DOUBLE-TRACER SCINTIGRAPHY WITH

^{67}Ga-CITRATE AND ^{99m}Tc-SULFUR COLLOID IN

THE DIAGNOSIS OF HEPATIC TUMORS

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A method of liver scanning based on a subtraction technique with simultaneous use of two tracers, ^{67}Ga-citrate and ^{99m}Tc-sulfur colloid, is described. The subtraction technique isolates radiogallium uptake by the space-occupying hepatic lesions by subtracting interference due to tracer uptake by healthy hepatic tissue. In 82 patients, the method yielded a correct result in 94.7% of the positive scans and in 97.7% of the negatives. Two false positives and one false negative occurred. Very poor results were obtained in the same patients using conventional technetium and gallium scans: only 20.7% of these interpretations were correct. The method proved very helpful in differentiating malignant from benign lesions.

Conventional radiocolloid scanning for the diagnosis of hepatic tumors often demonstrates the site and size of space-occupying lesions but not their nature. In recent years several attempts have been made to increase the specificity of liver scanning. Of great interest are techniques using either tracers with high uptake in tumor tissue or those with an exclusively intravascular distribution. In the latter case, the tumor is likely to appear as a cold area on a radiocolloid scan (1,2). However, this may also happen even if the tumor actively concentrates the tracer, since all the tumor-seekers currently available attain high concentrations in the surrounding healthy liver tissue. If the resulting interference is not eliminated, the scans are difficult to interpret. Elimination can be achieved by using two tracers simultaneously, one of which is taken up by the hepatic parenchyma only and the other by the tumor as well (3). The image due to the former is then subtracted from that of the latter.

Selenium-75 compounds have been used in conjunction with radiocolloids for this purpose (4,6). Our method uses ^{67}Ga-citrate and ^{99m}Tc-sulfur col-

loid scans in a computer-operated technique; this subtraction method is described together with the results obtained in a group of patients.

MATERIALS AND METHODS

The patients examined had been shown by conventional liver scanning with radiocolloids to have focal hepatic lesions. With the new approach, an
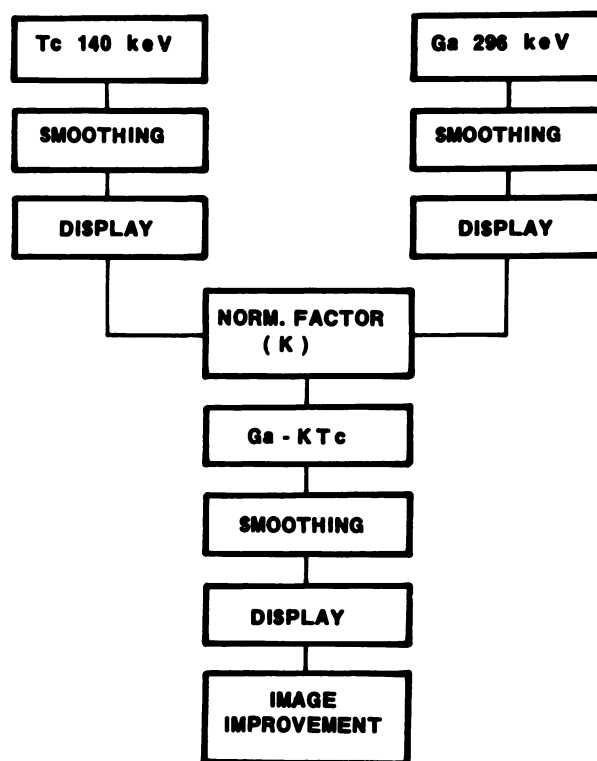
FIG. 1. Flow chart for processing scan data.

intravenous injection of 3 mCi of ^{67}Ga-citrate was given 48 hr before the examination and an intravenous injection of 1 mCi of ^{99m}Tc-sulfur colloid 15 min beforehand. The examinations were done with a Searle Radiographics Pho/Gamma III scintillation camera connected on-line to a DEC PDP-8m computer with a 12K core memory. The results were displayed on a television monitor using a scale of eight intensity levels. The system (Nukab 2530) was controlled by teletype. A parallel-hole collimator (Model 820-821517: 410 keV, medium fine) was used.

