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The functional hepatic volume assessed by ^{99m}Tc-GSA hepatic scintigraphy

Jin Wu,* Nobuyoshi Ishikawa,* Tohoru Takeda,* Yumiko Tanaka,** Xiao qing Pan,* Motohiro Sato,* Takeshi Todoroki,* Rokurou Hatakeyama** and Yuji Itai*

**Institute of Clinical Medicine, University of Tsukuba*
*** Department of Radiology, Tsukuba University Hospital*

The accuracy of measurement of the functional hepatic volume by single photon emission computed tomography (SPECT) with ^{99m}Tc-galactosyl serum albumin (^{99m}Tc-GSA) was evaluated. ^{99m}Tc-GSA planar scintigraphic images were obtained dynamically and the hepatic SPECT imaging was then performed in 25 patients with hepatobiliary tumors. The patients were divided into 4 groups with normal hepatic function, and mild, moderate and severe hepatic dysfunction. The functional hepatic volume determined by SPECT was compared with the morphological hepatic volume determined by computed tomography. The ratio of the hepatic volumes obtained by the two methods was calculated. The mean hepatic volume ratio was 96.6 ± 2.3% in the normal hepatic function group and 95.9 ± 2.2% in the mild dysfunction group (n.s.). In both the moderate and severe hepatic dysfunction groups, the hepatic volume ratio was smaller than that in the normal group (87.9 ± 5.2%, $p < 0.001$, and 71.9 ± 7.6%, $p < 0.0001$, respectively). There was a linear correlation between the hepatic volume ratio and various indices of reserve hepatic function, such as LHL_{15} ($r = 0.83$, $p < 0.0001$), HH_{15} ($r = 0.74$, $p < 0.0001$), and ICG_{15} ($r = 0.75$, $p < 0.0005$). These results indicate that the hepatic volume ratio is proportional to the severity of hepatic dysfunction, and suggest that the functional hepatic volume measured with ^{99m}Tc-GSA faithfully reflects the functioning hepatocyte mass. ^{99m}Tc-GSA scintigraphy and hepatic SPECT therefore provide information regarding global and regional reserve hepatic function.

Key words: ^{99m}Tc-galactosyl serum albumin (^{99m}Tc-GSA), ^{99m}Tc-GSA scintigraphy, hepatic SPECT, functional hepatic volume, reserve hepatic function

INTRODUCTION

With the progress in hepatic surgery and hepatic radiotherapy, various new treatments have become available. It is important to evaluate the hepatic functional volume accurately in order to predict the risk of hepatic failure before selecting one of these treatments. At the present time, numerous methods of estimating the hepatic volume are available, including those based on computed tomography (CT),[1–5] ultrasonography[6] and radionuclide scanning with ^{99m}Tc-sulfur colloid,[7] ^{99m}Tc-phytate,[8] ^{99m}Tc-N-pyridoxyl-5-methyl tryptophan (^{99m}Tc-PMT),[9] and ^{99m}Tc-DTPA-human serum albumin (^{99m}Tc-HSA).[10] The measurement of functional hepatic volume with ^{99m}Tc-galactosyl serum albumin (^{99m}Tc-GSA) was recently attempted.[11–13]

^{99m}Tc-GSA is a receptor-binding ligand that specifically binds to the asialoglycoprotein-receptor (ASGP-R) on the hepatocyte membrane.[14–16] ^{99m}Tc-GSA scintigraphy, which reveals the functioning hepatocyte mass, can be used to assess the reserve hepatic function under various physiological and pathological conditions.[14,17] As this agent is retained by the hepatocyte for a long period, the distribution of the functioning hepatocyte mass can be assessed by single photon emission computed tomography (SPECT).[11–13,18]

In this study, the functional hepatic volume obtained by hepatic SPECT with ^{99m}Tc-GSA and the morphological hepatic volume determined from CT scans were compared in patients with hepatobiliary tumors.

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For reprint contact: Tohoru Takeda, M.D., Institute of Clinical Medicine, University of Tsukuba, 1–1–1 Tennodai, Tsukuba, Ibaraki 305, JAPAN.

