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Comparison of Tc-99m-GSA scintigraphy with hepatic fibrosis and regeneration in patients with hepatectomy

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Objective: Liver regeneration after hepatectomy is correlated with liver fibrosis. Retrospectively, we compared three quantitative indices (HH15, LHL15 and LU15) of Technetium-99m-diethylenetriaminepentaacetic acid-galactosyl-human serum albumin (Tc-99m-GSA) liver scintigraphy with liver fibrosis; in particular, we compared the HH15 index and the rate of remnant liver regeneration. ***Methods:*** Fifty-three patients who had undergone hepatectomy were enrolled in this study. The non-neoplastic parts of their resected specimens were divided into 5 groups (F0–F4) according to the degree of liver fibrosis, as determined using the New Inuyama classification system: F0, no fibrosis (n = 12); F1, portal fibrosis widening (n = 12); F2, portal fibrosis widening with bridging fibrosis (n = 14); F3, bridging fibrosis plus lobular distortion (n = 7); F4, liver cirrhosis (n = 8). ***Results:*** When the cases were divided into a no or mild fibrosis group (F0 and F1) and a moderate or severe fibrosis or cirrhosis group (F2, F3 and F4), all of the indices were significantly different between the two groups. In this analysis, the areas (Az) under the receiver operating characteristic (ROC) curves for the HH15 and LHL15 indices were very similar, while the Az for the LU15 index was smaller. An HH15 index equal to 0.52 was the most accurate, producing a 79.3% sensitivity and a 75.0% specificity rating. When 18 patients that had received a CT scan one month after hepatectomy were divided into 2 groups according to their HH15 value (group A, HH15 ≤ 0.52; group B, HH15 > 0.52), group A exhibited a better regeneration rate. ***Conclusion:*** Tc-99m-GSA scintigraphy is well correlated with liver fibrosis and may be useful for non-invasive, preoperative evaluations of liver fibrosis. The HH15 index, in particular, may be useful for predicting the rate of liver regeneration after hepatectomy.

Key words: Tc-99m-GSA, liver fibrosis, liver regeneration, hepatectomy, ROC curve

INTRODUCTION

ASIALOGLYCOPROTEIN RECEPTOR (ASGPR) exists only on mammalian hepatocytes; asialoglycoprotein (ASGP) is specifically taken up by hepatocytes through the ASGPR and catabolized by hepatic lysosomes.[1–3] Technetium-99m-diethylenetriaminepentaacetic acid-galactosyl human serum albumin (Tc-99m-GSA; Nihon Medi-Physics, Nishinomiya, Japan) is a liver scintigraphy agent that is an analogue ligand of ASGP and specifically binds to ASGPR.

Some authors have reported that liver regeneration after hepatectomy is well correlated with liver fibrosis.[4–7] Therefore, the preoperative evaluation of liver fibrosis is likely to be very important. Correlations between liver fibrosis and several blood laboratory data have been reported, including the clearance of indocyanine green

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Table 1 Patient characteristics

Liver disease		Free	Chronic hepatitis			Cirrhosis	
Group		F0	F1	F2	F3	F4	Total
Number		12	12	14	7	8	53
Age	Range	40–83	58–77	47–72	45–70	46–61	40–83
	Mean	60.5	65.8	61.3	63.6	56	61.6
Sex	Male	7	10	11	5	5	38
	Female	5	2	3	2	3	15
Diagnosis	HCC	1	8	13	7	8	37
	Met	10	3	1			14
	CCC		1				1
	Simple cyst	1					1
Hepatectomy	Subsegmentectomy	4	10	10	4	6	34
	Monosegmentectomy	3	1	1	1	2	8
	Disegmentectomy	4		3	2		9
	Extended disegmentectomy	1	1				2

HCC: hepatocellular carcinoma
Met: metastatic liver tumor
CCC: cholangiocellular carcinoma

(ICG)[8–10]; in this study, we considered the correlation between Tc-99m-GSA, which directly evaluates liver function, and liver fibrosis.