A block diagram for data acquisition and processing is shown in Fig. 1. Using a double-channel analyzer, conventional liver scans were obtained on the 140-keV ^{99m}Tc peak and on the 296-keV ^{67}Ga peak. The method of subtraction required that the two scans be normalized. An area of 100 cells of normal hepatic tissue, in which the activity distribution is almost homogeneous, is chosen for normalization of the counts from both radionuclides. The ratio of the counts from ^{67}Ga to those from ^{99m}Tc in this region is the normalizing factor used in image subtraction.

TECHNICAL CONSIDERATIONS

Statistical error. If the standard deviation of the count density is used to indicate the error of measurement, then the relative increase in uncertainty arising from subtraction of the two nuclides (relative to a single-nuclide measurement) is given by

$$\sigma(N_1 - kN_2) = \sqrt{N_1 + k^2 N_2}, \qquad (1)$$

where N_1 is the count from a single nuclide (^{67}Ga), N_2 is the count from the second nuclide (^{99m}Tc), and k is the normalizing factor.

Spread function. In order to minimize the difference in septal penetration of photons measured for gallium (296 keV) and for technetium (140 keV), a collimator suitable for measuring higher-energy (410 keV) radiation was chosen from among those available. Under these conditions we obtained the spread functions of the two radioisotopes: gallium had a full width half maximum of 11 mm and technetium had FWHM = 13 mm.

Attenuation. The attenuation in paraffin of photons of the two selected energies was evaluated by setting the analyzer of the Anger camera on the respective energy peaks. Attenuation coefficients were determined to be

$$\mu(\text{Ga}) = 0.100 \text{ cm}^{-1} \text{ and } \mu(\text{Tc}) = 0.128 \text{ cm}^{-1}.$$

A 10-cm thickness of tissue reduces the counts of gallium to 38% and those of technetium to 29%, while a 20-cm thickness reduces the counts to 14% and 8%, respectively.

The pulse-height spectra were taken after administration of one or both of the tracers (Fig. 2): when the technetium scan was recorded on the 140-keV peak, there was clearly interference due to scattered Ga radiation. The contribution of gallium to the count in the 140-keV channel was estimated to be about 5%.

Image display. Image enhancement is applied after the subtraction step and does not influence the diagnostic judgment in any way. Its goal is to clarify the result through selection of optimal contrast. The operator chooses upper and lower cutoff levels, expressed as percentages of the maximum intensity. The computer then searches out the maximum intensity, determines the absolute values for the two cutoffs, and displays only those intensities that lie within the chosen range. The computer then divides the range into eight equal intensity levels, each rep-
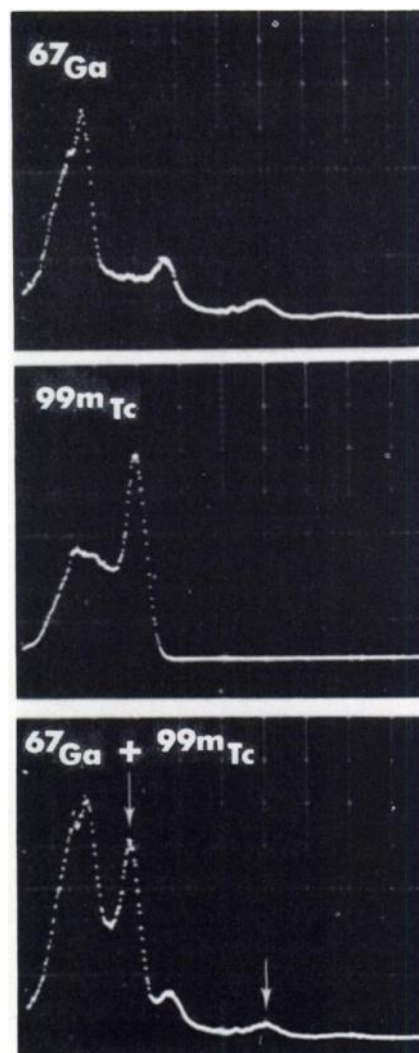