Table 1 Patient classification by severity

	Criteria*		n	Patients	
	HH_{15}	LHL_{15}		HH_{15}	LHL_{15}
Normal	0.537 ± 0.037	0.942 ± 0.017	8	0.531 ± 0.029	0.937 ± 0.014
Mild	0.631 ± 0.080	0.909 ± 0.044	3	0.627 ± 0.047	0.905 ± 0.027
Moderate	0.741 ± 0.076	0.844 ± 0.066	9	0.733 ± 0.052	0.831 ± 0.032
Severe	0.830 ± 0.054	0.706 ± 0.112	5	0.819 ± 0.022	0.714 ± 0.022

*Based on the criteria of the Liver Cancer Study Group of Japan.[19]

MATERIALS AND METHODS

Subjects

The subjects consisted of 25 patients with hepatobiliary tumors, including 13 patients with hepatocellular carcinoma (HCC) and liver cirrhosis (LC), 4 with gallbladder carcinoma (GB Ca) and 8 with hilar bile duct carcinoma (HBD Ca). Thirteen of them were males and 12 were females, and the age ranged from 42 to 79 years (mean age: 65.8 ± 9.0 years). The diagnoses of all patients with GB Ca and HBD Ca were histologically confirmed at surgery. Among the 13 patients who had HCC associated with LC, the diagnosis in 10 was confirmed histologically, either at surgery (n = 3) or by percutaneous biopsy under ultrasound guidance (n = 7), and that in three on the basis of the presence of the typical angiographic features, computed tomographic findings, and laboratory test results.

Based on the criteria of the Liver Cancer Study Group of Japan,[19] the patients were then divided into the following 4 groups (Table 1): the normal hepatic function group (n = 8), including 4 patients with GB Ca, 3 with HBD Ca and 1 with HCC and LC; the mild hepatic dysfunction group (n = 3), including 2 patients with GB Ca and 1 with HBD Ca; the moderate hepatic dysfunction group (n = 9), including 2 patients with HBD Ca and 7 with HCC and LC; and the severe hepatic dysfunction group, consisting of 5 patients who had HCC with LC.

Computed tomography

In all patients, serial transverse CT scans of the upper abdomen were obtained (CTT 9800 Advantage or Hilit units, GE) ten days before and after the ^{99m}Tc-GSA study. The slice thickness was 5 mm, with a slice interval of 7 mm. Each slice was displayed on a television monitor and the edge of the portion of the organ of interest which did not contain the tumor was traced with a cursor. The enclosed area was calculated by a computer. This process was repeated for each slice, and the morphological hepatic volume (MHV) was calculated by the sum of areas method[2] as follows:

$$MHV = dx\sum_{i=1}^{n} Area_i = dx(Area_1 + Area_2 + \ldots + Area_n)$$

dx = slice interval

Hepatic functional imaging

Following the bolus intravenous injection of 185 MBq of ^{99m}Tc-GSA, dynamic scintigrams were obtained with a large field-of-view gamma camera (RC-150DT, Hitachi Medical Corporation, Tokyo) fitted with a low-energy all-purpose parallel hole collimator. The acquisition parameters were an energy window of 20% and a peak at 140 keV. Sequential anterior abdominal images (64 × 64 matrix) including the heart and liver were acquired at 20-sec intervals for 18 min.

Hepatic SPECT images were acquired after the dynamic study. Each set of projection data was obtained in a 64 × 64 matrix, and 64 projections were acquired (5.6° steps, and 15 sec/projection). A Wiener filter was used as the pre-reconstruction filter, and final reconstruction was performed with a Ramachandran filter. Attenuation correction was performed with Chang's first-order compensation procedure, and a value of 0.10 cm^{-1} was used as the effective attenuation correction coefficient. The pixel slice thickness along the axis of rotation was 8 mm.

Data analysis

Data were processed by means of a HARP-II computer system (Hitachi Medical Corporation, Tokyo). In the case of dynamic imaging, time-activity curves for the heart and liver were generated from regions of interests (ROI) encompassing the whole organ. The blood pool clearance index (HH_{15}) and the hepatic uptake index (LHL_{15}) were then calculated from the time-activity curves.

For SPECT transaxial images, hepatic background correction was performed by the previously reported method.[9] The background ROI was set in the spleen, and the average count per voxel was measured. As the pooled liver/spleen ratio per unit, the averaged value used as reported in the cited study was 0.812 in the patients with LC.[9] Accordingly, in this study, the averaged count per voxel in the spleen was multiplied by 0.812 to give the hepatic background.

