

**<sup>99m</sup>Tc-galactosyl Syalil Albumin (GSA) scintigram adjusts hepatic resection range  
in ICG based estimation.**

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Indocyanin green

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## Abstract

**Background:** Indocyanin Green (ICG)-based decision was widely accepted in determination of hepatic resection range, however, we frequently encounter scattered results of preoperative assessment. The aim of this study is to clarify implication of  $^{99m}\text{Tc}$  Galactosyl sialyl albumin (GSA) scintigram in decision of resection range.

**Patients and Methods:** One hundred eighty patients underwent liver resection at department of surgery in Nagasaki University Hospital were investigated for this study. The patients was divided according to ICG R15 value as follows; Group 1 (n=64 ): ICG R15 <15%, Group 2 (n=32):  $15 \leq \text{ICG R15} < 20\%$ , Group 3 (n=32):  $20 \leq \text{ICG R15} < 25\%$ , Group 4 (n=8):  $\text{ICG R15} \geq 25\%$ . Each group was divided to two subgroups by GSA-LHL 0.9 and compared in liver function, portal pressure, and HAI score of background liver. Frequency of complication was also compared to previous cases without GSA-LHL estimation (n=100).

**Results:** In Groups 2 and 3,  $\text{GSA-LHL} \geq 0.9$  subgroup showed better platelet counts, portal pressure and lower HAI score. In total groups of  $\text{GSA-LHL} \geq 0.9$ , platelet counts showed higher value between below 20% of ICGR15 and above of that, while in  $\text{GSA-LHL} < 0.9$ , it showed no differences exceeded 15% of ICGR15. Overall complications less occurred in  $\text{GSA-LHL} \geq 0.9$  than previous cases.

**Conclusion:** Levels of GSA-LHL reflects severity of portal hypertension in moderately damaged liver preoperatively, and could contribute to decide range of resection with low morbidity.

## Introduction

Hepatocellular carcinoma (HCC) is one of the major causes of death. They mostly arise from injured liver, which contains viral infection, alcohol injury and metabolic overloads. The treatments of HCC are widely spreads such as surgical resection, radiofrequency ablation (RFA), transarterial catheter chemoembolization (TACE), and transplantation.<sup>1-4</sup> They have been well standardized by evidence based guideline, in which indicate treatment modality incorporating with hepatic function reserve.<sup>5</sup> According to the reports by Japan Study Group of Liver Cancer (JSGLC), surgical resection showed better survival in patients with well to moderately preserved liver function than another treatments.<sup>6</sup> The extent of hepatic resection is absolutely dependent on reserve of hepatic function. Accumulated experience and development of assessment modalities allows us to perform hepatic resection safely and results in low operative mortality. Galactosyl sialyl albumin (GSA) scintigram reflects hepatocellular function and is reported the correlation to several hepatic functions.<sup>7, 8</sup> However, a few analyses are available in determination to an extent of resection.<sup>5, 7, 8</sup> In this study, we investigate the contribution of GSA scintigram for an assessment of resection volume and attempt to clarify its implications in hepatic functional reserve.

## Patients and methods

From 1995 to 2009, 180 patients underwent liver resection at Department of Surgery in Nagasaki University Hospital were investigated for this study. Liver functional reserve was preoperatively estimated by counts of blood cells, conventional liver function tests, indocyanin green retention rate at 15 minutes after dye loading (ICGR15), and liver-heart ratio at 15 minutes after  $^{99m}\text{Tc}$ -GSA loading (GSA-LHL15). Portal venous pressure was measured intraoperatively. Briefly, the catheter was inserted from branch of jejunal vein into portal vein and measured manometrically as described previously.<sup>10</sup> The groups were divided into four based on the value of ICGR15 as follows; Group 1 (n=64 ): ICGR15 <15%, Group 2 (n=32):  $15 \leq \text{ICGR15} < 20\%$ , Group 3 (n=32):  $20 \leq \text{ICGR15} < 25\%$ , Group 4 (n=8):  $\text{ICGR15} \geq 25\%$ . The range of hepatic resection was classified according to the general rules for the clinical and pathological study of primary liver cancer.<sup>11</sup> The patients in each ICG group was classified into two subgroups by the value of LHL15, which were  $\text{LHL15} \geq 0.9$  (LHL-high) and  $\text{LHL15} < 0.9$  (LHL-low). Characteristics of the patients were shown in Table 1.

