Addition of transcatheter arterial chemoembolization decreased local recurrence but had no survival benefit to percutaneous ethanol injection therapy for patients with small hepatocellular carcinoma: A multicenter randomized control study

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Abstract. To assess the efficacy of the additional treatment of transcatheter arterial chemoembolization (TACE) to percutaneous ethanol injection (PEI) therapy for relatively small hepatocellular carcinomas (HCCs), a multicenter randomized control study (RCT) was performed. We conducted an RCT and follow-up study during the enrollment period from 1997 to 1999. Newly diagnosed patients with one to three HCC tumors measuring from 2 to 4 cm (4 cm maximum) in diameter were enrolled. A total of 30 patients initially underwent a combination TACE-PEI or PEI-alone therapies at eight randomly assigned Japanese hospitals. However, 3 patients withdrew. Of the 27 remaining patients, 13 were treated with the combination TACE-PEI therapy and 14 with PEI therapy alone. The patients were observed over several months [median (interquartile range) 33.2 (24.6) months]. There were no significant differences in the background of the patients between the two groups. Among the patients treated with TACE-PEI, the development of a local residual tumor was of significantly lower occurence, compared to the group receiving PEI alone (7.6 and 42.9%, respectively; P=0.024). However, the mean cancer-free time (absence of local or multiple nodule recurrence) or patient survival time was not significantly different between the two groups [PEI alone vs. TACE-PEI: cancer-free time 16.7 (95% CI 7.3-26.0) vs. 22.9 months (95% CI 12.4-33.4); survival time 57.2 (95% CI 37.2-77.2) vs. 42.4 months (95% CI 29.2-55.6)]. Although the combination of TACE and PEI had significant effects on the local tumor control, no efficacy of the addition of TACE to PEI was noted in the prognosis among patients with relatively small HCC tumors.

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Introduction

In Japan, hepatocellular carcinoma (HCC) is a major health concern with an incidence of two million patients infected with hepatitis C virus (HCV) and with 7-8% of patients with liver cirrhosis developing *de novo* HCC every year. Moreover, approximately 35,000 patients with HCC succumbed to the disease in 2009. A total of 70-80% of HCC patients are infected with HCV and approximately 20% with hepatitis B virus (HBV) (1). It is estimated that the number of HCC patients may increase in the next 10 years. Therefore, the establishment of effective treatment modalities for HCC is imperative.

Percutaneous ethanol injection (PEI) therapy is a useful type of therapy for patients with small HCC, particularly for those with poor hepatic functional reserve (2,3). PEI therapy involves the injection of absolute ethanol into HCC using ultrasound guidance, resulting in cellular dehydration, coagulation necrosis and vascular thrombosis within the treated tumor (4). Patient outcome for PEI therapy is comparable to the outcome of patients who undergo surgical resection (5,6). However, the recurrence of primary HCCs after PEI is common, and the rate of local residual recurrence after PEI therapy is reported

to range from 14 to 44% (7-10). Therefore, to control local recurrence, combination therapy with transcatheter arterial chemoembolization (TACE) and PEI has been proposed.

TACE is widely used and is considered to be an effective conservative treatment for HCCs. Embolization of the hepatic artery results in selective ischemic necrosis of the tumor tissue (11). However, complete necrosis of the tumor by embolization of the hepatic artery alone is almost impossible to achieve (12).

A number of clinical studies examined the non-surgical treatment of small HCCs including TACE alone, PEI alone and combined therapy with TACE and PEI (13-18). Certain investigators reported the superior efficacy of combined TACE-PEI therapy, compared to PEI alone. Koda *et al* attempted to clarify the efficacy of combination TACE-PEI therapy in patients with small HCCs (<3 cm) using randomized assignment (19). The results, however, revealed that patient survival was not different between combined TACE-PEI therapy and PEI therapy alone. Stratified analysis showed that for patients bearing HCC tumors <2 cm, combined TACE-PEI therapy was superior to PEI alone. Consequently, the efficacy of additional TACE to PEI as a recommended treatment for HCCs >2 cm has yet to be determined.

