

## **Evaluation of Transcatheter Arterial Chemoembolization for Unresectable Hepatocellular Carcinoma**

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### SUMMARY

The long-term results of transcatheter arterial chemoembolization (LP-TAE) for unresectable hepatocellular carcinoma (HCC) were evaluated in comparison with that of transcatheter arterial chemoinfusion (LP-TAI) and systemic chemotherapy. The cumulative survival rate in 29 patients who received LP-TAE at one-year, two-years and three-years were 70.9%, 54.0% and 25.2%, respectively. In contrast, the cumulative survival rate at one-year in patients who received LP-TAI was 20.6% and those who received systemic chemotherapy was 5.6%. The cumulative survival rate for LP-TAE was significantly higher than those for LP-TAI and systemic chemotherapy ( $p < 0.001$ ). The factor that affected the survival rate for LP-TAE was the size of the tumor. Patients with HCC of less than 5 cm in diameter lived significantly longer than those with HCC of more than 5 cm in diameter ( $p < 0.05$ ).

**Key words:** Transcatheter arterial embolization (TAE), Lipiodol, LP-TAE, Hepatocellular carcinoma

### INTRODUCTION

Hepatocellular carcinoma (HCC) is a relatively common malignant tumor in Japan. From 1980 to 1981 in Japan 83.2% of the patients with HCC had liver cirrhosis, therefore, surgical resection was performed in only 619 of the 1,760 cases of HCC (1). Recently, transcatheter arterial embolization (TAE) has been performed in patients with unresectable HCC due to advanced cirrhosis. The reports of TAE treated unresectable HCC have accumulated, and the cumulative survival rate for TAE has been superior or equivalent to that for surgical resection.

We have performed transcatheter arterial chemoembolization (LP-TAE) in 29

patients with unresectable HCC since 1983. In this report, we compare the prognosis of LP-TAE with those of transcatheter arterial chemoinfusion (LP-TAI) and systemic chemotherapy.

### PATIENTS AND METHODS

*Patients* : Sixty-eight patients with unresectable HCC from 1981 to 1988 were chosen for this study. The patients were classified into three groups according to treatment. Group A consisted of 29 patients treated with LP-TAE, group B of 21 patients with LP-TAI and group C of 18 patients with systemic chemotherapy. Details of each group are shown in Table 1.

*Treatment* : LP-TAE was performed by the following procedures. A vascular catheter was introduced superselectively into the hepatic artery that fed the tumors following conventional hepatic angiography. 20~40 mg of Adriamycin (doxorubin [ADM]) was dissolved in 60% Urografin and mixed with 10 ml of Lipiodol Ultra Fluid (LP). This emulsion was slowly injected through the catheter and particles of gelatin sponge (Gelform, Upjohn) measuring 1x1 mm were used for embolization of the artery. LP-TAEs were performed 1 to 6 times for an average of 2.1 times. For LP-TAI, a similar catheterization was performed and the ADM-Urografin-LP emulsion was injected through the catheter.

*Statistical analysis* : The cumulative survival rate was studied with Kaplan-Meier's method and statistical significance was determined using the generalized Wilcoxon's method.

**Table 1** *Clinical characteristics of patients*

Group	A	B	C
Treatment	LP-TAE	LP-TAI	Systemic Chemotherapy
No. of cases	29	21	18
Male	20	17	17
Female	9	4	1
No. still alive	16	3	0
Mean age (yrs)	59.3	59.9	60.6
HBsAg positive	7	6	1
AFP positive <sup>1</sup>	19	16	14
Coexistence of LC <sup>2</sup>	23	16	13

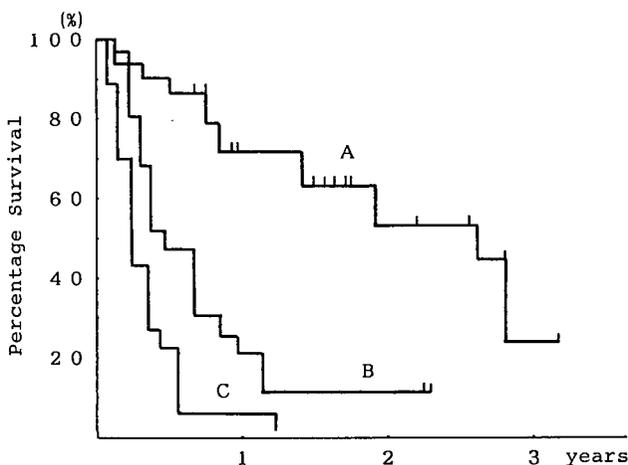
<sup>1</sup> AFP more than 20 ng/ml

<sup>2</sup> LC: liver cirrhosis

## RESULTS

*The cumulative survival rate of the 3 groups*

Fig. 1 shows the cumulative survival rate of the 68 patients with unresectable HCC. The cumulative survival rate at one-year, two-years and three-years for those who received LP-TAE (group A) were 70.9%, 54.0% and 25.2%, respectively. In contrast, the cumulative survival rate at one-year for those who received LP-TAI was 20.6% (group B), and for those who received systemic chemotherapy was 5.6% (group C). The cumulative survival rate for LP-TAE was significantly higher than that for LP-TAI ( $z=3.63$ ,  $p<0.001$ ). Furthermore, the cumulative survival rate for LP-TAI was significantly higher than that for systemic chemotherapy ( $z=2.89$ ,  $p<0.01$ ).

