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Evaluation of Hepatic Functional Reserve by ^{99m}Tc-GSA Scintigraphy before and after Treatment of Liver Cancer

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Abstract

Local therapies of liver cancer such as transcatheter arterial embolization (TAE), transcatheter arterial infusion (TAI) and radiofrequency ablation (RFA) are common. It has been pointed out that the liver function is reduced by repeating TAE and that in RFA the liver function is also reduced, especially in patients with a high Child-Pugh score after treatment. Therefore, the evaluation of preoperative hepatic functional reserve is vitally important for the selection of treatment methods. In the present study, the correlation between each index of scintigraphy with ^{99m}Tc-GSA, including HH15, LHL15 and LU15 as indices of hepatic functional reserve and conventional hepatic functional reserve was investigated before and after treatment of liver cancer. The subjects were 35 patients with liver cancer who were treated in hospital between April 2003 and January 2006 and examined by ^{99m}Tc-GSA scintigraphy before treatment. The total 35 patients were composed of 31 men and four women, aged 45 to 75 years (mean : 66.5 years), and details of background liver diseases were a positive HCV antibody in 32 patients, a positive HBV antigen in two and alcoholic liver disease in one. The methods of treatment of TAE in 27 patients and RFA in 8. Child-Pugh scores correlated with the respective indicators and the correlation with the LU15 value was the most significant. ICG scores also correlated with the respective indices and the correlation with theLU15 value was the strongest. In multiple regression analysis, the LU15 value showed a significant correlation in the three indices assessed in the present study and was considered to be the most useful. There were no significant differences between Child-Pugh scores before and after treatment. There were neither significant differences between HH15 values before and after treatment nor significant differences between LHL15 values before and after treatment. ^{99m}Tc-GSA scintigraphy has been used as a preliminary index of liver function in many medical institutions but is considered useful for predicting the progression to postoperative liver failure by improvement in analysis and analysis per liver area by SPECT.

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Introduction

The most radical treatment for liver cancer is considered to be surgical resection. Since the majority of the patients with liver cancer have underlying diseases of chronic hepatitis and hepatic cirrhosis, many have surgically unresectable cancer due to decreased hepatic functional reserve. Therefore, local therapies such as transcatheter arterial embolization (TAE), transcatheter arterial infusion (TAI) and radiofrequency ablation (RFA) are commonly selected. In Japan, most case liver cancer is due to hepatitis C virus infection. The pattern of relapse is frequently ectopic as well as local, which leads to a high frequency of treatment for liver cancer.

Liver function is reduced by repeated TAE[1] and that in RFA the liver function is also reduced, especially in patients with a high Child-Pugh score after treatment[2]. Therefore, the evaluation of preoperative hepatic functional reserve is vitally important for the selection of treatment methods.

In the present study, hepatic functional reserve was investigated using ^{99m}Tc-GSA scintigraphy as an index of hepatic functional reserve. Liver uptake 15 (LU15) is recommended as one of the indices of functional liver volume of ^{99m}Tc-GSA scintigraphy. Partial hepatic functional reserve is assessed by single photon emission computed tomography (SPECT) and is considered to be useful not only in deciding in surgical operation but also in the local treatment of liver cancer[3)4)].

Some reports assessed the correlation between Child-Pugh or hepatic injury classification[5] and HH15 or LHL15[6] but few reports investigated the correlation with LU15. In the present study, the correlation between each index of scintigraphy with ^{99m}Tc-GSA including LU15 as an index of hepatic functional reserve and conventional hepatic functional reserve was investigated before and after treatment of liver cancer.

Subjects

The subjects were 35 patients with liver cancer who were treated in the hospital between April 2003 and January 2006 and examined by ^{99m}Tc-GSA scintigraphy before treatment (Table 1).

The total of 35 patients were composed of 31 men and 4 women, aged 45 to 75 years (mean : 66.5 years), and details of background liver diseases were a positive HCV antibody in 32 patients, a positive HBV antigen in two and alcoholic liver disease in one.

The tumor sizes were about 1-6 cm in diameter (mean : 2.5 cm). The number of tumors was 1-6 nodes, and only one node was observed in 15 patients (mean : 2.3 nodes). The methods of treatment were transcatheter arterial embolization (TAE) in 27 patients and radiofrequency ablation (RFA) in 8. Preoperative CLIP (the Cancer of the Liver Italian Program) scores were 0 in 2 patients, 1 in 18, 2 in 11 and 3 in 4. JIS scores were 0 in 4 patients, 1 in 9, 2 in 10, 3 in 9 and 4 in 3.

