Breast-Specific Gamma Imaging: Correlations With Mammographic and Clinicopathologic Characteristics of Breast Cancer

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OBJECTIVE. The purpose of this article is to evaluate the correlations between breast-specific gamma imaging (BSGI) findings and mammographic and clinicopathologic characteristics of breast cancer.

MATERIALS AND METHODS. Our study included 56 breast cancers that had undergone BSGI between August 2010 and December 2012. We reviewed imaging findings (BSGI and mammography) with histopathologic findings, including tumor size, histologic type, nuclear grade, presence of ductal carcinoma in situ (DCIS), and presence of extensive intraductal component (EIC); and immunochemical features, including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (ERBB2, formerly HER2), Ki67, and p53. We classified cancers into positive or negative groups on the basis of BSGI visibility and investigated the statistical differences in mammographic and histopathologic characteristics between the BSGI-positive and -negative groups.

RESULTS. Among 56 malignancies, 48 (85.7%) were shown to be BSGI positive. Patients in the BSGI-positive group were statistically significantly older than those in the BSGI-negative group ($p = 0.027$). BSGI-positive cancers were statistically significantly larger than BSGI-negative cancers ($p = 0.002$). Cancers 1.0 cm or larger, unlike those of subcentimeter size, were statistically significantly more visible on BSGI ($p = 0.004$). The mammographic findings and mammographic densities did not statistically significantly differ between the BSGI-positive and -negative groups. Invasiveness of cancer showed no statistically significant difference on BSGI finding. Cancers with a DCIS component tended to be BSGI positive, but without statistical significance ($p = 0.051$). Visibility on BSGI was not statistically significantly associated with EIC, nuclear grade, ER, PR, ERBB2, Ki67, and p53.

CONCLUSION. The sensitivity of BSGI for breast cancer was 85.7%. Breast cancers in older patients, cancers larger than 1.0 cm, and cancers with the DCIS component tended to be visible on BSGI. BSGI was an equally sensitive tool to detect the breast cancer in women with fatty and dense breast.

Keywords: breast cancer, breast-specific gamma imaging, clinicopathologic characteristics, mammography

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Breast-specific gamma imaging (BSGI), or breast scintigraphy, is a radioisotopic imaging modality that is emerging as a useful complement to mammography for the diagnosis of breast cancer, especially in cases of dense breasts and multifocal or multicentric disease [1, 2]. BSGI is a physiologic, rather than an anatomic, approach to breast cancer diagnosis. BSGI using a high-resolution gamma camera is based on the increased uptake of ^{99m}Tc-sestamibi in cancer cells, compared with that in normal breast tissue, and the difference is thought to be due to the increased vascularity and mitochondrial activity in cancer cells [3–6].

Published studies have found that BSGI is also useful in the detection of ductal carcinoma in situ (DCIS), with a sensitivity of 87.5–93.9% [7–10]. Several studies have reported that BSGI has high sensitivity (88.8–96.4%) for the detection of breast cancer, including invasive cancer and DCIS [11, 12], and Brem et al. [13] showed that BSGI detects invasive lobular carcinoma (ILC) with 93% sensitivity. Furthermore, BSGI has been shown to be reliable regardless of breast density [14].

However, BSGI or breast scintigraphy can have limitations, such as false-positive and -negative findings. Several studies have investigated the correlations between ^{99m}Tc-sestamibi uptake and parameters such

as tumor grade or receptor status in breast cancer [15–17]. A negative correlation between ^{99m}Tc-sestamibi uptake and the presence of progesterone receptor (PR) and a borderline negative correlation between ^{99m}Tc-sestamibi uptake and estrogen receptor (ER) status have been reported [15]. However, Tiling et al. [16] found no statistically significant correlation between ER and PR statuses and scintigraphic tracer uptake. Tadwalkar et al. [17] reported that BSGI detected all invasive breast cancers of high pathologic grade, regardless of size. To our knowledge, no studies have yet correlated both mammographic and clinicopathologic results with BSGI-visible and -invisible breast cancers. Therefore, the purpose of this study was to evaluate the correlations of BSGI with mammographic and clinicopathologic characteristics of breast cancer.

