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Local recurrence is an important prognostic factor of hepatocellular carcinoma

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Abstract

AIM: To clarify the importance of complete treatment by PEIT.

METHODS: A total of 140 previously untreated cases of HCC were enrolled in this study from 1988 to 2002. The inclusion criteria were: a solitary tumor less than 4 cm in diameter or multiple tumors, fewer than four in number and less than 3 cm in diameter, without extrahepatic metastasis or vessel invasion. As general principles for the treatment of HCC, the patients underwent transcatheter arterial chemoembolization (TACE) prior to PEIT. After the initial treatment of the patients, ultrasonography and computed tomography were performed, and measurement of serum levels of α-fetoprotein (AFP) was determined. When tumor recurrences were detected, PEIT and/or TACE were repeated whenever the hepatic functional reserve of the patient permitted. We then analyzed the variables that could influence prognosis, including tumor size and number, the serum levels of AFP, the parameters of hepatic function (albumin, bilirubin, ALT, hepaplastin test, platelet number, and indocyanine green retention at 15 min [ICG-R15]), combined therapy with TACE, distant recurrence, and local recurrence.

RESULTS: Univariate analysis identified the ICG test, serum levels of AFP and albumin, tumor size and number, and local recurrence, but not distant recurrence, as significant prognostic variables. In multivariate analysis using those five parameters, the ICG test, tumor size, tumor number, and local recurrence were identified as significant prognostic factors. In both univariate and multivariate analyses, the relative risk for the ICG test was the highest, followed by local recurrence.

CONCLUSION: We found that local recurrence is an independent prognostic factor of HCC, indicating that achieving complete treatment for HCC on first treatment is important for improving the prognosis of patients with HCC.

Key words: Hepatocellular carcinoma; Local recurrence; Percutaneous ethanol injection therapy; Transcatheter arterial chemoembolization

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a highly malignant tumor with a high morbidity and mortality rate, carrying a poor prognosis[1]. Improvement of imaging techniques has enabled the diagnosis of HCC at an early stage, making it possible to treat tumors locally. The first local treatment for HCC consisted of percutaneous ethanol injection therapy (PEIT), which was reported by Livraghi *et al*., in 1986[2]. Although PEIT has been limited to small-sized HCC and liver resection remains a good treatment for HCC[3], the long-term prognosis due to recurrence or survival after treatment is close to that for hepatic resection[4-6]. Furthermore, PEIT can be used for HCC patients with reduced hepatic functional reserve attributable to pre-existing liver cirrhosis[7]. In 1996, however, Ishii *et al*., pointed out that a significant number of patients experienced local recurrence after PEIT[8]. This local recurrence is caused predominantly by intra-tumor septa, which may inhibit the infiltration of the injected ethanol into the entire tumor.

When the technique of percutaneous microwave coagulation therapy (PMCT) was established, it was expected that the rate of local recurrence would decrease because thermal coagulation should be achieved regardless of intra-tumor septa[9]. Contrary to that expectation, however, the effect of PMCT was limited to tumors of 15 mm or less in diameter. Radio frequency ablation (RFA) was later developed, which can achieve thermal necrosis throughout a mass of 35 mm in diameter[10,11]. Although the development of techniques for local treatment of HCC was aimed at decreasing the rate of local recurrence, it has remained unclear whether local recurrence does indeed worsen the prognosis

of patients with HCC[12], and whether an additional treatment for local recurrence can overcome the failure of initial treatment. Several studies have attempted to identify the significant prognostic factors for HCC[13-17]; however, to our knowledge, none of those studies considered local recurrence as a prognostic factor[18,19].

In this study, we aimed to clarify how local recurrence after initial treatment influences the prognosis of HCC patients. If the survival rate of patients with local recurrence is the same as that of those without local recurrence, the advantage of PMCT or RFA over PEIT would be diminished greatly, since PMCT and RFA were developed to reduce local recurrence.

