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Abbreviation:

BI-RADS = Breast Imaging Reporting and Data System

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See Materials and Methods for pertinent disclosures.

Author contributions:

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Occult Breast Cancer: Scintimammography with High-Resolution Breast-specific Gamma Camera in Women at High Risk for Breast Cancer¹

PURPOSE: To prospectively evaluate a high-resolution breast-specific gamma camera for depicting occult breast cancer in women at high risk for breast cancer but with normal mammographic and physical examination findings.

MATERIALS AND METHODS: Institutional Review Board approval and informed consent were obtained. The study was HIPAA compliant. Ninety-four high-risk women (age range, 36–78 years; mean, 55 years) with normal mammographic (Breast Imaging Reporting and Data System [BI-RADS] 1 or 2) and physical examination findings were evaluated with scintimammography. After injection with 25–30 mCi (925–1110 MBq) of technetium 99m sestamibi, patients were imaged with a high-resolution small-field-of-view breast-specific gamma camera in cranio-caudal and mediolateral oblique projections. Scintimammograms were prospectively classified according to focal radiotracer uptake as normal (score of 1), with no focal or diffuse uptake; benign (score of 2), with minimal patchy uptake; probably benign (score of 3), with scattered patchy uptake; probably abnormal (score of 4), with mild focal radiotracer uptake; and abnormal (score of 5), with marked focal radiotracer uptake. Mammographic breast density was categorized according to BI-RADS criteria. Patients with normal scintimammograms (scores of 1, 2, or 3) were followed up for 1 year with an annual mammogram, physical examination, and repeat scintimammography. Patients with abnormal scintimammograms (scores of 4 or 5) underwent ultrasonography (US), and those with focal hypoechoic lesions underwent biopsy. If no lesion was found during US, patients were followed up with scintimammography. Specific pathologic findings were compared with scintimammographic findings.

RESULTS: Of 94 women, 78 (83%) had normal scintimammograms (score of 1, 2, or 3) at initial examination and 16 (17%) had abnormal scintimammograms (score of 4 or 5). Fourteen (88%) of the 16 patients had either benign findings at biopsy or no focal abnormality at US; in two (12%) patients, invasive carcinoma was diagnosed at US-guided biopsy (9 mm each at pathologic examination).

CONCLUSION: High-resolution breast-specific scintimammography can depict small (<1-cm), mammographically occult, nonpalpable lesions in women at increased risk for breast cancer not otherwise identified at mammography or physical examination.

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Mammography remains the mainstay for breast cancer detection, with a sensitivity of 85%–90% but decreasing to 65% in women with dense breasts (1,2). As a result of the limitations of mammography, adjunct imaging modalities are being investigated to improve breast cancer diagnosis. The most commonly used adjunct imaging modality is

ultrasonography (US), which has been shown to improve breast cancer detection by 12% when used as a screening modality in women with dense breasts (3).

Mammography and US are anatomic approaches to breast cancer diagnosis. Nuclear medicine techniques, which rely on biochemical and physiologic characteristics of tumors, are currently being investigated and are increasingly being used. Technetium 99m (^{99m}Tc) sestamibi was approved in the United States in 1990 for clinical use as a cardiac perfusion agent for the detection of coronary artery disease. In 1994, Khalkhali et al (4) investigated the use of ^{99m}Tc sestamibi for the detection of breast cancer. Since that time, authors investigating scintimammography for the diagnosis of breast cancer have reported sensitivities ranging from 62% to 96% and specificities ranging from 69% to 100% (5–17). Of particular note is that the sensitivity of scintimammography for the detection of breast cancer is not adversely affected by increased breast density (6), which is a notable advantage.

Authors investigating scintimammography have used a general-purpose gamma camera, which is not optimally designed for breast imaging. Specifically, a general-purpose gamma camera has limited intrinsic resolution for cancers smaller than 1 cm. Most cancers diagnosed with scintimammography are larger than 1 cm, and the mean size of cancers included in one large multi-institutional trial was 2.2 cm (7). The reported sensitivity of scintimammography for cancers 1 cm or smaller is 35%–64% (17–22). In addition, the design of the gamma camera results in limited depiction of lesions in the medial portion of the breast. Finally, it is difficult to correlate mammographic findings with scintimammographic findings, because it is not possible to image the breasts in positions comparable to those used in mammography by using a general-purpose gamma camera.