MATERIALS AND METHODS

Study patients

Fifty-three patients (38 males, 15 females) of 103 patients who had undergone hepatectomy at the National Fukuyama Hospital during the period between April 1994 and September 2000, who underwent Tc-99m-GSA scintigraphy before hepatectomy, were enrolled retrospectively in this study. Written informed consent was obtained from each subject before the operation. The ages of the patients ranged from 40 to 83 years (mean 61.6 years). The diagnoses included hepatocellular carcinoma (HCC) in 37 patients, metastatic liver tumors (met) in 14 patients, cholangiocellular carcinoma (CCC) in 1 patient, and a simple cyst in 1 patient (Table 1).

Scintigraphy

After a bolus intravenous injection of 185 MBq of Tc-99m-GSA, a dynamic study was performed with the patient in a supine position using a large field-view gamma camera (PRISM-2000; Picker, Cleveland, OH) with a low-energy high-resolution collimator. The digital images obtained (128 × 128 matrix) were transferred to an on-line nuclear data processor (ODYSSEY; Picker, Cleveland, OH) at 30 seconds/frame for 30 minutes after the injection. Time-activity curves were generated from regions-of-interest (ROI) set over the whole liver and heart. The following parameters were calculated from the time-activity curves;

Parameter representing the retention of the tracer in the blood (HH15)[11]:

$$\mathrm{HH15} = \frac{\text{count for the heart at 15 minutes}}{\text{count for the heart at 3 minutes}}$$

Parameter representing the retention of the tracer in the liver (LHL15)[11]:

$$\mathrm{LHL15} = \frac{\text{count for the liver at 15 minutes}}{\text{sum of the counts for the heart and liver at 15 minutes}}$$

Cumulative liver uptake of the tracer from 15 to 16 minutes after injection (LU15)[12]:

$$\mathrm{LU15} = \frac{\int_{15}^{16} L(t)dt}{\text{total injected dose}} \times 100$$

$L(t)$ is the time-activity curve for the liver. The total injected dose was measured by counting the radioactivity of the syringe with a gamma-camera located 30 cm from the syringe before and after injection and calculating the difference.

Histopathology

The non-neoplastic parts of the resected specimens were divided into 5 groups (F0–F4) according to the degree of liver fibrosis as determined using the New Inuyama classification system,[13] which is widely used in Japan: F0, no fibrosis (n = 12); F1, portal fibrosis widening (n = 12); F2, portal fibrosis widening with bridging fibrosis (n = 14); F3, bridging fibrosis plus lobular distortion (n = 7); and F4, liver cirrhosis (n = 8). These groups correspond to the following New European classifications[14]: F0 = 0, no fibrosis; F1 = 1, mild fibrosis; F2 = 2, moderate fibrosis; F3 = 3, severe fibrosis; and F4 = 4, cirrhosis.

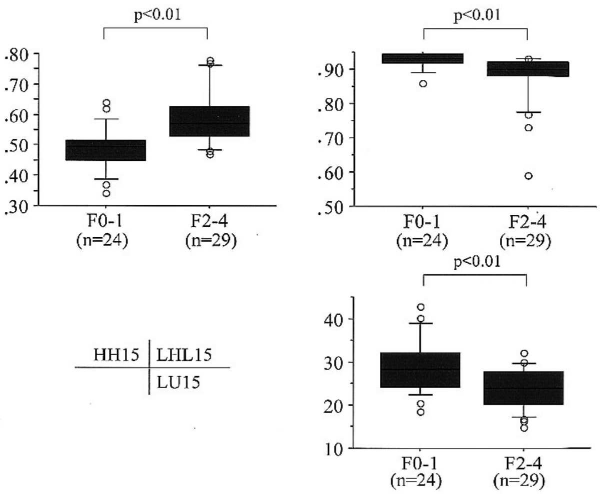

Fig. 1 Comparison of each index between two groups when the cases were divided into a no or mild fibrosis group (F0 and F1) and a moderate or severe fibrosis or cirrhosis group (F2, F3 and F4).

