Acta Medica Okayama

Volume 47, *Issue* 5 1993 *Article* 8

OCTOBER 1993

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Abstract

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KEYWORDS: hepatocellular carcinoma, prognosis, multrivariate analysis, Cox's proportional hazards model, simulation model

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*PMID: 8273457 [PubMed - indexed for MEDLINE]

Acta Med Okayama 47 (5) 339-346 (1993)

Survival Simulation of Hepatocellular Carcinoma Derived from Follow-up Studies of 450 Patients

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A simulation model to predict the survival probability of individual patients with hepatocellular carcinoma (HCC) after therapy was derived from the results of various therapies and follow-up studies of 450 HCC patients. Twenty-two prognostically important variables were analyzed by Cox's proportinal hazards model. The 9 significant variables that were extracted were used to build the simulation. In this model, S(t), the expected estimated survival rate for individual patient at time t (month), is calculated by the following equation: $S(t) = \{\exp(-0.03655t)\}^{\wedge}\{\exp[0.9479([\text{portal vein invasion}]-0.222)+0.3846([\text{tumor number}]-2.00)+0.2578([\text{tumor size}]-3.231)+0.0742([\log_e \text{AFP}]-5.647)+0.8184([\text{metastasis}]-0.036)+0.2810([\text{Child's class}]-1.689)-0.7088([\text{transcatheter arterial embolization}]-0.578)-0.9746([\text{percutaneous ethanol injection}]-0.153)-0.5377([\text{hepatectomy}]-0.109)]\}$ The validity of the model was assessed using a split-sample technique. This paper does not discuss the superiority or inferiority of the therapies, because some selection bias for prognostic factors among the therapies can not be completely excluded. But this model is proposed as a practical model to predict the survival of patients with HCC.

Key words : **hepatocellular carcinoma, prognosis, multivariate analysis, Cox's proportional hazards model, simulation model**

Hepatocellular carcinoma (HCC) arises in patients with chronic liver disease, particularly in those with liver cirrhosis. The first choice of therapy is hepatectomy, but HCCs are often unresectable at the time of diagnosis due to tumor size, invasion of major vessels, associated liver cirrhosis, or the anatomical singleness of the liver. Therefore, we are now striving to develop alternative treatments including transcatheter arterial embolization (TAE) and percutaneous ethanol injection (PEI). TAE for unresectable HCC was reported in 1983 (1), and the procedure is now broadly applied in most HCC cases because of the excellent therapeutic effect. PEI was introduced for patients with small HCC in 1983 (2, 3), and has also proved to have excellent therapeutic effect on HCC.

It is sometimes difficult to assess the clinical efficacy of each therapy, because the extent of HCC and the severity of coexisting liver injury are different in each patient. Several studies have defined the prognostic factors that affect survival in patients with HCC (4-15). Some preliminary mathematical models for the prediction of survival of patients with HCC were recently reported (11-13). This paper describes a model for the prediction of survival of patients with HCC and discusses the usefulness between the former studies and the present model.

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Subjects and Methods

Subjects and selection of 22 variables for analysis of the prognosis. Four hundred fifty patients with unequivocal HCC were admitted to our department in the 11-year period from July 1981 to December 1991. Diagnosis of HCC was based on histological findings in 199 cases, and other patients were diagnosed on the basis of elevated serum alpha-fetoprotein (AFP) with space-occupying lesions demonstrable by ultrasonography (US)

and computed tomography (CT), or by the typical arteriographic findings. The complete clinical records including physical examinations and laboratory data of all these patients were analyzed.