To optimize scintimammography, a high-resolution small-field-of-view gamma camera specific to breast imaging was developed to improve resolution and optimize breast imaging (23). Preliminary findings with use of the breast-specific gamma camera for evaluating women with breast lesions prior to biopsy demonstrated improved resolution and sensitivity in the detection of breast cancer, with the greatest improvement demonstrated in nonpalpable lesions and lesions smaller than 1 cm (6). Women at increased risk of breast cancer may bene-

fit from an adjunct to mammography, particularly if additional imaging is not affected by breast density. Thus, the purpose of our study was to prospectively evaluate a high-resolution breast-specific gamma camera for depicting occult breast cancer in women who are at high risk for breast cancer and who have normal mammographic and physical examination results.

MATERIALS AND METHODS

This study was supported by a grant from Bristol Myers Squibb (Billerica, Mass). The radiotracer used was an in-kind donation by Bristol Myers Squibb. The Dilon camera was provided by an in-kind donation from Dilon Technologies (Newport News, Va). No authors are employed by Bristol Myers Squibb or Dilon Technologies. Dr Brem has stock options in Dilon Technologies and has been on the speakers bureau for Bristol Myers Squibb (previously DuPont Pharmaceuticals). Dr Majewski has stock options and had been a consultant for Dilon Technologies. Dr Welch has stock options and stock and is a consultant to Dilon Technologies. No other authors have any other relationship with Bristol Myers Squibb or Dilon Technologies. The data reported in this study, as well as the submission of this manuscript, have always been in the sole control of the authors.

Patients

From September 2001 to March 2004, 94 women with a mean age of 55 years (range, 36–78 years) who had a calculated 5-year risk for the development of breast cancer of 1.66% or higher, as determined with the Gail Risk Model, were eligible (1). The calculated risk of 1.66% (range, 1.7%–7.6%; mean, 3.3%; median, 2.9%) was used since this was the criterion used for the inclusion in the BCPT1 Breast Cancer Prevention Trial 1 (24). Of the 94 women in this study, 27 had history of invasive carcinoma, three had history of ductal carcinoma in situ, three had atypical ductal hyperplasia, and two had lobular neoplasia. All women seen at our institution with normal mammographic and physical examination findings and with a calculated breast cancer risk of 1.66% or higher were offered participation. In addition, women were recruited from advertisements placed in the health section of a local newspaper. All patients had a normal mammogram (Breast Imaging Reporting and Data System [BI-RADS] category 1 or 2), and phys-

ical examination was performed by a health care provider within 6 months (mean, 2.4 months; median, 1.7 months) of scintimammography. The institutional review board approved our study, which was Health Insurance Portability and Accountability Act compliant, and informed consent was obtained from all participants.

Imaging

Patients received an injection of 25–30 mCi (925–1110 MBq) of ^{99m}Tc sestamibi into the dorsalis pedis vein of the foot or the antecubital vein, depending on clinical considerations. All injections were preferentially administered into the dorsalis pedis vein, unless the patient refused or it was not clinically possible. Approximately 10 minutes after the injection of the radiotracer, images were obtained in the craniocaudal and mediolateral oblique projections with a high-resolution small-field-of-view breast-specific gamma camera (model 6800; Dilon Technologies, Newport News, Va). The acquisition time for each image was approximately 10 minutes, with a total imaging time of approximately 40 minutes per scintimammographic study.

Image Evaluation

Scintimammograms were prospectively classified as normal (score of 1), with no focal or diffuse uptake (Fig 1); benign (score of 2), with minimal patchy uptake (Fig 2); probably benign (score of 3), with scattered patchy uptake (Fig 3); probably abnormal (score of 4), with mild focal radiotracer uptake (Fig 4); and abnormal (score of 5), with marked focal radiotracer uptake (Fig 5) (2). In addition, all mammograms were evaluated for breast density by using the BI-RADS criteria for density and were assigned a BI-RADS breast density category of 1–5. Mammograms and scintimammograms were reviewed and classified by two radiologists, one with 15 years of experience (R.F.B.) and one with 5 years of experience (J.A.R.). Any discrepancies in interpretation between the radiologists was resolved by consensus. Scintimammograms were interpreted without knowledge of the patient characteristics and mammographic reports. Scintimammograms assigned a score of 1, 2, or 3 were considered to be without evidence of disease, while those with scores of 4 and 5 resulted in directed US to the region of the breast in which there was focal radiotracer uptake. Patients with abnormal

