VISUALIZATION OF TUMORS IN HUMANS USING ^{67}Ga-CITRATE AND THE ANGER WHOLE-BODY SCANNER, SCINTILLATION CAMERA AND TOMOGRAPHIC SCANNER

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Recently gallium-citrate has been shown to accumulate sufficiently in a variety of tumors to allow for their visualization (*1,2*). The present communication summarizes our experience in visualizing the distribution of ^{67}Ga-citrate in 18 patients with a variety of neoplasias using the Anger whole-body scanner, scintillation camera and tomographic scanner.

MATERIALS AND METHODS

The Anger whole-body scanner (*3*), scintillation camera (*4*) and tomographic scanner (*5*) have been described previously. Carrier-free ^{67}Ga-citrate complex was prepared in a fashion identical to that described in another publication (*2*). Each patient received approximately 4 mCi of the ^{67}Ga-citrate added to 150 ml of normal saline and administered intravenously over a 15–30-min interval. In selected patients, the distribution of the ^{67}Ga in the body was visualized daily following its administration. In most patients, however, the distribution of the ^{67}Ga was visualized 2–6 days after its administration. Visualization of the ^{67}Ga by the Anger scintillation camera, whole-body scanner and tomographic scanner was performed at a variety of window settings corresponding to each of the major gamma emission peaks of gallium [0.296 MeV (22%), 0.184 MeV (24%) and 0.093 MeV (40%)] to evaluate the optimum gamma emission for visualization with the three instruments. All peaks gave acceptable results with the scintillation camera but in general with this instrument we used the 0.093 MeV peak because of the associated higher counting rate. A window including 0.184 and 0.296 MeV peaks was used with the tomoscanner and the whole-body scanner.

All patients had established diagnoses of malignant neoplasia before the study.

RESULTS

Patient EY had hepatoma with widespread hepatic involvement and pulmonary metastases. Figure 1 shows whole-body scans obtained with the Anger whole-body scanner 1 hr to 9 days after the administration of ^{67}Ga. In the initial scan obtained 1 hr after the administration of the ^{67}Ga the material appears to be widely distributed throughout the body with no apparent localization in tumor. One day later, localization in portions of the lungs, liver and skeleton has occurred. At 2 days after ^{67}Ga administration blood background has diminished further compared to that noted the previous day, and one sees with greater clarity uptake in the left chest and in an area in the region of the right diaphragm. The ^{67}Ga distribution did not change significantly thereafter, and satisfactory scans were obtained through the 9th and last day of the study. The lower portion of Fig. 2 shows the tomographic scan of the liver 3 days after the administration of the ^{67}Ga. In each figure the plane of best focus is 1, 2 and 3 in. beneath the detector head as read from left to right across the top of the figure and 4, 5 and 6 in. beneath the detector head as read from left to right at the lower portion of each figure. The distribution of the isotope in the liver is inhomogeneous with the most prominent uptake occurring in the region of

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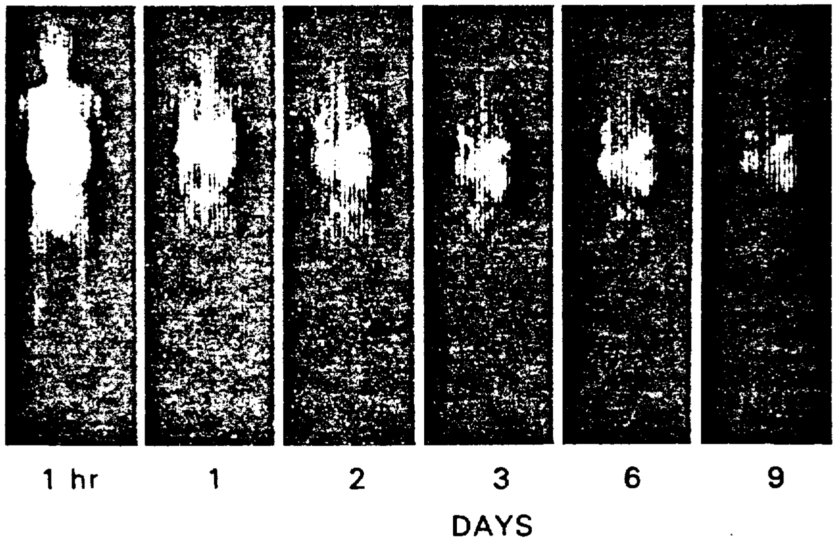

