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RAPID COMMUNICATION

Prognosis following transcatheter arterial embolization for 121 patients with unresectable hepatocellular carcinoma with or without a history of treatment

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Abstract

AIM: To retrospectively evaluate the prognosis of patients with hepatocellular carcinoma (HCC) with or without a history of therapy for HCC following transcatheter arterial embolization (TAE).

METHODS: One hundred and twenty-one patients with HCC treated with TAE from 1992 to 2004 in our hospital were enrolled in this study. Eighty-four patients had a history of treatment for HCC, while 37 did not. At the time of entry, patients with extra-hepatic metastasis, portal vein tumor thrombosis, or Child-Pugh class C were excluded. TAE was repeated when recurrence of HCC was diagnosed by elevated tumor markers, or ultrasonography or dynamic computed tomography findings.

RESULTS: Tumor size was larger and the number of tumors was fewer in patients without past treatment ($P < 0.01$). However, there were no differences in tumor node metastasis (TNM) stage or survival rate between the 2 groups. A bilobular tumor and high level of α-fetoprotein (AFP) (>100 ng/mL) were factors related to a poor prognosis in patients with a history of HCC.

CONCLUSION: The prognosis following TAE is similar between HCC patients with and without past treatment. Early diagnosis of HCC or recurrent HCC and obtaining good local control against HCC before entry to a repeated TAE course can improve prognosis.

Key words: Unresectable hepatocellular carcinoma; Prognosis; Repeated transcatheter arterial embolization

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INTRODUCTION

Liver transplantation is recognized as an effective therapy for hepatocellular carcinoma (HCC)[1]. However, a shortage of donors in Japan has led to the general use of transcatheter arterial embolization and transcatheter arterial chemoembolization (TAE) in patients with unresectable HCC without an indication of surgery and percutaneous therapy. Although disappointing results are published[2-4], the usefulness of TAE has been reconfirmed recently as some studies found that the procedure reduces the overall 2-year mortality rate and improves the survival rate of patients with unresectable HCC[5-8]. Past reports regarding the prognosis of patients with HCC are usually limited to the initial therapy, including surgery[9], percutaneous ethanol injection therapy (PEIT)[10], radiofrequency ablation (RFA)[11,12], and TAE. In previous studies of TAE, the subjects had no history of treatment for HCC. However, most patients with HCC have no indication for therapy such as surgery, PEIT and RFA due to multiple recurrences finally. No reports have evaluated prognosis and its related factors of patients with a history of HCC following a repeated TAE course. In the present study, we retrospectively evaluated the prognosis of HCC patients with or without a history of therapy for HCC following TAE.

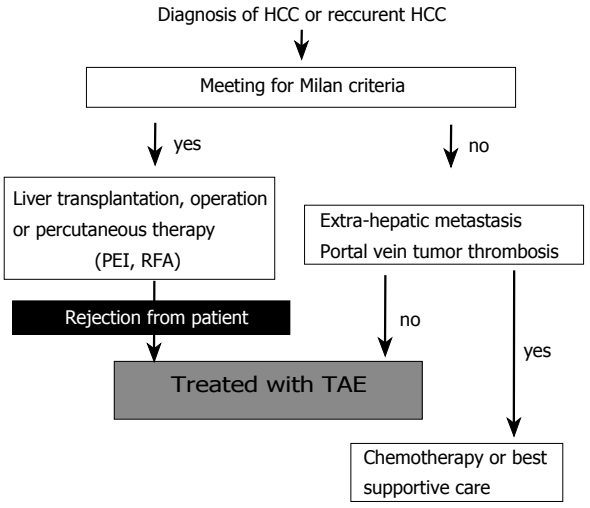

Figure 1 Strategy for treatment of HCC employed at our institution. Nearly all patients with HCC, which were outside of the Milan criteria, were recommended for a repeated TAE course.

MATERIALS AND METHODS

This was a single-center retrospective study conducted at Ehime University Hospital. One hundred and twenty-one patients with advanced HCC treated with TAE from 1992 to 2004 were enrolled in the study. After informed consent was obtained, the entry date was considered the day of the first TAE therapy after enrollment. The diagnosis of HCC was based on histological and cytologic findings or findings of dynamic computed tomography (CT). Tumor stage was established by dynamic CT, ultrasonography (US), angiography, chest CT, and bone scintigraphy examinations.