Methods

1. Diagnosis of liver cancer

Liver cancer was diagnosed comprehensively on the basis of tumor marker, abdominal ultrasonography, dynamic CT, contrast-enhancement MRI (gadolinium, superparamagnetic iron oxide) and angiography.

2. Method of treatment

The method of treatment selected considered the size and number of tumors and evaluation of preoperative hepatic functional reserve. The algorithm of the treatment in our department is shown in Fig. 1. In TAE, the artery was embolized with gelatin after the emulsion of epirubicin hydrochloride and lipidole was infused into the hepatic artery. The dose of epirubicin was 30-50 mg (mean : 33.1 mg). The range of treatment by TAE was segmental in 12 patients, subsegmental in six and lobular area in nine. In RFA, RITA model 90 and Cool-tip were used. RFA was performed subcutaneously in all patients under sonographic guidance.

3. ^{99m}Tc-GSA scintigraphy

It is well known that ^{99m}Tc-GSA scintigraphy is a radioisotope that combines specifically the asialoglycoprotein present on the surface of the hepatocytes and

Table 1 Back ground

gender (M/F)	31/8											
Age (yrs old)	45～75											
background	HCVpositive	32	HBVpositive	2	Alcoholic	1						
size of tumor	1 cm>	10	1<≧2	10	2<≧3	5	3<≧4	3	4<≧5	6	5<≧6	1
number of tumor	1	15	2	7	3	4	4and over	9				
Method of treatment	TAE	27	RFA	8								
CLIPscore	0 point	2	1 point	18	2 point	11	3 point	4				
JIS score	0 point	4	1 point	9	2 point	10	3 point	9	4 point	3		

