

Technetium-99m-DTPA-Galactosyl Human Serum Albumin Liver Scintigraphy Evaluation of Regional CT/MRI Attenuation/Signal Intensity Differences

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Regional attenuation/signal intensity differences seen on CT/magnetic resonance imaging can be a clue in detecting regional hepatic blood flow abnormality. Sometimes, however, they can be misinterpreted as a hepatic neoplasm or, in the case of a true neoplasm, they can lead to an overestimation of its size because these regions often have similar attenuation or signal intensity to hepatic neoplasms. We evaluated ^{99m}Tc -diethylenetriaminepentaacetic acid-galactosyl human serum albumin (^{99m}Tc -DTPA-GSA) liver scintigrams in patients manifesting regional attenuation/signal intensity differences to further analyze the findings. **Methods:** Technetium-99m-DTPA-GSA scintigrams of 23 patients with regional attenuation/signal intensity differences in the liver at dynamic contrast-enhanced CT/magnetic resonance imaging were evaluated. The causes of the differences were arterioportal (AP) shunts in seven patients, decreases in the portal venous flow in seven patients, occlusion of right hepatic vein in one patient, confluent hepatic fibrosis in one patient and unknown in seven patients. The accumulation of ^{99m}Tc -DTPA-GSA was compared with each known cause of attenuation/signal intensity difference. Count ratios of the regions to normal hepatic parenchyma also were calculated in all cases. **Results:** In AP shunts, none of seven patients showed any decreased accumulation in the region. Accumulation of ^{99m}Tc -DTPA-GSA decreased in six of seven patients who had decreases in portal venous flow; this incidence was significantly higher than that in patients who had AP shunts ($p < 0.005$). In cases of unknown cause, two of seven patients showed a decrease in accumulation, but the other five showed no such decrease. The one patient with occlusion of the right hepatic vein showed no decrease, but the confluent hepatic fibrosis showed a significant decrease. The count ratio in AP shunts was significantly larger than that of the decrease in the portal venous flow ($p < 0.005$). **Conclusion:** Technetium-99m-DTPA-GSA accumulation in AP shunts has a different pattern from that found in patients with a decrease in portal venous flow. Therefore, differentiation between AP shunts, which showed no decrease in ^{99m}Tc -DTPA-GSA accumulation, and hepatic neoplasms can be made more easily.

Key Words: liver; radionuclide studies; technetium-99m-DTPA-GSA; regional attenuation/signal intensity differences

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On CT and MRI, regional attenuation/signal intensity inhomogeneities in the liver have been reported. Most of these are caused by regional hepatic blood flow abnormalities, such as decreases in the portal venous flow and/or arterioportal (AP) shunts (1-3). Recently, whole-liver dynamic CT and MRI have become available and have proven useful for screening hepatic tumors, especially hypervascular tumors, such as hepatocellular carcinoma (4,5). On these images, we often encounter regional enhancement in the arterial phases. These regional attenuation/signal intensity differences can be clues for detecting regional hepatic blood flow abnormality, but they are sometimes misin-

terpreted as a hepatic neoplasm or they may lead to overestimation of the size of the neoplasm because these regions often have similar attenuation or intensity to hepatic neoplasms. Technetium-99m-diethylenetriaminepentaacetic acid-galactosyl human serum albumin (^{99m}Tc -DTPA-GSA) is a newly developed analog ligand to asialoglycoprotein receptor. Uptake of ^{99m}Tc -DTPA-GSA depends on the presence of normally functioning hepatocytes. This hepatocyte-oriented radioligand is used not only for hepatic radionuclide imaging but also for assessing liver function by analysis of the dynamic pattern of hepatic accumulation (6-8). Most hepatic neoplasms, except for some tumor-like conditions, such as focal nodular hyperplasia (9), show an accumulation defect on hepatocyte-oriented scintigraphy (10). A case of hepatocellular carcinoma in which ^{99m}Tc -DTPA-GSA was superior to ^{99m}Tc -pyridoxylated-5-methyl-tryptophan for clear depiction of accumulation defect also was reported (11). As for nontumor-related decrease in ^{99m}Tc -DTPA-GSA accumulation, there was a case report of localized decrease in accumulation due to segmental biliary obstruction (12). But there have been no detailed reports on accumulation of ^{99m}Tc -DTPA-GSA in regions of attenuation/signal intensity differences in the liver. We performed ^{99m}Tc -DTPA-GSA liver scintigraphy on patients with hepatic regional attenuation/signal intensity differences to further analyze these differences.

