Diagnostic Performance of Breast-Specific Gamma Imaging (BSGI) for Breast Cancer: Usefulness of Dual-Phase Imaging with ^{99m}Tc -sestamibi

Ji Sun Park · Ah Young Lee · Kyung Pyo Jung ·
Su Jung Choi · Seok Mo Lee · Sang kyun Bae

Received: 23 May 2012 / Revised: 27 August 2012 / Accepted: 18 September 2012 / Published online: 13 October 2012
© Korean Society of Nuclear Medicine 2012

Abstract

Purpose The aim of this study was to investigate the usefulness of breast-specific gamma imaging (BSGI) with dual-phase imaging for increasing diagnostic performance and interpreter confidence.

Methods We studied 76 consecutive patients (mean age: 49.3 years, range: 33–61 years) who received 925 MBq (25 mCi) ^{99m}Tc -sestamibi intravenously. Craniocaudal and mediolateral oblique planar images were acquired for all patients. Delayed images were obtained from all patients 1 h after tracer injection, except for patients with no definite abnormal uptake. All images were classified into four categories: group 1 (definite negative) = no definite abnormal uptake; group 2 (possible negative) = symmetrically diffuse and amorphous uptake; group 3 (possible positive) = asymmetrically mild and nodular uptake; group 4 (definite positive) = asymmetrically intense and nodular uptake. To evaluate diagnostic performance, the BSGI studies were classified as positive (group 3 or 4) or negative (group 1 or 2) for malignancy according to a visual analysis. The final diagnoses were derived from histopathological confirmation and/or imaging follow-up after at least 6 months (range: 6–14 months) by both ultrasonography and mammography.

Results The patients' ages ranged from 33 to 61 years, with an average of 49.3 years. Thirteen patients were diagnosed with malignancy, and 63 patients were diagnosed as negative for malignancy. Using early images, 43 patients were classified as group 1, 12 as group 2, 10 as group 3 and 11 as

group 4. Based on early images, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of BSGI were 77 %, 83 %, 48 %, 95 % and 82 %, respectively. Dual-phase BSGI had a sensitivity, specificity, PPV, NPV and accuracy of 69 %, 95 %, 75 %, 94 % and 91 %, respectively. The BSGI specificity was significantly higher with dual-phase imaging than with single-phase imaging ($p=0.0078$), but the sensitivity did not differ significantly ($p=1.0$). Based on dual-phase imaging, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of BSGI for the evaluation of US BI-RADS 4 lesions were 60 %, 86 %, 67 %, 83 % and 78 %, respectively.

Conclusion Dual-phase imaging in BSGI showed good diagnostic performance and would be useful for increasing interpreter diagnostic confidence, with higher specificity, positive predictive value and accuracy for breast cancer screening as well as the differential diagnosis of breast disease compared with single-phase imaging.

Keywords Breast · Breast cancer · Technetium-99 m-Sestamibi · Dual-phase imaging · Breast-specific gamma imaging

Introduction

Mammography has been shown to be effective in the diagnosis of breast cancer, both as a screening examination and when faced with clinical suspicion of the disease. Although mammography is the most commonly used procedure for breast cancer diagnosis, it is an imperfect examination, with a sensitivity of 70–90 %, which may be reduced in patients with dense breast tissue, implants, severe dysplastic disease or significant architectural distortion following breast surgery or radiation therapy [1–7].

J. S. Park · A. Y. Lee · K. P. Jung · S. J. Choi · S. M. Lee (✉) ·
S. kyun Bae
Department of Nuclear Medicine, Pusan Paik Hospital,
Inje University,
633-165 Gaegum-Dong, Pusanjin-Gu,
Pusan, South Korea
e-mail: narrowroad@inje.ac.kr

Furthermore, mammography is a relatively nonspecific diagnostic technique, which often does not distinguish malignant lesions from benign conditions. It has a high false-positive rate (60–80 %), which leads to an elevated number of biopsies being performed on benign lesions [6, 7]. Therefore, adjunct methods are needed to improve breast cancer detection and the differentiation of benign and malignant lesions.

Breast-specific gamma imaging (BSGI), a molecular breast-imaging technique, is a physiologic approach to breast imaging using a high-resolution gamma camera. BSGI is used as a complementary procedure to help detect breast cancer when more information is needed after questionable radiological examinations [8–10].

