BREAST SCINTIGRAPHY WITH ^{99m}Tc-PERTECHNETATE AND ^{67}Ga-CITRATE

Steven D. Richman, Philip A. Brodey, Robert S. Frankel,
Ernest V. de Moss, Douglass C. Tormey, and Gerald S. Johnston

National Institutes of Health, Bethesda, Maryland

Radionuclide breast scintigraphy was evaluated as a noninvasive tumor-localizing modality. Technetium-99m-pertechnetate ($^{99m}TcO_4$) demonstrated good correlation between malignancy and positive scintigraphy (88% accuracy in 16 cases of breast carcinoma). The high false-positive rate (29% of proven benign breast disease) limits the use of $^{99m}TcO_4$ as an aid to differential diagnosis. Gallium-67-citrate (^{67}Ga) is limited as a diagnostic adjunct (localizing in only five of ten breast malignancies). Refined techniques of positioning, shielding, gamma camera imaging, and computer assistance have helped in visualizing abnormal radionuclide accumulation.

Early and accurate detection of breast carcinoma is of major importance. In the past decade, refined radiographic techniques including mammography and xeroradiography have made it possible to obtain excellent diagnostic results. A possible complementary modality, radionuclide breast scintigraphy, was evaluated as a noninvasive tumor-localizing technique utilizing ^{99m}Tc-pertechnetate and ^{67}Ga-citrate.

Several attempts have been made to detect breast tumors and to differentiate benign and malignant lesions using isotopic methods. Mammary scintigraphy was first proposed utilizing surface measurements of ^{32}P (*1*) and ^{42}K (*2*). In 1965, Sodee, et al (*3*) demonstrated ^{197}Hg-chlormerodrin localization in two of three primary carcinomas using a rectilinear scanner. Buchwald, et al using $^{197}HgCl_2$ (*4*) studied 26 patients with breast malignancy, 18 of whom were positive and 4 were questionable. Sannazzari, et al (*5*) confirmed the usefulness of $^{197}HgCl_2$ in demonstrating positivity in nine of ten breast malignancies. Bonte, et al (*6*) using ^{131}I-human serum albumin had some difficulty with rectilinear image quality, demonstrating two fair and two poor scans in large primary breast carcinomas.

Technetium-99m-pertechnetate is widely recognized as a brain-scanning agent but its ability to localize in extracranial neoplasms has also received attention. Whitley, et al (*7*) demonstrated abnormal accumulation in 17 of 26 neoplasms, a positive finding occurring in the single breast carcinoma investigated. Cancroft and Goldsmith (*8*) reported focal accumulation in four patients with breast masses diagnosed as malignant. Technetium-99m-pertechnetate did not concentrate abnormally in two patients with proven benign breast disease. Villarreal, et al (*9*) studied six patients with breast malignancy, five of whom had positive ^{99m}Tc-pertechnetate scintiscans. The high false-positive rate (3 of 15 proven benign and 3 of 15 presumed benign disease) led the authors to conclude that pertechnetate mammography would not be useful as a screening agent.

Most recently, ^{67}Ga-citrate has gained widespread popularity as a positive indicator of malignancy. This study is intended to evaluate and compare the specificity and reliability of ^{99m}Tc-pertechnetate and ^{67}Ga-citrate when they are used in the scintigraphic diagnosis of primary breast carcinomas.

METHOD

Breast scintigraphy was performed 15–60 min following the intravenous injection of 10–15 mCi of $^{99m}TcO_4$. Lateral, medial, and craniocaudal views were obtained with a Searle Radiographics HP gamma camera. The camera was interfaced with a Hewlett-Packard Scintigraphic Data Analyzer for histogram collection and data manipulation.

The patient was placed in either the sitting or the erect position and draped with a specially designed lead apron. Shielding and positioning were selected to attenuate background radiations from the thoracic and abdominal regions and thereby to expose only

Received Sept. 25, 1974; original accepted Nov. 10, 1974.

For reprints contact: Steven D. Richman, Clinical Center, Bldg. 10, Room 1B44A, Dept. of Nuclear Medicine, National Institutes of Health, Bethesda, Md. 20014.