MATERIALS AND METHODS

Patients

The inclusion criteria were as follows: (1) the patients not diagnosed with HCC previously; (2) a solitary HCC less than 4 cm in diameter, or fewer than four tumors with diameter less than 3 cm; and (3) patients without extrahepatic metastasis or vessel invasion. Of the 452 consecutive patients who were diagnosed with HCC in Kyushu University Hospital between January 1988 and December 2002, a series of 140 consecutive HCC patients meeting the inclusion criteria were enrolled. The enrolled patients included 95 males and 45 females, ranging in age from 35 to 83 years (mean 63.2 years, Table 1). Computed tomography (CT) and ultrasonography (US) were performed on all of the patients. To confirm the findings obtained by CT and US, angiography was also performed on patients, who gave consent for angiography examination. The diagnosis of HCC was finally confirmed histologically by aspiration tumor biopsy using a 21 G needle prior to the PEIT procedure.

Table 1 Characteristics of 140 patients at base line (means±SD)

		(Range)
Age (yr)	63.3±8.54	(35-83)
Male/female	95/45	
Child (A/B/C)	77/48/15	
Albumin (g/dL)	3.56±0.43	(2.5-4.5)
Bilirubin (mg/dL)	1.19±0.99	(0.4-10.3)
Platelet (10^4/L)	9.74±6.0	(0.8-69.9)
ALT (U/L)	84.58±47.04	(14-266)
HPT (%)	60.98±17.14	(25-116)
ICG-R15 (%)	28.13±15.29	(3.5-76.5)
AFP (ng/mL)	155.37±565.3	(2-5 653)
Tumor size (mm)	20.51±8.26	
Tumor number	1.51±0.79	

In accordance with general principles for the treatment of HCC, the patients underwent transcatheter arterial chemoembolization (TACE) prior to local treatment to enhance the effects of PEIT. In total, TACE was carried out on 81 patients 7 to 14 d before local treatment. With a therapeutic goal of complete necrosis of HCC, PEIT was carried out on all tumors for each patient. Ethanol (4-8 mL) was injected into each tumor during one session of PEIT. The total number of PEIT sessions was decided based on achieving a total amount of injected ethanol for each HCC that was more than two times the mass volume and all tumors consequently received more than two sessions of PEIT. CT was performed to evaluate treatment after finishing all sessions of PEIT. Successful treatment with PEIT was confirmed by CT and demonstrated that the tumor was completely covered by at least a 5 mm region (i.e., the ethanol-injected region) that was non-enhanced with contrast medium. When evidence of treatment success was not obtained, additional PEIT was performed until success was achieved, as assessed by CT. Major complications, such as intraperitoneal bleeding, hemobilia or liver abscesses were not observed in any case after PEIT.

After the initial treatment of the patients, US and measurement of serum α-fetoprotein (AFP) levels were carried out on an outpatient basis. The patients were also observed regularly by CT at 1, 3, 6, and 12 mo after the initial treatment, and every 6 mo after the first year of the treatment. Whenever changes were observed on US or CT imaging, or in the serum AFP levels, CT and/or angiography were carried out to confirm the recurrence, which was verified by enhanced uptake of contrast medium. Among the cases of recurrence, we defined "local recurrence" as those cases in which tumors occurred within or in contact with the treated lesion as determined by CT findings (Tables 2 and 3). The number and size (diameter) of locally and/or distantly recurrent tumors were also determined by CT examination (Table 3). Where recurrences were detected, PEIT and/or TACE were repeated whenever the hepatic functional reserve of the patient permitted. Among the local recurrence group, four patients suffered rapid and diffuse tumor growth involving the portal and hepatic veins. Two of them had been treated only with PEIT and the other two patients had undergone both PEIT and TACE at first treatment. In the local recurrence-free group, on the other hand, venous invasion was not seen. Although PEIT and/or TACE were available for all patients in the local recurrence-free group, four patients in the local recurrence group could not be given further treatment because of their decreased hepatic functional reserve.

