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Quantitative evaluation of the regional hepatic reserve by ^{99m}Tc-GSA dynamic SPECT before and after chemolipiodolization in patients with hepatocellular carcinoma

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^{99m}Tc-DTPA-galactosyl human serum albumin (^{99m}Tc-GSA) hepatic scintigraphy was performed in 32 patients with hepatocellular carcinoma before and after chemolipiodolization, which was performed from the right hepatic artery (RHA) in 15 patients and the proper hepatic artery (PHA) in 17 patients. Following a bolus injection of ^{99m}Tc-GSA, dynamic SPECT was performed with 1 minute rotation for 16 minutes. Data analysis was conducted by setting a region of interest (ROI) on the right liver, left liver and heart and then their time-activity curves were generated. The regional hepatic accumulation index (LHL15) and the regional uptake constant index (KU) were also calculated from the time-activity curves. In the RHA group, regional LHL15 and KU of the left lobe significantly increased, but they did not significantly increase in the PHA group. In the right lobe, no significant change in regional KU or LHL15 was observed. In the poor prognosis group, all indices in both regions decreased after chemolipiodolization, especially the value for regional KU had a poor score before chemolipiodolization. A decrease in each index in both lobes after chemolipiodolization is considered to be a sign of a poor prognosis. ^{99m}Tc-GSA dynamic SPECT scintigraphy is a useful method for evaluating the changes in regional hepatic reserve before and after chemolipiodolization.

Key words: hepatocellular carcinoma, ^{99m}Tc-DTPA-galactosyl human serum albumin, chemolipiodolization, hepatic functional reserve

INTRODUCTION

CHEMOLIPIODOLIZATION for hepatic tumor results in a decrease in hepatic blood flow to the tumor and normal hepatic tissue. It is very difficult to evaluate the changes in regional hepatic function after chemolipiodolization with blood laboratory data. In patients with chemolipiodolization, assessment of regional hepatic functional reserve, especially in normal hepatic tissue, seems to provide information useful in the clinical management of these patients after chemolipiodolization.[1] Shuke et al.[2] have applied the Patlak plot to dynamic data for the liver and heart and calculated the uptake constant (KU) as a quantitative index. KU has shown significant correlation with the results of liver function tests. The quantitative assessment of the regional functional reserve of the liver is considered to be important for the clinical management of patients with hepatic malignancy. But the quantitative evaluation of the regional functional reserve of the liver by dynamic ^{99m}Tc-GSA single photon emission computed tomography (dynamic SPECT) has not been performed.[3–5]

The purpose of this study is to assess the regional liver function with each regional quantitative index derived from the dynamic SPECT before and after chemolipiodolization, and the usefulness of these indices for the clinical outcome after chemolipiodolization.

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MATERIALS AND METHODS

Study Patients

The study subjects were 32 patients with hepatocellular

Table 1 Changes in each ^{99m}Tc-GSA indices before and after chemolipiodolization in RHA and PHA group

	RHA			PHA		
	before	after	p-value	before	after	p-value
LHL15 (rt)	0.669 ± 0.091	0.703 ± 0.140	ns	0.742 ± 0.101	0.687 ± 0.105	ns
LHL15 (lt)	0.633 ± 0.088	0.711 ± 0.126	$p < 0.05$	0.690 ± 0.114	0.663 ± 0.127	ns
KU (rt)	0.132 ± 0.065	0.151 ± 0.107	ns	0.160 ± 0.097	0.150 ± 0.080	ns
KU (lt)	0.100 ± 0.041	0.143 ± 0.077	$p < 0.05$	0.128 ± 0.097	0.128 ± 0.081	ns

RHA; right hepatic artery, PHA; proper hepatic artery

Table 2 Changes in each ^{99m}Tc-GSA indices before and after chemolipiodolization in poor prognosis group

	before TAE	after TAE
LHL15 (rt)	0.715 ± 0.033	0.362 ± 0.036
LHL15 (lt)	0.664 ± 0.033	0.356 ± 0.141
KU (rt)	0.087 ± 0.008	0.026 ± 0.002
KU (lt)	0.070 ± 0.006	0.022 ± 0.011

carcinoma. They were 23 males and 9 females, and their ages ranged from 45 to 82 years (mean 66.3 years). The diagnosis of the hepatocellular carcinoma was made by echo-guided needle biopsy. The location of the tumor was in the right lobe in 15 patients and both lobes in 17 patients. Chemolipiodolization was performed from the right hepatic artery in the 15 patients and the proper hepatic artery in the others. Lipiodol (3–5 m*l*) and anticancer agents (cisplatin 60–100 mg) were used in 30 patients as embolic materials. Intraarterial infusion of an anticancer agent (cisplatin 100 mg) was performed in two patients because of a large A-P shunt. A dynamic ^{99m}Tc-GSA SPECT was performed in all patients before and after chemolipiodolization. ^{99m}Tc-GSA scintigraphy was performed within 1 week before treatment and 5 to 12 days after treatment. The liver function tests were also performed at the same time before and after chemolipiodolization.