Despite improved camera resolution and metabolic imaging using ^{99m}Tc sestamibi, benign lesions taking up sestamibi and physiologic activity mimicking nodules on BSGI are not unusual, and these often result in ambiguous conclusions.

We hypothesized that imaging at two time points would be helpful to differentiate malignant lesions from benign conditions, which can result in false-positive results on BSGI. The aim of this study was to investigate the usefulness of BSGI with dual-phase imaging for increasing diagnostic performance and interpreter confidence.

Materials and Methods

Patients

Seventy-six female patients were enrolled in the study. The patients' ages ranged from 33 to 61 years, with an average of 49.3 years. All of the patients received a conventional imaging examination (ultrasonography and/or mammography and/or MRI) and BSGI. The clinical indications for BSGI included the following: a palpable lesion, a diagnosis of multicentricity and/or multifocality in women with biopsy-proven cancer, screening of women for breast cancer, and determining the appropriate biopsy site in patients with multiple lesions detected by a mammogram and/or ultrasound.

Histopathological confirmation was performed for 35 patients, and imaging follow-up studies were performed for 41 patients prior to the final diagnosis. The biopsy results were classified as malignancy [invasive ductal carcinoma (IDC), ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS)] or benign conditions [fibrocystic change (FCC), fibroadenoma, intraductal papilloma or hamartoma].

Imaging Procedure

BSGI Each patient was given 925 MBq (25 mCi) of ^{99m}Tc -sestamibi intravenously as a single dose in the arm. We used a dedicated high-resolution, small field of view gamma camera optimized to perform BSGI (Dilon 6800 Gamma

Camera, Dilon Technologies, Newport News, VA, USA). A breast-specific gamma camera was used to acquire images while the patient was seated in a position similar to the mammogram position, and the breast was lightly compressed. Craniocaudal and mediolateral oblique planar images were acquired right after injection for all patients. More than 100,000 counts were acquired for craniocaudal imaging and more than 120,000 counts for mediolateral oblique imaging using a low-energy general-purpose collimator. The matrix size was 80×80 , and the energy window was ± 10 % centered on 140 keV for ^{99m}Tc -sestamibi. Delayed images were obtained 1 h after tracer injection, with the same acquisition time as early imaging.

Ultrasonography (US) US was performed using linear high-frequency transducers with 5–12 MHz broadband width (iU22 xMATRIX ultrasound system, Philips Medical Systems, Bothwell, WA, USA). Imaging data were analyzed according to the Breast Imaging Reporting and Data System (BI-RADS) lexicon.

Image Analysis

The uptake pattern of ^{99m}Tc -sestamibi was visually assessed by an experienced nuclear medicine physician according to uptake on the early images and the presence or absence of washout on the delayed images.

All images were classified into four categories by early images: group 1 (definite negative) = no definite abnormal uptake; group 2 (possible negative) = symmetrically diffuse and amorphous uptake; group 3 (possible positive) = asymmetrically mild and nodular uptake; group 4 (definite positive) = asymmetrically intense and nodular uptake (Fig. 1). To assess the diagnostic performance of BSGI using early images, a negative result for malignancy was defined as no definite abnormal uptake or symmetrically diffuse and amorphous uptake (groups 1 and 2), and a positive result for malignancy was defined as asymmetrically mild or intense nodular uptake in breast tissue in at least one view (groups 3 and 4). For the assessment of the diagnostic performance of dual-phase BSGI, patients in groups 3 and 4 with washout on the delayed image were classified as negative, and patients in groups 3 and 4 with persistent tracer uptake on delayed images were classified as positive for malignancy.

Reference Standard

The final diagnoses (nonmalignancy or malignancy) were derived from biopsies (fine-needle aspiration, core needle or excision biopsy), which were performed within 1 month of BSGI, and/or imaging follow-up studies, which were performed after at least 6 months (range: 6–14 months) by both

Fig. 1 Visual grading scale. **a** Group 1 (definite negative) = no definite abnormal uptake. **b** Group 2 (possible negative) = symmetrically diffuse and amorphous uptake. **c** Group 3 (possible positive) =

asymmetrically mild and nodular uptake. **d** Group 4 (definite positive) = asymmetrically intense and nodular uptake

ultrasonography and mammography. Lesions with increased size and showing a distinct malignant pattern on the follow-up images were considered suspicious for malignancy, and a biopsy was performed. In contrast, lesions showing a benign nature and unchanged size over the 6-month follow-up period were regarded as benign.

