Technetium-99m DISIDA Hepatobiliary Agent in Diagnosis of Hepatocellular Carcinoma: Relationship Between Detectability and Tumor Differentiation

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The present investigation was aimed to assess the usefulness of biliary agents scintigraphy in the diagnosis of hepatocellular carcinoma (HCC) and to ascertain the relationship between the uptake of these agents and the degree of HCC differentiation. Forty-four patients with this hepatic cancer were included in the study. Liver scans were performed 20 min and 3 hr after the administration of Tc-99m disopropyliminodiacetic acid (DISIDA). DISIDA scintigraphy could not be assessed in six cases. In 16 (42%) out of the remaining 38 patients, the tumor exhibited equal or greater radioactivity uptake than the surrounding liver. In six out of these 16 patients, tumor uptake was apparent in the early and delayed hepatic scans, while in the other ten subjects radioactivity uptake by the HCC could only be detected in the 3-hr delayed scans. In the remaining 22 patients, HCC appeared as a cold area. Tumor location by this technique did not differ from that observed by Tc-99m-sulfur colloid scan or ultrasound. DISIDA uptake was significantly related to tumor differentiation: 70% of those well differentiated tumors exhibited DISIDA uptake, whereas it was found in only 30% of those moderately differentiated and in none of those poorly differentiated (p < 0.05). These results show that DISIDA scintigraphy can be useful in the diagnosis of HCC. Since its sensitivity is related to the degree of tumor differentiation, it may be indicated when aspiration cytology is unable to distinguish between well differentiated HCC and reactive changes due to hepatic cirrhosis.


Recent investigations have explored the use of biliary agents in the isotopic diagnosis of hepatocellular carcinoma (HCC) (1–5). These primary hepatic tumors can retain the ability of taking up these kind of substances and, therefore, in radionuclide tagged biliary agents may identify HCC by identifying hot areas previously found to be cold in the isotopic scan with technetium-99m-sulfur colloid (99mTc-SC). In that regard, it has been reported that up to 36–57% of HCC show radioactivity uptake (3–5). Isotope accumulation seems to be more evident in delayed images, 3–5 hr after radioactive injection, when biliary agents have been excreted from the nontumoral liver to the biliary tract (2–4). The present study was aimed to confirm the usefulness of this technique in the diagnosis of HCC and to ascertain which factors may influence its sensitivity.

PATIENTS AND METHODS

The investigation was performed in 44 patients with HCC, 36 males and eight females, with a mean age of 58 ± 1.6 yr. HCC complicated liver cirrhosis in 40 patients: 21 were cryptogenic, 17 alcoholic, and two HBsAg positive. In four subjects, HCC developed in a normal liver. HCC was confirmed in 34 patients by liver biopsy or aspiration cytology. In the remaining cases, diagnosis of HCC was based on ultrasonographic findings associated with pathologic angiographic characteristics and/or increased alpha-fetoprotein (AFP) levels.

All subjects were submitted to the same procedures. The tumor was first located by hepatic scintigraphy with Tc-99m-SC (5 mCi) and/or ultrasound (US). Two days later, Tc-99m-labeled diisopropyliminodiacetic acid (DISIDA, 5 mCi) was injected i.v., and hepatic scans were obtained 20 min and 3 hr after radioisotope administration.
Liver scans were performed with a scintillation camera, and anterior, right lateral, and posterior hepatic images were recorded. Extrahepatic radioactivity uptake indicating metastatic sites was intentionally searched for by performing delayed anterior and posterior thoracic scans in all the cases and by performing skeletal scans in those cases with clinical or radiologic suspicion of bone metastasis.

According to the DISIDA uptake by the tumor, the scans were classified into two groups: those with no or minor uptake and those with equal or greater uptake than the surrounding liver tissue. The exploration was considered diagnostic of HCC when equal or increased radioactive uptake was observed.

