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Outcomes of 116 patients with hepatocellular carcinoma

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Abstract. We studied the outcomes of 116 patients with hepatocellular carcinoma (HCC) diagnosed in our hospital between January 1980 and August 1992. The patients were divided into groups according to the principal treatment procedure. The 3-year survival rates in the patients treated by percutaneous ultrasonically guided ethanol injection (PEI), operation (hepatic resection), and transcatheter hepatic arterial embolization (TAE) were 90.9%, 53.6%, and 29.0%, respectively. None of the patients treated by one-shot injection of an anticancer agent into the hepatic artery and chemotherapy survived for more than 2 years. The outcomes of the patients treated by PEI and hepatic resection were significantly better than those of the patients treated by the other procedures. There was no significant difference when the patients were stratified according to the year of detection. The 3-year survival rate was 57.3% for 19 patients in whom HCCs were detected during clinical follow-up for chronic liver disease and 17.3% for the other 97 patients. We concluded that hepatic resection in patients with good liver function and PEI for early HCC yielded significantly better survival rates than the other procedures. Moreover, for early detection and treatment of HCC, we recommend clinical follow-up of patients with chronic liver disease.

Introduction

Recent advances in real-time ultrasonography have contributed to the early detection of hepatocellular carcinoma (HCC) [8, 19], but many advanced cases continue to be detected. Only 18.1% of HCC cases in Japan undergo hepatic resection due to cirrhosis in the noncancerous portion of the liver. However, cirrhosis has been confirmed in 82.1% of autopsied cases [10]. On the other hand, transcatheter hepatic arterial embolization (TAE) [2, 5, 24], ultrasonically guided percutaneous ethanol injection (PEI) [4, 12, 20, 21], and hepatic arterial infusion of Lipiodol through a catheter (LpI) [14, 15, 22, 26] now play important roles in the treatment of unresectable HCC. In this study, we retrospectively analyzed the outcomes of HCC cases to evaluate various treatment procedures.

Patients and methods

Between January 1980 and August 1992, 116 patients were confirmed to have HCC in our hospital. The age of the patients ranged from 34 to 80 years (mean, 63.7 years). The male-to-female ratio was 2.52 (Table 1).

For the treatment of HCC, we employed PEI, operation (hepatic resection), TAE, LpI, one-shot injection of an anticancer agent (mitomycin C, Adriamycin, or epirubicin) into the hepatic artery via a catheter, and chemotherapy (injection of an anticancer agent into a peripheral vein or oral administration of fluorouracil, tegafur, or an anti-cancer agent preparation containing tegafur and uracil at a molar ratio of 1:4).

For the LpI treatment, a catheter was inserted into the tumor-feeding artery to allow administration of an anticancer agent (10–50 mg of mitomycin C, Adriamycin, or epirubicin) mixed with

Table 1. Age and sex distribution of 116 patients with hepatocellular carcinoma

	Sex	
Age (years)	Male	Female
30–39	1	0
40–49	6	0
50–59	23	5
60–69	30	19
70–79	21	9
80–89	2	0
Total	83	33

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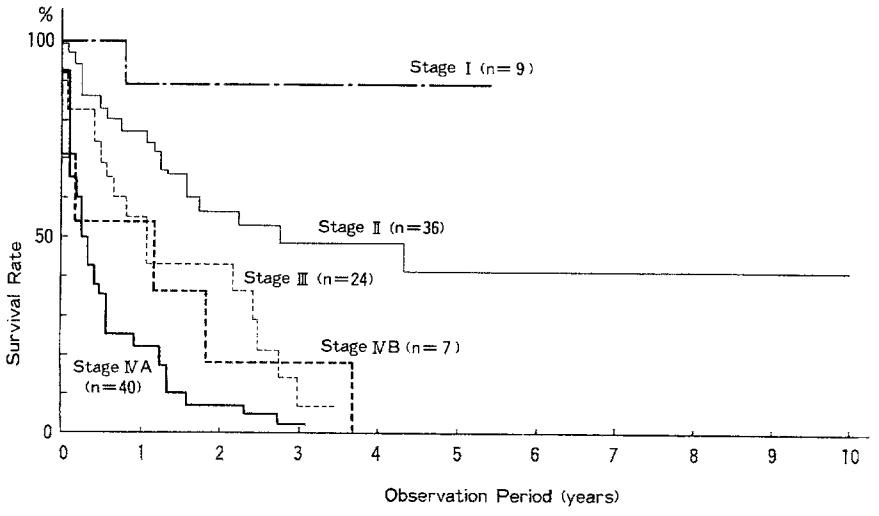