Twenty-two important variables which potentially affect the prognosis were selected (Table 1). The patients were 381 men (84.7 %) and 69 women (15.3 %) and their ages ranged from 25 to 83 years. The average age was 59.3 ± 8.2 (SD) years. All patients had either liver cirrhosis or chronic hepatitis. The patients were divided into 3 groups using Child's classification (16). The existence of ascites was assessed by US. TAE was carried out in 260 cases (57.8 %) as the first therapeutic modarity: PEI in 69(15.3 %), hepatectomy in 49 (10.9 %), transcatheter arterial injection chemotherapy without embolization (Infusion) in 84 (18.7 %). The other 44 patients (9.8 %) received no specific anti-cancer treatment due to the advanced stage of the disease. Both TAE and hepatectomy were performed in 19 patients as a combination therapy in the first series of therapy and both TAE and PEI were performed in 36 patients. The degree of tumor extension was evaluated by means of the images of US, CT, or angiography.

The value of main tumor size, the number of tumors, and portal vein invasions were disposed as the following semiquantative variables. Main tumor size of HCC was classified into 5 semiquantitative groups and scored according to its diameter on the US or angiographic images: less than 21 mm = 1, 21-30 mm = 2, 31-50 mm = 3, 51-100 mm = 4, and over 100 mm or diffuse type tumors = 5. The number of tumors was classified into 3 semiquantitative groups and scored by its number on their US and CT and/or angiographic appearance: solitary = 1, 2 or 3 tumors = 2, and more than 3 tumors = 3. Involvement of the portal vein was classified as positive, if the tumor thrombus was detected in the second or more proximal branch of the portal veins using US or angiography. According to the criteria of the Liver Cancer Study Group of Japan (17), macroscopic stage and intrahepatic metastasis (IM) factors were scored as followed: stages I, II, III, IVa, IVb = 1, 2, 3, 4, 5 and IM 0, 1, 2, 3 = 0, 1, 2, 3.

The time lag between the diagnosis and the first therapy varied; about 1-3 weeks in TAE, PEI and Infusion, and about 1-2 months in hepatectomy. Therefore, the time point from which the survival period was calculated was the day when the first therapy was performed, and the point was thought to be the day when the diagnosis was established in patients who did underwent no therapy. The follow-up study was closed on March 31, 1992. Three hundred sixteen patients (70.2 %) had died, and although the deaths of 16 patients (5.1 %) were not attributable to HCC or liver cirrhosis, death from any cause was treated as a failure for the purpose of survival analysis.

Statistical methods. The cumulative survival rates of whole patients and each of 3 therapies (TAE, PEI and hepatectomy) were calculated using the methods of Kaplan and Meier (18). The 22 variables were first studied individually using Cox's proportional

Table 1 Twenty-two important variables in relation to the prognosis of HCC

Demographic data		Tumor findings	No. patients(%)
1. Age (years; median)	56	17. Tumor size (mm)	
2. Sex, %male	84.7	0-20	59(13.1)
		21-30	84(18.7)
Clinical findings	No. patients (%)	31-50	98(21.8)
3. Child's classification		51-100	112(24.9)
Grade A	211(46.9)	over 100	97(21.6)
Grade B	167(37.1)	18. Tumor number	
Grade C	72(16.0)	Solitary	108(24.0)
4. Ascites	129(28.7)	2 or 3	144(32.0)
5. Encephalopathy	59(13.1)	More than 3	188(44.0)
6. HBsAg positive	89(19.8)	19. Portal vein invasion	
		Presence	100(22.2)
Laboratory data	Median	20. Macroscopic stage	
7. Alpha fetoprotein (ng/ml)	176	Stage I	34(7.5)
8. K-ICG(%)	0.09	Stage II	90(20.0)
9. Total bilirubin (mg/dl)	1.02	Stage III	76(16.9)
10. Albumin(g/dl)	3.6	Stage IV a	234(52.0)
11. Total cholesterol (mg/dl)	156	Stage IV b	16(3.6)
12. Prothrombin time (sec.)	14.4	21. IM factor	
		IM 0	102(22.7)
Therapy	No. patients (%)	IM 1	41(9.1)
13. TAE	260(57.8)	IM 2	121(26.9)
14. PEI	69(15.3)	IM 3	186(41.3)
15. Hepatectomy	49(10.9)	22. Distant metastasis	
16. Infusion	84(18.7)	Presence	16(3.6)

K-ICG: Indocyanine green plasma disppearance rate; TAE: Transcatheter arterial embolization; PEI: Percutaneous ethanol injection.

