Uptake of Tc-99m Di-isopropyliminodiacetic Acid by Hepatocellular Carcinoma: Concise Communication

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Uptake of Tc-99m di-isopropyliminodiacetic acid (DISIDA) by hepatocellular carcinoma was assessed in 30 patients showing obvious liver defects on a Tc-99m tin colloid image. In none of these patients was there complete "filling in" of the defects, and even partial "filling in" occurred in only 11 (36.7%). There was no uptake of Tc-99m DISIDA by the primary tumor in the remaining 19 patients (63.3%). In 19 of the 30 patients an attempt was made to correlate the degree of histologic differentiation of the tumor with the uptake of DISIDA by the tumor. No difference in uptake could be demonstrated between well, moderately, and poorly differentiated tumors. Tc-99m DISIDA was not taken up by pulmonary metastases in the only two patients tested. We conclude that imaging with Tc-99m DISIDA in conjunction with Tc-99m colloid is of no value in the specific diagnosis of hepatocellular carcinoma.

J Nucl Med 24: 1119–1122, 1983

Although Tc-99m tin colloid imaging will almost always show the presence of one or more defects in the liver in patients with hepatocellular carcinoma (HCC) (*1*,*2*), the images obtained are not diagnostic. Various radionuclides that are taken up by normal hepatocytes and might therefore be expected to be concentrated by HCC have been used in an attempt to increase the diagnostic accuracy of liver scintigraphy in HCC, but thus far have proved to be of limited value (*3–6*). The search continues for an agent that will improve the diagnostic capability of liver imaging in HCC. Recently, two case reports have hinted that hepatobiliary imaging agents might be useful in this regard. In the first, pulmonary metastases from a well-differentiated HCC concentrated Tc-99m *p*-isopropyliminodiacetic acid (PIPIDA) (*7*); in the second, the primary tumor took up Tc-99m pyridoxylidene isoleucine (*8*). In order to assess the uptake of hepatobiliary imaging agents by HCC, we have performed Tc-99m di-isopropyliminodiacetic acid (DISIDA) images in 30 patients with HCC who showed one or more obvious defects on a Tc-99m tin colloid image.

Received May 10, 1983; revision accepted June 27, 1983.

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PATIENTS STUDIED AND METHODS

Anterior, posterior, and right and left lateral images were recorded with a scintillation camera 15–20 min after an intravenous injection of 3–5 mCi (110–185 MBq) of Tc-99m tin colloid. Images were recorded with a low-energy, medium-resolution, parallel-hole collimator, 300,000 counts per image. After an interval of at least 24 hr, anterior and right lateral scans were recorded 30, 45, and 60 min after an intravenous injection of 3–5 mCi of Tc-99m DISIDA, containing 2 mg of DISIDA. The images obtained with the two agents were compared with respect to the uptake of Tc-99m DISIDA in the defect or defects present on the colloid study. Simple visual comparisons were made by two of the authors without any attempt at formally measuring the differences in concentration, and the results were expressed as complete, partial, or no uptake of DISIDA in the defects.

Multiple large pulmonary metastases were present in two of the patients. We took the opportunity to find out whether these metastases would take up Tc-99m DISIDA.

The patients studied comprised 30 southern African Blacks with histologically proved HCC. All but three of the patients were males, with ages ranging from 22 yr to