Dynamic SPECT

Dynamic SPECT was performed in patients after a bolus injection of a dose of 1 mg/185 MBq of ^{99m}Tc-GSA via an antecubital vein. A dual head SPECT (GCA 90B, Toshiba, Japan) with a low energy high resolution parallel hole collimator was used for the dynamic SPECT. The dynamic SPECT images acquired with 1 minute rotation were obtained with a 64 × 64 matrix for 16 minutes after injection. Sixty views were obtained over a 360 degree arc. at each rotation and were collected to an on-line computer (GMS 550U, Toshiba, Japan). Axial images were reconstructed by a filtered back projection method, with a Shepp and Logan filter with attenuation correction (Chang, $\mu = 0.15$). The slice thickness of a reconstructed axial image was 32 mm. These methods were used to obtain dynamic SPECT data every minute.

Data Analysis

Three rectangular regions of interest (ROI) of 3 × 3 pixel size were placed on the right lobe, the left lobe of the liver and the heart of dynamic SPECT images, and then their time-activity curves were generated. We set ROIs in the normal liver area in each lobe to evaluate the effects of chemolipiodolization on the normal tissue. We placed heart ROI in the left ventricle, and the following quantitative indices were calculated from the time-activity curves.

Two quantitative indices were calculated to evaluate regional hepatic function. First, the regional hepatic accumulation index (regional LHL15); LHL15 (rt), defined as the uptake ratio of the 3 × 3 pixel ROI on the right lobe of the liver to right lobe ROI (3 × 3) plus heart ROI (3 × 3) at 15 minutes. LHL15 (lt) is the same as the one used for the left lobe ROI instead of the right lobe ROI. Second, the uptake constant index (KU), representing hepatic blood flow and receptor affinity, was determined by Patlak plot. KU was calculated on the basis of the following theory. When the uptake of ^{99m}Tc-GSA into the liver is constant, and the catabolism and excretion of ^{99m}Tc-GSA bound to the receptor are disregarded, the amount of ^{99m}Tc-GSA in the liver is derived from the amount of ^{99m}Tc-GSA in the blood, as follows:

$$L(t)/Ca(t) = KU\int Ca(t)dt/Ca(t) + Vn$$

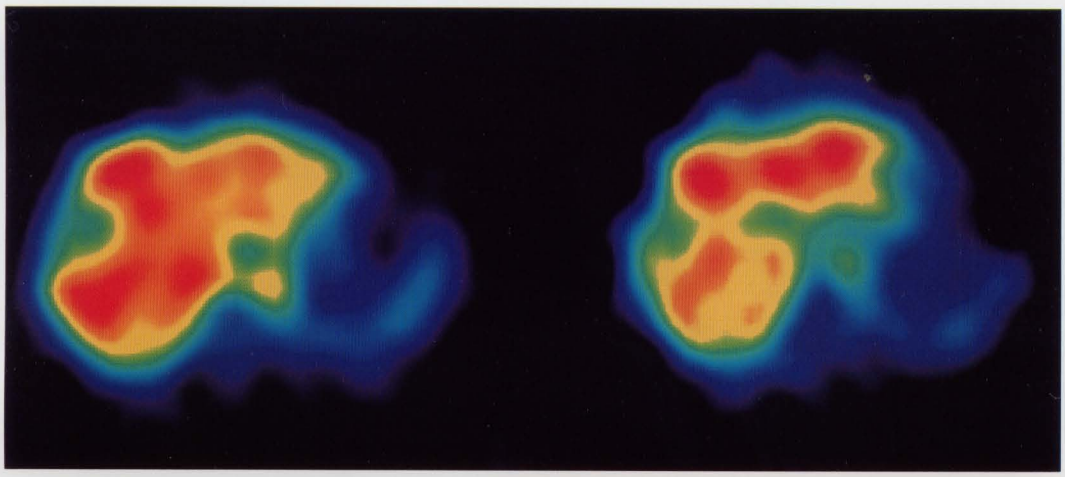
where L(t) is the time-activity curve for the liver, and Ca(t) is the time-activity curve for the heart. Vn represents the non-specific distribution volume of ^{99m}Tc-GSA in the liver. L(t)/Ca(t) was plotted against $\int Ca(t)dt/Ca(t)$, and KU was determined as the slope derived from simple linear regression analysis. The right lobe ROI was used to calculate KU (rt) and the left lobe ROI was used in KU (lt).

