Sustained Complete Response and Complications Rates After Radiofrequency Ablation of Very Early Hepatocellular Carcinoma in Cirrhosis: Is Resection Still the Treatment of Choice?

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If liver transplantation is not feasible, partial resection is considered the treatment of choice for hepatocellular carcinoma (HCC) in patients with cirrhosis. However, in some centers the first-line treatment for small, single, operable HCC is now radiofrequency ablation (RFA). In the current study, 218 patients with single HCC ≤ 2.0 cm (very early or T1 stage) underwent RFA. We assessed 2 primary end points that could be easily compared with those reported for resective surgery: (1) the rate of sustained, local, complete response and (2) the rate of treatment-related complications. The secondary end point was 5-year survival in the 100 patients whose tumors had been considered potentially operable. After a median follow-up of 31 months, sustained complete response was observed in 216 patients (97.2%). In the remaining 6, percutaneous ethanol injection, selective intraarterial chemoembolization, or resection were used as salvage therapy. Perioperative mortality, major complication, and 5-year survival rates were 0%, 1.8%, and 68.5%, respectively. Conclusion: Compared with resection, RFA is less invasive and associated with lower complication rates and lower costs. RFA is also just as effective for ensuring local control of stage T1 HCC, and it is associated with similar survival rates (as recently demonstrated by 2 randomized trials). These data indicate that RFA can be considered the treatment of choice for patients with single HCC ≤ 2.0 cm, even when surgical resection is possible. Other approaches can be used as salvage therapy for the few cases in which RFA is unsuccessful or unfeasible. (HEPATOLOGY 2008;47:82-89.)

Resective surgery, when feasible, is considered the treatment of choice for hepatocellular carcinoma (HCC) in patients with cirrhosis who are not candidates for liver transplantation.1 This position is based on the oncological assumption that resection is the more suitable option for obtaining the complete tumor ablation including a layer of tissue surrounding it.2,3 The importance of the local complete response (in other words, the absence of residual neoplastic tissue at the site of the tumor) on the overall survival in patients with HCC had been proved not only for surgery but also for percutaneous ablation therapies (PATs).4,5 PATs were originally reserved for HCCs that were, for one reason or another, unsuitable for resective surgery, but they are now proving their worth in small operable cases as well.6,7

Radiofrequency ablation (RFA) is currently considered the most effective PAT,8-11 and 2 recent randomized trials failed to reveal significant differences between the survival rates associated with resective surgery and RFA in patients with early HCC.12,13 These considerations have led some centers to adopt RFA as first-line treatment for single HCC nodules less than 3.0 cm in diameter,14-17 opening the debate over the best therapeutic option for these small tumors.

To clarify this issue, we conducted a multicenter study that included a consecutive series of patients with single HCC 2.0 cm or less in diameter accompanying cirrhosis...
who underwent percutaneous RFA. The primary end points were long-term rates of local tumor control and major, treatment-related complication rates. These end points, which are easy to evaluate, provide a reliable basis for comparing RFA with resective surgery. Because several of the patients enrolled were potentially suitable for resective surgery, we also calculated their 3-year to 5-year survival rates as a secondary end point.

Patients and Methods

Patients. This survey is a noncurrent cohort study conducted as a retrospective analysis of a prospective database in 5 hospital departments (1 Internal Medicine, 2 Gastroenterology, and 2 Radiology Departments) in which PATs are routinely performed. The protocol was preapproved by the local review boards, and written informed consent was obtained from all patients before treatment.

Patients were enrolled from October 1995 through June 2006 according to the following inclusion criteria: (1) presence of a single HCC nodule measuring 2.0 cm or less in diameter (“very early” or T1 stage, in accordance with the Barcelona-Clinic-Liver-Cancer or the Liver Cancer Study Group of Japan staging systems, respectively); (2) liver cirrhosis scored Child-Pugh class A; (3) performance status Eastern Cooperative Oncology Group 0 or 1. The exclusion criteria were: (1) poor or absent visualization of the nodule on ultrasound (US); (2) intestinal loops or main bile ducts adjacent to the tumor, because this presentation is considered a relative contraindication for RFA; (3) severe coagulation disorders (prothrombin activity < 40% or platelet count < 40,000/mL); (4) previous HCC treatment; (6) no foreseeable possibility for liver transplantation.

