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^{99m}Tc-GSA scintigraphy for assessing the functional volume ratio of the future liver remnant in the routine practice of liver resection☆

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ABSTRACT

Background: The significance of incorporating regional functional heterogeneity assessment by liver scintigraphy into the calculation of the future liver remnant has been reported. However, liver scintigraphy entails additional costs and radiation exposure. Nevertheless, studies describing when liver scintigraphy demonstrates an actual benefit over computed tomography liver volumetry are lacking. Thus, we evaluated the degree of agreement between future liver remnant % values calculated by technetium ^{99m}Tc diethylenetriaminepentaacetic acid-galactosyl human serum albumin scintigraphy (galactosyl human serum albumin–based future liver remnant %) and those by computed tomography volumetry and investigated the practical impact of performing regional functional heterogeneity assessment.
Methods: The Bland–Altman method was used to retrospectively analyze the agreement between computed tomography– and galactosyl human serum albumin–based future liver remnant % measurements in 84 patients.
Results: In ordinary patients with a computed tomography–based future liver remnant % greater than 50%, there was a good agreement between both measurements. However, in cases with a computed tomography–based future liver remnant % less than 40%, galactosyl human serum albumin–based measurements were significantly smaller than computed tomography–based values, with 88% of these patients exhibiting a galactosyl human serum albumin–based future liver remnant % less than 30%. After portal vein embolization, galactosyl human serum albumin–based measurements were primarily greater than or in agreement with computed tomography–based values, even in cases with a computed tomography–based future liver remnant % less than 40%.
Conclusion: Adding ^{99m}Tc diethylenetriaminepentaacetic acid-galactosyl human serum albumin scintigraphy to computed tomography liver volumetry is advised when deciding on hepatectomy in patients with a computed tomography–based future liver remnant % less than 50%. If the computed tomography–based future liver remnant % is smaller than 40%, it is strongly recommended to check future liver remnant % by ^{99m}Tc diethylenetriaminepentaacetic acid-galactosyl human serum albumin scintigraphy. In other cases, computed tomography–based future liver remnant % calculation alone can be regarded as the gold standard of safe hepatectomy.

INTRODUCTION

In patients undergoing massive hepatectomy, the amount of the liver that should be preserved to prevent posthepatectomy liver failure (PHLF) has always been an important issue. The limit for safe liver resection is reportedly a future liver remnant (FLR) volume between 20% and 30% of the total liver volume (TLV) in patients with normal liver function [1–3]. There is now no dispute that preoperative evaluation of the FLR/TLV ratio (expressed as FLR%) is a prerequisite for massive hepatectomy, with computed tomography (CT) liver volumetry representing the current golden standard for measuring FLR% [3].

Recent advances in computer technology have made it possible to assess the heterogeneity of liver function from region to region by the means of either ^{99m}Tc diethylenetriaminepentaacetic acid-galactosyl human serum albumin (^{99m}Tc-GSA) scintigraphy or ^{99m}Tc-mebrofenin scintigraphy [4–8]. Although there is certainly a theoretical rationale behind performing liver scintigraphy, it places considerable financial and medical burdens on patients, including additional costs and radiation

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exposure. The cost of a single ^{99m}Tc-scintigraphy exanimation is about US$300 in Japan (US$564–$2,534 in the United State for liver scan test). Radiation exposure is estimated to be about 90 mGy in the gallbladder and 6.5 mGy in the liver. The effective radiation dose by the International Commission on Radiological Protection is 1.5 mSv per test. In addition, unlike CT liver volumetry, liver scintigraphy alone cannot accurately distinguish the border between the liver segment that needs to be resected and the segment that could be preserved, thus necessitating image fusion with CT scans and consequently making CT volumetry inevitable. Nevertheless, there is a lack of studies exploring when liver scintigraphy offers an actual benefit over CT volumetry alone.

In this study, we retrospectively evaluated the degree of agreement and disagreement between the FLR% calculated by ^{99m}Tc-GSA scintigraphy (GSA-based FLR%) and that by CT volumetry (CT-based FLR%) to investigate the practical impact of adding regional functional heterogeneity assessment of the liver to FLR% calculation.

METHODS

Patients. All patients who received ^{99m}Tc-GSA scintigraphy at Akita University Hospital between June 2010 and May 2020 were first extracted. Whether or not to perform ^{99m}Tc-GSA scintigraphy before hepatectomy has been left to the discretion of the attending physician, so it has not been performed on all patients. Three inclusion criteria were used in this study: (1) patients who had undergone contrast-enhanced CT scanning at a time when comparison with ^{99m}Tc-GSA scintigraphy was possible, (2) their initial surgical plan involved typical anatomical hepatectomies of 1 liver section or more, and (3) they had no prior history of interventions other than portal vein embolization (PVE)/ligation and/or biliary drainage. In this study, portal vein ligation was regarded as a variant of PVE. However, the data after receiving PVE were separately analyzed from those without PVE. Exclusion criteria were as follows: (1) the initial surgical plan was partial resections (including segmentectomies and multiple resections), modified complex liver resections, and previous history of hepatobiliary pancreatic surgery, because the accuracy of CT volumetry was not enough in these patients, and (2) patients who had previously received interventions which would modify hepatic blood flow such as transcatheter arterial embolization, because they would significantly affect the functional reginal heterogeneity of the liver.