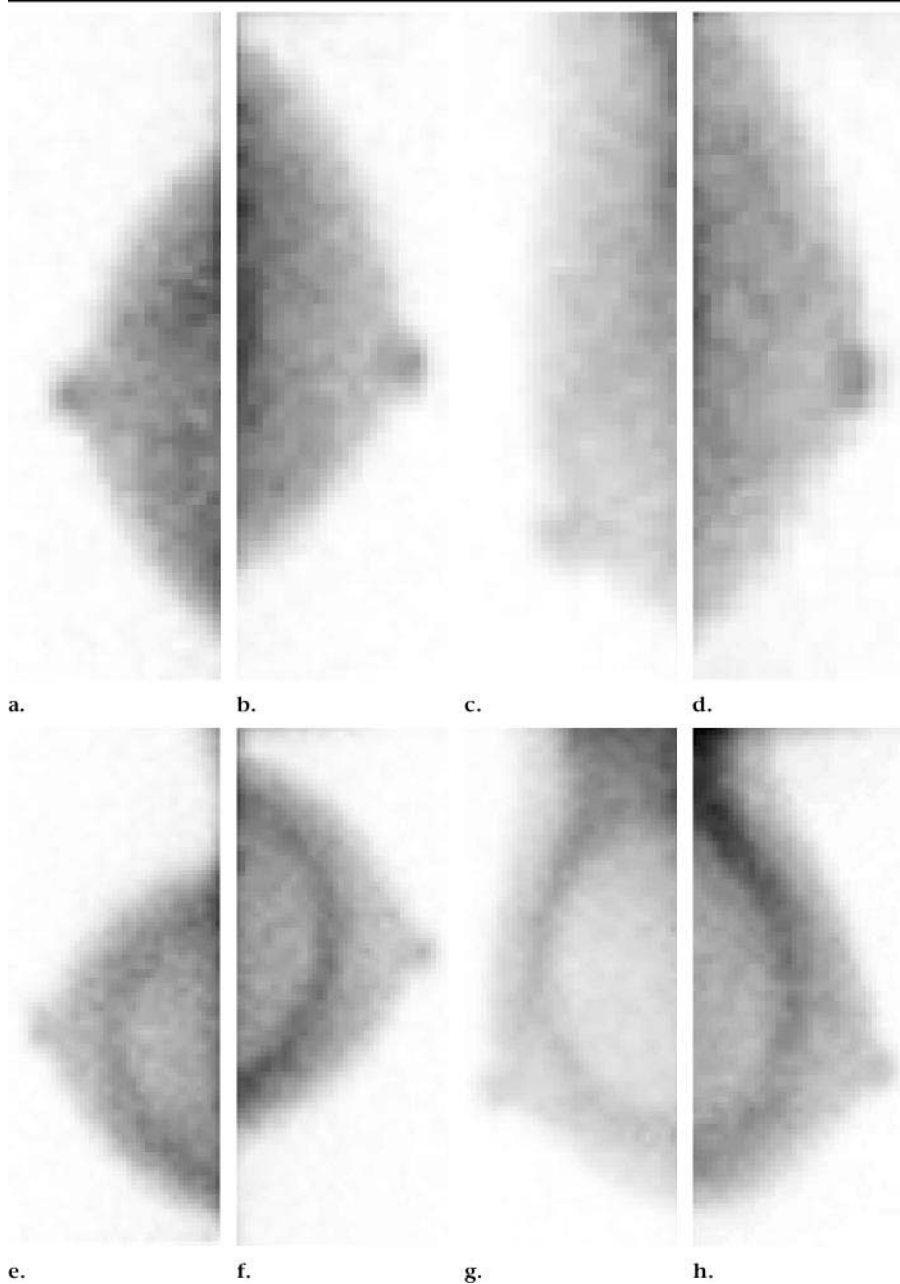


Figure 1. High-resolution breast-specific scintimammogram in a patient with breast implants. (a) Left craniocaudal, (b) right craniocaudal, (c) left mediolateral oblique, and (d) right mediolateral oblique implant displacement views. Normal scintimammograms in (e) left craniocaudal, (f) right craniocaudal, (g) left mediolateral oblique, and (h) right mediolateral oblique projections do not demonstrate focal or diffuse radiotracer uptake. The rim of increased radiotracer uptake is normal parenchyma adjacent to the breast implant.

scintimammograms (score of 4 or 5), in which the subsequent directed US demonstrated a focal hypoechoic area, underwent US-guided core-needle biopsy. US-guided core-needle biopsies were performed as previously described (25). Both the US examinations and subsequent US-guided core-needle biopsies were performed by the radiologists who had in-

terpreted the mammograms and scintimammograms for this study.