Patients with extra-hepatic metastasis, portal vein tumor thrombosis (PVTT), or Child-Pugh class C at entry were excluded from this study since the existence of PVTT and a high Child-Pugh score are poor prognostic markers and TAE can not improve these patients[5]. As a result, 37 patients with no history of treatment for HCC and 84 with such a history of surgery, PEIT, or RFA, were studied. During the 13-year study period, a total of 121 patients underwent 435 courses of TAE, with 99 (82%) outside of the Milan criteria[1]. In 37% of 121 patients, HCC was confirmed by histological examination. Others were diagnosed based on the increasing course of α-fetoprotein (AFP) and dynamic CT. All HCC nodules treated with TAE were hypervascular.

The patients treated with TAE were evaluated based on our strategy (Figure 1). TAE was repeated when HCC recurrence was diagnosed by the elevation of tumor markers, or US or dynamic CT examination findings. Experienced radiologists performed all the TAE procedures. A microcatheter was inserted into the artery feeding the tumor super-selectively after conventional hepatic angiography or angiography CT, and then a segmental or subsegmental TAE procedure[13] was performed. Before the procedure, antegrade flow in the portal vein and no obstruction of the main trunk of the portal vein were confirmed by US, dynamic CT, and portography findings via the superior mesenteric artery. Lipiodol and a gelatin sponge (Gelfoam, Upjohn, Kalamazoo, MI, USA) were used for embolization, and epirubicin hydrochloride was used together with Lipiodol in 25% of the cases. The goal of embolization was disappearance of tumor staining without complete obstruction of the hepatic artery. Patients that underwent additional chemotherapy via a subcutaneously implanted injection port, surgery, PEIT, or RFA for the purpose of reducing the size of the tumor after undergoing TAE were excluded from this study.

Table 1 Backgrounds of patients without or with history of treatment

	Patients without history of HCC ($n=37$)	Patients with history of HCC ($n=84$)	P value
Age (yr)	66.4 ± 9.9	67.0 ± 8.1	NS
Sex (male ： female)	32 ： 5	64 ： 20	NS
Frequency of positive for anti-HCV	72%	81%	NS
TNM stage (II ： III)	12 ： 25	35 ： 49	NS
Tumor size (mm)	46.4 ± 23.5	27.7 ± 16.1	$P<0.01$
Number of tumors (≤3 ： >3)	21 ： 16	23 ： 61	$P<0.01$
Monolobular ： bilobular	17 ： 20	27 ： 57	NS
Child-Pugh class (A ： B)	27 ： 10	48 ： 36	NS
Alanine transferase (IU/L)	63.8 ± 45.1	82.1 ± 64.3	$P=0.07$
AFP (≤100 ： >100 ng/mL)	23 ： 14	53 ： 31	NS
TAE with or without anti-cancer medication	13 ： 24	17 ： 67	NS
Average number of past treatments	-	2.9 ± 2.2	-
History of hepatectomy	-	18%	-
Average observation period (d)	557.6 ± 377.0	493.6 ± 390.6	NS

Anti-HCV: hepatitis C virus antibody; AFP: α-fetoprotein; TNM stage: tumor node metastasis stage.

The backgrounds of both groups at study entry are shown in Table 1. The group of patients without past treatment consisted of 32 males and 5 females, of whom 12 and 25 patients were in tumor node metastasis (TNM) stage[14,15] II and III, respectively. Furthermore, 27 were Child-Pugh class A and 10 were class B, of whom 72% were positive for the hepatitis C virus antibody (anti-HCV) and 14% for the hepatitis B surface antigen (HBs Ag).

As for the group of patients with treatment history, 64 were male and 20 female, of whom 35 and 49 were TNM stages II and III, respectively. Forty-eight patients in this group were Child-Pugh class A and 36 class B, of whom 81% were positive for anti-HCV and 16% for HBs Ag.

Determination of markers of hepatitis viruses

The presence of anti-HCV and HBs Ag was determined precisely using enzyme immunoassay kits (Imcheck-FHCV, Kokusai-Shiyaku, Kobe, Japan; AxSYM HBs Ag, Dainabot, Tokyo, Japan), according to the manufacturer's instructions.

