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Estimation of remnant liver function before hepatectomy by means of technetium-99m-diethylenetriamine-pentaacetic acid galactosyl human albumin

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Abstract. To improve the results of hepatectomy in cirrhotic patients, the likely reserve function of the liver was evaluated before surgery. Asialoglycoprotein receptor (ASGP-R) is a hepatic cell surface receptor specific for galactose-terminated glycoproteins. Technetium-99m-diethylene triamine pentaacetic acid-galactosyl human serum albumin (^{99m}Tc-GSA) is a newly developed analog ligand to ASPG-R. The probable functional reserve of the remnant liver after hepatectomy was estimated preoperatively as the hepatic binding protein (HBP) concentration specific for ASGP-R on the hepatocellular membrane of the remnant liver. This estimate was based on the effective liver volume rate, obtained by the uptake of ^{99m}Tc-GSA. In all, 3 normal volunteers, 3 patients with chronic hepatitis (CH), 9 patients with liver cirrhosis (LC), 2 patients with hepatic cystadenoma, 3 patients with hepatocellular carcinoma (HCC) associated with CH, and 21 HCC patients with LC were studied. The mean value ± SD obtained for HBP in normal volunteers (three cases) and in patients with mild (four cases), moderate (two cases), and severe liver damage (five cases) were 0.74 ± 0.03 μ*M*, 0.43 ± 0.042 μ*M*, 0.31 ± 0.05 μ*M*, and 0.20 ± 0.05 μ*M*, respectively. Most of the cases in which the preoperative HBP of the remnant liver was above 0.22 μ*M* had a good postoperative course irrespective of the type of hepatectomy. On the other hand, in subjects with a remnant liver HBP of between 0.22 and 0.11 μ*M*, postoperative severe liver dysfunction occurred in about 50% of cases. In all cases with a remnant liver HBP below 0.1 μ*M*, the prognosis was very poor, indicating that hepatectomy should be avoided. The HBP concentration detected by the ^{99m}Tc-GSA study is a very sensitive indicator of changes in the hepatic functional reserve, and the HBP value for the functional reserve of the remnant liver is extremely useful for estimating the liver function before and after hepatectomy.

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Introduction

Hepatocellular carcinoma (HCC) is the most prevalent type of primary liver carcinoma, and it is frequently associated with cirrhosis. The liver function is usually impaired in cirrhotic patients, sometimes with an accompanying increase in bleeding tendency and portal hypertension. Therefore, surgery on the cirrhotic liver is quite different from that on the noncirrhotic liver. To improve the operative results in cirrhotic patients, it is necessary to evaluate the functional reserve of the liver and predict the surgical results and long-term prognosis prior to surgery. On the basis of these findings, the safest and most suitable surgical procedure should then be selected. The purpose of this study was to evaluate the functional resectability of the liver, especially in cirrhotic patients, based on the functional reserve of the remnant liver using ^{99m}Tc-GSA scintiphotography.

Asialoglycoprotein receptor (ASGP-R), discovered by Ashwell and Steer [1], is a specific receptor for asialoglycoprotein (ASGP). ASGP-R recognizes and binds galactose-terminated glycoproteins by second-order chemical reactions [11]. Recent advances in receptor biochemistry [6, 13] have led to the synthesis of an analog ligand of ASGP-R by attaching galactosyl units to human serum albumin instead of removing the terminal sialic acid groups to expose the ASGP-R substrate, galactose. The radiolabeled compound is a member of a new class of tracers called receptor-binding radiopharmaceuticals. ^{99m}Tc-GSA is a newly-developed analog ligand for ASGP-R. Kudo et al. [5] reported finding a significant correlation between the receptor concentration and the hepatic binding protein (HBP) concentration by kinetic analysis based on pharmacokinetic modeling [15].

