ORIGINAL ARTICLE

# Molecular Breast Imaging: A New Technique Using Technetium Tc 99m Scintimammography to Detect Small Tumors of the Breast

DEBORAH J. RHODES, MD; MICHAEL K. O'CONNOR, PHD; STEPHEN W. PHILLIPS, MD; ROBIN L. SMITH, MD; AND DOUGLAS A. COLLINS, MD

OBJECTIVE: **To determine the sensitivity of molecular breast imaging (MBI) to detect small cancers of the breast.**

PATIENTS AND METHODS: **A cadmium-zinc-telluride gamma camera with a field of view of 20 × 20 cm was used. The detector elements were 2.5 × 2.5 mm. The gamma camera was mounted on a modified mammographic gantry. Between November 2001 and March 2004, we performed MBI on patients who were scheduled to undergo biopsy for a lesion suggestive of malignancy that was smaller than 2 cm on a mammogram. Patients were injected with 20 mCi of technetium Tc 99m sestamibi and underwent imaging immediately after injection. Using light pain-free compression, we obtained craniocaudal and mediolateral oblique views of each breast.**

RESULTS: **Of the 40 women included in the study, 26 had a total of 36 malignant lesions confirmed at surgery. Of these 36 lesions, 33 were detected by MBI (overall sensitivity, 92%). Of the 22 malignant lesions 1 cm or smaller in diameter, 19 were detected by MBI (sensitivity, 86%). Two patients had false-negative MBI results. Of the 14 malignant lesions larger than 1 cm in diameter, all were identified correctly by MBI. In 4 patients, MBI identified additional lesions not seen on mammography that were confirmed subsequently on magnetic resonance imaging and were true-positive cases at surgery. Three of these patients had lesions in the breast contralateral to the breast containing the initial mammographic finding suggestive of malignancy. Of 14 patients with no evidence of cancer at biopsy or surgery, 9 had true-negative (normal) scans and 5 had false-positive scans on MBI. False-positive results included benign fibroadenoma (2 patients), inflammatory fat necrosis (1 patient), benign breast parenchyma (1 patient), and complex sclerosing lesion (1 patient).**

CONCLUSION: **This prototype gamma camera system for MBI reliably detects malignant breast lesions smaller than 2 cm. Furthermore, we obtained the highest sensitivity (86%) yet reported for the detection of lesions smaller than 1 cm. These results suggest an important role for MBI, particularly for women in whom the sensitivity of mammography is reduced by the density of the breast parenchyma.**

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**CZT = cadmium-zinc-telluride; MBI = molecular breast imaging; MRI = magnetic resonance image**

Recent controversy regarding the efficacy of screening mammography highlights the need for more effective breast imaging techniques. The true sensitivity of breast cancer screening with mammography is uncertain, but estimates range from 66% to 88%.[1-9] A recent study of women with a familial or genetic predisposition to breast cancer found that the sensitivity of mammography was only 33% for detecting invasive breast cancers.[10]

Scintimammography with technetium Tc 99m sestamibi has been shown to be a good complementary technique to conventional mammography.[11,12] In 2 large multicenter studies of more than 2500 patients, the sensitivity and specificity of scintimammography for detecting malignant breast tumors were approximately 85%.[13,14] Although scintimammography has shown good overall sensitivity and specificity, the technology has never been fully optimized for breast imaging and performs poorly for small lesions. Mekhmandarov et al[15] reported a sensitivity of 55% for scintimammographic detection of nonpalpable breast tumors with a mean size of 1.34 cm. This limitation is particularly important in light of the finding that up to a third of breast cancers detected by screening mammography were smaller than 1.0 cm.[16]

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The poor sensitivity for small lesions found with conventional gamma cameras is due to several factors. The primary obstacle has been the large inactive area at the edge of the detector present on all conventional sodium iodide–based gamma camera systems. This area is typically 8- to 10-cm wide and prevents the gamma camera from imaging the area of breast tissue contiguous with the chest wall. Consequently, conventional scintimammography is performed with the patient supine and the detector positioned to obtain a lateral view of the breast. The absence of breast compression and the inability to position the detector close to the breast considerably degrade image quality and limit the ability of the gamma camera to detect small lesions. By comparison, positioning the detector to image the breast in the craniocaudal or mediolateral

From the Department of Internal Medicine and Division of Preventive and Occupational Medicine (D.J.R.), Department of Radiology (M.K.O., S.W.P., D.A.C.), and Department of Internal Medicine and Division of General Internal Medicine (R.L.S.), Mayo Clinic College of Medicine, Rochester, Minn.