Table 2 Univariate analysis of 22 variables and establishment of hazard ratio of each variable

Demographic data	HR[a] (95 % CI[b])	Tumor findings	HR (95 % CI)
1. Age	1.1(0.8-1.3)	17. Tumor size (mm)	
2. Sex	1.5(1.1-2.0)	0-20	1.0
		21-30	2.0(1.8-2.2)
Clinical findings	HR (95 % CI)	31-50	3.8(3.1-4.7)
3. Child's classification		51-100	7.4(5.4-10.3)
Grade A	1.0	over 100	14.5(9.5-22.4)
Grade B	1.5(1.3-1.8)	18. Tumor number	
Grade C	2.4(1.7-3.2)	Solitary	1.0
4. Ascites	2.0(1.5-2.4)	2 or 3	2.7(2.3-3.2)
5. Encephalopathy	1.8(1.3-2.4)	More than 3	7.2(5.2-10.1)
6. HBsAg	1.4(1.1-1.8)	19. Portal vein invasion	
		Presence	7.7(5.9-10.2)
Laboratory data	HR (95 % CI)	20. Macroscopic stage	
7. Alpha fetoprotein	2.0(1.6-2.5)	Stage I	1.0
8. K-ICG	0.7(0.5-0.8)	Stage II	2.0(1.8-2.3)
9. Total bilirubin	1.6(1.3-2.0)	Stage III	4.0(3.1-5.3)
10. Albumin	0.6(0.5-0.8)	Stage IV a	8.1(5.4-12.1)
11. Total cholesterol	0.8(0.7-1.0)	Stage IV b	16.3(9.5-27.9)
12. Prothrombin time	1.0(0.8-1.3)	21. IM factor	
		IM 0	1.0
Therapy	HR (95 % CI)	IM 1	1.8(1.6-2.0)
13. TAE	0.6(0.5-0.8)	IM 2	3.2(2.5-4.0)
14. PEI	0.2(0.1-0.4)	IM 3	5.7(4.1-7.9)
15. Hepatectomy	0.3(0.2-0.5)	22. Distant metastasis	
16. Infusion	3.5(2.7-4.7)	Presence	6.0(3.6-10.0)

a: HR; hazard ratio; *b*: 95 % CI; 95 % confidence interval. TAE, PEI: See Table 1.

hazards model for the univariate analysis. Some variables; presence or absence of TAE, PEI, were dichotomously divided. The continuous variables, age or biochemical data, were dichotomously divided by their median. The hazard ratio, defined as the influence of each variable on survival, was calculated by comparing patients with positive findings or presence of therapies to those with negative findings or absence of therapies. The hazard ratio of continuous variables was calculated by comparing patients with data above the median to those with data below the median. The hazard ratio of macroscopic stage, tumor number, main tumor size, and IM factor was calculated by comparing patients with least advanced tumor development to those with more advanced tumor development. The hazard ratio of Child's classification was similarly calculated (Table 2).

A multivariate analysis of the same 22 variables was performed to determine the significant prognostic factors. The number was used with the age data, and natural logarithmic transformation was used with the biochemical data, but other variables were scored in the same manner as the univariate analysis. Cox's proportional hazards model (19) and stepwise variable selection procedures were used to select variables for the model. Finally, the variables ratained in the model were calculated as statistically significant ($p < 0.05$). The appropriateness of the proportional hazards assumption was examined by the Z: PH statistics (20). A statistical analysis system (SAS) procedure, PHGLM (21), was used for the computer analysis. In this model, the hazard ratio (H) of each patient was shown in the equation below:

$$H = \lambda(t: x)/\lambda 0(t)$$
$$= \exp\{\beta 1(x1 - \bar{x}1) + \cdots + \beta k(xk - \bar{x}k)\}$$

