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Potential for qualitative diagnosis of tumors and tumorous lesions in the liver with Tc-99m-GSA SPECT —Correlation with pathological evaluation and MRI findings—

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To evaluate the effect of technetium-99m-labeled DTPA-galactosyl human serum albumin (Tc-99m-GSA) SPECT imaging for qualitative diagnosis of hepatic lesions.

The subjects were 29 patients with pathologically confirmed hepatic lesions (21 malignant and 8 benign lesions). SPECT data were obtained at about 30 minutes after injecting 185 MBq (5 mCi) of Tc-99m-GSA. The GSA SPECT findings were compared with those of pathological evaluation and T2-weighted MR images (T2WI).

Of 29 lesions, 17 showed decreased accumulation, and three exhibited increased accumulation. The other nine lesions were undetectable. The malignant lesions which showed increased accumulation were all well differentiated hepatocellular carcinomas (HCCs). One of the eight benign lesions exhibited increased accumulation. The three lesions which showed increased accumulation of GSA exhibited hypointensity on T2WI, whereas the malignant lesions which showed decreased accumulation of GSA exhibited hyperintensity on T2WI.

The GSA SPECT findings correlate well with those of T2WI. GSA SPECT may be useful for qualitative diagnosis of focal liver lesions. If a lesion is suspected of being HCC, increased accumulation may indicate well differentiated HCC.

Key words: liver, SPECT, MRI, hepatocellular carcinoma, Tc-99m DTPA-galactosyl human serum albumin

INTRODUCTION

TECHNETIUM-99m-labeled DTPA-galactosyl human serum albumin (Tc-99m-GSA) is a liver scintigraphic agent which binds specifically to asialoglycoprotein receptors (ASGPR) on the membrane of hepatocytes. It is mainly used for evaluating hepatic function,[1–4] and has the potential for use in the qualitative diagnosis of hepatic tumors on the basis of the presence or absence of normal hepatocytes in the lesions.[5–8] Several papers have reported that hepatocellular carcinoma (HCC) and metastatic liver tumors lack ASGPR on the cell membranes[9,10] and that Tc-99m-GSA SPECT consequently showed decreased accumulation in those tumors,[5,7,8,11] but there have been no reports of the use of Tc-99m-GSA SPECT imaging for the qualitative diagnosis of hepatic tumors, whereas magnetic resonance imaging (MRI) is useful for qualitative diagnosis of liver lesions. We compared the findings of Tc-99m-GSA SPECT with those of pathological evaluation and MRI, and evaluated the potential of Tc-99m-GSA SPECT imaging for qualitative diagnosis of hepatic tumors.

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MATERIALS AND METHODS

The subjects were 29 patients with hepatic lesions which were pathologically confirmed: 14 lesions by surgery, 14 by biopsy and one by autopsy. Surgery and biopsies were

Table 1 GSA findings for each lesion

Lesion	GSA SPECT findings		
	Increased	Decreased	Undetectable
HCC well differentiated	2 (30)	3 (46.7)	3 (15)
HCC moderately differentiated	0	2 (102.5)	0
Cholangiocellular carcinoma	0	2 (25)	0
Metastatic adenocarcinoma	0	4 (36.8)	3 (23.3)
Carcinoid tumor	0	2 (47.5)	0
Non-neoplastic lesion in alcoholic hepatitis	1 (40)	0	0
Chronic hepatitis or liver cirrhosis	0	0	5 (12.6)
Submassive necrosis	0	1 (30)	0
Angiomyolipoma	0	1 (30)	0
Total	3 (33.3: 25.0–40.0)	15 (46.5: 17.0–145.0)	11 (16.2: 5.0–40.0)

Numbers in parentheses are the mean size and range of the lesions (mm).

performed within 2 months of radionuclide studies and MRI. Of the 29 lesions, 21 were malignant lesions: 10 HCCs (8 well differentiated, 2 moderately differentiated), seven metastatic adenocarcinomas (all from colorectal carcinomas), two cholangiocellular carcinomas and two carcinoid tumors. The remaining eight lesions were benign and included five cases of chronic hepatitis or cirrhosis, one non-neoplastic lesion in alcoholic hepatitis, one angiomyolipoma and one submassive necrosis.