The three-dimensional hepatic image and the functional hepatic volume (FHV) were obtained from the SPECT data. The FHV was calculated by the outline extraction method, and the hepatic volume ratio for the SPECT and CT methods (FHV/MHV ratio) was calculated by the following formula:

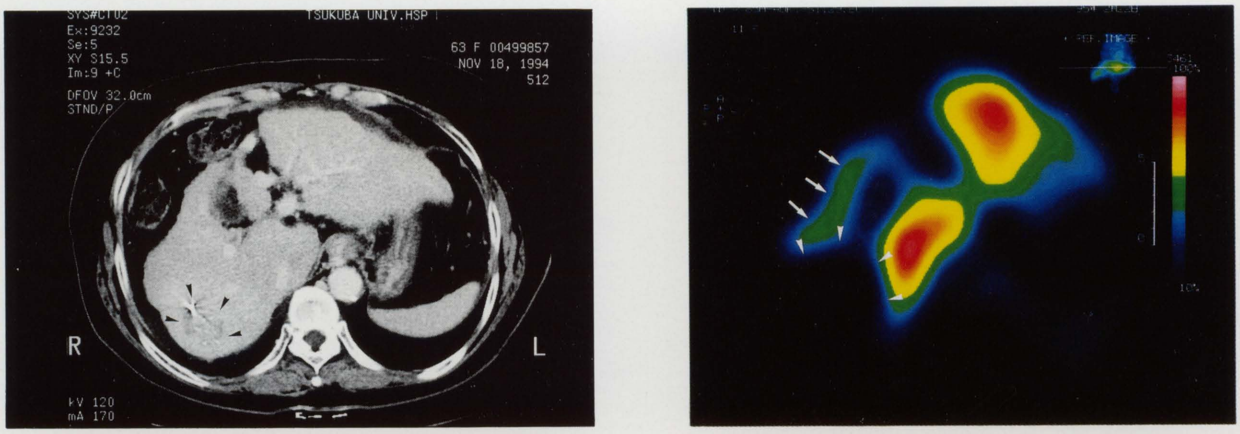

Fig. 1 An image obtained in a 63-year-old woman with hepatocellular carcinoma (arrow head: region of the tumor, arrow: region of mildly diminished uptake).

$$F\,(xyz) = \begin{cases} 1, & D(xyz) \geq Ct \\ 0, & D(xyz) < Ct \end{cases}$$

$$\text{FHV} = P^3 \sum_x \sum_y \sum_z F(xyz)$$

$$\text{Hepatic volume ratio (\%)} = \frac{\text{FHV}}{\text{MHV}} \times 100\%$$

Where, $D\,(xyz)$ is the pixel count at positions x, y, and z on the SPECT image, FHV is the functional volume (cm^3), Ct is the cut-off level, and P is the pixel size (cm). A cut-off level of 31% was used, because results closest to the true volume had been obtained at that value in a phantom study. In the patients with gallbladder accumulation, we set the ROI so that it encompassed the gallbladder and subtracted it from the transaxial images before the measurement of FHV.

Statistical analysis

The mean FHV/MHV ratio values for the 4 groups of subjects were compared statistically by Student's unpaired t-test (two-tailed). Linear regression analysis by the least squares method was performed to assess the relationship between the FHV/MHV ratio and various indices of reserve hepatic function. A P value of less than 0.05 was considered to indicate a significant difference.

RESULTS

Case presentation

The images obtained from a 63-year-old woman who had HCC with LC are shown in Figure 1. She had severe hepatic dysfunction ($HH_{15} = 0.821$, $LHL_{15} = 0.694$, ICG15 = 52%). A low density area in the right lobe of the liver was observed on CT with contrast enhancement, and the MHV was 861 cm^3. On the transaxial SPECT image, a defect in ^{99m}Tc-GSA accumulation was seen in the low density area visualized on the CT scan. A region of mildly diminished uptake was observed in S8, but it appeared almost normal on the CT image. Without background correction, the FHV was 748 cm^3 and the FHV/MHV ratio was 91.1%. There was no significant difference between the FHV and MHV, but a marked difference was observed between the ^{99m}Tc-GSA hepatic SPECT images and CT images. With background correction, both the FHV and the FHV/MHV ratio were decreased, to 557 cm^3 and 64.7%, respectively.