FIG. 1. Whole-body scans in patient with metastatic hepatoma obtained at various time intervals following i.v. administration of ^{67}Ga-citrate. Whole-body scans were performed over 3–11-min intervals at 1 hr and 1–9 days after i.v. administration of ^{67}Ga-citrate. All scans are posterior views. Note progressive accumulation of activity in left chest and region of right dome of liver.

the right dome of the liver beneath the diaphragm. The upper portion of Fig. 2 presents a tomographic scan of the liver subsequent to the administration of ^{99m}Tc-sulfur colloid. It can be seen that the area of maximum uptake of ^{67}Ga in the dome of the right lobe of the liver corresponds to a defect in the colloid uptake by the liver, suggesting that this region consists primarily of tumor mass. However, the large defect in the mid- and lateral portion of the right lobe of the liver seen on the colloid is also represented as a less well-defined defect in the ^{67}Ga study, indicating that this portion of the tumor is not concentrating the ^{67}Ga to the same extent as the surrounding liver. Similar tomographic scintiphotos of the lungs showed prominent uptake of ^{67}Ga in several of the pulmonary metastases. However, many of the pulmonary metastases defined radiographically failed to concentrate sufficient ^{67}Ga to allow their visualization.

JA had Hodgkin's granuloma with a tumor mass involving the anterior mediastinum and the right upper lung field. The large tumor mass in the chest was the only clinical and radiographic evidence of Hodgkin's disease in this patient. The left portion of Fig. 3 shows a whole-body scan 3 days after the administration of ^{67}Ga. The large amount of uptake in the chest region corresponds to the known area of tumor involvement. In addition to uptake of ^{67}Ga in the liver and portions of the skeleton, a localized area of high uptake is seen in the left upper quadrant of the abdomen. Visualization of the lesion in the chest (upper right) and in the abdomen (lower right) by use of the tomographic scanner are also shown in Fig. 3. The lesion in the chest appears in best focus at approximately 3 in. beneath the tomographic detector head, while the lesion in the abdomen comes into best focus approximately 5 in.