FIG. 2. In vivo spectrometry with scintillation camera during examination. Arrows mark peaks used for scanning: 140 keV for technetium and 296 keV for gallium.

resented by one color or gray shade on the monitor screen. Alternatively, the selected intensity range may be represented by a single color or gray shade, thus yielding an isocontour display.

RESULTS

The biologic assumption is that the two tracers are similarly distributed in healthy hepatic tissue. Since the mechanisms of hepatic uptake differ from Ga and Tc, there may well be differences of distribution, although these differences are not great in practice. In fact, in healthy livers, subtraction results in a scan in which only a few low-intensity points appear. These counts are statistically distributed about zero in accordance with Equation 1. Figure 3 illustrates four stages of the method in a patient in whom no hepatic disease was evident. The subtraction scan is almost uniformly zero in the hepatic area, whereas the surrounding regions are positive due to Ga accumulation in the abdominal organs.

The content of every cell displayed on the subtraction scan is expressed as a percentage of the maximum value and is assigned one of the eight intensity levels. Thus, the near-zero content of cells corresponding to healthy parenchyma is negligible compared with the cells corresponding to diseased tissue or to regions outside the liver. The hepatic region, represented by the low intensity level, can only be recorded photographically if the contrast is increased. The isocontour of the subtracted scan shows a well-defined zero image of the healthy liver,
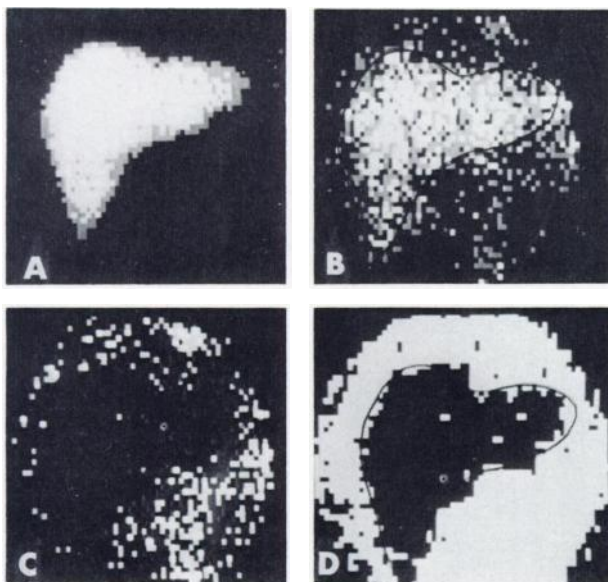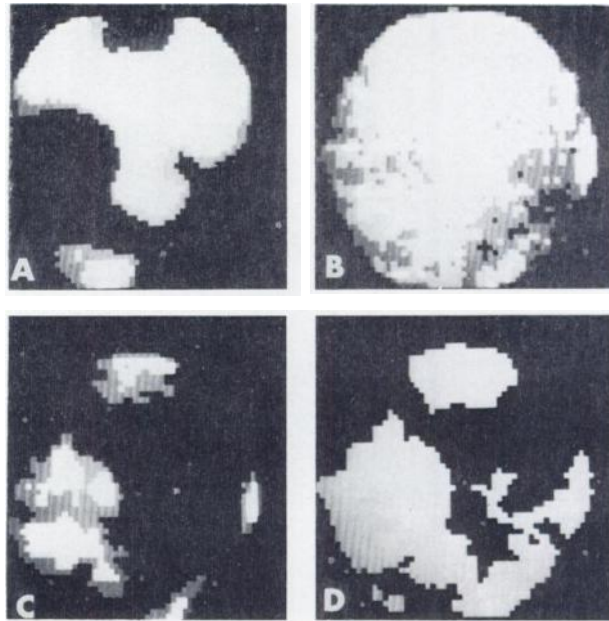

FIG. 4. Patient with hepatoma. (A) Technetium scan shows large cold area. (B) Gallium scan shows diffuse uptake in liver area. Subtracted scan (C) and its elaboration (D) give clear picture of Ga uptake in malignant tissue, showing size and location of lesions.