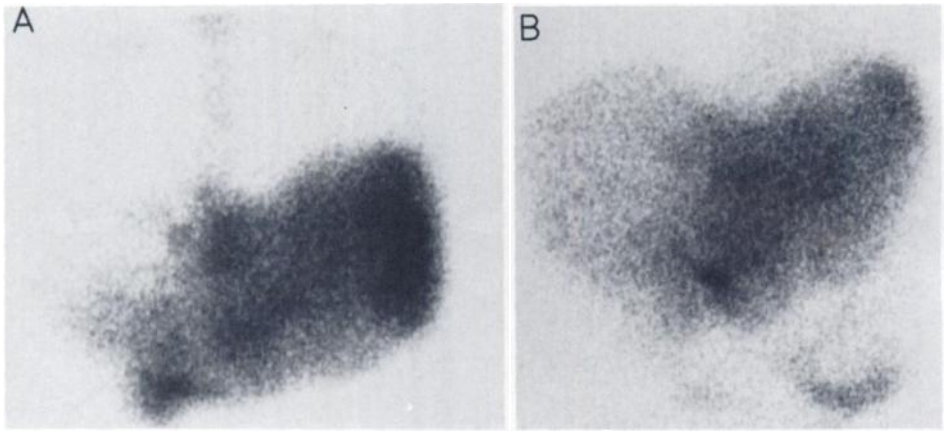

FIG. 1. Hepatocellular carcinoma: Defect, caused by tumor, is seen in right lobe of liver in Tc-99m tin colloid image (A). Same area shows partial uptake of Tc-99m DISIDA (B), with some also seen in bowel.

70 yr (mean 30.1). Alpha-fetoprotein was present in high concentration (>500 ng/ml) in the sera of 26 of the 30 patients (86.7%). All the patients had advanced disease, with large tumor burdens and evidence of muscle wasting. In 19 of the cases, histologic slides from liver biopsies were available for examination. In these patients the degree of histologic differentiation of the tumors was assessed by two of the authors who were unaware of the scintigraphic findings. An attempt was then made to correlate the degree of histologic differentiation with the scintigraphic findings.

RESULTS

In none of the HCC patients was there complete "filling in" of the defects seen on the colloid image. Partial "filling in," indicating some uptake of Tc-99m DISIDA in the tumor, occurred in 11 patients (36.7%) (Fig. 1). In the remaining 19 patients (63.3%) the colloid and DISIDA studies were identical i.e., there was no visible uptake of DISIDA by the tumor (Fig. 2). The relationship between the degree of histologic differentiation of the tumors and the uptake of DISIDA by 19 of the tumors is shown in Table 1. Well- or moderately differentiated tumors were no more likely to concentrate DISIDA than poorly differentiated tumors.

The pulmonary metastases present in two of our patients did not take up Tc-99m DISIDA.

DISCUSSION

Various radionuclides have been used in an attempt to increase the value of hepatic scintigraphy in the specific diagnosis of HCC. Selenomethionine (Se-75) is concentrated by normal hepatocytes, and early reports suggested that uptake of this radionuclide by HCC approached that of normal liver (*9,10*). Unfortunately, false-negative results were soon recorded in as many as 50% of patients (*3*), and occasional "false-positive" results also occurred (*10*). Gallium-67 citrate is selectively

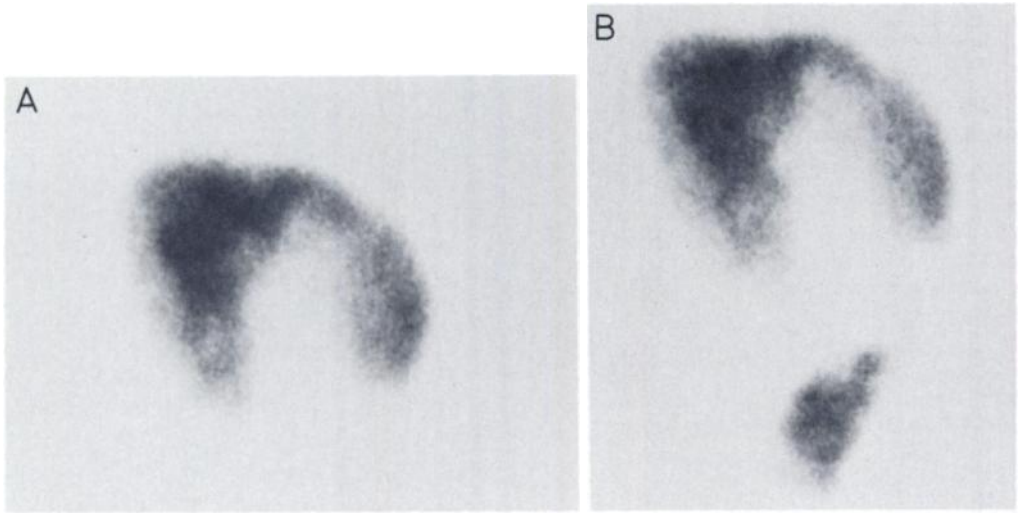

FIG. 2. Tc-99m tin colloid (A) and Tc-99m DISIDA (B) images in patient with hepatocellular carcinoma abscess appear identical. Tc-99m DISIDA uptake seen in bowel in (B).