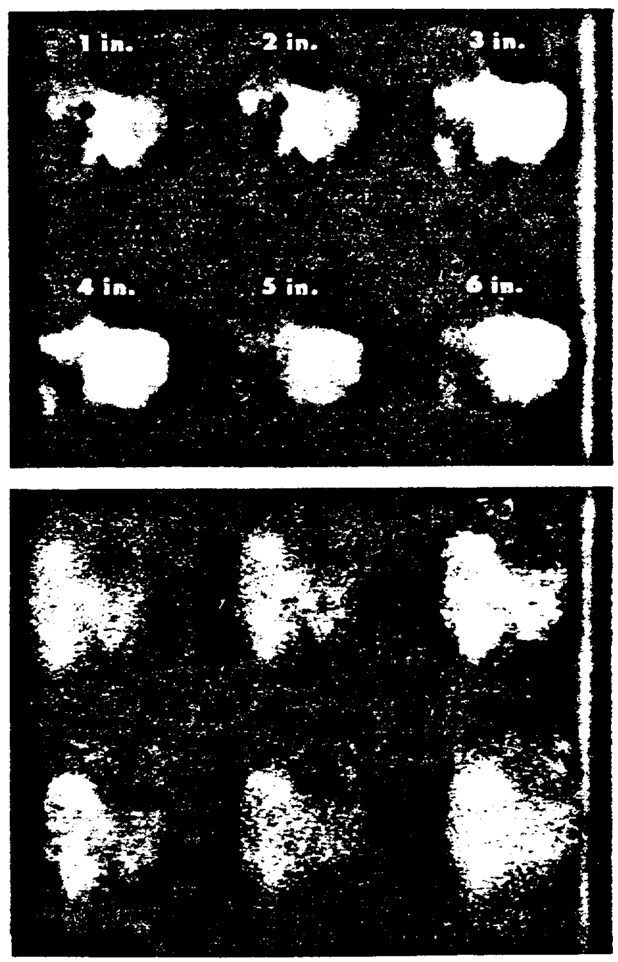

FIG. 2. Tomographic scans (anterior views) obtained in same patient shown in Fig. 1 following the administration of ^{99m}Tc-sulfur colloid (upper figure) and ^{67}Ga-citrate (lower figure). In each figure plane of best focus is 1, 2 and 3 in. beneath detector head as read from left to right across top of figure and 4, 5 and 6 in. beneath detector head as read from left to right at lower portion of each figure. It can be seen that large defect in dome of right lobe of liver seen on ^{99m}Tc-sulfur colloid scan corresponds to area of increased uptake of ^{67}Ga in lower scans.

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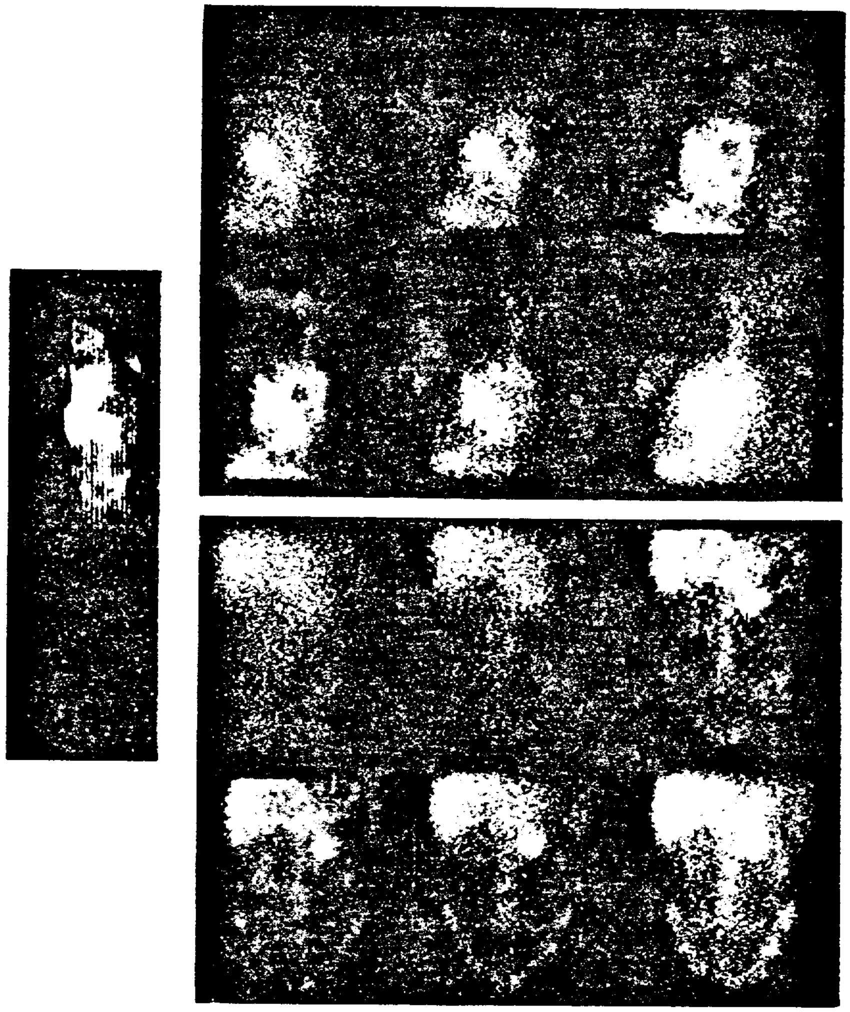

FIG. 3. Whole-body scan and tomographic scans (anterior views) of chest and abdomen in patient with Hodgkin's granuloma. Whole-body scan (left portion of figure) is anterior view showing localization of ^{67}Ga in lesions, in chest and in left upper quadrant of abdomen. ^{67}Ga also accumulated in liver and selected portions of skeleton. Tomographic scans show further details of chest (upper right) and left upper quadrant lesions (lower right).