Follow-up

Those with abnormal scintimammograms and negative US findings returned at 6 months for reimaging with scintimammography. All patients were followed up in the subsequent year with

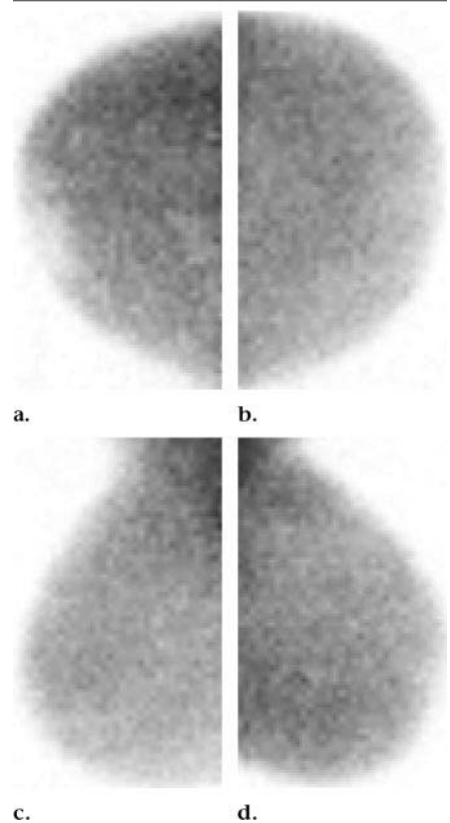


Figure 2. Benign scintimammograms in (a) left craniocaudal, (b) right craniocaudal, (c) left mediolateral oblique, and (d) right mediolateral oblique projections demonstrate minimal patchy radiotracer uptake compatible with physiologic uptake.

annual mammography, physical examination, and follow-up scintimammography by using high-resolution breast-specific gamma camera. All patients with new suspicious findings on a 2nd-year mammogram or with physical findings underwent biopsy as clinically indicated, regardless of scintimammographic findings.

Statistical Analysis

The data were analyzed for sensitivity and specificity of cancer detection, as well as for positive and negative predictive values. Sensitivity is the probability that results at imaging are positive in those patients who have the disease. Specificity is the probability that results at imaging are negative in patients who do not have the disease. Statistical analysis was performed with Microsoft Excel 2000 (Microsoft, Redmond, Wash) software. For the reference standard, we used either pathologic results of biopsy or follow-up imaging that did not demonstrate evidence of malignancy.

RESULTS

Ninety-four women initially underwent mammography, physical examination, and scintimammography, with 1-year follow-up that included mammography, physical examination, and repeat scintimammography. Seventy-eight (83%) of the 94 patients had normal scintimammograms (scores of 1, 2, or 3) at initial examination and were followed up for 1 year. Findings of follow-up mammography, clinical examination, and scintimammography at 1 year were normal in all 78 patients, confirming the absence of disease (true-negative findings). Ten of the 78 patients who had a normal scintimammogram at initial examination and at 1-year follow-up underwent biopsy as a result of suspicious findings at mammography, US, or physical examination. Histopathologic findings in all 10 patients were benign and confirmed the normal scintimammographic findings. These patients have been followed up mammographically for a minimum of 1 year subsequent to the biopsy, with no evidence of malignancy.

Sixteen (17%) of the 94 patients had positive scintimammograms at initial examination. All 16 of these patients underwent US to the region of the breast with focal radiotracer uptake, and 11 (69%) of these patients went on to undergo biopsy owing to a focal hypoechoic finding. Two (18%) of the 11 patients who underwent US-guided core-needle biopsy were found to have invasive carcinoma (true-positive findings). The other nine (82%) of 11 patients had benign pathologic findings at US-guided core-needle biopsy, with pathologic findings demonstrating fibrocystic change ($n = 6$), fat necrosis ($n = 1$), fibroadenoma ($n = 1$), and benign cyst content ($n = 1$). The remaining five (31%) of 16 patients did not have any focal US findings and, therefore, did not undergo biopsy. The five patients had a follow-up scintimammogram at 6 months, all of whom did not have any abnormal foci of radiotracer uptake. Furthermore, 6 months later (ie, 1 year from the initial abnormal scintimammogram), these five patients had normal scintimammograms as well.

