Invasive Lobular Carcinoma: Detection with Mammography, Sonography, MRI, and Breast-Specific Gamma Imaging

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OBJECTIVE. The objective of our study was to compare the sensitivity of mammography, sonography, MRI, and breast-specific gamma imaging (BSGI) in the detection of invasive lobular carcinoma.

MATERIALS AND METHODS. This is a retrospective multicenter study of women with biopsy-proven invasive lobular carcinoma. All patients had undergone mammography and BSGI, and the imaging findings were classified as positive or negative for invasive lobular carcinoma by experienced breast imagers. The results of MRI and sonography, if either was performed, were included. Final surgical pathology results were used as the reference standard and the lesion sensitivities of BSGI, mammography, sonography, and MRI were then statistically compared using CIs.

RESULTS. Twenty-six women ranging in age from 46 to 82 years (mean age, 62.8 years) with a total of 28 biopsy-proven invasive lobular carcinomas were included in the study group. Mammograms were negative in six of 28 (21%), yielding a sensitivity of 79%. In the 25 patients who underwent sonography, 17 had focal hypoechoic areas, yielding a sensitivity of 68%. In the 12 patients who underwent MRI, the sensitivity was 83%. BSGI had a sensitivity of 93%. There was no statistically significant difference in the sensitivity of BSGI, MRI, sonography, or mammography, although there was a nonsignificant trend toward improved detection with BSGI.

CONCLUSION. BSGI has the highest sensitivity for the detection of invasive lobular carcinoma with a sensitivity of 93%, whereas mammography, sonography, and MRI showed sensitivities of 79%, 68%, and 83%, respectively. BSGI is an effective technique that should be used to evaluate patients with suspected cancer and has a promising role in the diagnosis of invasive lobular carcinoma.

Mammography has been the gold standard for detecting breast cancer. It is an anatomic approach, relying on the relative densities of breast tissues to differentiate normal breast tissue from breast cancer. The sensitivity of mammography is limited, with an overall sensitivity of 85% that decreases to 68% in women with dense breasts [1]. Sonography, the most common adjunct imaging technique used in breast imaging, also uses an anatomic approach to detect breast cancer and is an imperfect technique for the diagnosis of breast cancer [2].

Invasive lobular carcinoma is the second most common breast malignancy, accounting for approximately 10% of breast cancers. Arising from the lobular epithelium, invasive lobular carcinoma tends to be insidious in onset because it does not invoke a vigorous desmoplastic response. Its incohesive histologic growth pattern, low likelihood of producing calcifications, and low opacity may account for the fact that invasive lobular carcinoma is frequently not apparent mammographically and is difficult to identify clinically [3, 4]. It is usually detected with mammography at a later stage, increasing the likelihood of large primary lesions and positive node status at biopsy [3].

Mammography [4–6], sonography [7], and MRI [8] have limitations in the diagnosis of invasive lobular carcinoma [3]. Although MRI has been found to have a higher sensitivity for invasive lobular carcinoma than mammography [8, 9], MRI's role in detecting invasive lobular carcinoma is still limited as the sensitivity for the detection of invasive lobular carcinoma is less than other invasive cancers. The lower sensitivity may be attributed to the fact that invasive lobular carcinoma shows only subtle enhancement and its distribution mimics that of normal breast parenchyma [3]. Similarly, sonography has limitations in the diagnosis of invasive lobular carcinoma, especially in detecting small lesions [3, 7]. With the limitations of mammography, sonography, and even MRI in detecting invasive lobular carcinoma, additional imaging techniques are needed to improve the detection of invasive lobular carcinoma.