A total of 84 patients, including 60 men and 24 women, were enrolled in the study. Patient characteristics and initial hepatic resection procedures are listed in Table 1 (left column). Hepatectomy indications were determined based on various factors, including anatomical tumor location, tumor size, background liver function, and prognostic factors; tolerance for hepatectomy was primarily evaluated using the CT-based FLR% and plasma clearance rate of indocyanine green (KICG). As a combined index of these parameters, remKICG = KICG × CT-based FLR% has been used [9,10]. The CT-based FLR% was calculated after subtracting the tumor volume from the TLV [11]. We principally considered a remKICG > 0.05 as a standard for safe hepatectomy, although some patients with marginally low remKICG values were treated with hepatectomy because of special circumstances [9]. These patients had received ^{99m}Tc-GSA scintigraphy as well, but we only used the HH15 (clearance index: count for the heart at 15 minutes/count for the heart at 3 minutes) and LHL15 (receptor index: count for the liver at 15 minutes/sum of the counts for the heart and liver at 15 minutes) as indices. The GSA-based FLR%, which was retrospectively calculated in the present study, had not been considered an indication for hepatectomy at the time of surgery.

Table 1
Patient characteristics

Age	67.7 ± 8.9 y
Hepatectomy planned	
Men/women	60:24
Disease	Total 84
Hepatocellular carcinoma	40
Intrahepatic cholangiocarcinoma	8
Perihilar cholangiocarcinoma	16
Broad bile duct carcinoma	2
Gallbladder carcinoma	5
Colorectal liver metastasis	13
Mode of hepatectomy	Total 84
Right trisectionectomy (r3HPD)	6 (1)
Left trisectionectomy	2
Right hepatectomy (rHPD)	50 (2)
Left hepatectomy	12
Central bisectionectomy	5
Posterior sectionectomy	5
Anterior sectionectomy	2
Medial sectionectomy	2

r3HPD, right trisectionectomy with pancreaticoduodenectomy; *rHPD*, right hepatectomy with pancreaticoduodenectomy.

After the first measurement of CT-based FLR% and remKICG, 48 patients directly underwent intended hepatectomy; however, in 3 patients, surgery was modified to limit the resection volume: from central bisectionectomy to anterior sectionectomy ($n = 1$) and to extended medial sectionectomy ($n = 1$) and from right hepatectomy to anterior sectionectomy ($n = 1$). Resection was aborted after laparotomy because of either peritoneal dissemination or duodenal invasion, with hepatic artery involvement in 2 gallbladder cancer patients. Twelve patients were switched to partial hepatectomies limited to less than 1 liver section, interventional therapies, or systemic chemotherapy. In 19 patients, PVE was performed. Several weeks after PVE, CT examination, ^{99m}Tc-GSA scintigraphy, and indocyanine green test were re-examined. In addition to these 19 patients, there were 4 patients for whom only ^{99m}Tc-GSA scintigraphy data after PVE were available. As a result, 103 measurements were analyzed in 2 separate groups: without/before PVE ($n = 80$) and post-PVE ($n = 23$).

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Data collection for the present analysis was approved by the ethics committee of Akita University, Graduate School of Medicine (Approval code: 2078). According to the IRB instruction, the study protocol was informed on the web page of Akita University Hospital and obtained consent of patients in an opt-out manner.

CT Liver Volumetry. Dynamic contrast-enhanced CT was performed using a CT scanner with 64-row (Revolution CT or Discovery CT 750 HD, GE Healthcare Japan, Co, Ltd, Tokyo, Japan) at 0.625–1.25-mm intervals. Under intravenous administration of a nonionic contrast agent (650 mg/kg of iodine in 30 seconds), images were obtained in early arterial, late arterial, portal, and equilibrium phases at 10, 20, 45, and 165 seconds after injection initiation, respectively. Digital Imaging and Communications in Medicine (DICOM) data were used to construct three-dimensional (3D) images for volumetric analysis by SYNAPSE VINCENT Ver.4.0 (Fujifilm Medical Co, Tokyo, Japan). After analyzing 3D vascular images of the portal branches, we simulated our intended hepatectomy on the display panel and computed the TLV, tumor volume, and FLR volume and their ratio to the TLV.

^{99m}Tc-GSA Scintigraphy. After 3 mg of ^{99m}Tc-GSA (1 mL, 185 MBq or more; Nihon Medi-physics Co, Ltd, Nishinomiya, Japan) was intravenously administered, dynamic scintigrams were acquired using a gamma camera (Symbia E, Siemens Healthcare, Erlangen, Germany) equipped with a low-energy, high-resolution collimator. During the first 30 minutes, dynamic scintigraphy data were obtained. Then, single-photon emission CT (SPECT) images were captured in 36 rotation steps of 5° (20 seconds/step) with 2 cameras placed opposite each other, which resulted in 360° images. SPECT images (128 × 128 matrix) were reconstructed using the filtered back projection method with a Butterworth filter to yield volume data.

Image Fusion. DICOM volume data from ^{99m}Tc-GSA SPECT scintigraphy were merged with CT volumetric data on SYNAPSE VINCENT by adjusting axial and coronal images. The workstation then automatically computed the ratio of radioactivity magnitudes detected from the corresponding compartments used for calculating the CT-based FLR%. In this study, the FLR/TLV ratio computed from the volumetry weighted by the GSA distribution was termed *GSA-based FLR%*. Figure 1 shows representative cases in terms of the difference in CT-based FLR% and GSA-based FLR%. In patient A, there is little disagreement between 2 measurements, but in patient B, the difference reaches 10.8% in a volume ratio.

Statistics

Agreement Analysis Between CT- and GSA-Based FLR% Measurements

The Bland–Altman method was employed to analyze the agreement between CT- and GSA-based FLR% measurements [12,13]. Because the clinical impact of disagreement between the 2 measurements depended on the magnitude of FLR% in each patient, differences in rates (rather than differences in raw values) were plotted on the *y* axis against the best estimate of FLR% on the *x* axis.

