USEFULNESS OF GALLIUM SCINTIGRAPHY IN PRIMARY AND METASTATIC BREAST CARCINOMA

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Gallium-67-citrate whole-body scintigraphy was incorporated into the evaluation of 125 patients with primary and metastatic breast carcinoma. A prospective analysis of these patients demonstrated gallium scanning to be limited in its corroborative value and of practical use only in detecting metastatic breast carcinoma in the mediastinum. Since the extent of tumor involvement is a significant prognostic factor, the gallium scan merits consideration for the detection of mediastinal metastases.

The detection of primary breast carcinoma and the documentation of the extent of the metastatic disease are of paramount importance for determining prognosis and therapy. Since ^{67}Ga scanning is a valuable adjunct in the diagnosis, staging, and therapeutic followup of Hodgkin's disease and the non-Hodgkin's lymphomas (*1,2*), malignant melanoma (*3*), hepatoma (*4*), and lung carcinoma (*5*), an evaluation of its localizing affinity for breast carcinoma was undertaken. This report presents our clinical experience with ^{67}Ga-citrate scintigraphy in 125 patients with primary and metastatic carcinoma of the breast.

FIG. 1. Anterior whole-body gallium scan in 62-year-old woman shows adenocarcinoma in left breast and left axilla. There is also increased activity in metastases in right breast.

METHOD

Gallium-67-citrate (35–50 μCi/kg) was administered intravenously 48–72 hr before scanning. Bowel purgatives were employed routinely to eliminate interfering gallium. A dual-probe 5-in. Ohio-Nuclear whole-body scanner with 5:1 minification and spectrometer window setting of 130–330 keV was used. Lateral rectilinear scans and scintillation camera images were obtained in equivocal cases.

The study population consisted of 125 female patients with breast carcinoma who were referred to the Department of Nuclear Medicine at the National Institutes of Health. The age range was from 20 to 70 years. All scintigrams (196) were interpreted by one of the authors (SML) without knowledge of the patient's clinical history. A group of 21 patients was scanned prior to biopsy or mastectomy, and 104 patients were studied either after mastectomy or, in cases deemed inoperable, before therapy. Scintigraphic findings were compared with clinical, roentgenographic, and histologic data.

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TABLE 1. GALLIUM UPTAKE IN METASTATIC BREAST CARCINOMA

Organ involvement	Gallium: Abnormal: Increased	Gallium: Abnormal: Decreased	Gallium: Normal	Number of patients
Bone	34		18	52
Liver	2	3	20	25
Lung	7		13	20
Brain	2		8	10

RESULTS

Gallium-67 whole-body scans revealed abnormal localization in 68 (54%) of 125 patients with breast carcinoma.

Of the 21 patients studied prior to surgery, 14 had abnormal scans. Gallium localization occurred in the primary lesion in 11 of these positive studies. In difficult diagnostic situations, lateral rectilinear views localized the relative thoracic hyperconcentration to the breast mass itself. In two cases, sites of suspected metastases were identified in addition to the primary lesion (Fig. 1). Gallium-67 demonstrated metastatic disease in three patients in whom the abnormal breasts did not reveal a focal accumulation of radionuclide.

Eighty-three postsurgical or inoperable patients had known metastatic tumor and 54 (65%) revealed gallium scan abnormalities. There was variable affinity of ^{67}Ga for breast carcinoma metastases in different organs (Table 1). Gallium scans demonstrated bone involvement in 34 (65%) of 52 patients with evidence of skeletal metastases. The bone scan, the most sensitive indicator of osseous metastases, was used in conjunction with the roentgenographic skeletal survey to determine bony involvement. While gallium asymmetries were apparent, abnormalities were more clearly defined with skeletal scintigraphy. Moreover, additional individual sites in the same patient were commonly identified with skeletal scintigraphy. An example of intense bone scan activity in multiple sites of metastases is given in Fig. 2 and is compared with less satisfactory gallium localization. In two instances, the gallium scan did visualize a site of skeletal metastasis prior to the bone scan and roentgenogram. Both patients, however, had multiple sites of known skeletal metastases.