SPECT images were obtained with a rotating single head gamma camera (ZLC-DIGITRAC Orbiter, Shimadzu-Siemens, Kyoto, Japan) interfaced with a computer (SCINTIPAC-24000, Shimadzu, Kyoto, Japan). Immediately after the injection of 185 MBq (5 mCi) of Tc-99m-GSA (Nihon Medi-Physics, Nishinomiya, Japan) into an antecubital vein, dynamic acquisition over the heart and liver was performed for 30 minutes with the patients in the supine position to obtain sequential planar anterior images and generate time-activity curves for the heart and liver. The SPECT data were obtained in a matrix size of 64 × 64, in 64 views taken with 360° rotation, with 10 seconds imaging for each view.

MRI was performed with a 1.0 or 1.5 T superconductive Magnex (Shimadzu, Kyoto, Japan) in 24 cases. T1-weighted image (T1WI: TR 500 msec/TE 20 msec), T2-weighted image (T2WI: TR 2000 msec/TE 90 msec) and dynamic images (TR 200 msec/TE 9 msec, flip angle 60°) were obtained.

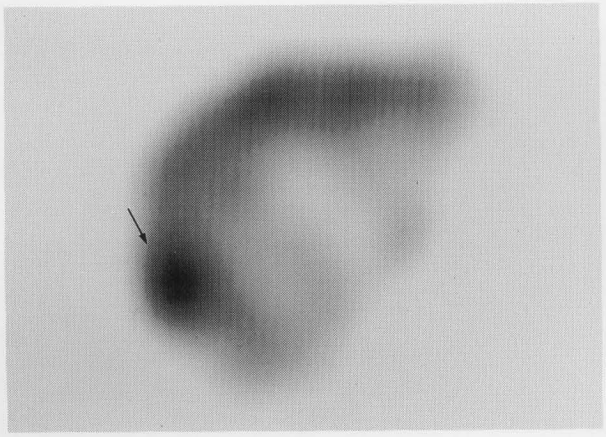
Lesion size was determined mainly with surgical specimens. In some unoperated cases, however, it was determined by MRI or ultrasonography (US). The largest diameter seen in these images was regarded as the lesion size.

The findings of Tc-99m-GSA SPECT were compared with those of pathological evaluation and MRI, especially T2WI. Statistical comparison of the detectable lesions and undetectable lesions was done by Student's t-test.

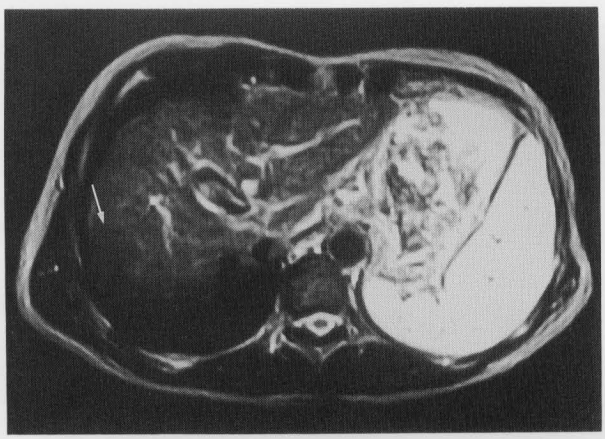
RESULT

Comparison with pathological findings

Table 1 shows the relationships between the Tc-99m-GSA SPECT findings and the pathological findings. Of the 29 lesions, 15 exhibited decreased accumulation and three showed increased accumulation. The other 11 lesions were undetectable. The mean size of the detectable lesions was 44.3 ± 29.2 mm (mean ± standard deviation), and that of the undetectable lesions was 16.2 ± 9.0 mm. A significant difference was found between the two groups ($p = 0.0047$). Regarding the 10 HCCs, five lesions (2 moderately differentiated, 3 well differentiated) showed decreased accumulation, but two well differentiated HCCs exhibited increased accumulation (Fig. 1). The other three well differentiated HCCs were not detected. Of the seven metastatic lesions, four showed decreased accumulation (Fig. 2) and the other three were not detected. All of the cholangiocellular carcinomas and carcinoid tumors exhibited decreased accumulation. Of the 21 malignant lesions, 13 (62%) showed decreased accumulation. The malignant lesions which exhibited increased accumula-