The limits of agreement were determined as follows: When FLR% was sufficiently large, the absolute magnitude of differences in FLR% did not significantly affect clinical judgment. By contrast, when FLR% was relatively small (eg, about 30%) and the small size of FLR% represented a contraindication to hepatectomy, even a measurement difference of ± 0.2 led to an approximately $\pm 6\%$ difference in the real value of FLR%. This is especially important because overestimation of FLR% by 6% could result in overlooking the fact that the actual FLR% was less than 25%, which is thought to be the minimum FLR% required for patients to survive [14,15]. Therefore, in anticipation of safety, the limits of agreement were set at ± 0.1.

Others

All data are expressed as mean $\pm$ standard deviation, unless otherwise stated. Statistical analyses were performed using SPSS version 26 (SPSS Inc., Chicago, IL, USA). Correlation analysis was done using Pearson's correlation coefficient (r) and P value. The Kolmogorov–Smirnov test was used to assess data normality. The Mann–Whitney U test and paired Student t test were applied as appropriate to compare mean values.

RESULTS

FLR% Estimation in Ordinary Patients Without/Before PVE. Of the 80 patients in this group, 19 were hepatitis B positive and 9 were hepatitis C positive. The underlying parenchymal quality of the liver in these patients was uniformly fairly good. All patients showed Child-A class with a Child–Pugh score of 5.250 (95% confidence interval: 5.155–5.345). ALBI scores were −2.488 (95% confidence interval: −2.596 to −2.380). Platelet count and prothrombin time INR were 201,300/μL (95% confidence interval: 185,100–217,500) and 0.986 (95% confidence interval: 0.962–1.01), respectively. KICG was 0.144 (95% confidence interval: 0.136–0.152). Accordingly, differences in the quality of background liver disease of this cohort were not thought to have a significant impact on the following analysis of differences in CT-based and GSA-based FLR% measurements.

As shown in Fig 2, there was a very strong correlation between GSA- and CT-based FLR% values. However, a strong correlation between 2 measurements—in this case, CT- and GSA-based FLR% values—does not necessarily mean that they are in agreement with each other and can therefore be used interchangeably [12]. The key to understanding the value of adding ^{99m}Tc-GSA scintigraphy to CT liver volumetry is to analyze how much discrepancy exists between CT- and GSA-based FLR% measurements. In other words, the use of ^{99m}Tc-GSA scintigraphy has no value if the difference between CT- and GSA-based FLR% values is too small; yet, it should be considered if the deviation between these values is significantly large.

To this end, the Bland–Altman plot was used to analyze the degree of deviations between GSA- and CT-based FLR% measurements. CT- and GSA-based FLR% values were regarded as 2 independent measurements of the true FLR% (the true value remains unknown). Figure 3 illustrates that the difference in measurements (rate) had a unique dependency on the magnitude of the best estimate of the true FLR%. Interestingly, most of the points below the lower limit of agreement were observed in the area where the best estimate of FLR% was small (inside the dotted circle). Other data points lay either within the limits of agreement or above the upper limit of agreement. In the former case, the CT-based

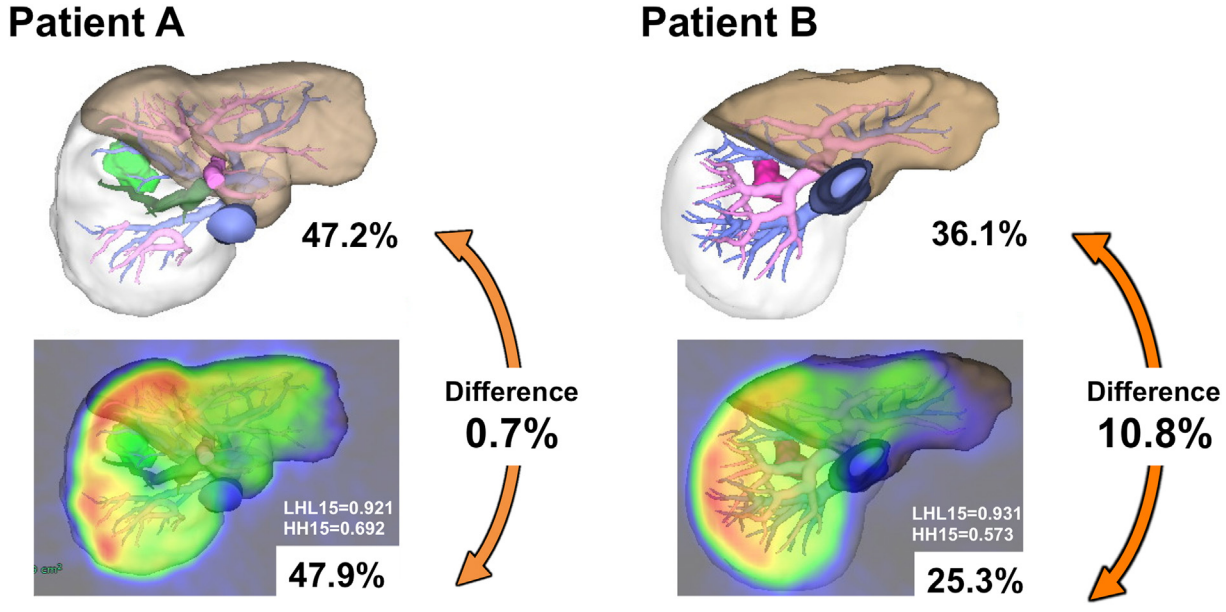

Fig 1. Representative cases of with and without difference in the ratio of future liver remnant to the whole liver. The difference is only 0.7% in patient A, but the difference reaches 10.8% in patient B.

