

Postoperative recurrence in hepatocellular carcinoma: Comparison between percutaneous ethanol injection and radiofrequency ablation

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Abstract

Aim: Recently percutaneous ethanol injection (PEI) turned into percutaneous radiofrequency ablation (PRFA), and it has become widely used for the treatment of hepatocellular carcinoma (HCC). The present study was to compare the incidence in postoperative HCC recurrence between these two therapeutic approaches.

Methods: One hundred and sixty-eight first-time HCC in patient cases were chosen for PEI ($n = 94$) and PRFA ($n = 74$). The localized recurrence rate based on the operator's experience in percutaneous treatment for HCC (on <5 years versus ≥ 5 years experience) was examined.

Results: The PRFA group demonstrated a significantly lower localized recurrence rate within 2 years than the PEI group (8% and 22%, respectively, $P < 0.01$). The local recurrence rate of HCC within 2 years after PEI was significantly lower in those for whom the operator's experience was more than 5 years compared to those for whom it was less than 5 years (12% versus 24%, respectively, $P < 0.05$). In contrast, after PRFA there was no significant difference between these two groups of <5 years and of ≥ 5 years experience (8% versus 8%, respectively, $P = 0.98$).

Conclusion: The present study demonstrated that PRFA resulted in a lower rate of local recurrence in comparison to conventional PEI, regardless of the operator's experience.

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Keywords: Hepatocellular carcinoma (HCC); Percutaneous radiofrequency ablation (PRFA); Percutaneous ethanol injection (PEI); Operator's experience; Local recurrence

1. Introduction

Hepatocellular carcinoma (HCC) is one of most common malignancies, occurring throughout the world, particularly in Asia [1]. HCC is the main cause of death in patients with liver cirrhosis [2]. Percutaneous ethanol injection (PEI) has been widely used as an effective treatment for small HCC since 1985 [3–6]. Recently, several novel

treatments involving tumor ablation for HCC, such as percutaneous microwave coagulation and percutaneous radiofrequency ablation (PRFA) have been developed [7–12]. The application of PRFA has generally been limited to hepatic lesions characterized by their smaller number ($n \leq 3$) and size (≤ 3 cm), similar to the criteria used to indicate the utility of PEI [13–18]. Therefore, many medical facilities that traditionally have conducted numerous PEI procedures have turned increasingly to novel PRFA. However, only a few studies comparing the PEI and PRFA treatments have been reported [19–22]. In the present study, we have compared PEI and PRFA with regard to the postoperative recurrence in HCC.

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2. Materials and methods

2.1. Subjects

From August 1999 to July 2003, among 484 cases with HCC displaying a Child-Pugh score of 5–9 points, 168 cases, whose tumor diameter was 1–3 cm and with no more than three tumor nodules present were treated with PEI or PRFA. PEI was performed from August 1999 to July 2001. According to the availability of the ablation devices, PRFA was performed from August 2001 to July 2003. Ninety-four receiving PEI (PEI group) and 74 cases receiving PRFA (PRFA group) were included in the present study.

2.2. Examination items

The following six items were examined in the two groups:

- (1) Number of treatment sessions.
- (2) Number of days from treatment to discharge from the hospital.
- (3) Incidence of severe complications (intra-abdominal bleeding, hepatic infarction, hepatic abscess, or sepsis).
- (4) Total HCC recurrence rate (including local recurrence and ectopic recurrence).
- (5) Local HCC recurrence rate (continuous with or near the primary treatment area).
- (6) In the two treatment groups, total and local HCC recurrence rates in patients treated by operating physicians who have experience of ultrasound guided treatment or biopsy for HCC either less than 5 year's, or 5 or more year's experience.
- (7) Survival rate for a short term in 3 years.

2.3. Procedure for PEI, and for PRFA

In the case of PEI, 3–10 ml/session of 99% ethanol was injected directly into each tumor using a 22-gauge 20-cm needle (PTC needle; Hakko, Tokyo, Japan), for three or four sessions. In the case of PRFA, a Cool-tip needle (Radionics, Burlington, MA) was inserted into the tumor, and the tumor was cauterized for 8–15 min/session, for only one or two sessions. The aim of the treatments was to completely destroy the tumor with a surrounding 0.5–1.0 cm safety margin on enhancement CT.

2.4. Follow-up

Following discharge, the patients were followed-up by examining serum tumor markers, ultrasound imaging and/or computed tomography every 3 months. When tumor recurrence was detected, the subsequent hospitalization day for the treatment was recorded as the day of recurrence.

