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Evaluation of the Effect of Age on Functioning Hepatocyte Mass and Liver Blood Flow Using Liver Scintigraphy in Preoperative Estimations for Surgical Patients: Comparison with CT Volumetry

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Background. **The effect of age on functioning hepatocyte mass and liver blood flow was examined using ^{99m}Tc-galactosyl-human serum albumin (GSA) liver scintigraphy in patients with liver tumors awaiting surgery.**

Materials and methods. **Seventy-two patients with liver tumors, but normal liver parenchyma, were included in this study; patients with compromised hepatic blood flow as a result of vascular invasion or thrombus were excluded. The liver volume, calculated liver volume, and liver blood flow index (*K* value) were preoperatively determined by liver scintigraphy using GSA. These three parameters and liver volume measured by computed tomography volumetry (CT-LV) and the standard liver volume (ST-LV), calculated from the patient's body surface area, were examined for correlations with the patient's age. The *K* value was compared with the indocyanine green dye retention rate, and both sets of results were examined for correlation with the patient's age.**

Results. **Both the CT-LV and the ST-LV decreased with age, resulting in an unchanged CT-LV/ST-LV ratio with aging. The liver volume and calculated liver volume measured by scintigraphy both decreased with age, even when body size was taken into account. Therefore, in elderly patients, the liver was not morphologically smaller, but the hepatocyte mass in the liver decreased. Furthermore, liver blood flow per unit of functional liver volume determined from the blood flow index did not change with age.**

Conclusions. **These results, suggesting a discrepancy between liver volume estimated by CT and actual functioning hepatocyte volume in the elderly, may have a critical impact on preoperative liver functional reserve evaluation prior to hepatic resection in elderly patients.**

Key Words: **99mTc-GSA; aging; liver volume; functioning hepatocyte mass; liver blood flow.**

INTRODUCTION

The effects of aging on the human liver have not been clearly determined [1]. The most frequently cited post-maturational change in the human liver is a decline in organ mass [2–4], although there is even disagreement about this basic parameter [5, 6]. Reduction of hepatic blood flow has also been reported [2, 4], but again is controversial [7]. The recent progressive increase in the geriatric population in society and the increased life span have forced surgeons to expand the operative indications to include geriatric patients. Even in liver surgery, the indication for hepatectomy has been expanded to include geriatric patients, and several studies have demonstrated acceptable long-term survival of elderly patients after surgery [8, 9]. It is therefore of primary importance to understand the effect of aging upon liver functional and morphological changes in considering the risk involved in hepatic resection.

Recent technological advances have resulted in the development of new equipment to evaluate human liver function noninvasively *in vivo*. In the field of liver surgery, liver scintigraphy using ^{99m}Tc-galactosyl-human serum albumin (Tc-GSA)[1] has recently been

[1] Abbreviations used: Tc-GSA, ^{99m}Tc-galactosyl-human serum albumin; CT-LV, liver volume measured by computed tomography volumetry; GSA-LV, liver volume measured by scintigraphy using ^{99m}Tc-galactosyl-human serum albumin; GSA-CLV, calculated liver volume measured by scintigraphy using ^{99m}Tc-galactosyl-human serum albumin; ST-LV, standard liver volume; *K* value, liver blood flow index.

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reported as a useful method for the quantitative measurement of functioning hepatocyte mass unaffected by liver tumors or bile obstruction [10–13], Tc-GSA measurement of the total amount of asialoglycoprotein receptor is reported to be proportional to the number of viable hepatocytes and therefore provides a valid assessment of functioning hepatocyte mass. In this study, we used this technique to evaluate the effect of aging on liver functional volume and blood flow in patients awaiting liver surgery.

PATIENTS AND METHODS

Patients. Of the patients who underwent a Tc-GSA liver scintigraphy study before liver surgery for hepatic and biliary malignancies between January 1993 and January 2001 at the First Department of Surgery, Kagawa Medical University, 72 with a histologically normal liver parenchyma were included in this study. Patients with an abnormal liver parenchyma as a result of hepatitis or cirrhosis were excluded. The diagnosis of a normal liver parenchyma was confirmed histologically postoperatively using a specimen of the resected liver. Patients with compromised hepatic blood flow, e.g., as a result of vascular invasion or thrombus, were also excluded. Patients with jaundice, whose serum total bilirubin level exceeded 2 mg/dl, were excluded.