A



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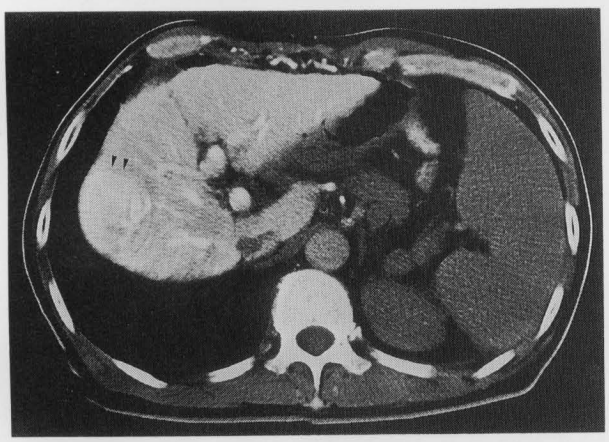
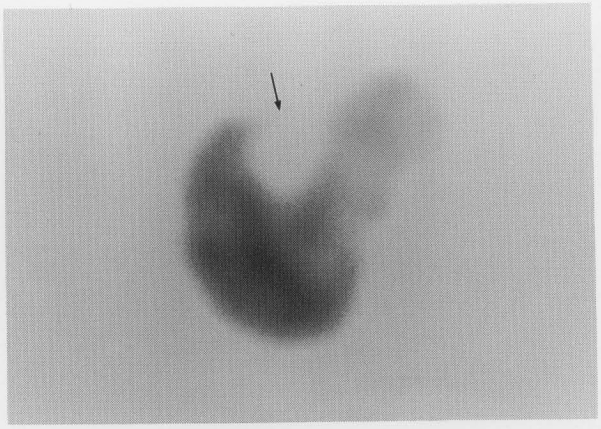


C

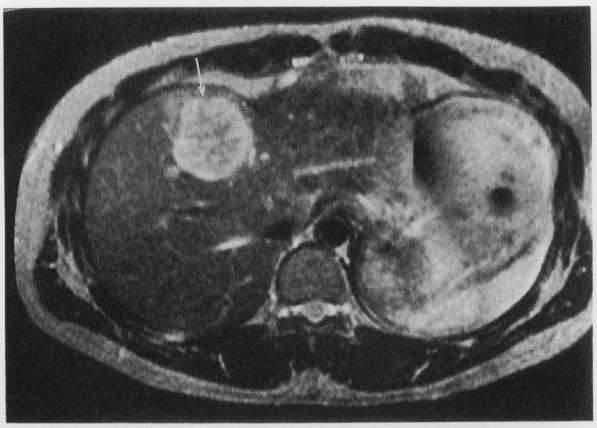
Fig. 1 Well differentiated HCC. A. GSA SPECT shows increased accumulation in segment VIII (arrow). B. The lesion exhibits hypointensity on the T2-weighted MR image (white arrow). C. CTAP shows increased portal perfusion (arrowheads).

tion were all well differentiated HCCs.

In the five cases of chronic hepatitis and cirrhosis, which were suspected of being HCC on US or CT, GSA SPECT was unable to detect any focal lesions. The final diagnoses of these lesions were confirmed to be non-



A



B

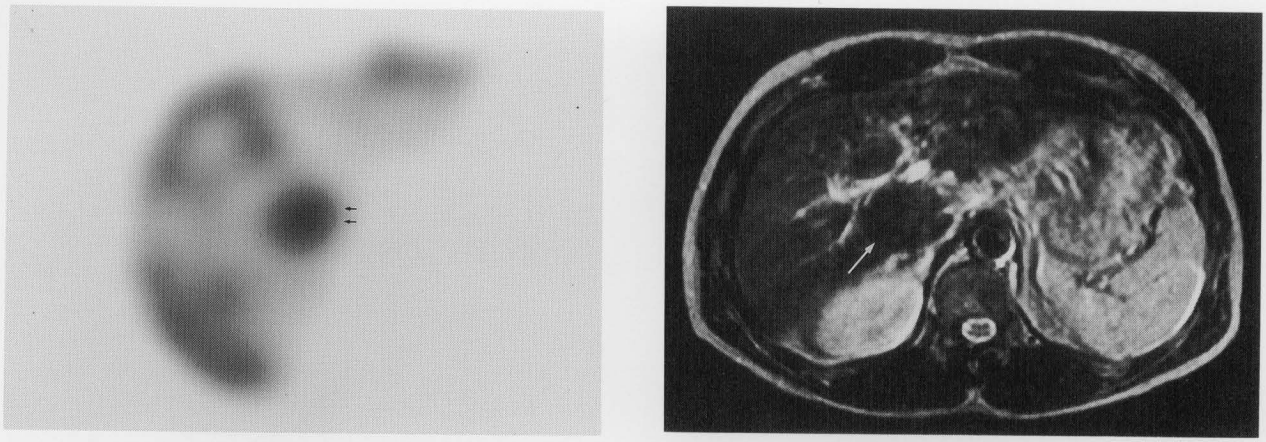
Fig. 2 Metastatic adenocarcinoma. A. GSA shows decreased accumulation in segment IV (arrow). B. T2-weighted MR image shows hyperintensity in segment IV (white arrow).