Statistical analysis

All statistical analyses were carried out using a personal computer with StatView version 5.0 (SAS Institute, Inc., Berkeley, CA, USA). Analyses were conducted using Student's t-test, Mann-Whitney U test, Cox's proportional hazards regression model, logrank test, and the Kaplan-Meier method. $P < 0.05$ was considered statistically significant.

Table 2 Univariate analysis of patients with past treatment for HCC ($n=84$)

Factors	Number	Hazard ratio	95% CI	*P* value
Age (= and <65 ： >65)	38：46	0.99	0.95-1.02	NS
Sex (male ： female)	64：20	1.02	0.54-1.93	NS
Anti-HCV (positive ： negative)	67：17	1.31	0.64-2.67	NS
TNM stage (II ： III)	35：49	1.57	0.83-3.00	NS
Tumor size (mm)	-	1	0.98-1.02	NS
Number of tumors (≤3 ： >3)	23：61	0.88	0.47-1.67	NS
Monolobular : bilobular	27：57	2	1.04-3.86	$P<0.05$
Child-Pugh class (A ： B)	48：36	1.07	0.59-1.95	NS
AFP (≤100 ： >100 ng/mL)	53：31	1.9	1.03-3.48	$P<0.05$
History of hepatectomy (negative ： positive)	69：15	1.63	0.72-3.70	NS
Number of past treatments	-	1.05	0.93-1.19	NS

CI: confidence interval; anti-HCV: hepatitis C virus antibody; AFP: α-fetoprotein; TNM stage: tumor node metastasis stage.

Table 3 Multivariate analysis of patients with past treatment for HCC ($n=84$)

Factors	Hazard ratio	95% CI	*P* value
Existence of bilobular tumors	2.37	1.19-4.71	$P<0.05$
AFP (>100 ng/mL)	2.24	1.19-4.23	$P<0.05$

CI: confidence interval; AFP: α-fetoprotein.

RESULTS

There were no significant differences in the background findings between patients with or without past treatments for HCC, except for tumor size and the number of tumors ($P<0.01$) (Table 1). There was also no significant difference in patient distribution for TNM staging between the groups. None of the patients died due to the TAE procedure. For patients with treatment history, the average number of past treatments for HCC was 2.9±2.2 (range 1-10) and a hepatectomy was performed before entry to the repeated TAE course in 18% of these patients.

The survival rate was not significantly different between the 2 groups (Figure 2). The 1-, 2-, and 3-year survival rates were 90%, 57%, and 20% respectively in patients without past treatment, and 75%, 43%, and 25% respectively in those with past treatment. The factors related to poor prognosis in the 84 patients with past treatment for HCC were evaluated. Seventy-four of them (88%) were outside of the Milan criteria. According to univariate analysis, variables significantly associated with survival were tumor location (bilobular) and a high concentration of AFP (>100 ng/mL) ($P<0.05$). There were no relationships between the prognosis of patients with a history of treatment for HCC and other factors, including history of past hepatectomy and the number of past treatments for HCC (Table 2). Multivariate analysis showed that the existence of bilobular HCC and high concentrations of AFP (>100 ng/mL) were the factors for poor prognosis ($P<0.05$, Table 3). The survival rate of patients without both risk factors was better than that of those with both risk factors ($P<0.01$, Figure 3). In all 121 patients, the existence of bilobular HCC was related to poor prognosis ($P<0.01$), while a high concentration of AFP ($P=0.059$) and other factors including past treatments, were not related to poor prognosis.

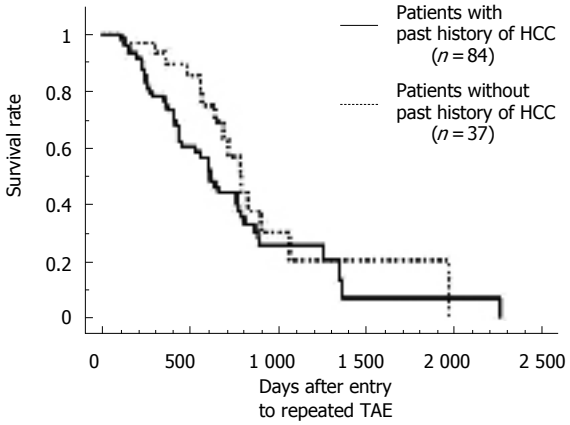

Figure 2 Survival rates of HCC patients with or without past treatment for HCC. There was no significant difference between the 2 groups. Survival rates after 1, 2, and 3 years were 90%, 57%, and 20% respectively for patients without past treatment, and 75%, 43%, and 25% respectively for patients with past treatment.