Fig. 1. Cumulative survival rates (Kaplan-Meier method) obtained in patients with HCC according to disease stage as proposed by the Liver Cancer Study Group of Japan [11]. Significant differences are observed as follows: stage I vs III, $P < 0.01$; stage I vs IV-A, $P < 0.002$; stage I vs IV-B, $P < 0.05$; stage II vs III, $P < 0.05$; stage II vs IV-A, $P < 0.002$; and stage II vs IV-B, $P < 0.05$

Table 2. Characteristics of patients and treatment procedures

	Principal treatment procedure							
	PEI[a]	Operation	TAE[b]	LpI[c]	One-shot[d]	Chemotherapy[e]	Unknown	None
Number	11	16	29	9	12	18	2	19
M:F	7:4	11:5	17:12	8:1	9:3	15:3	1:1	15:4
Age (years)								
Mean	66.0	60.6	62.7	63.9	60.7	65.6	–	66.3
Range	52–75	43–73	47–76	53–75	34–77	46–80	61–72	45–78
Combined procedure (numbers of cases are indicated):								
None	11	10	21	5	12	18	2	–
PEI	0	1[f]	3	4	0	0	0	–
Operation	0	–	1	0	0	0	0	–
TAE	0	5	–	0	0	0	0	–
LpI	0	1	4	–	0	0	0	–

[a] PEI: ultrasonically guided percutaneous ethanol injection
[b] TAE: transcatheter hepatic arterial embolization
[c] LpI: intra-arterial infusion of Lipiodol into the hepatic artery via a catheter
[d] One-shot: one-shot injection of anticancer agents into the hepatic artery via a catheter
[e] Chemotherapy: oral administration of anticancer agents or injection of anticancer agents into a peripheral vein
[f] One case underwent operation, TAE, and PEI

3–20 ml of iodized oil (Lipiodol Ultra Fluide, an ethylester of poppyseed oil fatty acid) through the catheter. For the TAE cases, infusion of the anticancer agent mixture was followed by injection of gelatin sponge cubes into the feeding artery.

We employed the clinical staging criteria presented in the General Rules for the Clinical and Pathological Study of Primary Liver Cancer as established by the Liver Cancer Study Group of Japan [11]. The stages were as follows: stage I – T_1, N_0, M_0; stage II – T_2, N_0, M_0; stage III – T_3, N_0 M_0 or T_{1-3}, N_1, M_0; stage IV-A – T_4, N_{0-1}, M_0; and stage IV-B – T_{1-4}, N_{0-1}, M_1.

The χ^2-test was used for the statistical analyses. The survival rates were calculated according to the Kaplan-Meier method and compared by the generalized Wilcoxon test. Statistical significance was defined as a P value of less than 0.05.

Results

Figure 1 shows the survival rates of the patients in each clinical stage. The 3-year survival rates of the patients in stages I, II, III, IV-A, and IV-B were 88.9%, 48.0%, 7.2%, 2.5%, and 17.9%, respectively. Although there was no statistically significant difference between the outcome of patients in stage I and those in stage II, the outcomes of the patients in stages I and II were significantly better than those of the patients in the other stages (I vs III, $P < 0.01$; I vs IV-A, $P < 0.002$; I vs IV-B, $P < 0.05$; II vs III, $P < 0.05$; II vs IV-A, $P < 0.002$; and II vs IV-B, $P < 0.05$).

Table 2 presents the treatment procedures and characteristics of the patients. The principal treatment procedures were PEI, operation, TAE, LpI, one-shot, and chemotherapy, which were performed in 11, 16, 29, 9, 12, and 18 cases, respectively. In 19 cases the HCC was left untreated. The treatment procedure was unknown in 2 cases. Figure 2 shows the stages of the patients. The percentage of stage I plus stage II was 91% for the patients treated by PEI and 88% for the surgically treated patients, whereas this rate was below 41% for the patients treated by the other procedures ($P < 0.005$).