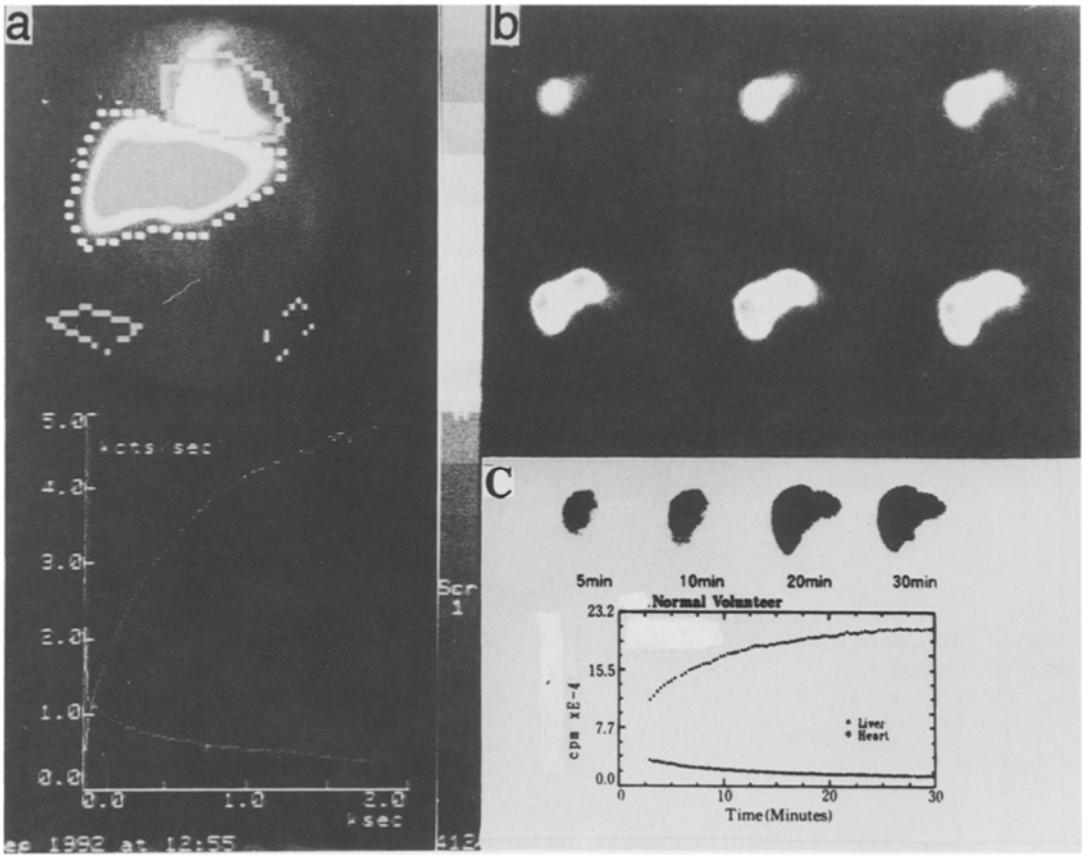

Fig. 1. Time-activity data from the ^{99m}Tc-GSA study. (a) ^{99m}Tc-GSA dynamic image and time-activity curve obtained for a normal volunteer after intravenous injection of a 3-mg dose of ^{99m}Tc-GSA. (b) At 30 min after injection, a SPECT image of the liver was obtained. (c) Receptor concentration (HBP) obtained by pharmacokinetic modeling is 0.714 in normal volunteer

Subjects and methods

Subjects

We investigated 26 hepatectomy cases, 3 normal volunteers, 3 cases of chronic hepatitis (CH), and 9 cases of liver cirrhosis (LC) in our department between October 1989 and December 1992. The age of these patients ranged from 24 to 79 years. The subjects consisted of 21 patients with HCC associated with LC, 3 HCC patients with CH, and 2 patients with cystic adenoma. Of the 26 hepatectomy cases, 6 were women and 20 were men, and their ages ranged from 46 to 79 years (mean, 63.8 years). The diagnosis was histologically confirmed by biopsy under laparoscopic examination in 3 cases of CH and 9 cases of LC, and the diagnosis was further confirmed by operation and autopsy in 21 HCC cases with LC and 3 HCC cases with CH. All cases were subjected to various hepatic function tests preoperatively and were followed for more than 1 year after surgery to detect any severe postoperative complications involved in disturbance of liver function. During the same period, patients who died of esophageal varix bleeding or postoperative cardiac infarction were excluded from the study. Preoperative estimation of the surgical risk of liver surgery was performed by clinical stage, liver-function test, and ICGRmax. On the other hand, the ^{99m}Tc-GSA study and ICGRmax test were carried out in three normal volunteers, three patients with CH, and nine patients with LC.