MATERIALS AND METHODS

Patients

Twenty-three patients (20 men, 3 women; age range 45-77 yr; mean age = 60 yr) who showed regional attenuation/intensity differences in at least one CT/MR scan had ^{99m}Tc -DTPA-GSA liver scintigraphy. It was arranged that the regions of attenuation/signal intensity differences should be larger than 2 cm in diameter, in deference to the sensitivity of SPECT for hepatic tumors (13). Fifteen patients had hepatocellular carcinomas and four had metastatic liver tumors. One patient had a pyogenic abscess. In the other three patients, the abnormalities in the hepatic parenchyma were not accompanied by hepatic masses. Causes of the differences in attenuation/signal intensity were, at some stage, determined by: angiograms; some CT findings, such as obvious portal venous thrombus (for decrease in the portal venous flow), opacification of portal venous branch in the arterial phase of dynamic study (for AP shunts) and so on; and surgery. These causes were AP shunts in seven of the patients, decreases in the portal venous flow in seven patients, stenosis of the right hepatic vein due to metastatic tumor in one patient and confluent hepatic fibrosis (14) in one patient, but in seven patients, the causes could not be clarified.

Imaging Techniques

CT images were obtained on a helical scanner. Precontrast scanning was done with 10-mm collimation and a table speed of 10 mm/sec. One hundred milliliters of 300 mg/ml iodine contrast

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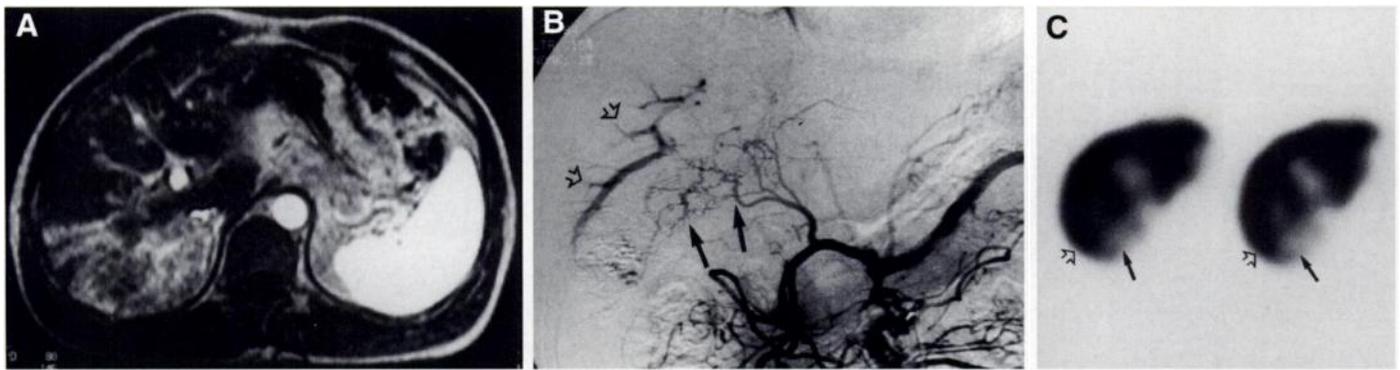


FIGURE 1. A 47-yr-old man with hepatocellular carcinoma. (A) Dynamic MRI shows enhancement in the posterior half of the right hepatic lobe, which suggests hypervascular tumor or AP shunt or both. (B) Hepatic arteriogram shows irregular vascular neoformation (arrows) in the right lobe, which indicates hepatocellular carcinoma and obvious AP shunting lateral to the tumor (open arrows). The enhancement on dynamic MRI proved to be hepatocellular carcinoma in the center and AP shunt in the periphery. (C) Transaxial SPECT images show decreased accumulation on hepatocellular carcinoma (arrows) and spared accumulation in the corresponding region of the AP shunt (open arrows).

material were administered at a rate of 3 ml/sec with a power injector. Triphasic whole-liver helical CT scans (with arterial, portal and equilibrium phases) were performed within a single held breath. Scans were done with 7-mm collimation and a table speed of 7 mm/sec at 30, 60 and 180 sec after initiating intravenous administration of the contrast material. Four serial scans (precontrast, arterial, portal and equilibrium phases) were evaluated.

