Complementary Role of Semiquantitative Analysis of Breast-Specific Gamma Imaging in the Diagnosis of Breast Cancer

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OBJECTIVE. We investigated whether the interpretation of breast-specific gamma imaging (BSGI) with visual and semiquantitative analyses can improve the diagnosis of breast cancer.

MATERIALS AND METHODS. The records of 114 women (mean age ± SD, 49.6 ± 9.8 years) who underwent BSGI, mammography, and ultrasound to evaluate a breast lesion or lesions were reviewed retrospectively. The breast lesions identified with BSGI were compared with those identified with mammography and ultrasound. BSGI was first interpreted visually, and then a semiquantitative analysis was performed. For the semiquantitative analysis, the uptake ratio for each breast lesion was calculated by dividing the tumor uptake by the contralateral normal breast uptake.

RESULTS. Four of the 114 patients had two breast lesions, so a total of 118 breast lesions (42 malignant lesions and 76 benign lesions) were evaluated. A BSGI uptake ratio cutoff of 1.5, with values less than 1.5 indicating negative for cancer, as determined by receiver operating characteristic curve analysis of our data (area under curve, 0.874), was used for semiquantitative analysis. The sensitivity and specificity of BSGI with visual analysis alone for assessing malignant breast lesions were 76.2% (32/42) and 81.6% (62/76), respectively. For BSGI with visual and semiquantitative analyses, the sensitivity and specificity were 76.2% (32/42) and 92.1% (70/76), respectively. The sensitivity and specificity for mammography were 57.1% (24/42) and 81.6% (62/76), respectively. For ultrasound, the respective values were 97.6% (41/42) and 61.8% (47/76). BSGI with visual and semiquantitative analyses had a significantly higher specificity than BSGI with visual analysis alone, mammography, and ultrasound (all, $p < 0.01$).

CONCLUSION. Semiquantitative analysis of BSGI with visual interpretation may be a useful complementary method for evaluating malignant breast lesions.

Keywords: breast cancer, breast-specific gamma imaging (BSGI), mammography, semiquantitative analysis, ultrasound

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The global incidence and mortality of breast cancer have increased steadily in the past decades, and breast cancer is recognized as an important health problem for women [1]. Mammography and ultrasound are commonly used anatomic imaging procedures to detect breast cancer, but they have several limitations. The sensitivity of mammography for breast cancer detection decreases substantially if the breast parenchyma is dense. In addition, false-positive diagnoses based on mammography result in many benign findings at biopsy. Ultrasound, the most commonly used adjunct breast imaging technique, can depict small node-negative breast cancers, which increases the probability of cancer detection, especially in women with mammographically dense breast tissue; however, ultrasound also has a high false-positive rate, and concerns have been expressed regarding its operator dependence [2–4].

Molecular imaging technologies have been developed recently to circumvent these limitations. Breast-specific gamma imaging (BSGI), also referred to as "molecular breast imaging," has been improved significantly in recent years with the development of breast-optimized, high-resolution, small-FOV gamma camera designs [5]. Unlike mammography and ultrasound, BSGI is a functional imaging examination that reflects the biochemical and physiologic characteristics of tumors. In particular, cellular mitochondrial density can be measured using ^{99m}Tc-methoxyisobutylisonitrile (MIBI) as a tracer; high cytoplasmic mitochondrial density is typical of hyperproliferative cell types and not of benign pathologic entities [6].

Several recent studies have concluded that BSGI has a high sensitivity for breast cancer detection and that its findings influence presurgical planning and management [7–12]. However, the specificity of BSGI is lower than its sensitivity [7–12]. We considered that a semiquantitative analytic approach might be helpful in determining whether a lesion is a tumor. For example, the standardized uptake value of ^{18}F-FDG PET/CT, which normalizes the FDG accumulation in a suspicious lesion with respect to the injected dose and the patient's body weight, is used widely as a semiquantitative method to evaluate questionable lesions [13, 14].

In this study, we investigated whether the interpretation of BSGI with visual and semiquantitative analyses provides a better means of detecting breast cancer than BSGI with visual analysis alone. We also compared BSGI with mammography and ultrasound in the diagnosis of breast cancer.