True-Positive Findings

Both cancers detected only with high-resolution scintimammography were in women with a history of breast carcinoma; one was a local recurrence in a

lumpectomy bed (Fig 4); the other, a contralateral malignancy (Fig 5). Both of these cancers were diagnosed histopathologically as infiltrating and intraductal carcinoma. The largest diameter of the two cancers measured at US was 6 and 8 mm, and both measured 9 mm in the greatest diameter at pathologic examination. The cancers were located in the upper outer quadrant and upper inner quadrant and occurred in breasts with mammographic BI-RADS density categories 2 and 3, respectively.

False-Positive Findings

Fourteen (88%) of the 16 patients with positive scintimammograms had either benign findings at biopsy (7) or no focal abnormality at US (false-positive findings) (3). Biopsy was not performed in five patients in whom there were no focal US findings. Among the nine patients with false-positive findings, pathologic examination demonstrated fibrocystic change (one with concomitant sclerosing adenosis) in seven patients, fibroadenoma in one, and fat necrosis in one. The five patients with no focal US findings were reimaged at 6 months, at which time scintimammographic findings were normal.

True-Negative Findings

Seventy-eight (83%) of the 94 patients had true-negative findings, which were defined as a normal mammogram, physical examination findings, and scintimammogram at 1 year and in the subsequent year. There were no false-negative findings in this study (ie, a patient with a normal scintimammogram who went on to biopsy because of suspicious mammographic, US, or physical examination findings and was found to have cancer).

Additional Findings

Three patients with four lesions (BI-RADS category 4 or 5) detected on a 2nd-year mammogram went on to undergo biopsy. Of these three patients, all had normal scintimammograms. Two lesions were proved at histopathologic examination to be benign tissue, and two lesions demonstrated fibrocystic change. The pathologic findings were determined to be concordant with the mammographic manifestation of the lesions. As per our protocol, patients with benign findings at breast biopsy, which was performed because of suspicious mammographic findings, and normal scintimammograms were followed up with mammog-

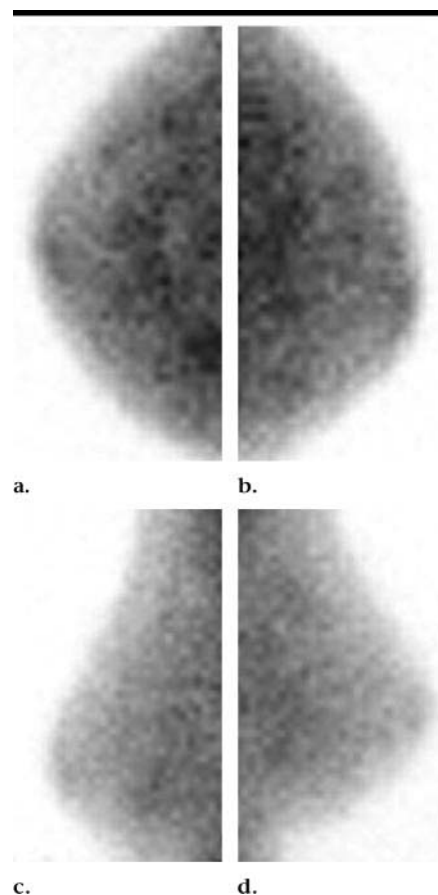


Figure 3. Probably benign scintimammograms in (a) left craniocaudal, (b) right craniocaudal, (c) left mediolateral oblique, and (d) right mediolateral oblique projections demonstrate scattered patchy radiotracer uptake.

raphy at 6 months to ensure that the targeted lesion was not missed. Mammographic findings for all of these patients were stable at 6-month follow-up.

Overall Results

In 94 patients with normal (BI-RADS category 1 or 2) mammograms, scintimammography performed with the high-resolution breast-specific gamma camera depicted two occult and otherwise undetected breast cancers. It had an overall sensitivity of 100% (95% confidence limit, 0.22, 1.0), specificity of 85%, positive predictive value of 12.5%, negative predictive value of 100%, and diagnostic accuracy of 85%. However, it is essential to emphasize that the 100% sensitivity is based on only two patients in this study in whom breast cancer was diagnosed with the high-resolution breast-specific gamma imaging.