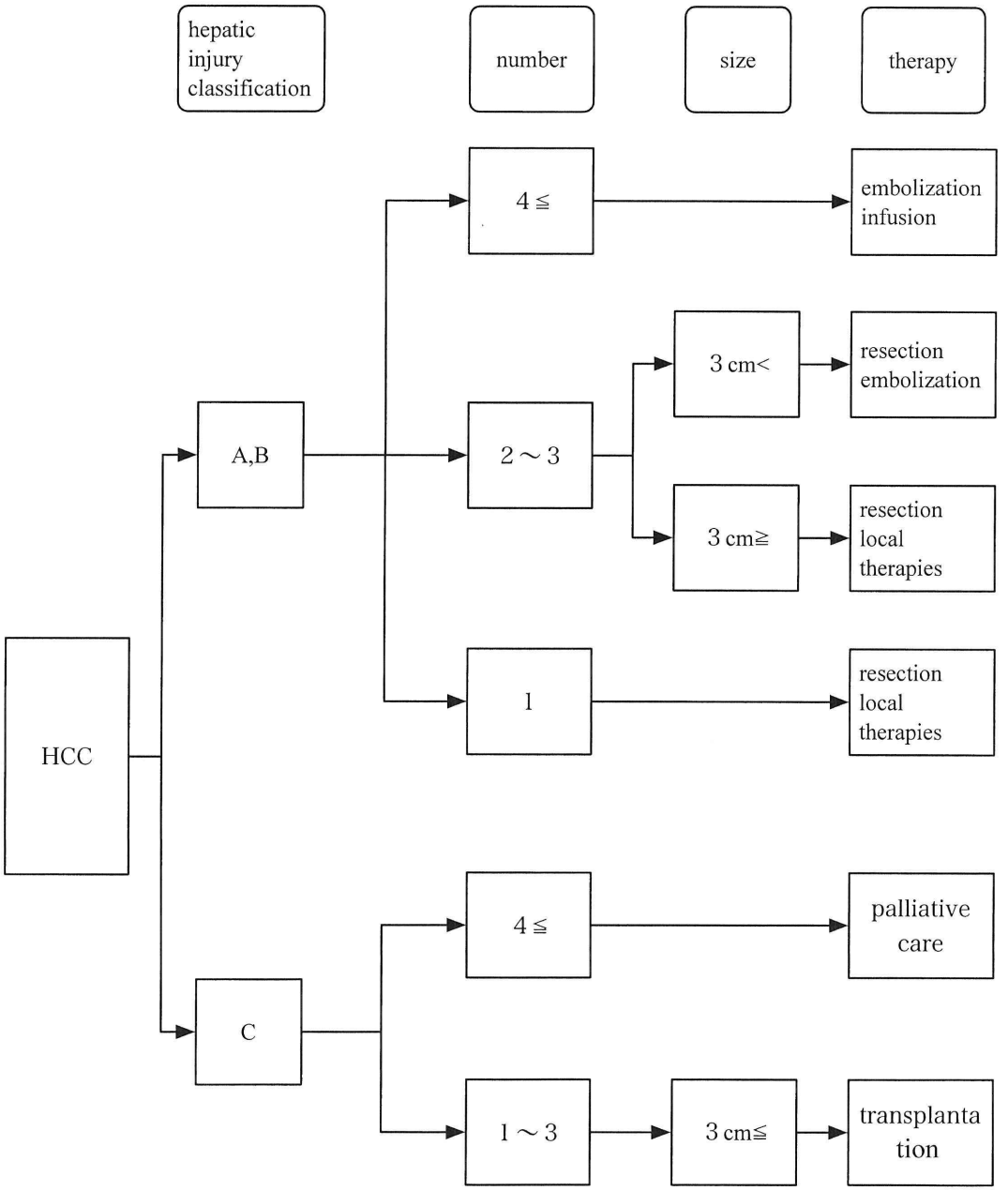

Fig. 1 The algorithm of the treatment in this department

reflects the amount and distribution of hepatocytes.

Tc-GSA (185 Mbq/mL, Nihon Mediphysics) was given intravenously to bed rest patients. Continuous dynamic images (at the rate of 30 seconds per frame) were recorded in patients in a supine position under a gamma camera from just before intravenous injection to 20 minutes after injection. The dose of ^{99m}Tc-GSA given intravenously to the body was calculated by measuring the ^{99m}Tc-GSA syringe count before and after intravenous injection. The calculation method of parameters (HH15, LHL15, and LU15) involved HH15 value, which is an index of blood clearance of ^{99m}Tc-GSA and is calculated as the count ratio (H15/H3) of the heart activity (H) at 3 minutes (H3) to that at 15 minutes (H15) after injection ; the LHL15 value, which is an index of the accumulation of hepatic receptor after injection of ^{99m}Tc-GSA and shows the count ratio [L15/(H15+L15)] of the liver activity [L] to the heart activity [H]+liver activity [L] at 15 minutes after injection (Fig. 2)[7] ; and the LU15 value, which is an index of accumulation of hepatic receptor and was calculated by dividing the accumulation amount for one minute between 15 and 16 minutes by the given ^{99m}Tc-GSA count, using the continuous 20-min image data.

4. Method of assessment

In conventional hepatic functional reserve test, the correlation among HH15, LHL15 and LU15, indices of ^{99m}Tc-GSA scintigraphy, were investigated using Child-

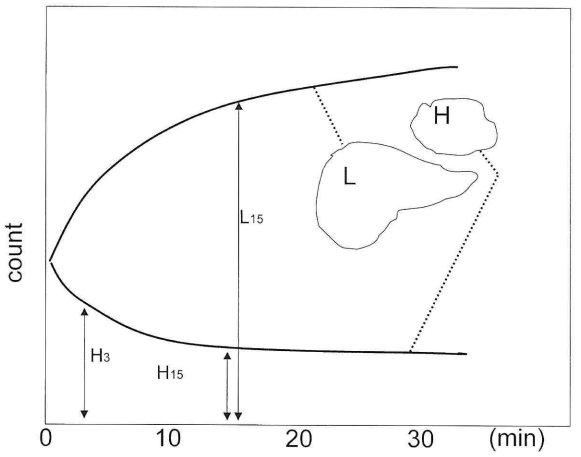

Fig. 2 Time-radiation curve
HH15 value is an index of blood clearance of ^{99m}Tc-GSA and is calculated as count ratio (H15/H3) of the heart activity (H) at 3 minutes (H3) to that at 15 minutes (H15) after injection.. LHL15 value is an index of the accumulation of hepatic receptor after injection of ^{99m}Tc-GSA and shows the count ratio [L15/(H15+L15)] of the liver activity [L] to the heart activity [H]+liver activity [L] at 15 minutes after injection.

Pugh classification, the ICG 15-min value and hepatic injury classification. Furthermore, changes in each index of Tc-GSA scintigraphy were investigated before and 4 and 12 weeks after treatment.

5. Statistical evaluation

Statistical analysis of the data was performed by Student's *t*-test, the chi-square test, the Wilcoxon signed-rank test and Spearman's rank-correlation coefficient (level of significance : $P<0.05$).