Postoperative complications were also evaluated, which were post operative bleeding, bile leakage, refractory ascites and pleural effusion (need for drainage more than a week or symptomatic), sustained liver dysfunction (AST or ALT >200IU/l for more than a

week). The frequency of complications were compared to the previous patients underwent ICG-based hepatectomy from 1991 to 1995 before introduction of GSA scintigraphy (n=100).

Back ground liver damage was evaluated by HAI score in noncancerous lesion<sup>12</sup>.

### **Statistical analysis**

Statistical analyses were commercially available softwares (Stat mate III, 2003 ATOMS, Tokyo, Japan) and  $p < 0.05$  was taken as significant.

## **Results**

### **Relationship between ICGR15 and GSA-LHL15**

In all patients, the positive correlation between ICGR15 and LHL15 was observed ( $R=0.59$ ,  $p < 0.05$ ). In one ICGR15 group includes relatively wide range of LHL15 value although average levels of LHL15 behaved parallel to that of ICGR15. In Groups 2 and 3, the ratio of LHL-high contained nearly 40 to 50% (Fig.1). The other factors including HH15 showed no significant correlations.

### **Comparison between LHL-high and LHL-low in each ICGR15 based group**

Serum total bilirubin, aspartate aminotransferase (AST), alanin aminotransferase (ALT) showed no differences between LHL-high and LHL-low in each group. Platelet count was significantly lower at LHL-low in Group 2 and showed same trend in Group 3. In group 2, LHL-low showed relatively high portal pressure and high HAI score of the background liver (Table 2).

Platelet counts showed significant differences between Group 1 and 2 in all LHL-high patients, while that of LHL-low patients showed no difference except Group 1 (Fig. 2).

Overall complications were found at 30% of operative cases. Procedure dependent complications such as postoperative bleeding and biliary leakage was almost 9%.

Since introduction of GSA scintigram, LHL-high group showed less complication in Group 3 in compared to the previous cases with the same grade ICGR15 ( $p<0.03$ ) without GSA assessment, whereas, LHL-low group showed no difference in compared to previous ones (Table 3).

## Discussion

On assessment of the liver functional reserve, we sometimes encountered that several parameters showed dissociated results. Indocyanin Green Elimination test reflects

hepatic clearance capacity and widely accepts as a marker of liver function reserve.

Hepatic binding activity (LHL) of GSA scintigram is reported to reflect liver function<sup>13,14</sup>. ICG and GSA should show the same trend on liver function, which was supported by several report<sup>15,16</sup>. In this study, mild correlation was observed between ICG and GSA-LHL, however, our results demonstrates one range of ICGR15 contains broad value of GSA LHL. Several studies demonstrated that the patients with LHL exceeded 0.9 could be torelable in major to moderate hepatectomy.<sup>17,18</sup> Nearly half of ICG exceeded 15% group contains LHL exceeded 0.9. It suggests some subgroups have more hypofunction than estimated one. Therefore, we had attempted to clarify an implication of LHL value in ICG based estimation. LHL-low subgroup showed lower platelet count than in LHL-high. Platelet count is known to be affected by portal hemodynamics. We previously reported that usefulness of measurement of intraoperative portal pressure to reduce postoperative morbidity.<sup>10</sup> In our study, LHL low subgroup also showed the same trend in intraoperative portal pressure, but not in the levels of total bilirubin, prothrombin time, and albumin. Taken together, it is suggested that LHL below 0.9 indicates portal hypertension even though another liver function test indicated better results. Theoretically, portal hypertension is correlated with cirrhotic liver damage. In our study, LHL-low subgroup showed relatively high



HAI, especially inflammatory (grading) score. Thus, GSA LHL15 can reflect histological damage as well as latent portal hypertension. It is reported that preoperative low platelet count or low platelet count immediately after hepatectomy were sensitive indicator for the postoperative morbidity.<sup>19-21</sup> To evaluate frequency of morbidity by incorporating preoperative LHL decision, we compared postoperative morbidity in ICG estimation alone (previous cases) and current ICG and LHL estimation. Postoperative morbidity was better reduced since induction of ICG and LHL estimation. Especially, it occurred less in LHL-high subgroup than LHL-low in moderately high value of ICG R15. In lower (<15%) ICGR15 group, almost patient showed LHL-high, suggesting no dissociation between two modalities. In LHL-high groups, platelet count showed no difference below 20% in ICG R15, while, in LHL-low groups, that was almost same above 15% in ICGR15. HAI score and portal pressure showed same trend in LHL-low of each ICG group. These results suggest the patients below 15% of ICG R15 can be achieved safer hepatic resection by ICG R15 based decision alone. Based on our result, in 15 to 20% of ICG R15 patients, wider resection than ICG based estimation could undergo if their -LHL15 exceeds 0.9, (e.g. segmentectomy converted to lobectomy). On the contrary, patients with LHL below 0.9 should undergo smaller resection to avoid severe complications although their

