Response to Percutaneous Transhepatic Portal Embolization: New Proposed Parameters by ^{99m}Tc-GSA SPECT and Their Usefulness in Prognostic Estimation After Hepatectomy

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Accumulation of ^{99m}Tc-galactosyl human serum albumin (GSA) in the liver correlates well with the parameters of hepatic function tests. We performed ^{99m}Tc-GSA SPECT before and after percutaneous transhepatic portal embolization (PTPE) to induce compensatory hypertrophy of the remnant lobe before extensive hepatic resection and analyzed the responses of new proposed parameters in the future remnant lobe that showed hypertrophy. The aim of this study was to evaluate the usefulness of these parameters in prognostic estimation after hepatectomy. **Methods:** We studied 10 patients with cholangiocarcinoma and 1 patient with metastatic liver tumor from sigmoid colon cancer. ^{99m}Tc-GSA SPECT was performed immediately before and 2 wk after PTPE. We analyzed the responses of the liver uptake ratio (LUR), functional volume (FV), and liver uptake density (LUD) in the future remnant lobe and evaluated their relationship with the prognosis after subsequent hepatic resection. **Results:** LUR and FV increased slightly but were not associated with the prognosis after hepatic resection. LUD increased significantly after PTPE in the group showing a good outcome after hepatic resection but decreased after PTPE in the group showing a poor outcome (post-PTPE LUD, 0.064 ± 0.017%/cm^3 versus 0.035 ± 0.006%/cm^3, $P < 0.05$; response rate, 22.2% ± 11.9% versus −8.9% ± 17.6%, $P < 0.01$). **Conclusion:** Responses of LUD to PTPE before hepatic resection in the future remnant lobe represent changes in asialoglycoprotein receptor activity per hepatocyte and predict responses to subsequent hepatic resection. LUD may be an important parameter for determining the outcome after hepatic resection.

Key Words: ^{99m}Tc-GSA SPECT; PTPE; hepatectomy; prognosis

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Galactosyl human serum albumin labeled with ^{99m}Tc (^{99m}Tc-GSA) is a radiopharmaceutical that binds to asialoglycoprotein receptors, which are specifically present in the hepatocyte membrane (*1–3*). Because these receptors are decreased in hepatopathy, the level of ^{99m}Tc-GSA accumulation in the liver correlates well with the parameters of hepatic function tests (*4–7*). For quantitative evaluation of the hepatic function and functional reserve, various parameters in ^{99m}Tc-GSA scintigraphy have been developed and used at many institutions (*8,9*). However, the methods used at each institution are complicated and have not been broadly accepted. Many of these parameters are used for evaluation of the entire liver, and there have been only a few studies on regional hepatic function (*10*).

Percutaneous transhepatic portal embolization (PTPE) is preoperative embolization of the portal branches in the hepatic lobe to be resected to induce hypertrophy of the remnant lobe (*11,12*). This procedure is performed before extensive hepatic resection for diseases such as cholangiocarcinoma in the porta hepatis or advanced gallbladder cancer for reduction of postoperative complications and prevention of hepatic failure. We developed an evaluation method by ^{99m}Tc-GSA SPECT that is readily performed and allows evaluation of regional accumulation or volume using an arbitrary region of interest (ROI). By this method, ^{99m}Tc-GSA SPECT was performed before and after PTPE, and changes in various parameters such as regional accumulation and volume in the future remnant lobe that showed compensatory hypertrophy were measured. The relationship between these changes and prognosis after hepatectomy or surgical risks of hepatectomy was evaluated.

MATERIALS AND METHODS

Subjects

We studied 10 patients with cholangiocarcinoma and 1 patient with metastatic liver tumor from sigmoid colon cancer who underwent PTPE before hepatic resection. Right lobectomy was performed in 6 patients, and extended right lobectomy was performed in 5 patients. Postoperative complications developed in 4 patients (hepatic failure in 2, intraperitoneal infection in 1, and portal thrombosis in 1). The 7 patients without postoperative complications were classified as the good outcome group (group A) and the 4 patients with complications were classified as the poor outcome group (group B) at discharge from the hospital (3–11 wk after hepatectomy). We obtained written informed consent from all patients to follow the protocol.

