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Comparative Diagnostic Utility of Low-Dose Breast-Specific Gamma Imaging to Current Clinical Standard

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■ **Abstract:** To retrospectively compare low-dose (7–10 mCi) to high-dose (15–30 mCi) breast-specific gamma imaging (BSGI) in the detection of breast cancer. A retrospective review of 223 consecutive women who underwent BSGI exam between February 2011 and August 2013 with subsequent pathologic analysis was performed. Women were divided into low-dose and high-dose groups. The results of BSGI and pathology were compared, and the sensitivity, positive predictive value (PPV), and negative predictive value (NPV) were determined. A subgroup analysis was performed to evaluate specificity using benign follow-up imaging to establish true-negative results. There were 223 women who met inclusion criteria with 109 patients with 153 lesions in the low-dose group and 114 patients with 145 lesions in the high-dose group. Pathologic correlation demonstrates sensitivities of 97.6% (95% CI = 90.9–99.6%) and 94.6% (95% CI = 84.2–98.6%; p = 0.093), PPVs of 62.1% (95% CI = 53.2–70.3%) and 50.5% (95% CI = 40.6–60.3%, p = 0.089), and NPVs of 90.5% (95% CI = 68.2–98.3%) and 92.5% (95% CI = 78.5–98.0%, p = 0.781) in the low-dose and high-dose groups, respectively. Subgroup analysis included 72 patients with 98 lesions in the low-dose group and 116 patients with 132 lesions in the high-dose group, with a specificity of 53.7% (95% CI = 39.7–67.1%) and 66.3% (95% CI = 56.2–75.2%%, p = 0.143), respectively. Low-dose BSGI demonstrated high sensitivity and NPV in the detection of breast cancer comparable to the current standard dose BSGI, with moderate specificity and PPV in a limited subgroup analysis, which was associated with a substantial number of false-positives. ■

Key Words: breast cancer detection, breast imaging, breast-specific gamma imaging, molecular imaging

Breast-specific gamma imaging (BSGI) is a physiologic imaging modality with a high sensitivity and specificity (1). The technology offers similar sensitivity with improved specificity compared to magnetic resonance imaging (MRI) with several advantages: fewer false-positives, decreased cost, decreased interpretation time, improved patient comfort, and the ability to image patients who cannot undergo MRI (2–4).

Breast-specific gamma imaging is utilized as an adjunct modality for the detection of breast cancer with diagnostic utility in patients with newly diagnosed breast cancer, high-risk populations, cases of diagnostic ambiguity, technically challenging breast imaging, and in monitoring treatment response in patients undergoing neo-adjuvant chemotherapy (5). BSGI is effective in detecting ductal carcinoma in situ (DCIS), infiltrating lobular carcinoma (ILC), sub-centimeter cancers, and high-risk lesions, such as atypical ductal hyperplasia (ADH) or lobular neoplasia (1–3,6–9).

Despite the numerous benefits of BSGI, its use is limited due to the risks associated with radiotracer exposure during imaging. BSGI utilizes the radiotracer Technetium-99m (Tc-99m)-sestamibi at a currently label-recommended dose of 20–30 mCi. Hendrick compared the lifetime-attributable risk of radiation-induced cancers of BSGI to that of mammography, concluding that a single BSGI study involves a lifetime risk of inducing a fatal cancer that is greater than or comparable to a lifetime of annual screening mammography (10). In addition, the systemic distribution of radiotracer used in BSGI exposes all organs to radiation, whereas in mammography radiation is directed only to the breasts.

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The current label-recommended dose of radiotracer used with BSGI is based on extensive cardiac studies. However, a number of institutions have begun reducing the dose of radiotracer administered to minimize the potential risk to patients. Recent studies have examined the diagnostic utility of low-dose radiotracer in molecular breast imaging (MBI), a technique similar to BSGI, with encouraging results (11–13). Following these findings, our institution began using Tc-99m-sestamibi at a dose of 7–10 mCi to minimize radioactivity for patients.

The purpose of our study was to retrospectively compare the diagnostic utility of low-dose BSGI (7–10 mCi) to the previously utilized high-dose (15–30 mCi) protocol in the detection of breast cancer.

MATERIALS AND METHODS

The Subjects

A retrospective review of the records of all patients who underwent BSGI between February 2011 and August 2013 was performed. Two-hundred and twenty-three patients were included in the analysis, meeting the following criteria: (i) Either low-dose (7–10 mCi) or high-dose (15–30 mCi) BSGI exam had been performed, (ii) pathologic diagnosis was available for correlation, and (iii) a complete medical record was available. Institutional Review Board approval was obtained with a waiver of informed consent and waiver of Health Insurance Portability and Accountability Act.