Breast-specific gamma imaging (BSGI) is a physiologic, rather than an anatomic, approach to breast cancer diagnosis. BSGI uses 99m-technetium sestamibi and a high-resolution breast-specific gamma camera for the detection of breast cancer. BSGI in the diagnosis of breast cancer is based on the differential uptake of radiotracer in cancer cells as compared with in the normal surrounding breast tissue; this increased uptake is thought to be due, in part, to increased vascularity and mitochondrial activity in cancer cells [10]. Although earlier studies investigated the use of a traditional gamma camera for breast imaging, the intrinsic size resolution did not allow reliable detection of subcentimeter and nonpalpable breast cancers. Furthermore, a traditional gamma camera does not allow imaging the breasts in positions comparable to mammography so that image correlation can more easily be undertaken. The use of a high-resolution gamma camera allows the reliable detection of subcentimeter cancers—even those smaller than 5 mm [10]. BSGI has been shown to be reliable regardless of breast density or pathologic type of breast cancer [11]. With the increasing use of BSGI, our observations have suggested that BSGI may allow the improved detection of invasive lobular carcinoma.

The purpose of this study was to compare the sensitivities of mammography, sonography, MRI, and BSGI in the detection of pure invasive lobular carcinoma.

Materials and Methods

Study Design

Institutional review board approval was obtained before the beginning of the study as well as a consent waiver. The study was performed as a multicenter retrospective chart review from four institutions: two academic centers and two private practices. All results and data were obtained solely from patients' medical records. Only women with biopsy-proven pure invasive lobular carcinoma who also underwent BSGI were eligible for inclusion in the study group. Twenty-six women who ranged in age from 46 to 82 years (mean age, 62.8 years) were included. Invasive lobular carcinomas with ductal components were excluded from the study. Surgical pathology reports were obtained to confirm the histopathology.

All patients were imaged with mammography and BSGI. The results of sonography and MRI, if performed, and the pathologic tumor size were included. All radiologists who interpreted the examinations were experienced breast imagers, each with a minimum of 5 years of experience interpreting BSGI. Patients underwent BSGI using a high-resolution breast-specific gamma camera (6800 Gamma Camera, Dilon Technologies) after IV injection of 20–25 mCi (740–925 MBq) of ^{99m}Tc sestamibi (Miraluma, Dupont Pharma) in an antecubital vein. The BSGI camera uses a detector mounted to an articulating arm so that the breast can be imaged in all projections, including those comparable to the positions used in mammography. Planar images were acquired in the craniocaudal (CC) and mediolateral oblique (MLO) projections for 7–10 minutes per image. The number of counts per image varies from patient to patient depending on the uptake of sestamibi in the breast tissue; however, a minimum number of 100,000 counts per image were obtained.

Mammography was performed with the equipment available at each institution (DMR, GE Healthcare; Diamond Analog, Instrumentarium Imaging; model 300, Siemens Medical Solutions; and M4, Elite, and Sophie, Lorad). Sonography was performed using a high-frequency transducer (12–13 MHz) with the equipment available at each institution (Elegra and Antares, Siemens Medical Solutions; models 5000 and IU22, Philips Healthcare). MRI was performed with a 1.5-T scanner and a dedicated breast coil with and without gadolinium using the standard breast protocol at each institution, which included unenhanced and contrast-enhanced T1 images as well as 3D volumetric sequential images after the administration of gadolinium. All images were obtained as part of the clinical evaluation of the patients, and imaging was deemed necessary by the referring physician, interpreting radiologist, or both.

Data and Statistical Analysis

The results of BSGI studies were classified as positive (focal increased radiotracer uptake) or negative (no focal increased radiotracer uptake or scattered heterogeneous physiologic uptake) by one of four radiologists experienced in all techniques of breast imaging including BSGI. Likewise, the results of mammography and, when applicable, MRI and sonography were classified as positive or negative for invasive lobular carcinoma; any discrepancies were resolved by consensus. The reports in the patients' medical records were used, and the results of imaging were not reevaluated for this study. The data were analyzed to determine the sensitivities of mammography, sonography, MRI, and BSGI for the detection of invasive lobular carcinoma. For the reference standard, the final surgical pathology report was used.