DISCUSSION

The prognosis of a patient with HCC is dependent on the hepatic reserve function and HCC staging[16,17]. A repeated TAE course is widely used for patients with unresectable HCC[18,19], though it was reported that TAE is not effective for improving the prognosis of such patients[2,3,4]. The reason for the disappointing results is that TAE is repeated within a fixed period of time although the liver reserves function and the patients have or have no recurrence of HCC. When TAE is repeated after a fixed period of time, embolization from the main trunk of the hepatic artery can lead to liver atrophy and deterioration of hepatic reserve function. Recently, the efficacy of TAE for patients with HCC has been reported, with good improvement of survival results[5-8]. Caturelli *et al*[20] reported that repeated TAE does not induce long-term deterioration of hepatic reserve function in HCC patients with Child-Pugh A and B but without PVTT.

Since repeated TAE for a fixed period without recurrence can lead to a reduction in hepatic reserve function, we think that it is important to perform TAE at the time

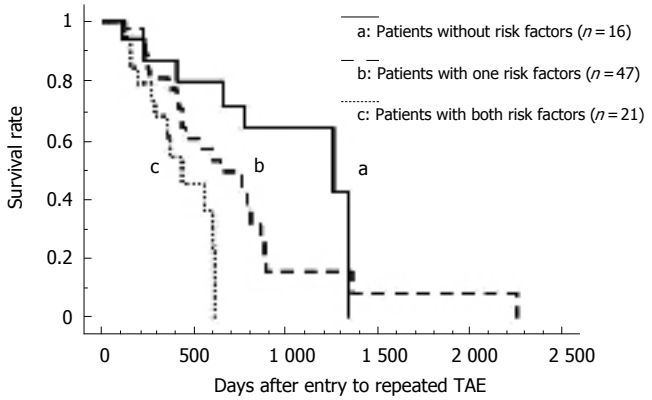

Figure 3 Survival rates of HCC patients with past treatment and with or without the 2 risk factors found in the present study. Significant differences were shown between "**a**" and "**b**" and between "**b**" and "**c**" ($P<0.01$ and $P=0.01$), while there were no significant differences between "**a**" and "**b**" ($P=0.08$). **a**: Patients without either factor [existence of bilobular tumors and high concentration of AFP (greater than 100 ng/mL; $n=16$)]; **b**: Patients with one of the factors ($n=47$); **c**: Patients with both factors ($n=21$).

when HCC recurrence is diagnosed by the elevation of tumor markers, or based on US or dynamic CT findings [21,22]. Recently, diagnostic progress of US and CT has made it easier to accurately diagnose new and recurrent HCC with low levels of AFP. Dynamic CT can offer detailed information about tumor vascularity and dynamic CT is useful to distinguish cholangiocarcinoma from HCC[23,24]. In our study metastatic liver tumor was denied from clinical course in all cases. In a large number of patients, HCC develops to an unresectable condition during the course of therapy and becomes outside of the Milan criteria. To our knowledge, the prognosis of patients with a history of HCC and factors for poor prognosis have not been reported after a repeated TAE course. In the present study, though the tumor maximum size and the number of tumors were different between the patients with or without past treatment, the survival rates of both groups after undergoing TAE did not show a significant difference, which might be due to no significant difference in TNM staging distribution between the groups.

As for the patients with past treatment, a past hepatectomy and the number of past percutaneous therapies (e.g. PEIT and RFA) did not influence the prognosis after repeated TAE in regard to maintaining liver reserve function. A high concentration of AFP and tumor location (bilobular) each had a significant influence. The elevation of AFP and existence of bilobular HCC are dependent on the malignant potential of HCC [25] and intra-hepatic metastasis, respectively.

Prognosis was not significantly different between HCC patients with or without a history of HCC following TAE. Our results show that diagnosis of HCC or recurrent HCC in the early stage and obtaining good local control against HCC before a repeated TAE course can reduce the time bias and improve prognosis.

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