BSGI Technique and Interpretation

A high-resolution, small-field-of-view breast-specific gamma camera (6800; Dilon Technologies, Newport News, VA) was used to obtain all images for this study. Patients received an injection of Tc-99m-sestamibi radiotracer in either the antecubital vein or dorsal venous complex of the hand. Patients received an injection of high-dose (15–30 mCi) radiotracer prior to December 2012 and low-dose (7–10 mCi) radiotracer following this time period. Craniocaudal and mediolateral oblique projections were obtained for all patients, with additional views performed as necessary without additional radiotracer injection. Average acquisition time for each image ranged from 6 to 10 minutes, with a minimum of 100,000 counts, for a total imaging time of approximately 40 minutes per study.

Breast-specific gamma imaging examinations were interpreted by experienced radiologists. The results in the medical record were used; examinations were not reinterpreted for this study. Images were read in the clinical setting with access to patient history and adjunct imaging studies. Images were assigned a score of 0–6, paralleling the BI-RADs assessment. Scores of 1, 2, or 3 were classified as a negative BSGI exam, and scores of 0, 4, 5, or 6 were classified as positive for purposes of analysis.

Data Collection and Analysis

Patients were stratified into two groups based upon the dose of radiotracer received. The patient's age, indication for BSGI study, BSGI interpretation, number of suspicious lesions, lesion size, and pathologic results were collected. Each BSGI-identified lesion was compared to pathologic results requiring the lesion on BSGI and pathology to be in the same quadrant and the same distance from the nipple. As several patients had two or more lesions, statistical independence is not assumed. Accordingly, the method of generalized estimating equations, which allows for nonindependent data, was used (14). The sensitivity, positive predictive value (PPV), and negative predictive value (NPV) of low-dose and high-dose BSGI were calculated. Statistical analysis for significant differences in sensitivity between groups was performed using Chi-squared tests, while PPV and NPV were compared using two-proportion z-tests, with a $p < 0.05$ considered significant.

Specificity Sub-Group Analysis

To evaluate specificity, a minimum of 6-month follow-up to assure absence of cancer was needed. Not all women included in the low-dose group had a 6-month follow-up. Therefore, a subgroup analysis was performed to assess specificity between low-dose and high-dose BSGI. A random 4-month period in the high-dose group with a minimum 6-month follow-up was compared with the 4-month period of the low-dose group which had a 6-month follow-up. In the low-dose group, the 4-month period between November 2012 and March 2013 for which follow-up imaging of at least 6 months duration was available, was utilized in analysis. In the high-dose group, a 4-month period between June 2011 and September 2011 for which follow-up imaging of at least 1 year was

available, was arbitrarily chosen for comparison. The sensitivity, PPV, NPV, and corresponding confidence intervals and statistical significance levels were recalculated using a two-proportion *z*-test.

RESULTS

Two-hundred and twenty-three women (34–84 years; mean, 58.8 years) met the criteria for inclusion in the study: 109 women (34–84 years; mean, 59 years) with 153 lesions in the low-dose (range 7.0–10.9 mCi) group and 114 women (40–83 years; mean, 58.5 years) with 145 lesions in the high-dose (range 16.7–25.7 mCi) group.

Low-Dose BSGI Analysis

Of 153 lesions identified in women imaged with low-dose BSGI, 84 (55.0%) were malignant with 60 (71.4%) invasive cancers and 24 (28.6%) DCIS (Table 1, Fig. 1). Of the 69 (45.0%) nonmalignant lesions, 61 (88.4%) were benign and 8 (11.6%) were high-risk lesions, including lobular carcinoma in situ (LCIS) and ADH (Fig. 2).

Of the 84 malignant lesions, 82 had a positive BSGI for a sensitivity of 97.6%. A positive BSGI was noted in 132 lesions of which 84 were invasive carcinoma or DCIS, resulting in a PPV of 62.1%. Nineteen of 21 negative BSGI exams had benign pathology while 2 positive BSGI examinations were in women with malignancy, resulting in a NPV of 90.5% (Table 2).

In the women who had cancer and who were imaged with low-dose BSGI examinations, 100% of the invasive cancers (62/62) (95% CI = 92.8–100.0%) and 20 of the 22 DCIS had positive BSGI for a sensitivity of 91.7% (95% CI = 71.5–98.5%).