The per-lesion sensitivities for BSGI, mammography, sonography, and MRI were determined along with corresponding exact binomial 95% CIs [12]. Estimates of the differences in per-lesion sensitivities between BSGI and each imaging technique—mammography, sonography, and MRI—were determined along with 98 ⅓% CIs for differences in correlated proportions [13]. The three hypotheses that BSGI is more sensitive than each other technique—that is, mammography, sonography, and MRI—were tested using the McNemar test for correlated proportions, providing p values that were compared with a significance-level alpha value of 0.01667. The 98⅓% CIs and alpha value of 0.01667 significance levels were used to protect against multiple comparisons, preserving the overall significance level for the study at an alpha of 0.05. Statistical analyses were performed using statistics software (Intercooled, version 8.0, Stata).

Results

Twenty-eight biopsy-proven pure invasive lobular carcinomas were detected in the 26 women in the study group; two had bilateral cancers. The mean pathologic size of the invasive lobular carcinomas was 22.3 mm (range, 2–90 mm). Mammographic findings were negative in six cancers. The abnormal mammographic findings, seen in 22 of 28 carcinomas, included 13 of 22 (59%) asymmetric densities, four (18%) architectural distortions, and five (23%) spiculated masses. In seven of the 22 patients (32%), the invasive lobular carcinoma manifested mammographically as microcalcifications. Mammography had an overall sensitivity of 79% for invasive lobular carcinoma.

In the 25 patients who underwent sonography, 17 focal hypoechoic areas were detected. Eight patients had negative sonography examinations. Tumor size as determined by sonography was available in 17 lesions (mean size, 14 mm; range, 7–32 mm). Of the eight lesions not visualized on sonography, one was also not seen on BSGI; the other lesion missed on BSGI was found on sonography. The sensitivity of sonography for the detection of invasive lobular carcinoma was 68%.

Twelve of the 26 patients had MRI examinations with 10 of 12 (83.3%) lesions enhancing after injection of gadolinium including four lesions that were not visualized on mammography. The mean size of the lesions detected on MRI was 19.9 mm (range, 2–77 mm). The sensitivity of MRI for the detection of invasive lobular carcinoma was 83%.

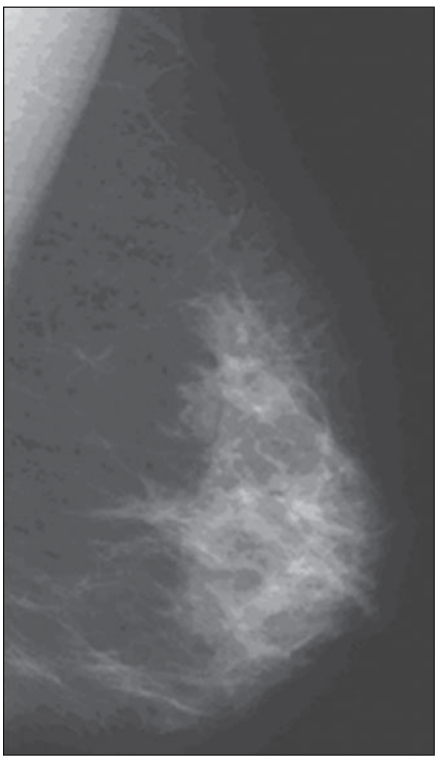
BSGI showed increased radiotracer uptake in 26 of 28 invasive lobular carcinomas with a sensitivity of 93%. Figure 1 shows a lesion that was detected by all imaging techniques. The mean size of the lesions detected by BSGI was 20.3 mm (range, 2–77 mm). The smallest invasive lobular carcinoma detected with BSGI was 2 mm. Two lesions were not detected on BSGI, measuring 5 and 90 mm, respectively. BSGI detected six cancers that were mammographically occult. Figure 2 shows a lesion that was detected by both MRI and BSGI but that was not detected on mammography. Two invasive lobular carcinomas were detected with BSGI, whereas the MRI findings were negative. These cancers measured 5 and 40 mm, respectively.