GSA study

1. Radiopharmaceutical preparation. The molecular weight of GSA was approximately 76,000 Da, and it contained 30–40 galactose residues. ^{99m}Tc-GSA was supplied by Nihon Medi-Physics Co., Ltd. (Nishinomiya, Japan).

2. Estimation of ASGP-R concentration (HBP) of remnant liver. Hepatic functional imaging of the functional reserve of the remnant liver after hepatectomy is shown in Fig. 1. All 38 patients and 3 normal volunteers received a dose of 3 mg of ^{99m}TcGSA intravenously. After injection of 185 MBq (5 mCi) of ^{99m}Tc-GSA, dynamic imaging was performed with the patient in the supine position under a large field-of-view gamma camera with a low-energy, all-purpose pallaler collimator using a General Electric Stacarm 400AT/T.

Computer acquisition of the gamma-camera data was started just prior to injection of ^{99m}Tc-GSA and held for 60 min. Digital images (128×128 pixels) were acquired in the byte mode at a rate of 20 s/frame. Data-analysis time-activity curves for the heart and liver were generated from regions of interest (ROI) for the whole liver and a precardiac region.

By means of a five-compartment analysis performed in accordance with Vera et al. [13, 14, 15], the parameter was estimated from the curve fit to the time-activity data from each ^{99m}Tc-GSA study (Fig. 1).

At 30 min after injection, a SPECT image of the liver was prepared. A cut line was entered into each section of the frontal SPECT image at 1-cm intervals using a teletype in accordance with the expected three-dimensional hepatectomy, permitting calculation of the effective liver volume rate (ELVR; Fig. 2). The ELVR was multiplied by HBP or ICGRmax, which was significant for quantitative evaluation of the hepatic function, so as to estimate the functional reserve of the remnant liver.

The severity of chronic liver damage was classified into three groups based on the criteria for clinical staging of hepatic functional capacity established by the Liver Cancer Group of Japan: mild damage (stage I), moderate damage (stage II), and severe damage (stage III).