Lesion size was available in 45 of 62 invasive cancers and 13 of 22 DCIS. Of the invasive cancers, 10 of the 45 lesions measured ≤1.0 cm. Of the DCIS lesions, seven of 13 measured ≤1.0 cm. The two false-negative lesions were 2 DCIS measuring 1.0 and 1.2 cm. The size of the true-positive lesions identified via low-dose BSGI ranged from 0.5 to 4.2 cm, mean 1.7 cm (Table 3).

Table 1. Comparison of Malignant Lesions Detected by Low-Dose and High-Dose BSGI

Malignant lesions detected by BSGI	Low-dose (# of cancers)	High-dose (# of cancers)
Infiltrating ductal carcinoma with a component of ductal carcinoma in situ	37	27
Infiltrating ductal carcinoma	14	7
Ductal carcinoma in situ	22	13
Infiltrating lobular carcinoma	5	5
Mixed infiltrating ductal and lobular carcinoma	3	1
Mucinous carcinoma	2	2
Micropapillary carcinoma	1	0
Paget's disease of the nipple with ductal carcinoma in situ	0	1
Total	84	56

High-Dose BSGI Analysis

Of 145 lesions identified in women imaged with high-dose BSGI, 56 (39.0%) were malignant with 42 (75.0%) invasive cancers and 14 (25.0%) DCIS (Fig. 3). Of the 89 (61.0%) nonmalignant lesions, 77 (86.5%) were benign with no associated risk of cancer, and 12 (13.5%) were high-risk lesions (Fig. 4).

Breast-specific gamma imaging was positive in 53 of 56 malignant lesions, for a sensitivity of 94.6%. A positive BSGI result was seen in 105 lesions of which 53 were invasive carcinoma or DCIS, resulting in a PPV of 50.5%. A negative BSGI result was identified for 40 lesions of which 37 had benign pathologic findings, resulting in a NPV of 92.5%.

Forty of 42 invasive cancers imaged with high-dose BSGI had positive examinations for a sensitivity of 95.2% (95% CI = 82.6–99.1%). Fourteen of 14 DCIS imaged with low-dose BSGI had positive examinations for a sensitivity of 100.0% (95% CI = 73.3–100.0%).

Pathologic size was available in 36 of 42 invasive cancers and 9 of 14 DCIS. Of the invasive cancers, 11 of the 36 lesions identified were ≤1.0 cm. Three of 9 DCIS were ≤5 mm. The 3 false-negative lesions were three invasive cancers measuring 0.4, 0.5, and 1.3 cm. The size of the true-positive cancers identified with high-dose BSGI ranged from 0.2 to 6.0 cm, mean 1.7 cm.

Comparative Analysis of Low-Dose and High-Dose BSGI

Statistical significance analysis of differences in sensitivity values with low-dose and high-dose BSGI yielded a Chi-squared value of 6.43 ($p = 0.093$). Low-dose BSGI demonstrated a higher sensitivity for cancer than high-dose BSGI examinations. Differences in PPV and NPV were compared via two-proportion *z*-test.