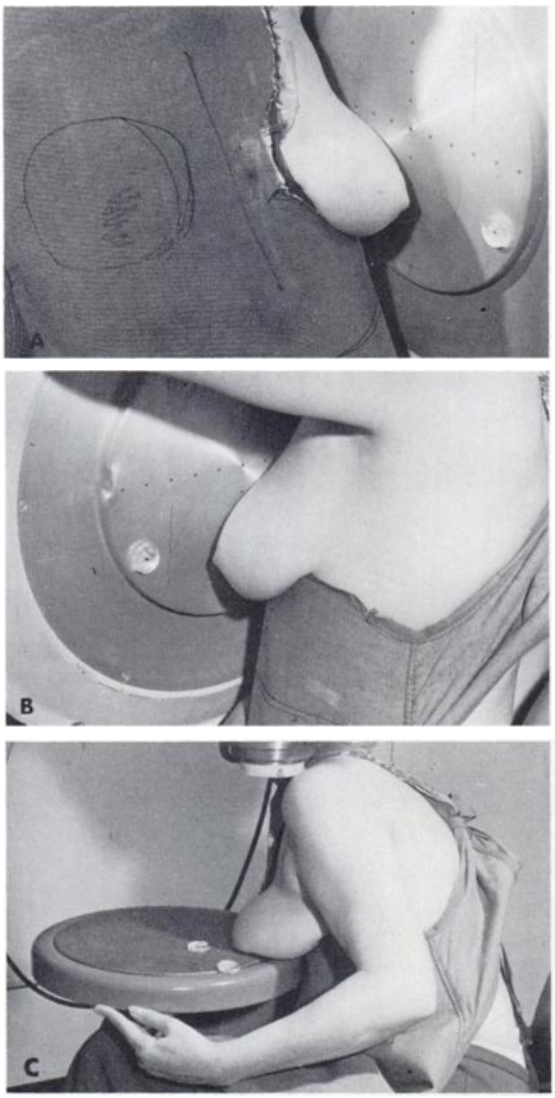

FIG. 1. Positioning of patient for lateral (A), medial (B), and craniocaudal (C) gamma camera breast scintigraphy. Cobalt-57 markers note nipple and axillary regions. Craniocaudal view is omitted in ^{67}Ga-citrate breast scintigraphy.

the breast for scintigraphic study. Cobalt-57 markers were placed on the collimator face to note the nipple and axillary regions. No compression device was used.

Using the high-resolution, low-energy collimator, 300,000 counts were obtained in lateral and medial views. Approximate scanning time was 200 sec for each view. In the lateral view, the breast was positioned in relief from the body wall and against the collimator face (Fig. 1A). In the medial view, the medial aspect of the same breast was positioned against the collimator and the ipsilateral arm was raised above the detector head (Fig. 1B). The craniocaudal view utilized the pinhole collimator with a 4.5-mm tungsten insert. Positioning was similar to conventional mammography with the collimator maneuvered as close to the breast as possible (Fig. 1C). Satisfactory images were obtained with 50–80,000 counts, which were accumulated in 250 sec.

After the intravenous injection of 50 μCi/kg ^{67}Ga-citrate, breast scans were performed at 48 hr. Patient positioning was identical to the pertechnetate scanning technique in the lateral and medial gamma camera views only. The high-energy collimator was used, accumulating 50,000 counts in approximately 300 sec. The counting rate was inadequate for the craniocaudal ^{67}Ga breast view.

Patients selected for scintigraphic study were those referred for radiographic breast evaluation. These patients included many with suspicious clinical findings and patients with a strong family history of breast cancer as well as those undergoing evaluation of the contralateral breast following previous mastectomy. Comparison of diagnostic accuracy was made with the proven techniques of mammography and xeroradiography. If brain scan was indicated, appropriate views were obtained following $^{99m}TcO_4$ breast scintigraphy. Potassium perchlorate (300 mg) was given prior to $^{99m}TcO_4$ administration. Gallium-67 breast views were most often obtained in conjunction with whole-body rectilinear studies.

