

## Hepatic artery embolization for inoperable hepatocellular carcinoma; prognosis and Risk Factors

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**Summary.** During a 7-year period in our hospital, 69 patients with inoperable hepatocellular carcinoma (HCC) underwent 111 courses of transcatheter hepatic artery embolization (TAE) and/or chemoinfusion with lipiodol. Patient survival was 0.5–37 months following therapy and the factors affecting prognosis were evaluated. Survival rates at 1, 2 and 3 years after TAE were 53%, 24% and 15%, respectively. Survival rates at 1, 2 and 3 years in relation to tumor size were 100%, 100% and 100% in 5 patients (tumor size <2 cm in diameter), 81%, 33% and 16% in 23 patients (2.1–5.0 cm), and 35%, 9% and 0% in 41 patients (>5.1 cm). An analysis of prognostic factors showed that the size of the main tumor significantly influenced the prognosis following TAE ( $P < 0.01$ ), whereas the frequency of TAE, intrahepatic metastasis and the degree of liver dysfunction showed a slight correlation ( $P < 0.1$ ). These results suggest that TAE has a significant potential for becoming the first choice of treatment for patients with small multiple HCCs (<2 cm), provided that neither severe hepatic dysfunction nor a tumor thrombus in the main portal vein is present.

### Introduction

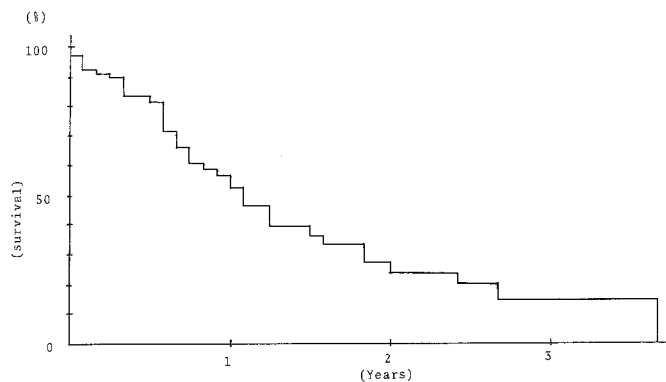
With the recent imaging modalities, such as ultrasonography and computed tomography, and the clinical follow-up of patients at high risk for development of hepatocellular carcinoma (HCC) [5], HCCs 3 cm or smaller in diameter have been found with relative ease in asymptomatic patients with negative or low level serum  $\alpha$ -fetoprotein both in Japan and Taiwan [1].

However, 56% of hepatectomized patients with HCC(s) 5 cm or smaller in diameter experience a recurrence in the residual liver within an average period of 14.5 months [10], in spite of an integrated imaging diagnosis including intraoperative-ultrasonography before resection. In this study, the tumor size and other factors influencing the prognosis of patients with inoperable HCC after transcatheter hepatic artery embolization (TAE) were analyzed.

### Patients and methods

During the period from October 1979 to August 1986, a total of 111 courses of therapeutic embolization of the hepatic artery were performed on 69 patients with inoperable HCC. The patients consisted of 54 men and 15 women, their ages ranging from 34 to 81 years. Three treatment protocols were followed. In the 22 patients undergoing TAE prior to 1984, gelatin-sponge particles measuring 1 × 1 mm (Gelfoam, Upjohn, Kalamazoo) mixed with 20 mg doxorubicin (or 10 mg mitomycin C in patients with cardiac disease) (group A) were used. Beginning in 1984, an emulsion of 5 ml ethyl ester of poppyseed oil fatty acids, containing 38% iodine by weight (lipiodol: Andre-Gelbe Laboratories, France), with 20 mg doxorubicin (group B) was administered to 14 patients, and an emulsion of iodized oil and doxorubicin followed by gelatin-sponge particles (group C) was administered to 33 patients. Our analysis of the therapeutic effects on HCC among the three groups, based on the resected specimens, suggested that the method used in group C had the best results both for the main tumor and the daughter tumors [11]. Therefore, beginning in 1984, most patients in groups A and B received repeated embolization therapy using the materials described above for group C. The follow-up period after TAE was from 0.5 to 37 months. Three patients (4.3%) died within 1 month after TAE. The survival rates were calculated using the Kaplan-Meier method [7]. The presence of a significant difference in the survival rates among the three groups, divided according to the size of the main tumor, was evaluated using Greenwood's formula.