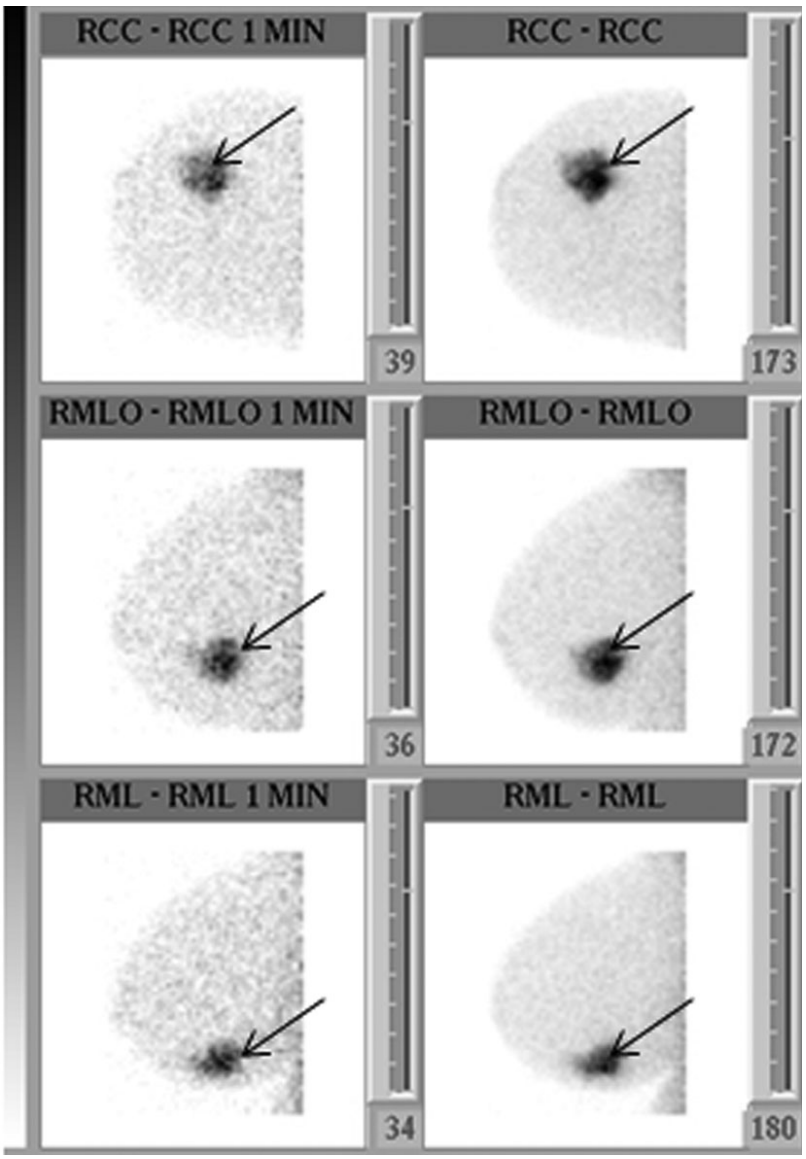

Figure 1. Infiltrating ductal carcinoma imaged via low-dose BSGI (7.2 mCi). Examination demonstrated marked radiotracer uptake in the index cancer in the lower outer quadrant (arrow).

Analysis of differences in PPV and NPV in low-dose and high-dose BSGI yielded z-scores of 1.7 ($p = 0.089$) and 0.3 ($p = 0.781$), respectively.

Subgroup Analysis for Specificity Analysis

Seventy-two women (31–83 years; mean, 60.2 years) with 98 lesions had BSGI examinations during the 4-month period, November 2012 to March 2013 used for analysis of BSGI specificity. Of the 54 (56.0%) nonmalignant lesions, 50 (92.6%) were benign with no associated risk of cancer, and 4 (7.4%) were high-risk lesions (ADH, ALH, or LCIS). Pathologic correlate was used to define benign status in 34 (63.0%) of the nonmalignant lesions, while 20 (37.0%) were confirmed via negative follow-up imaging.

In the 54 nonmalignant lesions, a negative BSGI was found in 29 lesions, yielding a specificity of 53.7%. BSGI was negative in 30 lesions, of which 29 were benign or had follow-up imaging, resulting in a NPV of 96.7% (95% CI = 80.9–99.8%).

The high-dose subgroup included 116 women (range, 40–83 years; mean, 58.5 years) with 101 (77.0%) nonmalignant lesions, of which 93 (92.1%) were benign with no associated risk of cancer, and 8 (7.9%) were high-risk lesions. Pathologic correlate was used to define benign status in 50 (49.5%) of the nonmalignant lesions, while 51 (50.5%) were confirmed via negative follow-up imaging.