Materials and Methods

Patients

This retrospective study was approved by our institutional review board; patient consent was not required. The records of patients who had at least one of the following indications for undergoing BSGI at our center from December 2009 to May 2012 were reviewed: clinical findings such as a palpable breast lesion, breast pain, or bloody nipple discharge; indeterminate or suspicious mammography or ultrasound findings; or high risk of breast cancer [10, 15, 16]. Patients with a personal history of breast cancer were excluded from this study. One hundred fourteen women who met the study criteria were enrolled. All had undergone BSGI, mammography, and ultrasound to evaluate the breast lesion or lesions. Four of the study subjects had two synchronous breast lesions, so a total of 118 breast lesions were evaluated in 114 patients.

Biopsy was performed when considered clinically necessary, and biopsy results were used as the reference standard. If the biopsy result was inconclusive, another biopsy was performed 3 months later. When a biopsy result was not obtained, the clinical follow-up results at least 1 year after BSGI were used as the reference standard. The results were classified as malignant or benign.

Breast-Specific Gamma Imaging

A high-resolution, small-FOV breast-specific gamma camera (Dilon 6800, Dilon Technologies) was used. Approximately 740–925 MBq of ^{99m}Tc-MIBI was administered via an upper extremity vein in the side contralateral to the suspected breast lesion if possible. Imaging began 5–10 minutes after administration of the radiopharmaceutical. Craniocaudal and mediolateral oblique images were acquired for 10 minutes each with the patient seated.

Images were assessed by two experienced nuclear medicine physicians who were unaware of the pathology results. Any discrepancies were resolved by consensus. The findings for breast lesions detected by BSGI were analyzed and compared with those identified by mammography and ultrasound. Initially, BSGI studies were interpreted visually. Each case was classified on the basis of radiotracer uptake on the BSGI study as normal (homogeneous uptake), benign (minimal patchy uptake), probably benign (minimal patchy uptake with some areas of more focal uptake), probably abnormal (mild focal uptake), or abnormal (marked focal uptake) [7, 15]. For statistical analysis, BSGI results were classified as negative (normal, benign, and probably benign) or positive (probably abnormal and abnormal).

After visual interpretation of the BSGI studies, a semiquantitative analysis of the BSGI studies was performed. The workstation software was used to draw a region of interest (ROI) around the breast lesion (tumor ROI) and a corresponding ROI of the same size and in the same location in the contralateral normal breast (background ROI). The radiotracer uptake ratio for each breast lesion was calculated by dividing the uptake count of the tumor ROI by the uptake count of the background ROI (Fig. 1). The craniocaudal or mediolateral oblique image that showed the breast lesion with the highest uptake ratio was selected for this analysis. For a breast lesion that was not visualized on BSGI, the uptake ratio was recorded as 1.

Mammography and Ultrasound

Mammography (Selenia system, Lorad) and ultrasound (IU22, Philips Healthcare) were performed as part of the clinical evaluation of the patients. The mammography and ultrasound studies were interpreted by one experienced radiologist unaware of the pathology results. Assessments for mammography and ultrasound were classified as either negative (BI-RADS categories 0–3) or positive (BI-RADS categories 4 and 5).

Statistical Analysis

For semiquantitative analysis of BSGI, the cutoff value of the uptake ratio for a malignant breast lesion was determined using receiver operating characteristic (ROC) curve analysis. The significance of differences in the sensitivities and specificities of BSGI with visual analysis alone, BSGI with visual and semiquantitative analyses, mammography, and ultrasound was identified using the McNemar test. Statistics software (PASW, version 17.0, SPSS) for Microsoft Windows was used for the analyses, and p values less than 0.05 were considered significant.

Results

Patient Characteristics

The clinical characteristics of the 114 women (118 breast lesions) and the pathologic results of the malignant lesions are summarized in Table 1. Biopsy results were available for 89 lesions, and the other 29 lesions underwent clinical follow-up (mean ± SD, 25.2 ± 11.0 months; range, 12.7–42.1 months). Overall, 42 lesions were found to be malignant and 76 were found to be benign.