Data Analysis

Abnormalities on BSGI were correlated with the clinical, pathological and radiological findings. Statistical analyses were performed using Medcalc version 12.0.0 (MedCalc Software, Mariakerke, Belgium). Diagnostic performance was evaluated based on the calculated sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy. The McNemar test was used to compare sensitivity and specificity. A P value less than 0.05 was considered to be statistically significant.

Results

Patient Characteristics

Thirteen patients were diagnosed with a malignancy, and 63 patients were diagnosed as negative for malignancy. There were a total of 16 pathologically confirmed cancers in 13 patients. These 16 malignant lesions included IDC ($n=10$), DCIS ($n=5$) and LCIS ($n=1$). Three patients had two separate cancer foci; one patient had two foci of IDC, and two patients had both DCIS and IDC. The 30 pathologically confirmed benign lesions included fibrocystic changes ($n=19$), fibroadenomas ($n=5$), intraductal papillomas ($n=4$), mastitis ($n=1$), and a hamartoma ($n=1$).

End Results of Each Scintigraphic Pattern

Using early images, 43 patients were classified as group 1, 12 as group 2, 10 as group 3 and 11 as group 4. The

histopathologic diagnoses of the enrolled patient population in relation to the BSGI uptake pattern are shown in Table 1.

One patient showed tracer washout on the delayed image in group 4 (1/11, 9 %), and this patient was identified as having three benign conditions (2 FCCs and 1 intraductal papilloma) following a biopsy (Fig. 2). In this patient, the lesion that showed washout of the tracer on the delayed images was pathologically confirmed as FCC. The other ten patients of group 4 showed persistent tracer uptake (Fig. 3). Nine of these ten patients (9/10, 90 %) were pathologically confirmed as having breast cancer, and the remaining one patient was diagnosed as negative for malignancy by an imaging follow-up (ultrasound and mammogram) examination at approximately 7 months.

Delayed tracer washout was found in nine patients in group 3 (9/10, 90 %) (Fig. 4). Eight of these nine patients were diagnosed as negative for malignancy (8/9, 89 %), and the remaining one patient was pathologically confirmed as having high-grade DCIS. One patient in group 3 had persistent tracer uptake on delayed images and was diagnosed with a hamartoma.

Six patients in group 2 showed tracer washout on delayed images (6/12, 50 %). Of these six patients, five were diagnosed as negative for malignancy (5/6, 83 %), and the remaining patient had two malignant lesions (low-grade IDC and low-grade DCIS).

Group 1 included 43 patients. One DCIS patient and one LCIS patient were included in group 1.

False-Positive and False-Negative Results

The false-positive results of single- and dual-phase BSGI are shown in Table 2. There were 11 false-positive results in single-phase BSGI. Eight of nine patients categorized as BSGI group 3 showed tracer washout on delayed images (8/9, 89 %), and their diagnoses were changed from malignant to benign. Three patients (patients 9, 10 and 11) presented false-positive results on dual-phase BSGI, and they had five benign lesions (1 hamartoma, 3 FCCs and 1 intraductal papilloma).

Table 1 Breast-specific gamma imaging and pathological results

BSGI		No. of patients who underwent biopsy	Histopathology (no. of lesions)
Group (no. of patients)	Delayed washout (no. of patients)		
4 (<i>n</i> =11)	1	10	IDC (9), DCIS (2), FCC (5), fibroadenoma (2), intraductal papilloma (1)
3 (<i>n</i> =10)	9	3	DCIS (1), FCC (1), fibroadenoma (1), hamartoma (1)
2 (<i>n</i> =12)	6	9	IDC (1), DCIS (1), FCC (6), intraductal papilloma (2), fibroadenoma (1), inflammation (1)
1 (<i>n</i> =43)	ND	13	DCIS (1), LCIS (1), FCC (8), fibroadenoma (2), intraductal papilloma (1)