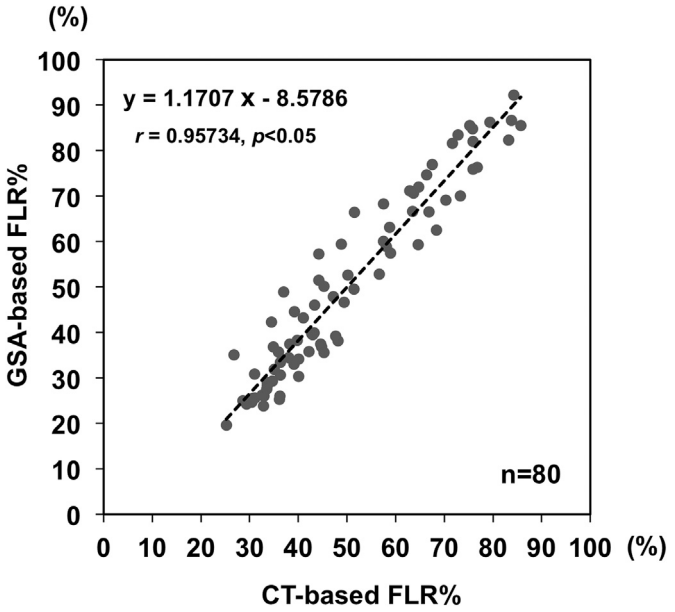

Fig 2. Correlation between CT- and GSA-based FLR% measurements. The dotted line represents the regression line.

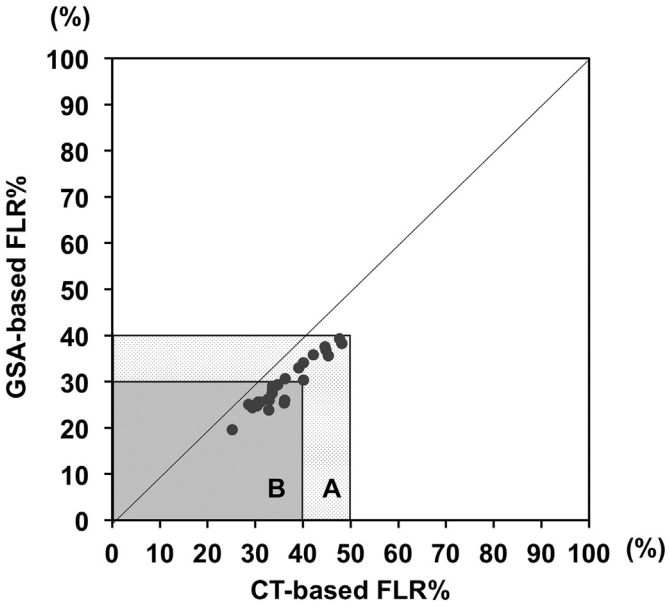

Fig 4. Correlation between CT- and GSA-based FLR% measurements in patients with a difference rate significantly smaller than the lower limit of agreement (ie, data points within the dotted circle in Fig 2). The solid line indicates the line of agreement for CT- and GSA-based FLR% measurements. Area A indicates the CT-based FLR% between 40% and 50%. Area B indicates the CT-based FLR% less than 40%.

FLR% could be considered equal to the GSA-based FLR%, diminishing the usefulness of ^{99m}Tc-GSA scintigraphy. In the latter case, however, the GSA-based FLR% turned out to be larger than the CT-based measurement. In these cases, patients found eligible for hepatectomy according to their CT-based FLR% would also qualify for hepatectomy based on their GSA-based FLR%. This suggests that, in such patients, CT-based FLR% calculation alone would suffice to guarantee a safe resection given that the purpose of FLR% calculation prior to hepatectomy is to avoid unreasonably excessive liver resection. Conversely, when the best estimate of FLR% was less than 30%, all data points lay below the lower limit of agreement; in this situation, only 1 patient underwent right hepatectomy as per initial decision. In 8 of 9 (89%) patients, surgery was aborted, and PVE or transcatheter arterial chemoembolization was undertaken instead.

Consequently, we strived to investigate when the GSA-based FLR% was smaller than the CT-based FLR%. In doing so, we evaluated the correlation between GSA- and CT-based FLR% measurements in patients whose data points were marked by a dotted circle in Fig 3 (Fig 4). We found that all patients lay below the line of agreement (the solid diagonal line from the left lower corner to the right upper corner). The maximum CT-based FLR% of patients whose GSA-based FLR% was less than the CT-based FLR% was 50%. Nevertheless, in patients with a CT-based FLR% within the 40%–50% range (area **A** in Fig 4), the corresponding GSA-based FLR% measurements were still greater than 30%, which is generally regarded as the threshold for indication of hepatectomy with a safe margin. There was no patient with a critically small GSA-based FLR% in this area. More importantly, however, 15 of 17 (88%)