tumor lesions by biopsy.

One non-neoplastic lesion caused by alcoholic hepatitis showed increased accumulation (Fig. 3). This lesion was confirmed to be liver fibrosis by biopsy and was pathologically not different from the surrounding liver parenchyma. Two other benign lesions, i.e., angiomyolipoma and submassive necrosis, exhibited decreased accumulation. Of the eight benign lesions, one showed increased accumulation, two exhibited decreased accumulation and five were undetected. The size of the undetectable benign lesions was also significantly smaller than that of the detectable benign lesions.

Comparison with MRI findings

Tables 2 and 3 show the relationships between the Tc-99m-GSA SPECT findings and the MRI findings. Three lesions which showed increased accumulation of GSA exhibited hypointensity on T2WI and hyperintensity on T1WI (Fig. 1, Fig. 3). Regarding the well differentiated HCCs, the hypointense lesions seen with T2WI also exclusively exhibited increased accumulation of GSA (Table 4). CT during arterial portography (CTAP) was



A B

Fig. 3 Non-neoplastic lesion in alcoholic hepatitis. A. GSA SPECT shows increased accumulation in the caudate lobe (arrows). B. The lesion exhibits hyperintensity on T1-weighted and hypointensity on T2-weighted MR image (white arrow).

Table 2 MRI T2WI findings for each lesion

Lesion	GSA SPECT findings		
	Increased	Decreased	Undetectable
HCC well differentiated	low, low	high, high, high	poor, high, iso
HCC moderately differentiated	0	high, (–)	0
Cholangiocellular carcinoma	0	high, high	0
Metastatic adenocarcinoma	0	high, high, (–), (–)	high, iso, (–)
Carcinoid tumor	0	high, high	0
Non-neoplastic lesion in alcoholic hepatitis	low	0	0
Chronic hepatitis or liver cirrhosis	0	0	iso, iso, iso, iso, (–)
Submassive necrosis	0	poor	0
Angiomyolipoma	0	high	0
Total	3	11	8

high: hyperintensity; iso: iso intensity; low: hypointensity; poor: impossible to evaluate because of poor image; (–): not performed. The total number excluded poor cases.

Table 3 MRI T1WI findings for each lesion

Lesion	GSA SPECT findings		
	Increased	Decreased	Undetectable
HCC well differentiated	high, high	low, high, high	poor, high, high
HCC moderately differentiated	0	low, (–)	0
Cholangiocellular carcinoma	0	low, low	0
Metastatic adenocarcinoma	0	low, low, (–), (–)	low, low, (–)
Carcinoid tumor	0	low, low	0
Non-neoplastic lesion in alcoholic hepatitis	high	0	0
Chronic hepatitis or liver cirrhosis	0	0	high, high, high, iso, (–)
Submassive necrosis	0	poor	0
Angiomyolipoma	0	high	0
Total	3	11	8

high: hyperintensity; iso: iso intensity; low: hypointensity; poor: impossible to evaluate because of poor image; (–): not performed. The total number excluded poor cases.

Table 4 Correlation of GSA SPECT findings with MRI T2WI findings in well differentiated HCCs

MRI T2WI finding	GSA SPECT finding	
	Increased	Decreased
Hypointensity	2	0
Hyperintensity	0	3

performed in one of the two well differentiated HCCs which showed increased accumulation of GSA, and this disclosed hyperperfusion of the lesion (Fig. 1).

The malignant lesions which showed decreased accumulation of GSA exhibited hyperintensity on T2WI.