The included patients consisted of 21 with peripheral, mass-forming-type cholangiocellular carcinoma, 31 with metastatic liver tumors from gastrointestinal malignancies, 9 with carcinoma of the gall bladder, 5 with biliary duct tumors, and 6 with benign tumors of the liver. The group was made up of 45 men and 27 women with ages ranging from 30 to 82 years (mean 63 years). Three patients were in the fourth decade of life, 5 in the fifth, 4 in the sixth, 27 in the seventh, 21 in the eighth, and 2 in the ninth.

Methods. After admission, every patient underwent preoperative computed tomography (CT) examination to confirm the diagnosis and evaluate disease development. At the same time, CT volumetry of the liver was performed to assess resectability and operation risk. Liver scintigraphy using Tc-GSA was also performed preoperatively on each patient to assess liver function and resectability. The indocyanine green dye retention rate 15 min after the injection of 0.5 mg/kg (ICGR15) was also determined.

Using Tc-GSA, liver volume (GSA-LV), calculated liver volume (GSA-CLV), and the liver blood flow index (K value) were measured as described in the next section, and then the GSA-LV and GSA-CLV were compared to the standard liver volume (ST-LV), estimated on the basis of body surface area, and the liver volume estimated by CT (CT-LV), while the K value was compared to the ICGR15. Correlations between all the values obtained and the age of the patient were examined statistically.

The ST-LV was estimated on the basis of the patient's body surface area using the formula liver volume (cm^3) = 706 × body surface area (m^2) + 2.4, according to Urata *et al.* [14]. The CT-LV was calculated by multiplying the parenchymal area of each cross-sectional liver image by the slice thickness of 1 cm, the volume of the tumor being excluded. Statistical analysis was performed using SPSS computer software (SPSS, Chicago, IL), and correlations between parameters were examined by Spearman rank correlations.

Liver volume and functional liver volume measured by Tc-GSA. The GSA-LV and GSA-CLV were calculated by serial transverse-scanning Tc-GSA scintigraphy. The acquisition parameters were an energy window of 20% and a peak at 140 keV, and hepatic single-photon emission CT (SPECT) images were acquired after a dynamic study. A dual-head SPECT (RC26001, Hitachi, Tokyo, Japan) with a low-energy high-resolution parallel hole collimator was used for the SPECT. Each set of projection data was obtained in a 64 × 64 matrix, and 64 projections were acquired (six steps and 15 s per projection). The SPECT field of view included the whole liver. The slice thickness for image reconstruction was 1.08 cm. The prereconstruction filter was a Wiener filter, and the final reconstruction was performed with a Shepp–Logan filter. Attenuation correction was performed by Chang's first-order compensation procedure, with a value of 0.1 cm^{-1} being used as the effective attenuation correction coefficient.

The GSA-LV was obtained from the SPECT data and was calculated by the outline extraction method. A cutoff level of 54%, determined by comparing the results with the true hepatic volume obtained by hepatectomy, was used. The liver volume in each slice (V) was calculated as the sum of the volume of the voxels in which the count exceeded the cutoff level and the total liver volume was calculated from the sum of the V values. The GSA-CLV was calculated by weighting each voxel in accordance with its count, i.e., a voxel with a count greater than 80% of the maximum count was counted as one voxel, but a voxel with a count less than 80%, but greater than 54%, was given a value between zero and 1, determined in proportion to its count given by an experimentally determined equation. Thus, in contrast to the GSA-LV, the GSA-CLV pays more attention to the actual amount of asialoglycoprotein receptor.

The K value was calculated from the time–activity curves for each liver slice created using the 1st to 35th projection liver images, as described elsewhere [15, 16]. Briefly, the K value was obtained using a simple two-compartment model using the equation $C_s(t) = C_0(e^{-K\mathrm{e}t} - e^{-K\mathrm{n}t})$, where K_e is the elimination rate from the liver and K_u is the uptake rate of the liver. Since Tc-GSA binding is irreversible [17] and the elimination of radioactivity into the bile is very slow [18], K_e in the above formula can be assumed to be zero during the early phase of the time–activity curve and the equation can be simplified to $C_t = C_{max}\ (1 - e^{-K\mathrm{u}t})$, where C_{max} is the plateau level. Therefore, the curves were fitted to the equation $C_s(t) = C_0\ (1 - e^{-Kt})$, where C_s is the ^{99m}Tc-GSA count and C_0 the plateau count of the Tc-GSA in the voxel. Typical accumulation curves are shown in Fig. 1. The Tc-GSA disappearance curve was then determined by subtraction from the saturation (plateau) value. From the curves, we determined the disappearance half time (T 1/2), the time taken for half the radioactivity to disappear from the blood. The disappearance rate constant (K value = 0.693/T 1/2) was then determined for each curve. The K value and functional slice volume were obtained for each slice, and then the average K value for the whole liver was obtained by taking the sum of the product of the K value and the functional liver volume for each slice and dividing by the sum of the functional liver volume for the whole liver.