FIG. 3. Double-tracer scan of healthy liver. (A) Technetium scan; (B) gallium scan; (C) result of subtraction; (D) isocontour after subtraction.

surrounded by a uniformly positive image due to the extrahepatic radioactivity. The technetium scan shows diseased hepatic tissue as a cold area, whereas the gallium scan shows a diffuse uptake in both normal and diseased parts of the liver. Although gallium does accumulate in the areas where technetium is not fixed, it is very difficult to recognize the location and size of the lesions from either scan alone. The subtracted scan gives a detailed picture of tumor since positive images then are seen in areas where the technetium scan was cold. Figure 4 illustrates the results obtained in a patient with large lesions due to hepatoma.

Similar results were obtained in all cases of hepatoma examined (Fig. 5) and in other tumors also, provided that they take up gallium as most malignant tumors do (Fig. 6). The subtraction procedure shows this uptake more definitely than the simple gallium scan; small lesions become identifiable and large ones stand out clearly. Those abnormal regions that do not take up gallium (benign lesions) are often obvious even with conventional ^{67}Ga scanning, especially if the lesion is large; however, they are clearer still after subtraction (Fig. 7).

This procedure was used in 82 patients in whom conventional scanning had shown focal lesions. In 39 of them, a biopsy was taken in the course of laparotomy or laparoscopy. In the other 43, confirmation emerged from the clinical course in the months that followed. The scans were "read" sep-
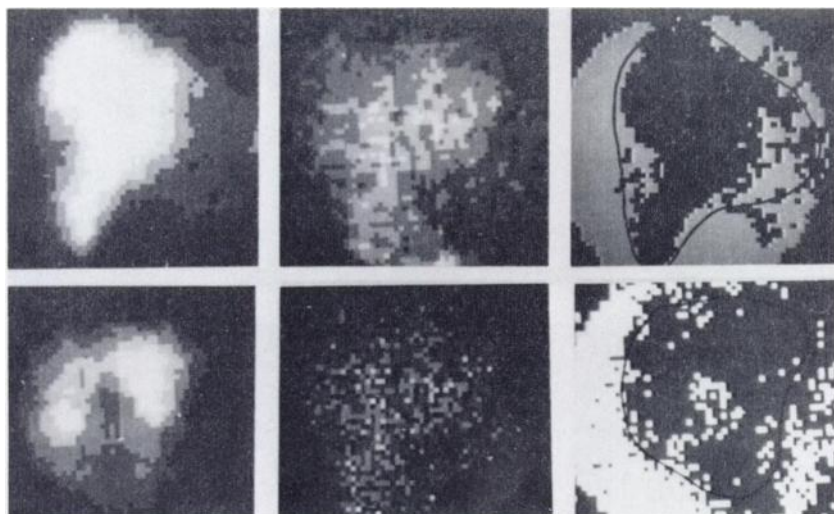
FIG. 5. Patient with hepatoma. Top: anterior views; bottom: lateral views. Technetium scans (left) show large cold area in right lobe and irregularities in left lobe; gallium scan (center) is inconclusive, whereas subtraction (right) clearly shows tracer uptake by lesions.

arately by two observers without knowledge of the clinical and pathologic findings. Conventional Tc and Ga scans and the subtraction scans were read separately. The interpretations of the subtraction scans were identical for both observers; disagreements occurred only in the interpretations of the conventional Ga scans. Moreover, many of the latter were inconclusive.