Intrahepatic disease was evaluated with standard US and triphasic spiral computed tomography (CT). Tumor size was expressed in terms of maximum diameter as measured on these studies, and the segmental location was defined according to the Couinaud nomenclature. The patient’s general health status was assessed with routine hematology, renal and liver function tests, and abdominal US studies. For each case, we recorded sex, age, hepatitis B surface antigens, antihepatitis C antibodies, alcohol consumption, total bilirubin level, coagulation parameters, serum alanine transferase level, portal hypertension (esophageal varices or splenomegaly with platelet count < 100,000/mL), recurrences (local and new lesions), and potential operability (age < 75 years, serum levels of alanine transferase < 3 times the normal value, and total bilirubin level < 1.5 ng/mL or absence of portal hypertension as defined by the guidelines suggested by the European and the American Associations for the Study of Liver Diseases). Some of these parameters were evaluated as possible predictors of survival.

Treatment Modality. In 3 of the 5 departments, RFA procedures were performed using a 17-gauge cooled-tip electrode (Cool-Tip, Valleylab, Burlington, MA) with a 3-cm exposed portion. Expandable-tip electrodes were used in the other 2 centers. These included 2 models (StarBurst, RITA Medical System, Mountain View, CA; Models RF 3000, Boston Scientific Corp., Natick, MA) consisting of a 16-gauge cannula containing 4 to 10 hook-shaped tines with a diameter of 3.5 cm when completely deployed, and in a third model (TAG100, Invatec, Roncadelle, Italy) consisting of an 18-gauge cannula containing a laterally deployed spiral measuring 1.5 cm in length.

In agreement with the Italian Healthcare System guidelines, patients were hospitalized for 2 days unless complications occurred. Depending on local policy, patients were treated under local anesthesia with conscious sedation or under general anesthesia. Power settings and exposure times were selected according to the standard recommendations provided by the manufacturers of the equipment used and the preferences of the individual operators. RFA was performed under US guidance, using a 3.5-MHz probe with an incorporated guide device. After cleansing the skin with iodized alcohol (which also served as a contact medium), the most appropriate approach for electrode insertion was selected. For tumors located in the left lobe, a subcostal approach was most often used. For tumors located in the right lobe, an intercostal approach with the patient in the left lateral decubitus was generally preferred. One or 2 insertions were performed, with or without the pullback technique, and care was always taken to include a 1.0-cm safety margin in each tumor ablation. As RF energy was delivered, the size and the shape of the hyperechoic zone that appeared at the area treated was monitored to assess the completeness of therapy. Treatment was stopped when the entire target (including the safety margin) was completely covered by the zone of hyperecogenicity, and when the zone did not increase in size for some minutes.
**Treatment Schedule and Follow-up Studies.**

1. Thirty to 40 days after the RFA, triphasic CT was performed. The response to treatment was classified as “complete radiological necrosis” (indicated by the absence of enhancing tissue at the tumor site) or “incomplete treatment” (when enhancing tissue was still observed at the tumor site). In the latter case RFA was repeated, as described, approximately 1 week later. Patients who had a “complete radiological necrosis” after the first or the second RFA treatment underwent follow-up studies.

2. For patients who still had residual enhancement after the second RFA, response to treatment was defined as “treatment failure.” These patients were scheduled for other types of therapy, that is, resective surgery, percutaneous ethanol injection (PEI), or selective transcatheter arterial chemoembolization (sTACE), depending on the individual features of the case, and then underwent follow-up studies.

3. After treatment, the follow-up program provided for imaging examinations (US, spiral CT), liver function tests, and measurement of AFP levels every 4 to 6 months.

4. During the follow-up, the persistence of “complete radiological necrosis” at the tumor site was regarded as evidence of sustained “complete local response,” whereas the reappearance of enhancing tissue within the ablation zone or less than 2.0 cm from its borders was defined as “local recurrence.” This definition was based on pathologic studies demonstrating that any microsatellites associated with HCC nodules up to 2 and 3 cm in diameters are located within 1 cm and 2 cm from tumor borders, respectively. When a local recurrence was observed, the case was reclassified as RFA “treatment failure.” HCC nodules found in other segments or more than 2.0 cm from the ablation zone were considered “new lesions.”

5. Patients with new lesions or local recurrence were scheduled for further treatment, that is, RFA, PEI, or sTACE, depending on the individual presentation.