MRI was performed using a 1.5-T scanner. Conventional T1-weighted spin-echo images [repetition time = 600 msec and echo time = 15(600/15)] and proton density/T2-weighted spin-echo images (2000/22-90) were obtained. After a manual bolus injection of 0.1 mmol/kg gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany), whole-liver dynamic MRI was performed with multisection fast low-angle shot (120-165/4; flip angle = 80°). Thirteen to 18 serial sections of the whole liver were obtainable within a single held breath. In a similar manner to helical CT, triple phases of whole-liver dynamic MRI were done at 25, 60 and 120 sec after administering the contrast material. Finally, postcontrast T1-weighted spin-echo images were obtained with the same sequence as the first scan. Six serial scans (T1-weighted/T2-weighted spin-echo images, triple phases of dynamic study and postcontrast T1-weighted images) were evaluated.

The patients fasted on the morning of ^{99m}Tc -DTPA-GSA liver scintigraphy. They were examined in the supine position with a dual-head rotating gamma camera interfaced to a minicomputer (model GCA7200A/DI; Toshiba, Tokyo, Japan). A parallel-hole, low-energy, high-resolution collimator was used. Immediately after intravenous administration of 185 MBq ^{99m}Tc -DTPA-GSA (Nihon Medipysics, Nishinomiya, Japan), dynamic images were acquired for 30 min. After dynamic imaging, SPECT was performed by the acquisition of 60 projection images over a 360° angle in a 128 × 128 matrix. Reconstruction for transaxial, coronal and sagittal sections of 6.9-mm thickness was done. A Chang attenuation correction was applied. Finally, serial sets of static planar views in the anterior, posterior, right lateral and right and left anterior oblique projections were obtained up to each preset count of 900,000.

Evaluation

Three side-by-side experienced readers evaluated the results and consensus was obtained. First, the readers investigated the regions of attenuation/signal intensity differences on CT/MRI, especially concerning their sites and sizes. Then they evaluated ^{99m}Tc -DTPA-GSA liver scintigrams (planar and SPECT images) for the presence of a significant decrease in accumulation in the corresponding regions. The incidences of significant decrease in accumulation for each cause were calculated and compared.

As a quantitative analysis, a comparison between counts in the regions of attenuation/signal intensity differences and the other normal hepatic parenchyma was performed in all cases. Count ratios were calculated by dividing the average counts of ROIs interest in the regions of attenuation/signal intensity differences by the average counts of ROIs in the normal hepatic parenchyma in the same transaxial section of SPECT.

Statistical Analysis

The incidence of decreased accumulation for each cause was analyzed by chi-square test. For comparison of count ratios, the unpaired Student's t-test was used. Probability values of <0.05 were regarded as significant.

RESULTS

A significant decrease in ^{99m}Tc -DTPA-GSA accumulation was seen in 9 of 23 patients. In the AP shunts, none of the seven patients showed any decreased accumulation (Fig. 1). With decrease in the portal venous flow, decreased accumulation (Fig. 2) was seen in six of seven patients. This indicated that AP shunts did not show any decrease in ^{99m}Tc -DTPA-GSA accumulation, whereas a decrease in the portal venous flow did show this ($p < 0.005$). In cases of unknown cause, two of seven patients showed a decrease in accumulation, but the other five did not. In two of these five patients, there were differences accompanied by metastatic liver tumors, and in one patient, the difference was concomitant with hepatocellular carcinomas. The other two regions were not accompanied by hepatic masses. The one patient with occlusion of the right hepatic vein did not show decreased accumulation. The patient with confluent hepatic fibrosis showed a significant decrease in accumulation.

Count ratios were 0.91 ± 0.12 in AP shunts, 0.53 ± 0.25 with decreases in the portal venous flow and 0.83 ± 0.17 in cases with unknown causes. Count ratios in AP shunts and in cases with unknown causes were larger than those with decreases in the portal venous flow ($p < 0.005$ and $p < 0.05$, respectively) (Fig. 3).