RESULTS

The correlations among ST-LV, CT-LV, and GSA-LV are shown in Fig. 2. Statistically significant correlations were found between ST-LV and CT-LV (r = 0.607, $P < 0.001$), ST-LV and GSA-LV (r = 0.654, $P < 0.001$), and GSA-LV and CT-LV (r = 0.736, $P <$ 0.001).

Figure 3 shows the correlations between the patient's age and the ST-LV, CT-LV, GSA-LV, and GSA-CLV. A negative linear correlation was found between the patient's age and the CT-LV (r = −0.410, P = 0.001), GSA-LV (r = −0.562, $P < 0.001$), and GSA-CLV (r = −0.614, $P < 0.001$); a negative correlation with age was also found for the ST-LV (r = −0.387, P = 0.001), which also declined linearly with age.

Figure 4 shows the CT-LV/ST-LV, GSA-LV/ST-LV, and GSA-CLV/ST-LV ratios as a function of the patient's age. No correlation was found between the CT-

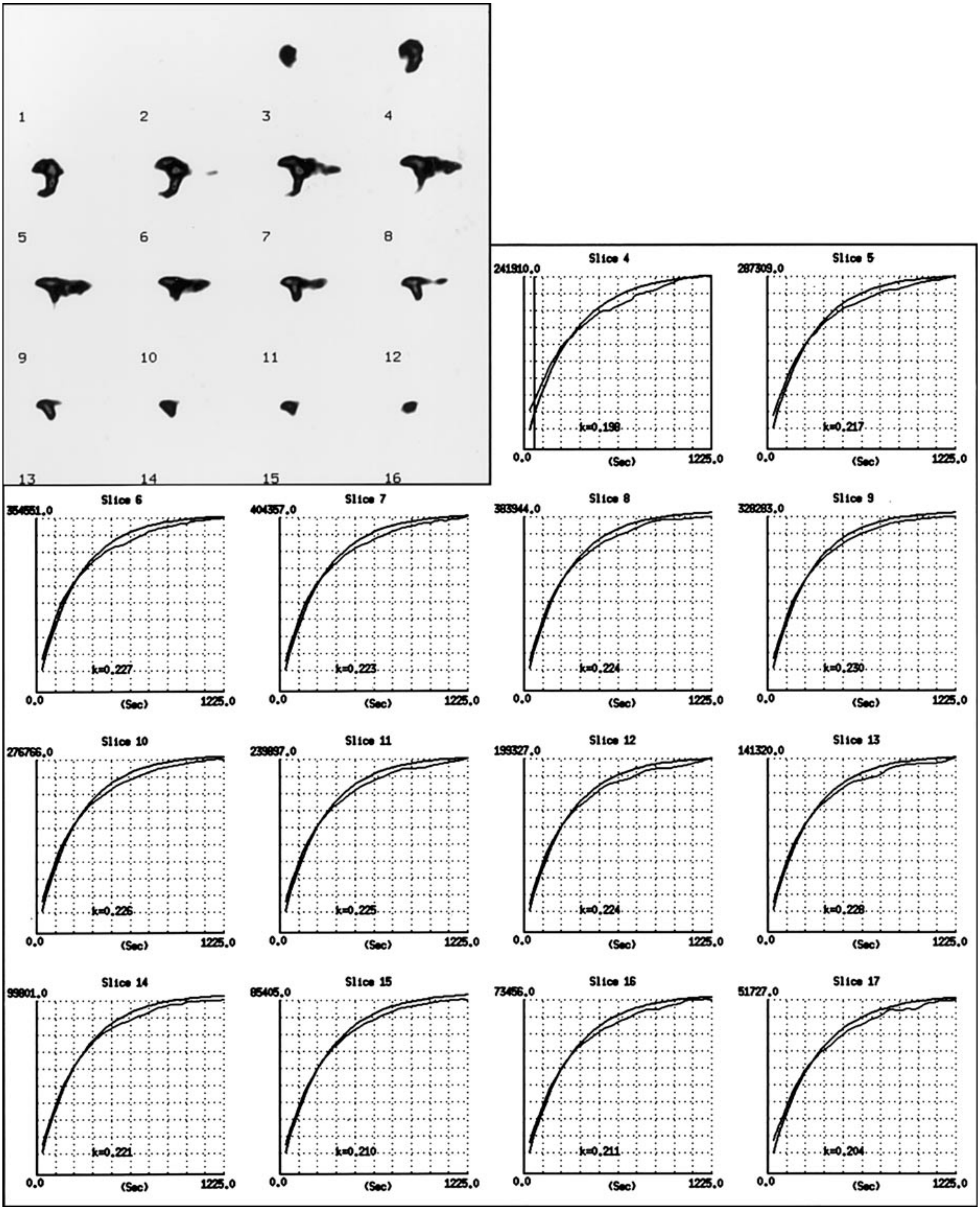

FIG. 1. A typical accumulation curve determining the K value is shown. The upper left shows SPECT images of each slice of the liver.

LV/ST-LV ratio and patient's age ($P = 0.2$). Since the ST-LV, determined taking into account the patient's body surface area, did not change with age and the CT-LV/ST-LV ratio did not change with age, the CT-LV and ST-LV declined by the same proportion. However, the GSA-LV/ST-LV and GSA-CLV/ST-LV ratios showed a statistically significant negative correlation with patient's age ($r = -0.402$, $P = 0.001$, and $r = -0.502$, $P < 0.001$, respectively), with the GSA-CLV/ST-LV ratio falling faster than the GSA-LV/ST-LV ra-