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Methods

PTPE was performed 2 wk before the resection as described (*11,12*). Under fluoroscopic control, the right branch of the portal vein and its ramifications were occluded. The embolizing material consisted of a mixture of gelatin sponges (Gelfoam; Upjohn, Kalamazoo, MI), cubes (1 mm in size) or powder, contrast medium, and gentamicin (40 mg).

^{99m}Tc-GSA SPECT was performed immediately before and 2 wk after PTPE (just before hepatic resection) using a triple-head γ camera (MULTISPECT 3; Siemens Medical Systems, Erlangen, Germany). SPECT images of the injection syringe were obtained for 20 s before injection of ^{99m}Tc-GSA. Subsequently, ^{99m}Tc-GSA (185 MBq) was injected as a bolus into a cubital vein, and SPECT data (72 steps, 360°) were obtained from 12 min 30 s to 17 min 30 s after injection. Image reconstruction was performed by the filter convolution method with a cutoff level of 34% of the maximum counts in the liver. The acquisition time of SPECT data was determined by ^{99m}Tc-GSA sequential scintigraphy according to analysis of the time–activity curves of the liver. We fixed the center of the acquisition time at 15 min after injection, just before the time–activity curves reach a plateau under the influence of saturation and metabolism. This is the time when the differences in activities between various curves showed the maximum values and their increase rates were low. When counts in the liver were sufficient, acquisition of SPECT data was continued for 5 min (72 steps, 360°).

The following regional parameters in the future remnant lobe were evaluated: the added SPECT count in the whole liver slices divided by the whole SPECT counts of the syringe SPECT value—i.e., the percentage of the hepatic SPECT value to the syringe value (liver uptake ratio using SPECT [LUR], %); the volume in the future remnant lobe (functional volume [FV], cm^3); and the liver uptake ratio divided by the volume— i.e., the liver uptake ratio per unit of volume in the regional liver (liver uptake density [LUD], $\%/cm^3$). For each parameter, the post-PTPE value minus the pre-PTPE value divided by the pre-PTPE value (×100) was calculated as the response rate to the PTPE. The ROI for the future remnant lobe was set on the entire left lobe (medial and lateral segments) for the cases of right lobectomy and on the lateral segment for the cases of extended right lobectomy. Figure 1 shows the method of setting the ROI on the entire left lobe in the case of right lobectomy.

Each parameter before and after PTPE and the response rate by PTPE were evaluated for groups A and B and were estimated using the unpaired Student *t* test to identify parameters affecting the prognosis after hepatectomy.

RESULTS

Responses of LUR, FV, and LUD to PTPE

Responses of LUR, FV, and LUD to PTPE are shown in Figure 2. LUR and FV increased slightly after PTPE in groups A and B. Values in both groups overlapped on the graph. The LUD tended to increase in group A but decrease slightly in group B. Although pre-PTPE LUD values in both groups overlapped, post-PTPE LUD values were $>0.04\%/cm^3$ in group A and $<0.04\%/cm^3$ in group B.

Pre- and Post-PTPE LUR, FV, LUD, and Their Response Rates

The pre- and post-PTPE LUR, FV, and their response rates did not differ significantly between the two groups when the mean values ± SD for LUR, FV, and LUD before

