BREAST SCINTIGRAPHY WITH

$^{99m}$Tc-PERTECHNETATE AND $^{67}$Ga-CITRATE

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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 $^{45}$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...
Satisfactory images were obtained with 50–80,000 counts, which were accumulated in 250 sec.

After the intravenous injection of 50 μCi/kg ⁶⁷Ga-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 ⁶⁷Ga 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 ⁹⁹ᵐTcO₄⁻ breast scintigraphy. Potassium perchlorate (300 mg) was given prior to ⁹⁹ᵐTcO₄⁻ administration. Gallium-67 breast views were most often obtained in conjunction with whole-body rectilinear studies.

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).
TABLE 1. COMPARATIVE STUDIES IN BREAST CANCER PATIENTS

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Clinical diagnosis</th>
<th>Radiographic diagnosis</th>
<th>99mTcO4</th>
<th>67Ga</th>
<th>Pathologic diagnosis</th>
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<tr>
<td>1</td>
<td>48</td>
<td>Carcinoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Infiltrating ductal</td>
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<td>2</td>
<td>57</td>
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<td>+</td>
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<td>Infiltrating ductal</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>Carcinoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>4</td>
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<td>Carcinoma</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Inflammatory</td>
</tr>
<tr>
<td>5</td>
<td>52</td>
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<td>-</td>
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<tr>
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<td>-</td>
<td>-</td>
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<tr>
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</tr>
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<td>8</td>
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<td>9</td>
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<td>+</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>11</td>
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<td>+</td>
<td>-</td>
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<tr>
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<td>+</td>
<td>-</td>
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<tr>
<td>14</td>
<td>43</td>
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<td>-</td>
<td>Infiltrating ductal</td>
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<tr>
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<td>50</td>
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<td>-</td>
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<td>-</td>
<td>Carcinoma in situ</td>
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<tr>
<td>17</td>
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<td>-</td>
<td>Carcinoma in situ</td>
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<td>13+/4—</td>
<td>14+/2—</td>
<td>5+/5—</td>
<td>17</td>
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</table>

RESULTS

The normal homogeneous breast images of 99mTc-pertechnetate and 67Ga-citrate are shown in Fig. 2.

Seventeen cases of breast carcinoma were investigated (Table 1). Of these, 16 cases underwent 99mTc-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 99mTcO4, 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 99mTc-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 99mTcO4, 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 99mTcO4 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 99mTc-pertechnetate in

FIG. 3. Craniocaudal mammography (A), xeroradiography (B), and 99mTc-pertechnetate breast scintigraphy (C) demonstrate malignant mass with excellent anatomic correlation. Computer representation (D) augments abnormal finding.
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 99mTcO 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 99mTcO 4 – than with 67Ga.

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 99mTc-pertechnetate (Table 2). Gallium-67-citrate uptake was increased in only one of ten cases of benign disease. Case 15 (Table 2) had abnormal 99mTcO 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 99mTcO 4 – and negative 67Ga 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 99mTc-pertechnetate breast scintigraphy may be a valuable diagnostic adjunct in breast cancer. There was excellent correlation between malignancy and positive breast scintigraphy with 99mTcO 4 – (88% accuracy). Among 17 patients with histologically proven benign breast disease studied to date, 5 demonstrated an abnormal concentration of 99mTcO 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 99mTc-pertechnetate localization in breast tumors is not known. Increased tumor vascularity, changes in capillary permeability, and altered cellular function as suggested by Can-croft and Goldsmith (8) are all tenable hypotheses for this observation. That 99mTc-diphosphonate may localize in breast carcinomas through similar mechanisms is plausible (10). Technetium-99m-polyphos-
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.
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, radiouclide 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.

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REFERENCES


4. BUCHWALD W, DIETHELM L, WOLF R: Scintigraphic