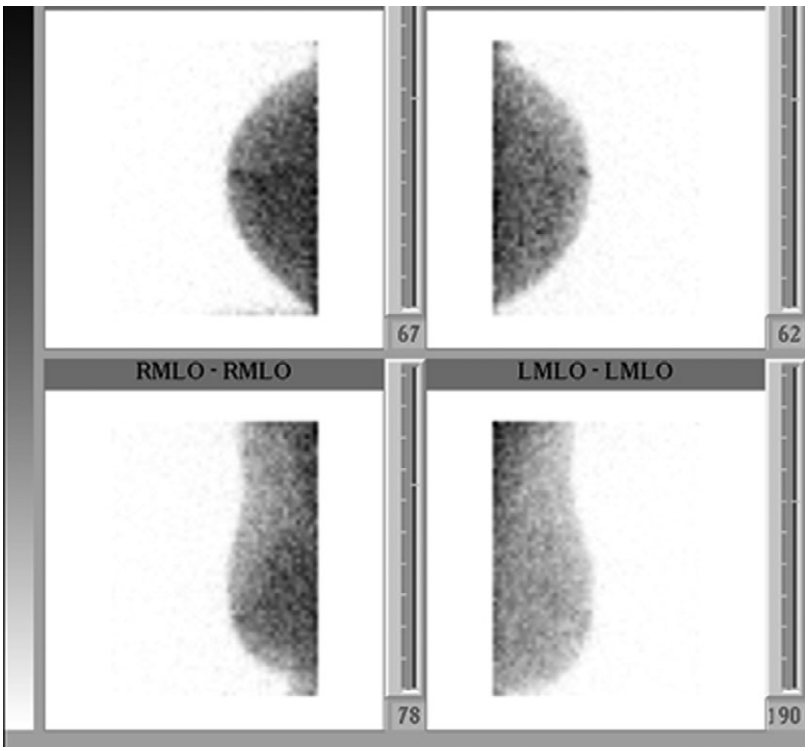

Figure 2. Dense stromal fibrosis and fibrocystic change imaged via low-dose BSGI (8.2 mCi). Minimal focus of radiotracer uptake is present in the retroareolar right breast.

Table 2. Comparison of the Diagnostic Accuracy of Low-Dose versus High-Dose BSGI

Metric	Low-dose BSGI	High-dose BSGI	p-value
Sensitivity	97.6% (82/84; 95% CI = 90.9–99.6%)	94.6% (53/56; 95% CI = 84.2–98.6%)	0.093
Specificity (subgroup analysis)	53.7% (29/54; 95% CI = 39.7–67.1%)	66.3% (67/101; 95% CI = 56.2–75.2%)	0.143
Negative predictive value	90.5% (19/21; 95% CI = 68.2–98.3%)	92.5% (37/40; 95% CI = 78.5–98.0%)	0.781
Positive predictive value	62.1% (84/132; 95% CI = 53.2–70.3%)	50.5% (53/105; 95% CI = 40.6–60.3%)	0.089

Table 3. Comparison of Lesion Size Detected in Low-Dose versus High-Dose BSGI

Lesion type	Low-dose BSGI (cm)	High-dose BSGI (cm)
True-positive	0.5–4.2 (1.7)*	0.2–6.0 (1.7)
Invasive cancers	0.5–4.2 (1.7)	0.2–6.0 (1.6)
Total <1.0 cm	10/45	11/36
Total <0.5 cm	1/45	8/36
DCIS	0.1–7.8 (1.5)	0.1–6.0 (1.8)
Total <1.0 cm	7/13	–
Total <0.5 cm	4/13	3/9
False-negative		
Invasive cancers	–	0.4–1.3 (0.7)
DCIS	1.0–7.8 (1.5)	–

*Mean of corresponding range is indicated in parentheses.

Sixty-seven of 101 nonmalignant lesions were negative in the high-dose group for specificity of 66.3%. Sixty-seven of 68 negative BSGI were benign for an NPV of 98.5% (95% CI = 91.0–100.0%).

Analysis of statistical significance for subgroup sensitivity and specificity parameters for low-dose and high-dose BSGI found no significant difference with chi-squared values of 2.25 ($p = 0.522$) and 5.43 ($p = 0.143$), respectively. Analysis of differences in PPV and NPV yielded z-values of 1.8 ($p = 0.065$) and 0.7 ($p = 0.469$).

False-Positive Lesions

A false-positive lesion is defined as a positive BSGI with no associated cancer. Forty-nine false-positive lesions occurred with low-dose BSGI, while high-dose BSGI had 52 false-positive lesions (false-positive rate: 58.4%, z-value = 2, $p = 0.051$).

In the subgroup analysis, low-dose BSGI yielded 25 false-positive lesions while high-dose BSGI yielded 34 false-positive lesions (false-positive rate: 33.7%,