ICGR15 was nearly 15%.

Recent study on GSA demonstrated to better estimate of remnant liver function and prediction of morbidity such as CT-SPECT and GSA max.<sup>22-24</sup> They can be useful for the decision in extensive hepatectomy such as metastatic tumor and cholangioma. However, an information of whole liver function is needed to decide limited extent of hepatic resection for Hepatocellular carcinoma. Moreover, analyses of CT-SPECT fusion image require special setting and skillful measurement for assessment. In order to get wider acceptance, simple manner appears to be better. Incorporating to LHL result to ICG based evaluation is simple and not complicated. Our results demonstrate that GSA-LHL result is useful adjustable marker for decision of resection range in patient with moderately high ICG R15 (above 15%). Of course, more experience would be necessary to get more accuracy.

In conclusion, levels of GSA-LHL reflect severity of portal hypertension in moderately damaged liver preoperatively, and could contribute to decide range of resection with less morbidity.

### **Conflicts of interest**

None declared.

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## FIGURE LEGENDS

### Figure 1 Relationship of ICGR15 and LHL15

From 15% to 25% of ICG R15, cases with  $LHL < 0.9$  and that with  $LHL \geq 0.9$  were almost same number and similar distribution.

ICGR15: indocyanin green retention rate at 15 minutes after dye loading

LHL15: liver-heart ratio at 15 minutes after  $^{99m}\text{Tc}$ -GSA loading

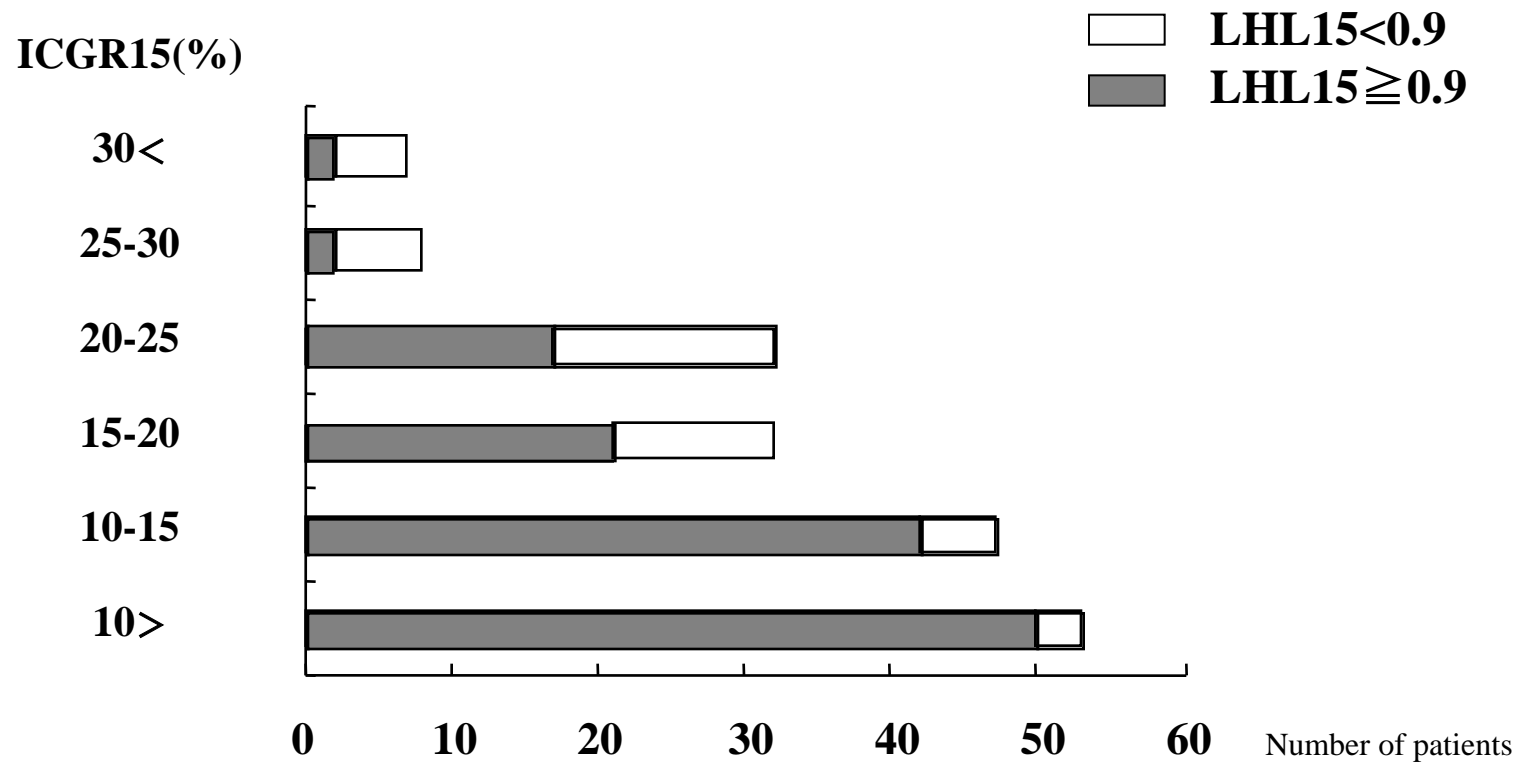
### Figure 2 Relationship of ICGR15 and platelet count in each group pf LHL15

