

Regular article

Prediction of Indocyanine Green Retention Rate at 15 Minutes by Correlated Liver Function Parameters before Hepatectomy

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Running title: HEPATIC FUNCTIONAL PREDICTORS FOR ICGR15

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Abstract

Background. Indocyanine green retention rate at 15 minutes (ICGR15) is a useful marker of liver function in deciding on the extent of hepatectomy. To determine ICGR15 regardless of liver condition, we sought to establish a formula for converted ICGR15 based on conventional blood tests and technetium-99m galactosyl human serum albumin (^{99m}Tc -GSA) scintigraphy.

Materials and methods. We measured liver function parameters, including ICGR15, in 307 patients, including 265 liver cancer patients without biliary obstruction (no obstruction group) and 42 with biliary obstruction (obstruction group).

Results. In the no obstruction group, multiple regression analysis identified blood pool clearance ratio (HH15), liver uptake ratio (LHL15) calculated by heart and liver activity between 3 and 15 minutes after injection of ^{99m}Tc -GSA, and serum hyaluronic acid as significant correlates ($P < 0.05$). The calculated Converted ICGR15 was then equal to $0.02 * \text{HA} + 0.276 * (\text{HH15} * 100) - 0.501 * (\text{LHL15} * 100) + 41.41$. The mean difference between actual and converted ICGR15 was significantly lower in the obstruction than in the no obstruction group ($P = 0.031$). A significantly larger proportion of patients of the obstruction group had lower converted ICGR15 than those of the no obstruction group ($P = 0.045$).

Conclusion. The converted ICGR15 is useful for evaluating hepatic function in patients with biliary obstruction who plan to undergo major hepatectomy.

Key Words: liver resection; indocyanine green retention rate at 15 minutes (ICGR15); technetium-99m galactosyl human serum albumin liver scintigraphy; serum hyaluronic acid; converted formula

INTRODUCTION

The incidence of postoperative hepatic failure has markedly decreased in recent years following the introduction of adequate preoperative evaluation of hepatic function and estimation of resected liver volume as well as improvement in perioperative management [1]. In addition, evaluation of hepatic functional reserve has been developed and Child-Pugh classification is still widely applied worldwide [2-4]. However, it is sometimes difficult to plan the extent of hepatectomy by such a comprehensive scoring system consisting of the blood biochemical parameters for liver function without load for drug administration to the liver. Therefore, Seyama and Kokudo [5] proposed systematic criteria for hepatectomy based on the indocyanine green retention rate at 15 minutes (ICGR15) [5], and Takasaki *et al.* [6] also proposed the formula of permitted liver volume for resection based on the ICGR15 values. We have applied the latter formula to plan the extent of hepatic resection, and the estimated liver volume for resection by computed tomography (CT) was compared to the permitted volume [7, 8]. Many investigators have also used the ICGR15 as the most reliable test for hepatic functional reserve before hepatectomy [3, 9, 10], but in cases of obstructive biliary diseases or vascular shunt of hepatic circulation, the results of ICG might be worse than the true functional reserve [11, 12]. Furthermore, some patients are allergic to indocyanine.

Recently, a new test that reliably assesses hepatic functional reserve, technetium-99m galactosyl human serum albumin (^{99m}Tc -GSA) scintigraphy, has been used in patients with liver diseases [13, 14]. This test is based on the fact that asialoglycoprotein receptors on hepatocytes reflect functional liver cells [15] and are not influenced by vascular shunt or obstructive jaundice [16, 17]. We confirmed previously that the results of ^{99m}Tc -GSA scintigraphy reflected impairment of background liver [11]. However, the range of the

liver uptake ratio (LHL15) was narrow, and therefore, it was sometimes difficult to decide on the extent of hepatectomy [11]. Therefore, ^{99m}Tc -GSA liver scintigraphy remains experimental in nature and has not yet replaced the ICGR15 test. To overcome the limitation of the ICG test described above, we sought to establish a modified formula for ICGR15 based on correlated parameters of conventional blood tests and ^{99m}Tc -GSA liver scintigraphy. We hypothesize that such a conversion formula can provide the true results of ICGR15 in patients with vascular shunt and obstructive jaundice.