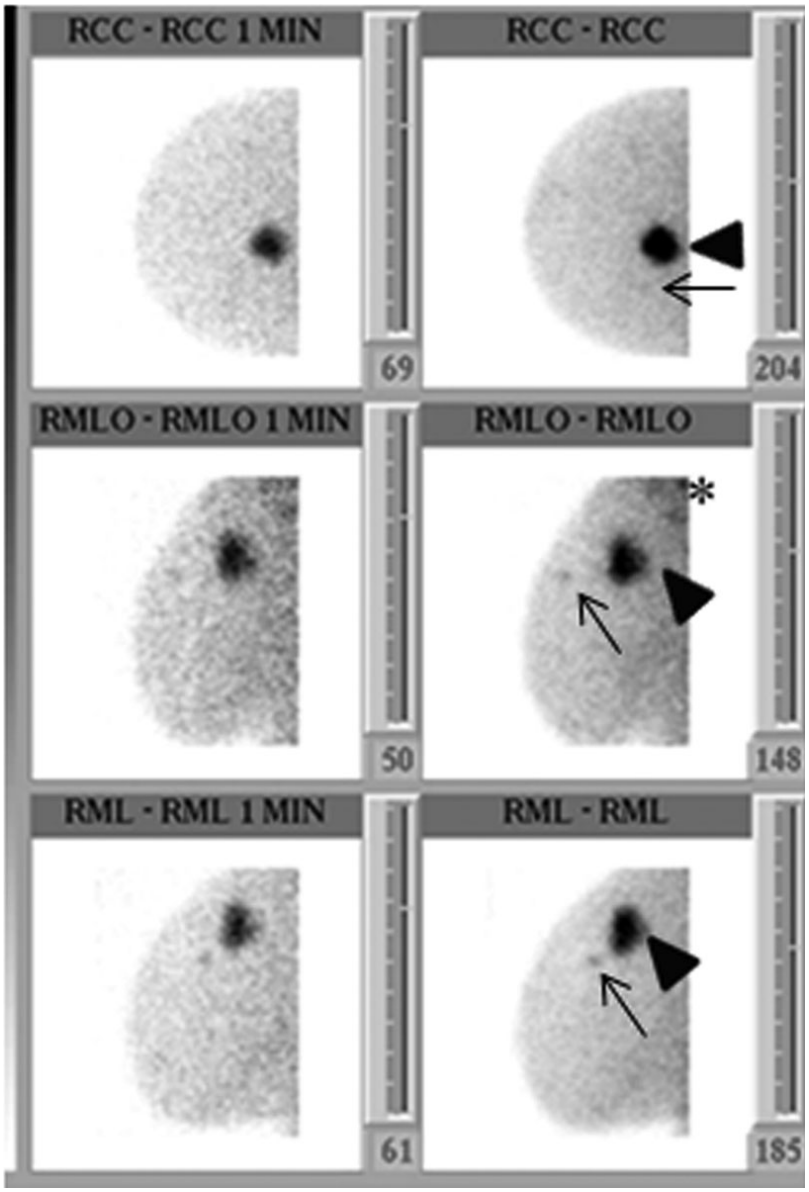

Figure 3. Infiltrating ductal carcinoma imaged with high-dose BSGI (21.1 mCi). Examination index cancer (arrowhead) in the upper inner quadrant with second focus of invasive cancer (arrow) anterior to the index lesion in the upper outer quadrant of the right breast. Metastatic axillary nodes are visualized as well (asterisk).

z-value = 1.5, p = 0.143). There is no significant difference in false-positive lesions with low-dose and high-dose BSGI. The most common pathologic diagnosis encountered was fibrocystic change (Table 4).

DISCUSSION

Breast-specific gamma imaging is a physiologic imaging modality with diagnostic utility in detecting multifocal disease in cases of newly diagnosed breast cancer, high-risk populations, and cases with remaining diagnostic concerns (4,15–18). A standard BSGI study using 20–30 mCi of Tc-99m-sestamibi results in the administration of a whole-body effective dose of 7.8–9.4 mSv compared to two-view bilateral mammography, which results in an effective dose of 0.44 mSv applied only to the breasts (10). By comparison the whole-body effective dose of a BSGI examination with 7–10 mCi results in a whole-body dose of 2.2–3.3 mSv, 5–7.5 times that of two-view bilateral mammography. Although this is higher than mammography, BSGI is not used as a screening tool, but rather, as a problem-solving adjunct imaging modality in properly selected cases.

Our study sought to compare the diagnostic performance of low-dose compared to standard high-dose BSGI in the detection of breast cancer. The overall sensitivity of low-dose and high-dose BSGI yielded

