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Treatment of small hepatocellular carcinoma*

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Summary. Of the 692 patients with hepatocellular carcinoma (HCC) who were admitted to our hospital between 1976 and 1990, 60 (8.8%) had small HCC with a maximal diameter of below 2 cm. The outcome of these 60 cases was analyzed after they had been divided into 4 groups based on the therapeutic method used: operation group (17 cases), percutaneous ethanol injection therapy (PEIT) group (20 cases), transcatheter arterial embolization (TAE) group (13 cases), and oral anticancer drug therapy (per os) group (10 cases). The 1-, 2-, 3-, 4-, and 5-year survival values obtained for the operation group (100%, 87.5%, 87.5%, 87.5%, and 87.5%, respectively) were significantly higher than those found for the per os group ($P < 0.01$). The best therapeutic results were achieved in the operation group. Although the follow-up period for the PEIT group was short, the 2-year survival of this group was nearly equal to that of the operation group. Whereas the duration of survival tended to increase in inverse proportion to the severity of the underlying liver cirrhosis, the survival values did not differ between solitary and multiple tumors or among the different histological grades of HCC. In this series, 20 patients died; 9 deaths (45.0%) were due to progressive disease and 3 deaths (15.0%) were attributed to hepatic failure. Because the operation group included many patients who displayed relatively good liver function, we cannot rule out the possibility that their excellent outcome may have been associated with this background factor. Therefore, further prospective investigation is necessary to compare the efficacy of various therapies in patient groups with a homogeneous background.

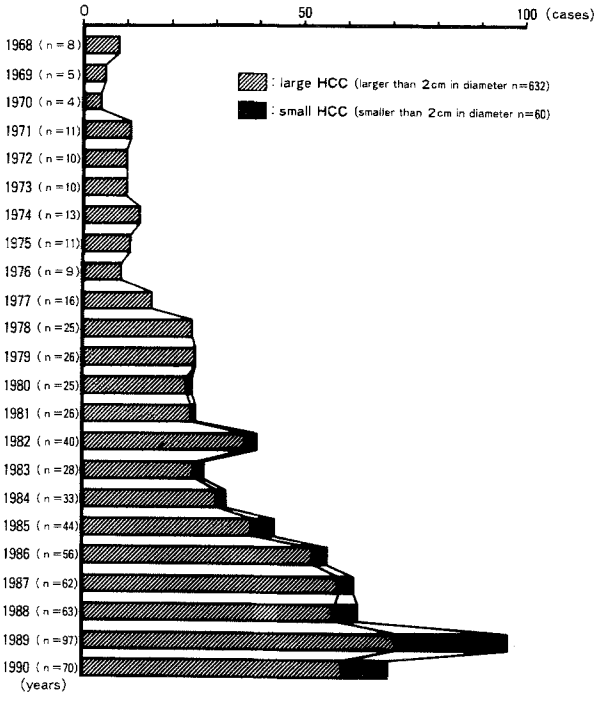

Fig. 1. Annual incidence of small HCC measuring less than 2 cm in diameter

Introduction

Due to recent progress in diagnostic modalities, the frequency of detection of small hepatocellular carcinoma (HCC) has increased. Of the 692 patients with HCC who were admitted to our hospital between 1976 and 1990, 60 (8.6%) had small HCC with a maximal diameter of less than 2 cm. The percentage of cases of small HCC among the total cases of HCC has increased over the last 3 years (Fig. 1).

The therapeutic approaches for HCC have also progressed markedly in recent years through the development of transcatheter arterial embolization (TAE) [7, 9] and

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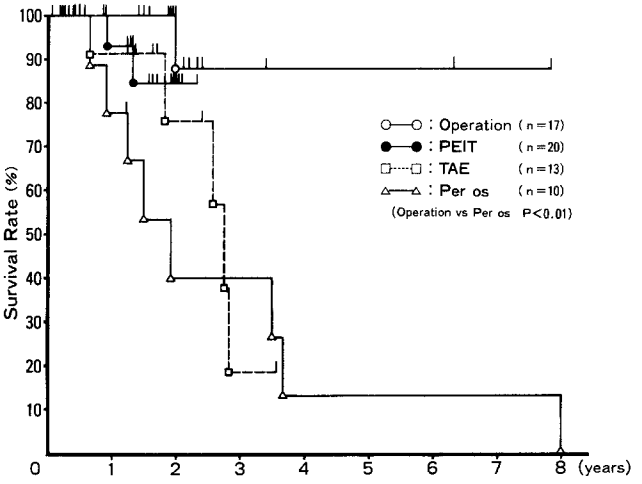