In the present study, we examined the correlation between hepatic functional reserve and ICGR15 in 265 patients with liver diseases who did not have biliary or vascular obstruction or a porto-systemic shunt. Based on this analysis, a regression equation for the converted ICGR15 was constructed. In addition, we examined the validity of the conversion formula in 42 patients who had biliary obstruction. Our overall aim was to establish a conversion formula for ICGR15 based on conventional hepatic functional parameters suitable for all patients, irrespective of background liver disease.

MATERIALS AND METHODS

Patients

The subjects included 307 patients who underwent hepatectomy in the Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Hospital (NUH) between January 1997 and June 2010. They included 222 males and 85 females with a mean age of 65.2 ± 10.6 years (\pm SD, range 28-87 years). The liver diseases included hepatocellular carcinoma (n=164), intrahepatic cholangiocarcinoma (n=35), metastatic liver carcinoma (n=63), bile duct carcinoma (n=24), gallbladder carcinoma (n=14) and others (n=7). The background liver diseases included normal liver function (n=108), fatty liver (n=10), chronic viral liver diseases (n=161; including 75 with liver cirrhosis) and obstructive jaundice (n=28). Clinical data were retrieved from both anesthetic and medical records, as well as the NUH database, for the duration of the initial hospitalization and post-hepatectomy period. The existing liver diseases were diagnosed by clinical examination of multi-detector computed tomography (CT) and magnetic resonance (MR) imaging. Biliary tract status was examined by MR cholangiography or direct cholangiography. The study design was approved by the Ethics Review Board of NUGSBS, and a signed consent was obtained from each subject.

Laboratory Tests

ICGR15 is routinely used in our hospital to determine the volume of the liver to be resected based on Takasaki's formula [6]. The estimated resected liver volume, excluding tumor volume (cm^3), is measured by CT volumetry [2]. The planned hepatectomy is performed when the permitted resected volume of the liver is greater than the estimated resected volume of the liver. The permitted resected volume was calculated as [6]:

$$= 100 \times (\text{LOG}(40) - \text{LOG}(\text{ICGR15})) / (2 - \text{LOG}(\text{ICGR15})) \text{ in cases of cirrhotic liver;}$$

= 100 x (LOG(50)-LOG(ICGR15))/(2-LOG(ICGR15)) in cases of non-cirrhotic liver.

Serum albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, choline esterase, total cholesterol and prothrombin activity were measured using standard procedures. To measure ICGR15, indocyanine green (ICG) was injected intravenously at a dose of 0.5 mg/kg body weight with the 15-minute retention rate measured by a photopiece applied to the fingertip (RK-1000, Sumitomo Electric, Tokyo, Japan) without blood sampling [7, 8, 11]. Peripheral blood samples were also collected before meals for analysis of hyaluronic acid (HA), a marker of hepatic fibrosis and endothelial cell function in hepatic sinusoids [18]. Blood samples were centrifuged at 3000 rpm for 15 min, and serum was stored at -80°C. HA was assayed using a sandwich binding protein assay (SRL, Inc, Tokyo; normal range <50 ng/ml).

Examination of ^{99m}Tc-GSA scintigraphy

For ^{99m}Tc-GSA scintigraphy, a bolus dose of 3 mg (185 MBq) of ^{99m}Tc-GSA (Nihon Medi-Physics, Nishinomiya, Japan) was injected into the antecubital vein. The hepatic uptake ratio of ^{99m}Tc-GSA (LHL15) and the blood pool clearance index (HH15) were then calculated after injection [19]. There was no limitation regarding the ^{99m}Tc-GSA test in patients with obstructive jaundice or hepatic vascular shunt. HH15 was then calculated as the uptake ratio of the heart at 15 min to that at 3 min, and LHL15 was calculated as the uptake ratio of the liver at 15 min to the liver plus the heart at 15 min (Figure 1a-b).