The sensitivities of BSGI, mammography, sonography, and MRI and the corresponding 95% exact CIs are provided in Table 1. BSGI has the highest sensitivity, followed by MRI, mammography, and sonography.

The overall sensitivity of BSGI was compared with the sensitivities of mammography, sonography, and MRI using the McNemar test for correlated proportions with a significance level of 0.01667. Estimates of the difference in sensitivity between BSGI and each of the other techniques (i.e., mammography, sonography, and MRI) with corresponding 98 ⅓% CIs and p values for comparisons between techniques are provided in Table 2. None of the differences in sensitivity was statistically significant at the alpha value of 0.01667 significance level, which preserves an overall alpha value of 0.05 significance level for the study. However, there was a nonsignificant trend for BSGI to have a higher sensitivity for the detection of invasive lobular carcinoma than mammography, sonography, or MRI.

Discussion

Invasive lobular carcinoma represents nearly 10% of all breast cancer diagnoses and is the second most common breast malignancy. Historically, it has presented a challenge in terms of its detection. It is believed that its elusive nature on imaging may be attributed to its growth pattern: Invasive lobular carcinoma is a slow-growing carcinoma and as it grows it fails to invoke a desmoplastic reaction. Its unique histology contributes to the difficulty in early detection, both clinically and radiographically.



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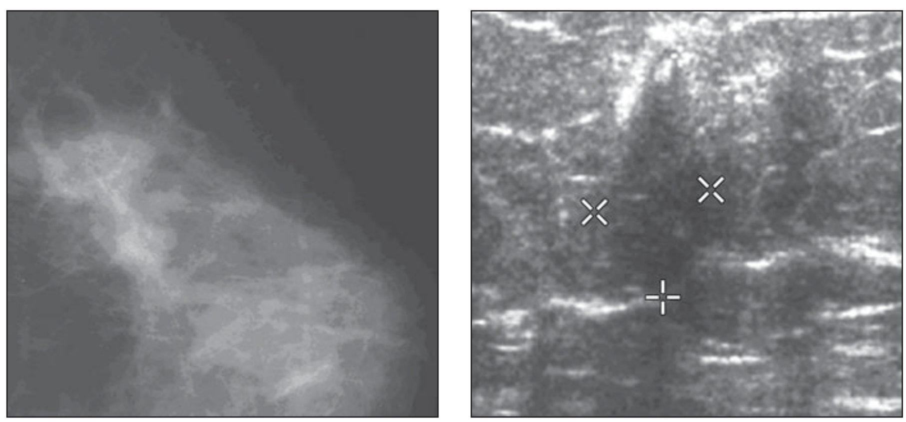

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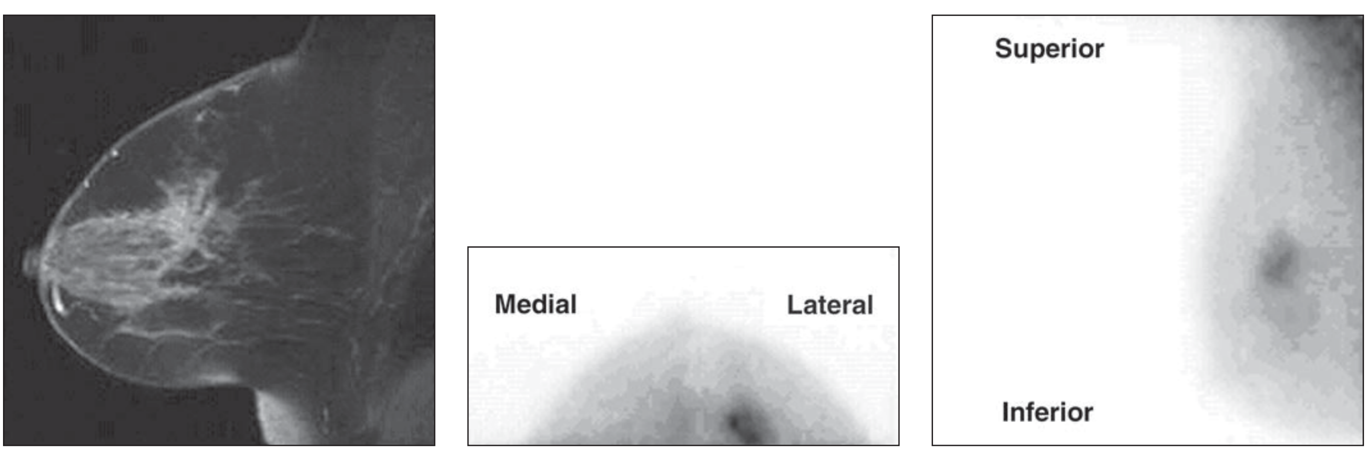