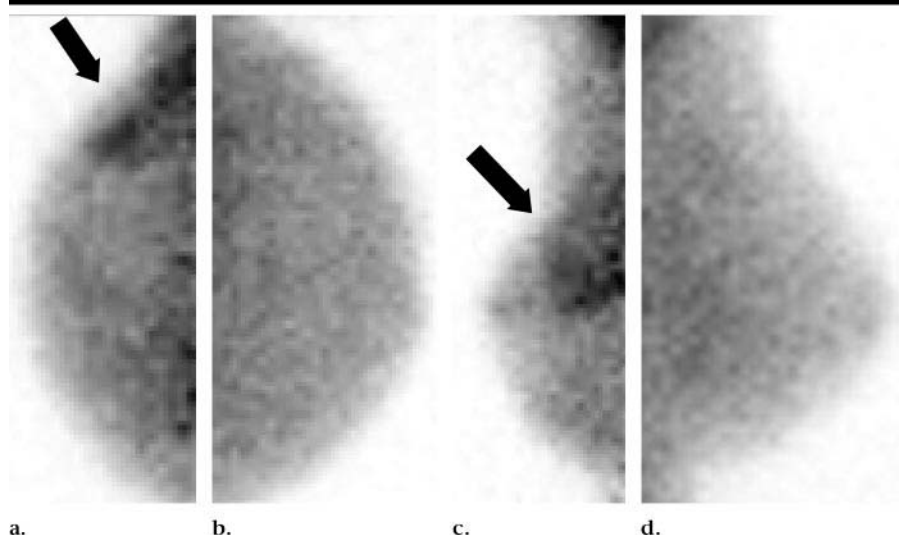


Figure 4. Probably abnormal scintimammograms in (a) left craniocaudal, (b) right craniocaudal, (c) left mediolateral oblique, and (d) right mediolateral oblique projections demonstrate mild focal radiotracer uptake (arrow). Pathologic examination demonstrated a 9-mm infiltrating ductal carcinoma in the lumpectomy bed of a patient with prior left lumpectomy.

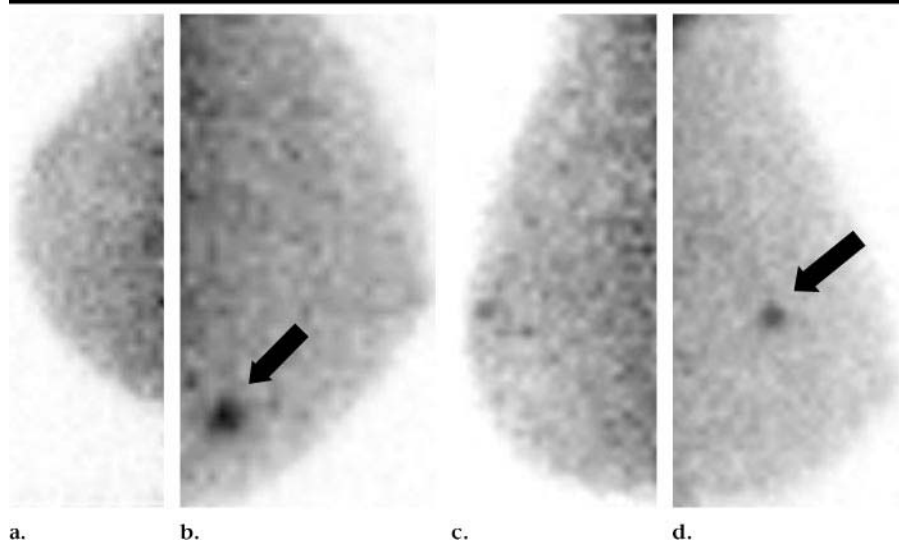


Figure 5. Abnormal scintimammograms in (a) left craniocaudal, (b) right craniocaudal, (c) left mediolateral oblique, and (d) right mediolateral oblique projections demonstrate marked focal radiotracer uptake (arrow). Pathologic examination demonstrated 9-mm infiltrating ductal carcinoma.

DISCUSSION

Recent studies in which nuclear medicine techniques that rely on biochemical and physiologic characteristics of breast tumors were evaluated have shown promising results as a potential adjunct to mammography (4–17). Scintimammography has demonstrated improved sensitivity and specificity in breast cancer detection, particularly in women with dense breasts and in women with architectural distortion or scarring from prior

biopsies (26,27). The sensitivity of scintimammography with a general-purpose gamma camera is decreased in cancers smaller than 1 cm, especially those located in the medial breast, with sensitivity decreasing to 35%–64% (17–22).