Of the eight lesions undetectable by GSA SPECT but evaluable by MRI, four lesions (50%) exhibited isointensity on T2WI and hyperintensity on T1WI. Biopsy confirmed three of these four lesions to be non-tumorous.

DISCUSSION

TC-99m-GSA has been used mainly for evaluating liver function.[2–4] There have been a few reports evaluating the use of this scintigraphic agent for qualitative diagnosis of hepatic focal lesions.[12] Because this scintigraphic agent binds specifically to ASGPR on the membrane of hepatocytes, evaluating the presence of hepatocytes in hepatic lesions offers the potential for qualitative diagnosis of the lesions.[5–8,11]

In this study, detectable lesions were significantly larger than undetectable lesions. SPECT imaging has been demonstrated to have poorer spatial resolution than other imaging procedures, such as US, CT and MRI. An earlier report pointed out that the rate detection of lesions smaller than 20 mm by SPECT is not very good,[13] and severe liver dysfunction makes the accumulation of scintigraphic agents in the hepatic parenchyma heterogeneous and consequently makes the detection of lesions difficult.

As another possibility, undetectable lesions might accumulate GSA equally with the surrounding liver, resulting in their escaping detection. Concerning the relationship with MR findings, 50% of the lesions which were undetectable with GSA SPECT showed isointensity on T2WI and hyperintensity on T1WI. This MR finding indicates that the lesions are adenomatous hyperplasia or early HCC, including well differentiated HCC.[14] GSA might accumulate these lesions equally with the surrounding liver parenchyma, probably because these lesions have ASPGR.[6]

Decreased accumulation suggests the absence of or a decrease in the number of normal hepatocytes.[8] All these lesions exhibited hyperintensity on T2WI. This MR finding is not specific to tumors, and it indicates the lesions are pathologically different from the surrounding liver parenchyma.

Three lesions exhibited increased accumulation of GSA. There might be two causes for this phenomenon. Well differentiated HCC is thought to have normally functioning hepatocytes and increased cellularity of the lesions, which causes increased accumulation of GSA. In fact, well differentiated HCC has been reported to show increased accumulation of GSA.[15] Hyodo et al. reported several well differentiated HCCs having ASGPR.[6] In the present study, these lesions exhibited hypointensity on T2WI, which indicates adenomatous hyperplasia or well differentiated HCC.[14,16,17] The pathological findings of these two lesions are similar: increased cellularity with or without structural atypia is recognized in both lesions.[18] From this viewpoint, it is expected that adenomatous hyperplasia also exhibits increased accumulation of GSA, but because the rate of cellularity in these two entities is different,[18] the accumulation also might be different. In this study, adenomatous hyperplasia was not detected. More experience is necessary to distinguish well differentiated HCC from adenomatous hyperplasia.

Another benign lesion also exhibited hypointensity on T2WI. Its GSA SPECT findings support hypercellularity. But when compared with the surrounding liver tissue, no specific finding was observed pathologically. Because the diagnosis was made by biopsy, only a portion of the lesion was evaluated; therefore, a precise pathological evaluation may not have been made. Pseudolesions are sometimes observed in the anterior portion of the medial segment and caudate lobe when using CTAP, and hyperplastic lesions arise in these lesions.[19,20] In earlier reports, these hyperplastic lesions showed hyperintensity on T1WI and hypointensity on T2WI. The lesion we examined showed similar intensity to those reported cases. During radiological diagnosis, a hyperplastic lesion was suspected. If a biopsy were able to show the character of the entire lesion, another reason for the increased accumulation might be able to be speculated.

The second cause of the increased accumulation may be increased blood perfusion. CTAP was performed in only one case of well differentiated HCC, and it confirmed increased portal blood flow. Previous reports discussed the accumulation seen in GSA as mainly being influenced by ASGPR, but there was no discussion of the blood flow.[1,3] If increased focal blood flow were maintained, increased accumulation might also occur.

In conclusion, GSA SPECT may be useful for achieving qualitative diagnosis of focal liver lesions as well as liver function. The findings of GSA SPECT correlate well with those of T2WI. Increased accumulation predicts hypercellularity and/or hyperperfusion of the lesions. If a lesion is suspected of being HCC, increased GSA accumulation may predict a well differentiated HCC.

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