Formulas for HH15 and LHL15 were as follows:

$$\text{HH15} = \text{H15}/\text{H3}$$

$$\text{LHL15} = \text{L15}/(\text{L15}+\text{H15})$$

Statistical Analysis

All continuous data were expressed as mean \pm SD. Data for different groups were compared using one-way analysis of variance (ANOVA) and examined by Student's *t*-test. Correlations between two parameters were examined by calculating Pearson's correlation coefficient. A two-tailed *P* value <0.05 was considered significant. The linear regression formula was calculated using the correlated parameters. PASW Statistics 18.0.0 for Windows (SPSS Inc., Chicago, IL) was used for all statistical analyses.

RESULTS

Patient Demographics and Background Liver Disease

Of the 307 patients, 265 (195 males and 70 females, age 64.9 ± 10.9 years) had no major vascular involvement or biliary obstruction. According to the Child-Pugh classification, 248 patients were classified as A (94%) and 17 as B (6%). Partial resection was performed in 98 patients (37%), segmental or sectional resection in 69 (26%) and hemihepatectomy or extended hemihepatectomy in 98 (37%).

Patients with biliary obstruction ($n=42$) included 25 males and 17 females (age 67.0 ± 8.2 years). In these patients, liver diseases included intrahepatic cholangiocarcinoma ($n=10$), bile duct carcinoma ($n=24$), gallbladder carcinoma ($n=5$) and others ($n=3$). The background liver diseases included normal liver function ($n=14$) and obstructive jaundice ($n=28$). According to the Child-Pugh classification, 35 patients in this group were classified as A (83%) and 7 as B (17%). Partial resection was performed in 1 patient (2%), sectional resection in 2 (5%), and hemihepatectomy or extended hemihepatectomy in 39 (93%).

Correlation between liver functional parameters and ICGR15

The mean ICGR15 in the 265 patients without biliary obstruction was $14.8 \pm 11.4\%$, and the mean in the 42 patients with biliary obstruction was $14.7 \pm 11.0\%$. There was thus no significant difference in actual volume between the groups ($P=0.82$). The mean total bilirubin levels at examination were 0.91 ± 0.49 and 2.1 ± 3.0 mg/dl in each group, respectively. Table 1 shows the correlation between each selected functional parameter of the liver (except total bilirubin level) and ICGR15 in 265 patients without biliary obstruction. The selected hepatic parameters were correlated against the ICGR15 using multiple linear regression analysis with the stepwise method (Table 2). In the first step,

HH15, LHL15, and serum HA levels correlated significantly with ICGR15. After 6 steps, these three variables were still significant (see model 2, Table 2). Based on this result, the regression equation was established as:

$$Y (\text{converted ICGR15}) = 0.02 \times \text{hyaluronic acid level (ng/ml)} + 0.276 \times (\text{HH15} \times 100) - 0.501 \times (\text{LHL15} \times 100) + 41.41$$

Differences between estimated and actual ICGR15

Using the above equation, a converted ICGR15 was calculated for all patients. Table 3 shows the comparison of clinical data between patients with and without obstructive jaundice. Patients with jaundice had bile duct carcinomas more frequently in comparison with those without jaundice ($p < 0.05$). Prevalence of Child-Pugh B patients in the jaundiced group were significantly more than that in the non-jaundiced group ($p < 0.05$). In addition, the mean converted ICGR15 in patients without biliary obstruction tended to be higher than in patients with biliary obstruction but not significantly so ($p = 0.092$). Furthermore, the variation of differences of ICGR15 in patients between the non-obstructed and obstructed jaundice groups was tended to be different but not statistically significant ($p = 0.066$).

In comparison with the actual ICGR15, the converted ICGR15 was reduced in 106 of 265 patients (40%) without biliary obstruction and in 24 of 42 patients (57%) with biliary obstruction, which was significant between the two groups ($p < 0.05$). Eighteen of the 106 patients (17%) without biliary obstruction and 10 of the 24 (42%) patients with biliary obstruction showed a significant reduction in the converted ICGR15 (over 10%) compared to the estimated value. Moreover, in comparison with patients without jaundice,

blood loss and presence of major hepatectomy were more frequent in patients with jaundice ($p < 0.05$), as was the associated hepatic failure ($p < 0.05$).