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Fig. 1—Breast images of 57-year-old woman with biopsy-proven lobular carcinoma in situ of left breast and invasive lobular carcinoma in right breast, about which findings from all imaging techniques agree.
A and **B,** Mediolateral oblique (**A**) and craniocaudal (**B**) mammograms of right breast show focal area of architectural distortion in upper outer quadrant.
C, Sonogram of right breast shows hypoechogenicity (*cursors*) with ill-defined margins in upper outer quadrant.
D, MR image shows enhancing spiculated mass in upper portion of right breast.
E and **F,** Breast-specific gamma images of right breast in craniocaudal (**E**) and mediolateral oblique (**F**) projections also show intense focus of uptake. All findings are concordant with biopsy-proven invasive lobular carcinoma.

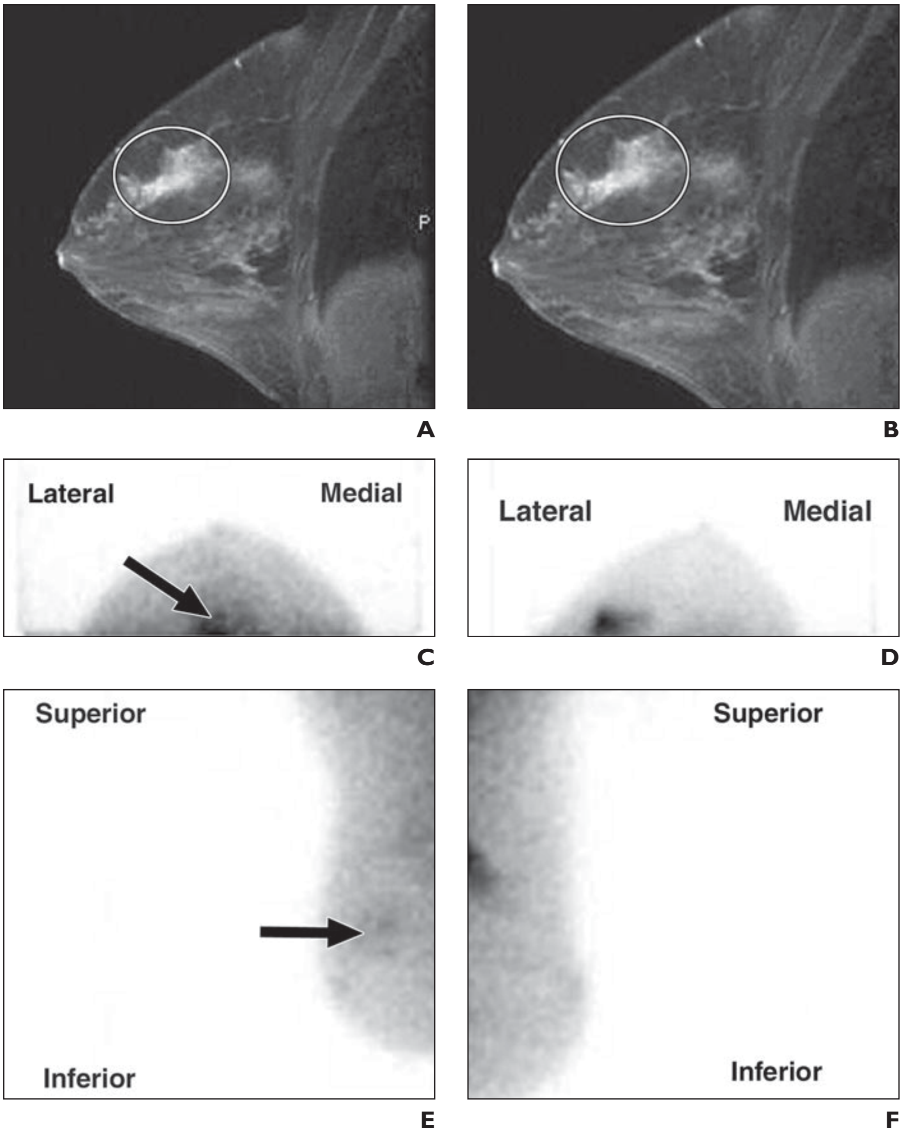

Fig. 2—Breast images of 46-year-old woman with biopsy-proven bilateral lobular carcinoma who presented with palpable left breast mass. MRI and breast-specific gamma imaging findings were positive. Mammogram of right breast (not shown) was negative, whereas mammogram of left breast (not shown) showed pleomorphic calcifications in upper outer quadrant.
A and **B,** Contrast-enhanced MR images of right breast show spiculated mass (*circle*) at 12-o'clock position.
C–F, Craniocaudal breast-specific gamma images of left (**C**) and right (**D**) breasts and mediolateral oblique images of left (**E**) and right (**F**) breasts show increased uptake at 12-o'clock position in right breast (*arrows,* **C** and **E**) as well as increased uptake in upper outer quadrant of left breast.

Studies using BSGI have shown the high sensitivity of this approach for the diagnosis of breast cancer as well as the ability to detect not only subcentimeter cancers, but also cancers smaller than 5 mm [10]. The possible improvement in detecting a difficult-to-diagnose breast cancer—invasive lobular carcinoma—with BSGI and the opportunity to compare the sensitivities of three imaging techniques with that of BSGI were the motivations to undertake this study.