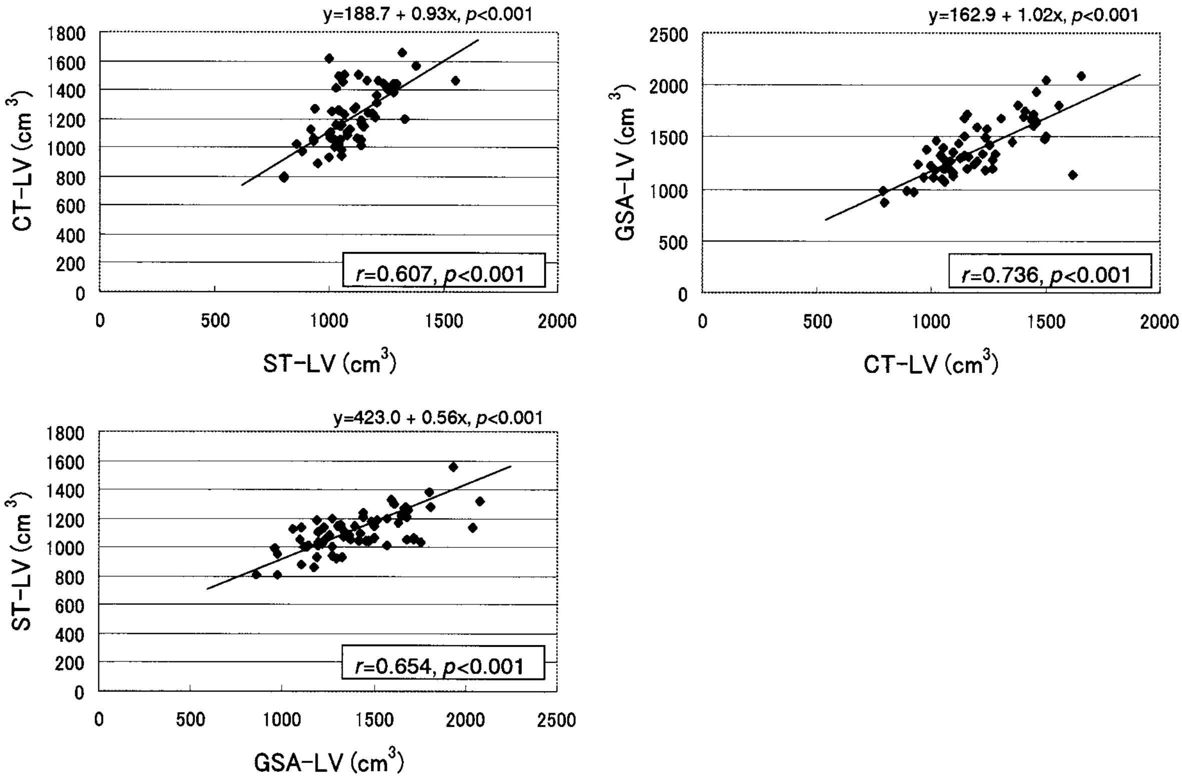

FIG. 2. Correlations between liver volume determined by CT volumetry (CT-LV), standard liver volume (ST-LV) calculated from the patient's body surface area, and liver volume obtained by liver scintigraphy using ^{99m}Tc-galactosyl-human serum albumin (GSA-LV).

tio. Thus, even when the decrease in body surface area with age was taken into account, the GSA-LV/ST-LV and GSA-CLV/ST-LV ratios both declined with age.

As shown in Fig. 5, there was a statistically significant negative correlation between the ICGR15 and the K value obtained by Tc-GSA ($r = -0.616$, $P < 0.001$). The ICGR15 value showed a weak positive correlation with patient's age ($r = 0.301$, $P = 0.017$), whereas the K value showed no statistically significant correlation with patient's age ($P = 0.412$).

DISCUSSION

In recent years, as the geriatric population in Japanese society and in most developed countries has progressively increased, the majority of patients admitted to hospitals are elderly. Furthermore, the increased life span and recent progress in perioperative management and operative techniques have forced surgeons to expand operative indications to include geriatric patients, although they are often compromised with cardiovascular diseases, metabolic disorders, or age-related respiratory problems. Even in liver surgery, the operative indication has been expanded to geriatric patients, and several studies have demonstrated acceptable long-term survival of this age after hepatectomy [8, 9]. Okamoto *et al.* [19] analyzed preoperative parameters predicting liver failure after major hepatectomy and selected patient's age as one predicting factor, in addition to parenchymal resection rates and the ICGR15. Thus, in liver surgery for elderly patients, it is of prime importance to understand the effect of age itself upon liver function and structure, in addition to carrying out a qualitative and quantitative evaluation of liver parenchyma and other organs.

However, there have been few comprehensive studies of liver morphology during aging, and most of these have been performed in rodents [1]. The most frequently cited postmaturational change in the human liver is a decline in organ mass [2–4], although there is even disagreement concerning this basic parameter [5, 6]. Recently, Marchesini *et al.* [3] reported that the maximal functional capacity of the liver, measured by galactose elimination, is reduced in the elderly. Further, Wynne *et al.* [4] observed a significant correlation between age and both liver volume and apparent liver blood flow measured using ICG, whether expressed in absolute terms or per unit of body weight. In both of the above studies, liver volume was assessed using ultrasound, which has an advantage in terms of simplicity. Although the morphological liver volume obtained by CT or ultrasound has been used to assess the functional reserve of the liver [19–22], this volume does not accurately represent the net quantity of hepatocytes,