Fig. 2. Survival according to therapeutic method

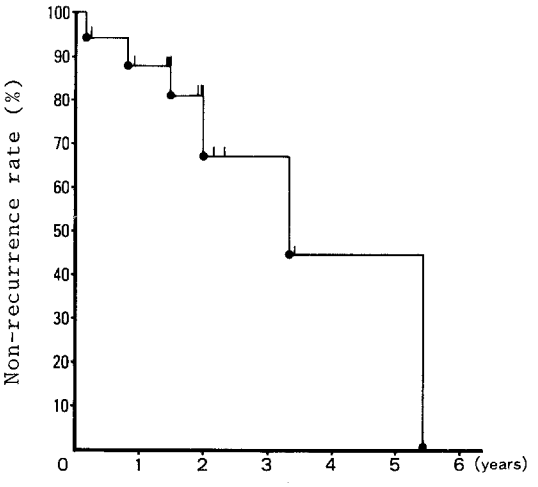

Fig. 3. Interval until recurrence after operation

Table 1. Patients' background characteristics

Characteristic	Treatment group			
	Operation	PEIT	TAE	Per os
Number of patients	17	20	13	10
Age (years, MV ± SD)	63.6 ± 7.1	62.0 ± 7.1	64.6 ± 8.9	60.7 ± 8.9
Sex (M/F)	8/9	14/6	9/4	6/4
Tumor size (mm, MV ± SD)	15 ± 4	15 ± 4	17 ± 4	18 ± 3
Tumor number (solitary/multiple)	14/3	11/9	9/4	8/2
$ICGR_{15}$ (%, MV ± SD)	19.2 ± 12.9	30.9 ± 19.5	30.2 ± 18.2*	37.7 ± 14.9**
Child's classification:				
A	13	6	5	1
B	4	10	7	6
C	0	4	1	3
Viral marker:				
B-type	4	3	0	5
C-type	8	14	6	1
NBNC-type	3	2	0	0
NB-type[a]	2	1	7	4
Esophageal varices:				
(+)	3	10	6	6
(−)	14	10	7	4
Edmondson and Steiner's grades:				
I	2	10	0	0
I–II	2	2	0	0
II	11	7	6	4
III	2	1	0	2
Unknown	0	0	7	4

* $P < 0.05$, operation vs TAE; ** $P < 0.01$, operation vs per os

[a] anti-HCV was not determined

percutaneous ethanol injection therapy (PEIT) [4, 8]. For these reasons, the prognosis of patients with HCC has been markedly improved. In this retrospective study, we analyzed the outcome of 60 patients with small HCC who received different therapies at our hospital.

Patients and methods

The study included 60 patients with small HCC (2 cm or less in diameter) who had been admitted to our hospital during the last 11 years. The diagnosis of small HCC was made histologically in 49 cases and clinically in 11 cases. Patients were divided into 4 groups as follows: operation group, 17 cases; PEIT group, 20 cases; TAE group, 13 cases; and oral anticancer drug therapy (per os) group, 10 cases. In the operation group, either partial resection or subsegmentectomy was carried out. In the PEIT group, the tumor was punctured with a thin needle under ultrasound guidance after the patient had been given a local anesthetic, followed by the injection of 1–3 ml 95.0% ethanol (containing mepivacaine hydrochloride), depending on the tumor size. In the TAE group, Adriamycin (20 mg/m^2) or epirubicin (60 mg/m^2) emulsified in lipiodol (an oily contrast material) was infused selectively into the hepatic artery, followed by embolization using Gelfoam powder or gelatin sponge. The per os group received oral doses of 100–300 mg 5-fluorouracil (5-FU) or 300–600 mg 1-hexylcarbamoyl-5-fluorouracil (HCFU) daily.