IDC invasive ductal carcinoma;
DCIS ductal carcinoma in situ;
FCC fibrocystic change; *LCIS* lobular carcinoma in situ

ND done

There were three false-negative BSGI results. All three patients underwent an ultrasound-guided core needle

biopsy, and the pathological results included two DCIS foci (0.1 cm and 0.6 cm), one LCIS (1.1 cm) and one low-grade

Fig. 2 A 42-year-old woman with a previous history of excisional biopsy for an intraductal papilloma in the left subareolar area. **a** Breast-specific gamma imaging. The images show intense ^{99m}Tc -sestamibi uptake and delayed washout in the subareolar area (*arrowhead*, known biopsy-proven intraductal papilloma and fibrocystic change) and the left upper-inner quadrant in the left breast (*arrow*). This case was classified as group 4 (definite positive) by early images, but the diagnosis was changed from malignant to benign using dual-phase imaging. **b** Mammography. MLO and CC images show extremely dense breast tissue with architectural distortion in the upper-inner quadrant of the left breast. **c** Ultrasonography. There is an architectural distortion (1.2×0.8 cm) in the left breast at the 11 o'clock position (BI-RADS category 4B). Pathology from a core-needle biopsy showed a fibrocystic change. (*CC* craniocaudal, *MLO* mediolateral)

Fig. 3 A 50-year-old woman with a palpable mass in the right breast. **a** Breast-specific gamma imaging. Early images (MLO and CC view) reveal intense ^{99m}Tc -sestamibi uptake in the lower-outer quadrant of the right breast (*arrow*). This case was classified as group 4 (definite positive). A delayed image (CC view) obtained 1 h after tracer injection shows persistent accumulation of the tracer in the lesion (*arrow*). **b** Mammography. CC and MLO images show heterogeneously dense breast tissue with no discernible abnormality. **c** Ultrasonography. There is an irregularly shaped, hypoechoic lesion (1.6 cm) with an indistinct and microlobulated margin in the right breast at the 8 o'clock position (BI-RADS category 4C). Pathology from a core-needle biopsy showed an invasive ductal carcinoma

IDC (1.1 cm) (one patient had both DCIS and IDC). One patient who had both low-grade DCIS and low-grade IDC was classified as group 2, and tracer washout was shown on the patient's delayed images. Delayed images were not available for the remaining two patients because their early images were classified as group 1 (definite negative).

Diagnostic Performance of Single- and Dual-Phase Imaging

The results and diagnostic performance of single- and dual-phase BSGI for breast cancer detection are shown in Tables 3 and 4 in a patient-based analysis. Using dual-phase imaging, the false-positive rate of BSGI decreased from 18 % (11/63) to 5 % (3/63), and the positive predictive value increased from 48 % to 75 %. The specificity of BSGI was significantly higher with dual-phase imaging than with single-phase imaging ($p=0.0078$), but there was no significant difference in sensitivity.

Scintigraphic Findings of Patients with US BI-RADS 4

Using the US BI-RADS classification system, 1 patient was classified as category 0, 1 was classified as category 1, 18 were classified as category 2 and 22 were classified as category 3. There were 41 category 4 lesions in 32 patients. Three patients had a category 5 lesion, and 1 patient had a category 6 lesion.

All of the 32 patients with BI-RADS category 4 lesions underwent biopsies to confirm the pathological diagnosis. The pathological and dual-phase BSGI results are shown in Table 5. There were five false-negative lesions and five false-positive lesions with dual-phase BSGI (Table 6).

Based on dual-phase imaging, the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of BSGI for the evaluation of US BI-RADS category 4 lesions were 60 %, 86 %, 67 %, 83 % and 78 %, respectively.