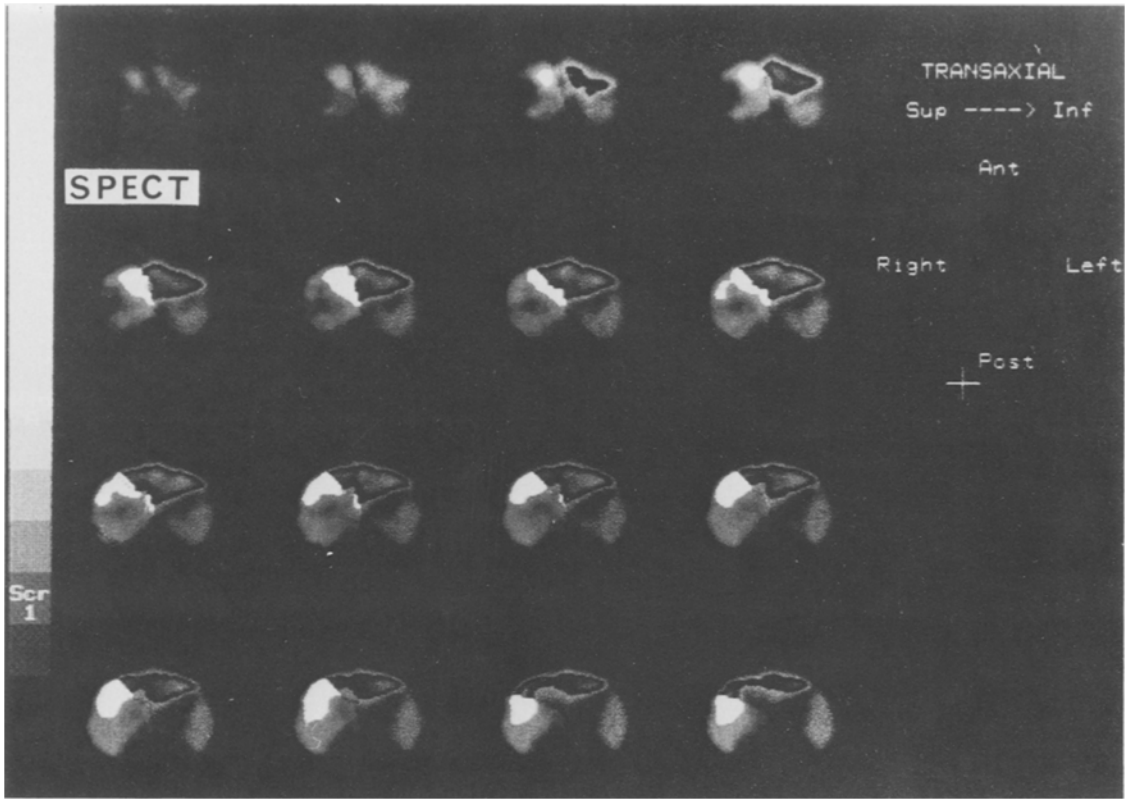

Fig. 2. A cut line of the expected hepatectomy in SPECT images. A cut line was entered into each section of the frontal image at 1-cm intervals using a teletype in accordance with the expected three-dimensional hepatectomy

Table 1. Summary of operated cases 15–26

Case No.	Age (y/o) Sex	No. of tumors	Location	Size of tumor (cm)	Diagram	LC	AFP (ng/ml)	OP	Sv (days)	Outcome
15	64 M	1	S8	3.9× 3.1		LC	160.1	Hr0(S8)	70	D
16	46 M	1	S6,8,7	15 ×12		CH	230.0	Hr3(PAM)	500	A
17	58 M	1	S,8	3.5× 3.5		LC	26500	Hr0(S8)	888	A
18	77 M	2	S8 S4	3.7× 3.2 2.2× 3.0		LC	2460	Hr2(AM)	104	D
19	53 F	2	S2,3	4.5× 3.8		LC	3250	Hr1(L)	225	A
20	51 F	2	S5	5.0× 3.0		LC	12.3	Hr2(PA)	176	D
21	65 M	1	S8,6	9.6× 7.9		LC	1600	Hr2(AP)	276	A
22	58 M	2	S8 S5	3.2× 2.0 2.2× 1.0		LC	50	Hr1(A)	509	A
23	57 M	1	S6	3.8× 4.2		CH	1856	Hr1(P)	528	A
24	31 M	1	S7	5.2× 4.5		CAH	104	Hr2(PA)	315	A
25	63 M	1	S5	2.2× 2.5		LC	9	Hr0(S5)	85	A
26	71 M	2	S8 S6	3.8× 4.5 2.4× 2.8		LC	2050	Hr2(AP)	70	D