DISCUSSION

When Inamoto et al. (1) first reported CT findings of hepatocellular carcinomas associated with obstruction of branches of the portal vein in 1981, the corresponding segment showed hypoattenuation on precontrast CT. In 1986, Itai et al. (2) reviewed the dynamic CT features of 42 patients with hepatocellular carcinoma having angiographically proven AP shunts with respect to the parenchymal attenuation. Transient high attenuation of lobar or segmental distribution in the lobe

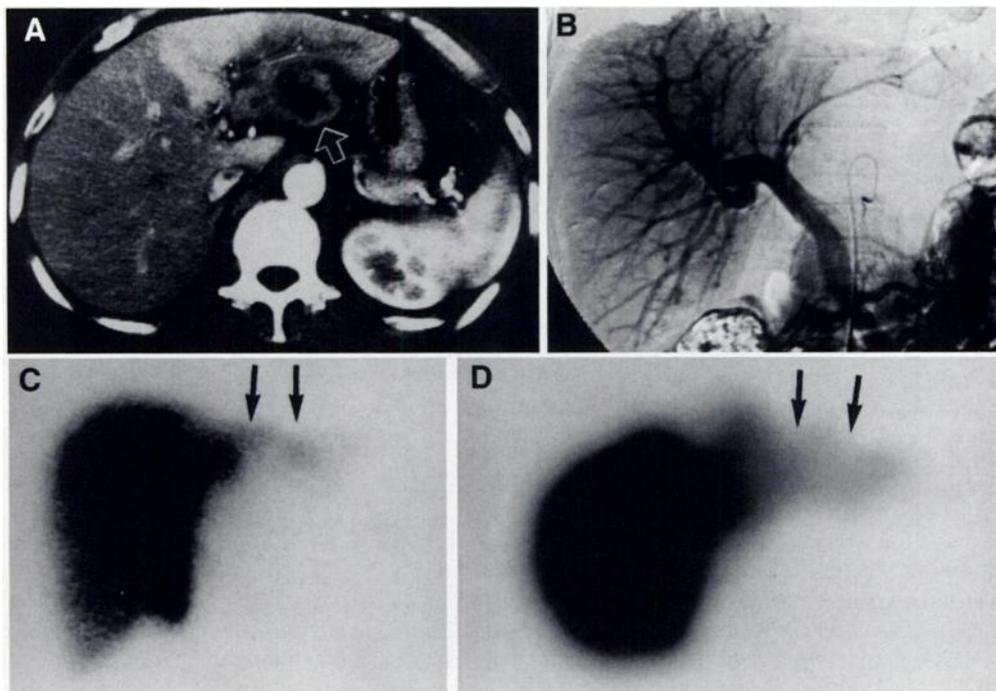


FIGURE 2. A 63-yr-old man with stenosis of the left portal branch due to pyogenic hepatic abscess. (A) Dynamic CT shows enhancement of the entire left lobe of the liver in the arterial phase. Note the abscess in the central portion of left lateral segment (arrow). (B) A portogram through the superior mesenteric artery shows stretching and stenosis of the left portal branch due to abscess. Portal venous perfusion is decreased in the left lobe. (C and D) Anterior view and transaxial SPECT images show decreased ^{99m}Tc -DTPA-GSA accumulation in the left lobe (arrows).

contralateral to the main tumor, and transient wedge-shaped enhancement peripheral to the tumor were findings typical of AP shunts. In 1988, Itai et al. (3) reported six cases with segmental intensity differences in the liver on MRI as a sign of intrahepatic portal venous obstruction. These findings of hepatic parenchyma can be a clue in detecting regional hepatic blood flow abnormality, but new diagnostic problems have occurred in which these findings are sometimes misinterpreted as hepatic neoplasm or lead to overestimation of the size of a neoplasm adjacent to the region.

We noticed the accumulation pattern of ^{99m}Tc -DTPA-GSA, which depends on the amount of asialoglycoprotein receptor, i.e., on the number of normally functioning hepatocytes. We decided to use this radioligand for analyzing attenuation/signal intensity differences.

Arterioportal shunts in the liver are common causes of regional attenuation/signal intensity differences. In this study, the region corresponding to AP shunts showed no significant decrease in accumulation. In AP shunts, the total amount of regional blood flow does not decrease, and regional enhancement in the arterial phase of dynamic study is the only finding of CT and MRI (15). Precontrast CT and conventional MRI demonstrate no attenuation/signal intensity difference. With AP shunts, functional damage of hepatocytes in the region tends not to occur easily, and accumulation of ^{99m}Tc -DTPA-GSA remains unaffected.