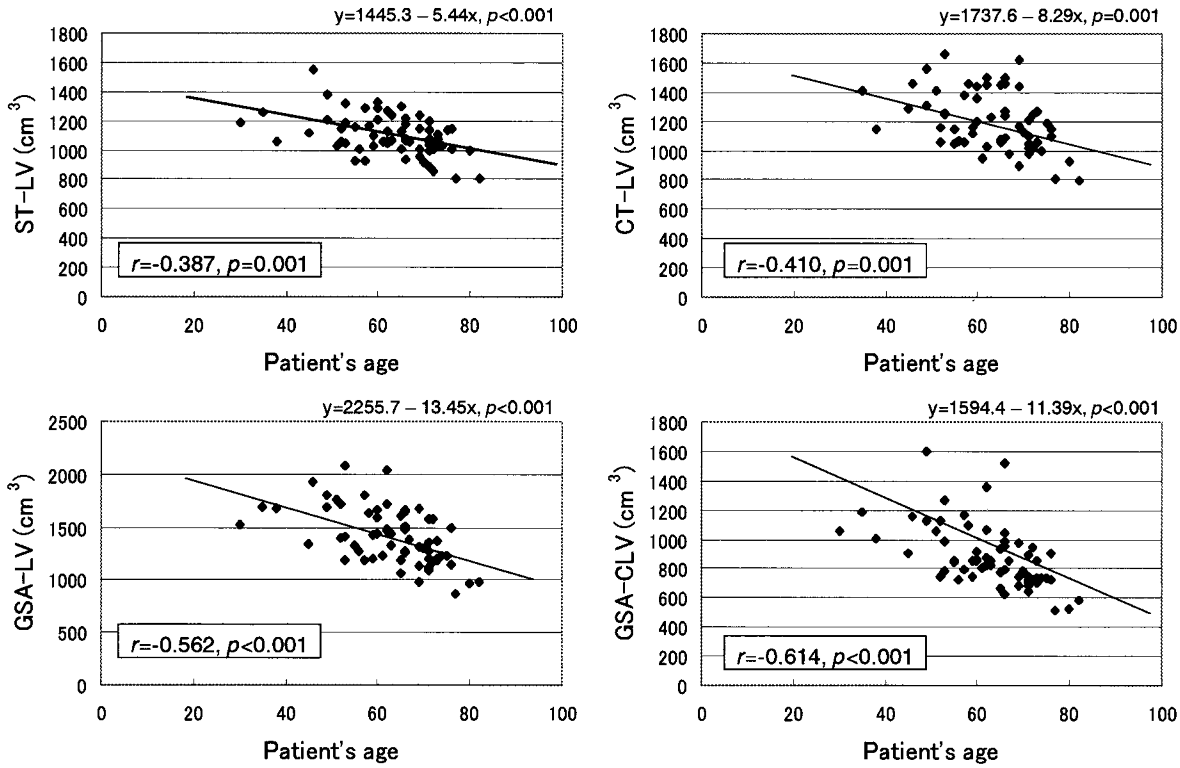

FIG. 3. Correlations between patient's age and liver volume determined by CT volumetry (CT-LV), standard liver volume (ST-LV) calculated from the patient's body surface area, and liver volume (GSA-LV) and calculated liver volume (GSA-CLV) obtained by liver scintigraphy using ^{99m}Tc-GSA.

particularly in cases of liver cirrhosis in which there is a reduction in hepatocyte volume [23, 24]. Furthermore, in the field of liver transplantation, a formula based on a close association between liver volume and body surface area has been reported [14] and its accuracy verified, allowing for a precise determination of the total liver volume in healthy adults. In the present study, the values for the liver volume, determined in various ways, were therefore compared to the ST-LV, calculated using the above formula, and not to the liver volume per unit of body weight.

Tc-GSA is a novel liver scintigraphy agent that binds to the asialoglycoprotein receptor on hepatocytes [25]. Tc-GSA scintigraphy has been reported to measure the viable hepatocyte mass and to be useful in assessing the reserve hepatic function under various physiologic and pathological conditions [10–13]. Even in liver-bearing tumors, such as hepatocellular carcinoma, cholangiocellular carcinoma, or metastatic tumors [10, 11], or in the jaundiced liver [13], Tc-GSA scintigraphy is reported to be useful in fully evaluating hepatic function based on hepatocyte volume. We have also evaluated liver function preoperatively by scintigraphy using Tc-GSA [16] or ^{99m}Tc-Sn colloid [15]. As the parameters to be evaluated, we chose liver volume assessed using GSA (GSA-LV), sometimes described as "the functional liver volume" by other researchers [10], and the calculated liver volume (GSA-CLV), which is calculated by paying more attention to the actual value of the Tc-GSA count, as described above.

In this study, we found that the CT-LV declined with age, as reported by others [1–4]. However, the CT-LV/ST-LV ratio did not change, indicating that liver volume evaluated by CT in elderly patients is not smaller when body size is taken into account. On the other hand, the GSA-LV and GSA-CLV declined with age, even when body size was taken into account. The GSA-CLV, which more closely reflects the amount of asialoglycoprotein receptor, was shown to have a greater negative correlation with age than the GSA-LV. Thus, in elderly patients, the liver was not morphologically smaller, but the hepatocyte volume decreased. This agrees with a previous report concluding that the liver in elderly humans has fewer, larger hepatocytes histologically [26]. This fact may have a critical impact on preoperative liver functional reserve evaluation prior to major hepatic resection. In recent years, in addition to the conventional criteria, such as Child–Pugh score [19–22], the remaining liver volume or the parenchymal resection rate estimated preoperatively using CT volumetry has become one of the major factors predicting risk accompanying major hepatic resection. However, our present results imply that there is a discrepancy between liver volume estimated by CT and the