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Address reprint requests and correspondence to Deborah J. Rhodes, MD, Division of Preventive and Occupational Medicine, Mayo Clinic College of Medicine, 200 First St SW, Rochester, MN 55905 (e-mail: rhodes.deborah@mayo.edu).

oblique projections, as in conventional mammography, could reduce breast thickness to 3 to 7 cm, using only light pain-free compression.[17] Thus, a detector designed specifically for breast imaging should improve the detection of both smaller and deeper lesions. Several laboratories have been working toward the development of such detectors.[17-19] Recently, Coover et al[19] performed scintimammography with a dedicated breast camera in patients with dense breasts and found a significant improvement in tumor detection with this system compared with a conventional gamma camera.

The aims of this work were to evaluate a new gamma camera system designed specifically for breast imaging and to determine the sensitivity of this system for detecting small cancers of the breast. We have termed this technique *molecular breast imaging* (MBI) to distinguish it from conventional scintimammography.

## PATIENTS AND METHODS

Consecutive patients referred for mammography at the Mayo Clinic in Rochester, Minn, between November 2001 and March 2004 were eligible for the study if they (1) had a lesion on mammography that was smaller than 2 cm and was considered highly suggestive of malignancy according to the Breast Imaging Reporting and Data System Atlas criteria and (2) were scheduled for biopsy (needle biopsy and/or surgical biopsy) of the lesion. Eligible patients were offered enrollment if the interval between mammography and scheduled biopsy allowed for performance of MBI. Patients who had undergone prior needle biopsy of the lesion were excluded from this study because such biopsies may effectively remove all or part of the lesion. After mammography, patients underwent MBI using a prototype gamma camera system. The longest interval between MBI and breast biopsy was 1 day. The same radiologist (S.W.P.) reviewed the mammogram and MBIs. If MBI revealed an additional lesion or lesions not seen on mammography, then additional mammograms, ultrasounds, and/or magnetic resonance images (MRIs) of the affected breast were obtained after consultation with the clinician and radiologist. If the additional lesion(s) appeared suggestive of malignancy on these images, biopsy of the area was performed.

Final diagnostic results were obtained from surgical excision or by core needle or vacuum-assisted biopsy. The size of malignant lesions was obtained from the surgical report, and the size of benign lesions was determined from either the mammogram or the ultrasound.

The prototype gamma camera system used in this study was a cadmium-zinc-telluride (CZT) semiconductor detector in place of a conventional sodium iodide detector.[20] The CZT detector was mounted on a modified mammographic gantry (Figure 1). The detector head was composed of an array of $80 \times 80$ CZT elements, each of dimensions $2.5 \times 2.5$ mm, giving a field of view of $20 \times 20$ cm. The system had an energy resolution of 6.5% (compared to approximately 10% for a conventional gamma camera), which allowed a reduction in scattered radiation present in the image data and improved image contrast. The system was equipped with a long-bore, high-resolution collimator matched to the CZT elements. The detector had approximately 2 to 3 mm of dead space between the edge and the active area of the detector, thereby allowing the system to be used in a manner comparable to a conventional mammographic unit. Data were acquired in an $80 \times 80$ matrix, which was padded to $128 \times 128$ for storage.

