AJR FOCUS ON:

Alternative Screening for Women With Dense Breasts: Breast-Specific Gamma Imaging (Molecular Breast Imaging)

Anna Holbrook[1]
Mary S. Newell

OBJECTIVE. Given mammography's limitations in evaluating dense breasts, examination with breast-specific gamma imaging (BSGI)—also called molecular breast imaging (MBI)—has been proposed. We review the literature pertinent to the performance of BSGI in patients with dense breasts.

CONCLUSION. Many studies have reported the sensitivity of BSGI in finding cancers even in dense breasts. However, BSGI has not yet been validated as an effective screening tool in large prospective studies. In addition, whole-body dose remains a significant concern.

Mammographic screening is a time-tested method of reducing breast cancer mortality but is less effective in women with dense tissue [1]. This limitation is likely related to masking of cancers by adjacent or overlapping normal tissue and the reliance on detection of often subtle morphologic disparities between malignant tissue and normal tissue. In patients with dense breasts, imaging modalities that detect cancer because of metabolic differences between the lesions and normal breast tissue may be of increased benefit. One such modality is breast-specific gamma imaging (BSGI), which is also known as molecular breast imaging (MBI) or breast scintigraphy. From our review of the literature, we found that the nomenclature is confusing and inconsistent, and we could not identify a clear consensus about the terminology of "BSGI" versus "MBI"; however, for simplicity and clarity, we chose to use "BSGI" in this article.

BSGI uses a radiotracer—most frequently, ^{99m}Tc-sestamibi—that accumulates within mitochondria. Both the greater number of mitochondria within the metabolically active cancer cells and their increased neovascularity result in the increased uptake of ^{99m}Tc-sestamibi within the tumors relative to the surrounding normal breast tissue [2].

Technique

Early work with nuclear imaging of the breast was called "scintimammography," which used a traditional gamma camera and obtained images in the lateral and anteroposterior projections while the patient was prone. Because the resolution of the detector was poor and the camera could not be positioned close to the breast, scintimammography was found to be unable to detect subcentimeter cancers [3], which is not acceptable performance for a screening tool. However, many technical improvements have led to enhanced results over time. The development of a dedicated breast-specific gamma camera allows an acquisition technique similar to traditional mammography: The patient's breast is compressed in the craniocaudal and mediolateral oblique positions with a high-resolution gamma camera directly in contact with the surface of the breast. Commercially available cameras use either sodium iodide scintillation crystal detectors (Dilon 6800, Dilon Technologies) or cadmium zinc telluride semiconductor detectors (Discovery NM 750b, GE Healthcare; and LumaGEM, Gamma Medica) [4]. From 8 to 30 mCi of ^{99m}Tc-sestamibi is injected IV, and each image is obtained to 100,000 counts. Each examination lasts approximately 40–45 minutes and is generally well tolerated by the patient because the breast is compressed only slightly and the patient is able to sit for the duration of the examination [2].

With the advent of this modern BSGI technique, the sensitivity for the detection of subcentimeter lesions has improved compared with scintimammography [5]. Additionally, because the breast is imaged in positions identical to those used for mammography,

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[1]Both authors: Department of Radiology, Emory University, 1365C Clifton Rd, NE, Bldg C, Ste C1104, Atlanta, GA 30322. Address correspondence to A. Holbrook (anne.holbrook@emoryhealthcare.org).