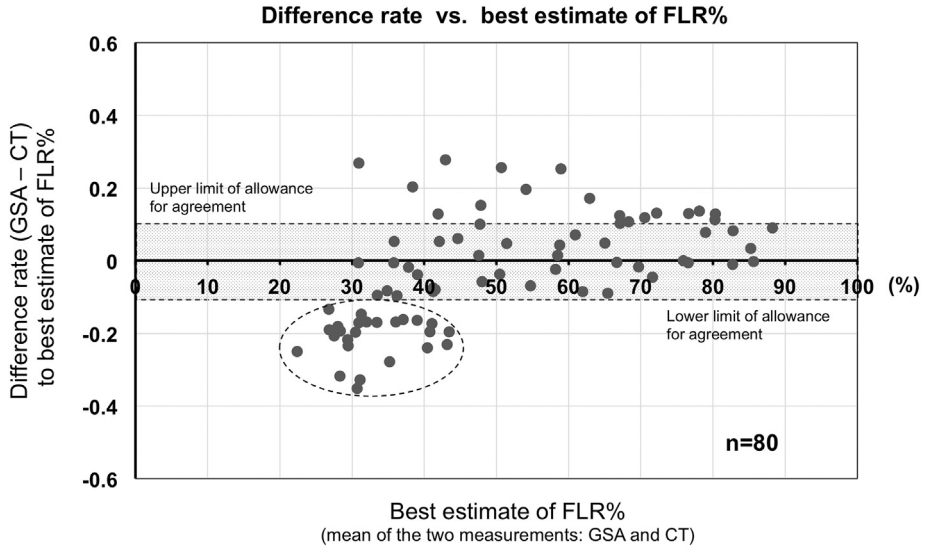

Fig 3. The Bland–Altman plot for 80 patients without PVE. The best estimate of FLR% is the mean of CT- and GSA-based FLR% measurements. The difference rate was determined as the difference between the 2 measurements against the best estimate of FLR%. The limits of agreement are within ±0.1 from the line of complete agreement.

patients with a CT-based FLR% less than 40% were found to have a GSA-based FLR% smaller than 30% (area **B** in Fig 4).

It is advised to perform ^{99m}Tc-GSA scintigraphy when the CT-based FLR% is less than 50% to avoid unexpected misjudgment of the true FLR%. When the CT-based FLR% is smaller than 40%, it is strongly recommended to conduct ^{99m}Tc-GSA scintigraphy to prevent overestimation of the true FLR%.

Clinical Consequence in the Patients with CT-Based FLR% < 40%. Table 2 shows the clinical consequence in 80 ordinary patients without/before PVE. Of 29 patients with CT-based FLR% < 40%, 11 patients (39.7%) underwent planned or reduced-size hepatectomy, but 15 patients (51.7%) were transferred to PVE; further consequence in these PVE patients differed because of the effectiveness of PVE and/or tumor progression. Three patients (10.3%) avoided hepatectomy and received transcatheter arterial chemoembolization or systemic chemotherapy. Of 11 patients who underwent hepatectomy, 3 patients (27.2%) developed PHLF (Grade A in 2 and Grade B in 1 according to the classification by the International Study Group of Liver Surgery). The incidence was higher than that in the patients of CT-based FLR% > 40% (20.9%, Grade A in 5 and Grade B in 4 of 43 hepatectomies), but it was difficult to evaluate this difference because the latter included more complicated surgeries. Because the clinical decision for therapeutic strategy at the time of their therapy was significantly influenced by remKICG >0.05, we retrospectively examined how the therapeutic strategies might have been changed if the remKICG (GSA) = KICG × GSA-based FLR% was also considered in addition to remKICG, assuming that the GSA-based FLR% was measured at that time. In 6 patients (20.7%), hepatectomy might have been hesitated and PVE would be chosen because of the low value of remKICG (GSA), and in 3 patients (10.3%), hepatectomy might have been bravely performed instead of PVE. However, not only because it has not been proven that the reference value of 0.05 for remKICG is valid for remKICG (GSA) itself but also because treatment decisions are multifactorial, this argument cannot escape the criticism of being very subjective.

Unit Density of ^{99m}Tc-GSA Uptake by the Right and Left Liver. Table 3 shows characteristics of patients who had a best estimate of FLR% less than 40%; among them, many patients had a significantly lower GSA-based FLR% value than CT-based FLR% value. Although background diseases varied from patient to patient, right hepatectomy and right trisectionectomy constituted 97% of the hepatic resection procedures planned. There was only 1 case of left trisectionectomy, where the best estimate of FLR% was found to be 31% owing to the remaining posterior section. Because there was a great tendency toward hepatectomy via right-sided approaches, we decided to compare the right and left livers in terms of their unit density of ^{99m}Tc-GSA uptake. The relative density of ^{99m}Tc-GSA uptake against anatomical volume (GSA-based FLR%/CT-based FLR%) was compared between the right and left livers by examining the cases of left and right hepatectomy, respectively. The unit density of ^{99m}Tc-GSA uptake by the left liver ($n = 47$) was significantly lower than that by the right liver ($n = 11$) (0.929 ± 0.153 vs 1.121 ± 0.035, respectively; $P < .05$). That is, the activity of the left liver per unit volume was suppressed to about 83% of that of the right liver. In addition, for the left liver, GSA-based FLR% measurements per se tended to be smaller than CT-based ones.

Table 2
Clinical consequence of 80 ordinary patients without/before PVE

CT-based FLR% < 40% patients			
Clinical consequence	*Total*	*Outside the dotted circle*	*Inside the dotted circle*
Hepatectomy	11 (37.9%)	6 (50.0%)	5 (29.4%)
As planned	9	6	3
Reduced size	2	0	2
PVE	15 (51.7%)	4 (33.3%)	11 (64.7%)
TACE/chemo	3 (10.3%)	2 (16.7%)	1 (5.9%)
	29	12	17
CT-based FLR% > 40% patients			
Clinical consequence	*Total*		
Hepatectomy	43 (84.3%)		
As planned	36		
Reduced size	7		
PVE	4 (7.8%)		
TACE/chemo	3 (5.9%)		
Exploratory laparotomy	1 (2.0%)		
	51		

TACE, transcatheter arterial chemoembolization; *chemo*, systemic chemotherapy. "As planned" means a hepatectomy as initially intended, and "reduced size" means a hepatectomy with more parenchymal preservation than initially intended.

Table 3
Characteristics of patients with a best estimate of FLR% less than 40%.

