

Natural History and Prognostic Factors of Primary Hepatocellular Carcinoma: Study of 70 Untreated Patients

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We carried out a study of the clinical courses of 70 untreated patients with primary hepatocellular carcinoma (HCC) in order to evaluate their survival period and the prognostic factors.

The median survival was two months.

We evaluated ten variables of biochemical parameters and findings of hepatic scintigraphy. Among them, six variables were chosen by univariate analysis. They were serum bilirubin (cut-off value 3.0 mg/dl), alkaline phosphatase (150 IU/ml), aspartate aminotransferase (AST) (200 IU/ml), alanine aminotransferase (ALT) (50 IU/ml), reticuloendothelial (RES) dysfunction (grade 1) and multiplicity of space occupying lesions (SOL). Multivariate analysis identified three variables. The RES dysfunction and multiplicity of SOL by hepatic scintigraphy and bilirubin were considered as important prognostic factors.

We found that the functional reservoir of the underlying liver and multiplicity of the origin of the tumor were the most important prognostic factors.

Key Words: *Primary hepatocellular carcinoma, Median survival, Prognostic factors, Hepatic scintigraphy*

INTRODUCTION

PRIMARY HEPATOCELLULAR CARCINOMA is one of the most serious medical problems in this country. It is very common and fatal. Many efforts to care for the patients turned out to be disappointing. Few patients can have a surgical operation and thus a chance of cure.¹⁾ As yet, many patients do not undergo any treatment for cancer at all. But by experience we know that some patients live longer than others. It is suggested that there must be several subgroups with different lengths of survival periods. It would be helpful to be able to distinguish these.

It is also important to know the prognostic factors influencing the outcome of the patients. This knowledge helps us to understand the basic biological differences and to make treatment plans. There have been many studies with no unanimous agreements. In domestic journals, few authors have analyzed the prognostic features. So we investigated the natural course and prognostic factors of untreated patients with HCC.

MATERIALS AND METHODS

The medical records of seventy patients with HCC were reviewed retrospectively in Korea Veterans Hospital. From January 1984 to April 1988, 134 patients with HCC visited our hospital. We excluded 54 patients who received specific therapy for cancer. Eight patients were lost to follow-up after one or two visits and they were also excluded.

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The diagnosis of HCC was done by percutaneous needle biopsy in 11 cases. In other cases, the diagnosis was made on the elevated levels of alpha-fetoprotein (more than 700 ng/ml by radioimmunoassay) and appropriate radiological imaging (angiography, ultrasonography, computerized tomography and hepatic scintigraphy). We used 99m Tc-phytate for hepatic scintigraphy.

The survival time was counted from the first day of diagnosis. We contacted the district offices and the Patriots and Veterans Affairs Agency by mail and phone to determine the date of death.

Ten prognostic factors were studied. Age, albumin, bilirubin, alkaline phosphatase, AST, ALT, hepatitis B surface antigen, ascites, and RES dysfunction and multiplicity of SOL in the hepatic scintigraphy were evaluated as to prognostic value. We assessed the severity of RES dysfunction arbitrarily according to the absorption of radioisotope by the RES system and the size of the whole liver. Grade 1 implied normal uptake, grade 2, decreased uptake, and grade 3, decreased uptake and shrunk size (Fig. 1). Scintigraphic data were available only in 49 patients.

The survival curve was drawn by the Kaplan-Meyer method.

To determine the independency of variables we carried out a correlation analysis, discriminant analysis and Spearman rank correlation analysis.

Univariate analysis was done with Student's t-test, analysis of variance (ANOVA) and multiple comparison test of Duncan. We divided the groups at the points with the least p value and the difference was considered significant when $p < 0.05$.

Multivariate analysis was done with regression analysis to determine the contribution of the individual independent variables to the survival.

We used SPSS/PC+ software (SPSS Inc., Chicago).²⁾

RESULTS

The mean age of the patients was 56 years (range 36-77 years). There were 65 men and 5 women.

The survival curve is shown in Fig. 2. The median survival time was two months (standard error, 0.39 month) and the one-year survival rate was 4.3%.