$\lambda(t: x)$: the hazard function of a particular patient at time t

$\lambda 0(t)$: the hazard function at the average values of the variable in the model, the so-called underlying hazard

$\beta 1, .., \beta k$: regression coefficients of the variables

$x1, .., xk$: the values of the variable of a particular patient

$\bar{x}1, .., \bar{x}k$: the average values of the variable in the model

Let S(t, x) give the probability that a patient with risk factors given as $x = \{x1, .., xk\}$ and with hazard ratio H will still be alive t months later. We obtained a very simple formula for S (t, x), given by

$$S(t, x) = \{S\ 0(t)\}\hat{}H,$$

where S0(t) is the survival function at the average value of each variable in the model. Here, exp and $\hat{}$ stand for exponential function, *e.g.*, $\exp(x) = e^x$ and $a\hat{}x = a^x$. S0(t) could be regarded as an exponential curve, which closely resembles the cumulative survival curve of the 450 patients.

The split-sample technique was used to validated the predictive power of model (22).

Results

The cumulative survival rates of each therapy. The cumulative survival curve of whole patients is shown in Fig. 1. The overall survival rates were 62 % at 1 year, 30 % at 3 years and 14 % at 5 years. The overall mean survival time was 27.1 months. An exponential curve, applying the cumulative survival curve of the all 450 patients was also shown in Fig. 1. The equation for the exponential curve is expressed as follows:

$S0(t) = \exp(-0.03653t)$.

Two cumulative survival curves of 205 HCC patients treated by TAE alone, and 98 patients with small HCC with a diameter less than 5 cm are shown in Fig. 2. The 1, 2, 3, 4 and 5-year survival rates of those 205 patients were 66 %, 42 %, 26 %, 17 % and 12 %, respectively, while those of 98 patients with small HCC were 84 %, 60 %, 37 %, 27 % and 17 %, respectively (Fig. 2).

Two cumulative survival curves of 69 HCC patients treated by PEI, and 52 patients with a diameter less than 3 cm are shown in Fig. 3. The 1-, 2-, 3-, and 4-year survival rates of 96 patients were 98 %, 83 %, 65 %, and 49 %, respectively, while those of 52 patients with HCC less than 3 cm were 100 %, 89 %, 66 %, and 66 %, respectively (Fig. 3).

The cumulative survival rates of 49 patients treated with hepatectomy were 87 % at 1 year, 80 % at 2 years, 74 % at 3 years, 56 % at 4 years and 38 % at 5 years (Fig. 4).

Results of univariate analysis. The results of univariate analysis of 22 prognostic variables are presented in Table 2. The hazard ratio 1.5 of the variable, Sex means that the risk of death of a man is 1.5 times higher than that of a woman. Many variables were significant factors in predicting survival as indicated by hazard ratio.

Results of multivariate analysis and construction of a simulation model. Twenty-two variables were analyzed by multivariate Cox's proportional hazards model with a

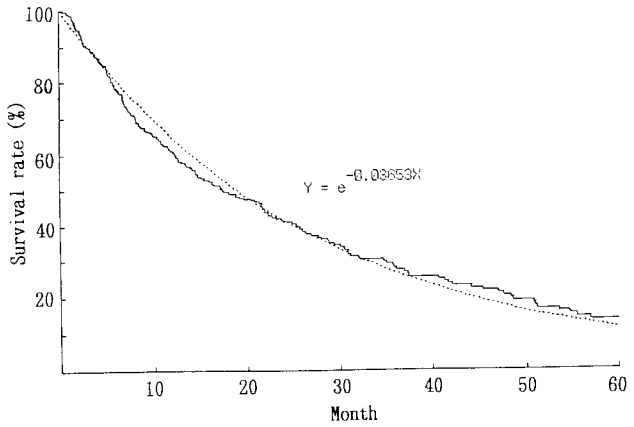

Fig. 1 Cumulative survival curve of the whole patients (—) and the applied exponential curve (····)