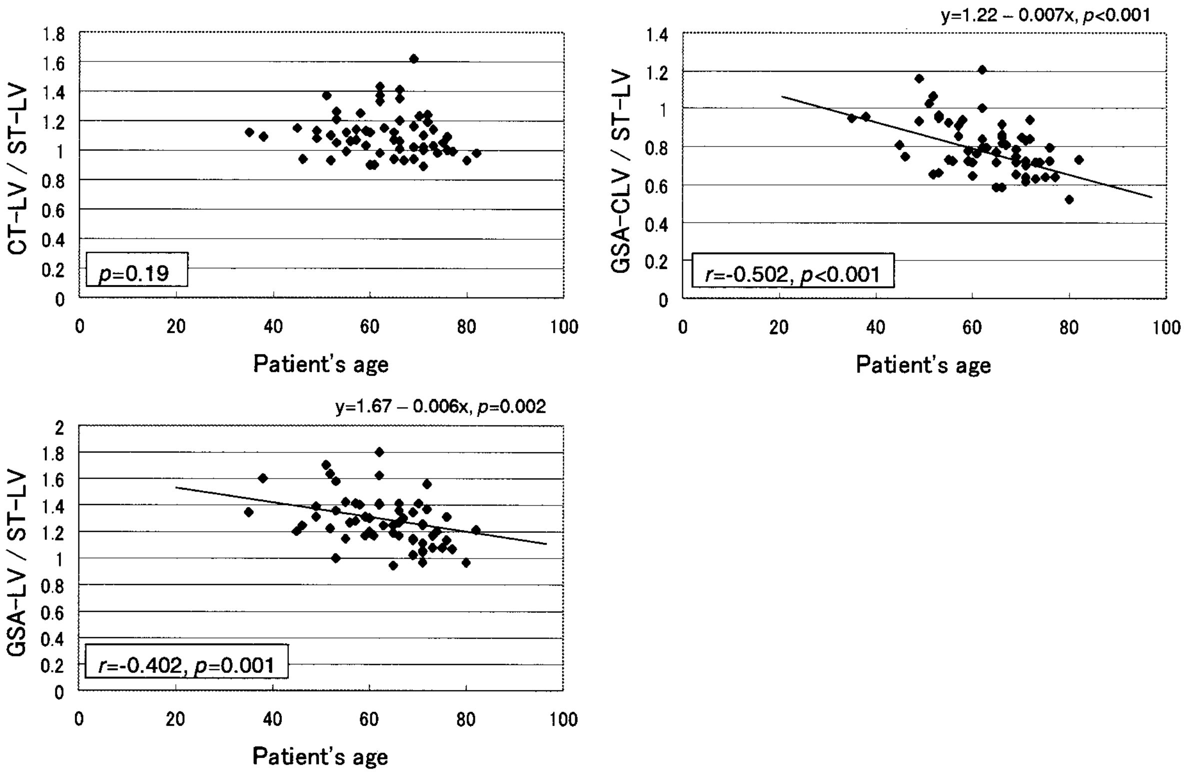

FIG. 4. Correlations between patient's age and the ratio of the liver volume determined by CT volumetry (CT-LV) and the liver volume (GSA-LV), and calculated liver volume (GSA-CLV) obtained by liver scintigraphy using ^{99m}Tc-GSA divided by the standard liver volume (ST-LV) calculated from the patient's body surface area.

actual hepatocyte volume in elderly patients. Actually, Matsui *et al.* [23] reported that the functional reserve of the cirrhotic liver was assessed more precisely by hepatocyte volume than by liver volume estimated by CT. Thus, in preoperative risk estimation prior to hepatic resection, it may be important to take age into account as one of the criteria, as reported by Okamoto *et al.* [19], or the functional volume estimated by Tc-GSA should be given priority over CT volumetry in elderly patients.

In addition, hepatic clearance of many drugs is reduced in elderly persons [1]. Traditional theories have attempted to attribute this to the age-related reduction in liver mass and blood flow [2–4], although a more recent study [7] suggests that it can be attributed to age-related changes in the sinusoidal endothelium and space of Disse, which may restrict the availability of oxygen and other substrates. Wynne *et al.* [4] analyzed ICG clearance in healthy men and showed that liver blood flow per unit volume of liver declined with age. In the present study, ICGR15 showed a weak positive correlation with age, whereas the K value, obtained by kinetic analysis of Tc-GSA accumulation, did not change. In the present study, the K value was found to correlate with the ICGR15, and we have previously reported that it correlates with the liver blood flow per unit volume of liver [16]. Currently, several different kinetic models and parameters for the analysis of Tc-GSA kinetics in the evaluation of hepatocyte mass and liver blood flow have been advocated [10–13, 18]. The five-compartment model advocated by Miki *et al.* [11] may be the most accurate representation of asialoglycoprotein receptor distribution but is rather complicated. In the present study, the K value was obtained using a simple two-compartment model, but we assumed the K value to be proportional to the hepatic blood flow per unit of functional liver volume [15, 16]. The results obtained in the present study suggest that liver blood flow per unit of functional liver volume may not change with age.