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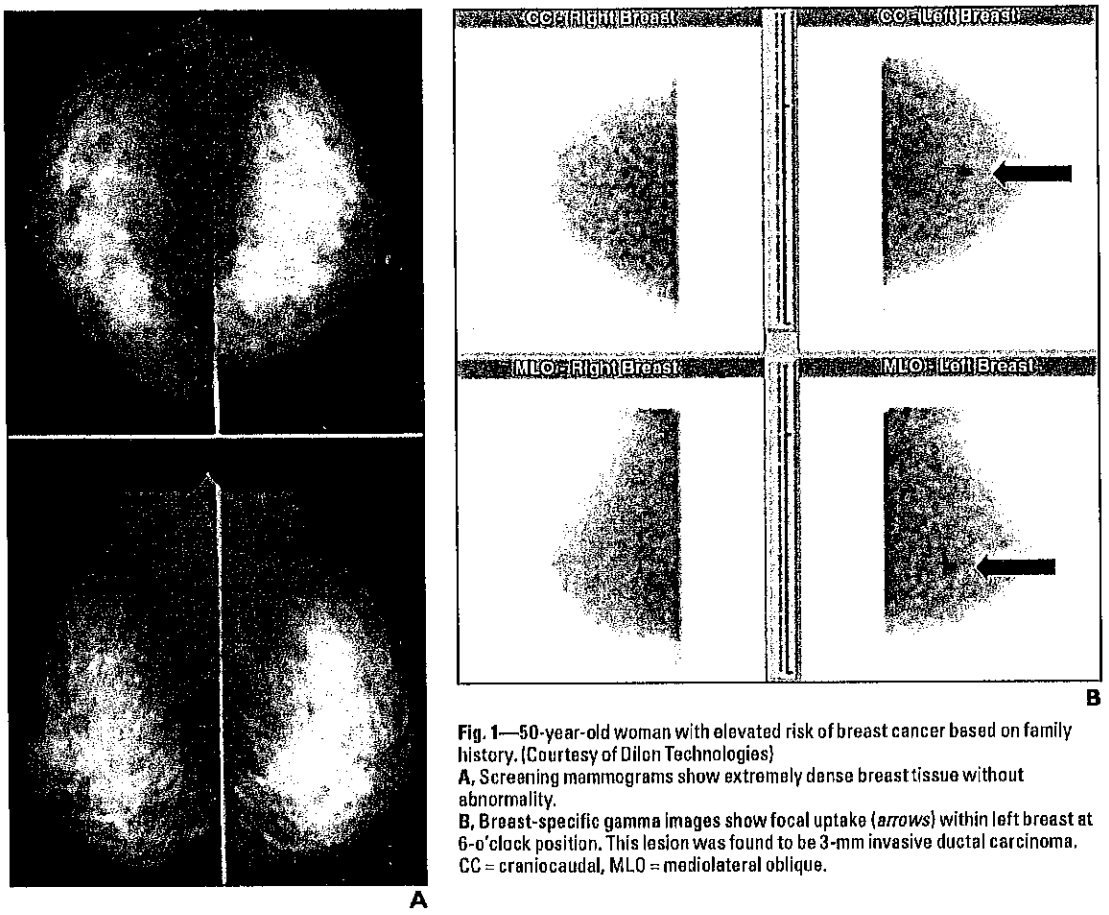

Fig. 1—50-year-old woman with elevated risk of breast cancer based on family history. (Courtesy of Dilon Technologies)
A, Screening mammograms show extremely dense breast tissue without abnormality.
B, Breast-specific gamma images show focal uptake (*arrows*) within left breast at 6-o'clock position. This lesion was found to be 3-mm invasive ductal carcinoma.
CC = craniocaudal, MLO = mediolateral oblique.

BSGI images can be directly correlated with mammograms [6]. If a suspicious lesion is identified on a BSGI examination, a second review of the mammography, directed ultrasound, or MRI study can be performed to identify the abnormality for biopsy. Alternatively, a gamma camera–guided stereotactic localization device has recently become available and can be used in cases in which the lesion is seen only with BSGI [2].

Another advance has been the development of dual-detector cameras, which are currently commercially available [4]. Hruska et al. [7] found that using a dual-head camera—with detectors on either side of the breast—increased sensitivity to 90% compared with 80% sensitivity with a single detector ($p < 0.0005$). The greatest increases were for the detection of lesions smaller than 5 mm and tumors in the upper inner quadrant of the breast. This increase in sensitivity is thought to be because the distance between lesions and the detector is decreased. Additional proposed benefits of the use of dual detectors are the ability to use the opposing views in combination with known breast thickness to perform quantitative analysis of size and uptake and the possibility of applying techniques that may permit a reduced acquisition time or a decreased dose [7].