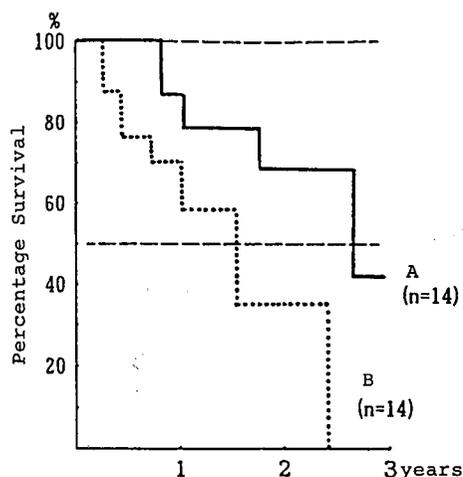


**Fig. 1** The cumulative survival rate of patients treated with LP-TAE (A), LP-TAI(B) and systemic chemotherapy(C).

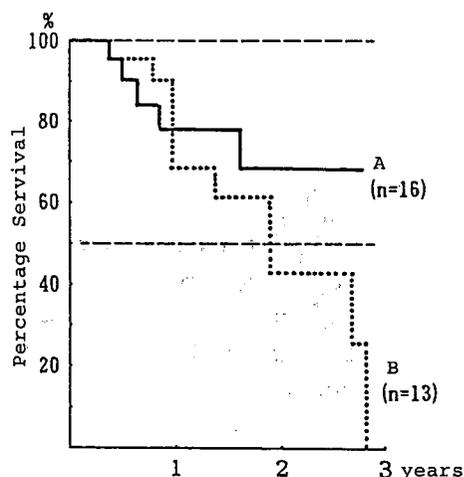
*The factors affecting the survival rate for LP-TAE*

In order to evaluate the factors that affected the survival rate for LP-TAE, the cumulative survival rates were calculated according to the following factors.

As shown in Fig. 2, the cumulative survival rate of patients with HCC of less than 5 cm in diameter was significantly higher than that of patients with HCC of more than 5 cm in diameter during the three-year study period ( $z=2.04$ ,  $p<0.05$ ). The number of tumors had no part in the survival rate during the one-year study period, however, the survival of patients with multi-nodule HCC was rather longer than those with single-nodule HCC after one year (Fig. 3). No significant difference of survival rate was observed for the number of tumors. The cumulative



**Fig. 2** The cumulative survival rate of patients treated with LP-TAE according to the difference of tumor size.  
A : less than 5 cm in diameter  
B : more than 5 cm in diameter

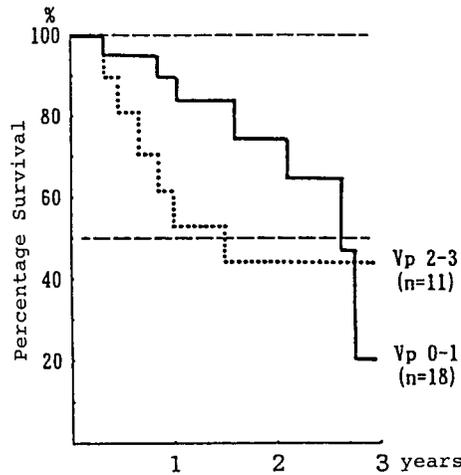


**Fig. 3** The cumulative survival rate of patients treated with LP-TAE according to the difference of the number of tumors.  
A : multi-nodule, B : single-nodule

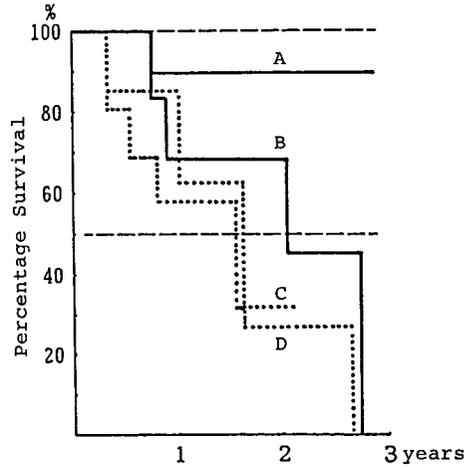
survival rate of patients with no tumor invasion (Vp 0) and tumor invasion in the 3rd order branch of the portal vein (Vp 1) was higher than that with tumor invasion in the 2nd (Vp 2) and the 1st (Vp 3) order branch during the two-year study period, but no significant difference was observed between the survival rates of the two groups (Fig. 4). As a result, in comparison of the size and number of tumors, the survival of patients with HCC of less than 5 cm in diameter was longer than those with HCC of more than 5 cm, regardless of the number of tumors (Fig. 5). It was also seen that the survival of the former was longer than that of the latter regardless of the degree of tumor invasion of the portal vein (Fig. 6).