DISCUSSION

Tests using ^{99m}Tc -GSA scintigraphy, such as the hepatic uptake ratio (LHL15) [19, 20] and the blood pool clearance index (calculated as the ratio of heart activity at 15 minutes to heart activity at 3 minutes (HH15) [19, 20]), are very reliable and noninvasive methods for evaluating hepatic functional reserve without requiring blood sampling.

Asialoglycoprotein is exclusively internalized into hepatocytes by a receptor [21]; thus, a decrease in the number of asialoglycoprotein receptors is specifically observed in injured livers [16]. Since 1996, our department has therefore used ^{99m}Tc -GSA scintigraphy preoperatively combined with ICGR15 and conventional liver function tests.

On the other hand, hepatic fibrosis is also an important determinant of liver damage and hepatic dysfunction in chronic liver disease and after liver resection [22]. Damage to the hepatic endothelial cells results in a high serum HA level [18, 23], which is thought to be a marker of hepatic fibrosis. If endothelial cell function in the injured liver deteriorates [23], the serum HA level could be a useful marker of nonparenchymal liver cell function. The findings of our study and those of others showed that serum HA concentrations correlated inversely with measurements of functional liver reserve and the degree of hepatic fibrosis, suggesting that measuring the HA level might be useful for monitoring liver damage or predicting postoperative complications after hepatic resection [18, 23]. We have referred to this parameter preoperatively to predict postoperative complications since 2004.

Here, we hypothesized that a converted ICGR15 could be calculated based on other hepatic functional parameters that are not affected by biliary obstruction. Kawamura *et al.* [9] measured converted ICGR15 using ^{99m}Tc GSA liver scintigraphy, with similar aims to the present study. As described above, the results of ^{99m}Tc GSA liver scintigraphy did not

seem to be affected by biliary obstruction [11, 12], and therefore, a more reliable estimation of liver functional reserve would be achieved. However, we decided that estimating the converted ICGR15 using only this parameter was problematic based on the availability of several other reliable liver function parameters. Therefore, we examined the correlations among various liver functions and ICGR15 in the present study.

All the selected parameters correlated significantly with ICGR15, and subsequently, three parameters were selected as candidates for the estimation equation. Total bilirubin level was not included in our analysis as a candidate parameter, although it also correlated significantly with ICGR15. To account for this omission, total bilirubin levels remained as a significant variable in the multiple linear regression analysis. However, such an equation would not be applicable in patients with biliary obstruction because, in many hospitals in Japan, surgical indication in patients with biliary carcinoma is a total bilirubin level of 2 mg/ml [9]; however, the converted ICGR15 could be lower even at 2 mg/dl total bilirubin. Total bilirubin levels were therefore excluded in the present analysis to avoid such an influence of biliary obstruction.

The remaining three parameters used for the multiple linear regression analysis were HA level and the two ^{99m}Tc GSA liver scintigraphy results, which were reliable parameters that have already been applied as referral parameters with ICGR15 [11, 18]. As a result, differences between actual and converted ICGR15, or differences of ICGR15 between patients with non-obstructed and obstructed jaundice, did not show remarkable significance. In addition, the standard deviation was large in comparison with the mean value. In some cases, other background factors might also have influenced the GSA or hyaluronic acid level, but we could not clarify these factors at this stage. It was necessary to revise the present formula for minimizing large standard deviation by applying other

associated parameters. As shown in the results, a decreased difference was more frequent in obstructive jaundice in comparison with non-obstructive jaundice, as we expected.

The goal of the present study was to apply the converted ICGR15 in patients with obstructive jaundice to accurately evaluate operative indication for the extent of hepatectomy. In the present study, for example, patient outcomes in jaundiced liver were worse than in patients without jaundice. However, by applying the more adequate evaluation of ICGR15, it was possible to improve these patient outcomes. At this stage, however, it is difficult to determine definite cut-off levels of the converted ICGR15 for decisions on major hepatectomy. A future prospective study using the converted ICGR15 presented here may clarify this problem.