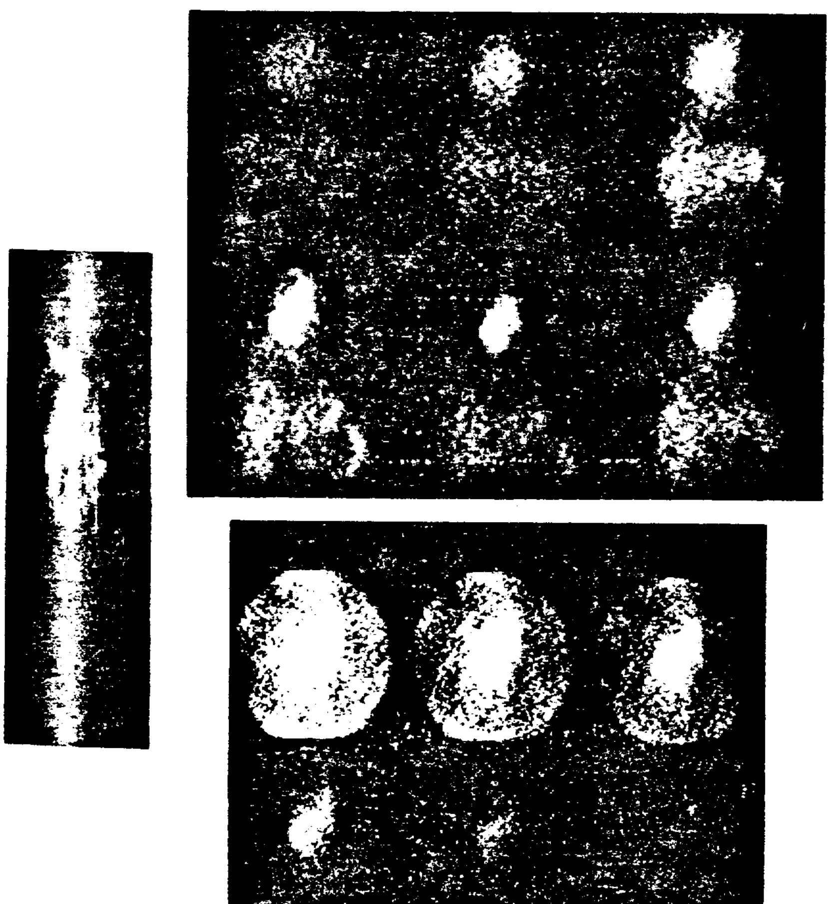

FIG. 4. Whole-body scan (shown on left) of patient with epithelial cell tumor of mediastinum showing localization of ^{67}Ga in lesion in chest. Liver, bowel and selected portions of skeleton are also visualized. Tomographic scans (upper right) and scintiphotos (lower right) of chest lesion are shown. All studies are anterior views.

beneath the detector head, suggesting that it is relatively posteriorly placed in the abdomen. Several weeks after these studies, the patient died and the abdominal lesion was found to correspond to infiltration of the upper pole of the left kidney by the lymphoma. Additionally, tumor infiltrations were found in the right kidney and certain abdominal lymph nodes, regions that were not discretely visualized in the ^{67}Ga study.

Patient BA had an epithelial cell tumor of the mediastinum. The left portion of Fig. 4 shows a whole-body scan of this patient showing a marked accumulation of ^{67}Ga in the mediastinum 2 days after its administration. Additionally, activity can be seen in the liver, bowel and portions of the skeleton. Tomographic scan of the chest lesion presented in the upper right portion of the figure shows that the lesion is located approximately 5 in. beneath the detector head. The scintillation camera picture of the chest shown in the lower right portion of the figure was taken with a 2.2-in. parallel-hole collimator and shows good resolution of the chest lesion.