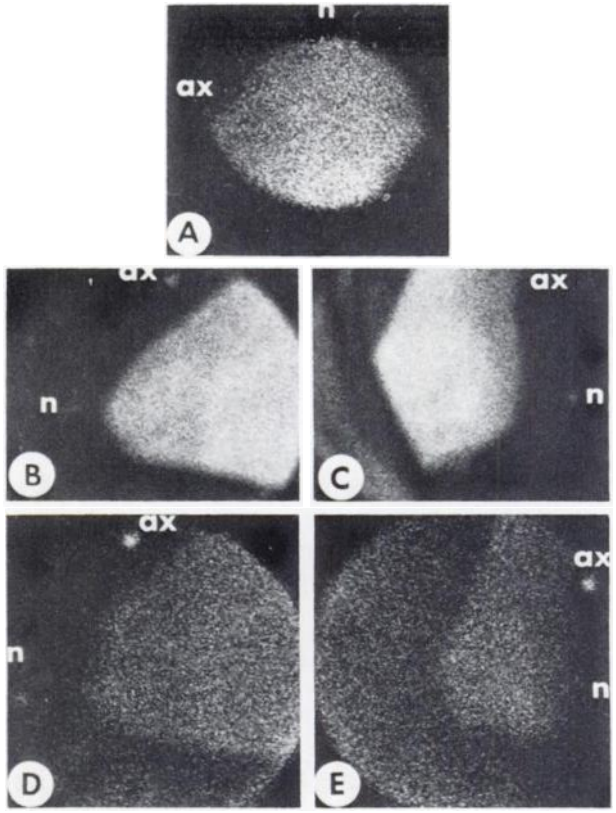

FIG. 2. Normal craniocaudal (A), lateral (B), and medial (C) ^{99m}Tc-pertechnetate breast scintigraphy demonstrate homogeneous radionuclide activity. Gallium-67-citrate lateral (D) and medial (E) views of same breast show uniform accumulation. There is often relative increase in radioactivity close to chest wall in all views. Sharp delineation in medial views is caused by lead shielding against chest wall. Axillary and nipple ^{57}Co markers are evident.

TABLE 1. COMPARATIVE STUDIES IN BREAST CANCER PATIENTS

Case No.	Age	Clinical diagnosis	Radiographic diagnosis	$^{99m}TcO_4$	^{67}Ga	Pathologic diagnosis
1	48	Carcinoma	+	+	+	Infiltrating ductal
2	57	Carcinoma	+	+	+	Infiltrating ductal
3	54	Carcinoma	+	+	+	Infiltrating ductal
4	47	Carcinoma	+	+	+	Infiltrating ductal
5	52	Carcinoma	+	+	−	Inflammatory
6	55	Carcinoma	+	+	−	Infiltrating ductal
7	40	Carcinoma	+	+	−	Infiltrating ductal
8	43	Carcinoma	+	+	−	Infiltrating ductal
9	47	Carcinoma	+	+		Infiltrating ductal
10	60	Carcinoma	+	+		Infiltrating ductal
11	53	Carcinoma	+	+		Infiltrating ductal
12	28	Carcinoma	+	+		Infiltrating ductal
13	58	Carcinoma	+		+	Infiltrating ductal
14	43	Carcinoma	Suspicious	+		Infiltrating ductal
15	50	Benign	Suspicious	−	−	Infiltrating ductal
16	45	Benign	Fibrocystic	+		Carcinoma in situ
17	45	Benign	Suspicious	−		Carcinoma in situ
		14+/3−	13+/4−	14+/2−	5+/5−	17

RESULTS

The normal homogeneous breast images of ^{99m}Tc-pertechnetate and ^{67}Ga-citrate are shown in Fig. 2.

Seventeen cases of breast carcinoma were investigated (Table 1). Of these, 16 cases underwent ^{99m}Tc-pertechnetate breast scintigraphy and 14 demonstrated abnormal radionuclide accumulation. There was excellent anatomic correlation with clinical, radiographic, and pathologic localization of malignancies. Discrete, focal localization of $^{99m}TcO_4$ was the most common finding.