Several studies have shown that a lower level of ^{99m}Tc -GSA clearance was associated with posthepatectomy complications [19, 24-27]. For example, Kokudo et al. [27] reported that levels of the hepatic receptor for ^{99m}Tc -GSA in the remnant liver were closely associated with morbidity after hepatectomy. The HA level was also correlated with posthepatectomy complications by previous reports, including a previous study of our own [18, 23]. Therefore, the converted ICGR15 calculated by these parameters may also be useful for predicting posthepatectomy complications or mortality.

The differences between the measured (actual) ICGR15 and the obtained converted ICGR15 were also examined. In some cases, a large difference between the actual and converted ICGR15 was observed, particularly in patients with biliary obstruction. A decrease in the converted ICGR15 was also frequently observed in such patients compared to those without biliary obstruction. Specifically, hepatic functional evaluation including the ICGR15 test was performed in 42 patients with biliary obstruction when the total bilirubin level was below 2 mg/ml. Therefore, the actual ICGR15 might still have been affected by bile congestion, and discrepancies with other hepatic functional

parameters might have occurred. In particular, previous reports including our preliminary study cited a discrepancy of 8% between ICGR15 and ^{99m}Tc -GSA liver scintigraphy, with these cases showing biliary obstruction or occult necroinflammatory or fibrotic findings [11]. Therefore, in patients with a large difference between the actual ICGR15 and ^{99m}Tc -GSA liver scintigraphy, the latter result might be more useful in evaluating surgical indications for hepatectomy.

The converted ICGR15 more closely reflects hepatic cellular function without the influence of a hepatic vascular shunt or a biliary obstruction. Regarding clinical application of the converted ICGR15, we have not yet decided to replace the conventional ICG test (=actual ICGR15) with the converted formula at our institute, as a conversion formula from a previous report [9] was different from our present formula. In addition, it is necessary to examine this conversion formula in a larger set of subjects through multi-center analysis before adoption. Another limitation is a higher cost for ^{99m}Tc -GSA liver scintigraphy in comparison with a ICGR15 test. Moving forward, we will measure both ICGR15 and ^{99m}Tc -GSA liver scintigraphy and apply the converted ICGR15 data to cases of biliary obstruction or cases with a large discrepancy between the actual ICGR15 and the LHL15.

In conclusion, we have provided a linear equation for calculating converted ICGR15 based on serum HA levels and ^{99m}Tc -GSA liver scintigraphy findings (HH15 and LHL15), both of which are unlikely to be affected by biliary obstruction. The converted ICGR15 tended to be lower in patients with biliary obstruction; however, this index could still be useful for evaluating hepatic function in patients with or without biliary obstruction who undergo major hepatectomy. This parameter is promising as a replacement of the conventional ICG test as the standard, reliable liver function test before hepatectomy.

References

1. Miyagawa S, Makuuchi M, Kawasaki S, Kakazu T. Criteria for safe hepatic resection. *Am J Surg* 1995; 169:589.
2. Kubota K, Makuuchi M, Kusaka K, et al. Measurement of liver volume and hepatic functional reserve as a guide to decision-making in resectional surgery for hepatic tumors. *Hepatology* 1997; 26:1176.
3. Schneider PD. Preoperative assessment of liver function. *Surg Clin North Am.* 2004;84:355.
4. Mullin EJ, Metcalfe MS, Maddern GJ. How much liver resection is too much? *Am J Surg.* 2005;190:87.
5. Seyama Y, Kokudo N. Assessment of liver function for safe hepatic resection. *Hepatol Res.* 2009;39:107.
6. Takasaki T, Kobayashi S, Suzuki S, et al. Predetermining postoperative hepatic function for hepatectomies. *Int Surg* 1980;65:309.
7. 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.
8. Nanashima A, Sumida Y, Takeshita H, et al. Parameters associated with changes in liver volume in patients undergoing portal vein embolization. *J Surg Res.* 2006 15;133:95.
9. Kawamura H, Kamiyama T, Nakagawa T, et al. Preoperative evaluation of hepatic functional reserve by converted ICGR15 calculated from Tc-GSA scintigraphy. *J Gastroenterol Hepatol.* 2008;23:1235.