Several additional factors affecting the prognosis following TAE were analyzed. A single-factorial analysis was carried out using the generalized Wilcoxon test, followed by a relative risk analysis utilizing the Cox regression model [4] with respect to the following factors: (a) age (<60, >60 years), (b) sex (male, female), (c) frequency of TAE (one to four times), (d) method of TAE (groups A, B and C), (e) size of the main tumor (<2 cm in diameter, 2.1–3 cm, 3.1–5 cm, 5.1–10 cm, >10.1 cm), (f) presence of intrahepatic metastasis (in one segment, one lobe, or both lobes), (g) presence of tumor thrombus in the portal vein (in the second order branch and in the first order branch), (h) the degree of liver dysfunction according to Child's classification [2] (A, B and C), (i) Indocyanine green 15-min retention test (normal <10%) ( $\leq 20\%$ , 21–39%,  $\geq 40\%$ ).



**Fig. 1.** The cumulative survival rates of the 69 patients with inoperable hepatocellular carcinoma following transcatheter hepatic artery embolization

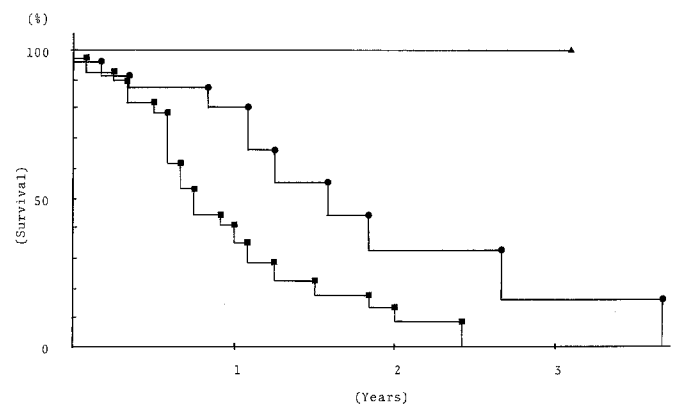
## Results

### Survival rate following TAE

The cumulative survival rates for all 69 patients undergoing TAE(s) were 53% at 1 year, 24% at 2 years and 15% at 3 years (Fig. 1). When these patients were divided into three groups in relation to tumor size, the survival rates for group 1 ( $n = 5$ , tumor size  $< 2$  cm), group 2 ( $n = 23$ , 2.1–5 cm) and group 3 ( $n = 41$ ,  $> 5.1$  cm) were 100%, 81% and 35% at 1 year, 100%, 33% and 9% at 2 years, and 100%, 16% and 0% at 3 years, respectively (Fig. 2). There was a marked difference in the survival rates among the three groups at 1, 2 and 3 years ( $P < 0.01$ ), except for a slightly significant difference between groups 1 and 2 at 1 year ( $P < 0.05$ ). The clinical data for group 1 are given in Table 1. These five patients are all alive, although the follow-up period was only 14–37 months. Their liver function according to Child's classification and indocyanine green retention was relatively good, and they were referred to our hospital for partial hepatectomy. However, they underwent TAE therapy because of newly found multiple lesions in the liver, or because of cerebrocardiac diseases.

### Analysis of factors affecting patient prognosis following TAE

On the basis of an analysis of possible prognostic factors using the generalized Wilcoxon test, significant differences



**Fig. 2.** The cumulative patient survival rates in relation to the size of hepatocellular carcinomas following transcatheter hepatic artery embolization. Survival rates of patients with small ( $< 2$  cm in diameter), intermediate (2.1–5.0 cm) and large lesions ( $> 5$  cm) are drawn in triangles, circles and squares, respectively

in survival were recognized for the following factors: (a) tumor size:  $< 2$  cm versus  $> 2.1$  cm ( $P < 0.05$ ), and  $< 5$  cm versus  $> 5.1$  cm ( $P < 0.01$ ); (b) the frequency of TAE: once versus more than twice ( $P < 0.05$ ), and twice versus more than three times ( $P < 0.05$ ); (c) the degree of liver function: Child A versus B ( $P < 0.01$ ) and Child A versus B plus C ( $P < 0.05$ ). A subsequent evaluation of the factors utilizing the Cox's multiregression model [4] (excluding indocyanine green retention) demonstrated (Table 2) that only the size of the main tumor was significant ( $P < 0.01$ ). The frequency of TAE, intrahepatic metastasis and Child's classification showed a slight but insignificant correlation ( $P < 0.1$ ).