Materials and Methods

Patients

An institutional review board approved our retrospective study. The review of pathologic records and images did not require patient approval or informed consent.

From August 2010 to December 2012, a total of 427 BSGI examinations were performed at our institution. We performed the BSGI on patients with newly diagnosed breast cancer before cancer surgery, patients who were undergoing regular follow-up after breast cancer surgery, patients with suspicious lesions who refused biopsy, and patients with multiple benign lesions. We included only patients with breast cancer newly confirmed by ultrasound-guided core needle biopsy or surgical excision in this study. We excluded cases of postoperative follow-up on patients with previous breast cancer, as well as cases of confirmed benign breast lesion. Our institution had 119 patients with newly diagnosed breast cancer between August 2010 and December 2012. Of these, 49 patients transferred to outside hospital and 16 patients did not undergo BSGI because they refused it. Finally, our study included 54 BSGI of 54 patients with 56 breast cancers.

Imaging Interpretation

Mammography was performed using a Mammomat Inspiration (Siemens Healthcare) in the craniocaudal and mediolateral oblique projections. Breast sonography was performed by one of two available breast radiologists with 5 and 15 years of experience with IU22 (Philips Healthcare) using a linear 7.5- to 12-MHz transducer. Patients were given 25–30 mCi (925–1110 MBq) of ^{99m}Tc-sestamibi (Sestamibi Injection Dong-A, Dong-A Pharma) through the antecubital vein contralateral to the breast lesion; 10 minutes after this radioisotope injection, BSGI was performed. The craniocaudal and mediolateral oblique images of bilateral breasts were obtained, with the patients in a seated position, using a high-resolution breast-specific gamma camera (6800 gamma camera, Dilon Technologies).

The BSGI results were reviewed retrospectively and classified as positive (focal increased radiotracer uptake or irregular radiotracer uptake) or negative (no focal increased uptake). We also reviewed the mammographic findings and mammographic densities. The mammographic findings were classified as mass, asymmetry, and calcifications only. The mammographic density was categorized as fatty or dense breast, according to whether the glandular-tissue component was less than 50% or 50% or greater of the whole breast tissue, respectively. Any discrepancies were resolved by consensus.

Pathologic Diagnosis

Ultrasound-guided core needle biopsy of all lesions that were visible on breast ultrasound was performed using a 14-gauge semiautomated core biopsy needle (Stericut, TSK) by one of two breast dedicated radiologists with 5 and 15 years of experience. At least four or five pieces per lesion were obtained.

Among the 56 cancers, 52 lesions were surgically excised at our institution. Forty-three cancers underwent breast-conserving surgery, and nine cancers underwent mastectomy. We reviewed the histologic type (invasive ductal carcinoma [IDC], DCIS, ILC, and others, including mucinous carcinoma and apocrine carcinoma), the presence of the DCIS component or extensive intraductal component (EIC), nuclear grade, ER status, PR status, human epidermal growth factor receptor 2 (ERBB2, formerly HER2) status, p53 status, Ki-67 index, and tumor size. The presence of the DCIS component was defined as "pathologic confirmed DCIS only" or "DCIS adjacent to main invasive cancer." Tumors of nuclear grade 3 were considered high grade, and those of grades 1 or 2 were considered low grade. The ER and PR statuses were scored according to the proportion (range, 0–5) and intensity (range, 0–3) of immunostained malignant cells. These proportion and intensity scores were then added to obtain a total score (range, 0–8). ER or PR positivity was defined as a total score of more than 2, using an Allred scoring system. The ERBB2 status was initially determined by immunohistochemical staining and was classified as positive for tumors with a score of 3 or more and negative for those with scores of 0 or 1 or higher. Tumors scored as 2 or higher by immunohistochemical staining were further evaluated by fluorescent in situ hybridization. A Ki67-positive tumor nuclei content of 14% or more was defined as Ki67 positive. Tumor size was determined with reference to the largest-diameter surgical specimen.