The survival rates for the principal procedures are shown in Fig. 3. The 3-year survival rates of the patients treated by PEI, operation, and TAE were 90.9%, 53.6%,

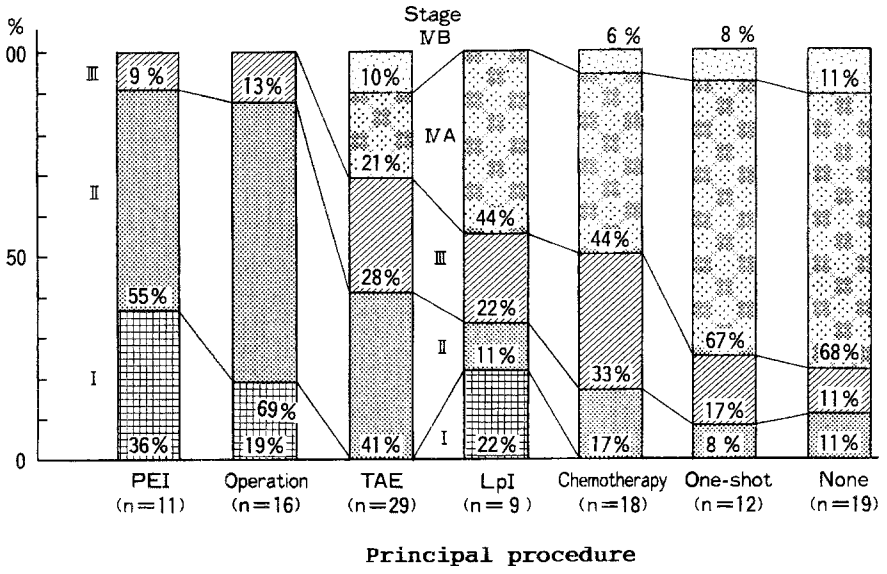

Fig. 2. Stages of the patients according to the principal treatment procedure

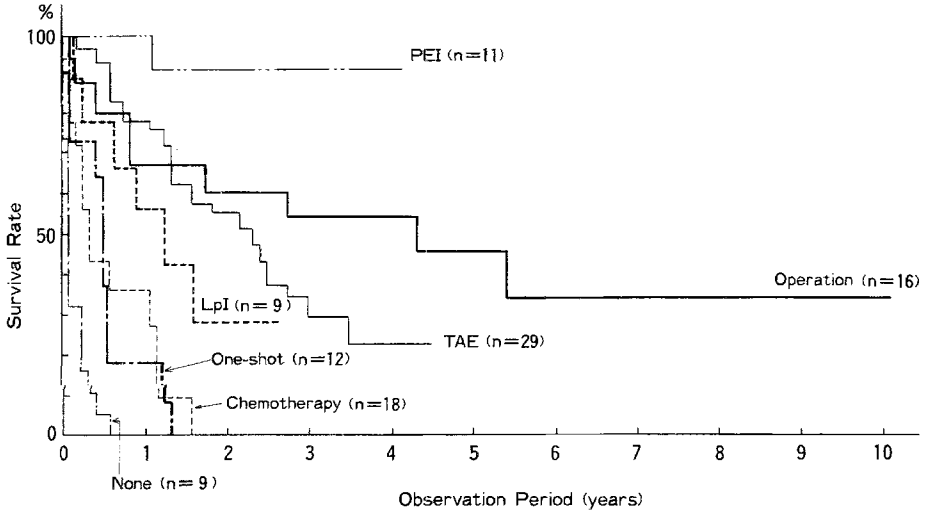

Fig. 3. Cumulative survival rates (Kaplan-Meier method) obtained in patients with HCC according to the principal treatment procedure. The outcome of the patients treated by PEI was significantly better than that of those treated by TAE, LpI, one-shot i.a. injection, or chemotherapy (P <0.05, P <0.01, P <0.005, and P <0.005, respectively). The outcome of the operated patients was significantly better than that of the patients treated by one-shot i.a. injection or chemotherapy (P <0.01 and P <0.01, respectively)

Table 3. Principal treatment procedures according to the year of detection

Principal treatment procedure	Year of detection						
	1980–1984	1985–1986	1987	1988	1989	1990	1991–1992
PEI	0	0	0	2	2	3	4
Operation	5	0	6	1	3	2	1
TAE	0	4	5	8	5	6	1
LpI	0	1	0	1	0	5	2
One-shot	3	3	2	0	0	0	2
Chemotherapy	3	2	3	1	3	2	4
Unknown	1	0	0	0	0	0	1
None	1	5	3	0	3	4	3
Totals	13	15	19	13	16	22	18

Numbers of cases are indicated

and 29.0%, respectively. None of the patients treated by either one-shot intra-arterial injection or chemotherapy survived for more than 2 years. The outcome of the patients treated by PEI was significantly better than that of the patients treated by TAE, LpI, one-shot intra-arterial injection, or chemotherapy (P <0.05, P <0.01, P <0.005, and P <0.005, respectively). The outcome of the operated patients was significantly better than that of the patients treated by one-shot intra-arterial injection or chemotherapy (P <0.01 and P <0.01, respectively). There was no significant difference in outcome between the patients treated by PEI and those treated by operation.

