Radiofrequency Ablation and Percutaneous Ethanol Injection in Patients with Small Hepatocellular Carcinoma: a Comparative Study

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Background: Radiofrequency ablation (RFA) is a novel thermal ablation technique to achieve coagulative necrosis of hepatocellular carcinoma. A study was conducted to compare the antitumor effect and adverse effect of RFA with those of percutaneous ethanol injection (PEI) in patients with solitary small hepatocellular carcinoma.

Methods: The study population consisted of 119 consecutive patients with solitary hepatocellular carcinoma smaller than 3 cm in diameter. Among these, 23 patients were treated with RFA and the remaining 96 patients were treated with PEI. The antitumor effects of both treatments were assessed by contrast-enhanced computed tomography 1 month after treatment.

Results: Complete tumor necrosis was achieved in 23 patients (100%) of the RFA group and 90 patients (94%) of the PEI group (p = 0.48) and local recurrence rates at 1 year were 15% in the RFA group and 14% in the PEI group (p = 0.80). RFA required an average of 1.5 sessions to achieve complete necrosis, whereas PEI required an average of 4.0 sessions. As a consequence, the hospital stay in the RFA group (median 10 days) was significantly shorter than that in the PEI group (median 17 days). There were no serious adverse effects or complications except for one case of cholangitis in the PEI group, although deterioration of serum transaminase after RFA was significantly more severe than that after PEI.

Conclusion: RFA achieved complete tumor necrosis for small hepatocellular carcinoma with fewer treatment sessions compared with PEI. There were no serious complications.

Key words: hepatocellular carcinoma – radiofrequency ablation – percutaneous ethanol injection

INTRODUCTION

Several local ablation therapies, most of which are performed percutaneously under imaging guidance, have been performed as minimally invasive therapy for hepatocellular carcinoma (HCC). Among them, percutaneous ethanol injection (PEI) has been most widely performed (1–4) and is now well established as an alternative to surgery in patients with small HCC; the prognosis of PEI for small HCC has been reported to be equivalent to that of surgical resection (5–8).

Radiofrequency ablation (RFA) is a novel thermal ablation technique to achieve coagulative necrosis of liver tumors (9–11). Several recent innovations in RFA technology have facilitated a larger volume of necrosis being obtained with one treatment session (12,13). Accordingly, RFA has come into prominence as an attractive local ablation modality for small HCC. The present study compared the antitumor effect and adverse effects of RFA with those of PEI in patients with a solitary small HCC.

MATERIALS AND METHODS

Patients

The study population consisted of 119 consecutive patients with solitary HCC smaller than 3 cm in diameter who had not received any prior treatment for HCC other than hepatic resection. Among these, 23 patients were treated with percutaneous RFA between February 1999 and January 2000 and the remaining 98 patients were treated with PEI between January 1995 and January 2000 at the National Cancer Center Hospital, Tokyo, Japan. Before the introduction of RFA to our hospital, all patients were treated with PEI. After the introduction of RFA, all patients, except those whose HCC nodules were diffi-
cult to approach or located in unsafe areas for RFA, were
treated with this technique. All patients were hospitalized
while they underwent RFA or PEI. Before treatment, all
patients were examined by ultrasonography (US), computed
tomography (CT) and angiography. Diagnosis of HCC was
based on histopathological findings of specimens (98 patients,
82%). The remainder (21 patients, 18%) were diagnosed with
HCC based on typical CT and angiographic findings. Written
informed consent was obtained from all patients before treat-
ment.

METHODS
For RFA, a radiofrequency ablation delivery system (RITA
Medical System, Mountain View, CA, Model: RITA 500PA)
was used. This system was a radiofrequency current generator
with 15-gage expandable needle electrode, which had ther-
nometers on their tips to monitor the temperature in the
surrounding tissue. After the electrode had been introduced
percutaneously under US guidance into the center of the tumor
and the hooks deployed, the power needed to maintain a tem-
perature of about 100°C at the hook tips was delivered for
8 min. Thereafter, the hooks were turned around the major axis
at an angle of 45° and the radiofrequency generator was acti-
vated again. At the end of the procedure, the hooks were
retracted and the electrode was removed while coagulating the
tract by a delivered power of 20 W. The coagulation was
repeated once weekly. If there were residual tumor stains
identified on contrast-enhanced CT 3–7 days after RFA, an
additional session was performed.

For PEI, a 22-gage needle (Top, Tokyo, Japan) was intro-
duced percutaneously into the tumor and/or its marginal area
under US guidance. The amount of absolute ethanol injected
each time was 2–8 ml, depending on ethanol diffusion, which
was monitored in real time by US. The injection was repeated
once or twice a week for four to six sessions. The number of
sessions depended on tumor size.