2.5. Training system for operators

Our institute incorporates 1 year of ultrasound examination practice and specialized training in hepatocellular carcinoma following residency. This regimen serves as a training system for ultrasound-guided operations (image guidance surgery). Both PEI and PRFA were conducted in accordance with our institutional guidelines after receiving informed consent from the patient. The operator on a treatment was chosen at random.

2.6. Statistical analyses

Comparisons in background characteristics between the two groups were conducted using χ^2 and Student's *t*-tests. A recurrence curve and the recurrence ratio were calculated using Kaplan–Meier estimates, and differences in the curves were tested using the log-rank test. A *P*-value of less than 0.05 was considered to be statistically significant.

3. Results

3.1. Clinical characteristics of subjects

No significant difference was observed in maximum tumor diameter, in number of tumors, or in liver function data, among the pre-treatment background factors, between the PEI group and the PRFA group (Table 1).

3.2. Number of treatment sessions

The number of treatment sessions in the PEI group was significantly higher than that in the PRFA group (4.0 ± 1.1 versus 1.2 ± 0.4 , respectively, $P < 0.001$) (Table 2).

Table 1
Clinical characteristics of patients

	PRFA group	PEI group	<i>P</i> value
Number of patients	74	94	
Gender (M/F)	49/25	65/29	NS
Age (years)	66.5 ± 11.6	66.6 ± 9.1	NS
Albumin (g/dl)	3.37 ± 0.52	3.39 ± 0.50	NS
Total bilirubin (mg/dl)	1.25 ± 0.81	1.17 ± 0.52	NS
Size of primary tumors (cm)	2.1 ± 0.8	2.0 ± 0.5	NS
Number of primary tumors	1.4 ± 0.6	1.3 ± 0.5	NS

PRFA: percutaneous radiofrequency ablation; PEI: percutaneous ethanol injection; NS: not significant.

Table 2
Differences according to treatment

	PRFA group	PEI group	<i>P</i> value
Number of treatments	1.2 ± 0.4	4.0 ± 1.1	<0.001
Complications	2/74 (2.7%)	3/94 (3.2%)	NS
Days from initial treatment to discharge	8.2 ± 3.0	20.4 ± 8.4	<0.001

PRFA: percutaneous radiofrequency ablation; PEI: percutaneous ethanol injection; NS: not significant.

Table 3
Therapeutic experience of operator and clinical characteristics of subjects

Operator's experience (years)	PRFA group (n = 74)		P value	PEI group (n = 94)		P value
	<5	≥5		<5	≥5	
Number of patients	36	38		47	47	
Primary tumor size (cm)	2.1 ± 0.6	2.2 ± 1.1	NS	1.9 ± 0.6	2.0 ± 0.4	NS
Number of primary tumors	1.4 ± 0.6	1.4 ± 0.6	NS	1.2 ± 0.4	1.4 ± 0.6	NS
Number of treatments	1.2 ± 0.5	1.2 ± 0.4	NS	4.1 ± 1.16	3.9 ± 1.03	NS
Complications	1/36 (2.8%)	1/38 (2.6%)	NS	3/47 (6.4%)	0/47 (0%)	NS
Days from initial treatment to discharge	8.0 ± 2.6	8.7 ± 3.4	NS	21.4 ± 6.7	18.8 ± 10.6	NS

PRFA: percutaneous radiofrequency ablation; PEI: percutaneous ethanol injection; NS: not significant.

3.3. Days from initial treatment to discharge

The average number of days from the initial treatment to discharge was 20.4 in the PEI group, and 8.2 in the PRFA group ($P < 0.001$, Table 2).

3.4. Complications

Three cases (3.2%) among the PEI group displayed severe complications; two cases suffered hepatic infarction, and the other case hepatic abscess. In the PRFA group, severe complications were recognized in two cases (2.7%); one case suffered intra-abdominal bleeding, while the other case suffered sepsis. No significant difference in complication occurrence rate was observed between the PEI group and the PRFA group (Table 2).

Concerning the experience of the operating physician, for those with experience of less than 5 years, then the overall incidence of a complication was 4.8% (occurring in 4 of the 83 cases). For those with five or more years of experience, then the overall incidence was only 1.2% (occurring in only 1 of the 85 cases) ($P = 0.35$).

3.5. Therapeutic experience of operator and clinical characteristics of subjects

No significant difference was found in tumor diameter, in number of tumors, number of treatment sessions, in the incidence of complications, or in the hospitalization period from initial treatment to discharge, according to the length of experience of the operator between the <5 years and the ≥5 years subsets, in the PRFA group, or in the PEI group (Table 3).