Preliminary results of scintimammography with the breast-specific gamma camera demonstrated an increase in sensitivity for breast cancer detection, ranging from 64.3% to 78.6%. In lesions smaller than 1 cm in size, the sensitivity increased from 46.7% with a traditional

gamma camera to 66.6% when the high-resolution breast-specific gamma camera was used (22).

In our study, the high-resolution breast-specific gamma camera demonstrated a 100% sensitivity by depicting the two histologically proved malignancies that were not identified with either mammography or physical examination. Both of these patients had prior breast cancers. Mammography and physical examination failed to depict cancer that was identified only with the high-resolution breast-specific gamma camera (27). Interestingly, both patients had minimal to moderate breast density (BI-RADS density categories 2 and 3), which suggests that the use of high-resolution scintimammography may be beneficial even in women who do not have dense breasts. In the patient with prior lumpectomy in whom a local recurrence was diagnosed with high-resolution scintimammography, the posttherapeutic changes, both mammographic and US, resulted in the inability to detect local recurrence. This physiologic approach of high-resolution scintimammography may be particularly beneficial in this group of patients. Further studies are needed to assess the role of high-resolution scintimammography in women who have undergone lumpectomy. The limited number of patients included in the study is likely the cause for the 100% sensitivity. Larger studies are needed to better define the true sensitivity for identification of occult breast cancer in high-risk women by using high-resolution scintimammography.

The occult cancers detected measured 6 and 8 mm at US and 9 mm each at pathologic examination, which demonstrates the ability of the high-resolution gamma camera to depict subcentimeter occult cancers. Prior studies with use of high-resolution breast-specific gamma camera have similarly demonstrated the detection of subcentimeter cancers in both phantoms (23) and clinically (6).

Pathologic findings of the false-positive lesions in this study included a fibrocystic change (with and without sclerosing adenosis), fibroadenoma, and fat necrosis. The increase in ^{99m}Tc sestamibi activity often seen in patients with proliferative breast lesions likely reflects the increased mitochondrial activity, as well as mitochondrial density (26). Gupta et al (28) demonstrated the ^{99m}Tc sestamibi uptake in benign breast disease to be highly associated with the presence of proliferative changes. In addition, radiotracer uptake increases in direct proportion to the degree of regional blood flow

(27). This may be the cause of the false-positive findings in the nonmalignant proliferative lesion, which results in increased vascularity and/or mitochondrial activity (29).

Currently, only 15%–30% of breast biopsies result in a diagnosis of cancer (25). Clearly it would be advantageous to improve the specificity of mammography and thereby decrease the number of biopsies performed for benign lesions identified at mammography. A high specificity, 90% or above, of breast-specific scintimammography may allow for improved differentiation of benign from malignant lesions and thereby allow for a reduction in the number of breast biopsies that are performed because of indeterminate findings, which are found to be benign. In our study, all 10 patients with normal scintimammograms at 1 year who underwent biopsy owing to mammographic or clinical findings had benign pathologic findings at biopsy. In addition, of the three patients with four lesions who had abnormal 2nd-year mammograms (BI-RADS category 4 or 5) that warranted biopsy, all had normal scintimammograms and benign pathologic findings. These 13 patients with 14 lesions warranting biopsy had normal scintimammograms and benign findings at pathologic examination. Scintimammography may potentially reduce the number of breast biopsies that result in a pathologic finding that is benign by improving specificity. This decrease in breast biopsies could result in substantial improvements in patient care, as well as substantial cost savings (30).

Indeterminate mammographic findings are commonly encountered in high-risk women, particularly those with dense breasts, prior lumpectomy, or radiation therapy (26,31). Therefore, the role of scintimammography as an adjunct to mammography in the screening of high-risk women should be considered, both for its ability to detect occult cancers and its potential to reduce the number biopsies that result in benign pathologic findings.

Our study with the high-resolution breast-specific gamma camera resulted in a negative predictive value of 100%, in contrast to the previously published studies of scintimammography with general-purpose gamma cameras, which reported a negative predictive value of 82%–96% (4,8,9,32). This difference may well be as a result of the ability of the high-resolution breast-specific gamma camera to depict subcentimeter tumors. However, our study was limited by the

small cohort of patients, as well as the small number of patients with cancer. Multi-institutional trials with a larger sample size are needed to more accurately evaluate scintimammography performed with high-resolution breast-specific gamma camera.