The antitumor effect was assessed by contrast-enhanced CT
1 month after completion of the treatments and thereafter
follow-up examinations including CT, US and α-fetoprotein
(AF) were performed at least every 3–4 months.

For the comparison between RFA and PEI groups, the fol-
lowing variables were analyzed: rate of complete tumor necro-
sis (%), rate of local recurrence at 1 year (%), treatment
sessions (times), hospital stay (days), rate of analgesic use (%),
differences between the pretreatment data and the worst data
after treatment in total bilirubin (d T-Bil), albumin (d Alb),
glutamic oxaloacetic transaminase (d GOT); glutamic pyruvic
transaminase (d GPT) and C-reactive protein (d CRP). The
antitumor effect was considered complete tumor necrosis when
the original extent of the tumor demonstrated on contrast-
enhanced CT was completely replaced by an avascular area
1 month after treatment. Local recurrence was defined as any
sign of progression in the treated tumor on follow-up CT, such
as development of tumor stain in the treated tumor or enlarge-
ment of the treated tumor. Pentazocine (Pentagin; Sankyo,
Tokyo, Japan) was used as an analgesic in all patients com-
plaining of severe pain.

STATISTICAL ANALYSIS
The frequency of each variable was analyzed by the chi-
squared test and continuous variables were compared by the
Mann–Whitney U test. The local recurrence rates were calcu-
lated by the Kaplan–Meier method and the differences were
evaluated using log-rank tests. A p-value < 0.05 was considered
significant in all analyses. Statistical analyses were performed
using Stat View Version 5.0 (SAS Institute, Cary, NC).

RESULTS
The baseline characteristics of the patients in both groups are
shown in Table 1. There were no significant differences in any
baseline characteristics, such as age, gender, alcohol abuse,
hepatic reserve and tumor size, between these two groups. The
median follow-up periods were 11.4 months (range: 1.4–20.7
months) in the RFA group and 30.8 months (range: 5.2–69.8
months) in the PEI group (p < 0.01).

Complete tumor necrosis was achieved in 23 patients
(100%) in the RFA group and 90 patients (94%) in the PEI
group (p = 0.48) (Table 2). Local recurrence at 1 year occurred
in 15% of the RFA group and in 14% of the PEI group (p = 0.80). RFA required an average of 1.3 sessions to obtain
complete necrosis, whereas PEI required an average of 4.0 ses-
sions. Moreover, the hospital stay in the RFA group (median
10 days) was significantly shorter than that in the PEI group
(median 17 days). There were significant differences in the
treatment sessions and the hospital stay between these treat-
ments.

Analgesic use was evaluated as an index of pain in this
study. If the patient complained of severe pain during and
immediately after the procedure, pentazocine was used as an
analgesic. The rate of analgesic use was higher in the RFA
group (52%) than in the PEI group (31%), but there was no sig-
nificant difference. The pain related to these treatments was
transient and relieved by pentazocine.

In most patients, blood chemistry tests worsened after treat-
ment, that is, levels of total bilirubin, transaminases and CRP
increased over baseline levels and albumin decreased below
the baseline level. There were no significant differences in d T-
Bil, d Alb or d CRP between these treatment groups. However,
d GOT and d GPT were significantly greater in the RFA group
than in the PEI group. All adverse effects observed in blood
chemistry tests were transient and all patients recovered to ini-
tial levels within 1 week after completion of treatment without
any specific treatment.