In  $LHL \geq 0.9$  group, platelet count were significantly more at  $ICGR15 < 20\%$  than at an exceeded 20% of that ( $p < 0.03$ ). In  $LHL < 0.9$  group, platelet count showed no difference at  $ICG R15 \geq 15\%$ .

ICGR15: indocyanin green retention rate at 15 minutes after dye loading

LHL15: liver-heart ratio at 15 minutes after  $^{99m}\text{Tc}$ -GSA loading

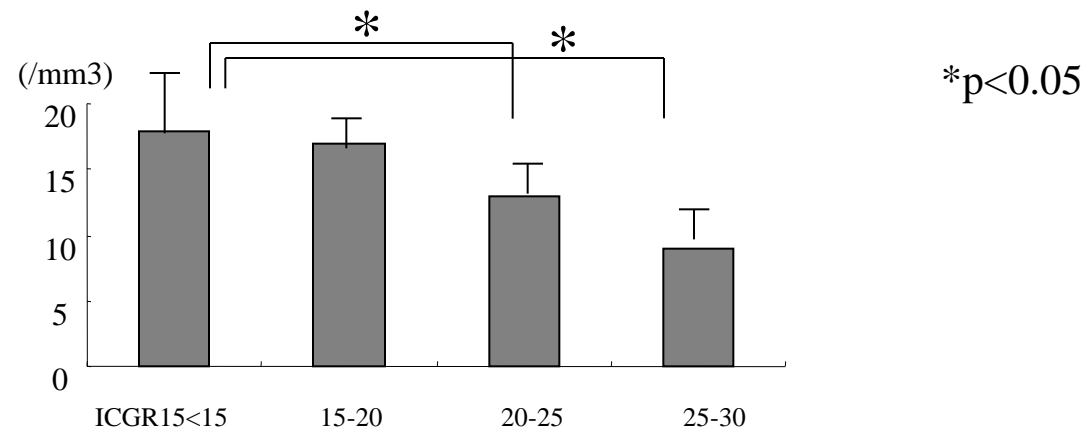
**Figure 1 Relationship of ICGR15 and LHL15**