Some investigators have suggested that a dual-phase BSGI protocol may be useful: Park et al. [8] found the specificity of BSGI significantly increased from 83% to 95% ($p = 0.0078$) when a second set of images was obtained 1 hour after injection. In their interpretation, they considered washout of radiotracer at the delayed phase to be a sign of benignity and persistence of radiotracer within an increased number of mitochondria to be a possible sign of malignancy [9]. Others think that a second phase may not be tolerable for patients because of the extended duration of breast compression [7].

Diagnostic Accuracy

Several retrospective studies evaluating BSGI for the detection of breast cancer have found a high sensitivity (91–96%) and moderate specificity (60–77%) [10–12]. A meta-analysis of studies investigating BSGI calculated a sensitivity of 95% and specificity of 80% [13]. The most common false-positive lesions seen on BSGI were fibrocystic changes, fibroadenoma, and benign breast tissue, and the most common false-negative lesions were subcentimeter invasive ductal carcinoma and ductal carcinoma in situ (DCIS). Brem et al. [14] performed a small prospective study evaluating BSGI of 94 women at an elevated risk of breast cancer who had normal findings on screening mammography. Of the 94 women, 16 (17%) had abnormal findings on BSGI, and of those patients, two (12%) mammographically occult cancers were detected.

Most studies of BSGI have been performed using a visual analysis of the images. Some investigators have suggested that a semiquantitative approach, calculating a ratio of lesion uptake relative to background uptake, may be helpful. Park et al. [15] found that the use of a lesion-to-background ratio of 1.5 or greater in combination with visual analysis increased the specificity of BSGI from 81.6% to 92.1% when compared with visual analysis alone. This improved specificity of BSGI (92.1%) was higher than the