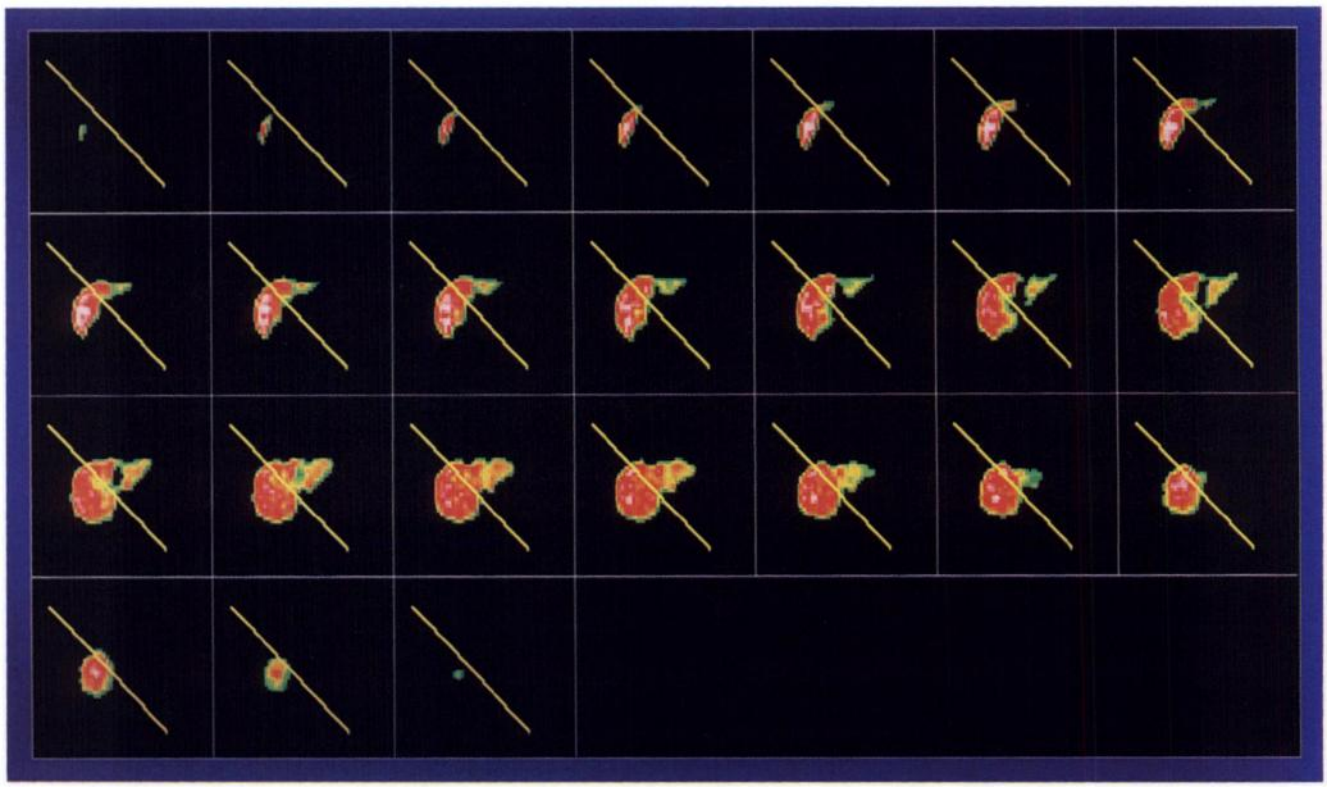

FIGURE 1. Method of setting ROI on entire left lobe in case of right lobectomy is shown. Borders were manually determined using gallbladder bed, inferior vena cava, and medial margin of right lobe as references.