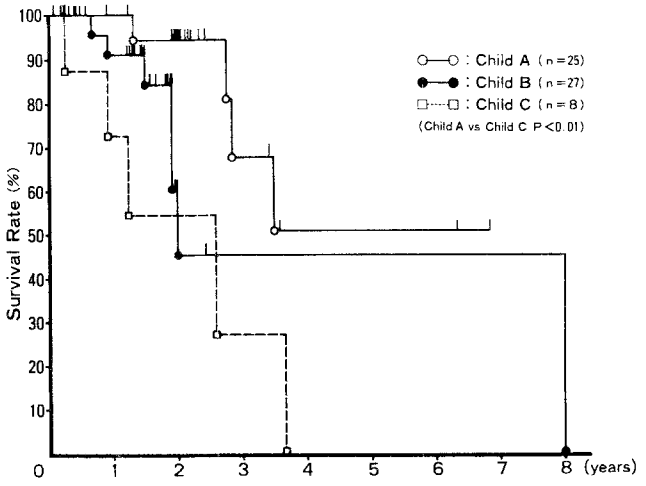

Fig. 4. Survival according to Child's classification

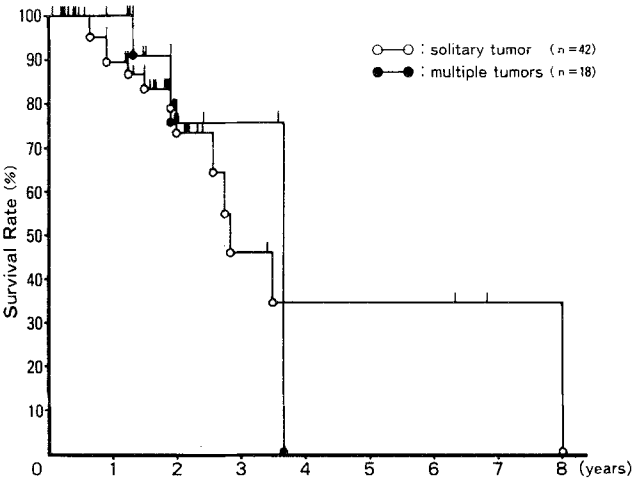

Fig. 6. Survival in relation to the number of tumors

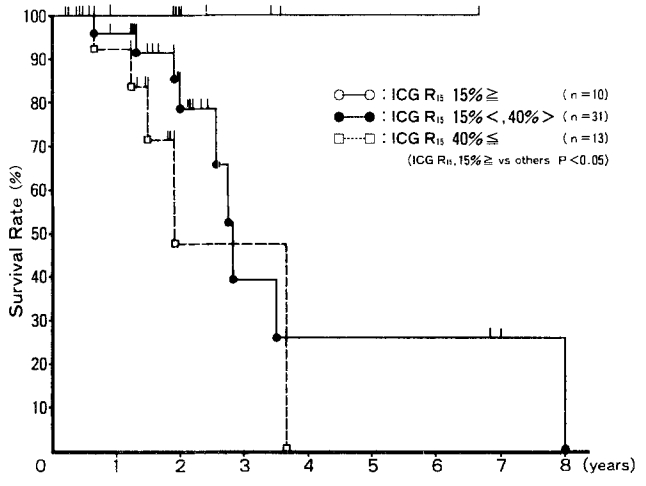

Fig. 5. Survival in relation to ICG values

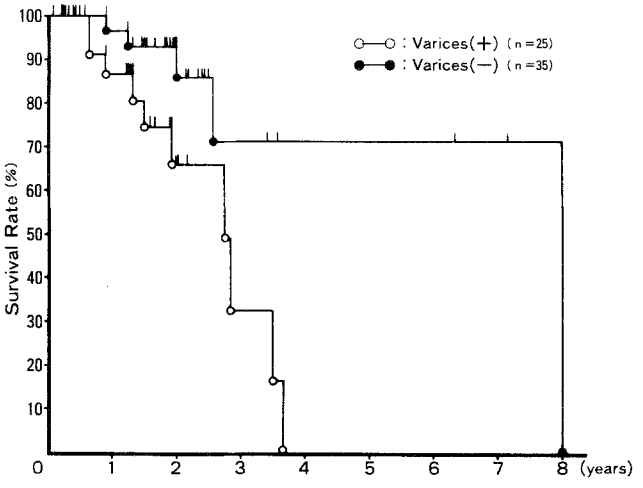

Fig. 7. Survival in relation to the presence/absence of esophageal varices

The outcome of the subjects was analyzed in relation to the therapy, the hepatic function, the number of tumors, the presence/absence of esophageal varices, and the histological grade of the HCC. The data were statistically analyzed by Wilcoxon's rank-sum test, and survival values were calculated using the Kaplan-Meier method. The statistical significance of differences was tested by the generalized Wilcoxon test.

Results

Table 1 summarizes the background characteristics of the patients. No significant intergroup difference was found in age, sex ratio, tumor size, number of tumors, or incidence of esophageal varices. However, the $ICGR_{15}$ value (15-min retention rate of indocyanine green) was significantly lower in the operation group than in the TAE group and the per os group. The percentage of Child's class A cases [1] was higher in the operation group than in the other groups. The percentage of grade I or I–II cases as determined according to Edmondson-Steiner's histological grading of HCC [2] was high in the PEIT group, whereas the percentage of grade II or III cases was high in the other groups.