Patient AB had inoperable uterine carcinoma with multiple pulmonary metastases. The left portion of Fig. 5 shows a whole-body scan (anterior view) of this patient taken 2 days after the administration of ^{67}Ga. The ^{67}Ga concentrated in an area of the pelvis just to the right of the midline. Additionally, there is activity noted in the liver and portions of the skeleton and bowel. A scintillation camera picture of the activity in the pelvis is shown in the right of the figure.

Patient SH had Hodgkin's granuloma and had received radiation to the neck, mediastinum and

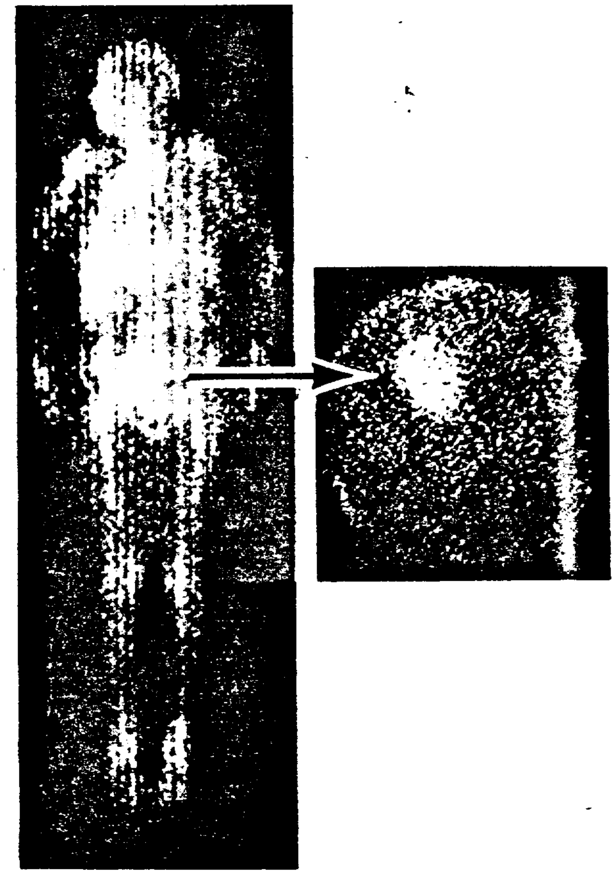

FIG. 5. Whole-body scans (anterior view) of woman with inoperable uterine carcinoma. Uptake of ^{67}Ga in lesion in pelvis is seen. ^{67}Ga accumulation also occurred in liver, selected portions of skeleton and probably in intestinal tract. Scintiphoto of lesion in pelvis is shown. Scintiphoto was anterior view and centered over pelvis. Lesion is seen to be to right of midline.