10. Jones SM, Roh MS. Results of surgical resection for hepatocellular carcinoma. *Cancer Treat Res.* 2001;109:59.
11. Nanashima A, Yamaguchi H, Morino S, et al. Relationship between indocyanine green test and technetium-99m galactosyl serum albumin scintigraphy in patients scheduled for hepatectomy: Clinical evaluation and patient outcome. *Hepatol Res.* 2004;28:184.
12. Nagino M, Nimura Y, Kamiya J, et al. Changes in hepatic lobe volume in biliary tract cancer patients after right portal vein embolization. *Hepatology.* 1995;21:434.
13. Kwon AH, Ha-Kawa SK, Uetsuji S, et al. Preoperative determination of the surgical procedure for hepatectomy using technetium-99m-galactosyl human serum albumin (^{99m}Tc-GSA) liver scintigraphy. *Hepatology* 1997;25:427.
14. Satoh K, Yamamoto Y, Nishiyama Y, et al. 99mTc-GSA liver dynamic SPECT for the preoperative assessment of hepatectomy. *Ann Nucl Med.* 2003;17:61.
15. Hwang EH, Taki J, Shuke N, et al. Preoperative assessment of residual hepatic functional reserve using 99mTc-DTPA-galactosyl-human serum albumin dynamic SPECT. *J Nucl Med.* 1999;40:1644.
16. Sawamura T, Nakada H, Hazama H, et al. Hyperasialoglycoproteinemia in patients with chronic liver diseases and/or liver cell carcinoma. Asialoglycoprotein receptor in cirrhosis and liver cell carcinoma. *Gastroenterology.* 1984;87:1217.
17. Kudo M, Todo A, Ikekubo K, Hino M. Receptor index via hepatic asialoglycoprotein receptor imaging: correlation with chronic hepatocellular damage. *Am J Gastroenterol.* 1992;87:865.
18. Nanashima A, Yamaguchi H, Tanaka K, et al. Preoperative serum hyaluronic acid level as a good predictor of posthepatectomy complications. *Surg Today.* 2004;34:913.

19. Kwon AH, Ha-Kawa SK, Uetsuji H, et al. Use of technetium 99m diethylenetriaminepentaacetic acid-galactosyl human serum albumin liver scintigraphy in the evaluation of preoperative and postoperative hepatic functional reserve for hepatectomy. *Surgery* 1995;117:429.
20. Kim YK, Nakano H, Yamaguchi Y, et al. Prediction of postoperative decompensated liver function by technetium-99m-labeled-galactosyl-human serum albumin liver scintigraphy in patients with hepatocellular carcinoma complicating chronic liver disease. *Br J Surg* 1997;84:793.
21. Ashwell G, Harford J. Carbohydrate –specific receptors of the liver. *Ann Rev Biochem* 1982; 51:531.
22. Kubo S, Tsukamoto T, Hirohashi K, et al. Correlation between preoperative serum concentration of type IV collagen 7s domain and hepatic failure following resection of hepatocellular carcinoma. *Ann Surg.* 2004;239:186.
23. Yachida S, Wakabayashi H, Okano K, Suzuki Y. Prediction of posthepatectomy hepatic functional reserve by serum hyaluronate. *Br J Surg.* 2009;96:501.
24. Hwang EH, Taki J, Shuke N, et al. Preoperative assessment of residual hepatic functional reserve using 99mTc-DTPA-galactosyl-human serum albumin dynamic SPECT. *J Nucl Med.* 1999;40:1644.
25. Sugai Y, Komatani A, Hosoya T, Yamaguchi K. Response to percutaneous transhepatic portal embolization: New proposed parameters by ^{99m}Tc-GSA SPECT and their usefulness in prognostic estimation after hepatectomy. *J Nucl Med* 2000;41:421.
26. Shiomi S, Iwata Y, Sasaki N, et al. Clinical need for both scintigraphy with technetium-99m GSA and per-rectal portal scintigraphy in some patients with chronic liver disease. *Ann Nucl Med.* 1999;13:241.

27. Kokudo N, Vera DR, Tada K, et al. Predictors of successful hepatic resection: prognostic usefulness of hepatic asialoglycoprotein receptor analysis. *World J Surg.* 2002;26:1342.