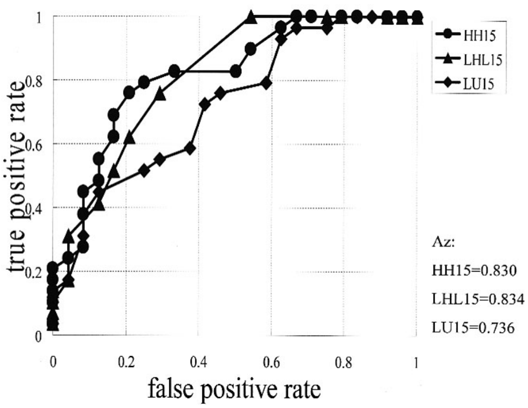

Fig. 2 ROC curves of HH15, LHL15 and LU15 when the cases were divided into a no or mild fibrosis group (F0 and F1) and a moderate or severe fibrosis or cirrhosis group (F2, F3 and F4).

Measurement of liver volume and hepatic regeneration rate

One-centimeter thick serial transverse section CT scans (900S; Toshiba, Tokyo, Japan, or SOMATOM PLUS4; Siemens, Hoffman Estates, IL) were taken of the entire liver in the 18 patients. The relative areas of each section were measured using a computer-linked planimeter or an image processing program (NIH image, Version 1.62; Public Domain Software). The areas of all the sections were then summed to estimate the total liver volume (cm^3). After estimating the remnant liver volume after hepatectomy using CT scans taken before hepatectomy, the regeneration rate of the remnant liver one month after hepatectomy was determined using the following formula:

Table 2 Patient population of Group A and Group B

Liver disease	Free	Chronic hepatitis			Cirrhosis	
Group	F0	F1	F2	F3	F4	Total
Group A	5	2	1			8
Group B		2	3	2	3	10

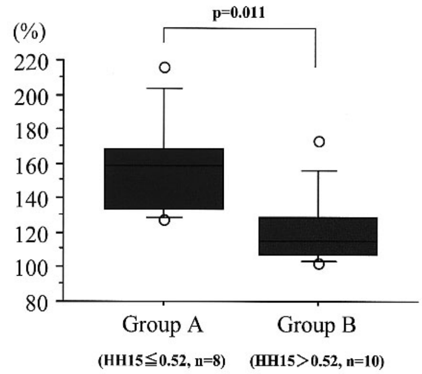

Fig. 3 Comparison of regeneration rates of two groups one month after hepatectomy.

Regeneration rate of remnant liver

$$= \frac{\text{liver volume one month after hepatoctomy}}{\text{estimated remnant liver volume after hepatectomy}} \times 100\,(\%)$$

Statistical analysis

When the cases were divided into a no or mild fibrosis group (F0 and F1) and a moderate or severe fibrosis or cirrhosis group (F2, F3 and F4), the Mann-Whitney test was used to compare each index between these two groups. In this analysis, the receiver operating characteristic (ROC) curve was also used to compare each index. Eighteen patients that had received a CT examination one month after their hepatectomy were divided into 2 groups according to a set cutoff value. The Mann-Whitney test was then used to compare the regeneration rates between the two groups.

The Rockit 0.90.1B program (University of Chicago, Chicago, IL)[15] was used to compare the areas (Az) under the ROC curves; the statistical program (Statview, Version 5.0; Abacus, Concepts, Berkley, CA) was used for the other statistical analyses. A p-value of less than 0.05 was considered significant.

RESULTS

When the cases were divided into a no or mild fibrosis group (F0 and F1) and a moderate or severe fibrosis or cirrhosis group (F2, F3 and F4), all of the indices were significantly different between the two groups (Fig. 1). In this analysis, the Az values for HH15 and LHL15 were very similar. The Az value for LU15 was smaller, but no