	Less than 40%	*Less than 30%*
Disease		
Hepatocellular carcinoma	12	2
Hilar cholangiocarcinoma	9	2
Liver metastasis	4	2
Intrahepatic cholangiocarcinoma	2	2
Gallbladder carcinoma	2	1
Broad cholangiocarcinoma	1	0
Hepatectomy plan		
Right hepatectomy	25	8
Right trisectionectomy	4	1
Left trisectionectomy	1	0
Actual consequence		
Right hepatectomy	10	1
Anterior sectionectomy	1	0
Partial resection (S8)	1	0
Portal vein embolization	16	7
Transcatheter arterial chemoembolization	2	1

FLR% Estimation in Patients Treated With PVE. The relationship between the anatomical volume of each liver segment and its regional function is significantly modified after vascular occlusion by PVE. Therefore, we extracted a cohort of 23 patients who were treated with PVE and studied the differences in their CT- and GSA-based FLR% measurements. Figure 5 illustrates the Bland–Altman plot for these patients, with no cluster of data points formed below the lower limit of agreement—unlike what was observed in patients without PVE treatment. All but 1 data point (to be exact, all but 2 data points) lay above the lower limit of agreement, indicating that GSA-based FLR% values were greater than or equal to CT-based measurements. This implies that additional examination with ^{99m}Tc-GSA scintigraphy is of limited value in patients treated with PVE.

Figure 6, *A* demonstrates an increase in paired CT- and GSA-based FLR% measurements before and after PVE in 19 patients. The mean increase in the GSA-based FLR% was significantly higher than that in the CT-based FLR% (18.495% ± 8.789% vs 9.479% ± 4.677%, respectively; $P < .05$). This indicates that PVE led to a greater rise in the GSA-based FLR% than in the CT-based FLR%, explaining the shift of measurement differences toward the positive direction (Fig 6, *B*).

DISCUSSION

Technological innovations may provide us with a tool for multiple evaluations, but it does not always benefit patients. Because CT scans are essential for every patient before surgery, it seems reasonable to trust the CT-based FLR% as a golden standard. However, if additional testing is significantly helpful in saving patients from unexpected PHLF, we should not spare it. A growing number of reports have

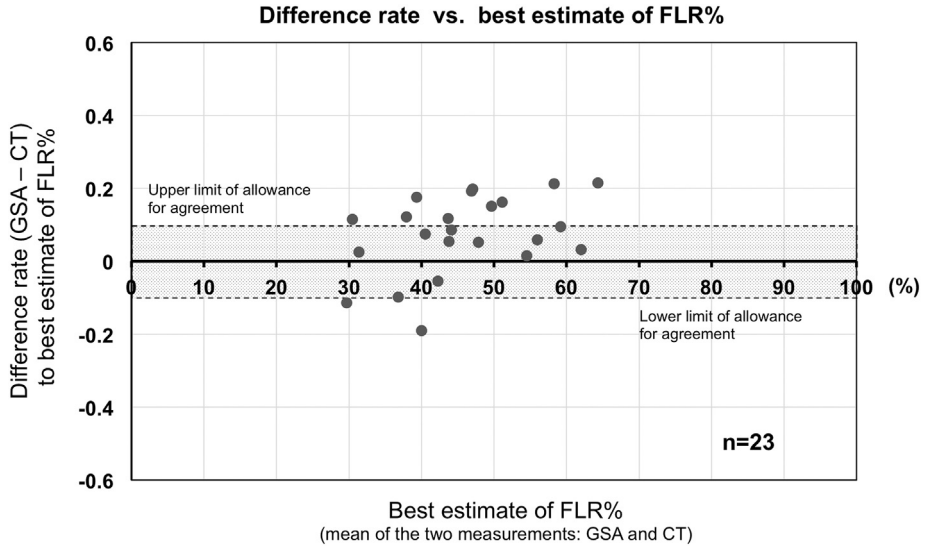

Fig 5. The Bland–Altman plot for 23 patients treated with PVE. The best estimate of FLR% is the mean of CT- and GSA-based FLR% measurements. The difference rate was determined as the difference between the 2 measurements against the best estimate of FLR%. The limits of agreement are within ±0.1 from the line of complete agreement.

suggested a discrepancy between the anatomical and functional volume ratios of the FLR [6–8]. Especially, the Amsterdam group emphasized the importance of including the regional heterogeneity of liver function in FLR% calculation [4,5,16].

In this study, we demonstrated that when the CT-based FLR% was larger than 50%, it basically agreed well with the GSA-based FLR%. A good agreement between these 2 FLR% measurements implies that the regional heterogeneity of liver function that is innately shared by everyone does not have a significant impact on hepatectomies. However, when CT-based FLR% measurements were less than 40%, CT volumetry showed an overestimation of FLR% compared with ^{99m}Tc-GSA scintigraphy. It is noteworthy that hepatectomies in this range correspond to the borderline area of tolerance [17,18]; therefore, surgeons should be particularly cautious about the threshold of indication for hepatectomy.

Obviously, the decision as to whether to perform hepatectomy should be individualized. Even in a patient with an FLR% of 30%, for example, hepatectomy might be either conservatively aborted or bravely enforced. In the latter case, given a measurement difference rate of −0.3, a CT-based FLR% of 30% might correspond to a true FLR% of 26%, which implies that FLR% calculation solely based on CT volumetry may carry a considerable risk of PHLF if it is overestimated. Herein, we demonstrated that when the CT-based FLR% was less than 40%, the GSA-based FLR% was likely to be critically small, with a probability of 88%.