Additionally, the informed consent was investigated in accordance with the spirit of the Helsinki Declaration, and the content of the study was explained sufficiently to the patients after approval by the Independent Ethics Committee of the hospital. Informed consent was obtained by the document from the patients.

Results

1. HH15 and index of hepatic functional reserve (Fig. 3)

There was a significant correlation between HH15 value and ICG15-min value ($r=0.52$, $p<0.001$). HH15 value increased significantly with a decrease in hepatic injury. There was a significant correlation between HH15 value and Child-Pugh score ($r=$s-0.3,

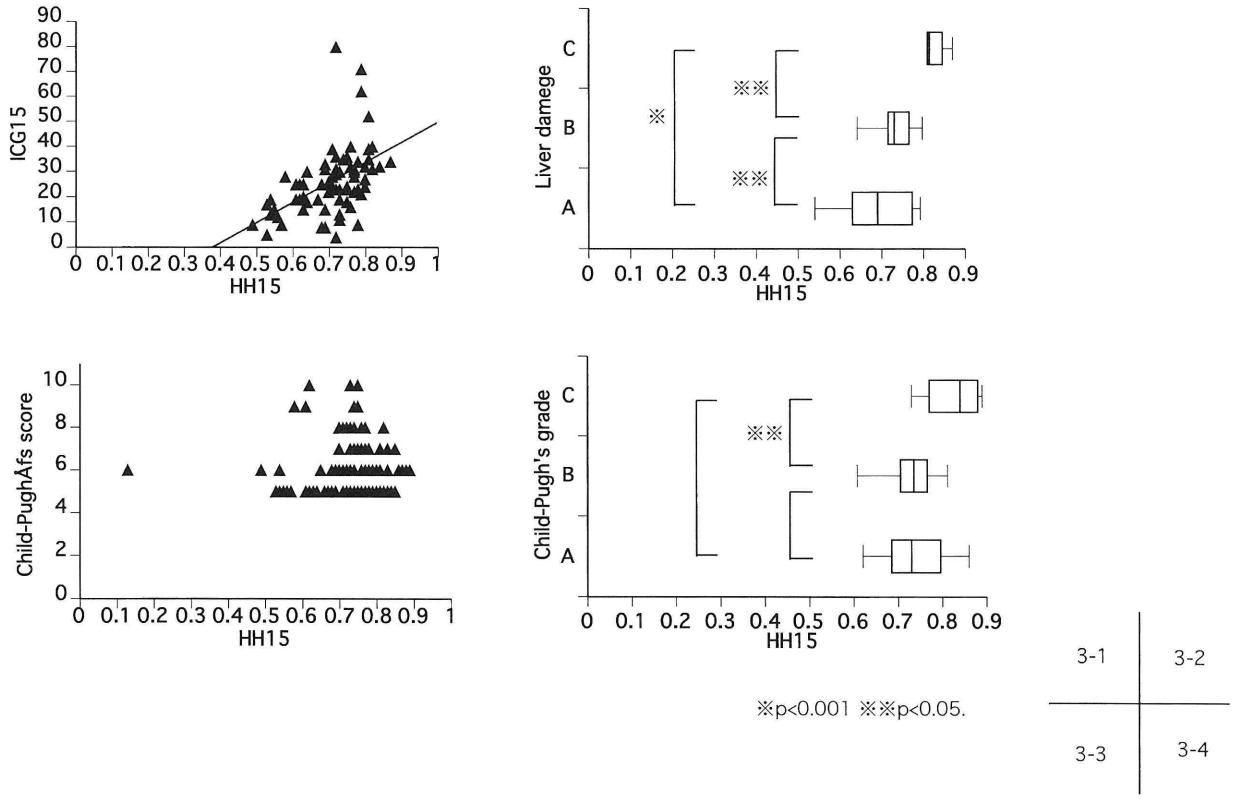

Fig. 3 HH15 and index of hepatic functional reserve.
Fig. 3-1 There were a significant correlation between HH15 value and ICG15-min value.
Fig. 3-2 HH15 value increased significantly with a decrease in hepatic injury.
Fig. 3-3 There was a significant correlation between HH15 value and Child-Pugh score.
Fig. 3-4 In Child-Pugh classification, there was significant differences between A and B. There were neither significant differences between B and C nor between A and C.