Fig. 4 A 52-year-old woman with a previous history of surgical excision for intraductal papillomatosis. **a** Breast-specific gamma imaging. Early images (MLO and CC view) reveal mild and nodular radioactivity (*arrow*) in the right breast (*arrow*). This case was classified as group 3 (possible positive). A delayed image obtained 1 h after tracer injection shows tracer washout in the area. **b** Ultrasonography. The image shows a hypoechoic lesion (0.7 cm) with a partially indistinct margin in the right breast at the 10 o'clock position (BI-RADS category 4A). Pathology from a core-needle biopsy showed a fibroadenoma

Discussion

Scintimammography is the functional imaging study of the breast. Several single-site and multicenter studies have demonstrated that scintimammography has improved specificity compared to mammography. The limitations of scintimammography performed with general-purpose gamma cameras did not allow for the reliable detection of small lesions (< 1 cm) [11–13]. In a meta-analysis by Lieberman, the overall sensitivity and specificity were 85.2 % and 86.6 %, respectively, in a total of 5,340 patients assessed for breast cancer with scintimammography. For patients with a palpable mass,

the sensitivity and specificity were 87.8 % and 87.5 %, respectively. For patients without a palpable mass, the sensitivity was 66.8 %, and the specificity was 86.9 % [13].

To overcome the limitations of a general-purpose gamma camera for the detection of breast cancer, a high-resolution, small field of view breast-specific gamma camera was developed. This technique is referred to as breast-specific gamma imaging (BSGI) [11, 12, 14]. Studies with BSGI have demonstrated the reliable detection of small cancerous lesions, including invasive and ductal carcinoma in situ (DCIS) as small as 1 mm [8, 15–17]. Furthermore, the BSGI camera allows for imaging in positions comparable to

Table 2 Change of interpretation for false-positive results using dual-phase BSGI

Patients	BSGI finding	US BI-RADS category	Diagnosis by single-phase BSGI	Washout	Diagnosis by dual-phase BSGI	Final diagnosis
1	Group 3	1	Malignant	+	Benign	Benign
2	Group 3	2	Malignant	+	Benign	Benign
3	Group 3	3	Malignant	+	Benign	Benign
4	Group 3	3	Malignant	+	Benign	Benign
5	Group 3	3	Malignant	+	Benign	Benign
6	Group 3	3	Malignant	+	Benign	Benign
7	Group 3	2	Malignant	+	Benign	Benign
8	Group 3	4A	Malignant	+	Benign	Fibroadenoma
9	Group 3	4A	Malignant	–	Malignant	Hamartoma
10	Group 4	3	Malignant	–	Malignant	FCC
11	Group 4	4A	Malignant	–	Malignant	FCC
	Group 4	4B	Malignant	+	Benign	FCC
	Group 4	4A	Malignant	–	Malignant	Intraductal papilloma

Table 3 Results of single- and dual-phase BSGI with final diagnosis

	Single-phase imaging		Dual-phase imaging		Total
	(+)	(−)	(+)	(−)	
Malignant	10	3	9	4	13
Nonmalignant	11	52	3	60	63
Total	21	55	12	64	76

mammography, which allows for a more direct correlation of mammographic imaging and BSGI [18].

The use of high-resolution, small field of view breast-specific gamma imaging (BSGI) has been shown to increase the sensitivity of nuclear breast imaging [9, 16, 19]. The sensitivity of BSGI ranges from approximately 78 % to 100 % for detecting breast cancer. The reported specificities of BSGI range from 59 % to 93 % [8–10, 14–18, 20]. In our study, using early images, the sensitivity and specificity were 77 % and 83 %, respectively, which were similar to those identified by previous studies. Brem et al. [8] reported that the PPV and NPV of BSGI were 68.8 % and 94.3 %, respectively, in a setting of 49.7 % disease prevalence. In our study, using early images, the PPV and NPV were 48 % and 95 %, respectively, in a setting of 17.1 % disease prevalence.

Brem et al. [8] evaluated 146 patients and showed a higher overall sensitivity (96.4 %) than previously reported BSGI studies. They suggested that one of the reasons for their high sensitivity was the early onset of imaging because patients in their study were imaged immediately after ^{99m}Tc -sestamibi injection, whereas the patients in the prior BSGI studies were imaged 1–1.5 h after injection. They proposed that delayed imaging (1–1.5 h) might have decreased the sensitivity because of increased ^{99m}Tc -sestamibi washout from the cancer. In our study, using dual-phase imaging, the sensitivity was decreased from 77 % to 69 %, but there was no significant difference between early and dual-phase imaging ($p=1.0$). However, the specificity, PPV and accuracy were increased using dual-phase compared to early imaging, and there was a significant difference in the specificity.