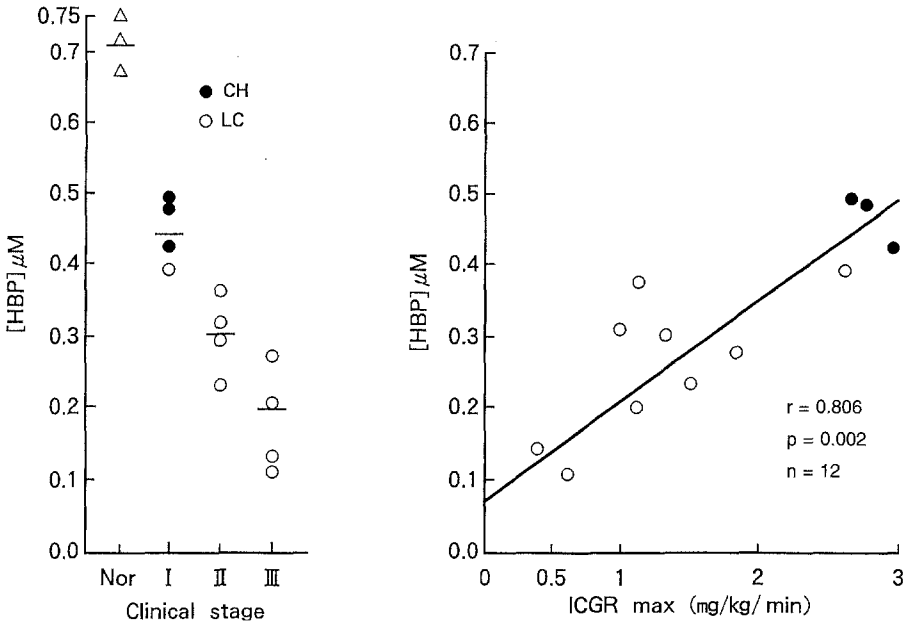

Fig. 3. Correlation between HBP and ICGRmax in patients with CH or LC

Results

1. Functional hepatic imaging

Figures 3 and 4 present the time-activity curves generated for a normal volunteer and a patient with LC, respectively. The liver- and heart-activity curves of a cirrhotic patient show inverse patterns as compared with those of a normal volunteer. Table 1 provides a clinical summary and the ^{99m}Tc-GSA data.

Good correlation was recognized between HBP and ICGRmax in the nine cases of LC and three cases of CH (r = 0.806; Fig. 3). A significant correlation was observed between LHL15 and the receptor concentration (HBP) obtained by kinetic analysis based on pharmacokinetic modeling [15].

HBP ranged from 0.5 to 0.10 μM in the cases with liver cirrhosis. The survival times of the operated HCC cases are shown in Fig. 6. In the cirrhotic patients, the main causes of death were hepatic insufficiency and tumor recurrence. In the noncirrhotic cases, the cancers were more advanced, and most of the patients died of tumor recurrence within 2 years. Severe liver dysfunction, including insufficiency after hepatectomy, was recognized in 5 of the 26 hepatectomy cases; among these 5 cases, 3 died of hepatic insufficiency within 6 months after hepatectomy, including 1 case of operative death within 1 month. Also, one of the hepatectomy cases with cirrhosis developed DIC after surgery, which led to severe liver dysfunction, and 1 died of esophageal varices bleeding.

2. Remnant liver HBP

The HBP of the functional reserve of the remnant liver changed during the clinical course of patients with HCC associated with LC. Figure 4 shows the changes in the HBP of the functional reserve of the remnant liver during the clinical course of HCC with LC before and after hepatectomy. The HBP values observed after hepatectomy were slightly lower than the preoperative HBP of the remnant liver (Fig. 4). Functional recovery of the liver was measured in terms of the HBP of the remnant liver, and morphological regeneration of the liver was examined by SPECT and CT. Two cases that had more than 0.6 μM of total liver HBP and more than 0.22 μM of remnant liver HBP showed good functional recovery and morphological regeneration of the remnant liver. Two cases that had between 0.5 and 0.7 μM of total liver and more than 0.22–0.10 μM of remnant liver HBP showed fair morphological

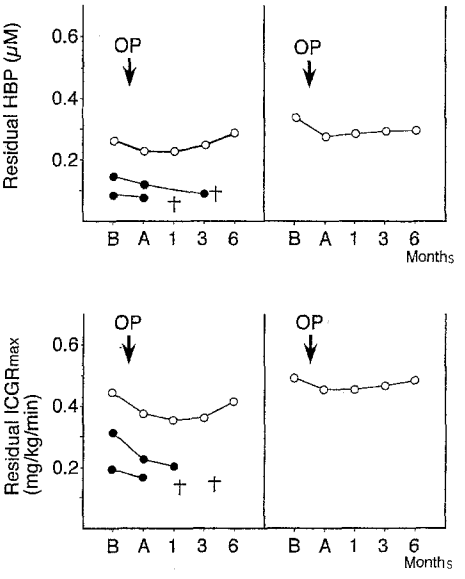

Fig. 4. Residual HBP and ICGRmax during clinical courses of four patients operated on for HCC with LC. ○ —— ○, alive; ● —— ●, dead after operation. Changes in HBP of the functional reserve of remnant liver during the clinical course of patients with HCC and LC before and after hepatectomy. HBP values observed after hepatectomy were slightly lower than the assumed preoperative HBP of the remnant liver. ^{99m}Tc-GSA was incorporated into the regenerated liver in living patients