Analysis of Breast-Specific Gamma Imaging, Mammography, and Ultrasound Findings

A BSGI uptake ratio cutoff of 1.5 was used for semiquantitative analysis as determined by ROC curve analysis of our data (area under curve, 0.874). The sensitivities and specificities of BSGI with visual analysis alone, BSGI with visual and semiquantitative analyses, mammography, and ultrasound for the diagnosis of a malignant breast lesion are shown in Figure 2. For the readings of the two nuclear medicine physicians of BSGI with visual analysis alone, the sensitivities were the same, 76.2% (32/42), whereas the specificities were 81.6% (62/76) and 78.9% (60/76), respectively. However, for BSGI with visual and semiquantitative analyses, no discrepancy was found between the

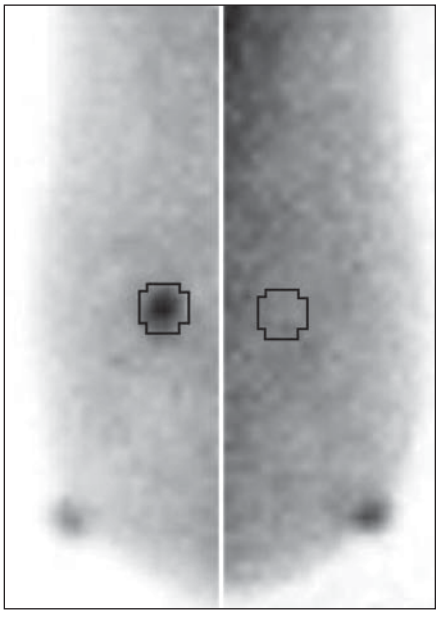

Fig. 1—For semiquantitative analysis of breast-specific gamma imaging, regions of interest (ROIs) encompassing breast lesion (left image) and corresponding ROI in contralateral normal breast (right image) were drawn. Breast-specific gamma images of 51-year-old woman are shown.

TABLE 1: Clinical Characteristics of the Patients (*n* = 114) and Pathologic Results of the Malignant Lesions (*n* = 42)

Characteristic or Result	Value
Age (y)	
Mean ± SD	49.6 ± 9.8
Range	22–76
Indication for BSGI (no. of patients)	
Indeterminate or suspicious findings on mammography or ultrasound	80
Palpable breast lesion, breast pain, or bloody nipple discharge	28
Cancer screening	6
Breast density (no. of patients)	
Extremely or heterogeneously dense	98
Almost entirely fat or scattered fibroglandular densities	16
Pathology results of malignant breast lesions (no. of lesions)	
Invasive ductal carcinoma	30
Ductal carcinoma in situ	10
Adenoid cystic carcinoma	1
Mucinous carcinoma	1

Note—BSGI = breast-specific gamma imaging.

two nuclear medicine physicians. We also evaluated 42 malignant breast lesions with available sizes, 12 of which were 1 cm or smaller. The sensitivity of BSGI was 41.7% (5/12) for lesions 1 cm or smaller and was 90.0% (27/30) for lesions larger than 1 cm. The sensitivities of BSGI with visual analysis alone and of BSGI with visual and semiquantitative analyses according to lesion size (≤ 1 cm and > 1 cm) were the same. Of 12 malignant breast lesions that were 1 cm or smaller, BSGI results for seven were false-negative. These false-negative lesions consisted of four ductal carcinomas in situ (DCIS) (size, 1, 1, 1, and 0.8 cm) and three invasive ductal carcinomas (1, 1, and 0.2 cm). Two false-negative invasive ductal carcinomas of 1 cm in diameter were located in the far periphery, close to the chest wall, and were not included in the FOV. All five true-positive subcentimeter lesions were invasive ductal carcinomas and were at least 0.5 cm.

The data for false-negative and false-positive lesions for each imaging modality are provided in Table 2. BSGI with visual analysis alone identified 72 of 118 (61.0%) breast lesions as negative for cancer; interestingly, all 72 showed uptake values of less than 1.5 after semiquantitative analysis. Ten of the 72 (13.9%) breast lesions with negative findings on BSGI with visual analysis alone were false-negatives (mean size ± SD, 1.1 ± 0.5 cm; range, 0.2–2.0 cm). These false-negative lesions were significantly smaller than the true-positive lesions identified by BSGI with visual analysis alone (2.9 ± 1.9 cm; range, 0.5–14.5 cm; p = 0.02). All 33 true-positive lesions identified by BSGI with visual analysis alone had uptake values of 1.5 or greater after semiquantitative analysis. Among the 46 positive breast lesions identified by BSGI with visual analysis alone, eight had uptake values of less than 1.5 and all eight were determined to be benign. No significant difference in tumor grade was found between the false-negative and true-positive lesions (both 2 ± 1).