Utilizing physical examination, liver function tests, percutaneous biopsy, and autopsy results as parameters of involvement, it was found that 25 patients had secondary hepatic neoplasms. Multiple focal defects were present on the ^{99m}Tc-sulfur colloid liver scan in 20 cases (Fig. 3). Gallium preferentially localized in only 2 (8%) of 25 patients. Two additional abnormal gallium scans had decreased activity corresponding to colloid defects. Advanced parenchymal replacement resulted in absent gallium uptake

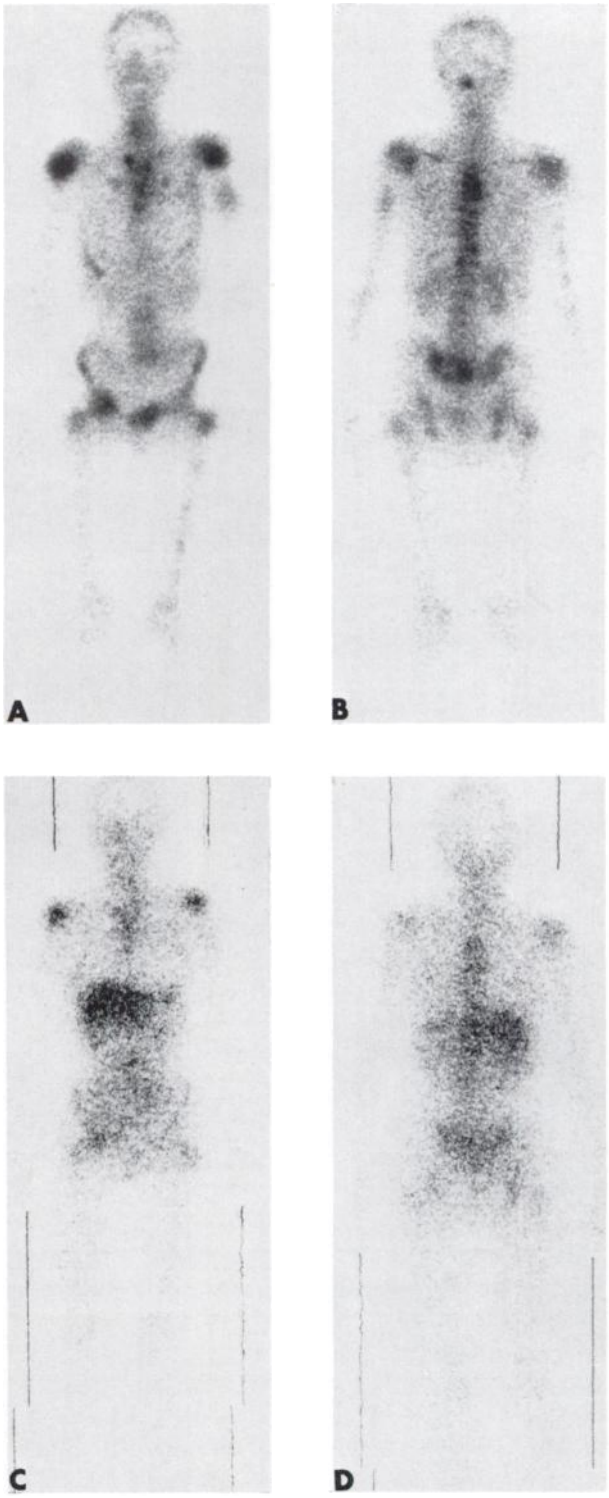


FIG. 2. Anterior (A) and posterior (B) whole-body ^{99m}Tc-diphosphonate scans demonstrate pronounced accumulation in multiple sites of metastatic breast carcinoma. Gallium scans (C and D) were far less rewarding showing increased activity in both shoulders, faint uptake in thoracic spine, and minimal asymmetry in right hip.