Statistics

The sensitivity of BSGI and mammography were calculated by comparing the imaging results with the pathologic diagnosis. We compared the differences of age and pathologic tumor size between the BSGI-positive and -negative groups using the Student *t* test. We also compared the differences in mammographic findings, mammographic densities, and histopathologic findings (including histologic type, presence of DCIS component, presence of EIC, nuclear grade, ER status, PR status, ERBB2 status, Ki67 index, and p53 status) between the BSGI-positive and -negative groups, using the chi-square test. A p value of less than 0.05 was considered statistically significant.

Results

Fifty-four patients (median age, 52 years; range, 28–76 years) with 56 breast cancers were included in this study. Two patients had cancer in both breasts. Among the 56 malignancies, 48 (85.7%) were BSGI positive and eight (14.3%) were BSGI negative. Patients in the BSGI-positive group (median age, 55 years; range, 28–76 years) were statistically significantly older than those in the BSGI-negative group (median age, 48 years; range, 41–52 years) ($p = 0.027$) (Table 1).

Breast-Specific Gamma Imaging Pathologic Characteristics

The pathologic characteristics of the breast cancers according to their visibility on BSGI are listed in Table 1. The median size of the 52 cancers measured by surgical specimen was 1.8 cm (range, 0.2–6.3 cm). The BSGI-positive cancers (median size, 2.0 cm; range, 0.4–6.3 cm) were statistically significantly larger than the BSGI-negative malignancies (median size, 0.9 cm; range, 0.2–1.4 cm) ($p = 0.002$). Forty-three cancers were 1.0 cm or larger, and 90.7% of those (39/43) were visible on BSGI; nine were of subcentimeter size, 55.6% (5/9) of which were visible on BSGI. The cancers 1.0 cm or larger were statistically significantly more visible on BSGI than were the cancers of subcentimeter size ($p = 0.004$).

With respect to the histologic subtypes of the 56 cancers, there were 42 (75.0%) IDC, five (8.9%) DCIS, two (3.6%) ILC, two (3.6%) invasive apocrine carcinomas, two

(3.6%) apocrine carcinoma in situ, one (1.8%) mucinous carcinoma, one (1.8%) metaplastic carcinoma, and one (1.8%) neuroendocrine carcinoma. There were 49 (87.5%) invasive cancers and seven (12.5%) noninvasive cancers. Forty-two (85.7%) of the invasive cancers and six (85.7%) of the noninvasive cancers were visible on BSGI. Invasiveness of cancer showed no statistically significant correlation with BSGI visibility ($p = 1.000$).

TABLE 1: Comparison of Clinicopathologic Characteristics Between Visible and Invisible Cancers on Breast-Specific Gamma Imaging (BSGI)

Characteristic	BSGI Positive ($n = 48$)	BSGI Negative ($n = 8$)	p
Patient age (y), median (range)	55 (28–76)	48 (41–52)	0.027
Tumor size (cm), median (range)	2.0 (0.4–6.3)	0.9 (0.2–1.4)	0.002
Invasiveness			1.000
Invasive cancer	42 (87.5)	7 (87.5)	
In situ cancer	6 (12.5)	1 (12.5)	
Combined ductal carcinoma in situ component			0.051
Positive	37 (77.0)	4 (50)	
Negative	7 (14.5)	4 (50)	
NA	4 (8.3)	0	
Extensive intraductal component			0.582
Positive	5 (10.4)	0 (0)	
Negative	39 (81.3)	8 (100)	
NA	4 (8.3)	0	
Nuclear grade			0.176
Low	34 (70.8)	8 (100)	
High	12 (25.0)	0 (0)	
NA	2 (4.2)	0	
Estrogen receptor			0.177
Positive	35 (72.9)	8 (100)	
Negative	13 (27.1)	0 (0)	
Progesterone receptor			1.000
Positive	32 (66.7)	5 (62.5)	
Negative	16 (33.3)	3 (37.5)	
ERBB2 oncogene			0.329
Positive	39 (81.2)	8 (100)	
Negative	9 (18.8)	0 (0)	
Ki67 index			0.712
Low	23 (47.9)	3 (37.5)	
High	25 (52.1)	5 (62.5)	
p53 Tumor-suppressor gene			1.000
Positive	38 (79.2)	5 (62.5)	
Negative	10 (20.8)	2 (25.0)	
NA	0	1 (12.5)	

Note—Except where noted otherwise, data are number (%) of patients. NA = not available, ERBB2 = human epidermal growth factor receptor 2.