For the diagnosis of malignant breast lesions, BSGI with visual and semiquantitative analyses reduced the number of false-positive findings compared with BSGI with visual analysis alone; the addition of the semiquantitative analysis significantly improved the specificity of BSGI (p = 0.008). Furthermore, the use of semiquantitative analysis did not affect the sensitivity of BSGI compared with BSGI with visual analysis alone. Representative BSGI examples from patients with a breast lesion are shown in Figure 3.

There were 17 malignant breast lesions that were mammographically negative but sonographically positive (12 invasive ductal carcinomas, four DCIS, and one mucinous carcinoma). The mean size of the 17 lesions was 1.9 ± 1.4 cm (range, 0.2–5.0 cm). Fifteen of the 17 lesions (88.2%) were in patients with heterogeneously or extremely dense breasts. Two breast lesions were identified in nondense

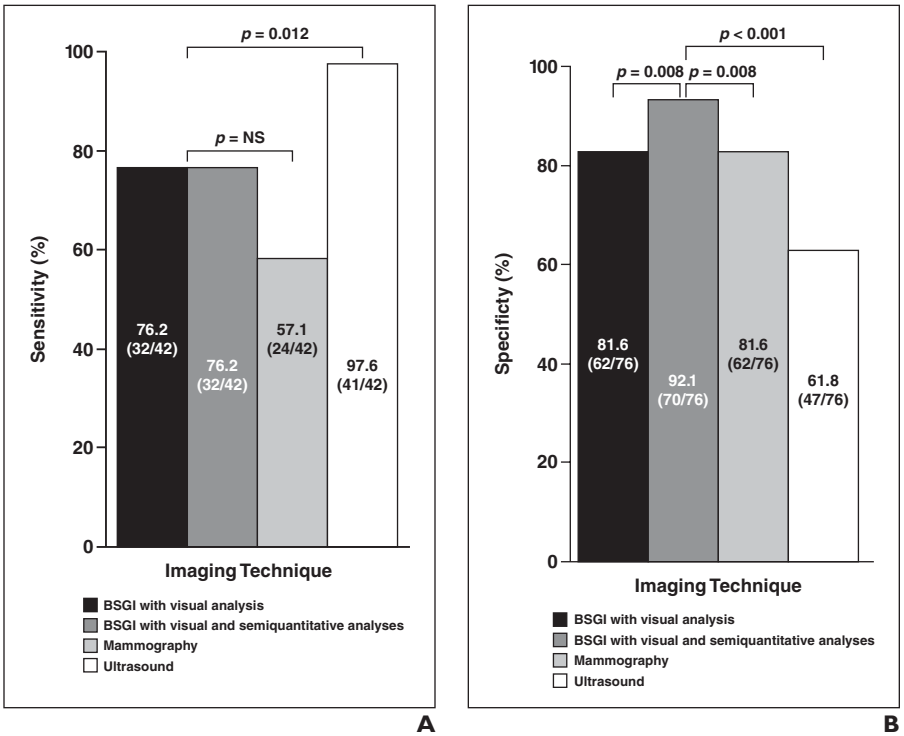

Fig. 2—Overall performance data for diagnosis of malignant breast lesions are shown for breast-specific gamma imaging (BSGI) with visual analysis, BSGI with visual and semiquantitative analyses, mammography, and ultrasound. NS = not significant. **A** and **B,** Bar graphs show sensitivity (**A**) and specificity (**B**) results for each imaging modality.

TABLE 2: False-Negative and False-Positive Imaging Findings for the Diagnosis of Breast Cancer

	False-Negatives				False-Positives								
	Final Pathologic Result				Final Pathologic Result								
Imaging Modality	IDC	DCIS	MC	Total	FD	FA	Intraductal Papilloma	Sclerosing Adenosis	Apocrine Adenosis	Benign Phyllodes Tumor	BL	DC	Total
BSGI with visual analysis alone	6	4	0	10	5	3	1	1	1	1	2	0	14
BSGI with visual and semiquantitative analyses	6	4	0	10	2	1	0	0	1	1	1	0	6
Mammography	13	4	1	18	7	1	1	0	0	1	4	0	14
Ultrasound	1	0	0	1	13	2	4	2	1	1	5	1	29

Note—IDC = invasive ductal carcinoma, DCIS = ductal carcinoma in situ, MC = mucinous carcinoma, FD = fibrocystic disease, FA = fibroadenoma, BL = benign lesion, DC = dermoid cyst, BSGI = breast-specific gamma imaging.

breasts: One was classified as invasive ductal carcinoma measuring 0.2 cm and one as DCIS without microcalcifications measuring 0.8 cm. Seven of the 17 breast lesions (two DCIS and five invasive ductal carcinomas) had microcalcifications identified by mammography but were interpreted as indeterminate or benign (BI-RADS categories 0–3).