**Statistical Analysis.** Univariate analysis was performed to identify parameters (sex, age, AFP, bilirubin level, serum alanine transferase level, portal hypertension, operability, recurrence) predicting survival. Survival curves were computed according to the Kaplan-Meier method and compared with the log-rank test. In addition, a univariate Cox proportional hazards model was fitted to each variable, and all variables with a P value < 0.20 were subjected to multivariate analysis to assess their value as independent predictors of survival. A disease-free survival curve was computed according to the Kaplan-Meier method. P < 0.05 was considered statistically significant. Data analysis was performed with STATA statistical package (release 9.0, 2006, Stata Corporation, College Station, TX).

**Results**

Of the 232 patients who met both of the inclusion criteria, 14 (6.0%) were excluded because their tumors were located in a high-risk area for RFA or were poorly detectable on US. The remaining 218 (93.3%) were enrolled in the study and treated with RFA. Their baseline characteristics are reported in Table 1. Three patients received liver transplants during the follow-up because of deteriorating liver function (in Italy, where there is a shortage of organ donors in comparison with the large number of patients with HCC, transplantation is generally reserved for patients with Child-Pugh classes B or C); for these patients the date of transplantation was considered the end of the study follow-up.

There were no perioperative deaths. Four of the 218 patients (1.8%) experienced major complications regarded as treatment-related (Table 2). These complications were treated as follows: peritoneal bleeding with blood transfusions, hemothorax with chest-tube drainage, and neoplastic seeding with 1 successful session of RFA.

Complete radiologic necrosis was achieved in 214 patients (98.1%), with 1 (188 cases, 86.2%) or 2 (26 cases, 11.9%) sessions of RFA. Four of the 218 patients (1.8%) had treatment failure after RFA, and their tumors were subsequently treated with resective surgery (n = 1), sTACE (n = 1), or PEI (n = 2). Histopathologic exam-
inations of the 3 explanted organs demonstrated complete necrosis of the nodules treated with RFA.

Follow-up for these patients ranged from 6 to 134 months (median, 31.0 months). The total risk time was 8411 months. During the follow-up, local recurrence was observed in 2 cases (0.9%), 24 and 84 months after RFA treatment, respectively. They were then treated with stTACE. In conclusion, sustained complete local responses to RFA were obtained in 212 of 218 cases (97.2%), and treatment failure occurred in 6 (2.7%). Two of the patients with unsuccessful outcome to RFA presented local progression at the end of the study.

During the follow-up, 63 of 218 patients (28.8%) died. As shown in Fig. 1, the estimated 3-year and 5-year survival rates were 76% and 55%, respectively. One hundred (45.8%) of the 218 participants had been regarded as potential candidates for resective surgery, whereas the other 118 (54.1%) were considered ineligible for surgery. As shown in Fig. 2, the estimated 3-year and 5-year survival rates for the potentially operable subgroup (89% and 68%) were significant better than those for inoperable patients (75% and 47%) ($P = 0.013$). The estimated 3-year and 5-year disease-free survival rates (82 patients) were 26% (95% confidence interval: 14-41) and 20% (95% confidence interval: 7-36), respectively (Fig. 3).

In univariate analysis, overall survival rates were not affected by sex, bilirubin or aminotransferase levels, or portal hypertension. Age, appearance of new lesions, and operability all had a statistically significant impact on survival (Table 3). Univariate analysis of the prognostic role of AFP levels could not be done because only 11 patients had significantly high values.

In multivariate analysis, appearance of new lesions (hazard ratio: 1.97; confidence interval: 1.13-3.5; $P = 0.017$) was the only factor significantly associated with survival (Table 3).

**Discussion**

In clinical practice, a single HCC nodule up to 2.0 cm in diameter is widely considered to represent the earliest stage of this tumor. Even at this stage, however, different degrees of tissue differentiation are possible. Histopathologic studies have shown that, although HCC nodules measuring 1.5 cm or less (considered the early stage for pathologists) are uniformly well differentiated, those between 1.5 and 2.0 cm in diameter often contain zones of less differentiated tissue with more intense proliferative activity (considered the small advanced-stage for pathologists). The less differentiated areas give rise to portal microinvasion in 10% of the cases, and to microsatellites in 3% of the cases, usually within 1.0 cm of the main tumor.