3.6. Recurrence rate

No significant difference was observed in total recurrence rate within 2 years between the PEI group (47%) and the PRFA group (39%) ($P = 0.62$) (Fig. 1). However, there was a significant difference in the local recurrence rate within 2 years between the PEI group (22%) and the PRFA group (8%) ($P < 0.01$) (Fig. 2). In the PEI group, the recurrence rate within 2 years under a operator with experience of

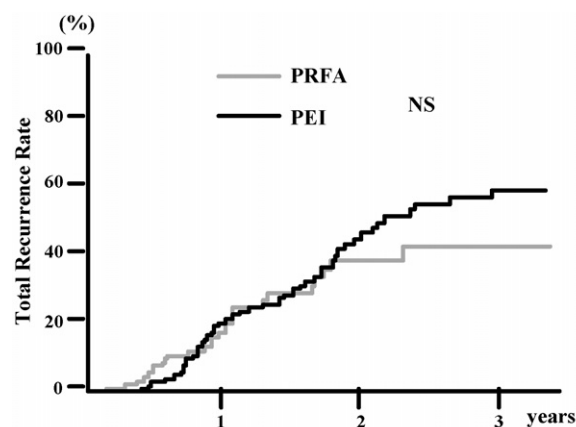


Fig. 1. No significant difference ($P = 0.62$) was found in total recurrence rate within 2 years between the PEI group (47%) and the PRFA group (39%).

less than 5 years was significantly higher than that under a operator with experience of ≥5 years (24% versus 12%, respectively, $P < 0.05$) (Fig. 3). On the other hand, in the PRFA group, the recurrence rate within 2 years under an operator with experience of less than 5 years was not significantly different from that under an operator with experience of ≥5 years (8% versus 8%, respectively, $P = 0.98$) (Fig. 4).

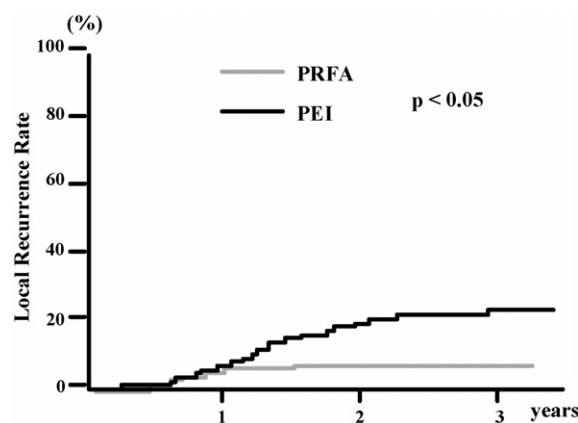


Fig. 2. A significant difference ($P < 0.01$) was found in local recurrence rate within 2 years between the PEI group (22%) and the PRFA group (8%).

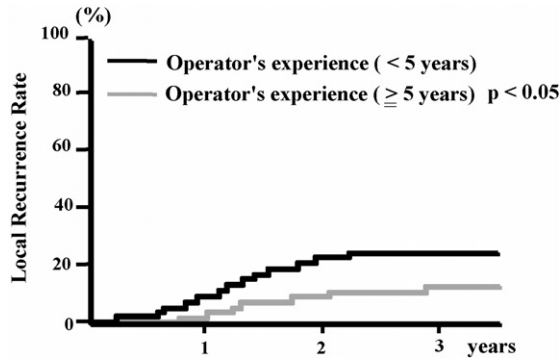


Fig. 3. In the PEI group, the local recurrence rate within 2 years under an operator with experience of <5 years (24%) was significantly higher ($P < 0.05$) than that under an operator with experience of ≥ 5 years (12%).

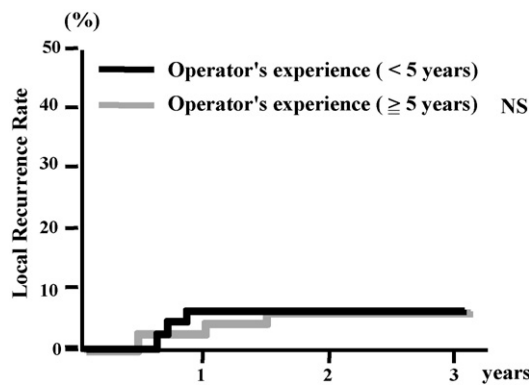


Fig. 4. In the PRFA group, the local recurrence rate within 2 years under an operator with experience of <5 years (8%) demonstrated no significant difference ($P = 0.98$) in comparison with that under an operator with experience of ≥ 5 years (8%).

3.7. Recurrence pattern of HCC in PRFA

Six cases of local recurrence occurred in the PRFA group. In two cases, the primary tumor was localized in the inferior margin of the liver, while in the other four cases the primary tumor was localized close to intrahepatic blood vessels.