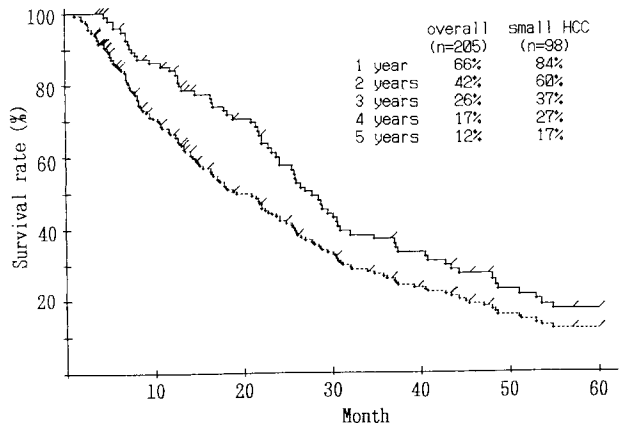

Fig. 2 Cumulative survival curves of HCC patients treated by transcatheter arterial embolization (TAE) alone; overall patients (····), small HCC patients with a diameter less than 5 cm (—).

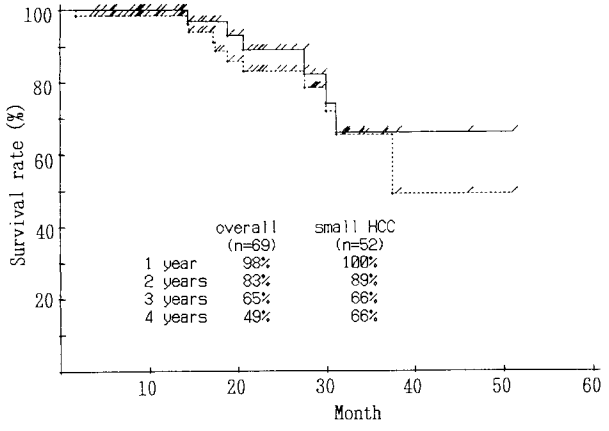

Fig. 3 Cumulative survival curves of HCC patients treated by percutaneous ethanol injection (PEI); overall patients (····), small HCC patients with a diameter less than 3 cm (—).

Table 3 Nine significant factors in relation to the prognosis extracted by multivariate Cox's proportional hazards model

Variables included	Scoring	Mean (SD[a])	β[b](SE[c])	χ^{2d} P^e	HR (95 % CI)
1. Portal vein invasion	Absence: 0	0.222(0.42)	0.9479(0.1649)	33.05***	1.0
	Presence: 1				2.6(1.9-3.5)
2. Tumor number	1 tumor: 1	2.200(0.80)	0.3846(0.1131)	11.55***	1.0
	2 or 3 tumors: 2				1.5(1.2-1.8)
	More than 3 tumors: 3				2.2(1.4-3.8)
3. Tumor size	0-20 mm: 1	3.232(1.33)	0.2578(0.0688)	14.06***	1.0
	21-30 mm: 2				1.3(1.1-1.5)
	31-50 mm: 3				1.7(1.3-2.2)
	51-100 mm: 4				2.2(1.4-3.3)
	Over 100 mm: 5				2.8(1.6-4.9)
4. Alpha fetoprotein	Log_e (value)	5.647(2.77)	0.0742(0.0224)	10.98***	1.3[f](1.1-1.4)
5. Distant metastasis	Absence: 0	0.036(0.19)	0.8184(0.2737)	8.94**	1.0
	Presence: 1				2.3(1.3-3.9)
6. Child's clasification	Child A: 1	1.689(0.73)	0.2810(0.0874)	10.34**	1.0
	Child B: 2				1.3(1.1-1.6)
	Child C: 3				1.8(1.3-2.5)
7. TEA	Unselection: 0	0.578(0.49)	−0.7088(0.1415)	25.10***	1.0
	Selection: 1				0.5(0.4-0.7)
8. PEI	Unselection: 0	0.153(0.36)	−0.9746(0.3290)	8.77**	1.0
	Selection: 1				0.4(0.2-0.7)
9. Hepatectomy	Unselection: 0	0.109(0.31)	−0.5377(0.2679)	4.03*	1.0
	Selection: 1				0.6(0.4-0.9)

a: Standard deviation of value; *b:* Regression coefficient; *c:* Standard error of cofficient; *d:* Chi-square test statistic for assessing significance of coefficient; HR, CI: See Table 2; *e:* p value for the test (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$) *f:* compared the values of AFP with 400 ng/ml to 20 ng/ml