TABLE 1. FAILURE OF CORRELATION BETWEEN UPTAKE OF Tc-99m DISIDA BY HEPATOCELLULAR CARCINOMA AND DEGREE OF HISTOLOGIC DIFFERENTIATION OF THE TUMOR

	Partial uptake	No uptake
Well-differentiated	2	4
Moderately differentiated	2	4
Poorly differentiated	2	5

concentrated in HCC but not in cirrhotic "pseudotumors." This radionuclide was therefore expected to be of value in the recognition of HCC occurring in a cirrhotic liver (*4*,*11*). However, in a study of patients with HCC coexisting with cirrhosis, one third of the defects caused by the tumor failed to concentrate Ga-67, and may have been wrongly attributed to cirrhosis (*5*). Isolated reports of selective uptake of cobalt-57 bleomycin in HCC prompted the use of this radiopharmaceutical as a tumor-seeking agent. It proved to be of limited value because selective concentration occurred in only 31% of patients (*6*).

Radionuclides used for hepatobiliary imaging are taken up by normal hepatocytes and excreted into bile. Malignant hepatocytes, particularly when well-differentiated, might be expected to have retained this property. Certainly, some HCCs retain the ability to secrete bile. If this were so, hepatobiliary imaging might be used in conjunction with colloid imaging in the specific diagnosis of HCC. In only about one third of our patients did some uptake of Tc-99m DISIDA by the tumor occur, and this was never enough to obliterate the defect or defects seen on the colloid image. It might have been anticipated that uptake would be more likely to occur with well- or moderately differentiated tumors than with poorly differentiated tumors. Our analysis showed, however, that there was no correlation between the degree of differentiation and the uptake of DISIDA by HCC. Of interest in this regard is the report of uptake of Tc-99m PIPIDA by pulmonary metastases from HCC (*7*), because the well-differentiated primary tumor in this case failed to concentrate the radionuclide. If concentration of Tc-99m DISIDA were dependent upon the ability of the malignant hepatocytes to produce bile, then only a small proportion of the tumors would be expected to give a positive result.

Even partial uptake of Tc-99m DISIDA in the defects seen on a colloid image does not necessarily indicate the presence of HCC. This tumor frequently coexists with cirrhosis, which is present in 60% of southern African Blacks with HCC and is known to produce defects on a colloid study. These so-called pseudotumors result from the disturbed architecture of the liver in cirrhosis, where fibrosis, regenerating nodules, and intrahepatic shunting of blood reduce the exposure of the radiocolloid to Kupffer cells. However, these pseudotumors do contain normal hepatocytes and partial concentration of Tc-99m DISIDA might therefore occur.

The use of radionuclides in the diagnosis of HCC is further hampered by the fact that their uptake by the tumor depends, among other things, on the circulation through the tumor. Interference with this circulation is not infrequent and may be caused by more than one mechanism. Large HCC masses frequently undergo central liquefaction, presumably on the basis of ischemic necrosis. In addition, the tumor often occludes portal and hepatic venous radicles with or without superimposed thrombosis. Finally, hemorrhage may occur into the tumor substance.

This study has shown that the hepatobiliary imaging agent, Tc-99m DISIDA, is of no value in the specific diagnosis of HCC in southern African Blacks. The same will almost certainly be found in other populations, even those in which this tumor is more likely to be well differentiated. Because the pictures obtained with other imaging modalities, notably computerized tomography and ultrasonography, are not diagnostic of HCC, and because no radionuclide that is selectively and consistently concentrated in HCC tissue is available, the diagnosis of this tumor must still depend upon the serum alpha-fetoprotein concentration and the arteriographic findings. Definitive diagnosis of HCC depends upon the demonstration of the histologic features of the tumor.

Uptake of Tc-99m PIPIDA by pulmonary metastases reported in one patient (*7*) was not confirmed in either of our two patients who showed multiple large pulmonary metastases.

ACKNOWLEDGMENT

This work was supported by the National Cancer Association of South Africa and the South African Chamber of Mines.

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