In this study, the patients analyzed were awaiting surgical treatment for liver tumors. Although the liver parenchyma in each patient was proven to be normal and although hepatocyte volume and blood flow analysis using Tc-GSA has been performed by many researchers on patient populations carrying liver tumors, the possibility that the liver tumor may affect the results cannot be excluded. The effects of aging on the liver should ideally be analyzed in healthy humans [3, 4]. However, the present study, analyzing the effect of aging on the basic parameters concerning liver function in patients awaiting surgery, will have clinical importance in actual preoperative estimation, al-

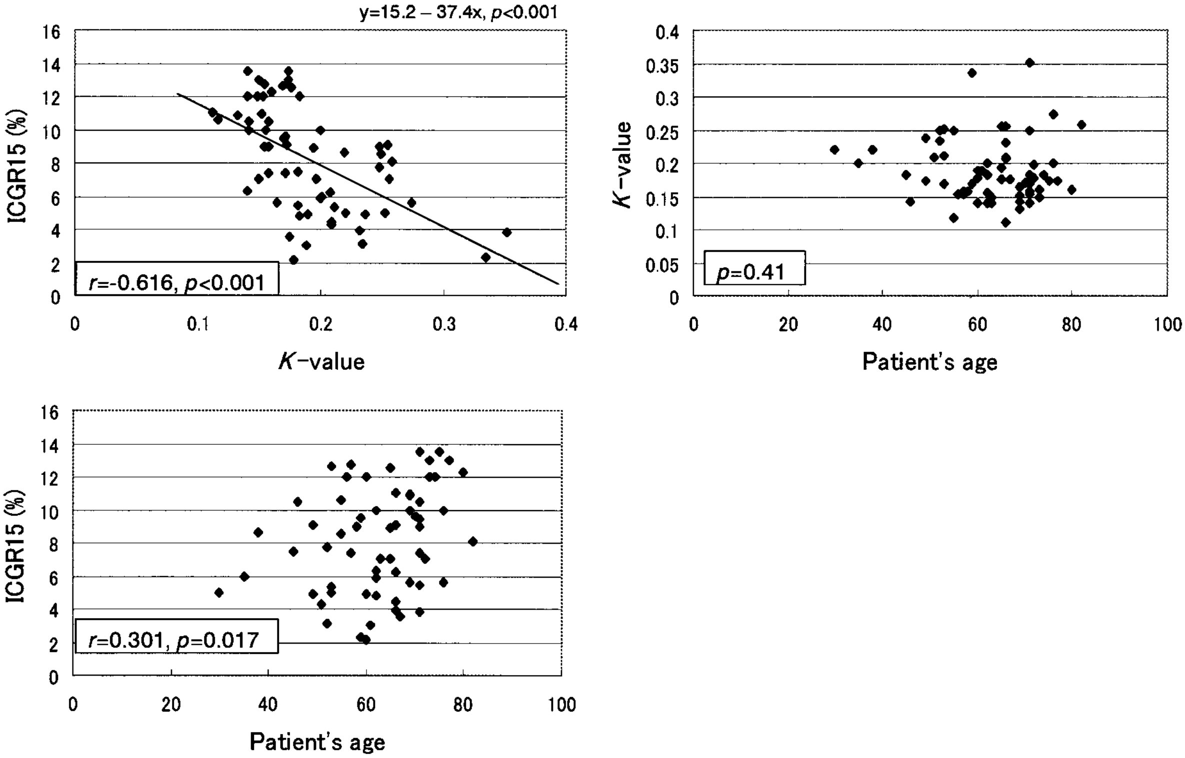

FIG. 5. Relationship between the *K* value and the indocyanine green retention rate and their correlation with patient's age.

though studies in a larger patient population will be needed to reach a definite conclusion.

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