Ten variables were tested for their independency. Above all, biochemical parameters had significant correlation coefficients between them (Table 1), and thus they were closely related variables, not independent variables. Scintigraphic data had a relationship with the other factors. In the discriminant

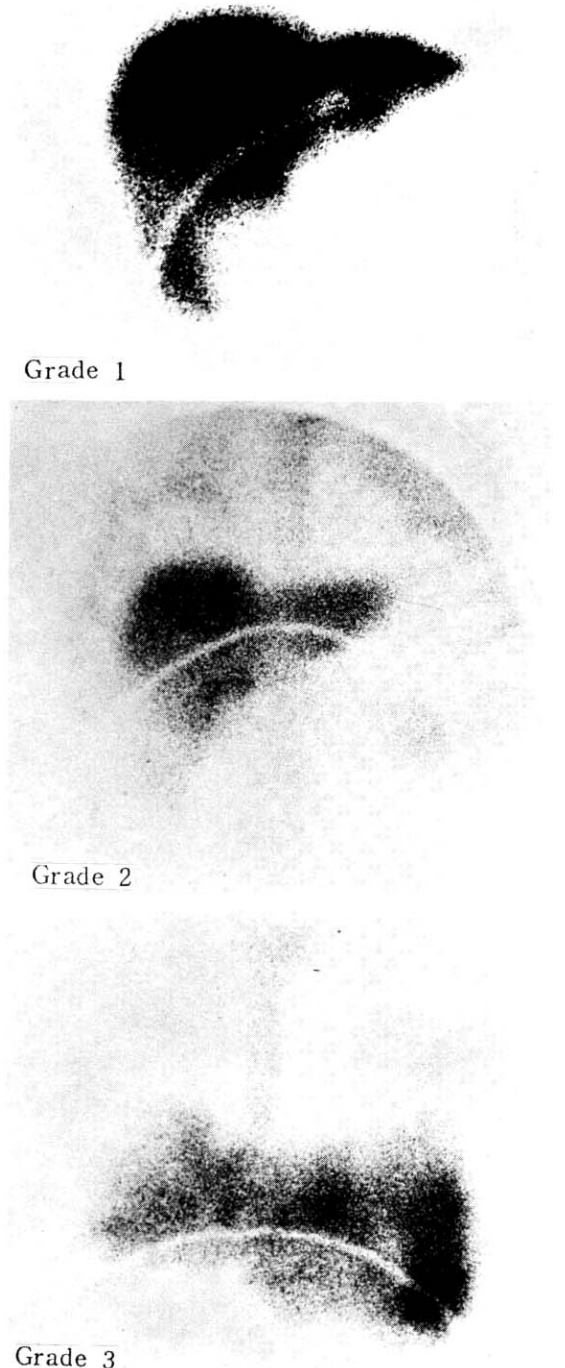


Fig. 1. Grades of Reticuloendothelial Dysfunction in Hepatic Scintigraphy

- 1) Grade 1 3) Grade 3
2) Grade 2 (See text for detailed description.)

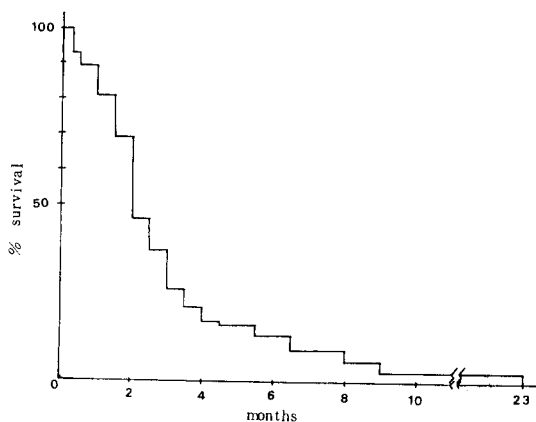


Fig. 2. Survival curve of 70 patients who did not receive specific treatment.