Acute cholangitis (1%) requiring percutaneous transhepatic
biliary drainage was observed in one patient treated with PEI,
but other severe complications, such as hemothorax, intraperi-
toneal bleeding and hemobilia, were not encountered in either
treatment group.
### Table 1. Characteristics of 119 patients treated with radiofrequency ablation or percutaneous ethanol injection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RFA</th>
<th>PEI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Median (range)</td>
<td>62 (50–83)</td>
<td>66 (23–81)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Male</td>
<td>18 (78%)</td>
<td>64 (67%)</td>
</tr>
<tr>
<td><strong>Alcohol abuse</strong></td>
<td>Positive</td>
<td>6 (26%)</td>
<td>24 (25%)</td>
</tr>
<tr>
<td><strong>HBs Ag</strong></td>
<td>Positive</td>
<td>3 (13%)</td>
<td>8 (8%)</td>
</tr>
<tr>
<td><strong>HCV Ab</strong></td>
<td>Positive</td>
<td>17 (74%)</td>
<td>85 (89%)</td>
</tr>
<tr>
<td><strong>Platelet (×10⁹/mm³)</strong></td>
<td>Median (range)</td>
<td>9.9 (4.3–19.9)</td>
<td>10.7 (2.9–25.9)</td>
</tr>
<tr>
<td><strong>T-Bil (mg/dl)</strong></td>
<td>Median (range)</td>
<td>0.8 (0.5–1.7)</td>
<td>0.9 (0.4–2.3)</td>
</tr>
<tr>
<td><strong>Alb (g/dl)</strong></td>
<td>Median (range)</td>
<td>3.5 (2.9–4.5)</td>
<td>3.6 (2.6–4.7)</td>
</tr>
<tr>
<td><strong>GOT (IU/l)</strong></td>
<td>Median (range)</td>
<td>67 (17–111)</td>
<td>61 (17–167)</td>
</tr>
<tr>
<td><strong>GPT (IU/l)</strong></td>
<td>Median (range)</td>
<td>78 (26–135)</td>
<td>64 (9–191)</td>
</tr>
<tr>
<td><strong>LDH (IU/l)</strong></td>
<td>Median (range)</td>
<td>426 (291–640)</td>
<td>407 (267–772)</td>
</tr>
<tr>
<td><strong>Cholinesterase (IU/l)</strong></td>
<td>Median (range)</td>
<td>194 (62–368)</td>
<td>189 (57–387)</td>
</tr>
<tr>
<td><strong>CRP (mg/dl)</strong></td>
<td>Median (range)</td>
<td>0.1 (0.1–1.2)</td>
<td>0.1 (0.1–1.2)</td>
</tr>
<tr>
<td><strong>Prothrombin time (%)</strong></td>
<td>Median (range)</td>
<td>84 (65–119)</td>
<td>81 (54–129)</td>
</tr>
<tr>
<td><strong>Tumor size (mm)</strong></td>
<td>Median (range)</td>
<td>18 (14–29)</td>
<td>19 (10–30)</td>
</tr>
<tr>
<td><strong>Tumor stain</strong></td>
<td>Positive</td>
<td>15 (65%)</td>
<td>80 (83%)</td>
</tr>
<tr>
<td><strong>AFP (ng/ml)</strong></td>
<td>Median (range)</td>
<td>40.9 (3.7–1220)</td>
<td>23.9 (1.7–4925)</td>
</tr>
<tr>
<td><strong>Follow-up period (months)</strong></td>
<td>Median (range)</td>
<td>11.4 (1.4–20.7)</td>
<td>30.8 (5.2–69.8)</td>
</tr>
</tbody>
</table>

RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody; T-Bil, total bilirubin; Alb, albumin; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; CRP, C-reactive protein; AFP, α-fetoprotein; well/mod./poor., well-differentiated/moderately differentiated/poorly differentiated.

*Ethanol intake, ethanol >80 g/day × 5 years.

### Table 2. Comparisons between radiofrequency ablation and percutaneous ethanol injection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RFA</th>
<th>PEI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete tumor necrosis [No. (%)]</strong></td>
<td>23 (100)</td>
<td>90 (94)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Local recurrence at 1 year (%)</strong></td>
<td>15%</td>
<td>13%</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>Treatment sessions (times)</strong></td>
<td>Average (range)</td>
<td>1.3 (1–2)</td>
<td>4.0 (4–6)</td>
</tr>
<tr>
<td><strong>Hospital stay (days)</strong></td>
<td>Median (range)</td>
<td>10 (4–16)</td>
<td>17 (12–72)</td>
</tr>
<tr>
<td><strong>Analgesic use [No. (%)]</strong></td>
<td>12 (52)</td>
<td>30 (31)</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>T-Bil (mg/dl)</strong></td>
<td>Median (range)</td>
<td>0.3 (0–1.0)</td>
<td>0.3 (0–6)</td>
</tr>
<tr>
<td><strong>Alb (g/dl)</strong></td>
<td>Median (range)</td>
<td>0.3 (0–0.8)</td>
<td>0.3 (0–1.2)</td>
</tr>
<tr>
<td><strong>GOT (IU/l)</strong></td>
<td>Median (range)</td>
<td>139 (66–223)</td>
<td>38 (0–594)</td>
</tr>
<tr>
<td><strong>GPT (IU/l)</strong></td>
<td>Median (range)</td>
<td>79 (16–194)</td>
<td>30 (0–524)</td>
</tr>
<tr>
<td><strong>CRP (mg/dl)</strong></td>
<td>Median (range)</td>
<td>0.9 (0–10.6)</td>
<td>1.0 (0–18.9)</td>
</tr>
</tbody>
</table>

RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; T-Bil, total bilirubin; Alb, albumin; GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase; CRP, C-reactive protein. d, differences between worst blood chemistry data after treatment and pretreatment data.
DISCUSSION

PEI has become the mainstay of ablation therapies for small HCC (1–4) because of its minimal invasiveness and simplicity. The long-term results of PEI for small HCC have been reported to be almost the same as those of surgical resection in comparable patients (5–8). PEI, however, has some disadvantages, i.e., the necessity for a large number of treatment sessions leading to a prolonged treatment period and uncertainty of tumor ablation due to the non-homogeneous distribution of injected ethanol within the tumor. In contrast, RFA has promising properties, such as fewer treatment sessions and the predictability of tumor ablation, because just one treatment session can produce regional necrosis with a diameter up to 3 cm (12,13). This study evaluated both the antitumor effect and the adverse effects of RFA compared with those of PEI.

Complete tumor necrosis was achieved in all patients (100%) treated with RFA and 90 patients (94%) treated with PEI. The result was similar to that of two prospective studies reported previously (14,15), which demonstrated that RFA achieved better local tumor control than PEI. With respect to local recurrence, there was no significant difference between the RFA group and the PEI group in our study, although RFA has been reported to show a lower local recurrence rate than PEI (15). The superiority of RFA over PEI in local tumor control may be due to the fact that RFA can achieve coagulative regional necrosis of HCC nodule including areas of extracapular invasion and/or adjacent intrahepatic metastasis. In this study, local recurrence after RFA may have been due to our limited experience with RFA treatment, because local recurrence was not observed in more recent patients treated with RFA.

Although the superiority of RFA over PEI in terms of local tumor control has been reported (14,15), the survival advantage of RFA over PEI remained to be determined (14–18). However, the survival of RFA is not expected to be worse than that of PEI because the rates of complete tumor necrosis and local recurrence were similar in both treatment groups. To elucidate the real effect of RFA on survival, long-term follow-up in a large number of patients is necessary.

Another important advantage of RFA over PEI is that fewer treatment sessions are required to achieve complete tumor necrosis; RFA required an average of 1.3 sessions, whereas PEI required an average of 4.0 sessions (p < 0.01). Consequently, the duration of hospital stay in the RFA group was also significantly shorter than that in the PEI group. Fewer treatment sessions and shorter hospital stay lessen the distress of the patients and result in an improved quality of life.

Concerning the rate of analgesic use, which may represent the severity of treatment-related pain, there was no significant difference between the RFA group and the PEI group, although the rate tended to be higher in the RFA group. RFA-related pain was transient and controllable by pentazocine, as is the case with PEI. Thus, percutaneous RFA under local anesthesia was feasible, although intraoperative RFA under general anesthesia was also performed to prevent severe pain and discomfort during the procedure (17).

With regard to changes in blood chemistry tests, d GGT and d GPT were significantly greater in the RFA group, and there was no difference in d T-Bil, d Alb or d CRP between these two treatment groups. Significant deterioration of serum transaminase after RFA may indicate that RFA induces a larger volume of necrosis including adjacent non-cancerous parenchyma compared with PEI. However, such deterioration may be regarded as being of little clinical importance, because it was transient and recovered to the initial level within 1 week after completion of treatment without any specific treatment. Thus, the current study demonstrated that RFA has no clinically significant adverse effect on liver function, particularly the hepatic reserve.

RFA has been reported to show higher complication rates than PEI (14), although there were no serious complications observed in our series. Locations of tumors treated with RFA may be closely related to these complications. Heat injuries to adjacent organs and Glisson’s sheaths caused complications, such as cholecystitis, intrahepatic abscess, biloma and pleural effusion. Moreover, the higher frequencies of complications in RFA, such as hemothorax and intraperitoneal bleeding, may be caused by a larger RFA needle electrode.

After the introduction of RFA, some patients, whose HCC nodules were difficult to approach or located in unsafe areas for RFA, were treated with PEI. We compared the results of RFA and PEI after excluding patients having masses which were difficult to approach or located in unsafe areas from the PEI group, because the results might be influenced by the difference in tumor location between the two groups. However, these results remained the same (data not shown).

We are encouraged by our experience with RFA as a treatment for small HCC, because RFA achieved complete tumor necrosis for small HCC in fewer treatment sessions without serious complications compared with PEI. The efficacy, safety and simplicity of PEI have made it now the choice among ablation therapies, but RFA may eventually replace PEI in the treatment of small HCC. Further studies, however, are required to clarify the optimal RFA method and proper patient selection. Moreover, to elucidate the real role of RFA therapy in the treatment of HCC, further trials, possibly randomized trials to compare the results of different therapeutic options, are necessary.

References