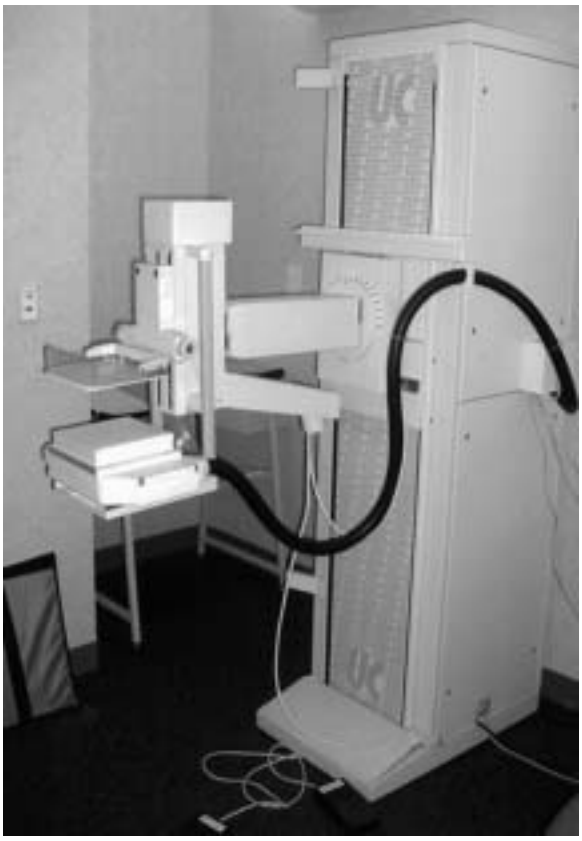

FIGURE 1. Prototype gamma camera mounted on a modified mammographic gantry.

For MBI, patients were injected with 20 mCi of $^{99m}$Tc sestamibi. The injection was given in the arm contralateral to the breast with the lesion suggestive of malignancy. A "cold start" (indwelling catheter or butterfly flush setup) was used to avoid infiltration of the radiopharmaceutical because such infiltration could lead to uptake in the axillary node. Patients underwent imaging 10 minutes after injec-

tion. Craniocaudal and mediolateral oblique views of each breast were obtained at 10 minutes per view, with the breast positioned between the detector and a compression paddle, as with conventional mammography. Light pain-free compression (15-lb force) was applied to both reduce breast thickness and limit movement artifact. Breast thickness and a subjective estimate of patient discomfort or pain during the procedure were recorded.

All MBI studies were evaluated visually for the presence of focal uptake. If present, focal uptake was scored as high, medium, or low. Normal or equivocal studies were scored as negative.

## RESULTS

This study enrolled 40 women (mean age, 61 years; age range, 39-86 years). Table 1 presents the MBI findings in the 40 patients. A total of 26 patients had breast cancer confirmed on biopsy and proceeded to surgery. Final diagnostic results (histopathologic testing) were obtained from surgical excision of the lesions in these patients and by core needle or vacuum-assisted biopsy in the remaining 14 patients. Three patients had bilateral breast cancer. In the 29 breasts with malignant disease, histopathologic tests confirmed the presence of 36 malignant lesions. These lesions included 23 cases of invasive ductal carcinoma, 4 cases of ductal carcinoma in situ, 3 cases of invasive lobular carcinoma, 4 cases of mixed invasive ductal carcinoma and invasive lobular carcinoma, 1 case of lobular carcinoma in situ, and 1 case of invasive papillary carcinoma.

Of the 36 malignant breast lesions, 33 were detected by MBI. False-negative results were obtained for 3 lesions in 2 patient studies. In 1 patient, the lesion was located deep within the breast (8 cm from nipple), whereas less than 7 cm of breast tissue had been included in the gamma camera field of view. Consequently, the lesion was missed on the MBI study because of this positioning error. In the other study, 2 small lesions (6 and 4 mm) were in the field of view on the MBI study but were not visualized on the scans. These results yielded an overall sensitivity of 92%.

Figure 2 presents a histogram of the distribution of malignant tumor diameters. There were a total of 22 malignant tumors 1 cm in diameter or smaller, of which 19 were detected on scintimammography for a sensitivity of 86%. All malignant tumors larger than 1 cm were detected. In 4 patients, MBI identified additional lesions not seen on mammography that were confirmed subsequently on MRI and were true-positive cases at surgery. Three of these patients had lesions in the breast contralateral to the breast containing the initial mammographic finding suggestive of malignancy. Figure 3 shows examples of MBIs obtained as part of this study, with lesions ranging from 5 to 15 mm in diameter.