Figure legends

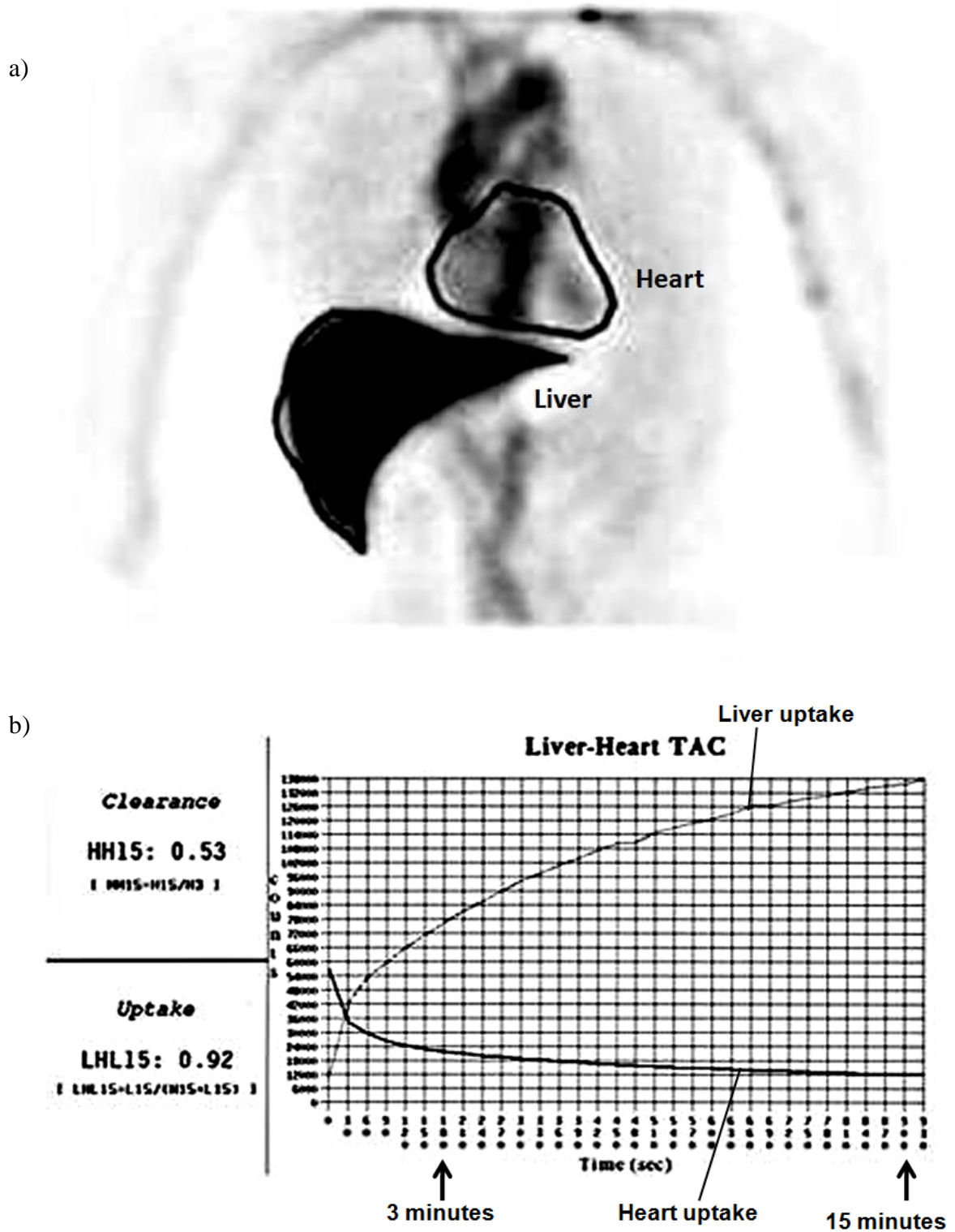


Figure 1. a) Uptake of ^{99m}Tc -GSA in the heart and liver. b) Changes in uptake of ^{99m}Tc -GSA in the heart and liver after injection.