The survival values calculated for each group are shown in Fig. 2. The duration of survival was longest in the operation group, which attained 1-, 2-, 3-, 4-, and 5-year survival values of 100%, 86.5%, 87.5%, 87.5%, and 87.5% respectively. The corresponding survival values obtained in the per os group (77.8%, 40.0%, 26.7%, 13.3%, and 13.3%) were significantly lower than those achieved the operation group (P <0.01, generalized Wilcoxon test). The survival values found for the PEIT group were similar to those calculated for the operation group, and the values determined for the TAE group were similar to those found for the per os group. However, the follow-up periods for the PEIT and TAE groups were too short for the analysis of possible significant differences.

The non-recurrence rates in the operation group are shown in Fig. 3. As determined at 1, 2, 3, 4, and 5 years after the operation, the non-recurrence rates were 87.5%, 67.1%, 67.1%, 44.7%, and 44.7%, respectively.

Figures 4 and 5 show the survival of patients in relation to their hepatic function. The survival period for Child's class A patients was significantly longer than that for Child's class C patients (P <0.01, generalized Wilcoxon test; Fig. 4). Similarly, the survival period for patients with

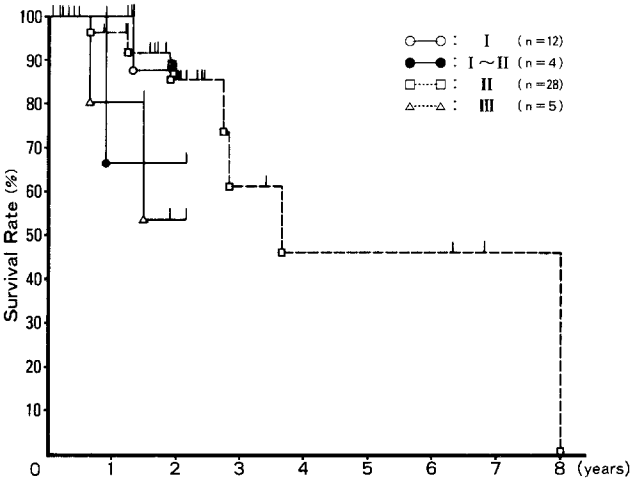

Fig. 8. Survival in relation to Edmondson-Steiner's histological grading

Table 2. Causes of death

	Operation	PEIT	TAE	Per os
Cancer death	1	1	1	6
Rupture of esophageal varices	0	0	3	1
Hepatic failure	0	1	1	1
Other disease	0	2	1	1

an $ICGR_{15}$ value of below 15% was significantly longer than that for patients with a value of between 15% and 40% or over 40% ($P < 0.05$, generalized Wilcoxon test; Fig. 5). Thus, the survival period was longer in patients with better hepatic function. There was no significant difference between solitary and multiple tumors (Fig. 6), also no difference between the presence and the absence of esophageal varices (Fig. 7).