The locations of the cancers detected only with the high-resolution breast-specific gamma camera were in the upper outer quadrant and upper inner quadrant. Although this study demonstrated a small number of cancers, one occurred in the upper inner quadrant, a region of the breast suboptimally visualized with mammography, and the other occurred in a prior lumpectomy site. Both cancers occurred in clinical situations in which mammography is suboptimal.

There has been dramatic progress in the field of breast magnetic resonance (MR) imaging since its initial introduction. Contrast material-enhanced MR imaging has demonstrated effectiveness in imaging and helping diagnose breast cancer, as well as in helping evaluate the extent of disease (33). In a study by Helbich et al (9), which compared MR imaging with planar and single photon emission computed tomographic (SPECT) scintimammography, MR imaging had a sensitivity and specificity for breast cancer detection of 96% and 82%, respectively. The respective sensitivities and specificities of planar and SPECT scintimammography were 62% and 88% and 83% and 80% (9). However, that study used a general-purpose gamma camera. It is likely that the sensitivity of scintimammography would increase with the use of a dedicated high-resolution gamma camera and may well be comparable to that of MR imaging. Further studies are needed to compare MR imaging and high-resolution scintimammography in the diagnosis of breast cancer.

Dynamic MR imaging of the breast currently allows evaluation of contrast material uptake and washout, resulting in additional analyses of breast lesions. Kuhl et al (34) reported a correlation between the contrast material washout curves in areas of contrast enhancement during breast MR imaging by using this method, with a reported a sensitivity of 91%, specificity of 83%, and accuracy of 86% in helping distinguish benign from malignant breast lesions. There are similarities between the principals of radiotracer uptake in scintimammography and contrast material uptake in MR imaging. Recently, the ability to obtain time-intensity curves with the high-resolution breast-specific gamma camera has

been developed. Future studies are being initiated to evaluate time-intensity curves obtained by using scintimammography with the high-resolution breast-specific gamma camera and their effect on the ability to differentiate benign from malignant breast lesions.

The decreased detector size and added maneuverability of the high-resolution breast-specific gamma camera increase the number of available views, reduce the amount of tissue and the distance between the lesion and the collimator, and permit acquisition geometries that minimize scatter radiation from nearby organs that exhibit high uptake, such as myocardium and liver (33). These refinements in design serve to eliminate some of the intrinsic limitations of scintimammography with a general-purpose gamma camera.

Optimally, patients with abnormal scintimammograms should undergo biopsy of the area of increased radiotracer uptake by using a directed approach to the region of interest. However, currently there is no minimally invasive method to directly target and perform biopsy on areas of focal radiotracer uptake. Therefore, the region of the breast with increased uptake was evaluated with US. If an abnormality was identified, the patient underwent US-guided core-needle biopsy. It is possible that the region with the increased radiotracer uptake could not be identified with US. It would certainly be optimal to perform a gamma camera-guided stereotactic biopsy of the region of increased radiotracer uptake. Although not yet available, we have begun preliminary studies on phantoms to develop this direct approach for the biopsy of the region of interest.

As reported earlier, additional patients underwent biopsy at 2 years following examinations performed because of mammographic or clinical findings. All of these patients had normal scintimammograms, and all had benign findings at biopsy. Although this suggests a possible role for scintimammography in the reduction of benign breast biopsies, in this study we did not address that question. Additional studies to specifically investigate the effect of scintimammography on the reduction of breast biopsies for benign lesions is needed.

Patients in this study were evaluated initially and at 1 year. We chose 1 year to evaluate for false-negative scintimammograms at the initial study. Although 1 year is appropriate to exclude a negative study finding in a patient with breast cancer, it might be optimal to evaluate

the patient at 2 years following initial examination. Finally, a multi-institutional study that would include a larger number of patients would allow for further and more definitive evaluation of high-resolution breast-specific scintimammography.

This study demonstrates that a high-resolution breast-specific gamma camera can depict small (<1-cm), mammographically occult, nonpalpable lesions in women at increased risk for breast cancer. The high specificity (84.8%–85.0%) and high negative predictive value (100%) indicate the potential of the high-resolution breast-specific gamma camera to distinguish benign from malignant lesions, thus potentially aiding in decreasing the number of benign-breast biopsies. We conclude that women at high risk for the development of breast cancer may benefit from the high-resolution breast-specific scintimammography as an adjunct to mammography. However, additional trials with inclusion of a greater number of patients are needed to further define the sensitivity and specificity of this approach to breast cancer diagnosis.

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