The 116 patients were divided into 7 groups according to the year when the HCC was detected. HCC was first

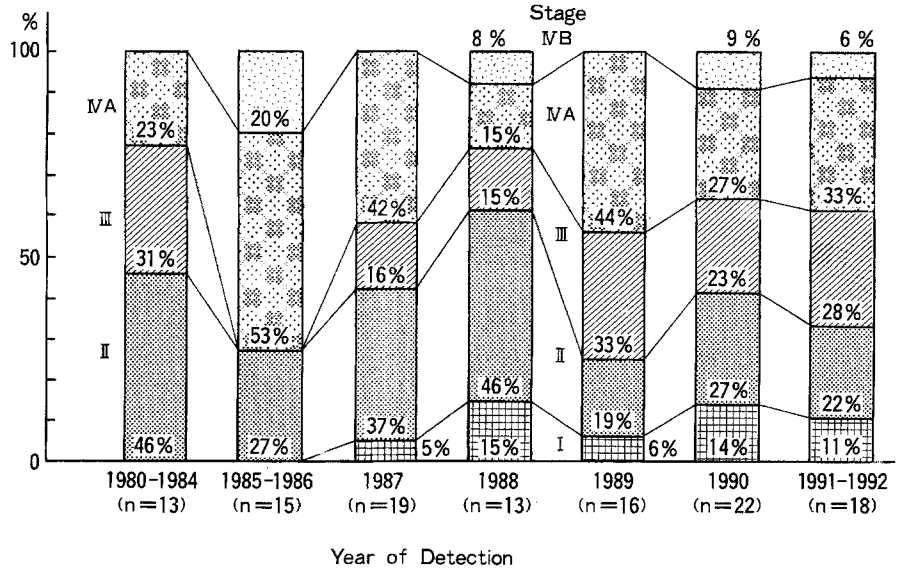

Fig. 4. Stages of the patients according to the year of detection

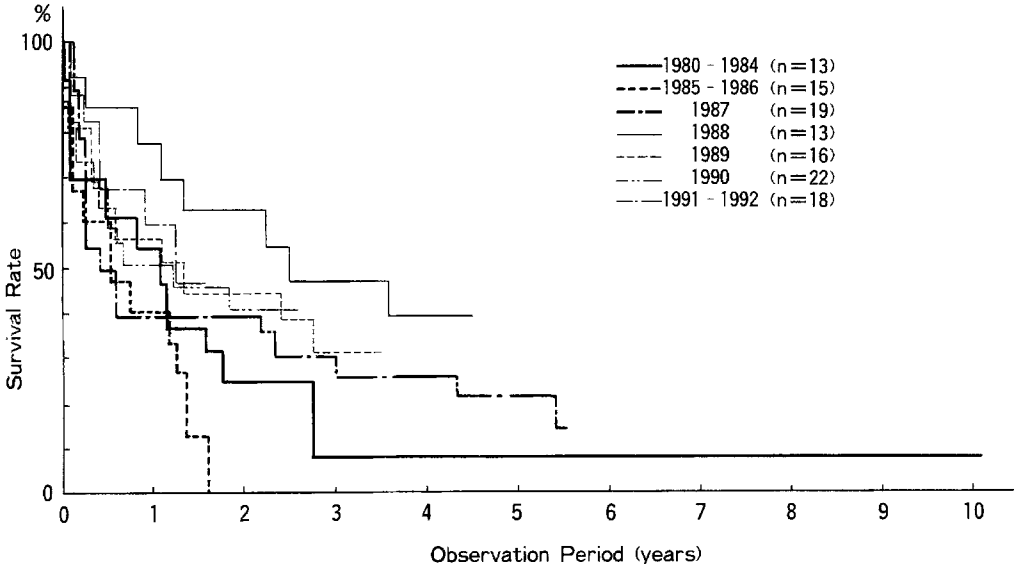

Fig. 5. Cumulative survival rates (Kaplan-Meier method) obtained in patients with HCC according to the year of detection. There was no statistically significant difference among the outcomes of the seven groups except for 1985–1986 vs 1988 (P <0.005)