Discussion

The performance of breast imaging modalities has improved in the past decades. Although mammography remains the primary imaging modality of choice for the detection of breast cancer, highly sensitive breast imaging modalities, such as ultrasound and MRI, are also widely available. However, highly sensitive findings must be considered carefully because of the risk of false-positive findings [17–19].

BSGI is now used as an adjunct functional imaging modality [20, 21]. The BSGI camera has a compact and portable detector that allows imaging in all mammographic positions and provides additional axillary views. Images from BSGI can be compared directly with the mammographic counterparts and can be obtained of a seated patient; minimal breast compression is needed for BSGI, which is considerably more comfortable for the patient during image acquisition than mammography. BSGI can be also used in patients with dense breast tissue, breast implants, or unexplained architectural distortion [15]. However, despite a consensus among reports regarding the high sensitivity of BSGI, the specificity of BSGI is considered somewhat variable [7–12], probably because of the visual interpretation criteria of BSGI suggested earlier. These criteria are rather subjective, particularly in terms of differentiating the probably benign lesions from the probably abnormal lesions.

Therefore, we investigated whether an additional method would be helpful in interpreting BSGI results in patients with a newly detected breast lesion for the diagnosis of malignancy. By use of an uptake ratio cutoff of 1.5 for semiquantitative analysis, the specificity was significantly better for BSGI with visual and semiquantitative analyses (92.1%) than for BSGI with visual analysis alone (81.6%, $p = 0.008$), mammography (81.6%, $p = 0.008$), and ultrasound (61.8%, $p < 0.001$). Of the 118 breast lesions, the number of false-positive findings was reduced to six when identified by BSGI with visual and semiquantitative analyses compared with 14 by BSGI with visual analysis alone, 14 by mammography, and 29 by ultrasound. To our knowledge, this study is the first to report that BSGI with visual and semiquantitative analyses can play a complementary role by improving the specificity of the diagnosis of malignant breast lesions when compared with BSGI with visual analysis alone, mammography, and ultrasound.

In this study, the sensitivity of BSGI (76.2%) was lower than in previous reports [7–12]. Several determinants may have contributed to the lower sensitivity of BSGI in our study. First, the sensitivity is highly dependent on lesion size. In the current study, false-neg-