Dual-phase imaging in BSGI is based on the assumption that ^{99m}Tc -sestamibi uptake by cancerous cells might persist on delayed images compared with benign conditions. Dual-phase imaging could help to discriminate between benign and malignant lesions in breast tissue. In their preliminary

study on palpable lesions, Cho et al. [21] suggested that delayed imaging had value in increasing the specificity of BSGI to determine breast lesions. They evaluated 19 breast cancer patients with 23 palpable lesions (18 malignant lesions and 5 benign lesions) using early (10 min) and delayed (30 min) double-phase, dedicated, high-resolution scintimammography using ^{99m}Tc -MIBI. They showed 100 % sensitivity and 60 % specificity for the evaluation of palpable breast lesions based on early images, and using short-interval delayed imaging (30 min) was useful for increasing the specificity from 60 % to 100 %. Two lesions showed increased ^{99m}Tc -sestamibi uptake on early images and a decrease in uptake on delayed images. Both lesions were confirmed as benign using histopathology.

To our knowledge, this is the first study investigating the usefulness of the addition of 1-h delayed imaging in BSGI to detect breast cancer among patients with palpable or nonpalpable breast lesions. Our study demonstrated that the use of dual-phase imaging increased the specificity of BSGI from 83 % to 95 % ($p=0.0078$). Although a statistical analysis was not performed, the results showed that the addition of delayed imaging increased the PPV from 48 % to 75 % and the accuracy from 82 % to 91 %.

Delayed imaging was particularly helpful for patients who had lesions with asymmetrically mild and nodular tracer uptake on early images (group 3 in this study). In these cases, the BSGI diagnoses were changed from malignant to benign for nine patients (9/10, 90 %) using dual-phase imaging. In these nine patients, there was only one false-negative case, and the pathologic result was DCIS. Moreover, the radiological findings of most patients in group 3 were regarded as physiological parenchymal activity. This is important for health screening because it reduces equivocal results.

Dual-phase imaging would be helpful to reduce false-positive BSGI results. Fibroadenomas, fibrocystic disease and inflammatory lesions are well-known causes of false-

Table 4 Comparison of diagnostic performance of single- and dual-phase BSGI for breast cancer detection

	Sensitivity ($p=1.0$)	Specificity ($p=0.0078$)	PPV	NPV	Accuracy
BSGI					
Single-phase imaging	77 %	83 %	48 %	95 %	82 %
Dual-phase imaging	69 %	95 %	75 %	94 %	91 %

PPV positive predictive value;
NPV negative predictive value

Table 5 BSGI findings and pathological results of 41 US BI-RADS 4 lesions

BSGI findings on early images	Pathology	No. of lesions with washout (+)
Group 1 (<i>n</i> =14)	FCC (9)	ND
	Fibroadenoma (2)	
	Intraductal papilloma (1)	
	LCIS (1)	
	DCIS (1)	
Group 2 (<i>n</i> =12)	FCC (6)	2
	Intraductal papilloma (2)	1
	Fibroadenoma (1)	1
	Inflammation (1)	1
	IDC (1)	1
	DCIS (1)	1
Group 3 (<i>n</i> =8)	IDC (3)	0
	Fibroadenoma (2)	2
	FCC (1)	1
	Hamartoma (1)	0
	DCIS (1)	1
Group 4 (<i>n</i> =7)	FCC (2)	1
	IDC (2)	0
	DCIS (1)	0
	Fibroadenoma (1)	0
	Intraductal papilloma (1)	0

Data are the number of lesions

ND not done

positive ^{99m}Tc -sestamibi uptake, and they compromise the specificity of scintimammography [21]. In this study, there were 11 false-positive BSGI results, and they included patients with FCC, fibroadenoma, intraductal papilloma and hamartoma. Of the 11 false positives, nine patients showed tracer washout 1 h after tracer injection (9/11, 82 %).

The identification of breast lesions on BSGI can be limited by the size and aggressiveness of the tumor [12]. In our study, there were three false-negative BSGI results (4 lesions). The pathological results included two DCIS foci (0.1 cm and 0.6 cm), one LCIS (1.1 cm) and one low-grade IDC (1.1 cm). A previous study reported BSGI sensitivities of approximately 92 % for lesions >1 cm and 67 % for lesions <1 cm, and tumors as small as 0.3 mm were detected [9]. Ductal cancers of the highest grade

(grade III) show the highest uptake of ^{99m}Tc -sestamibi, while lobular cancers show the lowest uptake or even no uptake. In this manner, ^{99m}Tc -sestamibi uptake reflects tumor aggressiveness [13, 22].