In Case 1 (Table 1), the craniocaudal views of mammography and xeroradiography demonstrate a malignancy (Fig. 3A and B). The ^{99m}Tc-pertechnetate scintiphoto (Fig. 3C) confirms the tumor demonstrating a focal accumulation in the subareolar region. A radical mastectomy was performed.

A lesion in the left breast, Case 2 (Table 1), was diagnosed as malignant on mammography and xeroradiography (Fig. 4A and B). The $^{99m}TcO_4$ scintiphoto and the computer representation (Fig. 4C and D) show the malignant mass. Computer assistance (Fig. 4D) demonstrates a larger abnormality than previously suspected by other studies. This latter finding was confirmed at surgery. Computer enhancement including background subtraction and smoothing techniques have proved useful in augmenting abnormalities.

A curvilinear peripheral $^{99m}TcO_4$ increase in Case 10 (Table 1) corresponds with marked skin thickening in that breast both clinically and radiographically. A very positive and diffuse increase in pertechnetate activity representing a large inflammatory carcinoma was found in Case 5 (Table 1). The mottled, irregular and increased uptake of ^{99m}Tc-pertechnetate in the left breast of Case 9 (Table 1) occurred 2 days after aspiration biopsy (Fig. 5). There was also abnormal uptake of ^{99m}Tc-polyphosphate in the soft-tissue tumor (Fig. 5D). Biopsy was positive for malignancy.

Two studies failed to demonstrate any abnormal ^{99m}Tc-pertechnetate accumulations. Both of these

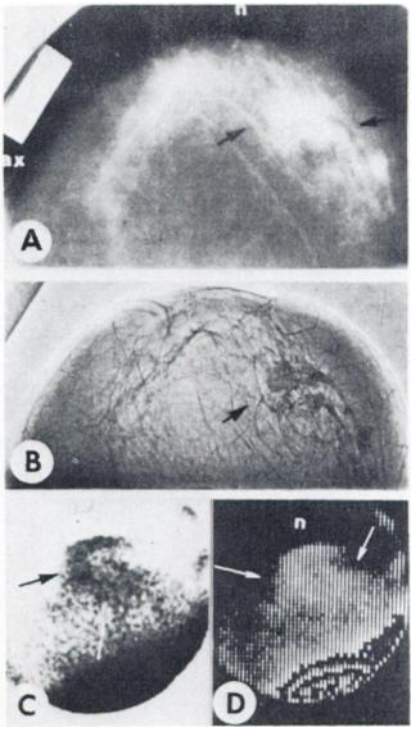

FIG. 3. Craniocaudal mammography (A), xeroradiography (B), and ^{99m}Tc-pertechnetate breast scintigraphy (C) demonstrate malignant mass with excellent anatomic correlation. Computer representation (D) augments abnormal finding.

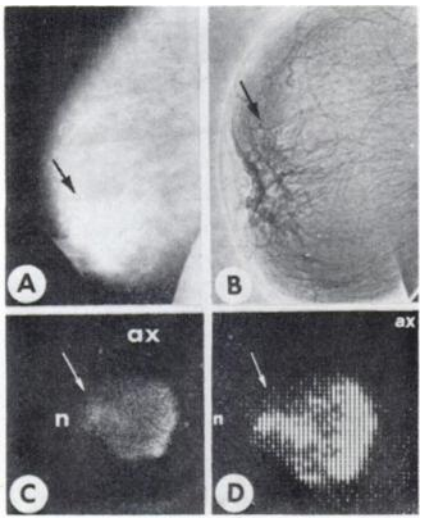

FIG. 4. Mediolateral mammography (A), mediolateral xeroradiography (B), and lateral ^{99m}Tc-pertechnetate breast scintigraphy (C) reveal carcinoma in left breast. Computer histogram (D) shows more extensive lesion confirmed at surgery.