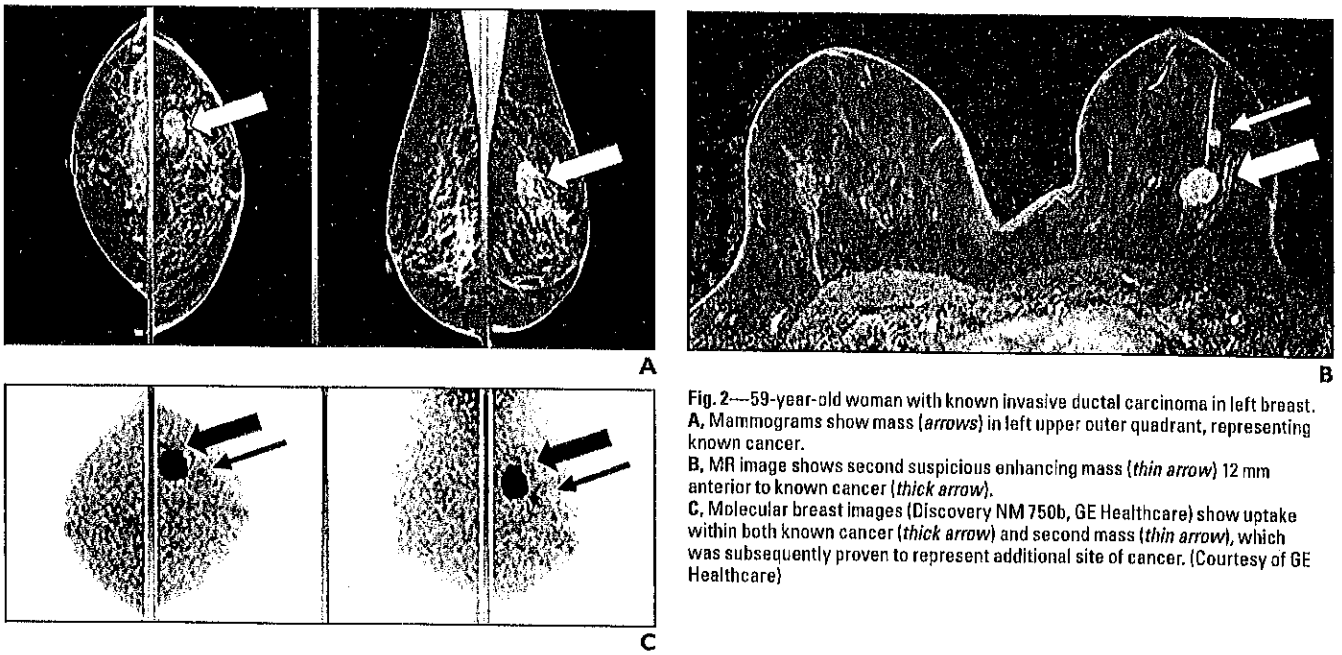

Fig. 2—59-year-old woman with known invasive ductal carcinoma in left breast.
A, Mammograms show mass (*arrows*) in left upper outer quadrant, representing known cancer.
B, MR image shows second suspicious enhancing mass (*thin arrow*) 12 mm anterior to known cancer (*thick arrow*).
C, Molecular breast images (Discovery NM 750b, GE Healthcare) show uptake within both known cancer (*thick arrow*) and second mass (*thin arrow*), which was subsequently proven to represent additional site of cancer. (Courtesy of GE Healthcare)

specificity of mammography (81.6%) and ultrasound (61.8%) [15].

Several authors have evaluated the utility of BSGI for the detection of breast cancer in patients with dense breasts. In a prospective study of BSGI as an adjunct to screening mammography in 936 women with dense breasts and at least one additional risk factor for breast cancer, the sensitivity of both modalities combined was significantly higher than that of mammography alone (91% vs 27%, respectively), and most detected cancers were node-negative [16] (Fig. 1). This increase in sensitivity was not at the expense of more recalls given that there was a nonsignificant trend toward a lower recall rate for BSGI. Additionally, the positive predictive value of BSGI-prompted biopsies was higher than that of mammography-prompted biopsies, although this difference in positive predictive values was not significant. Another study of 141 women with nondense breasts (fatty replaced and scattered fibroglandular tissue) and 206 women with dense breasts (heterogeneously or extremely dense) found that BSGI had a comparably high sensitivity for detecting known cancers (96.5% and 94.7%, respectively; $p = 0.459$) [12]. The investigators of that study also found that, in 20 of 347 (5.8%) mammographically occult cancers, BSGI was able to detect 100% of five cancers in nondense breasts and 14 of 15 (93.3%) cancers in dense breasts [12]. In a retrospective study, Kim et al. [17] found that BSGI was able to detect more additional sites of cancer than mammography in 28 of 121 women with dense breasts and cancer (sensitivity, 83.1% vs 44.1%, respectively) (Fig. 2). Overall, BSGI had a higher sensitivity than mammography (92.2% vs 53.6%) and equivocal specificity (89.3% vs 94.7%). However, one study found that patients with high-density breasts on mammography have greater and more heterogeneous background uptake of radiotracer on BSGI, which may confound results [18]. In contrast to the latter study, others found that sensitivity is not adversely affected by increased breast density [12, 17].

One concern that is raised about imaging modalities that rely on physiology rather than lesion morphology is their ability to detect DCIS. Studies suggest that BSGI is comparable to mammography in sensitivity for the detection of DCIS. Brem and colleagues [5] found in 22 biopsy-proven DCIS lesions that BSGI showed statistically equivalent sensitivity (91%) when compared with mammography (82%) and MRI (88%). In a study of 33 cases of DCIS, Spanu et al. [19] showed that BSGI had sensitivity equal to that of mammography (93.9% vs 90.9%, respectively), but BSGI findings better correlated with the histopathologic extent of disease. In another study [12], investigators found no statistical difference in the sensitivity of BSGI for DCIS (90.8%) compared with the sensitivity of BSGI for other subtypes of cancer (invasive ductal carcinoma, 96.1%; invasive lobular carcinoma, 100%).