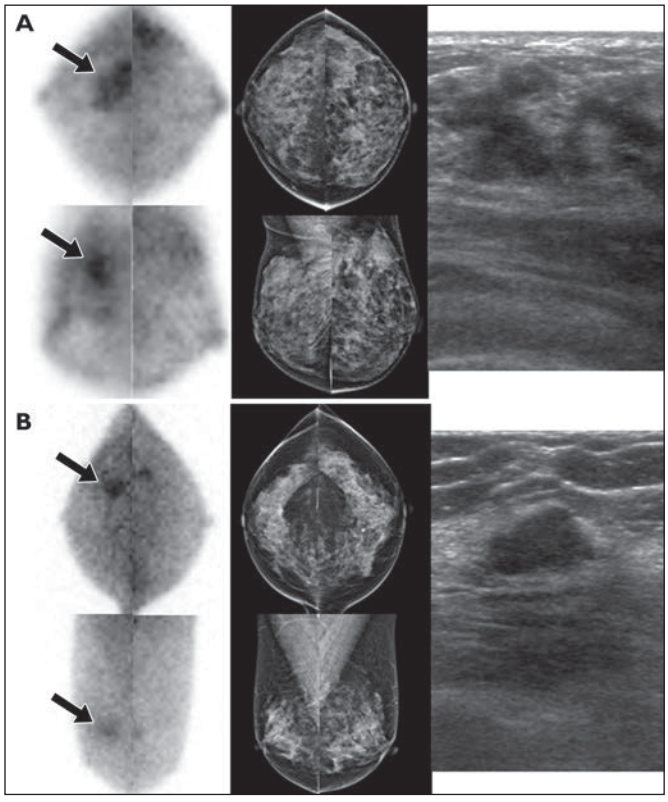

Fig. 3—Breast-specific gamma imaging (BSGI) of two patients.
A, BSGI (*left images*) of 51-year-old woman with right breast nipple discharge shows marked focal uptake (*arrows,* abnormal). Uptake ratio was 4.1 (10,570/2597). Mammograms (*middle images*) and ultrasound image (*right image*) were interpreted as BI-RADS categories 1 and 4, respectively. Pathology result was ductal carcinoma in situ.
B, BSGI (*left images*) of 53-year-old woman with palpable right breast lesion shows mild focal uptake (*arrows,* probably abnormal). Uptake ratio was 1.3 (2908/2286). Mammograms (*middle images*) and ultrasound image (*right image*) were interpreted as BI-RADS categories 1 and 4, respectively. Pathology result was fibroadenoma.

ative lesions were significantly smaller than true-positive lesions (1.1 ± 0.5 vs 2.9 ± 1.9 cm, respectively; $p = 0.02$). Although the tumor grade did not differ significantly between the false-negatives and the true-positives in this study, Tadwalkar et al. [22] reported that the detection rate of BSGI correlated with tumor size and grade. We found that the sensitivity of BSGI was also significantly lower for lesions 1 cm or smaller compared with lesions larger than 1 cm (41.7% and 90.0%, respectively). In the detection of malignant breast lesions 1 cm or smaller, BSGI was less sensitive for DCIS than for invasive ductal carcinoma. Although previous studies reported that BSGI is sensitive in the detection of DCIS [7, 12, 23], we suggest that DCIS is another important factor for determination of the sensitivity of BSGI, especially in small lesions. Breast lesion location also contributes to the sensitivity [24]. Of the 10 false-negative lesions identified by BSGI, two lesions (both 1.0 cm) were located in the far periphery close to the chest wall and, thus, were not included in the FOV. However, both lesions were detected by mammography. Lesion location may be a factor that increases the risk of false-negative BSGI findings, especially in women with small breasts, probably because of unfavorable breast compression.

There are several limitations of the current study. First, patient selection bias may have unduly influenced the determined sensitivities of BSGI, mammography, and ultrasound. Because of insurance coverage in Korea for BSGI, most of the included patients had suspicious or indeterminate mammography or ultrasound findings or an abnormal clinical finding before undergoing BSGI. This bias may have decreased the sensitivity of BSGI and increased the sensitivity of ultrasound. In addition, most patients had dense breast tissues, which may explain the low sensitivity of mammography in our study. Second, histologic confirmation was not acquired in all cases because we had to rely on a limited period of clinical follow-up observations in a proportion of cases. Validation of breast lesions by conventional imaging methods and serial follow-up may cause imprecise identification of malignant breast lesions. However, because all patients were followed for more than 1 year, it is unlikely that the conclusions of the current study would have differed significantly with further follow-up. Third, and most important, the results in this study were obtained by retrospective review and should be considered as preliminary findings. We used an uptake ratio of 1.5 as the threshold to differentiate benign from malignant breast lesions based on an ROC curve analysis of our data. Our camera consists of a sodium iodide activated with a thallium [NaI(Th)] scintillation detector. There is another type of BSGI camera that uses a different detector (solid-state semiconductor, cadmium zinc telluride) [11, 25]. We suggest that an appropriate uptake ratio cutoff should be determined in each center for the specific camera being used. Further multicenter studies are needed to establish the optimum uptake ratio cutoff and the role of BSGI in the assessment of breast lesions. These studies should include evaluations of the extent of known disease, detection of locoregional recurrence, comparison of the diagnostic accuracies, and effects of BSGI and other breast imaging modalities on patient management.

In conclusion, the use of visual and semiquantitative analyses of BSGI significantly improved the diagnosis of malignant breast lesions compared with BSGI with visual analysis alone. Interpretation of BSGI with visual and semiquantitative analyses had better specificity than mammography and ultrasound. It is a simple approach that can be integrated into clinical practice without additional imaging or radiation. Therefore, semiquantitative analysis of BSGI with visual interpretation may be a useful complementary method for the evaluation of malignant breast lesions.

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