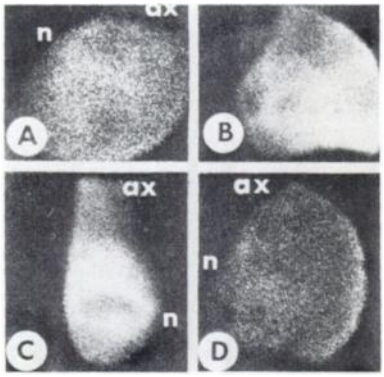

FIG. 5. Irregular, increased concentration of ^{99m}Tc-pertechnetate is demonstrated in craniocaudal (A), lateral (B), and medial (C) views. Technetium-99m-polyphosphate (D) also localized in this breast carcinoma complicated by recent aspiration biopsy.

patients had difficult diagnostic problems. Case 15 (Table 1) was seen 3 months following left radical mastectomy. A small, fibrocystic contralateral breast mass appeared unchanged clinically. Mammography was suspicious for malignant calcifications. Technetium-99m-pertechnetate breast scintigraphy was negative but biopsy demonstrated an intraductal carcinoma and a simple mastectomy was performed.

Cases 16 and 17 (Table 1) are in the same patient with bilateral carcinomas in situ. Technetium-99m-pertechnetate breast scintigraphy demonstrated one abnormal breast but the pertechnetate failed to localize abnormally in the other.

Gallium-67-citrate was less sensitive than $^{99m}TcO_4$ in detecting breast malignancy. Of ten patients with proven breast carcinoma, five had positive gallium breast scintigraphy, but five failed to demonstrate any abnormal concentration (Table 1). When both radionuclide mammograms were positive, lesions were better visualized with $^{99m}TcO_4$ than with ^{67}Ga.

Among the cases of proven carcinoma, many diagnoses were made with clinical palpation alone. Radiographic diagnosis including mammography and xeroradiography was accurate in 13 of 17 cases (Table 1).

Of 17 cases of biopsy-proven benign breast disease, 5 had abnormal accumulations of ^{99m}Tc-pertechnetate (Table 2). Gallium-67-citrate uptake was increased in only one of ten cases of benign disease.

Case 15 (Table 2) had abnormal $^{99m}TcO_4$ breast scintigraphy bilaterally (Fig. 6). The left breast contained carcinoma and a mastectomy was performed. Mirror-image biopsy of the right breast demonstrated only fibrocystic disease. Case 7 (Table 2) was clinically diagnosed as having fibrocystic disease with large cysts having been demonstrated at mammography. Calcium was noted to "layer" in one of these cysts in several radiographic views (Fig. 7). Technetium-99m-pertechnetate breast scintigraphy was negative and biopsy demonstrated a benign lesion.

An additional 15 patients with probable benign breast disease were evaluated with detailed clinical and radiographic study (Table 3). Biopsy was not performed in these cases. The evidence for benignity was confirmed by long-term followup. Both negative $^{99m}TcO_4$ and negative ^{67}Ga breast scintigraphy findings were highly reliable. The solitary false-positive gallium scan occurred in the same patient on three successive studies without explanation (Case 15, Table 3, Fig. 8). This shows a contralateral breast in a patient with previous mastectomy and the patient is neither pregnant nor lactating.

DISCUSSION

The patients studied thus far suggest that ^{99m}Tc-pertechnetate breast scintigraphy may be a valuable diagnostic adjunct in breast cancer. There was excellent correlation between malignancy and positive breast scintigraphy with $^{99m}TcO_4$ (88% accuracy). Among 17 patients with histologically proven benign breast disease studied to date, 5 demonstrated an abnormal concentration of $^{99m}TcO_4$ (29% false-positive rate). When the additional cases of presumed benign disease with no biopsy proof were included, however, the false-positive rate was 17%.