Patients from both groups were compared in regard to clinical findings, biochemical abnormalities, and tumor characteristics (size, location, and cell differentiation). This last item could be assessed in 34 cases, which were divided according to their degree of differentiation in three groups: well, moderately, and poorly differentiated. In the 11 patients with needle biopsy, tumor differentiation was graded according to the criteria of Edmondson and Steiner (6). In the remaining 23 cases, the tissue specimen was obtained by fine needle aspiration biopsy, thus allowing the examination of a reduced number of cells. The classification of Edmondson and Steiner was not feasible in these cases and, therefore, tumor differentiation was graded according to the following criteria:

1. Good differentiation: The neoplastic cells resemble normal or reactive hepatocytes and contain abundant cytoplasm with or without bile thrombi.
2. Moderate differentiation: The nuclei of the cells are larger and more hyperchromatic than in well differentiated tumors, occupying a large proportion of the tumor cell.
3. Poor differentiation: The nuclei are intensely hyperchromatic while the cytoplasm is markedly reduced and contains few granules. The cells are largely different from nontumoral hepatocytes.

In order to group patients stratified by these criteria and those divided by the criteria of Edmondson and Steiner, cases with grade I from the classification of Edmondson and Steiner were considered as well differentiated, grade II and III as moderately differentiated, and grade IV as poorly differentiated.

The Mann Whitney-U test and the chi-squared test were used for statistical analysis (7). Results were expressed as mean ± s.e.

RESULTS

In six patients, DISIDA uptake by the tumor and nontumoral liver was not evaluated because of extremely irregular isotope accumulation and/or overlapping of gallbladder or intestinal radioactivity.

Only 16 (42%) of the 38 cases with evaluated images exhibited DISIDA uptake by the tumor. In six patients, DISIDA uptake was apparent in early scans: one of them exhibited increased radioactivity and the other five showed equal DISIDA uptake than in the surrounding liver. The patient with increased DISIDA uptake continued to show this pattern in the 3-hr delayed scan, while three of those with equal uptake changed to increased pattern and the other two remained unmodified.

In ten patients, isotope accumulation in the tumor could only be detected in delayed examinations: six exhibited increased and four equal DISIDA uptake than in the surrounding liver.

In all cases, the area of radioactivity uptake corresponded to the filling defect observed in the 99mTc-SC scan (Fig. 1) or to the tumoral area detected by US.

In the 22 HCC cases without DISIDA uptake, HCC was identified as a cold area in the same location observed in 99mTc-SC scintigraphy or US. Nontumoral liver showed a heterogeneous uptake of DISIDA with no areas of increased radioactivity.

There were no clinical or biochemical differences between patients with DISIDA uptake by the tumor or those without (Table 1). Tumor size and location did not differ between the two groups, but isotope accumulation was significantly related to tumor differentiation (Fig. 2). As previously stated, tumor differentiation could be assessed in 34 patients. Seven of the ten (70%) well differentiated HCC exhibited DISIDA uptake, while this was only observed in six of the 20 (30%) moderately differentiated and in none of the four poorly differentiated (Table 1) (p < 0.05).

Only three out of the six patients with confirmed metastasis exhibited extrahepatic DISIDA uptake, in the lungs (two cases) or bone (one case), which also were detected by thoracic computed tomography (CT) and by bone scintigraphy, respectively.

DISCUSSION

The use of US and CT has reduced the employment of isotopic explorations in the detection of HCC (8). Hepatic scintigraphy with 99mTc-SC has been widely performed for many years, and it has been the main exploration in the setting of suspicion of HCC (9). However, this method is nonspecific and its interpretation is greatly hampered by the hepatic architectural distortion caused by liver cirrhosis (9,10), which frequently underlies HCC. The use of other radioactive isotopes, such as 67Ga citrate (11) or 75Se methionine (12) has increased the sensitivity and specificity, but while being more expensive than US, they are not more effective (8,13).