BSGI also depicts invasive lobular carcinomas at least as well as mammography, ultrasound, and MRI. Brem et al. [6] found a trend toward better sensitivity with BSGI of 93% as compared with 83% with MRI, 79% with mammography, and 68% with ultrasound, although the differences in sensitivities were not statistically significant.

Another alternative modality to mammography for patients with dense breasts is MRI. It is very sensitive, but its specificity is somewhat limited [20]. Several studies have found that BSGI is more specific than MRI without compromising sensitivity. When comparing BSGI and MRI in further evaluating 33 mammographically indeterminate lesions, BSGI was found to have an equal sensitivity to MRI (89% vs 100%, respectively; difference not statistically significant) but a higher specificity (71% vs 25%) [20]. These results were again seen when the two modalities were evaluated in a study of 66 patients with known cancer: BSGI had an equal sensitivity (BSGI vs MRI, 88.8% vs 92.3%) but higher specificity (90.1% vs 39%) [21]. Another advantage of BSGI over MRI is that there are no contraindications, whereas patients with certain metallic implants, claustrophobia, or renal disease may be unable to undergo MRI. Additionally, BSGI usually generates only 4–16 images per examination,

so the storage space requirements are much less than that for MRI, which routinely creates thousands of images. This characteristic of BSGI may also potentially decrease image interpretation time [2].

Limitations

Many studies show that BSGI can be effective for the detection of breast cancer, especially in patients with dense breasts. However, current recommendations from the American College of Radiology [22] do not support its use in routine screening. One reason for the exclusion of BSGI is that most of the studies that have been published to date have small sample sizes, are retrospective, or both. Few studies address the use of this technology in a screening setting. No data that indicate a mortality benefit have been reported to date. More large-scale multicenter prospective trials showing benefits will need to be performed in order for BSGI to be accepted into mainstream practice, especially for screening. Other proposed indications for BSGI include imaging patients with known breast lesions for preoperative staging, screening for recurrence, or monitoring response to therapy [23].

Care must be taken to train nuclear medicine technologists in mammographic technique [7]. In an early study, O'Connor et al. [24] found that inadequate inclusion of breast tissue near the chest wall led to several false-negative results.

Implementation of widespread screening with BSGI would be expected to dramatically change the workflow and throughput of a breast imaging department. This change in workflow and throughput is because a BSGI examination takes approximately 40 minutes to perform compared with several minutes for a mammography examination. Many fewer patients would be imaged per day, increasing the time that a patient waits for an appointment.

Another critical reason that BSGI is not widely accepted in its current state is because of its very high radiation dose, estimated to be 10–20 times that of mammography [25]. This high dose is particularly of concern in patients with dense breasts who have an increased risk of malignancy [26]. Younger patients are also at an increased risk of radiation-induced malignancy, and because many young patients are more likely to have dense breasts, any recommendations for screening must take this risk into account. Additionally, unlike mammography, the radiation exposure from BSGI is not limited to the breasts because the tracer is distributed throughout the body, exposing many organs to its effects [27]. It is estimated that with current typical protocols, one BSGI examination at age 40 portends a fatal radiation-induced cancer risk comparable to that of a lifetime of annual screening mammography examinations [25]. It is difficult to support the widespread use of BSGI with current typical doses. It is estimated that an administered dose of 2 mCi would result in an equivalent effective radiation dose compared with mammography. The efficacy of imaging at a reduced dose is being explored [28].

Conclusion

In the ongoing search for an optimized screening technique for women with dense breasts, BSGI has been proposed as a candidate technology, given its utilization of physiologic information rather than reliance on morphology. Many studies confirm its sensitivity in finding cancers, even in dense breasts, and suggest improved specificity compared with other technologies. However, BSGI has not yet been validated as an effective screening tool in large prospective studies. In addition, whole-body dose remains a significant concern.

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