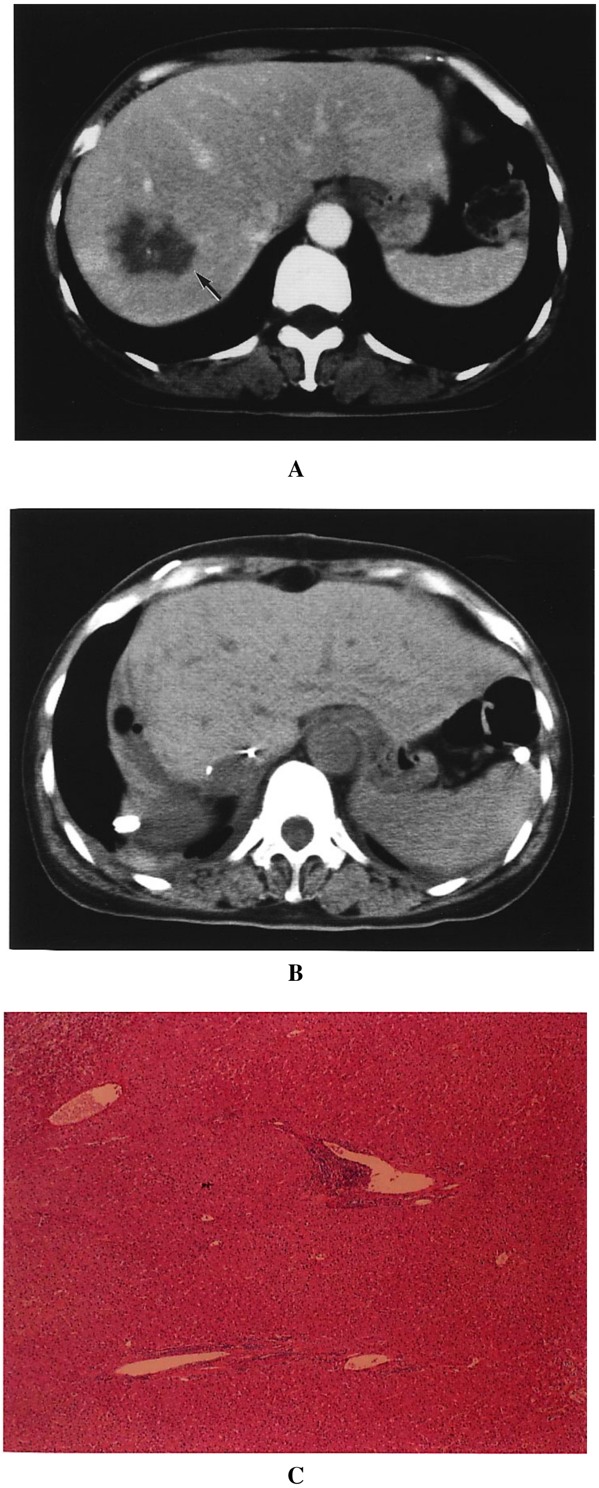

Fig. 4 A 56-year-old woman with metastatic liver tumor from rectum. HH15 was 0.49 and her degree of liver fibrosis belonged to F0. (A) CT image before hepatectomy shows a liver tumor in right lobe (*arrow*). (B) CT image one month after right lobectomy shows good regeneration. Her regeneration rate was 163.0%. (C) Histological finding shows no fibrosis (hematoxylin and eosin staining).