The results of this study show that BSGI has the greatest sensitivity (93%) for detecting invasive lobular carcinoma followed by MRI (83%), mammography (79%), and sonography (68%). Notably, in six instances in which the cancer was not seen on mammography, BSGI detected invasive lobular carcinoma lesions. In addition, MRI detected four lesions that were missed on mammography. Statistical analysis did not show a statistically significant difference in invasive lobular carcinoma detection between BSGI and mammography, sonography, or MRI. However, a nonstatistically significant trend toward improved detection using BSGI and MRI was seen, but additional and larger studies are needed to further investigate these trends. BSGI appears to be superior or comparable to MRI in the detection of invasive lobular carcinoma, but estimates for sensitivity and comparison of the sensitivities of BSGI and MRI should be interpreted with caution because the lesions for which MRI results were not obtained, more than half of the study lesions, may differ substantially from those imaged with MRI.

This study is the first, to our knowledge, to compare the sensitivity of four different breast imaging techniques for the diagnosis of invasive lobular carcinoma. This multiinstitutional study of 26 patients with 28 lesions is limited in the number of patients and invasive lobular carcinoma lesions. However, because invasive lobular carcinoma is an infrequent breast cancer, cases from numerous institutions would be required to obtain a sufficient number of cancers to more extensively evaluate and compare the different imaging techniques for the diagnosis of invasive lobular carcinoma. Nevertheless, a larger multiinstitution study including more patients than ours would certainly be of benefit to confirm the comparative sensitivities of mammography, sonography, MRI, and BSGI in the diagnosis of invasive lobular carcinoma. In addition, differences in sensitivity could be attributed to differences in MRI and sonography technique and equipment as well as to differences in the experience and ability of the interpreting radiologists at the various centers that participated in this study. This study does, however, show the high sensitivity of BSGI for the detection of invasive lobular carcinoma. Whether BSGI has a sensitivity that is equal to or greater than that of MRI for the detection of invasive lobular carcinoma awaits additional larger trials.