A total of 14 patients had negative findings at biopsy. Of these, 9 had true-negative results on the CZT gamma camera system and 5 had false-positive results, yielding a specificity of 64%. False-positive results occurred in 2 patients with benign fibroadenomas and in 1 patient with inflammatory fat necrosis. In 2 patients, faint focal uptake of sestamibi was seen. The biopsy specimen indicated a complex sclerosing lesion (radial scar) in one patient and benign breast parenchyma in the other.

The procedure was well tolerated by all patients. The mean pain score (on a scale of 0 to 10, with 0 indicating no pain) was 0.8±1.5. Mean breast thickness was 5.0±1.3 cm for craniocaudal views and 5.6±1.3 cm for mediolateral oblique views.

## DISCUSSION

In our study, a prototype gamma camera system for MBI had a sensitivity of 92% in detecting small malignant breast lesions. This is higher than the 85% sensitivity of conventional scintimammography in detecting breast cancers of any size and far higher than sensitivities reported previously in detecting small cancers.[13,15,18]

Knowledge of the mammographic findings may have biased the reading of the MBIs. However, 24 of the 33 lesions had medium or high uptake of sestamibi (Table 1), the classification of which requires minimal subjective input. There were only 9 cases with low uptake, in which the potential for subjective interpretation is higher: of these, 3 involved lesions missed by mammography, thus eliminating any bias from the mammogram. Therefore, the potential for bias due to foreknowledge of the mammographic location of lesions was minimal in this study.

Because eligible patients were identified on the basis of suspicious mammographic findings, this study was not designed to demonstrate superiority to mammography. However, several of our findings suggest that this gamma camera system for MBI will compare favorably to mammography. First, in 4 of 40 patients, malignant lesions were detected in the gamma camera images that were not visible, even retrospectively, on mammograms or ultrasounds. All 4 lesions were either ductal carcinoma in situ or lobular carcinoma in situ, lesions that historically have been more difficult to detect with conventional scintimammography.[21] Second, in 1 of the 2 false-negative cases, the lesion was missed because of technical errors in positioning. This type of error should be reduced with refinements in positioning technique and detector resolution.

The most important finding of this study is that MBI can detect small lesions of the breast, thus overcoming the main limitation of conventional scintimammography. This finding agrees with earlier work using dedicated breast cam-