Of the 52 cancers surgically excised, 41 (78.8%) had the DCIS component and five (9.6%) had the EIC component. Thirty-seven of 41 (90.2%) cancers with the DCIS component and seven of 11 (63.6%) of cancers without it were BSGI positive. Cancers with the DCIS component tended to show BSGI positivity without statistical significance ($p = 0.051$). The presence of the EIC component did not differ between the BSGI-positive and -negative groups ($p = 0.582$).

Of the 54 cancers with available nuclear-grade data, 42 (77.8%) were of low nuclear grade and 12 (22.2%) of high nuclear grade. Among the low-nuclear-grade cancers, 81% (34/42) were visible on BSGI, whereas 100% (12/12) of the high-nuclear-grade cancers could be detected on BSGI. As for the proportions of the immunochemical features visible on BSGI, the results were as follows: 100% (13/13) of cancers had negative ER, 81.4% (35/43) of cancers had positive ER, 84.2% (16/19) of cancers had negative PR, 86.5% (32/37) of cancers had positive PR, 100% (9/9) of cancers had negative ERBB2, 83.0% (39/47) of cancers had positive ERBB2, 88.5% (23/26) of cancers had negative Ki67, 83.3% (25/30) of cancers had positive Ki67, 83.3% (10/12) of cancers had negative p53, and 88.4% (38/43) of cancers had positive p53. The visibility of cancers on BSGI was not statistically significantly associated with nuclear grade ($p = 0.176$), ER status ($p = 0.177$), PR status ($p = 1.000$), ERBB2 status ($p = 0.329$), Ki67 index ($p = 0.712$), and p53 status ($p = 1.000$).

Breast-Specific Gamma Imaging Mammographic Characteristics

The mammography examinations of 47 cancers in 45 patients were available; the other nine patients did not undergo mammography at our institution. Thirty-nine of 47 (83.0%) cancers (45 patients) were visible on mammography and eight (17.0%) were not. Thirty-five of the 39 (89.7%) cancers visible on mammography also were visible on BSGI. Their mammographic findings were 20 (57.1%) masses, 10 (28.6%) calcifications only, and five (14.3%) asymmetries. Seven of the eight (87.5%) mammographically invisible cancers showed BSGI positivity. Of the 39 mammographically visible cancers, 22 (56.4%) had calcifications and 17 (43.6%) had no calcifications. Among the cancers with calcifications, 95.5% (21/22) were visible on BSGI, as were 82.4% (14/17) of the cancers without calcifications. The mammographic-density results