Table 2 Comparison of clinical backgrounds between local recurrence group and local recurrence-free group

	Local recurrence	
	(+)	(-)
n	44	96
Albumin (g/dL)	3.47±0.49	3.60±0.40
Bilirubin (mg/dL)	1.15±0.53	1.20±1.15
Platelets (10^4/L)	10.01±9.89	9.62±4.37
ALT (U/L)	85.16±41.76	84.31±49.50
HPT (%)	62.28±18.64	60.35±16.44
ICG-R15 (%)	29.04±15.23	27.72±15.39
AFP (ng/mL)	153.83±539.31	63.24±118.58
Tumor size (mm)	24.00±9.48	18.92±7.15[d]
Tumor number	1.77±0.94	1.39±0.69[b]
TACE prior to PEIT	22 (50%)	59 (61%)

[b]$P<0.01$ *vs* local recurrence (+); [d]$P<0.001$ *vs* local recurrence (+).

The variables that could influence the prognosis were compared between the local recurrence group and the local

Table 3 Comparison of features of recurrence after initial treatment for HCC between local recurrence group and local recurrence-free group

	Local recurrence	
	(+)	(-)
Recurrent tumor number	3.6±0.6[1]	2.3±1.9[d]
Recurrent tumor size	33.0±22.0[2]	19.4±8.8[d]
Recurrence-free period	325.6±216.8	710.5±813.3[b]
Treatment for recurrence		
PEIT (+/-)	25/16	65/16
TACE (+/-)	21/20	24/57

[1]Including both local and distant recurred tumors; [2]calculated from the size of locally recurred tumors; [b]$P<0.01$ *vs* local recurrence (+), [d]$P<0.001$ *vs* local recurrence (+).

recurrence-free group; these included tumor size and number, serum AFP levels, the parameters of hepatic function (albumin, bilirubin, ALT, hepaplastin test, platelet number, and ICG-R15), and combination with TACE.

Statistical analysis

Baseline data were presented as mean±SD for quantitative variables. Differences in baseline characteristics between the local recurrence group and local recurrence-free group were analyzed using the Wilcoxon rank sum test and the Fisher's exact test for qualitative variables.

The prognostic values of baseline characteristics, local and distant recurrence after initial treatment were assessed using the univariate and multivariate Cox proportional hazards regression models. Variables that met the selected cut-off value ($P<0.05$) in the univariate comparison were entered into the multivariate analysis. Both univariate and multivariate results were presented as relative risks with corresponding 95%CIs and *P* values from the Wald test. All significant tests were two-sided and differences with a $P<0.05$ were considered statistically significant.

RESULTS

Among the 140 patients enrolled, 44 (31.4%) suffered from local recurrence. Of the remaining 96 patients, non-local recurrence was found in 80, and only 16 patients (11.4%) remained free of recurrence throughout the period of observation.

For comparison of baseline characteristics, we divided the patients with recurrence into two groups, the local recurrence group and local recurrence-free group. There was no significant difference between these two groups with respect to the hepatic functional reserve (Table 2). The proportion of patients in the local recurrence group who underwent TACE was higher than that in the local recurrence-free group (50% *vs* 39%), but the difference was not significant. On the other hand, the differences in tumor size and numbers were significant between these two groups (Table 2). The local recurrence group had significantly larger average tumor size and greater tumor numbers compared to the local recurrence-free group (tumor size: 24.00±9.48 mm *vs* 18.92±7.15 mm, $P<0.001$; tumor number 1.77±0.94 *vs* 1.3±0.69, $P<0.01$). Combination with TACE did not affect the rate of local recurrence.

We then compared the features of recurrence after initial treatment between these two groups. At the time of recurrence, the tumor number in the local recurrence group was 3.6±0.6 and the largest tumor size among them was 33.0±22.0 mm in diameter, whereas the tumor number in the local recurrence-free group was 2.3±1.9 and the largest size was 19.4±8.8 mm in diameter (both $P<0.001$, Table 3). All cases of the local recurrence group ($n = 44$) showed