TABLE 1. **Results of Molecular Breast Imaging in 40 Patients***

| Case No. | Age (y) | Histopathologic test results | Additional studies | Surgical lesion size (mm) | Involved breast | MBI | Uptake |
|---|---|---|---|---|---|---|---|
| 1 | 67 | IDC | US | 15 × 10 × 8 | Left | TP | Medium |
| 2 | 74 | IDC | US | 13 × 10 × 8 | Right | TP | Low |
| 3 | 47 | BBP | US | Benign on biopsy | Left | TN | Negative |
| 4 | 59 | IDC | US | 8 | Left | TP | Low |
| 5 | 68 | BBP | US | Benign on biopsy | Right | TN | Negative |
| 6 | 56 | IDC | US | 13 × 9 × 7 | Right | TP | Low |
| | | DCIS† | US | ~10 | Right | TP | Low |
| 7 | 67 | IDC | US | 12 × 10 × 8 | Right | TP | High |
| 8 | 59 | IDC | US + MRI | 53 × 34 × 28 | Left | TP | High |
| | | IDC | US + MRI | 7 × 5 × 5 | Left | TP | Medium |
| | | IDC | US + MRI | 6 × 4 × 4 | Left | TP | Medium |
| | | DCIS† | US + MRI | 10 | Right | TP | Low |
| 9 | 70 | BFA | US | Benign on biopsy | Left | FP | Low |
| 10 | 86 | IDC/ILC | US | 17 | Right | TP | Medium |
| | | IDC | US | 12 | Right | TP | Medium |
| | | IDC/ILC | US | 5 | Right | TP | Low |
| | | IDC | US | 12 × 12 × 14 | Left | TP | Medium |
| 11 | 78 | IDC | US | 12 × 8 × 7 | Right | TP | Low |
| 12 | 39 | BFA | None | Benign on biopsy | Right | TN | Negative |
| 13 | 58 | IDC | US | 13 × 10 × 6 | Right | FN | Negative |
| 14 | 65 | IDC/ILC | US | 15 × 13 × 13 | Left | TP | High |
| 15 | 73 | IDC | US | 22 × 18 × 17 | Left | TP | High |
| 16 | 57 | IDC | US | 8 | Left | TP | Medium |
| 17 | 69 | IPC | US | 10 × 10 × 10 | Left | TP | High |
| 18 | 67 | IDC | US + MRI | 8 | Left | TP | Medium |
| 19 | 67 | ILC | US | 18 × 18 × 16 | Left | TP | Medium |
| | | ILC | US | 6 × 6 | Left | TP | Medium |
| 20 | 40 | IDC | US | 10 | Left | TP | Medium |
| 21 | 79 | IDC | US + MRI | 10 × 9 × 7 | Right | TP | Medium |
| | | LCIS† | US + MRI | 11 × 7 × 7 | Left | TP | Low |
| 22 | 66 | IFN | US | Benign on biopsy | Left | FP | Medium |
| 23 | 40 | BBP | US + MRI | Benign on biopsy | Left | FP | Low |
| 24 | 67 | IDC | US | 18 × 17 × 17 | Left | TP | High |
| 25 | 47 | BBP | US | Benign on biopsy | Right | TN | Negative |
| 26 | 71 | IDC | US | 15 | Right | TP | High |
| 27 | 46 | BFA | US | Benign on biopsy | Right | FP | High |
| 28 | 61 | IDC | US | 6 | Left | FN | Negative |
| | | IDC | US | 4 | Left | FN | Negative |
| 29 | 48 | BBP | US only | Benign on biopsy | Left | TN | Negative |
| 30 | 67 | ILC | None | 11 × 8 × 7 | Right | TP | Medium |
| 31 | 43 | CSL | US | Benign on biopsy | Right | FP | Low |
| 32 | 70 | BFA | US | Benign on biopsy | Right | TN | Negative |
| 33 | 51 | IDC | US | 10 × 7 × 5 | Left | TP | Medium |
| 34 | 84 | IDC/ILC | US | 28 × 18 × 13 | Right | TP | Low |
| 35 | 48 | DCIS | US + MRI + PET | 90 × 60 × 60 | Right | TP | High |
| 36 | 61 | DCIS† | US + MRI | 12 | Right | TP | Medium |
| 37 | 45 | BBP | US + MRI | Benign on biopsy | Right | TN | Negative |
| 38 | 80 | BBP | US | Benign on biopsy | Left | TN | Negative |
| 39 | 68 | IDC | US | 13 × 13 × 12 | Left | TP | High |
| 40 | 57 | Cyst | US | Benign on biopsy | Left | TN | Negative |

*BBP = benign breast parenchyma; BFA = benign fibroadenoma; CSL = complex sclerosing lesion; DCIS = ductal carcinoma in situ; FN = false negative; FP = false positive; IDC = invasive ductal carcinoma; IFN = inflammatory fat necrosis; ILC = invasive lobular carcinoma; IPC = intracystic papillary carcinoma; LCIS = lobular carcinoma in situ; MBI = molecular breast imaging; MRI = magnetic resonance imaging; PET = positron emission tomography; TN = true negative; TP = true positive; US = ultrasonography.

†Tumors missed on mammography and detected by MBI.

eras. Scopinaro et al[17] developed a prototype breast camera with a 12.5-cm field of view. Although the small field of view makes this camera impractical for routine clinical use, this system increased sensitivity from 50% to 81% for detecting breast lesions smaller than 10 mm. A similar, more recent study by Brem et al[18] that used a small multicrystal sodium iodide–based system showed an increase in sensitivity from 47% to 67%. With the improved energy resolution of a semiconductor-based system, we obtained the highest sensitivity (86%) yet reported for de-