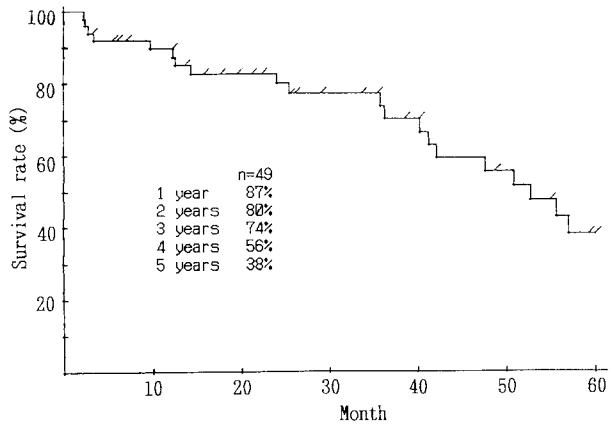

Fig. 4 Cumulative survival curves of HCC patients treated by hepatectomy.

stepwise variable selection procedure (Table 3). The 9 significant factors which correlated to survival extracted included portal vein invasion, tumor number, main tumor size, alpha fetoprotein (AFP), distant metastasis, Child's classification, TAE, PEI and hepatectomy. The scoring and mean level of each of the 9 factors, and the regression coefficients on a simulation model are shown in Table 3. The simulation model was constructed using these 9 factors:

$$S(t) = \{\exp -(0.03655t)\}^{\wedge}\{\exp [0.9479([\text{portal vein invasion}] - 0.222) + 0.3846([\text{tumor number}] - 2.00) + 0.2578([\text{tumor size}] - 3.231) + 0.0742([\log_e \text{AFP}] - 5.647) + 0.8148([\text{metastasis}] - 0.036) + 0.2810([\text{Child's class}] - 1.689) - 0.7088([\text{transcatheter arterial embolization}] - 0.578) - 0.9746([\text{percutaneous ethanol injection}] - 0.153) - 0.5377([\text{hepatectomy}] - 0.109)]\}$$

Hazard ratios of each factor are also shown in Table 3. Portal vein invasion, main tumor size, tumor number, Child's classification, AFP, and distant metastasis were identified as unfavorable prognostic variables. Favorable prognostic variables were PEI, TAE, and hepatectomy.

Assessment of validity of the simulation model. The predictive power of the simulation model was tested using the split-sample technique (22). According to the method of Schlichting *et al.* (22), 450 patients were divided into 2 groups using a stratified sampling method to avoid bias in the cancer stages or therapies. Group A

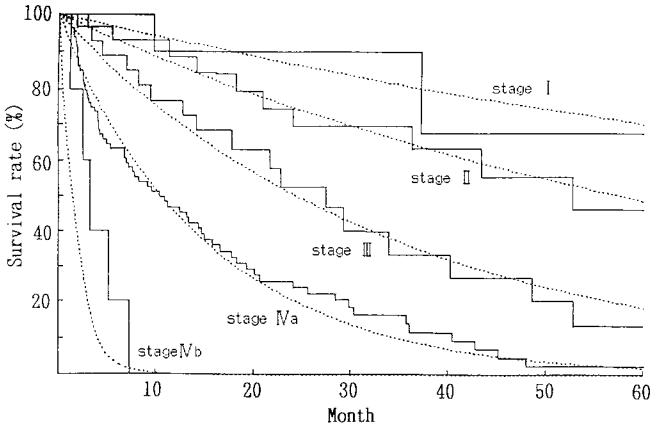

Fig. 5 Test of the simulation model by split-sample technique. Actual (——) and predictive (……) survival curves for five groups of patients divided according to macroscopic stage.