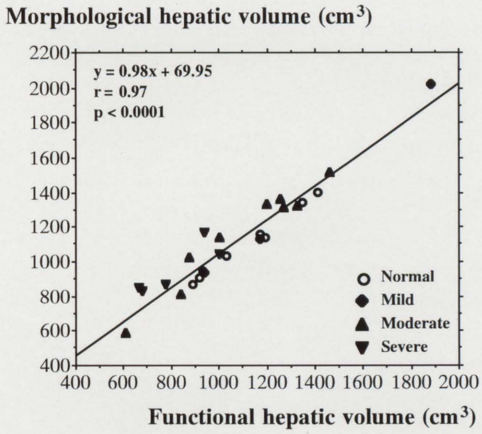

Fig. 2 Relationship between the functional hepatic volume obtained by ^{99m}Tc GSA hepatic SPECT and the morphological hepatic volume obtained by CT scanning.

Morphological hepatic volume and functional hepatic volume

The MHV and FHV determined by hepatic CT and SPECT imaging, respectively, showed a good linear correlation ($r = 0.97$, $p < 0.0001$) (Fig. 2). In comparison to the normal hepatic function group, both MHV and FHV tended to be increased in the mild hepatic dysfunction group, but with progressive hepatic damage they tended to be decreased (Fig. 3).

The mean MHV values in the normal hepatic function, mild, moderate and severe hepatic dysfunction groups were 1105 ± 198 cm^3, 1359 ± 578 cm^3, 1154 ± 198 cm^3 and 947 ± 198 cm^3, respectively, without any statistical

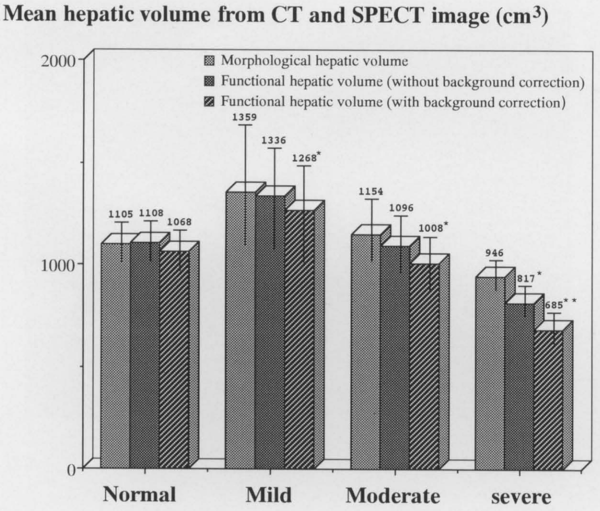

Fig. 3 Morphological hepatic volume and functional hepatic volume (without and with background correction) in hepatobiliary tumor patients with varying degrees of hepatic damage. *: $p < 0.05$, **: $p < 0.005$

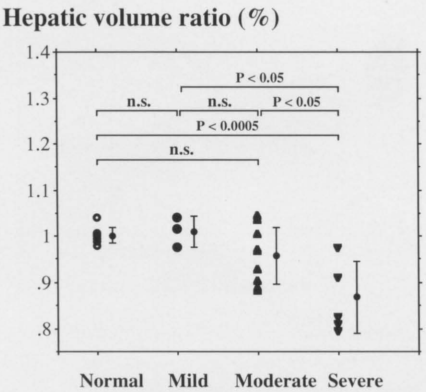

Fig. 4 The hepatic volume ratio in hepatobiliary tumor patients with varying degrees of hepatic damage calculated without background correction.

difference among the groups. Whereas, in the normal hepatic function, mild, moderate and severe hepatic dysfunction groups, the mean FHV values without background correction were 1108 ± 200 cm^3, 1336 ± 490 cm^3, 1096 ± 278 cm^3 and 817 ± 152 cm^3, respectively, and the mean FHV values with background correction were 1068 ± 193 cm^3, 1268 ± 473 cm^3, 1008 ± 260 cm^3 and 685 ± 152 cm^3 respectively. In severe hepatic dysfunction group, the FHV without and with background correction was smaller than that in the normal hepatic function groups ($p < 0.05$ and $p < 0.005$, respectively), and in the FHV with background correction, significant differences were also observed among the other groups ($p < 0.05$).