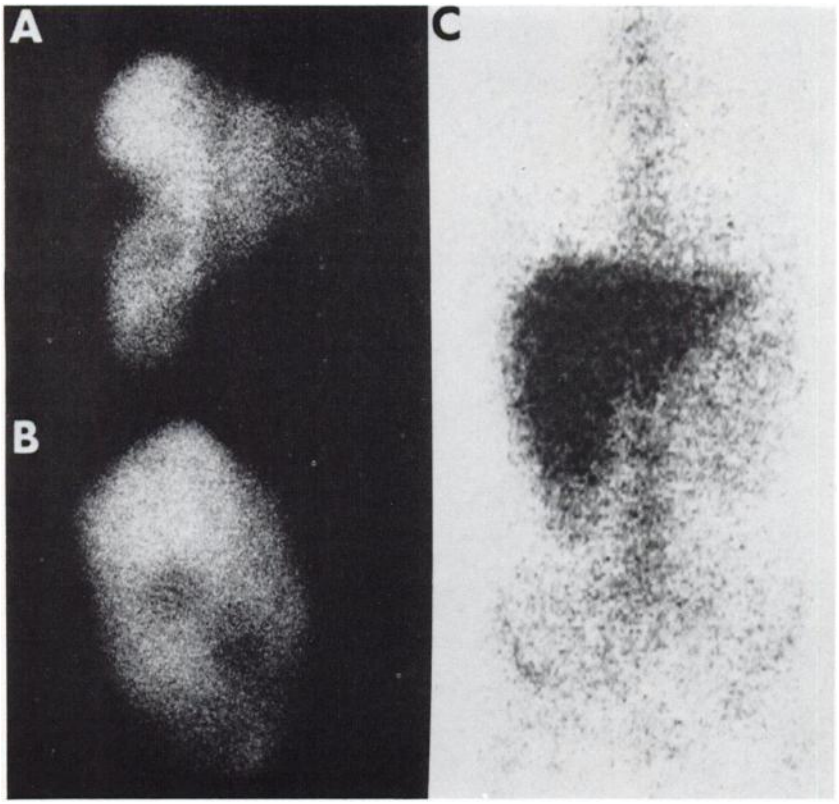


FIG. 3. Anterior (A) and right lateral (B) ^{99m}Tc-sulfur colloid scans show two large focal filling defects in right lobe of liver. Gallium activity (C) is homogeneous throughout, failing to differentiate biopsy-proven metastatic breast carcinoma.

by the liver in one instance. The technetium scan provided much greater reliability for demonstrating subtle changes in hepatic size.

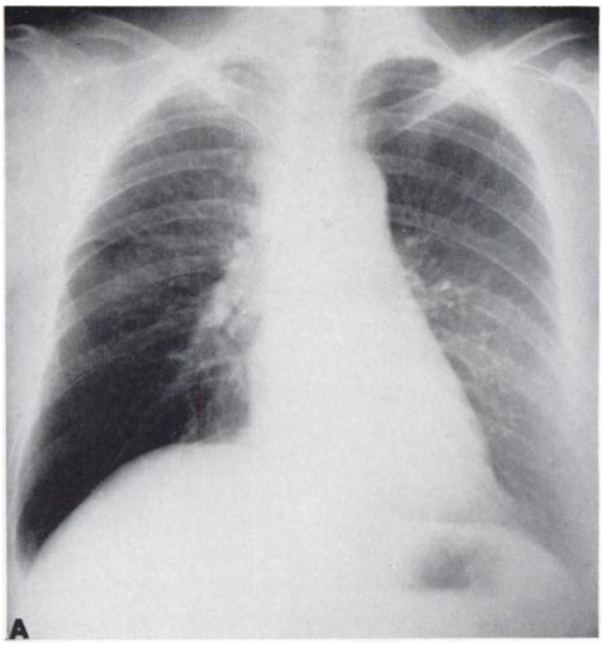
Of ten patients with autopsy-proven brain metastases, gallium localization was noted in two (20%). Better sensitivity was demonstrated with $^{99m}TcO_4^-$ with positive uptake in four patients.

Twenty patients had chest roentgenograms showing evidence of metastatic breast carcinoma including multiple pulmonary nodules, lymphangitic interstitial disease, pleural effusions, and extrapleural masses. The gallium scan confirmed metastases in only seven (35%).

The single most promising contribution of gallium scintigraphy was the detection of mediastinal tumor. Eight (10%) of the 83 patients with metastatic breast carcinoma had abnormal gallium localization in the mediastinum (Table 2). Autopsy performed on two patients was positive for metastases. Mediastinoscopy confirmed breast carcinoma metastases in four of five patients who underwent this procedure. In three cases, biopsy proof was obtained along with roentgenograms and tomograms that were unremarkable with regard to the mediastinum. Four of these eight patients entered remission on combination chemotherapy. The gallium scan returned to normal

TABLE 2. GALLIUM UPTAKE IN THE MEDIASTINUM IN PATIENTS WITH METASTATIC BREAST CANCER

Patient	^{67}Ga scan	Chest roentgenogram	Mediastinal tomography	Mediastinoscopy biopsy	Autopsy
CT	+	Normal	Normal	+	
MS	+	Normal	Normal	+	
RW	+	Parenchymal nodules	Normal	+	
LF	+	Parenchymal nodules, right hilar adenopathy	Right hilar adenopathy	+	
RH	+	Hilar adenopathy	Hilar adenopathy	−	
MF	+	Widened mediastinum			+
AW	+	Parenchymal nodules, radiation fibrosis			+
ID	+	Right upper lobe and right hilar masses	Right hilar masses		
EC	−	Hilar adenopathy	Hilar adenopathy	+	