Table 4 Univariate analysis of prognostic factors for HCC

Variables		*n*	*P*	Exp	95%CI
Albumin (g/dL)	>3.5	74	0.0455	1.694	1.011-2.841
	≤3.5	60			
Bilirubin (mg/dL)	<1.0	62	0.4059	1.246	0.742-2.091
	≥1.0	70			
Platelet (10^4/L)	>8.0	79	0.8301	1.057	0.637-1.753
	≤8.0	60			
ALT (U/L)	<75	65	0.2317	1.373	0.817-2.310
	≥75	74			
HPT (%)	>55	76	0.1665	0.688	0.406-1.168
	≤55	59			
ICG-R15 (%)	<30	67	0.0003	2.905	1.637-5.156
	≥30	45			
AFP (ng/mL)	<30	59	0.0269	1.879	1.075-3.287
	≥30	56			
Tumor size (mm)	<20	73	0.0174	1.882	1.117-3.170
	≥20	67			
Tumor number	1	91	0.0170	1.863	1.117-3.106
	≥2	49			
Local recurrence	(+)	45	0.0003	2.579	1.540-4.317
	(-)	95			
Distant recurrence	(+)	111	0.2250	1.630	0.740-3.951
	(-)	29			
TACE	(+)	81	0.5885	1.156	0.683-1.958
	(-)	59			

solitary local recurrence, but 31 cases also showed distant recurrence, in addition to local recurrence, when the recurrence was confirmed. In all cases of local recurrence combined with distant recurrence, the tumor size of local recurrence was larger than that of distant recurrence. Therefore, the recurrent tumor size (33.0±22.0 mm) in the local recurrence group was derived from the locally recurrent tumor (Table 3). The period from the initial treatment to the detection of recurrence (recurrence-free period) was 325.6±216.8 d in the local recurrence group, which was significantly shorter than that in the local recurrence-free group (710.5±813.3 d, $P<0.01$, Table 3). There was no significant difference between the two groups in the method of treatment after recurrence (Table 3).

Using univariate analysis, we identified the ICG test, serum levels of AFP and albumin, tumor size and number, and local recurrence, but not distant recurrence, as significant prognostic variables (Table 4). Additionally, in multivariate analysis using those five parameters, the ICG test, tumor size and number, and local recurrence were identified as significant prognostic factors (Table 5). In both univariate and multivariate analyses, the relative risk for the ICG test was the highest, followed by local recurrence.

Table 5 Multivariate analysis of prognostic factors for HCC

Variables	*P*	Exp	95%CI
Albumin	0.2424	1.490	0.764-2.906
ICG-R15 (%)	0.0074	2.498	1.278-4.882
AFP (ng/mL)	0.1816	1.557	0.813-2.983
Tumor size (mm)	0.0124	2.267	1.193-4.308
Tumor number	0.0469	1.845	1.008-3.375
Local recurrence	0.0081	2.362	1.250-4.462

DISCUSSION

Multivariate analysis showed that the ICG test, tumor size, tumor number, and local recurrence after initial treatment were significant prognostic factors. Those factors could be classified into three categories: the hepatic functional reserve, the progression of HCC, and local recurrence. In this study, "local recurrence" was defined as those cases in which tumor (s) occurred within or in contact with the treated lesion as detected by CT. It is impossible to determine whether local recurrence was attributable to residual HCC that had not been detected after initial evaluation or to newly developed HCC. We believe that local recurrence reflected failure (residual HCC) not recognized initially after treatment, since it seemed to be rare to newly develop within or in contact with the treated lesion, and because the recurrence-free period in the local recurrence group was significantly shorter compared to the local recurrence-free group. In earlier reports investigating the prognostic factors of HCC, tumor size and hepatic functional reserve were commonly identified as significant factors[15-19]. Those results, however, depended on the hypothesis that the treatment for HCC was performed completely. On the other hand, it has been reported repeatedly that a significant number of patients experience local recurrence after non-surgical treatment, which indicates that it cannot be expected that all treatments are performed completely. Therefore, multivariate analysis of HCC prognosis should be performed, and it should include factors relating to the completeness of the treatment, which is directly referable to local recurrence. Local treatments, including PEIT, require technical skill in both US and puncture, and it is well known that considerable variation in the PEIT technique occurs among different surgeons. In our univariate and multivariate analyses, the relative risk of local recurrence was the greatest, next to the ICG-R15 value, indicating that cautious PEIT technique is required when treating new cases of HCC.