Analysis of percent hepatic volume

Without background correction, the FHV approximated the MHV in the normal hepatic function and mild hepatic dysfunction groups, and the mean FHV/MHV ratio was 100 ± 1.8% and 100 ± 3.3%, respectively. In contrast diminished values for the mean FHV/MHV ratio were observed in the moderate and severe hepatic dysfunction groups (95.8 ± 6.2% and 86.2 ± 8.8%, respectively) (Fig. 4). But the standard deviation was increased in the latter two groups, and differentiation between the patients with moderate to severe hepatic dysfunction and those with the normal function or mild dysfunction was difficult.

A weak correlation was seen between the FHV/MHV ratio and the indices of reserve hepatic function: HH_{15} ($r = 0.52, p < 0.01$); LHL_{15} ($r = 0.58, p < 0.005$); and ICG_{15} ($r = 0.70, p < 0.005$) (Fig. 5a, b and c).

In the analysis with background correction, the mean FHV/MHV ratio in the groups with normal hepatic function and mild hepatic dysfunction was 96.6 ± 2.3% and 95.9 ± 2.2% (n.s.), respectively; they were significantly greater than those in the moderate and severe hepatic dysfunction groups (87.9 ± 5.2% and 71.9 ± 7.6%, respectively) (Fig. 6). The standard deviation value in the moderate and severe hepatic dysfunction groups was smaller than that without background correction. A stronger correlation was also observed between the FHV/MHV ratio and the indices of reserve hepatic function: HH_{15} ($r = 0.74, p < 0.0001$); LHL_{15} ($r = 0.83, p < 0.0001$); and ICG_{15} ($r = 0.75, p < 0.0005$) (Fig. 5d, e and f).

DISCUSSION

With advances in hepatic surgery and hepatic radiotherapy, various treatments have become available. In particular, with the expansion of the operative indications for hepatic surgery, the resection rate for hepatobiliary tumors has markedly increased. It has accordingly become important to evaluate the operative risk corresponding to the reserve hepatic function, and to select the proper operative techniques based on this risk.[4,10–13,20]

The morphological hepatic volume is usually determined by CT[1–5] or ultrasound.[6] These methods have advantages in terms of simplicity, reproducibility, high resolution and ease of detection of the hepatic edge,[1–6] but these techniques cannot be used to evaluate the functional hepatic volume because they do not demonstrate the regional hepatocyte function. Moreover, a conflicting relation between the functional distribution and the morphological imaging appearance is frequently encountered in patients with hepatobiliary tumor.[12] Consequently, in clinical practice, a method which can be used to assess both reserve hepatic function and volume simultaneously is desirable.

Several methods for determining the hepatic functional volume with ^{99m}Tc-sulfur colloid,[7] ^{99m}Tc-phytate,[8] ^{99m}Tc-PMT,[9] and ^{99m}Tc-HSA[10] have been reported, but ^{99m}Tc-sulfur colloid and ^{99m}Tc-phytate hepatic scintigraphy mainly reflect reticuloendothelial function and do not always indicate hepatocyte function. ^{99m}Tc-PMT is a hepatobiliary imaging agent, but with this agent it is