Thus, using multicenter randomized assignment, this study was conducted to examine the efficacy of TACE-PEI therapy instead of PEI alone for patients with relatively small HCC tumors, 2-4 cm in diameter.

Patients and methods

Study design. This was a multicenter randomized control (RCT) study. The study protocol was approved by the review board of each hospital, and all patients provided informed written consent.

Patients. Between July 1997 and April 1999, patients diagnosed with small HCCs for the first time were eligible to be enrolled as study subjects. The criteria for enrollment to this study were: i) age <70 years; ii) HCC nodules measuring 2-4 cm in maximum diameter; iii) number of HCC nodules ≤3; iv) no portal thrombosis or extrahepatic metastasis; v) hypervascular nodules, as determined by dynamic computed tomography (CT) scan and/or arteriography; and vi) no previous treatment for HCC prior to entry. Exclusion criteria included any severe comorbidity (such as uncontrolled diabetes mellitus, heart failure, renal failure or other cancer), as well as any patient who was unable to understand the protocol or manage self-care.

The diagnosis of HCC was made by dynamic CT and/or abdominal sonography. To assist the diagnosis of HCC, a needle biopsy was performed in all 27 patients. Tumor vascularity was also evaluated by dynamic CT and/or angiography from the hepatic artery.

Randomization was performed using a sealed-envelope method. Patients were divided into two groups: the TACE-PEI group, in which patients were treated with TACE followed by PEI and the PEI-alone group, in which patients were treated with PEI therapy alone.

Treatment procedure. Patients with HCC were treated by trained specialists at each institution. The precise techniques of ethanol injection are described elsewhere (7). Briefly, after local anesthesia, one 21-gauge needle was inserted into the lesion under ultrasound (US) guidance, and absolute ethanol was injected. In one session, 2-8 ml of ethanol was injected into several sites in and around the lesion according to the lesion size. After the procedure, the patients remained in bed for 3 h. This procedure was performed twice a week. The treatment was repeated until dynamic CT demonstrated entire tumor necrosis.

In addition, TACE [precise techniques are described elsewhere (12,13)] was performed by super-selectively introducing a catheter into the hepatic artery that fed the tumor. A mixture of an ionized oil and doxorubicin hydrochloride (0.6-1.0 mg per kg of body weight) was injected, followed by a gelatin sponge.

Diagnosis of the remaining tumors was based on image findings, particularly dynamic CT. In addition, the positivity of serum α-fetoprotein (AFP >10 ng/ml) or serum protein induced by vitamin K absence II (PIVKA-II >40 mAU/ml) facilitated the diagnosis.

Follow-up. The patients were under regular observation for the detection of recurrence by measurement of tumor markers (AFP and/or PIVKA-II), ultrasonography and/or dynamic CT scans every 3 months. The primary endpoint was a recurrence indicated in any of the above examinations. The secondary endpoint was patient death. The recurrence of HCC was classified as local residual or new nodular recurrence in lesions other than the tumor treated. Local recurrence was defined as tumors within or adjacent to the tumor being treated. The recurrent tumors were treated with PEI or TACE-PEI. In the PEI-alone group, however, TACE was performed when ≥3 recurrent tumors developed.

Statistical analysis. The statistical significance of the patient characteristics between the two groups was determined by the Chi-square or Mann-Whitney U test. The mean cancer-free time and survival time were calculated using the Kaplan-Meier method, and significance was determined by the generalized Wilcoxon's test. $P<0.05$ was considered to be significant.

Results

A total of 30 patients fulfilled the criteria for enrollment in this study. Patients were stratified and randomized into two treatment arms: 16 patients were treated with a combination of TACE and PEI (TACE-PEI group) and 14 received only PEI therapy (PEI-alone group). However, three patients withdrew from the study, and the final number of patients analyzed was 27 (TACE-PEI group, 13; PEI-alone group, 14). Of the 27 patients, 4 had cirrhosis and 23 had chronic hepatitis. Hepatitis B surface antigen was positive in 5 of the 27 patients (18.5%) and the HCV antibody was positive in 20 of the 27 patients (74.1%). No significant differences were noted between the two groups in the baseline characteristics (Table I).

