jnm/DIAGNOSTIC NUCLEAR MEDICINE

Scintigraphic Criteria for Hepatic Metastases from Cancer of the Colon and Breast

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Scintigraphic criteria for hepatic metastases were studied by examination of 333 liver scintigrams performed on 275 patients with primary cancers of the colon or breast. Focal defects in radiocolloid distribution correctly signaled the presence of metastatic colon carcinoma in 88% of the patients with that disease and incorrectly pointed to only 6% of the patients without such metastases. In contrast, the same criterion detected only 67% of hepatic metastases from breast carcinoma. This lower sensitivity could be improved to 87% by adding heterogeneity or hepatomegaly to the criteria for abnormality when patients with breast cancer are examined. Scintigraphic indicators of metastatic disease may vary according to the site of primary cancer.

J Nucl Med 17: 677–680, 1976

Scintigraphy of the liver plays a major role both in detecting hepatic metastases and in evaluating their response to cancer chemotherapy. Despite evidence that the features of biologic growth of various primary tumors differ widely (*1*), no effort has been made to discern whether such variations are reflected in the scintigraphic properties of their hepatic metastases.

Recently, hepatic scintigraphy was reported to be 77% accurate in the detection of tumor metastases when the primary disease was breast carcinoma and 85% accurate in the detection of metastatic colon cancer (*2*). These data raise the question of whether the growth features of metastases from these two common primary sources are sufficiently different to generate intrinsically different scintigraphic images, with the implication that the criteria for abnormality may depend upon the nature of the primary tumor. In order to investigate this hypothesis, we studied the medical charts of 275 patients whose livers had been directly examined shortly after hepatic scintigraphy.

MATERIALS AND METHODS

Data base. The scintigraphic findings from 208 examinations of 167 patients with primary adenocarcinoma of the colon or rectum and from 125 examinations of 108 patients with primary carcinoma of the breast formed the basis for the analyses. No patient had more than one primary tumor. All repeat examinations were made more than 1 month apart.

Each liver was examined either by closed needle biopsy, surgical observation, surgical biopsy, or postmortem examination within 4 weeks of scintigraphy. Any liver proven by these methods to contain metastatic deposits was assumed to have contained them at the time of scintigraphy. Further, any liver proven free of metastases at postmortem examination was considered to have been free of metastases at the time of imaging.

Hepatic scintigraphy. Hepatic scintiscans were begun 10–30 min after intravenous injection of 3–5 mCi of ^{99m}Tc-sulfur colloid. An Anger scintillation camera with 19 photomultiplier tubes, a 25-cm-diam

Received Dec. 3, 1975; revision accepted Feb. 23, 1976.

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crystal, and a 140-keV diverging collimator was employed in all cases. Anterior (650,000 counts), posterior (650,000 counts), and right lateral (540,000 counts) views were obtained for every patient. For all examinations two point sources, 10 cm apart, were photographed at the collimator face to aid estimation of organ size.

The scintigraphic images of the liver were evaluated for the following features:

Focal defect(s): One or more clearly delimited areas of absent or minimal radiocolloid accumulation surrounded by areas of normal radiocolloid uptake.

Heterogeneity: Irregular distribution of radiocolloid within the liver.

Hepatomegaly: Any liver image with a vertical height greater than 17 cm and a horizontal width greater than 18 cm (*3*).

In order to judge which scintigraphic features most accurately reflected the presence or absence of hepatic metastases, two kinds of criteria were employed:

Strict: The scintigram was considered positive for metastases only when one or more focal defects could be seen (*2–8*).

Liberal: The scintigram was considered positive for metastases when focal defects, heterogeneity, hepatomegaly, or any combination of these was apparent.

Data analyses. The scintigraphic data were analyzed for accuracy, sensitivity, and specificity according to the following definitions:

True-positive ratio: The fraction of livers that generated abnormal scintigraphic images and were proven to have metastatic disease (a measure of sensitivity).

False-positive ratio: The fraction of livers without metastatic disease that generated abnormal scintigraphic images.

True-negative ratio: The fraction of livers without metastatic disease that generated normal scintigraphic images (a measure of specificity).

False-negative ratio: The fraction of livers that generated normal scintigraphic images in spite of proven metastatic disease.