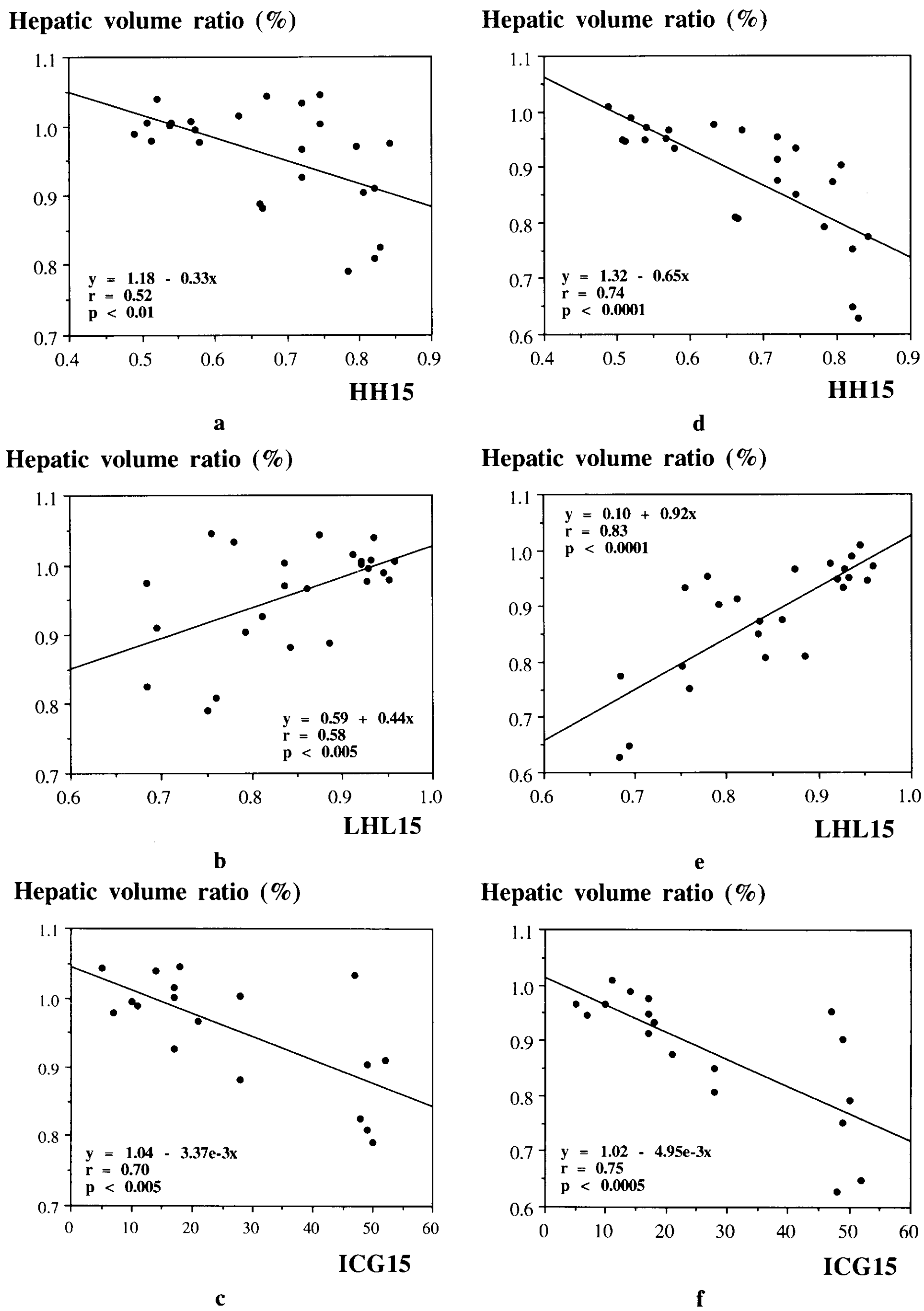

Fig. 5 Relationship between the hepatic volume ratio and the indices of reserve hepatic function calculated without (a, b and c) and with (d, e and f) background correction.

difficult to obtain satisfactory SPECT images for volume measurement because it is excreted rapidly into the biliary system. ^{99m}Tc-HSA is a vascular imaging agent, and does not reflect hepatocyte function.

In 1979, ^{99m}Tc-GSA was developed as a hepatic receptor-binding ligand that specifically binds to the ASGP-R on the hepatocyte membrane.[14–16,21] The uptake of ^{99m}Tc-GSA is an independent biochemical process,[21] and allows direct estimation of the functioning hepatocyte mass.[14] ^{99m}Tc-GSA scintigraphy has therefore been recognized to be the best method for evaluation of reserve hepatic function.[17] In our study, the FHV was very similar to the MHV in the patients with normal hepatic function and mild hepatic dysfunction, and a linear correlation was observed between FHV and MHV. But the FHV tended to be smaller than the MHV, probably because ^{99m}Tc-GSA accumulates in functioning hepatocytes and not in the interstitial tissue. Furthermore, we also observed that both MHV and FHV tended to be increased in the mild hepatic dysfunction group, and decreased with progressive he-