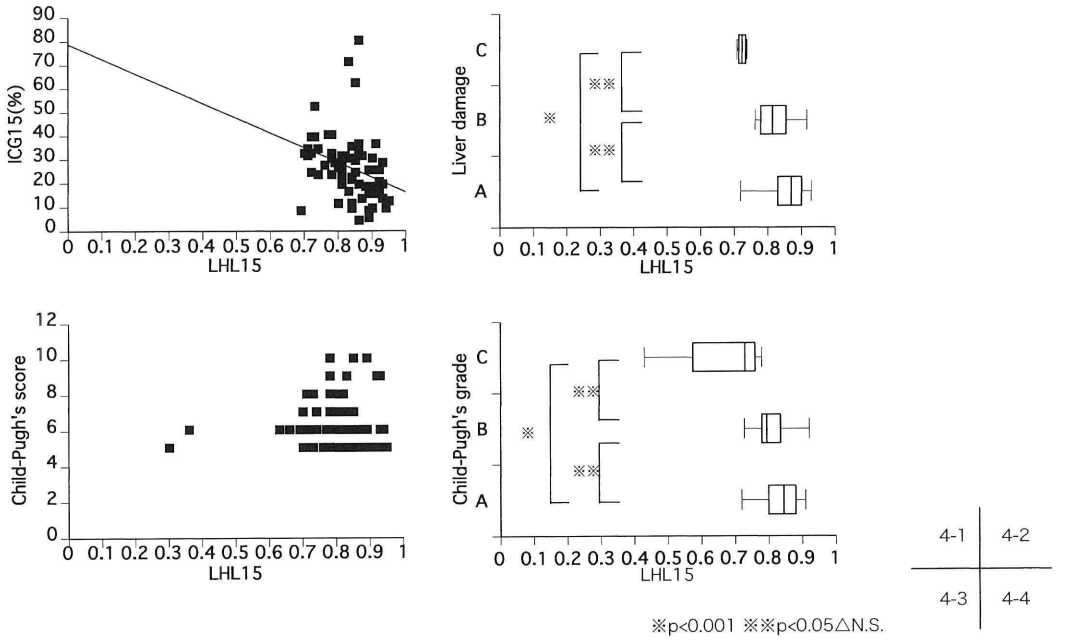

Fig. 4 LHL15 and index of hepatic functional reserve
Fig. 4-1 There was a significant correlation between LHL15 value and ICG15-min value.
Fig. 4-2 LHL15 value decreased significantly with a decrease in hepatic injury.
Fig. 4-3 There was a significant correlation between LHL15 value and Child-Pugh score.
Fig. 4-4 In Child-Pugh classification, LHL15 value decreased significantly with a decrease in liver function.