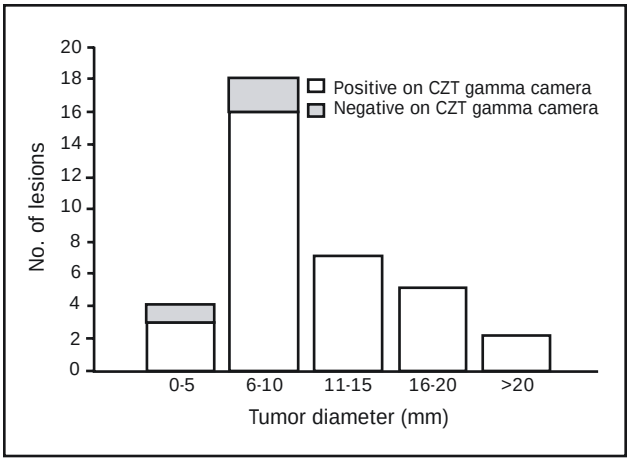


FIGURE 2. Histogram of the distribution of malignant tumor diameters in the 26 patient studies. Mean ± SD tumor diameter was 12.8±11.6 cm. CZT = cadmium-zinc-telluride.

tecting lesions smaller than 10 mm. It is clear from this body of work that dedicated breast imaging systems can play a useful role in detecting small lesions of the breast.

Using a CZT gamma camera, Coover et al[19] recently detected cancers in 13% of patients with dense breast parenchyma who had no suggestive clinical or mammographic findings. The evaluation of patients with dense breast parenchyma is likely to be one of the most important applications of MBI. Numerous studies have confirmed that the sensitivity of mammography is reduced in women with dense breast parenchyma.[22-26] In one large prospective study of screening mammography, the sensitivity of mammography in patients classified as having extremely dense breast tissue was 44%.[26]

Unlike mammography, the sensitivity of scintimammography is not influenced by breast density. Because mammography uses low-energy x-rays (15-25 keV), the quality of the images is highly dependent on breast composition. Fat appears radiolucent or dark on a mammogram, whereas connective and epithelial tissues are radiologically dense and appear lighter or white. Because mammography relies on small differences in radiological density, the presence of a substantial amount of connective and epithelial tissue may impair tumor detection. In contrast, scintimammographic detection of tumors relies on the relative difference in sestamibi uptake by the tumor compared with healthy breast tissue.

This inverse relationship between breast density and the sensitivity of mammography has important implications. First, although breast density decreases after menopause, the rate of fatty involution after menopause appears to be declining.[27] This trend has been seen even in patients not receiving hormone therapy and may be related to changes in childbearing patterns. A recent study found that one quarter of women aged 50 to 69 years had a dense mammographic breast pattern.[28] Thus, an increasing proportion of women may be at risk for missed cancers on screening mammography as a result of breast density.

Second, in addition to reducing the sensitivity of mammography, breast density is an independent risk factor for the development of breast cancer. Women with mammographically dense breast tissue have a risk of breast cancer that is 1.8 to 6.0 times that of women of the same age with little or no density.[29] These factors underscore the importance of developing a breast imaging modality that performs well in women with dense breast tissue.

Other imaging modalities have been studied in women with dense breast tissue. The sensitivity of MRI of the breast is not impaired by dense parenchyma.[30-33] Ultrasonography combined with mammography has a higher sensitivity than mammography alone in women with dense breast tissue.[26,34] However, these modalities are operator dependent and labor and time intensive and thus may not be well suited for screening purposes.

In addition to screening and diagnostic breast imaging for women with dense breast parenchyma, this technology has many other potential applications. Molecular breast imaging may be ideally suited for screening women who have an increased risk of breast cancer because of a history of breast atypia, family history of breast cancer, breast cancer gene mutations, or prior chest or mantle irradiation. It may also be a useful adjunct for surveillance in women with a history of breast surgery, in whom postoperative mammographic distortion can confound the detection of recurrent or de novo breast cancer. Moreover, MBI is likely to be useful in women with biopsy-proven breast cancer to exclude multifocal or contralateral involvement before definitive surgery.

Standard mammograms use compression forces of 35 to 45 lb, causing considerable discomfort in some women. In contrast, the light compression (maximum of 15 lb) used with this system was well tolerated, with minimal discomfort on a standard pain scale.