Ultrasonography has emerged as the most important adjunct to mammography in the diagnosis of breast diseases. BI-RADS category 4 is used to stratify a wide range of lesions recommended for biopsy [23]. In our study, there were 32 patients with 41 US BI-RADS category 4 lesions. In these patients, 4 of the 15 lesions (27 %) in groups 3 and 4 showed washout on dual-phase imaging (Table 5). Based on dual-phase imaging, the specificity, negative predictive value and accuracy were 87 %, 84 % and 78 %, respectively. The SNM Practice Guideline for Breast Scintigraphy with Breast-Specific Gamma Cameras includes interpretation criteria using BI-RADS classification. In the criteria, small focal areas of increased uptake in the breast or axilla (in the absence of radiopharmaceutical infiltration) represent an equivocal result, which is consistent with malignancy, inflammation, atypia or fat necrosis, and are classified as BI-RADS category 4 [24]. According to our results, dual-phase imaging would be helpful to reduce false-positive BSGI results, and the use of delayed washout for breast lesion assessment may help to reduce equivocal diagnoses.

There were limitations to our study. First, this study was retrospective in design. Second, it had a small sample size. Third, pathological confirmation was not performed on all patients with an abnormality identified using BSGI. In this study, patients with lesions with abnormal findings identified using BSGI and definitive benign findings identified using both mammography and ultrasonography did not undergo a biopsy. Instead, careful imaging follow-up studies were performed in these patients after at least 6 months. Fourth, immunohistochemical staining for p-glycoprotein, which is known as a regulator of MIBI accumulation in malignant tumors, was not performed.

In conclusion, dual-phase imaging in BSGI had good diagnostic performance and would be useful for increasing interpreter diagnostic confidence, with higher specificity, positive predictive value and accuracy for breast cancer screening as well as the differential diagnosis of breast disease compared with single-phase imaging. However, it could not replace or reduce biopsies for US BI-RADS category 4 lesions because of false-positive results for small or low-grade malignant lesions.

Table 6 The pathology and diagnosis of dual-phase BSGI in 32 patients with 41 US BI-RADS category 4 lesions

BSGI	Histopathology (no. of lesions)
True positive (<i>n</i> =6)	IDC (5), DCIS (1)
True negative (<i>n</i> =26)	FCC (18), fibroadenoma (4), intraductal papilloma (3), inflammation (1)
False positive (<i>n</i> =4)	FCC (1), fibroadenoma (1), hamartoma (1), intraductal papilloma (1)
False negative (<i>n</i> =5)	DCIS (3), LCIS (1), IDC (1)

Acknowledgments This research was supported by 2011 Collaborative Research Program of Nuclear Medical Sciences through the Dongnam Institute of Radiological & Medical Sciences (DIRAMS) funded by the Ministry of Education, Science and Technology (MEST) and Busan Metropolitan city.