Both BSGI and MRI are physiologically based imaging techniques, and both use, in part, tumor vascularity to image breast cancer. A recent study comparing BSGI and MRI for the detection of breast cancer showed equal sensitivity and greater specificity for BSGI over MRI [14]. However, beyond the greater specificity of BSGI over MRI, BSGI has other advantages. A BSGI examination is performed with the patient sitting comfortably as opposed to being confined in an MRI scanner and therefore there is no issue of claustrophobia. A BSGI examination generates from four to 16 images at

TABLE 1: Test Results for the Detection of Invasive Lobular Carcinomas Using Each Imaging Technique

Imaging Technique	No. of Lesions That Underwent Imaging	Imaging Findings		Sensitivity (%)	95% Exact CI
		Positive	Negative		
Breast-specific gamma imaging	28	26	2	93	76.5–99.1
Mammography	28	22	6	79	59.1–91.7
Sonography	25	17	8	68	46.5–85.1
MRI	12	10	2	83	51.6–97.9

TABLE 2: Cross-Tabulations of Breast-Specific Gamma Imaging and Other Test Results for Invasive Lobular Carcinomas

Imaging Technique	Breast-Specific Gamma Imaging		Estimated Differences in Sensitivities (98 ⅓% CI)	Exact McNemar p^a
	Positive	Negative		
Mammography			0.14 (–0.13 to 0.42)	0.29
Positive	20	6		
Negative	2	0		
Sonography			0.24 (–0.05 to 0.53)	0.07
Positive	16	7		
Negative	1	1		
MRI			0.17 (–0.19 to 0.53)	0.50
Positive	10	2		
Negative	0	0		

[a]All p values were not statistically significant at alpha = 0.01667 significance level; overall alpha = 0.05.

most as compared with hundreds or even thousands of images for a breast MRI examination. Although there has not been, to our knowledge, a study formally comparing the time for interpretation of BSGI versus breast MRI, our clinical experience is that the interpretation time for a BSGI examination is less than that required for breast MRI. In our practice, the cost of a BSGI examination is less than that of a breast MRI examination. Further cost-effectiveness studies will better define the comparative costs of these two studies. Finally, with the increasing concern of renal complications with the administration of gadolinium, the IV injection of ^{99m}Tc sestamibi has not been reported to be associated with significant complications.

The issue of which technique should be used to biopsy lesions detected with BSGI has been raised. In our practice, we perform second-look directed sonography in the region of the breast showing focal increased radiotracer uptake on BSGI. We can localize the region based on the quadrant where radiotracer uptake is increased as well as the distance from the nipple. This examination is essentially the same as directed second-look sonography after a focal finding is seen on MRI examination. If a lesion is detected with sonography, then a sonographically guided biopsy is performed. If no lesion is identified with careful, directed second-look sonography, then an MRI examination can be performed to determine whether an MRI-guided minimally invasive breast biopsy can be performed. Of course, direct gamma imaging–guided minimally invasive breast biopsy would be optimal and such a device is currently under development. In the near future, direct gamma imaging guidance for minimally invasive breast biopsy should be available.

In summary, our study shows that BSGI has a higher sensitivity (93%) for the detection of invasive lobular carcinoma than mammography (79%), MRI (83%), and sonography (68%). BSGI should be considered in evaluating patients with indeterminate breast lesions. Additional larger multi-institutional studies are needed to further evaluate BSGI's utility in the diagnosis of invasive lobular carcinoma.

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