Each ratio was calculated twice: once with the strict criterion for scintigraphic evidence of metastases and once with the liberal criteria.

RESULTS

Among the 208 scintigrams of patients with primary carcinoma of the colon or rectum, the strict criterion yielded a true-positive ratio of 0.88 and a false-positive ratio of 0.06 (Table 1). The liberal scintigraphic criteria resulted in a similar true-positive ratio (0.89), but the false-positive ratio was considerably larger (0.27). Thus, either strict or liberal criteria detected metastatic colon carcinoma with equal sensitivity. The liberal criteria were less specific, however, and would have indicated incorrectly the presence of metastases in some livers when they were in fact absent. The general accuracy of scintigraphy, expressed as the ratio of correctly identified normal and abnormal livers to the total number examined, was 91% with the strict criterion and 79% with the liberal criteria.

Carcinoma of the breast exhibited distinctly different accuracy parameters (Table 2). The strict criterion for scintigraphic abnormality led to a true-positive ratio of only 0.67 and a false-positive ratio of 0.09. In contrast, the liberal criteria generated a true-positive ratio of 0.87 and a false-positive ratio of 0.29. Thus, for breast carcinoma the liberal criteria were more sensitive to the presence of hepatic metastases than were focal defects alone. This enhanced detection was accomplished at the expense

TABLE 1. PARAMETERS FOR EVALUATION OF THE LIVER SCINTIGRAM OF PATIENTS WITH COLON CARCINOMA*

	Criteria for metastases	
Analysis	Focal defects only (strict criterion)	Focal defects, heterogeneity, or hepatomegaly (liberal criteria)
True-positive ratio	0.88	0.88
False-positive ratio	0.06	0.27
False-negative ratio	0.12	0.11
True-negative ratio	0.94	0.73

* A total of 208 livers were imaged: of these, 88 were found to have metastases.

TABLE 2. PARAMETERS FOR EVALUATION OF THE LIVER SCINTIGRAM OF PATIENTS WITH BREAST CARCINOMA*

	Criteria for metastases	
Analysis	Focal defects only (strict criterion)	Focal defects, heterogeneity, or hepatomegaly (liberal criteria)
True-positive ratio	0.67	0.87
False-positive ratio	0.09	0.29
False-negative ratio	0.33	0.13
True-negative ratio	0.91	0.71

* A total of 125 livers were imaged: of these, 60 were found to have metastases.

of a considerable increase in false-positive interpretations. Consequently, the general accuracy was similar for scintigrams interpreted by either strict or liberal criteria (Table 2): 80% and 79%, respectively.

Livers without metastases generated similar scintigraphic features regardless of the nature of the primary tumor. Judged by the strict criterion, the false-positive ratio was 0.06 for patients with colon primaries and 0.09 for patients with breast primaries. According to the liberal criteria, the corresponding ratios were 0.27 for colon carcinoma and 0.29 for breast carcinoma. Among the patients with colon primaries whose scintigrams were judged by the strict criterion, three of seven false-positive interpretations arose from fatty infiltration, two from portal inflammatory infiltrates, one from macroscopic cirrhosis, and one from severe systemic and abdominal sepsis. Three of these images exhibited significant extrahepatic radiocolloid localization. Two of the seven false-positive images arose from single focal defects in the portal and left lobe areas, respectively.

Six instances of focal hepatic radiocolloid defects were observed in the absence of metastatic cancer among patients with breast primaries. Two of these livers were examined histologically and showed fatty infiltration and abnormal hepatocyte regeneration. The three livers recorded as normal by surgical inspection had single peripheral defects and increased splenic sequestration of radiocolloid.

For most of the total of 13 false-positive scans (strict criterion), plausible and potentially detectable reasons for the misleading scintigram findings were evident. None were found to be due to benign space-occupying lesions or to impinging adjacent disease.

Among the 11 false-negative interpretations that arose from application of the strict criterion to liver scintigrams of patients with colon primaries, none exhibited discernible focal defects and only one showed any hepatic image abnormality (hepatomegaly). Only two of the livers with undetected colon metastases were so diagnosed histologically; the others were identified by surgical examination. Observation at laparotomy was also the basis for establishing the presence of metastases in seven of the eight patients with carcinoma of the breast whose hepatic scintigrams were normal by the liberal criteria and in six of 12 cases with hepatomegaly or heterogeneous and/or extrahepatic abnormalities of radiocolloid distribution.