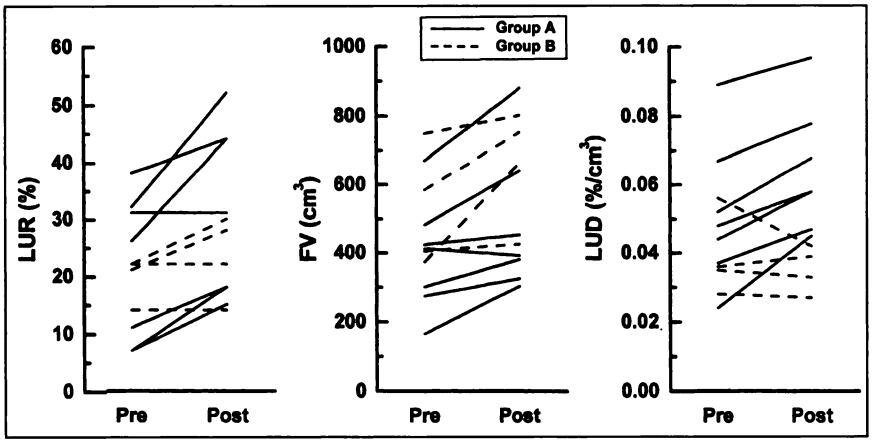

FIGURE 2. Responses of LUR, FV, and LUD to PTPE. LUR and FV increased slightly after PTPE in groups A and B. LUD tended to increase in group A but decreased slightly in group B. Post-PTPE LUD values were >0.04%/cm³ in group A and <0.04%/cm³ in group B.

and after PTPE and the response rates in the future remnant lobe were compared. The post-PTPE LUD and its response rate differed significantly between the two groups (LUD, 0.064 ± 0.017%/cm³ [group A] versus 0.035±0.006%/cm³ [group B], $P < 0.05$; response rate, 22.2% ± 11.9% [group A] versus −8.9% ± 17.6% [group B], $P < 0.01$) (Fig. 3). The post-PTPE LUD was >0.04%/cm³ in group A but was <0.04%/cm³ in group B, whereas an increase of >10% was observed in group A and an increase of <10% or a decrease was observed in group B.

Case Presentation

The patient was a 52-y-old man with a cholangiocarcinoma in the porta hepatis (Fig. 4; Table 1). After PTPE, LUR, FV, and LUD decreased in the right lobe that was treated by PTPE but increased in the untreated left lobe. Subsequently, the patient underwent right lobectomy and showed a good postoperative course. The third ^{99m}Tc-GSA SPECT examination was performed 4 wk after hepatic resection. In the remaining liver, the LUR and FV after resection were higher than the post-PTPE values before resection, but the LUD after resection was the same as the post-PTPE value.

DISCUSSION

Preoperative evaluation of the prognosis after hepatectomy—i.e., the surgical risk of hepatectomy—is one of the most important problems in terms of hepatic functional reserve. However, only a few evaluations by ^{99m}Tc-GSA scintigraphy have been reported, and consistent results have not been obtained (*13*). Difficulty in determining the outcome on the basis of the preoperative accumulation rate in the liver in the static state is also questionable. We speculate that the condition evaluated using parameters such as the accumulation rate or clearance rate represents not the response or functional reserve of the residual liver after hepatic resection but only the regional liver function before resection. On the other hand, responses to PTPE of the liver portion on the non-PTPE (nonresection) side are not associated with survival but may be regarded as the results of a type of loading test by which responses to hepatic resection can be estimated. For these reasons, this study was performed.

The purpose of PTPE is the prevention of complications and extension of the resection limits. Its effects have been evaluated by the degree of hypertrophy in the future remnant lobe. The increases in LUR and FV observed in this study are rational in terms of compensatory hypertrophy, but no difference was found between the good outcome and poor outcome groups, contrary to our expectation. These findings suggest difficulties in determining the outcome on the basis of changes in the accumulation rate or volume. On the other