A decrease in portal venous flow is also a common cause of these regional differences. Portal venous compression and tumor thrombosis of hepatocellular carcinoma are the most common causes of a decrease in the portal venous flow. When this flow decreases, arterial blood flow compensates for the decrease. Hence, regionally increased enhancement is shown in the arterial phase of the dynamic study, as with the AP shunts. Histologically, edema, depletion of hepatocytes or fibrosis occurs, probably because full compensation by arterial blood flow cannot be completely achieved (15). In some cases, mild hemorrhagic infarction (Zahn's infarction) occurs in the region. Lobar atrophy due to portal vein obstruction also was reported (16). Precontrast CT shows regional hypoattenuation (1) and MRI shows regional abnormal signal. The T1-weighted spin-echo image demonstrates iso- or hypointensity, and the T2-weighted image shows hyperintensity (3). In this study, accumulation of ^{99m}Tc -DTPA-GSA decreased in the region of decreased portal venous flow. This may indicate that normally functioning hepatocyte numbers decreased in line with the histological changes mentioned above.

Results in cases with unknown causes were intermediate between AP shunts and portal venous flow decrease. These cases probably included AP shunts and/or decrease in portal

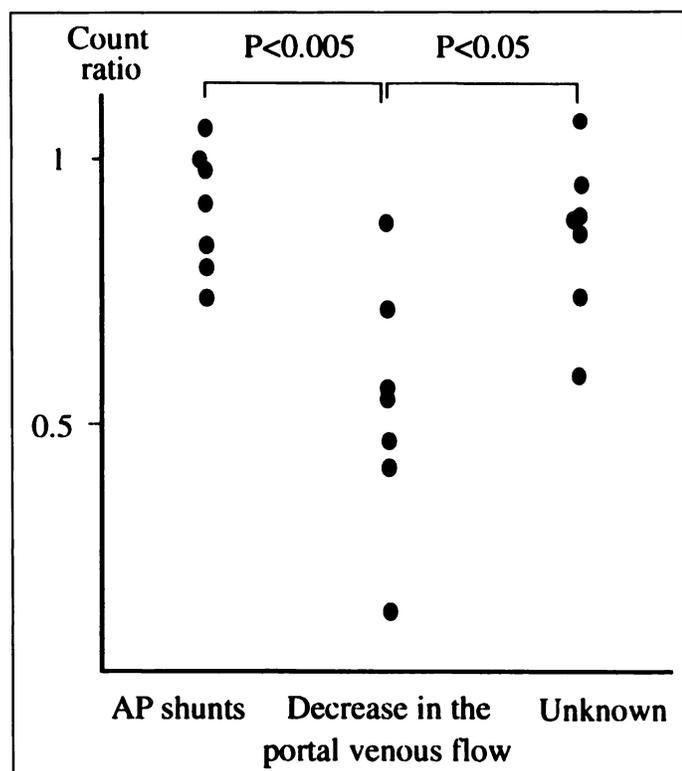


FIGURE 3. Count ratios in cases with AP shunts, in cases with decrease in the portal venous flow and in cases with unknown causes.