detected in 13 patients between 1980 and 1984, in 15 patients in 1985 and 1986, in 19 patients in 1987, in 13 patients in 1988, in 16 patients in 1989, in 22 patients in 1990, and in 18 patients in 1991 and 1992. Table 3 compiles the principal treatment procedures performed in the seven groups. Figure 4 shows the data on the stages of the patients. Although HCC cases in stage I represented 5%–15% of the HCC cases detected every year since 1987, cases in stages IV-A and IV-B accounted for 23%–44% of the detected cases. There was no statistically significant difference among the rates of the clinical stages in the seven groups. Figure 5 presents the data on survival rates in those groups. There was no statistically significant difference among the outcomes of the seven groups except for 1985–1986 vs 1988 (P <0.005).

In 19 of the 116 patients, the HCC was detected during clinical follow-up in the outpatient clinic for chronic liver diseases. Clinical follow-up was performed for patients with liver cirrhosis or chronic hepatitis using ultrasonography and the measurement of tumor markers (alpha-fetoprotein and/or PIVKA-II). The mean interval between ultrasonographic examinations in these patients was 5.4 ± 3.3 months. Figure 6 compiles the data on the stages of the patients: 19 cases of HCC detected during clinical follow-up in the outpatient clinic and 97 cases detected elsewhere. The percentages of patients in stages I and II were 32% and 47%, respectively, in the 19 follow-up patients, whereas these rates were 3% and 27%, respectively, in the other 97 patients (P <0.005). For the 19 patients with HCCs detected during clinical follow-up, the 1-, 2-, 3-, 4-, and 5-year survival rates were 89.5%, 73.7%, 57.3%, 57.3%, and 57.3%, respectively. For the other 97 patients, the 1-, 2-, 3-, 4-, and 5-year survival rates were 45.8%, 28.7%, 17.3%, 15.1%, and 13.0%, respectively. There was a significant difference (P <0.001) between the outcomes of these two groups (Fig. 7).

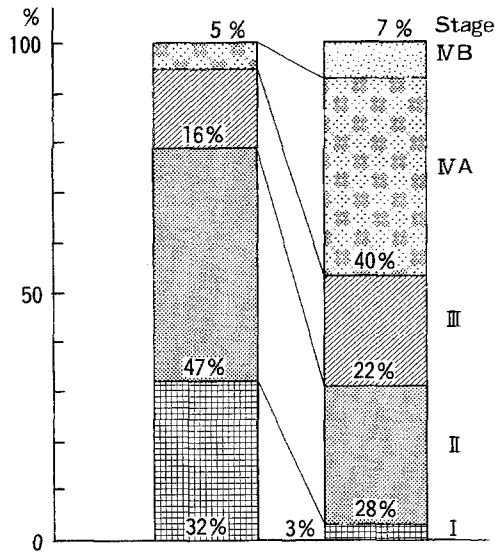

Fig. 6. Stages of the patients with HCC detected in an outpatient clinic for chronic liver diseases. *Left column:* Detected in outpatient clinic for chronic liver diseases (n = 19); *right column:* Others (n = 97)

Discussion

Hepatitis B virus [1, 9, 10, 13] and hepatitis C virus [6, 18, 23, 25] have been recognized to have close relationships with HCC in Japan. HBsAg, HBsAb, and HBcAb were positive in 26.0%, 26.9%, and 69.1% of Japanese HCC patients, respectively [10]. Hepatitis C virus was positive in 46%–94% of HCC cases [6, 18, 23, 25]. Cirrhosis and fibrosis were observed as accompanying changes in the noncancerous portion of the liver at autopsy in 73.8% and 7.9% of HCC cases, respectively. Only 10.1% of HCC cases did not show accompanying changes. According to the Liver Cancer Study Group of Japan [10], the rate of hepatic resection was only 18.1%, mainly because the accompanying liver cirrhosis was often too far advanced to permit surgery. On the other hand, PEI [4, 12, 20], TAE [2, 5, 24], and LpI [14, 15, 22, 26] have been widely accepted as treatment procedures for unresectable HCC.