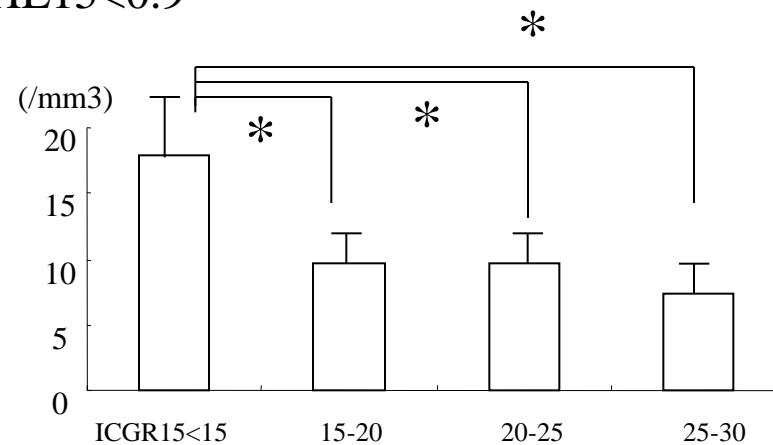


**Figure 2 Relationship of ICGR15 and platelet count in each group pf LHL15**

**LHL15  $\geq 0.9$**



**LHL15 < 0.9**



**Table 1 Patient Characteristics**

	n	Gender (M/F)		Age	HBsAg(+) / HCVAbs(+)		
<hr/>							
Group1							
LHL-low	7	5/2	N.S.	63±9	N.S.	1/4	N.S.
LHL-high	93	81/12		64±12		31/36	
Group2							
LHL-low	11	7/4	N.S.	63±6	N.S.	5/4	N.S.
LHL-high	21	19/2		69±8		6/10	
Group3							
LHL-low	15	10/5	N.S.	66±8	N.S.	2/9	N.S.
LHL-high	17	15/2		69±5		4/9	
Group4							
LHL-low	4	2/2	N.S.	65±9	N.S.	2/2	N.S.
LHL-high	4	2/2		61±7		2/2	

N.S. between LHL-low and LHL-high

**Table 2 Background data of each group**

	Albumin (g/dl)	Prothrombin time (%)	Platelet counts ( $\times 10^4$ )	Portal pressure (cmH <sub>2</sub> O)	HAI score
Group 1					
LHL low	4.0 $\pm$ 0.4	94.2 $\pm$ 12.2	19.0 $\pm$ 14.2	15.1 $\pm$ 5.1	7.5 $\pm$ 3.6
high	3.8 $\pm$ 0.5	85.4 $\pm$ 0.4	16.8 $\pm$ 5.2	16.8 $\pm$ 3.7	6.0 $\pm$ 4.7
Group 2					
LHL low	3.7 $\pm$ 0.4	90.0 $\pm$ 9.6	16.9 $\pm$ 14*	20.3 $\pm$ 0.6#	9.0 $\pm$ 4.0*
high	3.8 $\pm$ 0.4	85.0 $\pm$ 6.5	10.3 $\pm$ 2.1	17.7 $\pm$ 3.0	11.0 $\pm$ 4.0
Group 3					
LHL low	3.9 $\pm$ 0.3	88.0 $\pm$ 9.6	13.8 $\pm$ 3.7*	15.3 $\pm$ 6.0#	8.0 $\pm$ 4.0*
high	3.8 $\pm$ 0.4	86.0 $\pm$ 12.0	9.9 $\pm$ 3.0	14.3 $\pm$ 8.2	10.0 $\pm$ 4.0
Group 4					
LHL low	3.6 $\pm$ 0.3	70.0 $\pm$ 11.0	11.3 $\pm$ 6.2	N/A	9.0 $\pm$ 2.0
high	3.3 $\pm$ 0.2	74.0 $\pm$ 11.0	8.1 $\pm$ 3.7	24.8 $\pm$ 6.3	11.0 $\pm$ 2.0

ICGR15: indocyanin green retention rate at 15 minutes after dye loading

LHL15: liver-heart ratio at 15 minutes after 99mTc-GSA loading

HAI: hepatitis activity index

\*p<0.03, #p=0.06

**Table 3      Postoperative complications**

ICGR15<15%		(-)	(+)	
w/o GSA GSA		31	22	N.S.
	LHL15 $\geq$ 0.9	63	31	
ICGR15 15-20%				
w/o GSA GSA		7	7	*p<0.03
	LHL15 $\geq$ 0.9*	15	5	
	LHL15<0.9	5	5	
ICGR15 20-25%				
w/o GSA GSA		3	2	*p<0.03
	LHL15 $\geq$ 0.9	9	7	
	LHL15<0.9*	4	10	

ICGR15: indocyanin green retention rate at 15 minutes after dye loading

LHL15: liver-heart ratio at 15 minutes after 99mTc-GSA loading