The results of subtracted-scan interpretation are summarized in Table 1. Of the 82 cases examined, 37 had primary or secondary malignant tumors and 45 had benign lesions (cirrhosis, chronic hepatitis,

x-ray damage, cysts). Of the 38 positive results, 36 (94.7%) were correct and two (5.3%) were wrong; of the 44 negative results, 43 (97.7%) were correct and only one (2.3%) was wrong.

The results obtained from two observers examining conventional gallium scans are reported in Table 2. In only 20.7% of the examinations was it possible to give a response, which was concordant in nine positive scans and in eight negative scans. In 65 examinations (79.3%) it was not possible to conclude that there was significant uptake of gallium in the lesions.
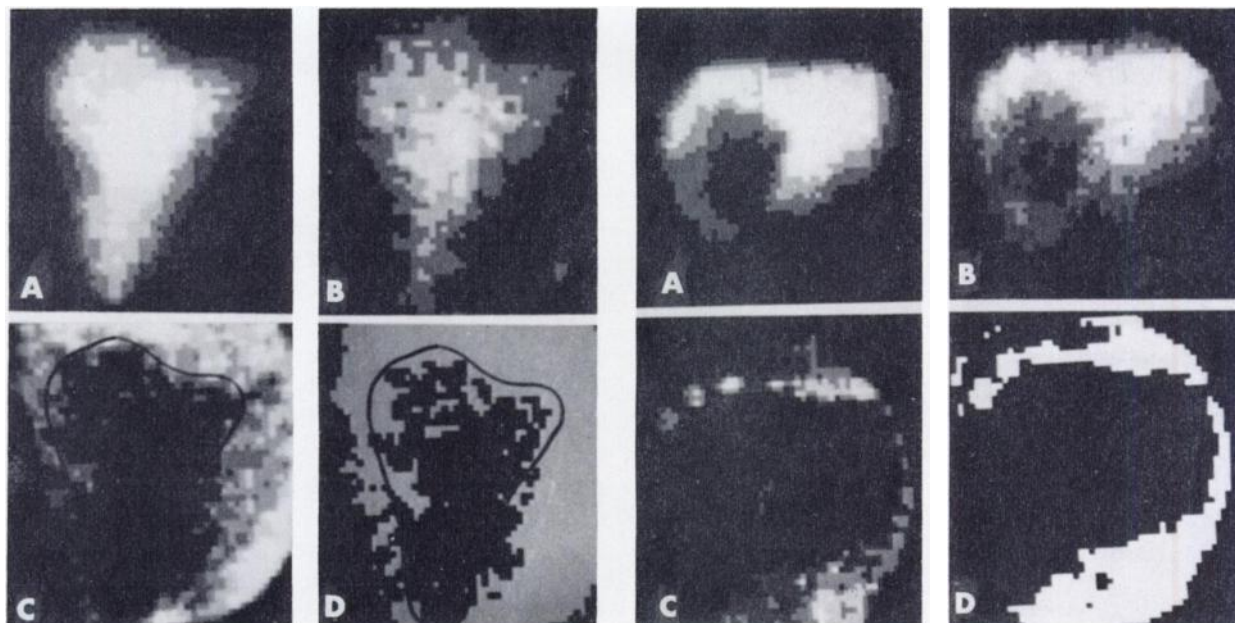

FIG. 6. Patient with histiocytic lymphoma. (A) Technetium scan shows cold areas in upper right lobe; (B) gallium scan seems to confirm these. Subtraction (C,D) shows Ga uptake in lesions.

FIG. 7. Patient with hepatic cyst. Lesion is quite clear both in Tc (A) and Ga (B) scans; both show lesion as lacunar area. Subtraction (C,D) shows no Ga uptake in lesion.