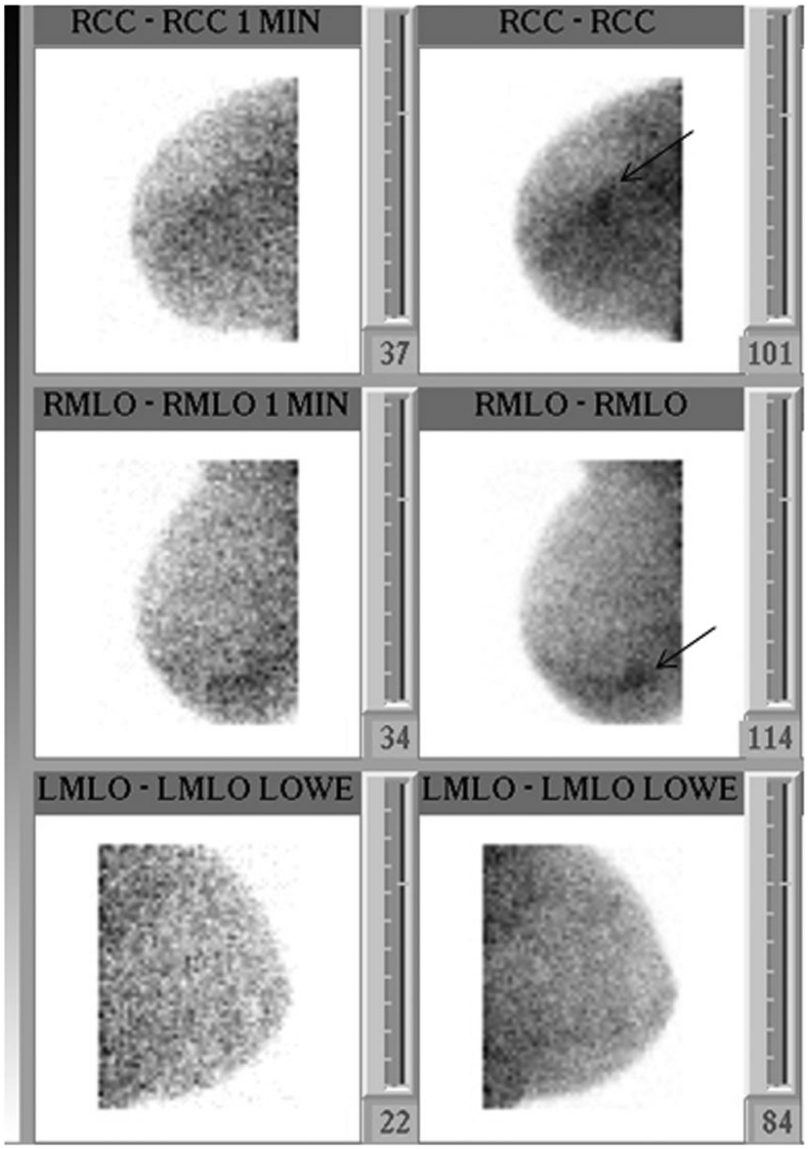

Figure 4. Benign fibro-fatty tissue imaged via high-dose BSGI (19.0 mCi). Suspicious focus of radiotracer uptake is in the lateral inferior right breast (arrows).

comparable results with sensitivities of 97.6% and 94.6%, respectively ($p = 0.093$). These values correspond with the previously reported sensitivity range BSGI (85.0–100.0%) (1) and are comparable to reported values for MRI of 85.7–99.0% (2,19,20).

Both low-dose and high-dose BSGI resulted in moderate specificity with values of 53.7% and 66.3%, respectively ($p = 0.143$). These values are lower than that previously reported, with prior reports noting specificity of 60.0–95.0% (1), but comparable to reported data for MRI, which ranges between 37.0% and 97.0% (21). This analysis was limited by a small sample size, which may in part explain the lower than-expected specificity. In addition, the specificity for both groups was tempered by a relatively high number of false-positive results with 32.7% (50 of 153 lesions) and 35.9% (52 of 145 lesions) of findings representing false-positive outcomes in the low-dose and high-dose groups, respectively. The most common benign pathology resulting in a false-positive BSGI was fibrocystic change, which is consistent with prior studies reporting on false-positive lesions with BSGI (9,22–24).

The disease prevalence in our population was 54.9% (84/153) and 38.6% (56/145) in the low-dose and high-dose groups, respectively. This resulted in differing PPVs with low-dose BSGI yielding a value of 62.1% and high-dose BSGI a value of 50.5% ($p = 0.089$). Variation in the indications for BSGI between groups may explain this observation (Table 5). When comparing the low-dose to the high-dose group, it was noted that 63.3% versus 32.5%

were referred to assess for extent of disease in cases of newly diagnosed breast cancer, 20.2% versus 44.7% were referred for annual surveillance for personal or family history of breast cancer, and 10.1% versus 16.7% referred for a new abnormality on imaging or physical exam. Accordingly, a higher pretest probability of malignancy was present in the low-dose group, resulting in a higher PPV. These findings may also reflect the change in indications for BSGI over time in our practice. In contrast, a high NPV was observed in both groups with values of 90.5% and 92.5% ($p = 0.781$), respectively.