Table 1. Correlation Coefficients between Biochemical Parameters

	Bilirubin	AP	Albumin	AST	ALT
Bilirubin	—				
AP	0.3088 (p=0.005)	—			
Albumin	-0.2794 (p=0.010)	-0.2803 (p=0.009)	—		
AST	0.2319 (p=0.027)	0.6423 (p=0.000)	-0.2945 (p=0.007)	—	
ALT	0.3221 (p=0.003)	0.4950 (p=0.000)	-0.2441 (p=0.021)	0.5856 (p=0.000)	—

AP : alkaline phosphatase
 AST: aspartate aminotransferase
 ALT: alanine aminotransferase
 p<0.05: significant

analysis, we knew that RES dysfunction was not significantly related with other variables (p=0.2136). The multiplicity of SOL had relation with alkaline phosphatase and ALT (p=0.0025). RES dysfunction and multiplicity of SOL were not related in the Spearman rank correlation analysis (p=0.4432).

Six variables were related to the survival period in the univariate analysis. These were alkaline phosphatase (mean survival 4.7 versus 2.2. months), bilirubin (4.1 vs 2.2 months), AST (4.7 vs 2.2 months), ALT (4.3 vs 2.0 months), RES dysfunction and multiplicity of SOL (4.6 vs 1.9 months) (Table 2). With respect to RES dysfunctions, we executed the multiple comparison test of Duncan. Mean sur-

Table 2. Prognostic Significance of Variables in Univariate Analysis

Variables	Cut-off Value	p value
Age	55	0.200
HBsAg	positive	0.989
Ascites	presence	0.063
Bilirubin	3.0 mg/dl	0.023
Alkaline phosphatase	150 IU/ml	0.004
Albumin	2.5 g/dl	0.106
AST	200 IU/ml	0.010
ALT	30 IU/ml	0.008
RES dysfunction	grade	0.0013*
Multiplicity of SOL	multiple	0.020

HBsAg: hepatitis B virus surface antigen
 AST : aspartate aminotransferase
 ALT : alanine aminotransferase
 RES : reticuloendothelial system
 SOL : space occupying lesions
 IU : international units
 p<0.05: significant
 * : F probability in the analysis of variance (ANOVA)

Table 3. Prognostic Significance of Variables in Multivariate Analysis

Variables	Coefficient	SE	p value
Multiplicity of SOL	-2.61	0.92	0.0069
R2*	-5.67	1.38	0.0001
R1*	-4.81	1.25	0.0004
Bilirubin	-0.34	0.14	0.0196
constant**	9.97	1.27	0.0000

SOL: space occupying lesions
 R2*, R1*: dummy variables of reticuloendothelial dysfunction
 constant**: constant of regression equation
 SE: standard error

vival of grade 1 (7.4 months) was different from that of grade 2 (2.8 months) and 3 (1.6 months). There was no difference between Grades 2 and 3.

The multivariate analysis found that three variables were related to the survival time. Those were RES dysfunction, multiplicity of SOL and bilirubin (Table 3).

DISCUSSION

We have confirmed the poor outcome of HCC.

The median survival of these untreated patients from the time of diagnosis to death was only two months. Three patients lived more than one year. Other studies have revealed that the natural history is the same all over the world^{3-6,10)}.

We wanted to know how to distinguish the subgroups with different life expectancies and the factors affecting the outcome. This information might give us insights of the fundamental characteristics of tumor behavior. The prognostic factors would be used as a guide in the care of patients and the design of clinical study.

There have been quite a few studies about the following prognostic factors: ascites, weight loss, portal hypertension, bilirubin,³⁾ encephalopathy, alcohol consumption, AST, blood urea nitrogen,⁴⁾ tumor size, albumin,⁵⁾ age, lung metastasis,⁶⁾ presence of capsule, invasion into parenchyma, satellite formation, portal vein involvement,⁷⁾ multiple sites of origin, coexistence of cirrhosis,⁸⁾ fibrolamellar variants⁹⁾ and so forth. In Korea, bilirubin, albumin, tumor size, ascites, and cell-mediated immunity were reported.¹⁰⁾

We took several aspects into account in choosing prognostic factors. First, our study was a retrospective one and we did not perform histological examinations (11 patients were confirmed by biopsy), so we had to rely on the objective laboratory data.

We knew Japanese reports that many patients died from hepatic failure rather than cancer itself.⁵⁾ So we tested the prognostic value of the biochemical measurements of liver function. We have an idea that hepatic scintigraphy basically reflects hepatic function. Hepatic scintigraphy is always considered as one of the morphologic studies but the image is related to the Kupffer's cells. Uptake of isotope and liver size have much to do with the reservoir of the underlying liver function.¹¹⁾ So we studied the RES dysfunction as one of the variables of liver function.

