig. 2). In this study, the mean greatest short-axis dimension of the coagulated necrotic areas was 25.5 mm. It has been reported that the size of an area coagulated by RFA is dependent on tumor size and is larger than expected within the tumor (called the "oven effect"). In the present study, 68 of 99 tumors were less than 25.5 mm in diameter; thus, the mean greatest short-axis dimension of the coagulated areas was 25.5 mm. However, it is possible to obtain a larger coagulated necrotic area than 25.5 mm from a single session of RFA in tumors larger than 25 mm because of the oven effect. Several small satellite nodules might have existed around tumors larger than 25 mm in diameter. It is suggested that these satellite nodules could not be completely treated by single-session RFA in tumors larger than 25 mm. These small satellite nodules were not always able to be detected by transcutaneous US, dynamic CT, or dynamic MRI.[15] It was difficult to evaluate whether the main tumor and satellite nodules were completely replaced by the coagulated necrosis just after single-session RFA. Therefore, several sessions of RFA or a single session with multiple-electrode insertion is necessary to replace both the main tumor and the satellite nodules to complete the process of coagulation of the necrotic area.

In the tumors located close to the liver surface, the local recurrence rate was significantly higher compared with that in the tumors situated deep within the liver (Fig. 3). When the tumors were located close to the liver surface, it was difficult to insert the RFA electrode and open the multiple-array at the center of the tumor. In the present study, 5 of the 68 tumors less than 25 mm in diameter were observed for their local recurrence. Four of the 5 tumors were located close to the liver surface. Therefore, tumors located close to the surface should be carefully treated using an expandable RF electrode, such as the Rita Medical Systems model 30. Recently, it was reported that the laparoscopic approach and artificial ascites method for percutaneous treatment were effective techniques for the treatment of patients with HCC located just beneath the diaphragm.[14,16–18] These techniques are recommended for the treatment of tumors located close to the surface.

A coagulated necrotic area was not rounded in tumors situated near vessels that were detected by abdominal imaging (CT, MRI, or US).[19] This is because a vessel (portal vein or hepatic vein) may influence the extent of the coagulated necrotic area produced by RFA, via a well-known cooling effect. This prevention of extending the necrotic area by the cooling effect raises the possibility that the local recurrence rate is higher in tumors situated near a vessel. However, in the present study, the location in relation to a vessel showed no significant relationship to the local recurrence rate.

The final size of the coagulated necrotic area depends on heat loss due to convection through blood flow. The reduction or elimination of blood flow during RFA is known to increase the volume of the coagulated area.[7] Recently, Yamasaki et al.[20] reported the efficacy of RFA with balloon occlusion of the hepatic artery in the treatment of tumors greater than 30 mm in diameter. However, in the present study, tumor vascularity, represented by tumor staining, showed no significant relationship to local recurrence after single-session RFA. These results suggest that, in HCC smaller than 3.0 cm in diameter, the arterial blood flow is not so high as to decrease the volume of the coagulated necrosis.

Fibrosis surrounding a tumor (tumor capsule) may increase heat retention and influence the size of the coagulated necrosis. Livraghi et al.[21] reported that the size of the coagulated area conformed to the size of the tumor, with a coagulation diameter larger than expected within the tumor (the oven effect) and smaller than expected in the surrounding cirrhotic tissue. The presence of a tumor capsule may influence the local recurrence rate after a single RFA session. However, in our study, no significant difference was observed between tumors with capsules and those without them. On the other hand, a tumor capsule may prevent heating outside the tumor. Satellite nodules existing outside the tumor may influence the local recurrence rate.

In the present study, it was revealed that the most important variables influencing the local recurrence rate were tumor size and tumor location relative to the liver surface. Consequently, it is suggested that single-session RFA with a single insertion should be limited to HCC nodules smaller than 25 mm in diameter; other treatment procedures (e.g., a laparoscopic approach) are recommended for the treatment of HCC tumors located close to the liver surface.

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