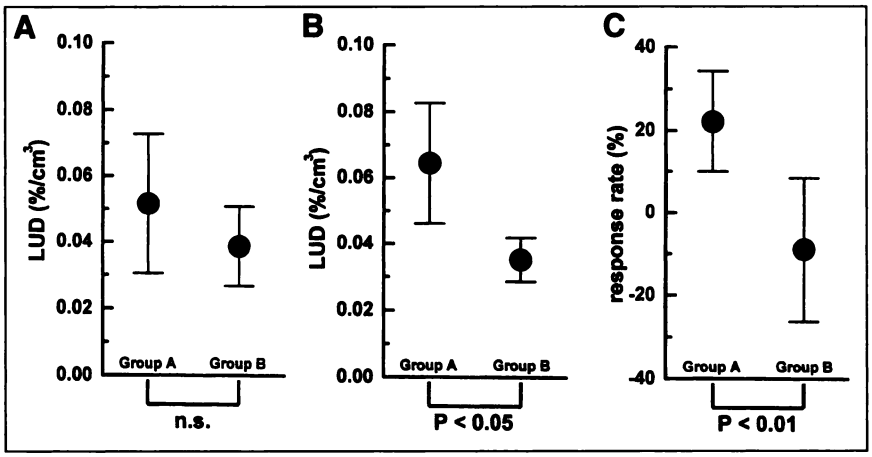

FIGURE 3. Comparison of mean values ± SD for pre-PTPE (A), post-PTPE (B), and response rates in future remnant lobe (C) in groups A and B. Post-PTPE LUD and response rate differed significantly between 2 groups. Post-PTPE LUD was >0.04%/cm³ in group A and <0.04%/cm³ in group B, whereas increase of >10% was observed in group A and increase of <10% or decrease was observed in group B. n.s. = not significant.