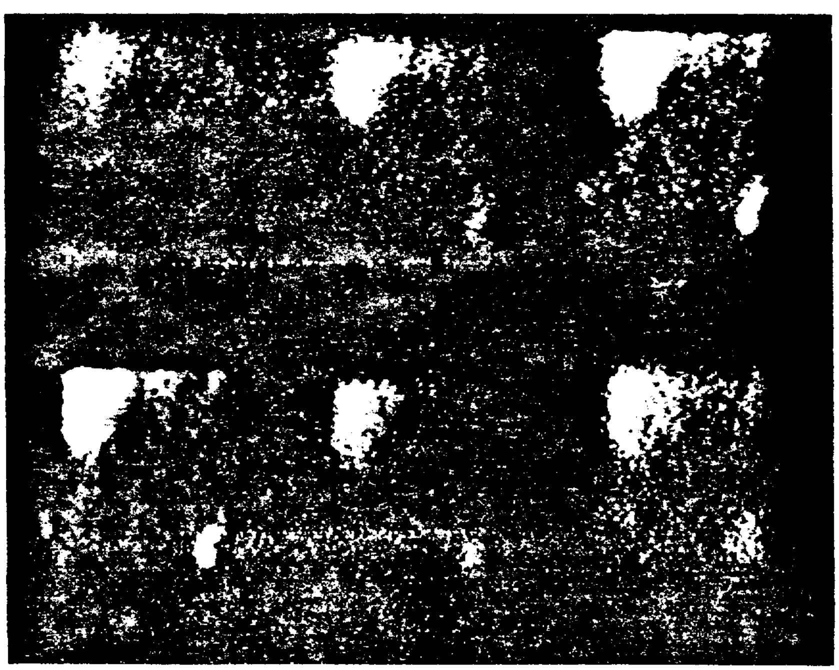

FIG. 6. Tomographic scans (anterior view) of abdomen and pelvis in patient with Hodgkin's granuloma. Accumulation of radioactivity in region of left anterior-superior iliac spine is seen.

posterior abdomen for tumor involvement in these areas. At the time of the ^{67}Ga study the patient was having nocturnal febrile episodes but no evidence of Hodgkin's lymphoma could be obtained by routine clinical techniques. Tomographic scans of the abdomen and pelvis showed an area of increased uptake in the region of the left iliac crest (Fig. 6). Subsequent to obtaining the scans, a biopsy of this region was obtained which generally showed myeloid hypoplasia and fibrosis with the presence of plasma cells and eosiniphilic and neutrophilic granulocytes in a pattern suggestive, but not diagnostic, of Hodgkin's granuloma. Subsequent to this study a ^{85}Sr bone scan was obtained which also showed abnormal localization in the left iliac crest.

RM had giant follicular lymphoblastoma with known involvement of mesenteric nodes. These nodes were irradiated immediately before the ^{67}Ga study. Prior to irradiation the patient had pericardial effusion and suspected pericardial involvement by the lymphoma. Subsequent to aspiration of the pericardial effusion, air was instilled in the pericardial sac. Radiographs obtained immediately thereafter failed to show any thickening of the pericardium nor any evidence of pericardial or mediastinal involvement with the lymphoma. Figure 7 shows a tomoscan of this patient 6 days after ^{67}Ga administration. Localized areas of increased uptake in the region of the heart can readily be seen.

WP had a history of seminoma treated successfully with surgery and radiation and was taking androgenic steroids. A clinical diagnosis of pheochromocytoma had been made, and the ^{67}Ga study was performed in an attempt to localize the lesion. A whole-body scan 1 day after the administration of ^{67}Ga-citrate failed to show any abnormal localization of ^{67}Ga, except for two areas in the chest. Tomographic scans of the upper abdomen and lower chest on this patient are present in Fig. 8. In addition to uptake of activity in the liver, increased activity is seen in two discrete areas. in the left and right chest. These areas of increased uptake of ^{67}Ga are placed anteriorly on the chest in this patient since the region of maximum localization is within 2 in. of the tomographic detector head. The patient had gynecomastia, and lateral views of the chest demonstrated that the ^{67}Ga uptake was localized to flat plaque-like areas corresponding to the gynecomastia.

Table 1 summarizes the results obtained in 18 patients with various neoplastic disorders. Eleven of these subjects showed sufficient localization of the ^{67}Ga in tumors to be useful in tumor localization. In several of these cases ill-defined accumulation of ^{67}Ga in pelvis (female), mediastinum and throughout the abdomen was noted. The significance and mechanism of such accumulation is yet to be determined. The variable amount of ^{67}Ga found in the bowel presented problems in interpretation of abdominal lesions during the study.