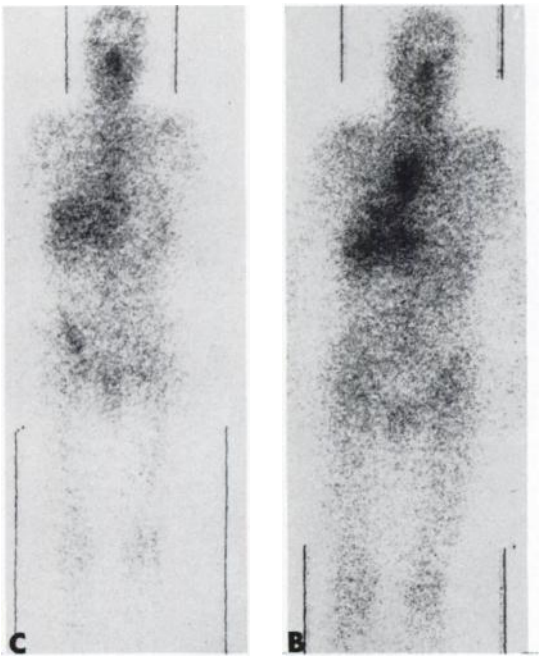


FIG. 4. Chest roentgenogram (A) demonstrates right mastectomy and chronic radiation changes in right upper lung. Gallium scan (B) shows intense mediastinal uptake. Following positive biopsy for metastatic breast carcinoma and subsequent chemotherapy, gallium scan is normal (C).

in all four cases. One additional patient (EC) had roentgenographic evidence of biopsy-proven hilar tumor but had no gallium uptake in the mediastinum.

CASE REPORTS

Case 1. MS, a 62-year-old woman, was diagnosed as having breast carcinoma 14 years prior to admission. On admission she presented with osseous metastases and small soft-tissue nodules at the mastectomy site. A chest roentgenogram (Fig. 4A) and full lung tomograms demonstrated no metastatic disease. Gallium failed to localize in the bony or soft-tissue tumor but was markedly positive in the mediastinum (Fig. 4B). Mediastinoscopy confirmed metastatic breast carcinoma. Following combination chemotherapy, the soft-tissue tumor regressed and the gallium scan reverted to normal (Fig. 4C).

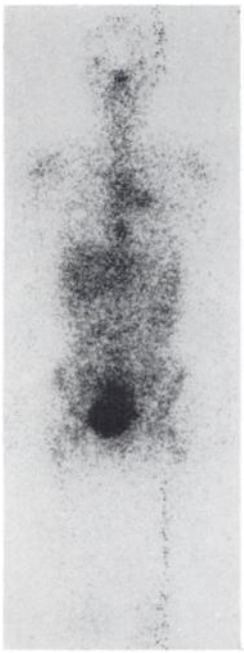


FIG. 5. Intense gallium concentration in sternum and mediastinum extending into left hilum is shown. Gallium was sole means of detection of mediastinal tumor. (Abdominal gallium cleared following laxatives.)

Case 2. CT, a 31-year-old woman with a history of bilateral mastectomies, was admitted with osseous metastases. Gallium localized in a known sternal metastasis and also concentrated in the mediastinum extending into the left hilar region (Fig. 5). Mediastinoscopy confirmed breast carcinoma in the presence of normal chest roentgenography and tomography.

Case 3. LF, a 44-year-old woman who had a right radical mastectomy 2 years prior to admission, presented with suspected pulmonary metastases. A chest roentgenogram and tomography demonstrated multiple lung nodules, the most prominent being in the right upper lobe and in the right hilum (Fig. 6A). The gallium scan was positive in the right hilum (Fig. 6B). Fiberoptic bronchoscopy was inconclusive, and mediastinoscopy was performed with biopsy corroborating metastatic breast carcinoma. A gallium scan 3 months later showed progression of mediastinal tumor commensurate with the radiographic findings (Fig. 6C). Following chemotherapy, the gallium scan showed minimal residual mediastinal