Molecular breast imaging has some disadvantages relative to mammography. It requires an injection of a small amount of radiotracer. The radiation dose delivered to the breast is comparable to or slightly less than that with mammography. Currently, performing MBI takes approximately 3 times longer than mammography (40 to 50 minutes vs 15 minutes). Future developments, such as optimized collimation and use of opposing dual detector heads, may cut imaging time in half. False-positive results were obtained in 2 cases of fibroadenomas, 1 case of inflammatory fat necrosis, 1 case of benign breast parenchyma, and 1 case of complex sclerosing lesion. However, the distinction between these entities and cancer can also be difficult to

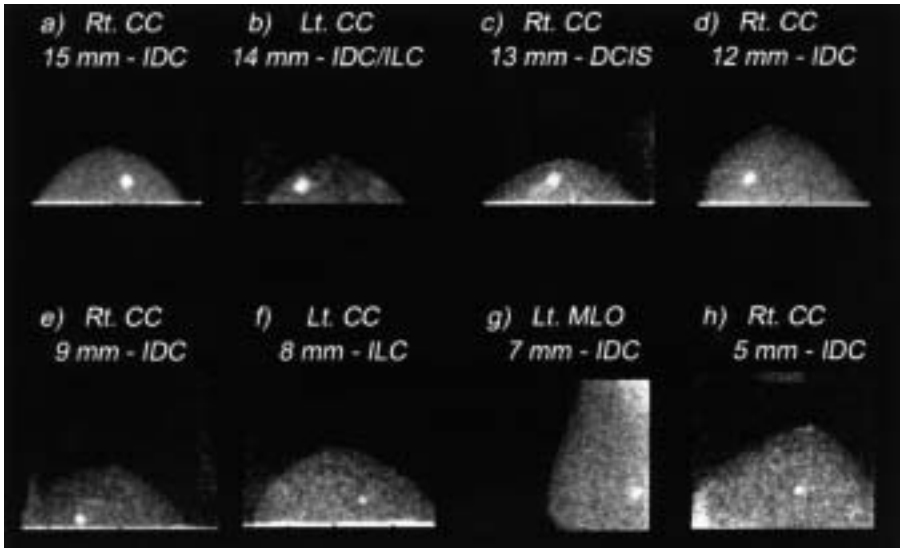


FIGURE 3. Examples of clinical studies that demonstrate the appearance of breast tumors in the scintigraphic studies. Tumor sizes ranged from 5 to 15 mm. DCIS = ductal carcinoma in situ; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; Lt. CC = left craniocaudal; Lt. MLO = left mediolateral oblique; Rt. CC = right craniocaudal; Rt. MLO = right mediolateral oblique.

appreciate on mammography, ultrasound, and MRI. Indeed, in a recent study of MRI of the breast prior to biopsy, the specificity of MRI was 68%. The authors concluded that MRI does not obviate the need for subsequent tissue sampling in the evaluation of suspicious breast lesions.[35] Thus, biopsy may be necessary to exclude cancer in these instances, regardless of the imaging technique. Furthermore, with the exception of these benign, inflammatory processes that can mimic the radiotracer uptake seen in breast cancers, interpretation of MBIs requires minimal subjective input (Figure 3). This may minimize dependence on interpreter skill and experience, factors that have been shown to lead to variability in the accuracy of interpretation for other breast imaging modalities.[36-38]

Several technical challenges remain before this imaging device is fully optimized. Efforts are under way to improve the collimation and energy resolution. Developing a direct means of lesion localization for biopsy will be critical because this device currently depends on ultrasonography or MRI to localize biopsy abnormalities not seen on mammography. The development of a radio-guided technique for biopsy may further increase the value of MBI by delineating lesions that may not be visible on a mammogram, ultrasound, or MRI.

## CONCLUSION

Molecular breast imaging with a prototype gamma camera system can reliably detect malignant breast tumors smaller than 1 cm with a sensitivity of 86%. By optimizing the camera to detect smaller and deeper breast lesions, this technique overcomes the primary limitations of conventional scintimammography in breast imaging. The results of this study suggest an important adjunctive role for MBI, particularly for women in whom the sensitivity of mammography is reduced because of dense breast parenchyma or a familial predisposition to breast cancer.

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