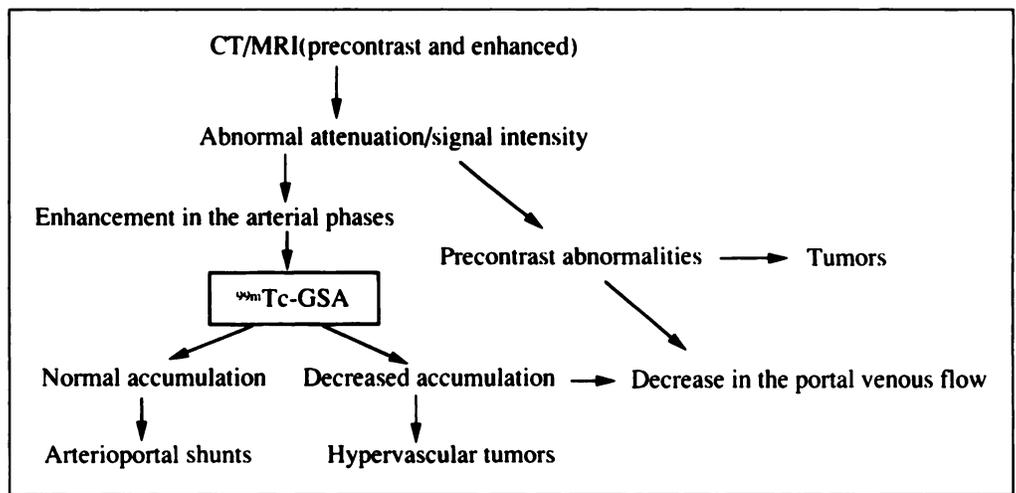


FIGURE 4. A new diagrammatic approach with ^{99m}Tc -DTPA-GSA scintigraphy to the work-up of attenuation/signal intensity abnormalities in the liver is suggested.

venous flow, which could not be proven. This could be why the results were intermediate.

There was no significant decrease in accumulation of ^{99m}Tc -DTPA-GSA in the patient with hepatic venous occlusion due to metastatic liver tumor, but the general tendencies of ^{99m}Tc -DTPA-GSA accumulation in occlusion of the hepatic vein cannot be determined by just this one case. A decrease in ^{99m}Tc -DTPA-GSA accumulation in this condition may have been expected, considering the pathophysiology of Budd-Chiari syndrome. In one case of confluent fibrosis in liver cirrhosis, the region of fibrosis showed decrease in ^{99m}Tc -DTPA-GSA accumulation. In this region, it is known that portal venous flow decreases and hepatic arterial flow increases slightly (15). Normally functioning hepatocyte numbers in this fibrous region may decrease, and ^{99m}Tc -DTPA-GSA accumulation also may decrease accordingly.

In this study, ^{99m}Tc -DTPA-GSA accumulation decreased in the region corresponding to portal venous flow decrease but not in the regions corresponding to AP shunts. It can be suggested that discrimination between AP shunts and decrease in the portal venous flow might be possible by observing accumulation patterns of ^{99m}Tc -DTPA-GSA. What should be emphasized in this article is the real possibility of discriminating between AP shunts (in which significant decrease in ^{99m}Tc -DTPA-GSA accumulation does not occur) and hepatic neoplasms.

Recently, whole-liver dynamic CT/MRI has proven useful for screening hepatic tumors, especially hypervascular tumors such as hepatocellular carcinoma. Therefore, they are routinely performed in many institutions. With these imagings, small hepatocellular carcinomas that only show enhancement in the arterial phase of dynamic study and isoattenuation or iso-intensity on the other scans are often detected. AP shunts also show enhancement of the corresponding region in the arterial phase. Typically, the enhancing regions in the AP the shunt are wedge-shaped and located peripherally. When the enhancing regions in AP shunts are round-shaped or located centrally, discrimination between AP shunts and hepatocellular carcinomas is often difficult. Even on angiograms, these two different conditions often can be indistinguishable if obvious opacification of the portal venous branch in the arterial phase (definite finding of AP shunt) is not seen. Even on CT during arterial portography, they are indistinguishable from the findings of localized portal perfusion defect. On these occasions, discreet course observation is the sole method of dealing with them, and there is no known constructive diagnostic procedure.

In this study, AP shunts were proven not to decrease accumulation of ^{99m}Tc -DTPA-GSA. On the other hand, ^{99m}Tc -DTPA-GSA accumulation decreases on most hepatic tumors, including hepatocellular carcinoma. These scintigraphic findings can be used to distinguish these two conditions, although it is probably not applicable to changes smaller than 2 cm in diameter because of the limited spatial resolution of SPECT. We now suggest a new diagrammatic approach with ^{99m}Tc -DTPA-GSA liver scintigraphy to the work-up of attenuation/signal intensity abnormalities in the liver (Fig. 4).

CONCLUSION

Technetium- ^{99m}Tc -DTPA-GSA accumulation in AP shunts has a different pattern from those found in patients with a decrease in the portal venous flow. Differentiation can be expected between AP shunts, which do not show any decrease in ^{99m}Tc -DTPA-GSA accumulation, and hypervascular tumors.

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