Many authors, especially pathologists, have suggested that the prognosis might be determined in advance by the biology of HCC itself.⁷⁾ They have underscored the characteristics of the gross growing patterns. Okuda et al reported that a solitary mass differed from multiple masses in several aspects.¹²⁾ It was frequently surrounded by a fibrous capsule. Multiple masses were seldom contained in a capsule. Despite some doubts, a single tumor might obtain a membrane by expansile growth.¹³⁾ Single tumors often grew steadily to a huge size but multiple masses rarely grew like that. It was suggested that there might be a basic difference between them

but the clinical implication was not studied in detail.¹²⁾

We paid attention to the real prognostic value of tumor growth patterns. It is well known that various imaging techniques correspond to pathologic findings. But a shortcoming of this retrospective study was that sensitive ultrasonographic data¹⁴⁾ were not available for analysis. Instead, we had to make use of hepatic scintigraphy. Hepatic scintigraphy correlates with other imagings to a reasonable degree.^{14,15)} As a result, we regarded scintigraphy as a test of both function and morphology. We doubted that tumor size had a real significance without consideration of the growth pattern or doubling time. According to a recent report, tumor size had no influence on the survival of surgical patients.¹⁶⁾ Also the conventional cut-off value of 50% of liver size^{5,10)} was too crude and there were no proposals for objective quantification of the tumor mass. We cancelled the investigation of tumor size.

There has been an emphasis on the microscopic findings of HCC. Many researchers particularly emphasized the histology of the boundary of the mass. Tumor invasion into the capsule or parenchyma was associated with recurrence after operation.⁷⁾ A solitary mass was also known to have either an encapsulated or spreading margin. There was a suggestion that an expanding mass differed from the spreading type as well as the multifocal type.¹²⁾ In our study, it was difficult to distinguish the expanding mass from the spreading mass due to the limited resolution of the scintiscan.

We progressed in the various statistical analyses. In validating the independency of the factors we found that they were intermingled to a degree and one should be careful in interpreting the results. In univariate study, the following six variables were important: bilirubin, alkaline phosphatase, AST, ALT, RES dysfunction and multiplicity of SOL. Age and sex distribution might be deviated because most of our patients were veterans of the Korean War. Ascites and albumin were omitted from choice. It is reasonable to think that the nature of ascites would be more important than the presence per se.¹⁷⁾ We had the same result as the previous observation on AST and the ratio of AST to ALT in HCC.¹⁸⁾ In multivariate analysis, the three factors of RES dysfunction, multiplicity of SOL and bilirubin were identified as prognostic factors. We have confirmed the importance of bilirubin as a prognostic factor.^{3,6,10,19)} But we found RES dysfunction and multiplicity of SOL were more important. In other words, the functional reservoir of the underlying liver and tumor growth pattern proved to be of important

prognostic value. As expected, hepatic scintigraphy had a good prognostic value. Scintiscan was not only a screening test but also a predictive test and it reflected that the destiny of a patient might be determined at the very beginning of the disease. In the analysis of biochemical parameters without scintiscan data, alkaline phosphatase was important but after including scintiscan data in the analysis, it was rejected from the regression equation. Regression analysis of alkaline phosphatase as a dependent variable showed that it was related to the multiplicity of SOL. We thought it might be substituted by scintigraphic data. Our regression equation was much more satisfactory than that of previous report.¹⁹⁾ The r factor was 0.658. Explanation power (square number of r factor) by three factors was 43.3%. But we failed to devise a useful clinical staging. The mean survival of patients with grade 1 RES dysfunction, single mass and low bilirubin was 14.0 months, but the mean survival of all other groups was below 3.8 months, so we were not able to separate them into several subgroups.

It is interesting that our prognostic factors coincided with operability.²⁰⁾ Patients with a single mass, least RES dysfunction and low bilirubin were the best candidates for operation. But by our analysis, they had the longest survival even without any treatment. We suggest that patients who could undergo an operation might represent a distinguished subset of HCC. Usually they had a slowly growing solitary tumor, good underlying liver function and greater chance of operation. These characteristics might be determined from the beginning. Further study of their features might give us a better understanding of the disease.

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