## Discussion

Our results of TAE for inoperable HCC showed a survival rate of 53% at 1 year, 24% at 2 years and 15% at 3 years (Fig. 1). This is very similar to the findings reported by Yamada et al. [13] of 44% survival at 1 year, 29% at 2 years, and 15% at 3 years in 120 patients with unresectable HCC. The result of TAE as a palliative therapy is extremely good when compared with the reported 1 year survival rate of

**Table 1.** Clinical data on five patients with inoperable small hepatocellular carcinoma ( $< 2$  cm) who underwent therapeutic embolization

Case	Size (cm)	Location <sup>a</sup>	Child's class	ICG $R_{15}$ (%) <sup>b</sup>	Reason why inoperable	No. of TAE	Survival (months)
1	1.7	S-VII	A	17.0	Multiple lesions	3	37
	1.7	S-VII					
2	2.0	S-VIII	B	22.0	Arrhythmia	5	36
3	1.7	S-VIII	A	24.2	Brain infarction, coronary insufficiency	2	23
4	2.0	S-VI	A	17.5	Multiple lesions	2	19
	1.2	S-VIII					
5	1.5	S-VIII	A	40.5	Multiple lesions	1	14
	1.0	S-VII					
	0.8	S-VIII					

<sup>a</sup> Location of lesion is based on the Couinaud's segment numbering [3]

<sup>b</sup> ICG  $R_{15}$  = 15-min plasma retention of i.v. indocyanine green

**Table 2.** Cox's multiregression model of risk factors for the prognosis of patients with inoperable hepatocellular carcinomas after transcatheter artery embolization (TAE)

Risk factor	Relative value	Significance
Age	0.08	N.S. <sup>a</sup>
Sex	0.77	N.S.
Frequency of TAE	1.87	N.S. ( $P < 0.1$ )
Method of TAE	0.15	N.S.
Size of main tumor	3.23	$P < 0.01$
Intrahepatic metastasis	1.80	N.S. ( $P < 0.1$ )
Tumor thrombus	0.33	N.S.
Child's [2] classification	1.71	N.S. ( $P < 0.1$ )

<sup>a</sup> N.S., not significant

only 3% for 511 patients who did not undergo laparotomy or TAE [12]. The 100% 3-year survival rate for the five patients in this study who had relatively good liver function and a small tumor (2 cm or less in diameter) is remarkable. They were surgical candidates, but underwent TAE because of cerebrocardiac diseases or multiple intrahepatic lesions found following admission. When compared with the survival rates of the 22 patients with HCC(s) of the same size treated by Ikeda et al. [6] with repeated TAE every 3 months, for which the 1-year, 2-year and 3-year survival rates were 100%, 38.1% and 38.1%, respectively, our five cases tolerated well the repeated TAE, which resulted in excellent survival rates, even though damage to non-cancerous parenchyma secondary to repeated TAE could have induced liver dysfunction. In their study, the main cause of the poor prognosis was the decreased liver function. The 3-year survival rate of all HCCs 2 cm or less ( $n = 18$ ) in diameter following operation in the National Cancer Center Hospital was 72.2%. In this group, the 3-year survival rates for solitary HCCs ( $n = 9$ ) and multiple HCCs ( $n = 9$ ) were 100% and 64.0%, respectively [14]. Despite the above-mentioned results, surgical resection is still thought to be the best treatment for HCC. However, postoperative recurrence in the residual liver was frequent (56%) within a short mean period of 14.5 postoperative months for HCCs no larger than 5 cm, and clearly TAE was the only means of treating the recurrence, as we have reported previously [10]. Moreover, it became clear in this study that multiple lesions, and even a solitary HCC larger than 3 cm in diameter, confirmed by preoperative diagnosis and the resected specimen, had a high recurrence rate. On the basis of these results, we believe that if a patient has multiple small HCCs no larger than 2 cm and good liver function, TAE should be the treatment of choice.

In this study, the size of the main tumor ( $P < 0.01$ ) was found to be the most important prognostic factor in patients treated with TAE. The degree of liver dysfunction [9], intrahepatic metastasis and frequency of TAE were not as significant ( $P < 0.1$ ) as we had expected. The analysis did not show any significant differences in other factors such as tumor thrombus, a potential cause of hepatic failure following TAE [8, 13]. This may be due to the small number of patients ( $n = 4$ ) with tumor thrombus in the portal vein trunk or the first-order branches. The various

TAE techniques have been previously shown by us to result in different degrees of tumor necrosis [11]. However, our analysis did not detect a significant difference in survival of patients receiving the various therapies, most likely because most patients received a combination of therapies.

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