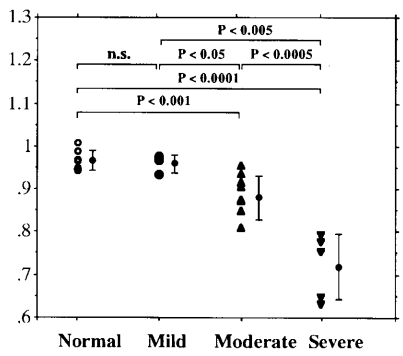

Fig. 6 The hepatic volume ratio in hepatobiliary tumor patients with varying degrees of hepatic damage calculated with background correction.

patic damage, but only in the FHV the difference between the severe hepatic dysfunction and the normal hepatic function groups was statistically significant. These results indicate that the FHV can accurately reflect the degree of hepatic damage. By means of these characteristics, the residual reserve hepatic function and hepatic volume can be predicted with ^{99m}Tc-GSA hepatic SPECT prior to surgery, catheter interventions or radiation therapy in patients with hepatobiliary tumors.

A linear correlation was found between the FHV/MHV ratio and HH_{15}, LHL_{15}, and ICG_{15} as indices of reserve hepatic function, but the FHV/MHV ratio in the patients with severe and moderate hepatic dysfunction was smaller than that in the other groups. These results indicate that the FHV/MHV ratio is proportional to the severity of hepatic dysfunction and that the functioning hepatocyte mass decreases as hepatic damage progresses, although the differences in the FHV/MHV ratio were not sufficient to differentiate among the hepatic dysfunction groups.

Hepatic background subtraction

The ASGP-R is present only on the hepatocyte membrane of mammals.[22] In the moderate and severe hepatic dysfunction groups in our study, mild accumulation in the spleen was observed on the SPECT images despite the absence of this receptor in this organ. It has been pointed out in previous reports that the clearance of ^{99m}Tc-GSA from the blood circulation is rapid in patients with normal hepatic function, but is delayed as hepatic dysfunction progresses.[13–19,21] This indicates that, in patients with hepatic dysfunction, the counts due to intrahepatic blood may influence the measurement of the hepatic volume by radionuclide techniques, and the intrahepatic blood activity should be taken into consideration in the interpretation of the SPECT study.

Nakamura et al. used ^{99m}Tc-PMT to determine hepatic function volume, and reported that hepatic background correction was important for obtaining an accurate value for functional hepatic volume.[9] In the present study, the FHV with background correction in the severe hepatic dysfunction group was significantly smaller than that in the normal hepatic function, mild and moderate hepatic dysfunction groups. On the other hand, in FHV without background correction, there was a significant difference only between the severe hepatic dysfunction and normal hepatic function groups. Moreover, background correction produced a marked improvement in differentiation in the FHV/MHV ratio among the patients with various degrees of hepatic dysfunction. It also improved the correlation coefficients for the relation between the FHV/MHV ratio and the indices of reserve hepatic function.

Limitations

In this study, hepatic background correction was performed by the method previously reported by Nakamura et al.[9] Although this method can be applied easily and can improve the strength of the correlations between the FHV/MHV ratio and the indices of reserve hepatic function, it is not without problems. In this study, a specific correction coefficient was used in all patients, but the degree of the hepatic damage differed considerably from patient to patient. The adjustment in the value of pooled liver / spleen ratio per unit from subject to subject may be necessary to evaluate reserve hepatic function accurately. For this purpose, ^{99m}Tc-HSA SPECT may be useful for hepatic background correction.

The FHV is thought to be underestimated when ^{99m}Tc-GSA is rapidly excreted into the biliary system. In addition, our background correction method cannot be used in splenectomy patients.

Clinical implications

It considered that the measurement of functional hepatic volume with ^{99m}Tc-GSA hepatic SPECT is an excellent method for evaluating reserve hepatic function, and it is extremely easy to perform. Both the parameters for FHV and the FHV/MHV ratio well reflect the reserve hepatic function. The FHV faithfully reflects the global functioning hepatocyte mass, whereas the FHV/MHV ratio provides a ratio for the functioning hepatocyte mass and the morphological hepatic volume. In this study, we examined only the global reserve hepatic function, but in the future, with computer techniques, it may be possible to accurately estimate the regional reserve hepatic function in relation to the morphological imaging findings.

We anticipate that ^{99m}Tc-GSA scintigraphy and SPECT will become useful in fully evaluating global and regional reserve hepatic function.

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