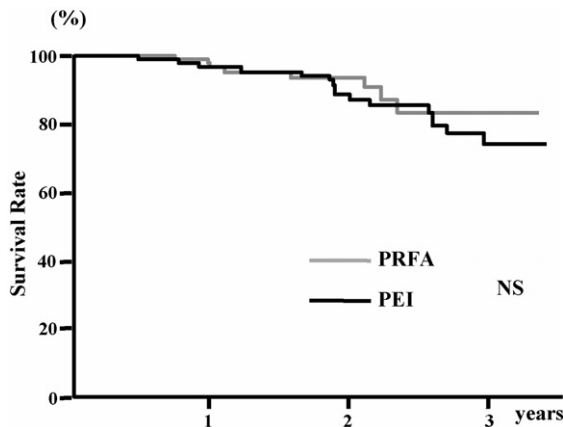


Fig. 5. No significant difference ($P = 0.44$) was found in survival rate within 3 years between the PEI group (78%) and the PRFA group (83%).

3.8. Survival rate for a short term in 3 years

No significant difference was observed in survival rate within 3 years between the PEI group (78%) and the PRFA group (83%) ($P = 0.44$) (Fig. 5).

4. Discussion

We have determined and compared the local and total recurrence rates after PEI, and after PRFA, for the treatment of HCC. To date, there have been only a few reports comparing the recurrence between PEI and PRFA within a same institution. Furthermore, we have determined the recurrence rates with reference to the length of the operating physician's experience.

With regard to the total recurrence rates within 2 years, there was no significant difference between the PEI group and the PRFA group. These recurrence rates within 2 years were similar to other results from PEI and from surgical resection reported elsewhere [23–29]. With regard to local recurrence rates within 2 years, however, the recurrence rate in the PRFA group was significantly lower than that in the PEI group.

In the PRFA group, the local recurrence rate was low, regardless of the length of the operator's experience, while PEI performed by an operator whose experience with percutaneous local therapy was less than 5 years led to a significantly higher local recurrence rate compared to therapy by an operator with longer experience. Because PEI produces a limited necrotic area following a single session, several sessions are necessary for the treatment of larger HCCs which are 2–3 cm in diameter [8]. Since PEI treatment needs several sessions, the operator has to consider the structure of the tumor and whether the tumor has invaded beyond the tumor capsule [30–33]. It thus follows that the operator is required to gain more experience to ensure successful treatment of larger HCC by PEI. On the other hand, PRFA can treat an HCC of up to approximately 3 cm in diameter with a single session, and can treat a tumorous lesion which has progress beyond the capsule. PRFA can achieve coagulated necrosis for an area up to 3 cm in diameter in the tumor region by a single session, while PEI can only treat a more limited area, thereby leading to a decreased rate of local recurrence in the PRFA group. An improvement in the PRFA needle may reach a larger coagulated necrosis area. However, enlargement in the coagulated necrosis area may not always result in decrease in local recurrence, because of the cooling effect due to the abundance of hepatic vessels [34–37].

In this study, six cases among the PRFA group showed local recurrence. In four of these six cases, primary tumors were adjacent to the portal vein or hepatic vein, indicating that the cooling effect may have prevented extension of the necrotic area. In one of the remaining cases, the tumor was difficult to detect by ultrasonography. In the other case, insertion of the RFA needle into the deep region of the tumor was difficult because the tumor was located close to inferior mar-

gin of the liver. When the tumor on the liver surface is adjacent to another organ, PRFA may lead to injury to that organ. In a tumor located near vessels or close to the liver surface, we require some other device such as PRFA in combination with PEI or in combination with an artificial ascites method [38].

As for the benefits of PRFA, we have shown that PRFA required fewer sessions of treatment as well as a shorter period of hospitalization, compared to PEI reported elsewhere [18–21]. In our five patients, the period of hospitalization was prolonged due to severe complications. In the PRFA group, such severe complications were seen in two cases, while in the PEI group, two cases developed hepatic infarction and one case developed a liver abscess. All the patients with severe complications improved following adequate treatment. These incidences of complications in each group were lower than those reported elsewhere [39,40].

In this study, we evaluated consequence of the PEI group and the PRFA group on survival rate in 3 years. We could not clarify the superiority in the PRFA therapy on short term survival. However, Kudo [22] have indicated that an increased rate of local recurrence reflects decreased survival rate.

In this study, we have determined that local recurrence following PRFA was rare compared with that following PEI: with a low recurrence rate in PRFA regardless of the operator's experience. However, this does not mean that PRFA is a simple treatment that can be carried out by anyone without careful planning. It is necessary to be extremely careful to avoid complications, and it is essential to gain experience with regard to the techniques involved in PRFA, in order to ensure the best possible outcome for patients with HCC.

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