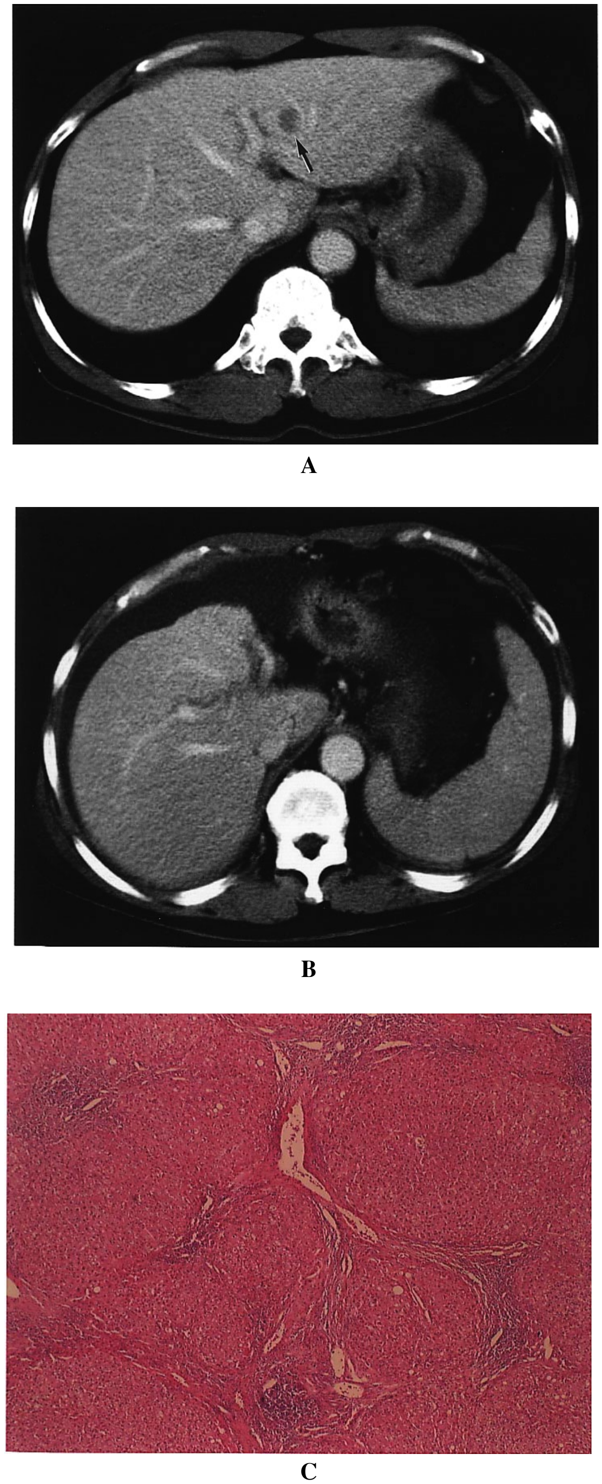

Fig. 5 A 59-year-old man with hepatocellular carcinoma. HH15 was 0.77 and his degree of liver fibrosis belonged to F4. (A) CT image before hepatectomy shows a liver tumor in left lateral segment (*arrow*). (B) CT image one month after left lateral segmentectomy shows poor regeneration. His regeneration rate was 102.2%. (C) Histological finding shows cirrhosis (hematoxylin and eosin staining).

significant differences were observed (Fig. 2). In LHL15, an index equal to 0.93 was the most accurate, producing a 75.5% accuracy. On the other hand, in HH15, an index equal to 0.52 was the most accurate, producing a 77.4% accuracy. Therefore, the cutoff value was set at HH15 = 0.52 for the following analysis, and the HH15 index had a sensitivity rating of 79.3% and a specificity rating of 75.0%. When the 18 patients who had received a CT scan one month after their hepatectomy were divided into 2 groups according to their HH15 value (group A, HH15 ≤ 0.52; group B, HH15 > 0.52; Table 2), group A exhibited a better regeneration rate; this difference was statistically significant (Fig. 3).

Representative cases are shown in Figures 4 and 5.

DISCUSSION

Reports on liver regeneration after hepatectomy have described several factors that affect regeneration, including liver fibrosis, hepatic removal rate, hepatic blood flow, hepatocyte growth factor, and nutrition after the hepatectomy.[4–7,16–18] Malignant tumors, such as HCC, frequently occur in chronically injured livers with some fibrosis, such as in patients with chronic hepatitis or cirrhosis. This prompted us to investigate liver fibrosis in this study. While some authors have estimated liver fibrosis using fibrotic markers, such as hyaluronate and type IV collagen,[5,19] or serum markers, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT),[20] instead of performing an invasive biopsy, in this study we used Tc-99m-GSA to estimate liver fibrosis. The Inuyama histological classification system for assessing chronic hepatitis has a long history of use in Japan; this system has now been replaced by the New Inuyama classification system, which is similar to the New European classification,[14] and is now widely used.[13] Assessments are made according to the grading (necro-inflammatory activity) and staging (fibrosis) of chronic hepatitis. In this study, the degree of liver fibrosis was classified according to this system. The regeneration ability of the remnant liver depends on the degree of liver fibrosis; cirrhotic livers tend to regenerate slowly and incompletely after hepatectomy.[4–7] Therefore, the preoperative evaluation of liver fibrosis, which can be used to predict liver regeneration after hepatectomy, is one of the most important factors in planning a strategy of hepatectomy.