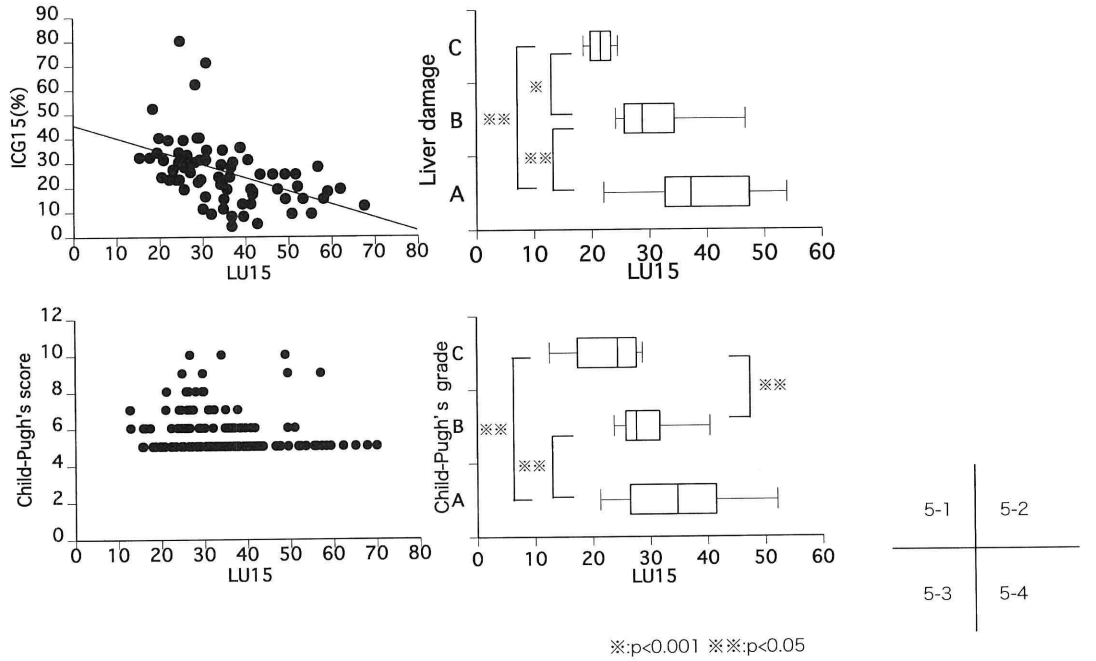

Fig. 5 LU15 and index of hepatic functional reserve.
Fig. 5-1 There was a significant correlation between LU15 value and ICG15-min value.
Fig. 5-2 LU15 value decreased significantly with a decrease in hepatic injury.
Fig. 5-3 There was a significant correlation between LU15 value and Child-Pugh score.
Fig. 5-4 In Child-Pugh classification, LU15 value decreased significantly with a decrease in liver function.

$p<0.005$). In Child-Pugh classification, there were significant differences between A and B ($p<0.05$). However, there were neither significant differences between B and C nor between A and C.

2. LHL15 and index of hepatic functional reserve (Fig. 4)

There was a significant correlation between LHL15 value and ICG15-min value ($r=-0.40$, $p<0.001$).

Table 2 Multiple regression analysis with Child-Pugh score and the respective indices of GSA were performed but correlation with LU15 was the strongest.

Independents variables	Partial regression coefficients	Standarized regression coefficients	*P* value
HH15	−0.857	−0.084	0.509
LHL15	0.529	0.045	0.743
LU15	−0.032	−0.372	0.021

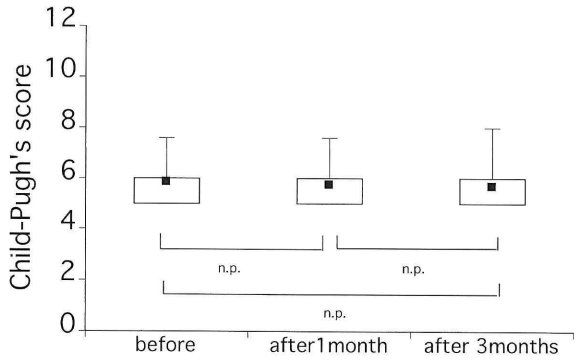

Fig. 6 There were no significant differences between Child-Pugh scores before and after treatment.

LHL15 value decreased significantly with a decrease in hepatic injury. There was a significant correlation between LHL15 value and Child-Pugh score ($rs=-0.43$, $p<0.001$). In the Child-Pugh classification, LHL15 value decreased significantly with a decrease in liver function.

3. LU15 and index of hepatic functional reserve (Fig. 5)

There was a significant correlation between the LU15 value and ICG15-min value ($r=-0.53$, $p<0.001$). The LU15 value decreased significantly with a decrease in hepatic injury. There was a significant correlation between the LU15 value and the Child-Pugh score ($rs=-0.43$, $p<0.001$). In the Child-Pugh classification, LU15 value decreased significantly with a decrease in liver function.

4. Multiple regression analysis with the Child-Pugh score (Table 2)

Multiple regression analysis with the Child-Pugh score and the respective indices of GSA were performed but correlation with LU15 was the strongest ($p<0.021$).

5. Evaluation before and after treatment

There were no significant differences between Child ? Pugh scores before and after treatment (Fig. 6). ICG15 increased significantly before operation and three months after operation (Fig. 7). On the other hand, HH15 and LHL15, indices of ^{99m}Tc-GSA scintigraphy, before the treatment were compared with those at one month and three months after treatment, and showed no

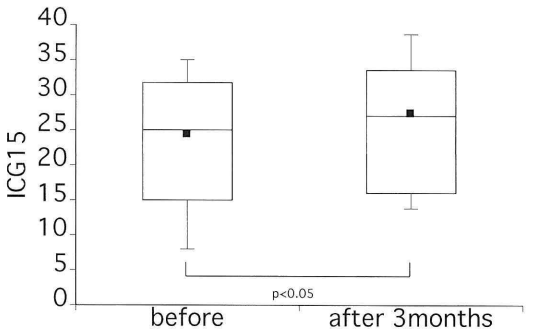

Fig. 7 ICG15 increased significantly before operation and three months after operation.