TABLE 1. AGREEMENT OF TWO OBSERVERS USING SUBTRACTION SCANS*

	Total	Concordant	Discordant
Positive scans	38	36 (94.7%)	2 (5.3%)
Negative scans	44	43 (97.7%)	1 (2.3%)
Total	82	79 (96.3%)	3 (3.7%)

* Data reported on 37 patients with malignant hepatic tumors and 45 patients with benign hepatic lesions.

TABLE 2. AGREEMENT OF TWO OBSERVERS USING Tc AND Ga SCANS*

Positive concordant	9 (11.0%)
Negative concordant	8 (9.7%)
Not conclusive	65 (79.2%)
Total	82 (100.0%)

* Data reported on 37 patients with malignant hepatic tumors and 45 patients with benign hepatic lesions.

DISCUSSION

The described method presents no particular difficulties either of execution or of interpretation. Its basic requirements (namely, the similar distribution of the two tracers in healthy hepatic parenchyma and the possibility of recording the two scans separately are fulfilled well enough for correct execution of the examination. The similarity of the normal distributions of the two tracers is shown by the almost complete deletion of the liver image in the subtraction scan, in which only a low content due to statistical fluctuation can be recognized.

The differences between the spread functions that characterize the two energies used is very small and does not seem to interfere with the results. The differences in attenuation of the radiations emitted by the two nuclides appears more important. The contribution to the scan given by the deeper regions of the liver is smaller for technetium than for gallium, but it is difficult to evaluate the practical consequence of this phenomenon.

Gallium scatter into the technetium window proved to be around 5% with the doses chosen, resulting in an underestimate of gallium uptake after subtraction and hence a higher probability of false negatives. The error could be reduced by increasing the technetium

dose, or eliminated altogether by administering the technetium after recording a gallium scan on 140 keV and then subtracting it from the technetium scan. There are drawbacks to this procedure, however. First, the gallium scan is always less sharply defined than the technetium scan, so the latter has to be centered beforehand; second, only one projection can be taken; and third, the investigation takes appreciably longer.

Such refinements would seem to be unnecessary anyway, since we have only one false-negative examination to date and that was due not to underestimation of the gallium uptake after subtraction, but to genuine absence of uptake by the hepatic lesions. The patient had Hodgkin's disease with multiple localizations, but the hepatic lesions failed to show any clear uptake of radiogallium. The two false-positives were difficult to interpret: one patient had polycystic disease of the liver and the other histiocytic lymphoma. In neither did laparotomy reveal malignancy in the liver.

The method is relatively simple to use and is indicated for the specific diagnosis of hepatic lesions detected by conventional scanning. No useful information is gleaned if conventional scanning fails to detect a space-occupying lesion, since both methods have the same resolving power. The favorable results obtained by the subtraction procedure, contrasted with the difficulties of interpreting the conventional gallium scan, seem to us ample justification for its further evaluation.

REFERENCES

1. EDDLESTON AL, RAKE MO, PAGALTSOS AP, et al: 75Se-selenomethionine in the scintiscan diagnosis of primary hepatocellular carcinoma. Gut 12: 245-249, 1971
2. LUBIN E, LEWITUS Z: Blood pool scanning in investigating hepatic mass lesions. Semin Nucl Med 2: 128-132, 1972
3. BEN-PORATH M, CLAYTON G, KAPLAN E: Modification of a multi-isotope color scanner for multipurpose scanning. J Nucl Med 8: 411-425, 1967
4. MOMBELLI L, FAVARO L, MELDOLESI U: Una nuova tecnica scintigrafica con doppio tracciante (198Au colloidale e selenito di sodio marcato con 75Se) per la diagnosi di lesioni neoplastiche del fegato. Radiol Med 56: 913-923, 1970
5. KAPLAN E, DOMINGO M: 75Se-selenomethionine in hepatic focal lesions. Semin Nucl Med 2: 139-149, 1972
6. SPINELLI RESSI F, CANTONI L, BANFI F, et al: Valutazione clinica della scintigrafia con doppio tracciante nella diagnosi differenziale delle aree fredde epatiche. Radiol Med 59: 946-958, 1973