DISCUSSION

The reason for the apparent concentration of trace elements in tumors is not known. In the present study with ^{67}Ga-citrate the carrier-free metal form was administered bound to a metabolizable chelate. The gallium-citrate complex readily dissociates particularly if the pH is lowered. The uptake of the gallium in the liver may be due to hepatic metabolism of the citrate liberating the free gallium to form proteinate complexes within the liver. Moreover, in the absence of a specific binding protein for a given metal, the metalo-proteinate complex is frequently removed from the blood by the liver, and this could also contribute to the hepatic uptake of this material. Since the gallium appears to bind readily to bone apatite crystals, the ^{67}Ga uptake in bone in the present studies could have resulted from gallium-apatite crystal association competing with the other materials binding the gallium in the blood perfusing the bone. The variation in uptake in various bones throughout the body may reflect variable bone-blood flow to given regions of bone or variations in metabolic activity in these regions.

Many investigators have reported that the pH in the intracellular and interstitial fluid around many tumors is lower than around normal tissue because of the preponderance of anaerobic to aerobic glycolysis in tumors resulting in a local lactic acidosis. It is possible that the uptake of the ^{67}Ga in the tumors presented in this and previous papers is a reflection of the increase in the gallium-citrate dissociation which occurs when the pH is lowered. This would allow for local formation of gallium proteinate complexes. Alternatively, the diminished aerobic glycolysis noted in some tumors may reflect heme enzyme deficiency within the tumor (cytochromes, etc.), and accumulation of trace metals and hematoporphyrins by tumors (*6*) may represent attempts at heme enzyme synthesis.

Although it is clear that ^{67}Ga administered as a citrate complex can localize in a wide variety of human tumors, this localization frequently occurs only in some of the tumors present in the patient with other tumors not showing such localization. Whether such variation in localization reflects metabolic activity within the tumor, such as that described above, remains to be determined. The variation in the ^{67}Ga uptake in various regions of bone (e.g. around joints and pelvis) in the spleen and in pelvis

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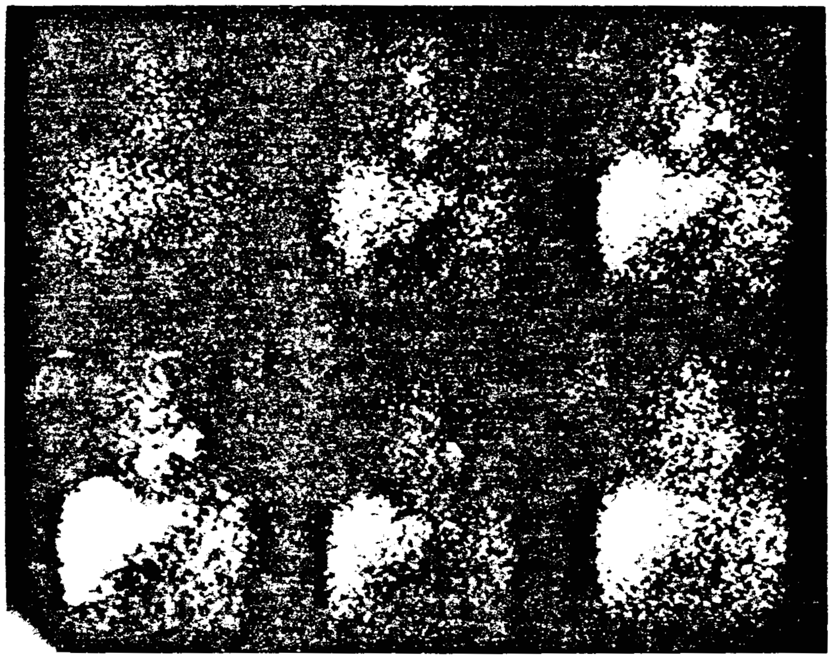

FIG. 7. Tomographic scans (anterior view) of chest in patient with giant follicular lymphoblastoma and pericardial effusion. Concentration of ^{67}Ga in region of heart is seen.

of female patients makes it difficult to determine whether tumors are present in these regions.

In this study the ^{67}Ga was shown to localize in the breast of a patient with gynecomastia and in the region of the vagina and uterus in female patients without demonstrable pelvic pathology. The highest uptake of tumor compared to nonspecific background activity was obtained 48 hr oı more after the administration of the ^{67}Ga-citrate. Little change in the distribution of ^{67}Ga was observed after 48 hr.