ASGPR exists only on mammalian hepatocytes, and the receptor is almost always located on the sinusoidal and lateral surfaces of the hepatocytes in normal liver.[21] In patients with chronic liver injuries, the number of ASGPR decreases in accordance with the degree of liver injury.[22,23] The number of receptors in cirrhotic tissues is about 28% of the number in normal liver tissues.[22] Nearly all HCC tissues and all metastatic liver tumor tissues do not contain these receptors.[22] Tc-99m-GSA levels are well correlated with other laboratory tests of liver function,[11,24] and no extrahepatic metabolism and little extravascular distribution occurs.[25,26] Therefore, Tc-99m-GSA can be used to directly evaluate liver function, unlike other laboratory tests. HH15, LHL15 and LU15 are widely used as clinical indices in Tc-99m-GSA; HH15 values increase and LHL15 and LU15 values decrease when liver function reserves are reduced.[11,12] LHL15 reportedly reaches a plateau as the liver function improves and does not exceed 1.0; therefore, precise functional discrimination among cases with almost normal liver function may not be possible.[11] On the other hand, HH15 also appears to reach a plateau in cases of severe liver dysfunction; thus, these indices should be evaluated in conjunction with each other.[11] Fibrosis, inflammation and necrosis are all present in damaged liver tissue, and Tc-99m-GSA is well correlated with the histological activity index (HAI) score[27] for histopathologic findings,[11,24] especially for fibrosis.[28,29] Fibrosis results in necrotic cells replacing fibrotic tissue. Therefore, when hepatic fibrosis proceeds, the total number of surviving hepatocytes and ASGPR seems to be reduced. We also demonstrated a good correlation between Tc-99m-GSA levels and liver fibrosis.

Clinically, liver regeneration after hepatectomy is better in patients with no or mild fibrosis.[4] When the patients were divided into a no or mild fibrosis group (F0 and F1) and a moderate or severe fibrosis or cirrhosis group (F2, F3 and F4), all of the indices were significantly different between the two groups. By comparing each index using ROC curves, the Az value for HH15 was found to be as large as that of LHL15, and these indices seem to be suitable for dividing the patients into 2 groups. The Az value for LU15 was smaller, but was not significantly different from those of the other indices. LU15 has been reported to be a good clinical index,[12] and our results showed that it was well correlated with liver fibrosis. In fact, the liver function reserve was estimated in the patients before hepatectomy by referring to their LU15 index, the results of which are similar to those of ICG, serum bilirubin levels, serum albumin levels and coagulation studies. The decision to perform hepatectomy and the pattern of the hepatectomy was then made based on the patient's liver functional reserve. Consequently, none of the patients in this study had an extremely poor LU15 index, which is one of the limitations of this study.

When the cutoff value was set at HH15 = 0.52 and the cases were classified into 2 groups, the HH15 index had a sensitivity rating of 79.3% and a specificity rating of 75.0%. When 18 patients that had received a CT scan one month after their hepatectomy were divided into 2 groups on the basis of their HH15 value, the HH15 ≤ 0.52 group exhibited better regeneration of the remnant liver. Consequently, the HH15 index may be useful for predicting liver regeneration after hepatectomy. As mentioned above, however, liver fibrosis is not the only factor that affects liver regeneration after hepatectomy. Miyazaki et al. reported that in the moderate and severe fibrosis group, the hepatic removal rate was not closely associated with the regeneration rate, but an increased hepatic removal rate was associated with an increased regeneration rate in the no fibrosis and mild fibrosis group.[4] In this study, we could not include the hepatic removal rate in our analysis because our patient number was too small. However, in cases with a good HH15 value, reflecting a good liver function reserve, the hepatic removal rate might have a significant influence on the regeneration rate. In addition, it is known that hepatic volume expansion is not always accompanied by functional restoration, while a good correlation between liver fibrosis and regeneration of remnant liver volume was reported.[4,30] We intend to investigate these points in the future.

In conclusion, Tc-99m-GSA is well correlated with liver fibrosis and can be used not only to estimate liver function reserve as a non-invasive and preoperative test, but also to predict liver regeneration after hepatectomy using the HH15 index. Although we cannot conclude simply, because postoperative liver regeneration may be inadequate in some cases, we think that it is necessary to plan particularly carefully the strategy of hepatectomy in a patient with HH15 > 0.52.

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