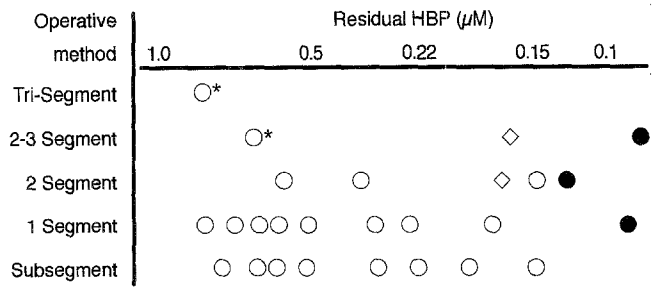

Fig. 5. Relationship between the HBP of the remnant liver estimated preoperatively and the postoperative clinical course. ○, Well; ◇, severe liver dysfunction without improvement for more than 1 month after operation; ●, death due to hepatic insufficiency within 6 months after surgery; *, benign hepatic tumor

regeneration but no functional recovery. In one case that had 0.5 μ*M* of total liver HBP and 0.1 μ*M* of remnant liver HBP, the function of the remnant liver did not recover but decreased instead, indicating an unfavorable prognosis.

In 19 of the 26 cases the preoperative remnant liver HBP was above 0.22 μ*M*; they survived for more than 6 months and the long-term prognosis was good, with no severe liver dysfunction occurring after hepatectomy. These 19 cases also showed a good postoperative course irrespective of the type of hepatectomy. On the other hand, in four cases with a remnant liver HBP of between 0.22 and 0.11 μ*M*, severe postoperative liver dysfunction occurred in two cases (Fig. 5). All cases with below 0.1 μ*M* of remnant liver HBP died within 6 months. In such cases the prognosis is very poor and hepatectomy should be avoided.

Discussion

^{99m}TC-GSA hepatic functional imaging is a new diagnostic approach for assessment of the function of the hepatocyte mass by the novel biochemical concept of a receptor-ligand system [2]. GSA dynamic data have the potential to provide valuable diagnostic information with regard to the ASGP-R function. The function of ASGP-R remains normal even in regenerated hepatocytes [5].

Vera et al. [13] developed a new kinetic analysis method for estimating the concentration of ASGP-R based on a radiopharmacokinetic model of ^{99m}Tc-NGA dynamic data using a computer. Kudo et al. [5] showed that assuming the concentration of ASGP-R estimated by the method of Vera et al. [13], a kinetic analysis model of ^{99m}Tc-NGA could also be applied to kinetic analysis of ^{99m}Tc-GSA.

Intravenous injection of ^{99m}Tc-GSA produces hepatic images based on the hepatocyte function (function hepatic imaging), which reflects the total number of functioning cell-surface ASGP-Rs, i.e., the functioning hepatocyte mass.

Therefore, if properly analyzed, time-activity data can also be assumed to reflect the functioning hepatocyte mass. The receptor concentration (HBP) parameter obtained via this technique was validated on the basis of showing a strong correlation with the clinical data [3, 10], and by in vitro binding assay data from biopsied tissues [4]. Kinetic analysis based on this pharmacokinetic model provides extremely accurate information concerning the receptor biochemistry.