The median (interquartile range) follow-up period was 33.2 (24.6) months [TACE-PEI group, 39.7 (46.7) months and PEI alone group, 33 (42.7) months].

Primary endpoint: Recurrence. Tumor recurrence was detected in 10 patients treated with PEI alone and in 11 patients

Table I. Clinical characteristics according to the treatment group.

	PEI (n=14)	TACE-PEI (n=13)	P-value
Age (years) (mean ± SD)	63.6±6.2	65.8±7.3	NS
Gender (M/F)	7/7	9/4	NS
Etiology of liver disease			
HBV	3	0	
HCV	9	9	
HBV + HCV	1	1	
NBNC	2	3	NS
Chronic hepatitis	13	10	
Cirrhosis	1	3	NS
Albumin (g/dl)	3.5±0.3	3.8±0.4	NS
Total bilirubin (mg/dl)	1.1±0.6	1.2±0.8	NS
ALT (UI/l)	82±50	145±99	NS
AST (UI/l)	65±53	129±65	NS
Prothrombin time (%)	63±3.6	77±15	NS
α-fetoprotein (ng/ml) [median (range)]	13 (4-97)	16 (4-373)	NS
Tumor lesions			
Single nodule	11	8	
2-3 nodules	3	5	NS
Greatest tumor dimension (mm)	26.4±7.4	26.5±6.8	NS

TACE, transcatheter arterial chemoembolization; PEI, percutaneous ethanol injection; M, male; F, female; NS, not significant; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non HBV-non HCV; ALT, alanine aminotransferase and AST, aspartate aminotransferase.

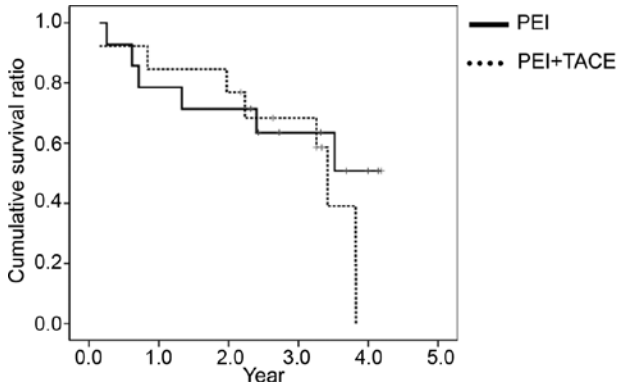

Figure 1. Comparison of the cumulative cancer-free time between the group that received TACE-PEI and the group that received PEI therapy alone. The mean cancer-free time was 16.7 months (95% CI 7.3-26.0) for the PEI-alone group and 22.9 months (95% CI 12.4-33.4) for the TACE-PEI group. No significant difference was noted between the two groups.

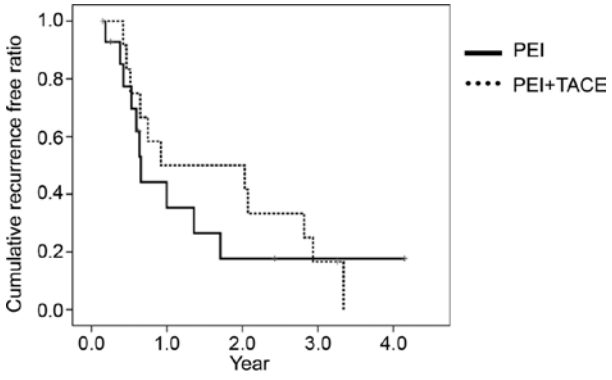

Figure 2. Comparison of the survival rates between the TACE-PEI group and the PEI-alone group. The mean survival time of the TACE-PEI group was 42.4 months (95% CI 29.2-55.6) and that of the PEI-alone group was 57.2 months (95% CI 37.2-77.2). No significant difference was found between the two groups.

treated with TACE-PEI. The cumulative cancer-free time was calculated using the Kaplan-Meier method (Fig. 1). The mean cancer-free time was 16.7 months (95% CI 7.3-26.0) for the PEI alone group and 22.9 months (95% CI 12.4-33.4) for the TACE-PEI group. No significant difference was found between the two groups. However, the pattern of recurrence was significantly different (P<0.05). During follow-up, the detection of a local residual lesion was observed in 1 of 13 nodules (7.6%) in the TACE-PEI group and in 6 of 13 nodules (46.1%) in the PEI-alone group. No local residual tumor was detected after 2 years of follow-up in the TACE-PEI group. On the other hand, new nodular recurrences were observed in 8 of 13 patients (61.5%) in the TACE-PEI group and in 3 of 14 patients (21.4%) in the PEI-alone group.