The exact mechanism of ^{99m}Tc-pertechnetate localization in breast tumors is not known. Increased tumor vascularity, changes in capillary permeability, and altered cellular function as suggested by Cancroft and Goldsmith (*8*) are all tenable hypotheses for this observation. That ^{99m}Tc-diphosphonate may localize in breast carcinomas through similar mechanisms is plausible (*10*). Technetium-99m-polyphos-

TABLE 2. COMPARATIVE STUDIES IN BENIGN BREAST DISEASE

Case No.	Age	Clinical diagnosis	Radiographic diagnosis	$^{99m}TcO_4$	^{67}Ga	Pathologic diagnosis
1	64	Benign	Fibrocystic	—	—	Fibrocystic
2	39	Benign	Fibrocystic	—	—	Fibrocystic
3	41	Benign	Fibrocystic	—	—	Fibrocystic
4	37	Benign	Fibrocystic	—	—	Fibrocystic
5	29	Benign	Fibrocystic	—	—	Blue dome cyst
6	20	Benign	Fibroadenoma	—		Fibroadenoma
7	43	Benign	Suspicious (Ca^{++})*	—		Fibrocystic
8	51	Benign	Suspicious	—	—	Fibrocystic
9	38	Suspicious	Fibrocystic	—		Fibrocystic
10	52	Suspicious	Multiloculated cyst	—	—	Fibrocystic
11	53	Suspicious	Benign cyst	—		Fibrocystic
12	36	Suspicious	Fibrocystic	—		Sclerosing adenosis
13	30	Suspicious	Fibrocystic	+		Fibroadenoma
14	30	Suspicious	Fibrocystic	+		Fibrocystic
15	43	Benign	Fibrocystic	+	—	Fibrocystic
16	46	Suspicious	Fibrocystic	+	—	Fibrocystic
17	51	Suspicious	Suspicious	+	+	Sclerosing adenosis
		8+/9—	3+/14—	5+/12—	1+/9—	17

* Ca^{++} is milk of calcium in large cyst.

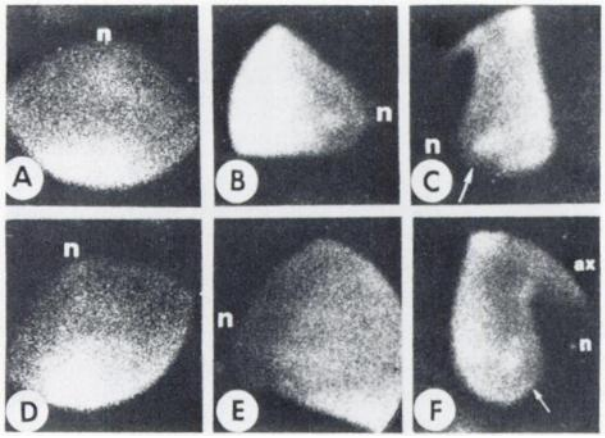

FIG. 6. Craniocaudal (A), lateral (B), and medial (C) $^{99m}TcO_4$ scintiphotos of right breast demonstrate focal concentration similar to abnormal accumulation in left breast; craniocaudal (D), lateral (E), and medial (F). Left was carcinoma. Right demonstrated only fibrocystic disease.

phate has accumulated in the breast on whole-body bone scans in several of these patients with breast carcinoma. In such cases, special camera views as described for ^{99m}Tc-pertechnetate breast scintigraphy confirmed localization of abnormal uptake in the breast tissue.

As an anion of Group VII of the periodic table, the pertechnetate ion like its analog iodide is concentrated in breast secretions. Lactating patients will concentrate $^{99m}TcO_4$ in breast milk (*11*) as will patients with breast secretions of the amenorrhea–galactorrhea syndrome (*12*).

Neoplastic and inflammatory tissue localization of ^{67}Ga-citrate is well established (*13–16*). The affinity of ^{67}Ga for soft-tissue tumor varies with the origin of the neoplasia. Primary breast cancer has proved less detectable than lymphoma or lung cancer. Higasi, et al (*17*) studied 16 cases of breast carcinoma in whom 8 were positive with ^{67}Ga scintigraphy.