TABLE 1

**Relationships among Various Hepatic Function Parameters and Indocyanine Green
Retention Rate at 15 Minutes.**

	Mean±SD	Correlation coefficient (r)	P value
HH15	0.603±0.100	0.583	<0.01
LHL15	0.909±0.055	-0.620	<0.01
AST (IU/L)	46±37	0.271	<0.01
ALT (IU/L)	46±46	0.156	0.012
Total cholesterol (mg/dl)	173±40	-0.248	<0.01
Platelet count (/mm ³)	18±10	-0.271	<0.01
Prothrombin activity (%)	93±14	-0.391	<0.01
Hyaluronic acid (ng/ml)	140±153	0.538	<0.01

P values are based on Pearson's correlation analysis.

HH15 and LHL15: Blood clearance index: uptake ratio of the heart at 15 min to that at 3 min, and hepatic uptake ratio by ^{99m}Tc-GSA; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

TABLE 2

**Multiple Linear Regression Stepwise Method Output using Data of 265 Patients
without Biliary Obstruction.**

Model	Unstandardized coefficients		Standardized coefficient	t value	Significance (p value)
	β	Standard error	β		
Model 1 (Constant)	37.78	25.17		1.50	0.135
Total cholesterol	0.006	0.015	0.021	0.398	0.691
HH 15*100	0.31	0.11	0.255	20.79	0.006
LHL15*100	-0.50	0.22	-0.221	-20.28	0.023
AST	0.028	0.037	0.085	0.76	0.45
ALT	-0.029	0.026	-0.116	-0.10.12	0.27
Platelet count	0.073	00.052	0.076	10.42	0.16
Prothrombin activity	-0.008	0.045	-0.010	-0.178	0.86
Hyaluronic acid	0.021	0.005	0.271	40.12	<0.001
Model 2 (Constant)	410.41	240.67		10.679	0.094
HH 15*100	0.276	0.104	0.230	20.648	0.009
LHL15*100	-0.501	0.213	-0.222	-20.35	0.020
Hyaluronic acid	0.020	0.005	0.263	40.135	<0.001

Dependent variable: Step 6 total.

The standardized β coefficient provides a measure of the contribution of each variable to the model. The t and p values provide an indication of the impact of each predictor variable.

Abbreviations as in Table 1.

TABLE 3

**Relationships between the Converted Indocyanine Green Retention Rate at 15
Minutes and the Presence of Obstructive Jaundice in the Liver.**

	Non-jaundiced liver (n=265)	Jaundiced liver (n=42)	P value
Age	65±11	67±8	0.44
Gender (Male/female)	197/68	25/17	0.071
Diseases			
Benign liver disease	5	2	
Hepatocellular carcinoma	164		
Intrahepatic cholangiocarcinoma	25	10	
Liver metastasis	62	1	<0.001
Gallbladder carcinoma	9	5	
Bile duct carcinoma	0	24	
Child-Pugh classification (A/B)	248/17	35/7	0.047
Actual ICGR15	14.8±11.2%	14.7±11.0%	0.99
Converted ICGR15	18.6±15.4%	12.9±5.3%	0.092
Difference of actual and converted ICGR15	3.7±16.3%	-1.87±9.9%	0.066
Decrease of converted ICGR15 compared to actual ICGR15 (No/yes)	159/106	18/24	0.036
Total bilirubin level at operation (mg/dl)	0.92±0.50	2.07±3.01	<0.001
HH15	0.60±0.10	0.58±0.08	0.38
LHL15	0.91±0.05	0.93±0.03	0.26
Hyaluronic acid level (ng/ml)	135±146	138±138	0.55
Blood loss (ml)	1068±819	1467±722	0.002
Hemihepatectomy or more extended hepatectomy			
No/Yes	180/49	3/39	<0.001
Postoperative outcomes			
Prolonged ascites*	197/68	29/13	0.59
Hepatic failure [#]	250/15	34/8	0.006

* Ascites over 500 ml prolonged at 1 week after hepatectomy with use of diuretics.

[#] Total bilirubin level over 5 mg/dl at 2 weeks after hepatectomy.