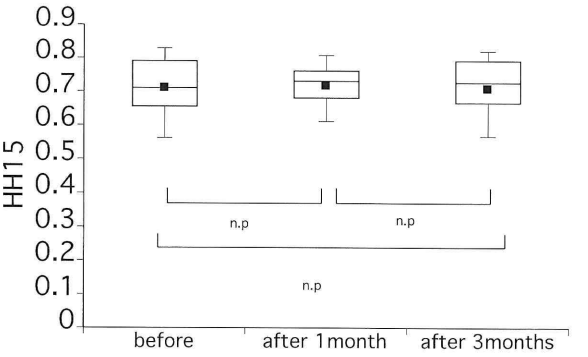

Fig. 8 Before the treatment were compared with HH15 at one month and three months after treatment, and showed no significant differences.

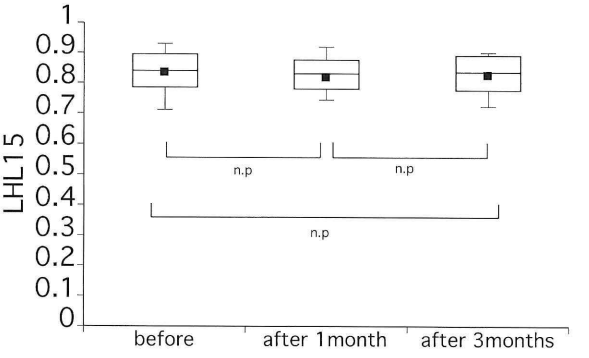

Fig. 9 Before the treatment were compared with LHL15 at one month and three months after treatment, and showed no significant differences.

significant differences (Figs. 8 and 9). There were no differences between LU15 values at one month after treatment and that at three months; however, LU15 value decreased significantly before, at one month after, and at three months after treatment (Fig. 10).

The index of ^{99m}Tc-GSA scintigraphy by TAE was compared with that by RFA but there were no differences between the two groups in manipulation of the treatment.

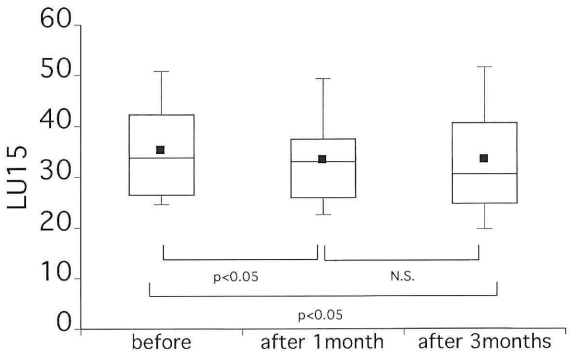

Fig. 10 There were no differences between LU15 values at one month after treatment and that at three months ; however, LU15 value decreased significantly before, at one month after, and at three months after treatment

Discussion

Child-Pugh classification, hepatic injury classification, CLIP score and JIS score, which were used as the test for hepatic functional reserve, have been judged based on many factors such as serum bilirubin, prothrombin activity, platelet count and ICG test. ICG test is especially important as an index at the time of hepatic resection[7]. However, when jaundice and portal vein-systemic circulation shunt are observed, there are problems with ICG test in reproducibility. This is because of the test values showing higher than the actual values, dispersion of blood collection time and operator's manipulative technique[8][9]).

In recent years, GSA scintigraphy has been used as one of the assessments of liver function. HH15 and LHL15 values are generally known to correlate with ICG test and Child-Pugh scores[8][9]. Yasutomi et al. have reported that only LHL15 and HH15 can be used as indices of selection of hepatic resection[10]. The LHL 15 value is specially emphasized, and when the value is not more than 0.9-0.92, the risk of postoperative hepatic failure is generally known to be high[11)-13)]. However, it is generally said that the LHL15 value is low in ability discrimination the favorable liver function area and HH15 value is low for discrimination ability in the hepatic dysfunction area[6]. Kawa et al. showed favorable results in patients with hepatic dysfunction and normal liver function, using GSA index (LHL15/HH15) to correct the disadvantage[14].

In the present study, the respective indices of ^{99m}Tc-GSA scintigraphy were investigated. Child-Pugh scores correlated with the respective indicators and the correlation with LU15 value was the most significant. ICG scores also correlated with the respective indices and the correlation with LU15 value was the strongest. In multiple regression analysis, the LU15 value showed a significant correlation in the three indices assessed in the present study and was considered to be the most useful.