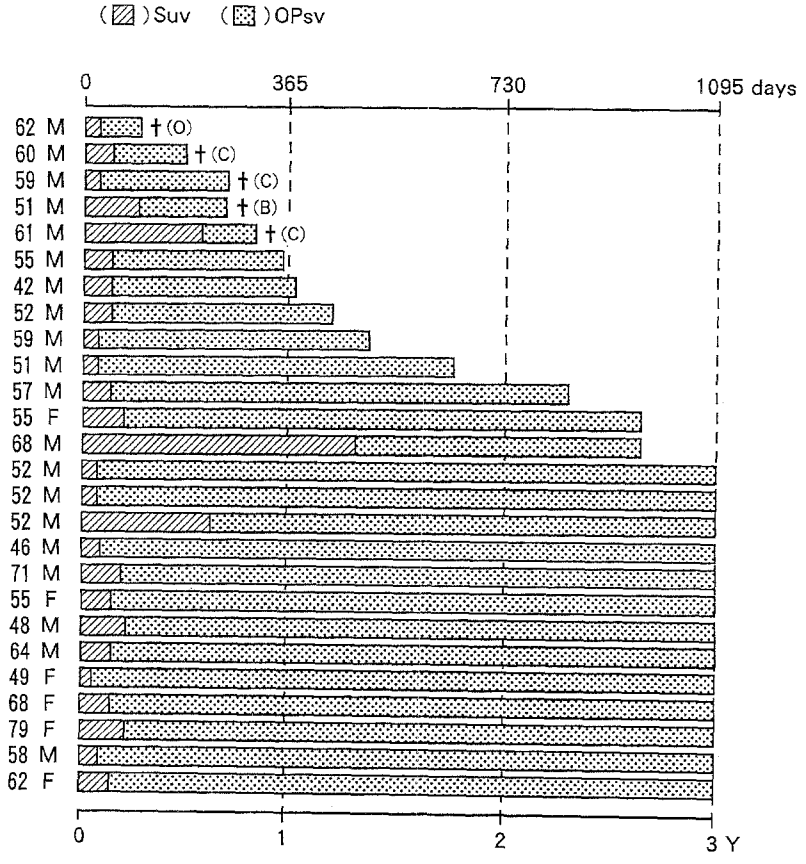

Fig. 6. Survival times of 24 operated patients with HCC associated with CH or LC and 2 cases of hepatic cystadenoma after treatment with Lp-TAI. *O*, Operation death; *B*, esophageal varices bleeding; *C*, cancer death; † dead

To perform safe surgery in cirrhotic patients, it is necessary to estimate the hepatic functional reserve preoperatively. Also, evaluation of the surgical risk must include the prediction of both postoperative complications such as hepatic insufficiency and long-term survival on the recovery of hepatic function. The ICGRmax, which was proposed as an indicator for evaluating the resectability of the liver by Paumgartner et al. [9] and then established by Moody et al. [7], has been evaluated as a theoretical index of the hepatic functional capacity. Noguchi et al. [8] also used ICGRmax as an extremely reliable parameter of hepatic functional reserve. In addition, various other tolerance tests for evaluation of the hepatic functional reserve have been attempted.

For instance, the highly quantitative nature of ICGRmax results in a very sensitive response to changes in the hepatic functional reserve, and it is extremely useful for estimating liver pathogenesis before and after surgery. In the present study, Fig. 3 indicates a good correlation between ICGRmax and HBP. However, these results reflect whole-liver function, and this may diminish after hepatectomy. Therefore, if the remnant liver function following hepatectomy could be measured preoperatively, it would be useful for estimating the advisability of hepatectomy.

To achieve this, it is necessary to measure the functional resection rate of the liver prior to hepatectomy. The liver volume has been measured using various imaging modalities such as X ray-CT and scintiphotography with ^{99m}Tcsn colloid, but these also fail to take the functional aspect into account. Therefore, in the present study the effective liver volume rate was measured on the basis of the degree of hepatocyte uptake of radioisotope, and this method provides very useful information for preoperative evaluation of the functional reserve in the expected remnant liver. This method was capable of clearly showing the functional resectability of the liver.

It has been pointed out that there is a discrepancy between morphological regeneration and functional restoration of the liver after hepatectomy. Noguchi et al. [8] measured the ICGRmax per unit hepatic volume and found that is correlated closely with the hepatic regenerative capacity. They suggested that this may be a useful index for preoperative estimation of the long-term prognosis of patients scheduled to undergo hepatectomy.

Conclusion

The HBP concentration determined by ^{99m}Tc-GSA studies is a very sensitive index of changes in the hepatic functional reserve, and the HBP value for the functional reserve of the remnant liver is extremely useful for estimating the liver function before and after hepatectomy.

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