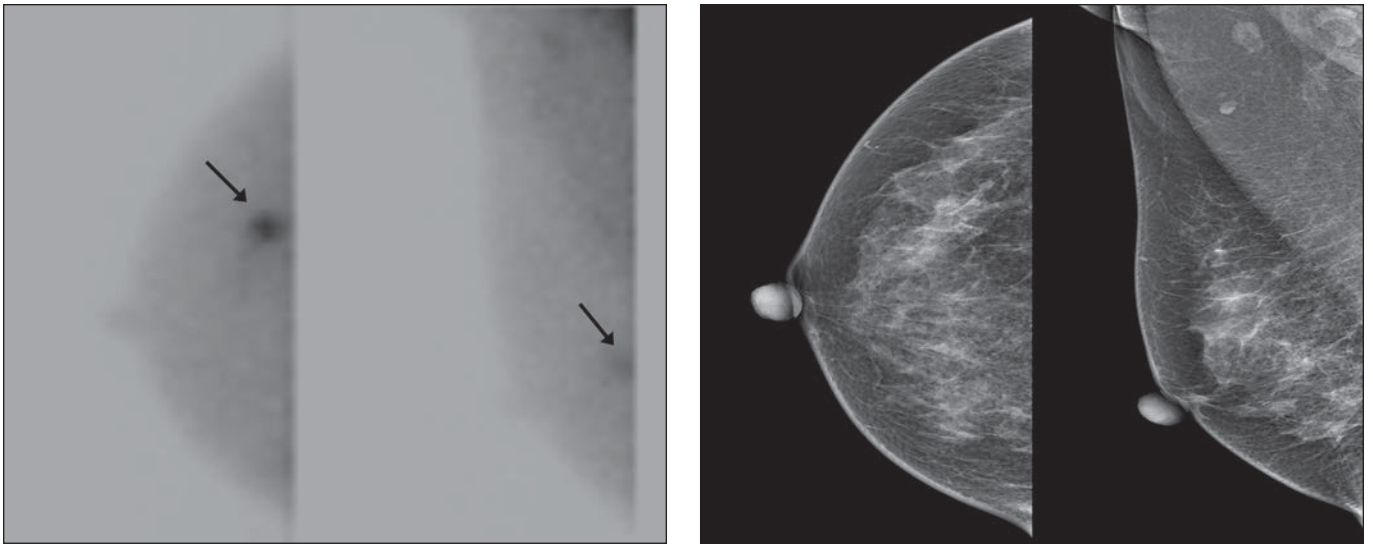

Fig. 1—52-year-old woman with invasive ductal carcinoma (0.4 cm).
A, Breast-specific gamma images show intense focal increased uptake (*arrows*) in right breast.
B, Mammography shows no abnormality in right breast.

included 19 cancers in fatty breast and 28 in dense breast among 47 cancers of 45 patients. On BSGI, all breast cancers in fatty breast were visible, as were 23 (82.1%) of the dense breast cancers. The mammographic findings and densities showed no statistically significant differences between BSGI positivity and negativity ($p = 0.274$ and $p = 0.072$), and neither did the presence of mammographic calcifications ($p = 0.300$) (Table 2).

Seven cases were visible on BSGI but not on mammography (Fig. 1). The mean size of these lesions was 1.4 cm (range, 0.4–3.4 cm), and six of them were dense breast cancers. Five of the seven lesions were invasive cancers, and two were noninvasive.

TABLE 2: Comparison of Mammographic Characteristics Between Visible and Invisible Cancers on Breast-Specific Gamma Imaging (BSGI)

Characteristic	BSGI Positive ($n = 42$)	BSGI Negative ($n = 5$)	p
Mammographic density			0.072
< 50% glandular tissue	19 (45.2)	0 (0)	
≥ 50% glandular tissue	23 (54.8)	5 (100)	
Mammographic visibility			1.000
Positive	35 (83.3)	4 (80)	
Negative	7 (16.7)	1 (20)	
Mammographic findings			0.274
Mass	20 (47.6)	1 (20)	
Focal asymmetry or asymmetry	5 (11.9)	2 (40)	
Calcification only	10 (23.8)	1 (20)	
NA	7 (16.7)	1 (20)	
Calcifications on mammography			0.300
Calcifications	21 (50.0)	1 (20)	
No calcifications	14 (33.3)	3 (60)	
NA	7 (16.7)	1 (20)	

Note—Except where noted otherwise, data are number (%) of patients. NA = not available.

There were eight false-negative BSGI cases, four of which were positive on mammography (Fig. 2). The sizes of these lesions were 0.2, 0.7, 1, and 1.4 cm, respectively. Two lesions were visible as asymmetry, one lesion was visible as a mass, and one was clustered calcifications on mammography. Three were IDCs, and one lesion was DCIS. One of the four false-negative BSGI cases was not visible on mammography, and three cases did not undergo mammography at our institution.

Discussion

BSGI is a useful modality that is complementary to mammography in the diagnosis of breast cancer. It has been proven that this examination is able to overcome mammography's limitations in cases of dense breasts or multifocal or multicentric disease [1, 2].