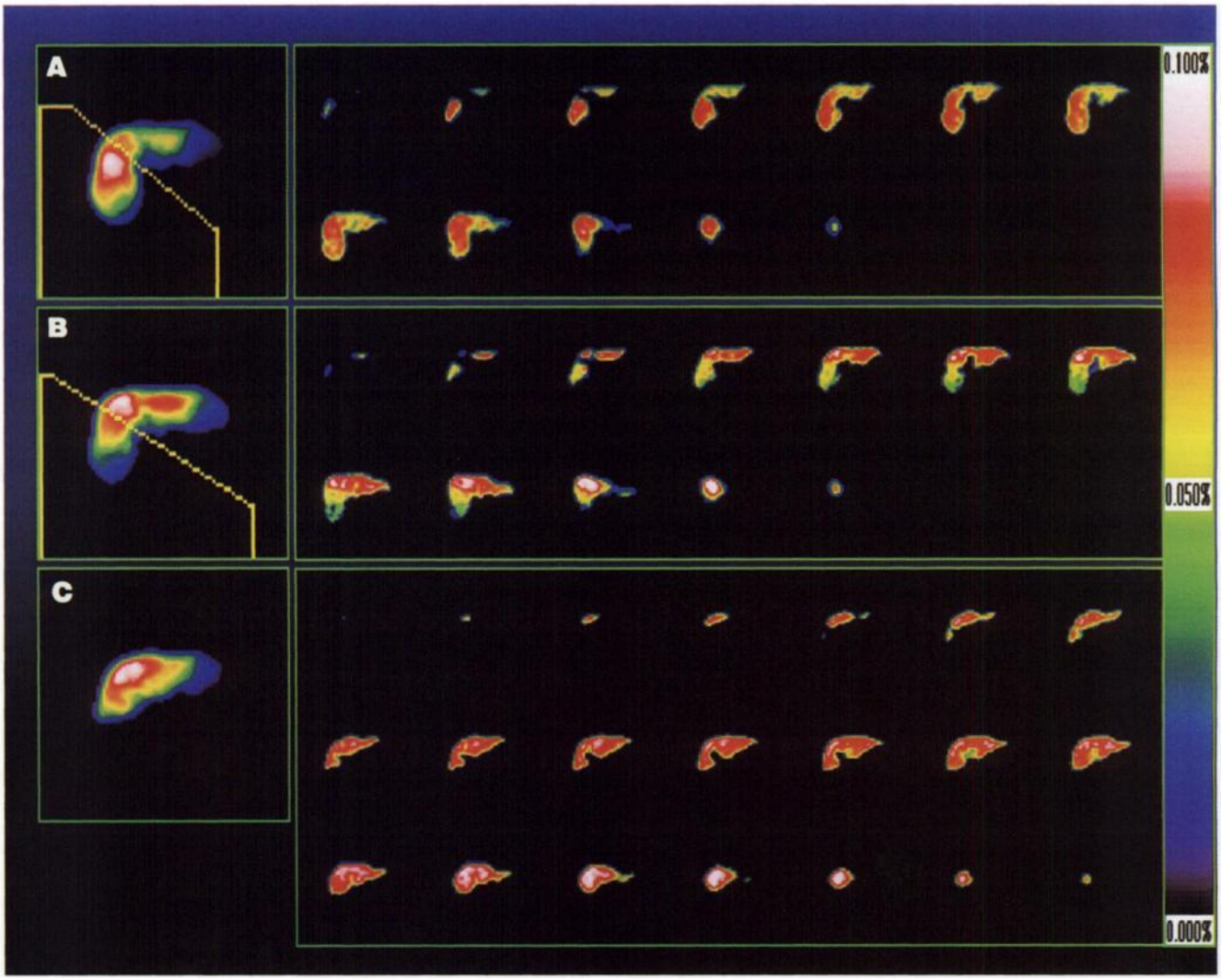

FIGURE 4. A 52-y-old man with cholangiocarcinoma in porta hepatis. SPECT images of ^{99m}Tc-GSA before (A) and after (B) PTPE and after hepatic resection (C) are shown. Left lobe showed hypertrophy after PTPE, and its radioisotope uptake was increased, although uptake of right lobe was decreased unevenly. After right lobectomy, remnant liver showed remarkable hypertrophy.

hand, the increase in LUD was an interesting finding that, to our knowledge, has not been reported previously. As shown in the case presentation, LUD alone did not change with further progression of hypertrophy after hepatic resection, which suggests that responses of LUD to PTPE reflect responses to hepatic resection. LUD appears to be an important parameter for determining the outcome after hepatic resection. However, because the number of patients was small, the LUD value after PTPE, or its response rate by PTPE, is still unclear. These results are preliminary and must be validated by studying a larger population.

TABLE 1
Responses of Parameters to PTPE and Lobectomy in 52-Year-Old Man with Cholangiocarcinoma in Porta Hepatis

	Before PTPE		After PTPE		After lobectomy
Parameter	R	L	R	L	Remnant lobe
LUR (%)	43	26	26	44	51
LUD (%/cm^3)	0.064	0.052	0.054	0.068	0.068
FV (cm^3)	671	483	474	642	736

An increase in LUD partly reflects an increase in portal blood flow after PTPE and the intrahepatic blood pool (*9*) but generally represents an increase in asialoglycoprotein receptors per unit volume. In other words, increased LUD indicates that the degree of the increase in asialoglycoprotein receptors is higher than that of the increase in FV (increase in cell count plus cell hypertrophy). This finding indicates a more marked increase in asialoglycoprotein receptors than in the cell count—i.e., an increase in asialoglycoprotein receptors per cell. This hypothesis is inconsistent with the intact hepatocyte theory (*14*), which postulates that the number of receptors per hepatocyte remains constant, or the theory that the number of asialoglycoprotein receptors reflects the number of functional hepatocytes (*15–17*). If these theories cannot be applied to the hyperfunctional state at the time of compensation, the degree of increase in

asialoglycoprotein receptors—i.e., the ability to increase them in an emergency—may reflect the hepatic functional reserve. Conversely, if these theories can be applied, the number of receptors remains constant but may not be proportional to receptor activity. Whether the increased LUD indicates an increase of activity in each receptor or an increase in the number of active receptors in all (active and inactive) receptors is unclear. The difference in the distribution ratio of receptors on the cell surface to those in cells between the growth phase and stationary phase should be also taken into consideration (*18–21*). The number of receptors on the cell surface in each phase also affects the functional reserve. However, dynamic changes and metabolism of asialoglycoprotein receptors are still unclear, and further studies are necessary.

Is it possible to evaluate beforehand the degree of compensatory responses to loads such as surgical invasion? Our results suggest that LUD is an important parameter for determining the outcome after hepatic resection. However, changes in LUD after PTPE are responses to an irreversible great load, and this evaluation method cannot be applied to other diseases. Although milder and reversible loading tests are required, there are no safe methods, such as loading myocardial scintigraphy, and further studies are necessary.

CONCLUSION

We evaluated the relationship between regional parameters by ^{99m}Tc-GSA SPECT before and after PTPE and the prognosis after hepatectomy. The results suggest that LUD may be an important parameter for determining the outcome after hepatic resection.

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