Among surgical procedures, anatomic resection seems to offer the best chances for eliminating satellite nodules and neoplastic emboli in small portal branches jointed to the tumor neovascularity. However, some studies have demonstrated that the width of the resection margin around small HCC does not influence postoperative recurrence rates, probably because satellites are rare with
HCC of this stage. Nonetheless, free surgical margins are an independent predictor of favorable outcomes for patients with cirrhosis who have had resective surgery for HCC. These data have led both the European and American Associations for the Study of Liver Diseases to recommend that PAT be used for very-early-stage HCC only "for patients who cannot undergo resection." The underlying assumption that surgery is superior to PATs for local disease control was undoubtedly true a few years ago, when PEI was considered the most effective PAT. In fact, its use with HCC nodules smaller than 2.0 cm in diameter was associated with a local recurrence rate of approximately 10%. This rate of failures associated with PEI is probably related to limited operator skill, difficult tumor sites, and above all tissue characteristics (septa, capsular microinfiltration) that impede uniform diffusion of the injected ethanol.

In recent years, RFA has surpassed PEI in terms of the local tumor control it offers and for overall patient survival. RFA performed with expandable-tipped or cool-tipped electrodes can eliminate most of the problems related to the correct placement of the PEI needle. A single electrode insertion can produce a necrotic area of up to 3.0 cm in diameter, thus allowing full ablation of a 2-cm tumor plus a 0.5-cm to 1.0-cm safety margin.

Our study confirms that RFA is more effective than PEI for local tumor control. Complete local responses were sustained through follow-up (median, 31 months) in 97.2% of the treated cases. However, certain tumors remain difficult to treat with RFA because of their location. A limited number of patients (6%) had to be excluded from this study because their tumors could not be visualized on US or were close to anatomic structures that might be damaged by the treatment. Moreover, 3 of the

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Reg. Total Fail Survivor Function Std. Error [95% Conf. Int.]</th>
</tr>
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<tbody>
<tr>
<td>12</td>
<td>43 26 0.66 0.0552 0.54 0.75</td>
</tr>
<tr>
<td>24</td>
<td>22 10 0.48 0.0638 0.35 0.60</td>
</tr>
<tr>
<td>36</td>
<td>8 7 0.26 0.0711 0.14 0.41</td>
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<tr>
<td>48</td>
<td>4 1 0.20 0.0779 0.07 0.36</td>
</tr>
<tr>
<td>60</td>
<td>4 0 0.20 0.0779 0.07 0.36</td>
</tr>
<tr>
<td>72</td>
<td>3 1 0.13 0.0744 0.03 0.31</td>
</tr>
<tr>
<td>84</td>
<td>1 0</td>
</tr>
</tbody>
</table>

Table 3. Cox Survival Analysis of Predictors for Survival in 218 Patients with T1 HCC After RFA

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate HR 95%CI</th>
<th>P</th>
<th>Multivariate HR 95%CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>1.09 0.66-1.79</td>
<td>0.742</td>
<td>NE</td>
<td>0.63 0.31-1.26</td>
</tr>
<tr>
<td>Age (per 1 year)</td>
<td>1.04 1.00-1.08</td>
<td>0.028</td>
<td>1.04 0.99-1.07</td>
<td>0.074</td>
</tr>
<tr>
<td>Operability (yes/no)</td>
<td>0.52 0.31-0.88</td>
<td>0.015</td>
<td>0.63 0.31-1.26</td>
<td>0.192</td>
</tr>
<tr>
<td>ALT (≥100 / ≤100 IU/L)</td>
<td>1.72 0.88-3.35</td>
<td>0.210</td>
<td>NE</td>
<td>1.97 1.13-3.46</td>
</tr>
<tr>
<td>New lesions (yes/no)</td>
<td>2.00 1.15-3.50</td>
<td>0.015</td>
<td>1.97 1.13-3.46</td>
<td>0.017</td>
</tr>
<tr>
<td>Bilirubin (≥1.5/ &gt;1.5 mg/dL)</td>
<td>1.51 0.91-2.48</td>
<td>0.108</td>
<td>1.03 0.54-1.96</td>
<td>0.938</td>
</tr>
<tr>
<td>Portal hypertension (yes/no)</td>
<td>1.33 0.78-2.30</td>
<td>0.310</td>
<td>NE</td>
<td></td>
</tr>
</tbody>
</table>
treatment failures occurred in patients whose tumors were located near a large blood vessel whose flow probably caused excessive heat loss in the ablation zone (the so-called “heat sink effect”). These cases were successfully treated by PEI or sTACE. Surgery was used as salvage therapy in only 1 case characterized by multiple contiguous micronodules with a blackberry appearance, and some of them remained viable even after a second RFA session.