In recent years, several authors have paid attention to the role of biliary agents in the diagnosis of HCC (1–5). The use of iodine-131 (131I) rose bengal (I) and 99mTc-labeled iminodiacetic acid derivatives or other biliary agents (2–5) has allowed the location of tumors that took up these substances. Hasegawa et al. (4) have shown that nearly 60% of the HCC are able to retain the biliary agent 99mTc-(Sn)-N-pyridoxyl-5-methyl tryptophan ([99mTc]PMT), and therefore, can be identified

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FIGURE 1
(A) Hepatic scintigraphy with $^{99m}$Tc-SC in a patient with HCC complicating liver cirrhosis. A filling defect is observed in the posterior view. (B) Hepatic scintigraphy with DISIDA 15 min after radioisotope administration (posterior view). A marked radioactivity uptake refills the cold area previously observed. (C) Hepatic scintigraphy with DISIDA 3 hr after radioisotope administration (posterior view). DISIDA has been excreted from the nontumoral liver, while it is clearly retained in the HCC area.

in hepatobiliary scans performed after radioisotope injection. These authors, as also observed by Lee et al. (2) using DISIDA, have found that tumor accumulation of $[^{99m}$Tc]PMT is more clearly observed in delayed imaging. This has been explained by the fact that biliary agents can not be removed from the tumoral cells because of the lack of biliary drainage. Since nontumoral liver progressively eliminates these substances to
in the diagnosis of HCC. As found in previous studies by other authors, this technique is able to detect only 36–57% of the tumors (2–5). In our study, imaging just after DISIDA administration showed tracer accumulation in only 16% of the cases, while in scans obtained 3 hr later, the proportion of tumors detected increased to 42%.

Previous reports have suggested the possible usefulness of DISIDA scintigraphy in the detection of metastasis (14,15), but in the present series only half of the cases with confirmed metastasis could be detected. Accordingly, this technique is of limited usefulness in the screening of extrahepatic spread.

These results indicate that this exploration cannot be considered for the screening of high risk populations. Early recognition of HCC is one of the major health problems in some countries like Japan (8) and China (16). HCC detection is usually based on a regular follow-up by US examination and AFP determination (17,18). This combined control has increased the number of tumors diagnosed in asymptomatic patients and has expanded the number of patients suitable for surgical treatment. In our study, we did not find a relationship between biliary agents imaging sensitivity and tumor size. However, we included only a reduced proportion of small HCC (5 cm) and therefore, the usefulness of DISIDA scintigraphy in the detection of small HCC cannot be ascertained from our data. On the other hand, it must be considered that large tumors are prone to undergoing necrosis, and this may explain why some of them are not identified as hot areas. However, taking into account that this exploration does not attain the same sensitivity as US, it can be concluded that biliary agents imaging is not indicated in HCC mass surveys.

In addition, previous reports have shown that focal nodular hyperplasia (19), hepatic adenomas (20), and liver metastasis from a breast cancer (21) may exhibit a radioactivity uptake pattern similar to that of HCC, thus diminishing the specificity of this technique.

The main interest of our study is the demonstration that the sensitivity of biliary agents imaging is related to the degree of tumor differentiation. Seventy percent of well differentiated HCC exhibited radioactivity uptake, whereas only 30% of those moderately differentiated and none of those poorly differentiated were found to take up DISIDA. This relationship between tumor differentiation and biliary agents uptake has not been previously demonstrated (5). Savitch et al. (5) did not find any correlation in a series of 19 patients. Perhaps the difference in the number of patients can explain the discrepancy between the findings of Savitch et al. (5) and those of the present study. Our results suggest that well differentiated tumors would retain some of the functions of nontumoral cells, such as the uptake of biliary agents. The ability of well differen-
differentiated HCC to take up biliary agents may have clinical relevance. HCC are frequently diagnosed by US guided aspiration cytology, which enables the examination of small pieces of the suspected tumoral area. Moreover, in some cases, it is hard to distinguish between cells from a well differentiated HCC and hepatocytes with reactive changes to an underlying cirrhosis. In these circumstances, DISIDA scintigraphy could be a non-invasive exploration leading to diagnosis by demonstrating isotope uptake in the area of suspected HCC.

REFERENCES