In this study, BSGI showed a sensitivity of 85.7% for detecting breast cancer, which is similar to the 88.8% and 89% sensitivities previously reported [12, 18] and lower than the sensitivities of 92.2% and 98% reported in other studies of more than 100 cases of breast cancer [17, 19]. The sensitivity of BSGI for cancers 1.0 cm or larger was 90.7%, and the sensitivity for subcentimeter cancers was 55.6%. The sensitivity for subcentimeter cancers was lower than the previously reported 88.9% for invasive cancers and DCIS [11]; the difference may be caused by our small number of cases. However, in our study, the two smallest cancers detected by BSGI were 0.4-cm IDCs, and of these

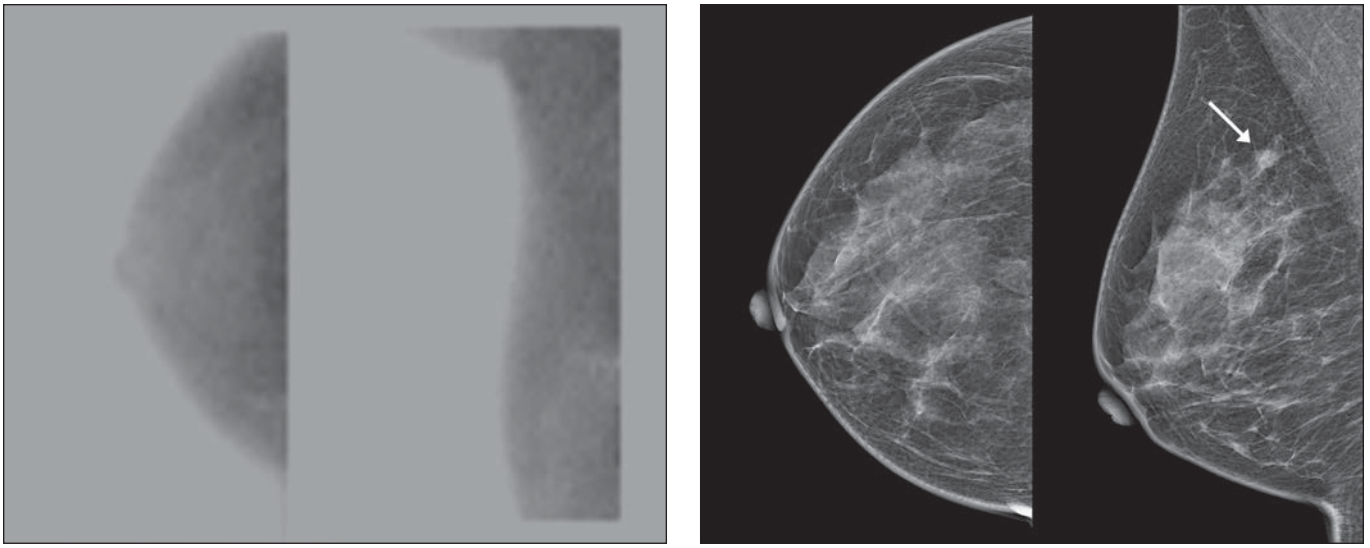

Fig. 2—49-year-old woman with invasive ductal carcinoma (0.7 cm).
A, Breast-specific gamma images show no abnormal uptake.
B, Mammography shows asymmetry (*arrow*) in right breast.

two cancers, a 0.4-cm cancer was detected by BSGI only, not mammography.

We also evaluated the association between pathologic findings and cancer visibility on BSGI, and the detectability was not associated with invasiveness, EIC, nuclear grade, or ER, PR, ERBB2, Ki67, and p53 status. We could not compare pathologic subtypes and visibility on BSGI because our study included only a limited number of them, except IDC. Spanu et al. [10] had reported a higher sensitivity to low-to-intermediate grade DCIS than to intermediate-to-high or high-grade DCIS (100% vs 91.3%), though the difference was not statistically significant. According to our results, 100% (12/12) of high-nuclear-grade cancers and 81% (34/42) of low-nuclear-grade were visible on BSGI, but without statistical significance. Tadwalkar et al. [17] reported that BSGI detected all invasive high-pathologic-grade breast cancers regardless of size (102/102) but detected low-grade cancers with a sensitivity of only 83.3% (15/18), results that are similar to our own. Our present data also corroborate two previous studies that found no correlation between ^{99m}Tc-sestamibi uptake and ER or PR status [15, 20].