SUMMARY

The ^{67}Ga-citrate was administered to 18 patients with a variety of malignant neoplasias. In 11 patients definite abnormal localization of the ^{67}Ga in tumors occurred. Positive results were obtained in all five patients with lymphoma. The Anger whole-body counter, scintillation camera and tomographic scanner all generally showed good resolution of the tumor from surrounding tissue. However, the tomo-

FIG. 8. Tomographic scans (anterior view) of lower chest and upper abdomen in patient with gynecomastia. Concentration of ^{67}Ga in two discrete areas is seen just above level of diaphragm. This proved to be ^{67}Ga in gynecomastia.

TABLE 1. RESULTS IN 18 PATIENTS WITH NEOPLASTIC DISORDERS

Patient/sex	Diagnosis	Therapy to tumor prior to study	Findings
JA/M	Hodgkin's granuloma	None	Good uptake in lesions in mediastinum and L.U.Q.
RG/M	Hodgkin's granuloma	Radiation to known lesions (~6 years prior to study)	Good uptake along left chest wall in region of previous radiation Rx, minimal equivocal uptake in palpable left axillary nodes
GB/M	Hodgkin's granuloma	None	Good uptake in mediastinal lesion, unusual prolonged retention of activity (6 days) in abdomen
SH/F	Hodgkin's granuloma	Radiation to known lesions (6–9 months prior to study)	Uptake in left anterior superior iliac spine and in pelvis
RM/M	Giant follicular lymphoblastoma	Radiation to abdomen nodes (immediately prior to study)	Uptake in heart region and L.U.Q.
JV/M	Carcinoma of stomach	None	Minimal but definite uptake in gastric lesion
HS/F	Carcinoma of stomach	None	No uptake in tumor
HH/F	Carcinoma of pancreas	None	No uptake in pancreatic tumor, minimal, ill-defined uptake in mediastinum
EY/M	Hepatoma	None	Good uptake in some of the lesions in liver and lungs
AW/F	Carcinoma of uterus	None (post-bilateral oophorectomy)	Uptake in L.L.Q. not felt to correspond to carcinomatous spread
AB/F	Carcinoma of uterus	None	Good uptake in uterine tumor and in some of the lung metastases
MS/F	Ovarian carcinoma	Chemotherapy	Moderate uptake in pelvis and Mediastinum. No uptake in lung lesions
MB/F	Ovarian carcinoma Rx 10 years previously. Presently has lesions in lung	Chemotherapy	No uptake in pelvic or lung lesions
VL/F	Carcinoma of breast (multiple skin and liver metastases)	Chemotherapy	No uptake in known tumors
GG/M	Alveolar cell carcinoma of lungs	Chemotherapy	No uptake in tumor
BA/F	Epithelial cell tumor of mediastinum	None	Good uptake in tumor
CP/M	Brain tumor	None	Poor but definite uptake in tumor
WP/M	Seminoma (cured) Pheochromocytoma (clinical diagnosis)	(androgens) None	Uptake in gynecomastia

graphic scanner had the advantage of also indicating the depth of tumor within the body. Generally when the ^{67}Ga localized in tumors, not all of the tumor mass within the body of the patient showed such accumulation, suggesting that variations in metabolic activity or vascular perfusion of the tumor were responsible for the localization.

Gallium-67 administered as the citrate can localize in a variety of non-neoplastic soft tissues. In the present study ^{67}Ga was noted in gynecomastia and variably in the pelvis of female patients. In several cases, the marked localization of the ^{67}Ga within the body appeared to give information concerning the presence of a tumor which could not be obtained by use of other clinical detection methods. These results suggest that chelated carrier-free metals, such as ^{67}Ga, will prove clinically useful in evaluating the presence and distribution of malignant neoplastic tissue in human subjects.

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LETTER TO EDITOR Improvements in the Preparation of ^{99m}Tc-Labeled Macroaggregated Ferrous Hydroxide (Tc-MAFH)
R. E. Boyd