Secondary endpoint: Death. Of the 13 patients (61.5%), 8 treated with TACE-PEI and 6 of the 14 patients (44%) treated with PEI alone succumbed to the disease during the

follow-up period. In the TACE-PEI group, causes of death included development of HCC in 2 patients, variceral bleeding in 3 patients and hepatic failure in 3 patients. In the PEI-alone group, causes of death were development of HCC in 2 patients, hepatic failure in 3 patients and other diseases (tuberculosis) in 1 patient. The cumulative survival curves of the two groups are shown in Fig. 2. The mean patient survival time of the TACE-PEI group was 42.4 months (95% CI 29.2-55.6) and that of the PEI-alone group was 57.2 months (95% CI 37.2-77.2). No significant difference was noted between the two groups.

Adverse events. In all 30 cases, serious adverse effects or complications, such as acute liver failure, liver infarction, abscess, cholecystitis, gastrointestinal mucosal lesions, pulmonary embolism, variceral bleeding, iatrogenic dissection or perforation of the celiac artery and its branches, were not related to treatment with TACE and/or PEI.

Discussion

This RCT study failed to show the anticipated efficacy of TACE-PET therapy compared to PEI treatment alone on survival time for patients with relatively small HCCs of 2-4 cm in diameter. Together with the previous RCT result by Koda *et al*, it was found that a tumor size smaller than 2 cm may be critical in obtaining significant effectiveness by combining TACE therapy to PEI (19).

The present study showed marked differences in recurrence patterns after initial treatment. Our results indicate that TACE-PEI is superior to PEI therapy alone regarding local tumor control. The addition of TACE, however, evoked new tumors in different lesions other than the original tumor. We believe that the induction of growth factors such as VEGF and HGF (20-23), due to ischemia by TACE, are involved in the development of new nodules. A liver with HCCs larger than 2 cm in diameter may be prone to develop HCCs in whole liver lesions. Stimulation by TACE may enhance the progression of small nodules that are not detected by CT examination. When the stage of HCC is evaluated using more sensitive methods, such as CT during arterial portography and/or superparamagnetic iron oxide-enhanced gradient-recalled echo MRI (24-29), extremely small focal nodules can be detected.

The main causes of patient death in the present study were related to hepatic failure and not to tumor progression in either group. Although it is reported that TACE improves tumor control in large-size HCCs, our data suggest that the prognosis of patients with HCCs of 2-4 cm in diameter depends on residual liver function, and not on tumor progression. No statistical significance was found in the present study which showed that the mean patient survival time was shorter in the TACE-PEI group than that in the PEI-alone group. Therefore, local tumor control may not directly contribute to patient survival time.

A number of limitations should be noted. Although patients were enrolled at different sites, a relatively small number of patients was unable to participate, and the follow-up period was short. All but two tumors were virus-related HCCs. Recently, the incidence of HCC from non-alcoholic steatohepatitis has been on the increase and its characteristics are reportedly different from HCCs resulting from HCV and HBV (30). However, this study used random assignment, providing us with important information regarding the treatment of relatively small-size virus-related HCCs. For HCCs of 2-4 cm in diameter, the additional TACE to PEI did not markedly improve patient survival. Moreover, the additional TACE treatment appeared to shorten the patient survival time as the treatment did not (at least notably) damage residual liver function and stimulated new tumor growth in lesions other than the primary one. Additionally, other modalities, such as radio frequency ablation (RFA), are available. Such treatment modalities are considered to be superior to PEI in local tumor control and attack tumors in a pin-point manner (31-35). Thus, our data suggest that RFA alone as well as PEI may be recommended in the treatment of relatively small HCCs of 2-4 cm in diameter.

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