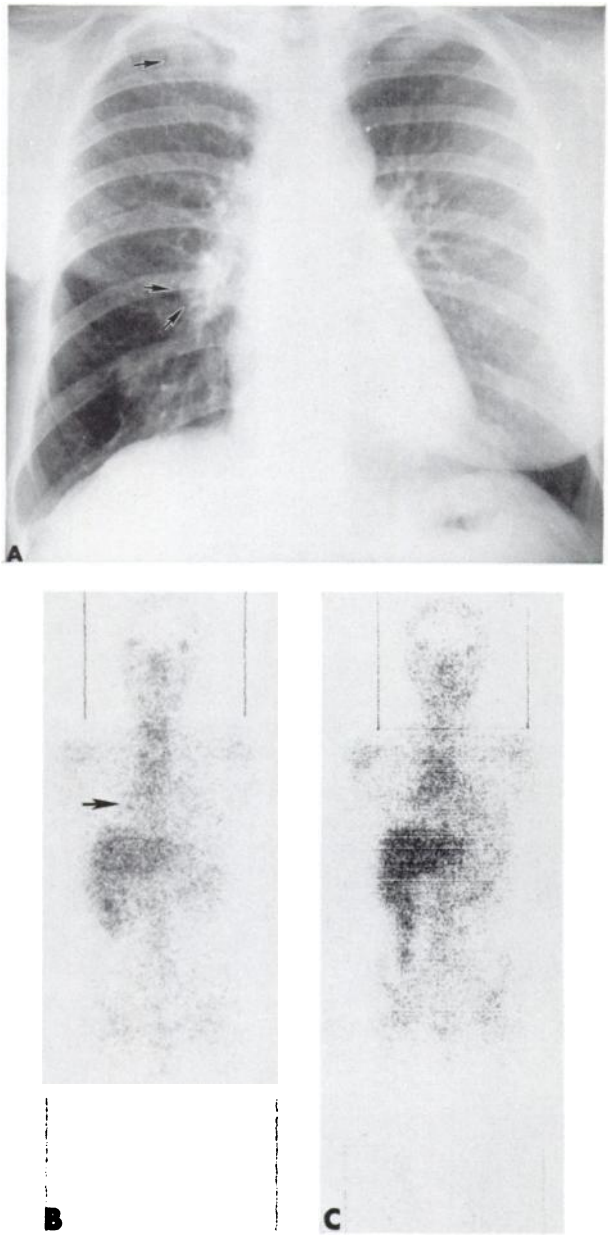


FIG. 6. Multiple pulmonary nodules are demonstrated in right upper lobe and right hilar region in patient 2 years after right radical mastectomy (A). Gallium showed uptake in mediastinum extending into right hilum (B). Followup scan shows more intense, diffuse mediastinal metastases (C).

activity in agreement with roentgenographic and clinical improvement.

Gallium-67 scans were obtained on 21 postoperative patients without evidence of metastases. Thirty normal studies corroborated disease-free status in 20 cases. In one patient, gallium scanning showed increased uptake in the mediastinum as the only evidence for presumed metastatic breast cancer (Fig. 7). After therapy, followup gallium scan was normal.

Thorough diagnostic followup of all sites of positive gallium uptake in 125 patients revealed no false-positive gallium scans. Inflammatory lesions accounted for abnormal gallium localization in three patients. Physiologic gallium activity was noted in the contralateral breast of a 35-year-old woman 2 months after a left mastectomy was performed. The patient was lactating in the postoperative period with unexplained elevated prolactin levels.

DISCUSSION

Routine gallium whole-body scintigraphy was incorporated into the evaluation of 125 consecutive breast cancer patients studied at the National Institutes of Health in order to determine its usefulness in breast carcinoma. With 90,000 new cases of breast cancer diagnosed each year, approximately 33,000 deaths anually, and essentially no statistical improvement in survival over the past 25 years, a sensitive tumor-scanning procedure would be most welcome. Gallium-67-citrate scanning was evaluated to determine its diagnostic capabilities as well as its contribution in metastatic followup.