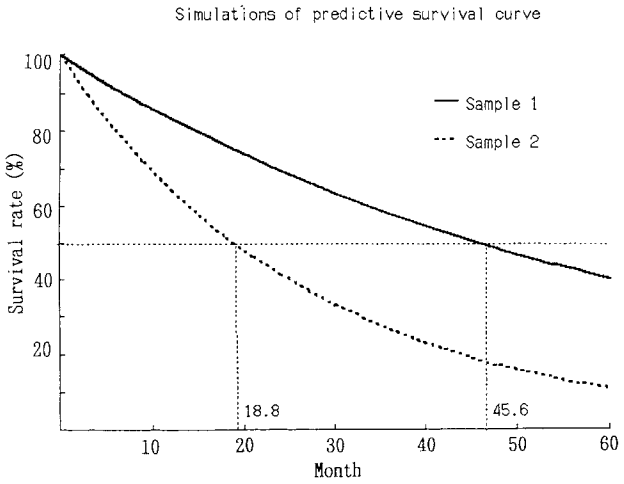

Fig. 6 Simulations of the expected survival probability for the sample cases. (sample 1; ——, sample 2; ……)

(300 patients) was used for making a test survival model using the same 9 factors and group B (remaining 150 patients) was used for calculation of the actual survival rate. Group B was divided into 5 subgroups according to macroscopic stage, and actual survival curve of each subgroups which was calculated by the Kaplan-Meier method. The predictive survival curve of each subgroup of group B was plotted using the test survival model constructed from group A. Both survival curves were compared, and validation was assessed by measurement of the difference between these paired survival curves. No significant difference was observed in the paired survival curves of the 5 subgroups (Fig. 5).

Actual practice of the simulation model. The formula of the simulation model was programmed into a personal computer (PC-9801, NEC Corporation, Tokyo), and predictive survival curve was graphically demonstrated. The commercial softwares, (Multiplan and MS-Chart, Microsoft Corporation, Tokyo), were used for the calculation and the diagram. Hazard ratios were calculated by the regression coefficients shown in Table 3 and the value of the 9 factors of a sample case. Predictive survival rate after t months; S(t), was calculated by putting the hazard ratio into the formula.

Sample 1. In an HCC patient with Portal invasion (−) = 0, Tumor number (2 tumors) = 2, Tumor size (25 mm) = 2, AFP (400 ng/ml) = 5.99, Distant metastasis (−) = 0, Child's class B = 2, TAE (−) = 0, PEI (+) = 1, and Hepatectomy (−) = 0, hazard ratio is 0.415, $S(t) = \{\exp(-0.03655t)\}^{0.415}$, and a predicted simulation curve is obtained (Fig. 6).

Sample 2. In another patient with Portal invasion (−) = 0, Tumor number (over 3 tumors) = 3, Tumor size (70 mm) = 4, AFP (400 ng/ml) = 5.99, Distant metastasis (−) = 0, Child's class A = 1, TAE (+) = 1, PEI (−) = 0, and Hepatectomy (−) = 0, the simulation is $S(t) = \{\exp(-0.03655t)\}^{1.006}$, and another survival curve was obtained (Fig. 6).

The simulation of predictive survival curves presented in the Fig. 6 showed that the expected survival rates of Sample 1 were 83.3 % at 1 year, 57.9 % at 3 years and 40.2 % at 5 years, while those of Sample 2 were 64.3 % at 1 year, 26.6 % at 3 years and 11.0 % at 5 years, and the predictive times for 50 % survival were 45.6 months in Sample 1 and 18.8 months in Sample 2, respectively. Only the comparison of each hazard ratio was useful, but the graphic demonstration of predicted survival curve was more impressive.