The reason why hepatectomies requiring examination of regional functional liver heterogeneity were limited to patients with a small FLR%, especially smaller than 40%, seemed to be differences in the physiological function of the right and left livers—as evidenced by the fact that the density of ^{99m}Tc-GSA uptake by the left liver was often lower than that by the right one. Furthermore, previous studies have demonstrated that, in the homeostatic state, activity per unit volume of the left liver is lower than that of the right liver [19,20]. Most of the hepatectomies that entail more than 60% of the liver parenchyma are right-sided hepatectomies, including standard right hepatectomy. In such hepatectomies, the remaining parenchyma (40% or less) belongs primarily to the left liver, which has less activity per unit volume than the resected liver. As a consequence, the GSA-based FLR% becomes smaller than CT-based FLR% in most hepatectomy candidates with an FLR% less than 40%. However, it should also be noted that the actual activity of the left liver is significantly modified after right hepatectomy or right portal vein ligation. Thus,

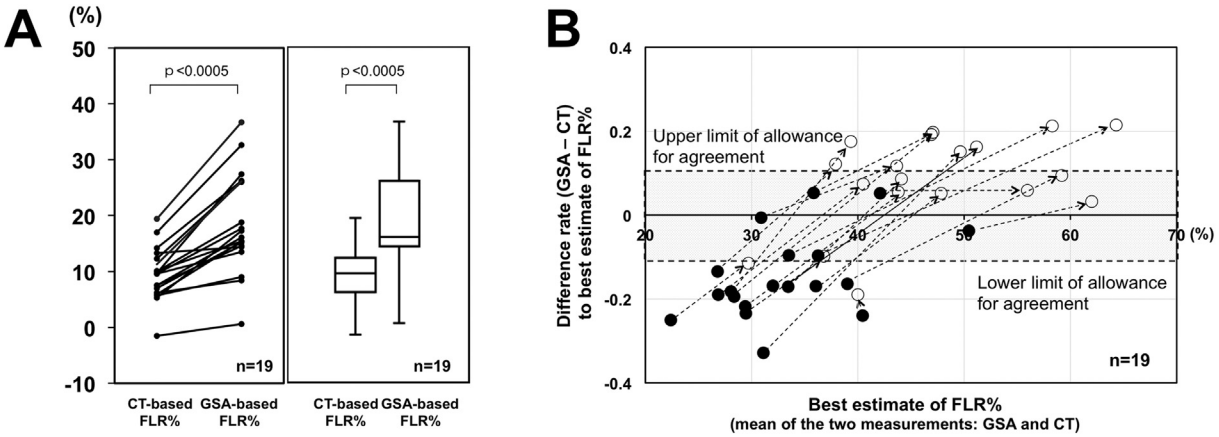

Fig 6. A, Increase in FLR% after PVE (the difference in FLR% values before and after PVE) on CT volumetry and ^{99m}Tc-GSA scintigraphy. Left column: individual difference; right column: box-and-whisker diagram. B, Changes in the difference rate between the CT- and GSA-based FLR% measurements before and after PVE in 19 paired patients. Filled circle, before PVE; empty circle, after PVE.

we must exercise caution when interpreting the predictive functional FLR ratio calculated using preoperatively suppressed activity of the left liver. The relatively low activity of the left liver before hepatectomy, which is perceived as heterogeneity on preoperative examinations, does not always remain low postoperatively. Therefore, it is important to not exclude such patients, who could be eligible for hepatectomy, based on the FLR% calculated using the relatively low preoperative activity of the left liver.

In patients treated with PVE, ^{99m}Tc-GSA scintigraphy proved to be of little use because GSA-based FLR% values were generally larger than CT-based FLR% measurements. As shown in Fig 6, *A*, when comparing CT- and GSA-based FLR% measurements before PVE with those after PVE in paired samples, we noticed that the rate of increase in FLR% was larger for GSA-based than CT-based values. This result is consistent with previously reported studies documenting the importance of ^{99m}Tc-GSA scintigraphy in the assessment of FLR% [21,22]. Nonetheless, it should be borne in mind that the rise in the GSA-based FLR% after PVE does not necessarily indicate an actual increase in the number of liver cells in response to PVE, but rather, it is partly due to a decrease in the uptake of ^{99m}Tc-GSA molecules by the embolized liver [23]. Reliable substantial improvement of FLR% after PVE is only due to increased CT volume and may not be comparable to the improvement in the uptake rate of GSA; however, establishing this was beyond the scope of the present study.

One of the main limitations of this study had to do with its single-center, retrospective design and relatively small sample size, especially in the PVE cohort. Second, the patients' postoperative prognosis was not explored. Third, PVE was performed only in the right liver in all cases. Finally, liver scintigraphy was carried out using merely ^{99m}Tc-GSA because ^{99m}Tc-mebrofenin was not available in Japan. Hence, ^{99m}Tc-mebrofenin scintigraphy, which has a different mechanism, is likely to produce different results.

In conclusion, we elucidated the usefulness of regional heterogeneity of liver function in assessing FLR% prior to hepatectomy. In patients without PVE, ^{99m}Tc-GSA scintigraphy is advised when FLR% is estimated to be less than 50%. Moreover, confirmation of the GSA-based FLR% is strongly recommended when the CT-based FLR% is less than 40%. In other cases, the CT-based FLR% can always be regarded as a gold standard for safe hepatectomy. In patients treated with PVE, ^{99m}Tc-GSA scintigraphy is of limited value. Nevertheless, this does not exclude the possibility of calculating the GSA-based FLR% if the CT-based FLR% still remains too small to perform a safe hepatectomy after PVE. Despite technological advances and modality development, efforts must be made to use the right method in the right place to mainly benefit the patients.