In analyses of the patients' outcome in relation to Edmondson-Steiner's HCC histological grades, the survival values did not differ among grades I, I–II, II, and III (Fig. 8). The follow-up periods were short for grade I and I–II cases because the diagnosis of these two grades became possible only recently. In analyses of the cause of death in 20 patients, the percentage of deaths due to progression of HCC (including deaths due to increased jaundice or to rupture of esophageal varices) was high in the per os group (66.6%; Table 2). Death due to rupture of esophageal varices occurred frequently in the TAE group (50.0%).

Discussion

It is known that there is a close relationship between HCC and chronic liver disease. This carcinoma seems to be detectable at a relatively early stage when patients with chronic liver diseases (chiefly liver cirrhosis) are followed up by diagnostic modalities such as ultrasound and computed tomography at least every 3 months [5]. However, in cases of small HCC with a diameter of less than 2 cm (especially HCC with a diameter of below 1.5 cm), characteristic findings are seldom obtained using diagnostic modalities, and diagnosis frequently requires liver biopsy [6].

In the past, patients in whom ultrasound-detected intrahepatic small masses could not be confirmed by other diagnostic imaging techniques such as computed tomography and angiography were carefully followed up at our hospital. Many of these cases were diagnosed as having HCC when either an increase in tumor size or number or other changes were observed during the follow-up. Therefore, in 1988 we started to perform liver biopsy under ultrasound guidance when a small mass had been found in the liver on ultrasound examination, and it became possible to detect even small HCC with a diameter of about 1.0 cm [3]. Over the past 3 years, we have detected small HCC in a large number of patients, as shown in Fig. 1.

Patients with small HCC usually have a better prognosis than those with larger HCC. The prognosis for small HCC has further improved due to recent advances in many therapies such as aggressive hepatic resection, PEIT, and TAE. In the present study, analysis of the patients' outcome in relation to the therapeutic method applied showed that the best survival was achieved in the operation group. The 1-, 2-, 3-, 4-, and 5-year survival values found for this group were significantly higher than those calculated for the per os group. Although follow-up period for the PEIT group was short, the 2-year survival of this group was close to that of the operation group. Therefore, we look forward to obtaining long-term follow-up data on the PEIT group. In almost all cases, HCC recurred within 6 years after operation, but it was very difficult to differentiate true recurrence from the development of a new tumor.

Because most Japanese patients with HCC have liver cirrhosis as an underlying disease, there are many factors that seem to affect the prognosis of HCC, including the severity of liver cirrhosis and portal hypertension. Therefore, we analyzed the survival of patients in relation to two indices of liver function: Child's classification and the $ICGR_{15}$ value. This analysis revealed the survival period to be longer in patients with better liver function. On the other hand, patients who did not have esophageal varices tended to survive longer than those who had esophageal varices, although the difference did not reach statistical significance. This may have been partially associated with the administration of prophylactic endoscopic sclerotherapy prior to treatment of HCC in patients with severe varices.

Although the degree of malignancy also seems to be an important factor affecting the prognosis of HCC, the outcome of HCC in the present study did not differ among different histological grades according to the classification of Edmondson-Steiner. However, as the diagnosis of grade I and I–II HCC by this histological classification became possible only recently and the follow-up period for these cases was thus short, the correlation of the patients' survival with this classification requires additional study.

In all, 20 patients died during the follow-up period; 9 deaths were attributed to progressive disease, and 6 of these 9 patients were in the per os group, suggesting the necessity of more aggressive therapy even for patients with liver cirrhosis. At the same time, careful selection of the therapy is necessary because of these deaths due to hepatic failure.

In summary, we analyzed the outcome of patients with small HCC in relation to the therapeutic method applied. The outcome was best in operated cases presenting with mildly severe underlying liver cirrhosis. These results indicate that a prospective comparison of the outcome of HCC treated by different therapies should be performed in a patient population with a homogeneous background.

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