Our results are unique, however, in that cancers with an associated DCIS component tended to correlate with BSGI positivity ($p = 0.051$). We can suggest that when even small invasive cancer has the DCIS component, it will tend to be readily visible on BSGI. In fact, our two smallest (0.4 cm) invasive cancers detected by BSGI had the DCIS component. To our knowledge, our study is the first to analyze the relationship between the combined DCIS component and cancer visibility on BSGI. Additional studies including larger numbers of cancers will be necessary to more precisely define the association between pathologic features (including the DCIS component) and BSGI findings.

Among our other results, breast density, mammographic findings, and the presence of calcifications showed no statistically significant differences between the BSGI-positive and -negative groups. On BSGI, all fatty breast cancers were visible, as were 23 (82.1%) dense breast cancers. Our BSGI detected seven cancers that were not visible on mammography, and six were dense breast carcinomas. These results support the previous report that scintimammography has a high breast cancer detection sensitivity, particularly for women with dense breasts [2]. Scopinaro et al. [21] described the mammographic BI-RADS category of breast lesions for which ^{99m}Tc-sestamibi scintimammography was performed, and 31 of 41 patients with BI-RADS category 5 had positive scintimammography. However, no study had yet evaluated the correlation between mammographic findings and visibility on BSGI.

Our data also included eight false-negative BSGI results, of which four were revealed on mammography. Among these four lesions, the sizes of which ranged from 0.2 to 1.4 cm, two were visible as asymmetries, one was seen as a mass, and the other was seen as clustered calcifications. Three of these cancers were invasive, and one was in situ. One of the other four false-negative BSGI cases was not visible on mammography. This patient had a 0.7-cm cancer in the right breast, at first. The preoperative breast MRI found another small suspicious lesion in the left breast. Left breast cancer was confirmed by breast ultrasound and ultrasound-guided biopsy. After surgery, this was found to be a 0.2-cm IDC. Three cancers with false-negative BSGI finding were detected by breast ultrasound at our institution. These cases did not undergo mammography at our institution, and these patients' examinations were not available to review at our PACS. They were a 0.7-cm IDC, a 1.2-cm IDC, and a 1.2-cm ILC. We think that such false-negative findings are mainly due to the small tumor size. The BSGI mechanism depends on tumor neoangiogenesis and abundant cytoplasmic mitochondria within tumor cells [3, 4]. Accordingly, lesions less than 10 mm in diameter can lead to false-negative BSGI findings, and parameters such as low cell count, low vascularity, or the absence of inflammation in carcinomas can produce false-negative malignancy results [16].

Patients in the BSGI-positive group (median age, 55 years) were statistically significantly older than those in the BSGI-negative group (median age, 48 years). Our results were similar to those of Lee et al. [22], who reported that BSGI was more diagnostically effective with patients 50 years and older

than with those younger than 50 years. Certainly, women younger than 50 years have relatively dense breast tissue [23], and in patients with dense breast tissue, ^{99m}Tc-sestamibi can bind with normal breast tissue more intensively than in patients with fatty breast tissue. This factor might play a role in generating false-negative results, and it might also be a factor affecting the lower sensitivity of BSGI with younger women [22]. In fact, our BSGI data included eight patients with false-negative cancers, of which seven patients were younger than 50 years. Further studies will be required for more comprehensive analysis of BSGI results with respect to breast density and the patient's age and menstrual status.

Our study has several limitations. First, it was a retrospective study of a small number of breast cancer samples. Further studies on a larger number of patients are needed to confirm our data. Second, all of our BSGI examinations were performed within 2 weeks after ultrasound-guided core needle biopsy, not before. Our BSGI-positive or -negative findings might have been affected. Third, because BSGI was not performed on all of the patients with breast cancer at our institution, selection bias could have occurred.

In conclusion, the diagnostic sensitivity of BSGI for detecting primary breast cancer was 85.7%. Breast cancers in older women, cancers 1.0 cm or larger, and the DCIS component tended to correlate with BSGI positivity. BSGI was equally sensitive in detecting breast cancer in women with fatty and dense breasts.

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