## DISCUSSION

Since HCC is fed only through hepatic arteries, TAE which blockades the feeding arteries of the tumor is an appropriate and useful treatment for those HCC which are unresectable due to the presence of advanced liver cirrhosis or multiple tumor nodules. The first application of TAE to unresectable HCC in Japan was reported by Yamada *et al.* (2). In their method of TAE, particles of gelatin sponge that were permeated with an anti-cancer drug (MMC or ADM) were used for embolization. On the other hand, it has been reported that a lipid lymphographic agent (LP) injected into a hepatic artery selectively remains in HCC tissues for a long time (3, 4, 5). Thereafter, TAE using LP in combination with an anti-cancer



**Fig. 4** The cumulative survival rate of patients treated with LP-TAE according to the difference of tumor invasion of the portal vein.  
 Vp 0-1: no tumor invasion and tumor invasion in 3rd order branch  
 Vp 2-3: tumor invasion in 2nd and 1st order branch

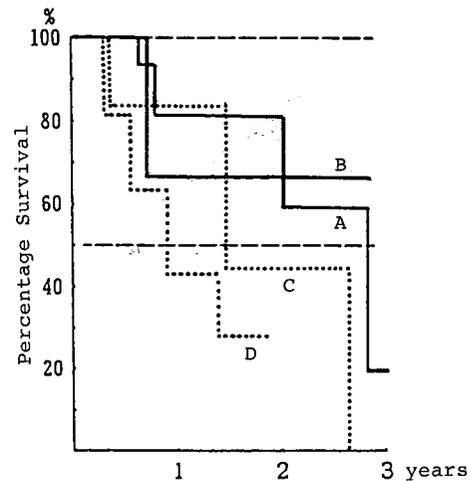


**Fig. 5** Influence of the number of tumors on the survival rate of patients treated with LP-TAE according to the difference of tumor size.  
 A : less than 5 cm and multi-nodule  
 B : less than 5 cm and single-nodule  
 C : more than 5 cm and multi-nodule  
 D : more than 5 cm and single-nodule

drug has been widely applied for HCC treatment. This combined method is called transcatheter arterial chemoembolization (LP-TAE).

In our study, the cumulative survival rate in 29 patients who received LP-TAE at one-year, two-years and three-years were 70.9%, 54.0% and 25.2%, respectively. The survival rate for LP-TAE worsens after a two-year study period, as reported by different research groups. Yamada *et al.* reported that the one-, two- and three-year cumulative survival rates of 120 patients receiving TAE were 44%, 29% and 15%, respectively(2).

We analyzed the factors affecting the prognosis of LP-TAE. The main factor was found to be the size of tumor.



**Fig. 6** Influence of tumor invasion of the portal vein on the survival rate of patients treated with LP-TAE according to the difference of tumor size.  
 A : less than 5 cm and Vp 0-1  
 B : less than 5 cm and Vp 2-3  
 C : more than 5 cm and Vp 0-1  
 D : more than 5 cm and Vp 2-3

The survival of patients with HCC of less than 5 cm in diameter was significantly longer than that of more than 5 cm. Tanabe *et al.* reported that the cumulative one-, two- and three-year survival rates of 34 patients with HCC of less than 5 cm in diameter were 88.4%, 72.3% and 43.4%, respectively(6). Statistically, the number of tumors and the degree of tumor invasion of the portal vein (Vp factor) were not significantly associated with the prognosis. The reason why the survival of multi-nodule HCC was rather longer than that of the single-nodule HCC after a one-year study period, may be due to the smaller tumor size of the former than the latter. Moreover, the trends shown in the survival curves of Fig. 5 and Fig. 6 suggest that the number of tumors and Vp factor had no influence on the survival of patients with HCC of less than 5 cm in diameter.

The contraindications of LP-TAE were 1) an occlusion of the main portal vein due to tumor invasion, 2) an occupancy rate of HCC larger than 80% of the liver, and 3) poor liver function tests (e. g. an elevation of serum bilirubin level more than 2 mg/dl and ascites). In those cases, LP-TAI was performed. As stated above, LP remained in HCC tissues for a long time, and the injection of LP with anti-cancer drug into the hepatic artery was a useful method for targetting chemotherapy of HCC. However, since embolization with LP alone was incomplete, the survival rate for LP-TAI was significantly lower than that for LP-TAE. One-shot chemotherapy to the hepatic artery was widely performed, but the survival rate at one-year was poor(7). Therefore, LP-TAI was carried out instead of one-shot chemotherapy.

The therapeutic effects of systemic chemotherapy have been reported by many investigators, but its application has declined because of the poor prognosis and the high frequency of side effects(8). In our study the cumulative survival rate for systemic chemotherapy was significantly lower than that for LP-TAI.

In conclusion, the cumulative survival rate of patients who received LP-TAE was excellent, but it was difficult to sustain life for more than two-years with LP-TAE alone. To improve the therapeutic effects of LP-TAE, a combination with other new treatments, such as percutaneous ethanol injection to HCC(9), will be required.

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