References

- van Dijk JA, Verbeek AL, Hendriks JH, Holland R. The current detectability of breast cancer in a mammographic screening program. A review of the previous mammograms of interval and screen-detected cancers. *Cancer*. 1993;72:1933–8.
- Lehman CD, Blume JD, Weatherall P, Thickman D, Hylton N, Warner E, et al. Screening women at high risk for breast cancer with mammography and magnetic resonance imaging. *Cancer*. 2005;103:1898–905.
- Bird RE, Wallace TW, Yankaskas BC. Analysis of cancers missed at screening mammography. *Radiology*. 1992;184:613–7.
- Ganott MA, Harris KM, Klamann HM, Keeling TL. Analysis of false-negative cancer cases identified with a mammography audit. *Breast J*. 1999;5:166–75.
- Morton MJ, Whaley DH, Brandt KR, Amrami KK. Screening mammograms: interpretation with computer-aided detection—prospective evaluation. *Radiology*. 2006;239:375–83.
- Williams MB, Pisano ED, Schnall MD, Fajardo LL. Future directions in imaging of breast diseases. *Radiology*. 1998;206:297–300.
- Kopans DB. The positive predictive value of mammography. *AJR Am J Roentgenol*. 1992;158:521–6.
- Brem RF, Floerke AC, Rapelyea JA, Teal C, Kelly T, Mathur V. Breast-specific gamma imaging as an adjunct imaging modality for the diagnosis of breast cancer. *Radiology*. 2008;247:651–7.
- Brem RF, Schoonjans JM, Kieper DA, Majewski S, Goodman S, Civelek C. High-resolution scintimammography: a pilot study. *J Nucl Med*. 2002;43:909–15.
- Brem RF, Petrovitch I, Rapelyea JA, Young H, Teal C, Kelly T. Breast-specific gamma imaging with ^{99m}Tc sestamibi and magnetic resonance imaging in the diagnosis of breast cancer—a comparative study. *Breast J*. 2007;13:465–9.
- Tafreshi NK, Kumar V, Morse DL, Gatenby RA. Molecular and functional imaging of breast cancer. *Cancer Control*. 2010;17:143–55.
- Schillaci O, Buscombe JR. Breast scintigraphy today: indications and limitations. *Eur J Nucl Med Mol Imaging*. 2004;31 Suppl 1:35–45.
- Liberman M, Sampalis F, Mulder DS, Sampalis JS. Breast cancer diagnosis by scintimammography: a meta-analysis and review of the literature. *Breast Cancer Res Treat*. 2003;80:115–26.
- Brem RF, Kieper DA, Rapelyea JA, Majewski S. Evaluation of a high-resolution, breast-specific, small-field-of-view gamma camera for the detection of breast cancer. *Nucl Instrum Meth Phys Res A*. 2003;497:39–45.
- Brem RF, Shahan C, Rapleyea JA, Donnelly CA, Rechtman LR, Kidwell AB, et al. Detection of occult foci of breast cancer using breast-specific gamma imaging in women with one mammographic or clinically suspicious breast lesion. *Acad Radiol*. 2010;17:735–43.
- Brem RF, Rapelyea JA, Zisman G, Mohtashemi K, Raub J, Teal CB, et al. Occult breast cancer: Scintimammography with high-resolution breast-specific gamma camera in women at high risk for breast cancer. *Radiology*. 2005;237:274–80.
- Brem RF, Fishman M, Rapelyea JA. Detection of ductal carcinoma in situ with mammography, breast specific gamma imaging, and magnetic resonance imaging: a comparative study. *Acad Radiol*. 2007;14:945–50.
- Brem RF, Michener KH, Zawistowski G. Approaches to improving breast cancer diagnosis using a high resolution, breast specific gamma camera. *Phys Med*. 2006;21 Suppl 1:17–9.
- Scopinaro F, Schillaci O, Scarpini M, Mingazzini PL, Di Macio L, Banci M, et al. ^{99m}Tc sestamibi: an indicator of breast cancer invasiveness. *Eur J Nucl Med*. 1994;21:984–7.
- Sung Mo Hur SHK, Lee SK, Kim WW, Choi JH, Kim S, Lee S-J, et al. The preoperative role of breast-specific gamma imaging for the breast cancer patients: In comparison with conventional imaging modality. *J Breast Cancer*. 2010;13:198–205.
- Arthur Cho HC, Yun M, Park B-W, Kim MJ, Kim E-K, et al. The value of dedicated ^{99m}Tc MIBI scintimammogram in the evaluation of patients with palpable breast lesions in comparison with mammogram: Preliminary result. *Nucl Med Mol Imaging*. 2009;43:48–54.
- Scopinaro F, Schillaci O, Ussof W, Nordling K, Capoferro R, De Vincentis G, et al. A three center study on the diagnostic accuracy of ^{99m}Tc MIBI scintimammography. *Anticancer Res*. 1997;17:1631–4.
- Reporting BI. Data System. Breast Imaging Atlas. 4th ed. Reston: American College of Radiology. 2003
- Goldsmith SJ, Parsons W, Guiberteau MJ, Stern LH, Lanzkowsky L, Weigert J, et al. SNM practice guideline for breast scintigraphy with breast-specific gamma-cameras 1.0. *J Nucl Med Technol*. 2010;38:219–24.