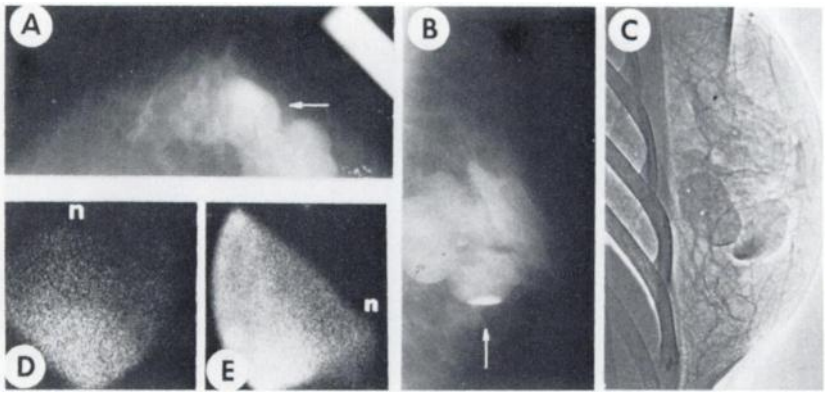

FIG. 7. Craniocaudal mammography (A), mediolateral mammography (B), and mediolateral xeroradiography (C) demonstrate fibrocystic disease with "milk of calcium" in one large cyst. Craniocaudal (D), and lateral (E) $^{99m}TcO_4$ breast scintigraphy is negative. Fibrocystic disease was confirmed at surgery.

TABLE 3. COMPARATIVE STUDIES IN PROBABLE BENIGN BREAST DISEASE

Case No.	Age	Clinical diagnosis	Radiographic diagnosis	$^{99m}TcO_4$	^{67}Ga	Clinical and radiographic followup (months)
1	58	Benign	Fibrocystic	—		8
2	56	Benign	Fibrocystic	—		8
3	59	Benign	Fibrocystic	—	—	9
4	50	Suspicious	Fibrocystic	—	—	6
5	40	Benign	Fibrocystic	—	—	6
6	43	Benign	Fibrocystic	—	—	7
7	48	Benign	Fibrocystic	—	—	8
8	41	Benign	Fibrocystic		—	5
9	32	Suspicious	Fibrocystic	—	—	7
10	52	Benign	Fibrocystic	—	—	5
11	60	Benign	Fibrocystic		—	6
12	45	Benign	Fibrocystic	—	—	5
13	48	Benign	Fibrocystic	—	—	8
14	41	Benign	Fibrocystic	—		5
15	50	Suspicious	Fibrocystic	—	+	8
		3+/12—	/15—	/13—	1+/11—	15

FIG. 8. Anterior whole-body ^{67}Gallium scan demonstrates abnormal accumulation in left breast. "False-positive" localization occurred on three successive studies during 8-month period.

Among 14 patients with metastatic breast carcinoma, Edwards and Hayes (*13*) demonstrated 10 with abnormal concentration of ^{67}Ga. The technique of using special gamma camera views described here does not seem to improve the degree of accuracy noted with rectilinear scanning, which is about 57% (*18*).

The diffuse increase in ^{67}Ga activity in the mammary glands during pregnancy or puerperium makes diagnosis in these patients extremely difficult (*19,20*).

When used as an adjunct to radiographic and thermographic evaluation of breast diseases, radionuclide breast scintigraphy may enhance diagnostic accuracy. At present, ^{67}Ga appears limited in its role as a primary breast cancer localizing agent. It is necessary to be cautious in supporting the validity of $^{99m}TcO_4$ breast scintigraphy. The high false-positive rate limits the use of ^{99m}Tc-pertechnetate breast scintigraphy for screening purposes and in differential diagnosis. Technetium-99m-pertechnetate localization may prove useful in the preoperative documentation of the extent of breast cancer or the evaluation of the response to therapy.

Refined techniques of positioning and shielding have helped to better visualize abnormal accumulations. Improvements of gamma camera imaging and better applications of computer assistance may further define abnormalities.

More selective radionuclides, perhaps related to hormones and their receptor sites in breast neoplasia, would prove invaluable in the detection and treatment of breast cancer.

ACKNOWLEDGMENT

The technical excellence and cooperation of Sybil J. Swann and Camille L. Boyce are gratefully acknowledged.

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