Table 4. Pathologic Findings Encountered in False-Positive Lesions in Low-Dose and High-Dose BSGI

			Subgroup analysis frequency	
Pathologic findings in false-positive lesions	Low-dose frequency	High-dose frequency	Low-dose	High-dose
Fibrocystic change	21	25	17	17
Stromal fibrosis	9	6	0	4
Fibroadenoma	6	7	3	6
Benign breast tissue	4	4	1	3
Benign cyst	2	2	0	0
Reactive lymphoid tissue	1	0	1	0
Atrophic breast tissue	0	1	0	0
High-Risk Lesions				
Atypical ductal hyperplasia	5	4	0	1
Atypical ductal hyperplasia with lobular carcinoma in situ	1	0	2	3
Atypical lobular hyperplasia	0	2	1	0
Mixed atypical ductal and lobular hyperplasia	0	1	0	1
Lobular carcinoma in situ	1	0	0	0
Total	50	52	25	34

Table 5. Comparison of the Indications for BSGI Exam in Patients Receiving Low-Dose versus High-Dose Radiotracer

Indication/Reason for referral for BSGI	Low-dose frequency	High-dose frequency
New diagnosis of breast cancer		
Evaluate for the extent of disease	63	35
S/p neo-adjuvant chemotherapy	7	2
Preoperative assessment	6	2
Postoperative assessment	1	4
Personal history of breast cancer	14	32
Abnormal findings on recent breast imaging	9	12
Family history of breast cancer	5	16
History of high-risk lesion (e.g., atypical ductal or lobular hyperplasia)	3	3
New onset breast pain	1	2
New palpable breast mass	1	5
New onset bloody nipple discharge	0	1
Total	109	114

Breast-specific gamma imaging has also shown utility in the diagnosis of DCIS with a sensitivity ranging from 67.0% to 94.0% (9,23–26). The reported sensitivity of mammography in the detection of DCIS ranges from 27% to 82% (26–28), while the sensitivity of MRI has been reported as 91.4% (29). In our study, low-dose BSGI had a sensitivity of 93.3% (28 of 30 DCIS), while high-dose BSGI had a sensitivity of 100.0% (14 of 14 DCIS), which exceeds previously reported values for BSGI and MRI. The finding of all DCIS lesions with high-dose BSGI is likely due to the smaller sample size, and undoubtedly, a larger series would result in sensitivity lower than 100%. In the detection of invasive cancers, BSGI and MRI have previously reported sensitivities of 97.0% and 90.9%, respectively (2,9). Our study demonstrated sensitivity for invasive cancers comparable to those previously reported of 98.4% (60 of 61 invasive cancers) and 93.3% (42 of 45 invasive cancers) in the low-dose and high-dose groups, respectively.

Differences in the size of lesions detected by low-dose and high-dose BSGI were also evaluated. The observed mean lesion size was comparable between groups (low-dose, 1.7 cm; high-dose, 1.6 cm). High-dose BSGI detected the smallest lesion at 0.23 cm, but both low-dose and high-dose BSGI exhibited similar ability to detect sub-centimeter cancers.

There were several limitations to our study. This was a retrospective analysis of two populations with differing prevalence of disease, indications for BSGI, and pretest probability of malignancy. However, we chose the population based on time of BSGI study and not on these other factors, reflecting the differences in indication for BSGI during different time periods. The ability to evaluate the specificity of BSGI in the two populations was limited due to small sample size, reducing the statistical power of our analysis. In addition, BSGI examination results were based on a single radiologist interpretation and not reread by multiple readers. Furthermore, this was a retrospective, observational study in its design, and the number of included cases was based on time, not on predetermined statistical power.

In conclusion, low-dose BSGI demonstrated high sensitivity and NPV in the detection of both invasive breast cancers and DCIS that is comparable to the current standard dose BSGI as well as values reported for MRI. Low-dose BSGI and high-dose BSGI had comparable moderate specificity and PPV in a subgroup analysis, which was associated with a signifi-

cant false-positive rate. The results demonstrate that low-dose BSGI is equally effective as high-dose, and although additional studies are needed, low-dose BSGI should be considered in clinical practice.

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None.

DISCLOSURE

Rachel Brem, MD is on the Board of Managers of and has stock in Dilon Technologies.

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