Regarding primary carcinoma of the breast, gallium scanning has been most unrewarding when com-

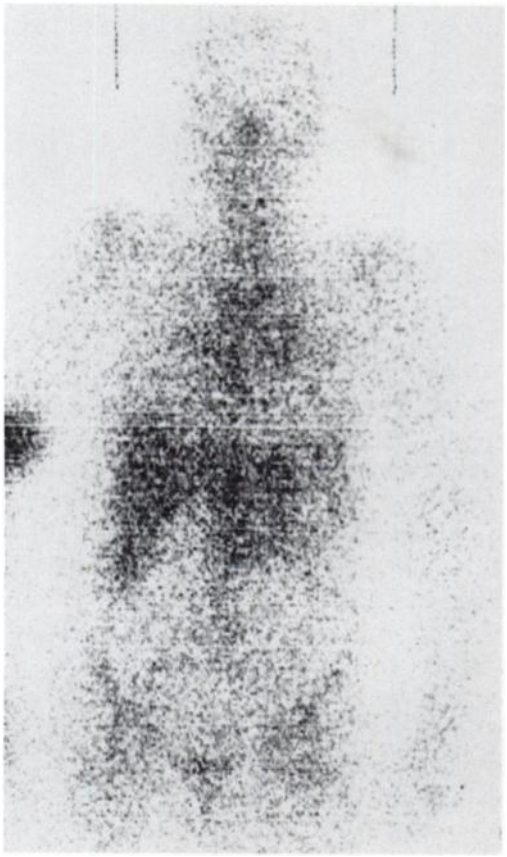


FIG. 7. Gallium uptake in mediastinum was only evidence of metastatic breast carcinoma in 50-year-old woman. After chemotherapy, gallium scan returned to normal.

pared to roentgenographic procedures. Sensitivity ranging from 20% to 72% has been reported by several authors (*6–9*). Our results with 21 documented cases was a disappointing 52%. Furthermore, the physical characteristics of ^{67}Ga are suboptimal for scintillation camera scintigraphy, and special breast views in our clinic have not added to overall accuracy (*10*).

In metastatic breast carcinoma, gallium was found to be less sensitive than organ-specific radionuclide procedures. Skeletal scintigraphy provided more superior information in the detection of osseous metastases. Technetium-99m-sulfur colloid scintigraphy was a more reliable indicator of secondary hepatic neoplasm and $^{99m}TcO_4^-$ was more sensitive than gallium in the detection of central nervous system metastases.

As a diagnostic adjunct in breast carcinoma patients, gallium scintigraphy is of unique value for the detection of mediastinal neoplasms. In cases of radiographically suspected but incompletely evaluated mediastinal involvement, gallium uptake is particularly useful for delineating the extent of mediastinal metastases. At the present time, whole-body gallium scans are included in the diagnostic workup of breast carcinoma patients as an effective noninvasive modality for studying the mediastinum.

REFERENCES

1. HOFFER PB, TURNER D, GOTTSCHALK A, et al: Whole-body radiogallium scanning for staging of Hodgkin's disease and other lymphomas. *Natl Cancer Inst Monogr* 36: 277–285, 1973

2. JOHNSTON G, BENUA RS, TEATES CD, et al: ^{67}Ga-citrate imaging in untreated Hodgkin's disease: Preliminary report of cooperative group. *J Nucl Med* 15: 399–403, 1974

3. MILDER MS, FRANKEL RS, BULKLEY GB, et al: Gallium-67 scintigraphy in malignant melanoma. *Cancer* 32: 1350–1356, 1973

4. LOMAS F, DIBOS PE, WAGNER HN: Increased specificity of liver scanning with the use of ^{67}gallium-citrate. *N Engl J Med* 286: 1323–1329, 1972

5. DELAND FH, SAUERBRUNN BJ, BOYD C, et al: ^{67}Ga-citrate imaging in untreated primary lung cancer: Preliminary report of cooperative group. *J Nucl Med* 15: 408–411, 1974

6. HIGASI T, NAKAYAMA Y, MURATA A, et al: Clinical evaluation of ^{67}Ga-citrate scanning. *J Nucl Med* 13: 196–201, 1972

7. LANGHAMMER H, GLAUBITT G, GREBE SF, et al: ^{67}Ga for tumor scanning. *J Nucl Med* 13: 25–30, 1972

8. LAVENDER JP, LOWE J, BARKER JR, et al: Gallium-67 citrate scanning in neoplastic and inflammatory lesions. *Br J Radiol* 44: 361–366, 1971

9. FOGH J: ^{67}Ga-accumulation in malignant tumors and in the prelactating or lactating breast. *Proc Soc Exp Biol Med* 138: 1086–1090, 1971

10. RICHMAN SD, BRODEY PA, FRANKEL RS, et al: Breast scintigraphy with ^{99m}Tc-pertechnetate and ^{67}Ga-citrate. *J Nucl Med* 16: 293–298, 1975