In the treatment of HCC using PEIT, there are three difficulties that prevent the achievement of complete tumor necrosis. The first is the existence of septa in the tumor which partitions it into several closed spaces. The existence of septa is very common when the diameter of the tumor is larger than 20 mm. When a tumor has septa, injected ethanol is not able to spread across the tumor and it is necessary to repeat the puncture, aiming at each separate partition[20,21]. Such a tedious procedure would risk that viable HCC cells may remain. The second problem relates to the location of the tumor. Because PEIT is performed under the guidance of US, it is sometimes difficult to image tumors located close to the diaphragm. Poor imaging of the tumor leads inevitably to insufficient injection of ethanol. Tumors on the surface of the liver also are difficult to puncture because a direct puncture of the projecting area should be avoided to prevent bleeding from the needle track. Furthermore, the tumors located near the portal vein or gall bladder are not easy to be treated completely without the possibility of viable HCC cells remaining. In such situations, surgeons tend to hesitate to inject a sufficient volume of ethanol (more than twice the mass volume)[22,23], fearing the possibility of causing inflammation in the wall of the intrahepatic vessel or gall bladder. The third problem is that the injected ethanol does not always spread fully into the target space. When the tumor includes a relatively large vein, injected ethanol leaks out through the vessels before it can infiltrate the tumor. Taking into account the aforementioned difficulties, multiple sessions are required to decrease the local recurrence after PEIT.

When we compared the local recurrence group and the local recurrence-free group, the latter had smaller diameter and fewer numbers of tumors; whereas there were no significant differences in the variables indicating their hepatic functional reserve (Table 2). Considering the difficulties in the PEIT procedure mentioned above, our results are clinically acceptable. As the number of tumors increases, the probability of tumor occurrence in the areas difficult to puncture also increases. Similarly, larger HCCs contain more septa and are more likely to involve vessels as compared with smaller HCCs. Furthermore, as the number of tumors to be treated increases, it becomes more difficult for the surgeon to maintain concentration.

There are several possible explanations for the poor prognosis of patients with local recurrence. The first possible explanation is that the residual part of the tumor might change to a poor differentiation after treatment. It is well known that there are cases in which rapid sarcomatous change

developed from residual HCC after TACE[24]. Recently, similar results also have been reported after RFA[12,25]. These phenomena are considered to be the result of the hypoxemia caused by TACE. HCC cells basically require a rich blood supply. Therefore, artificial hypoxic pressure could result in undifferentiation of malignant cells. In our study, it should be emphasized that the recurrences in the local recurrence group were more likely to be multiple and emerged more rapidly than that in the local recurrence-free group, indicating that the character of the residual tumor cells had changed to a more malignant one. On the other hand, it is well known that locally recurrent HCC often occurs with an extrahepatic arterial supply. Such vessel reconstruction is observed after treatments that could damage the original feeding artery. In short, all TACE, PEIT, PMCT and RFA procedures could be a cause of revascularization. Once the residual tumor is supplied by blood flowing from the extrahepatic artery, it is very difficult to perform complete treatment following chemoembolization.

Combined TACE and PEI is a therapeutic option that has been proposed to overcome the weakness of each of the two procedures in the treatment of HCC[21,26-30]. The rationale for a combination of these two treatments relies on the fact that tumor consistency is markedly decreased and intratumoral septa are usually disrupted after TACE. Consequently, these changes make subsequent treatment with PEIT easier, as they provide enhanced ethanol diffusion within the tumor and higher doses of ethanol than those used in conventional PEIT. In our general principles for the treatment of HCC, the patients underwent TACE prior to local treatment to enhance the effects of PEIT, however, combining with TACE did not affect the rate of local recurrence or the prognosis in our study. Koda *et al*.[21], reported that in patients with HCC less than 2 cm in diameter, combination with TACE showed lesser rate of local and distant recurrence and better prognosis than PETI alone. Further study will be needed including more number of cases and/or longer observation.

In conclusion, we showed that, in addition to factors such as the hepatic functional reserve and tumor size, it is important to achieve complete necrosis upon initial treatment in order to improve the prognosis of HCC patients. This result warrants the surgeons to be more cautious when performing the first treatment. New RFA devices that cover a greater volume might contribute to this goal, and further study of local recurrence after RFA is critical for improving the local treatment of HCC.

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