Each index is expressed as the mean ± one standard deviation. The significant difference for each index before and after chemolipiodolization was determined by Student's t-test (two-tailed, paired). A p-value of less than 0.05 was considered significant.

RESULTS

Changes in ^{99m}Tc-GSA indices in embolized and non-embolized lobes before and after chemolipiodolization

In 13 patients in whom chemolipiodolization was performed from the right hepatic artery, the regional LHL15



a b

Fig. 1 A 64-year-old male patient with hepatocellular carcinoma in the right lobe. Scintigraphic images of ^{99m}Tc-GSA before (a) and after (b) chemolipiodolization. The radioisotope uptake of the left lobe is increased after chemolipiodolization, though the uptake of the right lobe is decreased.

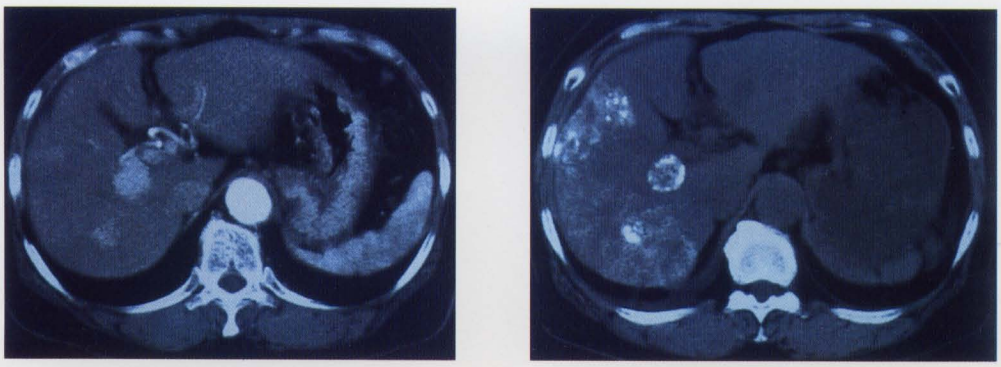


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Fig. 2 Abdominal CT images of the same patient with Figure 1. (a) Dynamic study in early phase before chemolipiodolization. Multiple early enhancements are observed in the right lobe. (b) Lipiodol CT, 7 days after chemolipiodolization. There are accumulation of lipiodol in the right lobe. There are no apparent changes of the hepatic size and shape.

Table 3 Changes in blood laboratory data before and after chemolipiodolization

	RHA		PHA	
	before	after	before	after
albumin (g/d*l*)	3.35 ± 0.37	3.36 ± 0.50	3.46 ± 0.58	3.00 ± 0.47*
t-bilirubin (mg/d*l*)	0.82 ± 0.46	1.08 ± 0.66	0.84 ± 0.43	0.95 ± 0.60
GOT (u/*l*)	50.6 ± 26.7	52.2 ± 15.1	45.2 ± 20.8	49.5 ± 31.2
GPT (u/*l*)	47.0 ± 32.5	62.1 ± 40.9	36.6 ± 15.4	44.2 ± 23.2
ChE (u/*l*)	93.3 ± 30.4	69.8 ± 30.5*	97.2 ± 39.3	68.8 ± 31.7*
platelets ($\times 10^3$)	110 ± 46.0	93.6 ± 30.0	117 ± 74.1	89.0 ± 49.7

*; $p < 0.05$, ChE; cholinesterase, RHA; right hepatic artery, PHA; proper hepatic artery

and regional KU of the non-embolized lobe were significantly increased (0.633 ± 0.088 to 0.711 ± 0.126 and 0.100 ± 0.041 to 0.143 ± 0.077, $p < 0.05$, respectively) (Table 1). In 17 patients in whom chemolipiodolization was performed from the proper hepatic artery, regional KU and regional LHL15 did not show significant changes (Table 1). A scintigraphic image and abdominal CT performed before and after chemolipiodolization from the right hepatic artery are shown (Figures 1 and 2). In this scintigraphy, the radioisotope uptake of the left lobe

Table 4 Changes in blood laboratory data before and after chemolipiodolization in poor prognosis group

	before	after
albumin (g/dl)	2.95 ± 0.21	2.90 ± 0.14
t-bilirubin (mg/dl)	1.90 ± 0.57	4.40 ± 2.12
GOT (u/l)	103.5 ± 57.3	186.0 ± 33.9
GPT (u/l)	73.0 ± 59.4	105.0 ± 18.4
ChE (u/l)	61.5 ± 19.1	48.0 ± 7.1
platelets ($\times 10^3$)	98.5 ± 82.7	85.5 ± 64.3

ChE; cholinesterase

increases after chemolipiodolization. As for two patients who had a poor prognosis, the values for regional KU and LHL15 were extremely decreased after chemolipiodolization in both lobes, though statistical analysis was not performed in these patients because there were too few patients in this category (Table 2).