DISCUSSION

These data support the confidence currently felt in the capability of the liver scan to detect metastatic liver disease (*9*). In particular, when the primary tumor was carcinoma of the colon, the overall accuracy of the liver scan was 90%. This figure is unsurpassed by any other noninvasive technique. Metastatic breast carcinoma appeared to cause focal defects in this series less frequently than colon carcinoma. Hence, its detection accuracy was lower (i.e., 80%).

When the strict criterion of focal defects was employed as an indication of metastases, the false-positive ratios were identical for patients with colon or breast primaries. Livers not involved with metastatic deposits were so defined by the liver scan independently of the nature of the primary cancer and of the regimen used in managing these patients.

Application of more liberal scintigraphic criteria for detecting metastatic colon carcinoma *diminished* overall accuracy by increasing the false-positive ratio. Thus, heterogeneity or hepatomegaly are seldom unique manifestations of metastatic colon carcinoma, a deduction consistent with the absence of these features from our false-negative patterns. From Table 1 the following may be deduced in regard to colon cancer: If there are focal scintigraphic defects, there is a 92% chance that the patient has metastases; if there is only heterogeneity or hepatomegaly, there is only one chance in 26 that metastases are present. According to either set of criteria, a negative scintigram means that the chances are 91% that the liver is free of metastases.

In contrast to the situation for colon carcinoma, adoption of the more liberal criteria for metastatic breast carcinoma had little effect on overall accuracy. Both the true-positive and the false-positive ratios increased, the former because certain instances of metastatic breast carcinoma were manifest only as heterogeneity or hepatomegaly.

The probability that a patient has metastases from the colon when focal defects are observed is $(0.88 \times 88)/[(0.88 \times 88) + (0.06 \times 120)] = 0.92$. Applying the liberal criteria, one additional case of metastases was detected, but the false-positive ratio increased from 0.06 to 0.27, indicating that $0.21 \times 120 = 25$ instances of heterogeneity or hepatomegaly did not represent metastases.

For patients with breast primaries, a focal scintigraphic defect gives an 87% probability of metastatic cancer (Table 2). However, if only heterogeneity or hepatomegaly are observed, the chance of hepatic metastases is 48%, hardly a negligible figure. Thus, the liberal criteria would more frequently detect metastatic breast disease but at the price of a higher false-positive ratio. In the context of modern breast-cancer management, this error would appear less serious than false-negative reports. Moreover, closed

needle liver biopsy or laparoscopy with directed liver biopsy should identify the nonmalignant parenchymal diseases that cause hepatic enlargement and heterogeneous radiocolloid distribution in the absence of cancer (*10*).

Should the criteria for abnormality be deliberately varied according to the nature of the primary tumor? In part, the answer depends upon the implications of false-positive and false-negative interpretations for patient management. The requirement of focal defects or space-occupying lesions for the scintigraphic diagnosis of metastatic liver disease is the criterion most commonly employed in published studies for any form of cancer (*2–8*). Although little is gained by employing any but such strict criteria when the primary tumor originates in the colon or rectum, further studies may be required to establish the validity of this approach for the detection of all forms and stages of metastatic cancer.

The data also raise an important technical question: for small metastatic deposits, is the in vivo resolution of the diverging collimator (used with a 19-photomultiplier scintillation camera at the information densities employed here) inferior to that of alternative methods of imaging? A definitive answer to this question would be important.

Direct examination of the livers in this series resulted in considerable dependence upon correct diagnosis by the surgeon, a potentially fallible measure of histologic changes (*11*). Although the limitations of both inspection and needle biopsy (*12*) are well known, these means of diagnosing hepatic metastases nevertheless play major roles in determining cancer management throughout the world. In view of the disagreements between the scintigraphic and gross surgical diagnoses of liver disease, operating surgeons should be encouraged to employ biopsy methods that afford maximal histologic accuracy.

ACKNOWLEDGMENTS

The author is indebted to S. J. Adelstein and B. J. McNeil for helpful discussions. The quality of scintigrams permitting this study is a tribute to the technologists of the Joint Program in Nuclear Medicine. This study was supported by NIH Grant GM-18674.

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