RFA was associated with no mortality. The major complication rate was 1.8%, and the single case of neoplastic seeding (0.5%) was successfully controlled by repeat RFA. The negligible mortality after RFA has been noted by other investigators, whereas surgical resection of HCCs is associated with mortality rates ranging from 0% to 15%, with a mean of 5%. Bilirubin elevations and portal hypertension have already been identified as negative prognostic factors for HCC patients who have undergone resection, in terms of both postoperative complications and decreased survival. However, our experience did not statistically confirm this fact, probably because of the lower invasiveness of RFA.

Two recent randomized trials showed that survival rates in patients with early HCC were similar after RFA and surgery. The first included 180 patients with single HCC nodules measuring less than 5.0 cm, and 4-year survival rates after surgery and RFA were 67% and 64%, respectively. In the second trial, 105 patients with 2 to 3 nodules smaller than 3 cm were treated, and 3-year survival rates were 86% in the RFA group and 87% for those who had surgical resection. The efficacy of RFA is known to be size dependent. Therefore, because most of the nodules treated in these 2 trials were larger than 2 cm, it would be reasonable to expect better survival rates among the patients who underwent resection, which is seemingly the only method capable of ensuring complete ablation of nodules accompanied by peritumoral microinvasion. The fact that survival rates in the RFA and resection groups were equivalent probably reflects the compensatory effects of certain advantages of RFA with respect to surgery, that is, less destruction of nonneoplastic tissue, greater repeatability, and lower complication rate. In terms of survival, the superiority of RFA should be more evident in the treatment of nodules up to 2 cm, because the advantages cited above are combined with local efficacy that is comparable to that of resection.

The patients we studied all had single nodules up to 2.0 cm in diameter, and although the limitations of historical comparisons are well known, it is worthwhile to note that the 5-year survival rate in our study (68%) was comparable to that reported by 3 studies after surgical treatment of HCCs of the same stage. The first study reported 67 patients, 15 with early HCC type at pathology and 52 with overt HCC. Five-year survival rates were 93% in the former subgroup and 54% in the latter (mean survival, 62%), and the perioperative mortality rate for the entire group was 1.4%. The second study revealed a 5-year survival rate of 67% among 84 patients. In this study, tumors located at the borderline of the segment were treated with bisegmentectomy or hepatic lobectomy, and the perioperative mortality rate for the entire group was 2.7%. The third study, which reports the experience of the Liver Cancer Study Group of Japan, revealed a 5-year survival rate of 70% among 2078 patients.

The best way to determine whether RFA is more effective than, or at least as effective as, resection for very early stage HCC is an obvious direct comparison in a randomized, controlled trial. However, the results obtained in the studies just reviewed indicate that the difference between the 2 approaches may be fairly small, and the sample size required to ensure meaningful results to be quite large. For this reason, a trial of this sort is probably not feasible. Our high overall recurrence rate at 5 years (80%) was comparable to those reported by other authors in patients with early clinical stage treated with either partial resection or PAT. It would be reasonable to expect a lower rate in patients with very early stage, but some studies have revealed rates that are even higher than our own. In a surgical study, recurrence rates were 53% for tumors classified as early type at pathology and 84% for those that were overt, and rates as high as 93% were observed in a histopathologic study. The tumors of our series were diagnosed by biopsy or by imaging, and therefore most belonged to the overt type. In terms of survival, the timing of new lesions’ appearance resulted in the only significant factor at multivariate analysis. This fact means that, above all, it is the natural history that governs the prognosis. HCC is an organ disease, and the first nodule treated is usually only a prelude to others. Therefore, all the survival curves reported in the literature, whatever the initial therapy, are generally the result of multimodality repeated treatments as required by the individual disease evolution.

In conclusion, compared with surgical resection, RFA of small HCCs has a number of clear advantages. For one thing, it is much less invasive and associated with a lower complication rate. In addition, RFA significantly lowers treatment costs by reducing treatment times, hospital stays, and the need for blood transfusions. Our experience now shows that RFA is just as effective as surgery for the treatment of very early HCC, in terms of sustained local disease control and survival. These data add support to the view that RFA is the treatment of choice for patients with single HCC nodules measuring 2.0 cm or less, even when there are no con-
indications to resective surgery. The latter approach, along with other treatment options such as PEI or sTACE, can be reserved for those patients whose tumors are not amenable to RFA or used as salvage therapy for the few cases in which RFA is unsuccessful.

References