Evaluation of blood laboratory data and changes in scintigraphic indices before and after chemolipiodolization in each grade

All study subjects underwent a standard battery of routine laboratory tests including albumin, total bilirubin, GOT, GPT, cholinesterase and platelet count. As shown in Table 3, albumin decreased after TAE in the proper hepatic artery group and cholinesterase in both groups, but no significant change was observed in the others after TAE. In the poor prognosis group, there was a tendency for all the blood laboratory data to deteriorate after chemolipiodolization (Table 4).

DISCUSSION

The assessment of regional liver function by ^{99m}Tc-GSA is important for the clinical management of patients with hepatocellular carcinoma, because chemolipiodolization results in the deterioration of normal liver tissue in the embolized region. Kosuda et al.[6] have been reported the changes in HH15 and LHL15 after chemolipiodolization. Dynamic data for the whole liver and total liver function have been evaluated in their study, but they did not show a significant correlation between these indices and liver damage caused by chemolipiodolization. In the evaluation of liver damage after chemolipiodolization, we have used the quantitative indices LHL15 and KU which reflect regional liver blood flow and regional receptor quantity. Regional KU and regional LHL15 of the left lobe increased after chemolipiodolization in the RHA group, but not in the PHA group. In the right lobe, neither index changed significantly after chemolipiodolization. The liver damage after chemolipiodolization was mainly caused by a decrease in hepatic blood flow and the toxicity of anticancer agents. Although chemolipiodolization causes hepatocytes to deteriorate, by the ^{99m}Tc-GSA indices in the non-embolized lobe indicated an increase in hepatic functional reserve. We believe that this is caused by the relative increase in hepatic blood flow in the non-embolized lobe after chemolipiodolization. Hepatocyte growth factor is identified as the factor that promotes cell proliferation in the regenerated liver. In an experiment on carbon tetrachloride disordered model rats, hepatocyte growth factor activity reached a peak in 24 hours after administration. DNA synthesis of hepatocytes reaches a peak at 24–48 hours later.[7] In a clinical examination, it was reported that hepatocyte growth factor in plasma had increased 3 days after transarterial embolization.[8] The rate of hepatic uptake of ^{99m}Tc-GSA increased in the non-embolized lobe more than in the embolized lobe in our study. We think the second reason for the mechanism is that hepatocyte growth factor acts on the non-embolized lobe which is not affected by chemolipiodolization. Hepatocyte growth factor was not measured in our study. We believe that in future we should measure the index to support our results.

The blood laboratory data worsened after chemolipiodolization, especially in albumin and cholinesterase. Blood laboratory data are mainly used for the evaluation of early hepatic damage after chemolipiodolization, but regional liver function cannot be evaluated with these data.[9]

^{99m}Tc-GSA indices in two patients were much worse after chemolipiodolization. Patients in this group had a poor prognosis and died of hepatic insufficiency 3 months after chemolipiodolization. It is a very useful if we can recognize such patients before chemolipiodolization. Although we could not perform statistical analysis because there were too few patients in the poor prognosis group, there was tendency for the regional KU value in these patients to worsen before chemolipiodolization. Regional LHL15 did not change before chemolipiodolization. Regional KU was thought to be a more sensitive index than regional LHL15 in the evaluation of the difference between regional liver function before and after chemolipiodolization. Regional KU and regional LHL15 in the poor prognosis group decreased not only in the embolized lobe but also in the non-embolized lobe. We considered that the effect of the hepatocyte growth factor was insufficient in these patients because of the reduction in hepatic functional reserve, and the marked toxicity of the anticancer drugs. It may be possible to postulate a poor outcome by means of these indices.

In conclusion, regional LHL15 and KU were considered to be useful indices in the evaluation of liver function and correlate closely with each other. Regional KU was thought to be a more sensitive index than regional LHL15 in evaluating of the changes in regional liver function before and after chemolipiodolization. Dynamic SPECT may be a useful method for quantitatively evaluating both the total and the regional function of the liver.

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