Discussion

HCC is a common malignacy with poor prognosis in Japan. The number of patients with HCC is gradually and definitely increasing. Recently, both regular examinations in high risk patients, and advances in imaging techniques

have made it possible to detect HCC at an earlier stage. Furthermore, TAE and PEI, which can cause tumor necrosis by direct action, have been developed and used widely for patients with unresectable HCC. Therefore, the prognosis of HCC have been altered by these recent advances in diagnosis and treatment. In our series, only 49 patients (10.9 %) underwent hepatectomy, but mean survival period of all 450 patients was 27.1 months. This result is better than that of an earlier report (8).

This study was designed to determine the important prognostic factors in a large series of Japanese patients with HCC and to develop a model for survival simulation. Other institutions have recently published HCC survival rates. Yamada (23) described the results of 66 patients with small HCC with a diameter less than 5 cm treated by TAE alone, and the 1, 2, and 3-year survival rates were 72 %, 55 %, and 47 %, respectively. Ebara (3) described the results of 95 patients with HCC with a diameter 3 cm or smaller treated by PEI, and 1-year survival rate was 93 %, 2-year 81 %, 3-year 65 %, 4-year 52 %, and 5-year 28 %. The Liver Cancer Study Group of Japan (24) reported the survival rate of HCC patients treated by hepatectomy, and the 1-year, 3-year, and 5-year survival rates were 67.1 %, 39.6 %, and 28.5 %, respectively. Our results were similar. The large number of patients with HCC in various stages that were admitted and received various therapies in our department, appears to be suitable for a simulation study of HCC.

Only 9 variables were identified in the multivariate analysis as significant in the prediction of survival of patients with HCC. These 9 variables can be subdivided into 3 groups. The first correlates the extension of the tumor (portal vein invasion, tumor number, main tumor size, AFP, distant metastasis), and the second correlates to the severity of liver disease (Child's classification), and the third includes therapeutic factors (TAE, PEI and hepatectomy). This result appears to confirm the expection of a more favorable prognosis when the HCC is detected in a less advanced stage, the careful maintenance of concomitant liver disease and the development of each of 3 therapies. Previous prognostic studies for patients with HCC used histological data or tumor factors recorded in surgery (4-7), and were analyzed by univaliate methods (8-10). Several other studies included analyses by multivaliate methods (11-15), but therapeutic factors were rarely selected as a prognostic factor in these studies (11, 12). Researchers may find our model interesting because 3 therapeutic factors are included. Of course, this model does not discuss the superiority or inferiority of these 3 therapies, because therapy selection is based on other variable conditions of tumors and patients. Consequently the indication of each therapies were differrent, and some selection bias of prognostic factors can not be excluded completely among these therapies. Surgically treated patients are highly selected with a correct diagnosis of absence of intrahepatic metastasis or non-multifocal tumorgenesis at the time of operation and with a good reserve liver function for hepatectomy. The unresectable cases undergo TAE, PEI, Infusion or other conservative therapy, independently or combined. A good indication of TAE is for an expanding type of HCCs, particularly an encapsulated HCC. PEI is applicable for small HCCs, generally no larger than 3 cm in diameter and less than 3 in number.

Recently reported mathematical models for the prediction of survival of individual patients with HCC (11-13) stratified the patients by means of a prognostic index or relative risk. In contrast, our model is a mathematical simulation of survival and its graphic presentation for individual patients. This model sould be able to present more definite and impressive information of the expected survival probability. Although this model is not a decision making tool for optimal therapy for HCC, the survival of individual patients in various situations can be predicted by using this simulation model. In conclusion, the present simulation model is available for clinical management of HCC, and it could be used to provide more easily understood information to patients and their families. The authors hope this model will be widely used for management of cases of HCC.

Acknowledgments. This work was supported by a grant from the Comprehensive 10-year Strategy for Cancer Control by the Japanese Ministry of Health and Welfare. The authors would like to express their profound thanks to Ohtsuka Pharmacentical Company for assistance in the statistical analysis.

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Received January 19, 1993; accepted June 14, 1993.