As a conventional nonoperative therapy for HCC, percutaneous ethanol injection therapy (PEIT), percutaneous local therapy (e.g. RFA), and IVR therapy (e.g. TAE) are used widely. These treatments have been reported to scarcely affect hepatic functional reserve[2)15)16)] but investigations of complications have been performed in many of these studies. There are few reports for changes in hepatic functional reserve. Koda Y et al. evaluated hepatic functional reserve according to Child-Pugh score of PEIT and confirmed that there were no significant changes at six months after treatment16). The evaluation of hepatic functional reserve before and after RFA was continued at a high level in 33% of the patients according to Child-Pugh score at six months after treatment and the decrease in hepatic functional reserve was greater than that in PEIT[2]. Hama et al. also have used a calculating formula as a clearance index, which is similar to that of HH15 value but there are no changes at one month after treatment[17]. In the present study, there were no significant differences between Child-Pugh scores before and after treatment. There were neither significant differences between HH15 values before and after treatment nor significant differences between LHL15 values before and after treatment. Because of these insignificant differences, the treatment level was considered to have been adjusted considering hepatic functional reserve beforehand in the treating liver cancer. However, ICG 15-minute and LU15 values decreased after operation and the liver function was presumed to be aggravated.

When single photon emission computed tomography (SPECT) is applied to ^{99m}Tc-GSA scintigraphy, remnant liver function can be measured. Yokota, et al. assessed the liver function before right hepatic lobectomy by ^{99m}Tc-GSA SPECT scintigraphy, making use of left lobe GSA index[18]. In addition, Kubo et al. performed hepatic portal embolization in the right lobe of a patient in whom right lobe resection was scheduled to be performed and examined LHL15 values before and after the embolization and SPECT was performed. They reported that the major activity of the liver function was transferred from the embolized right lobe to the left lobe[19]. Since measurement of the remnant liver function became possible, the remnant liver function is considered useful as a pretreatment test. Since the remnant liver function can be easily measured by LU15 making use of SPECT, LU15 can be used as an index of preoperative test.

^{99m}Tc-GSA scintigraphy has been used as a preliminary index of liver function in many medical institutions but is considered useful for predicting the progression to postoperative liver failure by improvement in analysis and analysis per liver area by SPECT.

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肝癌治療前後での ^{99m}Tc-GSA シンチグラフィーによる肝予備能の評価についての検討

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肝癌の治療は肝動脈塞栓術肝動脈動注療法及び経皮的ラジオ波焼灼療法などの局所療法が選択されることが多い。しかし、肝細胞癌は再発などにより頻回の治療を余儀なくされるが、治療を繰り返すことにより、肝予備能の低下を指摘されている。このため治療の選択で術前の肝予備能の評価が重要となる。今回、肝予備能の指標として ^{99m} TcTc-GSA-GSA シンチグラフィーを用いて検討した。^{99m}TcTc-GSA-GSA シンチグラフィーの指標 Tc-GSA シンチ 2) 3) として、機能的な肝容量の指標の一つとしてあげられる LU15 値を含め、HH15 値、LHL15 値と、従来の肝予備能との相関を肝癌治療前後で検討した。

対象は平成 15 年 4 月から平成 18 年 1 月までに当院で加療した肝癌患者で、患者背景は男性 31 例、女性 4 例、年齢は 45 歳から 75 歳、平均 66.5 歳であった。治療方法は TAE 27 例、RFA 8 例であった。

結果として ^{99m}Tc-GSAGSA シンチグラフィーと Child-Pugh スコアではそれぞれの指標で相関を認めたが、LU15 値が最も有意な相関を認めた。ICG15 値との関係もそれぞれの指標と相関を認めたが、LU15 値が最も強い相関を認めた。重回帰分析では今回評価した 3 指標の中で LU15 値が有意な相関を認め、最も有用と考えられた。今回の治療前後での検討で、Child-Pugh スコアや HH15 値、LHL15 値において治療前後で有意差が認められなかった。この理由として治療の際に事前の予備能を考慮し、治療程度が加減されているためと思われた。しかし、ICG15 分値と GSA シンチグラフィーにおいての LU15 値は術後に低下しており、肝機能は増悪していると推測された。これまで、^{99m}Tc-GSA シンチグラフィーは多くの施設において肝機能の予備的な指標として用いられてきたが、解析の工夫や SPECT による肝区域ごとの解析により術後の肝不全への進行の予知などに有用と思われた。

〈キーワード〉 ^{99m}Tc-GSA シンチグラフィー、肝細胞癌、肝予備能