Ebara et al. [3] reported that the 3-year survival rate of patients with untreated HCCs measuring less than 3 cm in diameter was 12.8%. The 3-year survival rates of the stage I and II patients in our earlier study were high in comparison with the data reported by Ebara et al. [3]. Treatment of HCC in the early stage (especially in stages I and II) is expected to improve the prognosis.

The resectable rate in our hospital was also low (13.8%) due to many cases of severe liver dysfunction caused by liver cirrhosis. Accordingly, we performed PEI, TAE, and LpI in 42.2% of the unresectable cases. In our study, the patients treated by PEI or operation had better outcomes than those treated by other procedures. We surmise that this reflects the high rates of patients with stage I or II disease in this study.

Although the development of ultrasonography has contributed greatly to increasing the number of patients diagnosed in the early stage, advanced cases continue to be detected. There was no statistically significant difference among the rates of the various clinical stages when the patients were stratified according to the year of detection, and this is considered to be the reason why there was no significant difference among the outcomes of the seven groups that were divided according to the year of detection. In contrast, the rate of patients in stage IV-A and IV-B was largest (73%) in 1985–1986 and smallest (23%) in 1988, and this observation is considered to be responsible for the significant difference in outcome noted between patients with HCCs detected in 1985–1986 and those detected in 1988.

One method for improving early detection is mass survey. An ultrasonic mass survey was conducted by the Miyagi Cancer Society to detect hepatic, biliary tract, and pancreatic cancers. In all, 16 cases of HCC were detected among 7,022 examinees: 1 case (6%) in stage I, 10 cases (63%) in stage II, 2 cases (13%) in stage III, and 3 cases (19%) in stage IV-A. The 1-, 2-, 3-, and 4-year survival rates were 83.3%, 72.9%, 60.8%, and 48.6%, respectively [16, 17]. Mass survey by ultrasonography is one method for detecting HCC in the early stage.

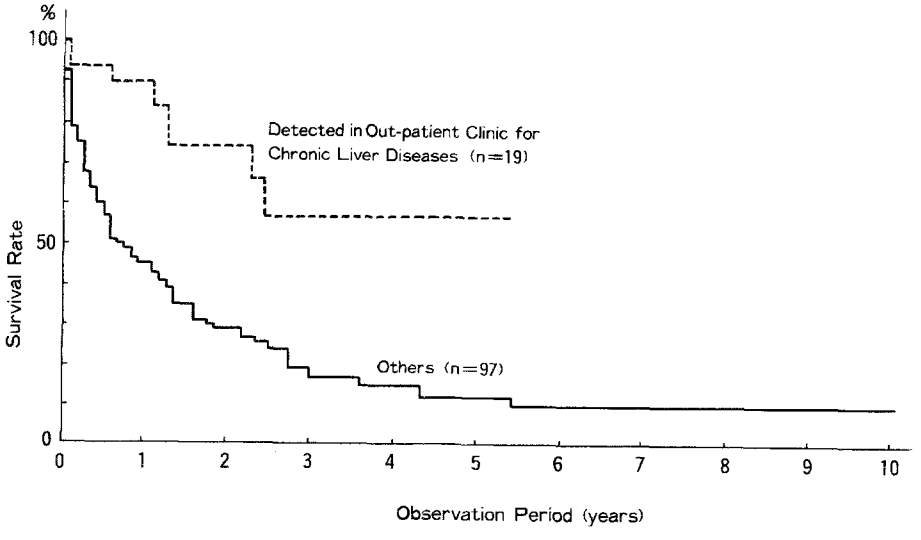

Fig. 7. Cumulative survival rates (Kaplan-Meier method) obtained in patients with HCC detected in an outpatient clinic for chronic liver diseases and others. There was a significant difference (P <0.001) between the outcomes of these two groups

Another method for early detection is clinical follow-up of cases of chronic liver disease [7, 8, 19]. In Japan, patients with chronic liver disease are considered to be at high risk of developing HCC [3]. In our outpatient clinic for chronic liver diseases, ultrasonography is performed at 3- to 4-month intervals for liver cirrhosis patients and at 6- to 7-month intervals for chronic hepatitis patients, and tumor markers are measured at 1- to 3-month intervals. In all, 32% of the HCC cases detected during this clinical follow-up were in stage I. This rate is superior to that obtained in the mass survey described above.

On the basis of our findings, we conclude that PEI for early HCC and hepatic resection in patients with good liver function result in a significantly better chance for survival than to other procedures. Furthermore, for early detection, we strongly recommend strict clinical follow-up of patients with known chronic liver disease.

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