Author Contribution

The authors confirm contribution to the paper as follows: study conception and design: all authors; data collection: MI, YY, HK, and NT; analysis and interpretation of results: MI, YY, YA, KK, and HU; draft manuscript preparation: MI, and YY. All authors reviewed the results and approved the final version of the manuscript.

Conflict of Interest

The authors have no related conflicts of interest to declare.

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Ethics Approval

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Data collection for the present analysis was approved by the ethics committee of Akita University, Graduate School of Medicine (Approval code: 2078). According to the IRB instruction, the study protocol was informed on the web page of Akita University Hospital and obtained consent of patients in an opt-out manner.

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References

[1] Guglielmi A, Ruzzenente A, Conci S, Valdegamberi A, Iacono C. How much remnant is enough in liver resection? Dig Surg. 2012;29:6–17.
[2] Yigitler C, Farges O, Kianmanesh R, Regimbeau JM, Abdalla EK, Belghiti J. The small remnant liver after major liver resection: how common and how relevant? Liver Transpl. 2003;9:S18–25.
[3] Vauthey JN, Chaoui A, Do KA, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. Surgery. 2000;127:512–9.
[4] de Graaf W, van Lienden KP, van Gulik TM, Bennink RJ. (99m)Tc-mebrofenin hepatobiliary scintigraphy with SPECT for the assessment of hepatic function and liver functional volume before partial hepatectomy. J Nucl Med. 2010;51:229–36.
[5] Olthof PB, Coelen RJ, Bennink RJ, et al. ^{99m}Tc-mebrofenin hepatobiliary scintigraphy predicts liver failure following major liver resection for perihilar cholangiocarcinoma. HPB (Oxford). 2017;19:850–8.
[6] Hayashi H, Beppu T, Okabe H, et al. Functional assessment versus conventional volumetric assessment in the prediction of operative outcomes after major hepatectomy. Surgery. 2015;157:20–6.
[7] Yoshida H, Makino H, Yokoyama T, et al. Preoperative liver functional volumetry performed by 3D-^{99m}Tc-GSA scintigraphy/vascular fusion imaging using SYNAPSE VINCENT: a preliminary study. Hepatoma Res. 2016;2:187–92.
[8] Tsuruga Y, Kamiyama T, Kamachi H, et al. Significance of functional hepatic resection rate calculated using 3D CT/(99m)Tc-galactosyl human serum albumin single-photon emission computed tomography fusion imaging. World J Gastroenterol. 2016;22:4373–9.
[9] Yokoyama Y, Nishio H, Ebata T, Igami T, Sugawara G, Nagino M. Value of indocyanine green clearance of the future liver remnant in predicting outcome after resection for biliary cancer. Br J Surg. 2010;97:1260–8.
[10] Kobayashi Y, Kiya Y, Sugawara T, Nishioka Y, Hashimoto M, Shindoh J. Expanded Makuuchi's criteria using estimated indocyanine green clearance rate of future liver remnant as a safety limit for maximum extent of liver resection. HPB (Oxford). 2019;21:990–7.
[11] Farges O, Belghiti J, Kianmanesh R, et al. Portal vein embolization before right hepatectomy: prospective clinical trial. Ann Surg. 2003;237:208–17.
[12] Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;1:307–10.
[13] Giavarina D. Understanding Bland Altman analysis. Biochem Med (Zagreb). 2015;25:141–51.
[14] Schindl MJ, Redhead DN, Fearon KC, Garden OJ, Wigmore SJ. Edinburgh Liver Surgery and Transplantation Experimental Research Group (eLISTER). The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. Gut. 2005;54:289–96.
[15] Shoup M, Gonen M, D'Angelica M, et al. Volumetric analysis predicts hepatic dysfunction in patients undergoing major liver resection. J Gastrointestinal Surg. 2003;7:325–30.
[16] Yamamoto Y. Evaluation of liver function and the role of biliary drainage before major hepatic resections. Visc Med. 2021;37:10–7.
[17] Glantzounis GK, Tokidis E, Basourakos SP, Ntzani EE, Lianos GD, Pentheroudakis G. The role of portal vein embolization in the surgical management of primary hepatobiliary cancers. A systematic review. Eur J Surg Oncol. 2017;43:32–41.
[18] Elias D, Ouellet JF, de Baère T, Lasser P, Roche A. Preoperative selective portal vein embolization before hepatectomy for liver metastases: Long-term results and impact on survival. Surgery. 2002;131:294–9.
[19] Sumiyoshi T, Shima Y, Tokorodani R, et al. CT/99mTc-GSA SPECT fusion images demonstrate functional differences between the liver lobes. World J Gastroenterol. 2013;19:3217–25.
[20] Sugahara K, Togashi H, Takahashi K, et al. Separate analysis of asialoglycoprotein receptors in the right and left hepatic lobes using Tc-GSA SPECT. Hepatology. 2003;38:1401–9.
[21] Sumiyoshi T, Shima Y, Okabayashi T, et al. Liver function assessment using 99mTc-GSA single-photon emission computed tomography (SPECT)/CT fusion

imaging in hilar bile duct cancer: A retrospective study. Surgery. 2016;160: 118–26.

[22] Beppu T, Hayashi H, Okabe H, et al. Liver functional volumetry for portal vein embolization using a newly developed 99mTc-galactosyl human serum albumin scintigraphy SPECT-computed tomography fusion system. J Gastroenterol. 2011;46:938–43.

[23] Nanashima A, Yamaguchi H, Shibasaki S, et al. Relationship between CT volumetry and functional liver volume using technetium-99m galactosyl serum albumin scintigraphy in patients undergoing preoperative portal vein embolization before major hepatectomy: a preliminary study. Dig Dis Sci. 2006;51:1190–5.