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REVIEW ARTICLE

Clinical usefulness of breast-specific gamma imaging as an adjunct modality to mammography for diagnosis of breast cancer: a systemic review and meta-analysis

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Abstract
Purpose The purpose of this study was to assess the diagnostic performance of breast-specific gamma imaging (BSGI) as an adjunct modality to mammography for detecting breast cancer.
Methods Comprehensive searches of MEDLINE (1984 to August 2012) and EMBASE (1994 to August 2012) were performed. A summary receiver operating characteristic curve (SROC) was constructed to summarize the overall test performance of BSGI. The sensitivities for detecting subcentimetre cancer and ductal carcinoma in situ (DCIS) were pooled. The potential of BSGI to complement mammography was also evaluated by identifying mammography-occult breast cancer.
Results Analysis of the studies revealed that the overall validity estimates of BSGI in detecting breast cancer were as follows: sensitivity 95 % (95 % CI 93–96 %), specificity 80 % (95 % CI 78–82 %), positive likelihood ratio 4.63 (95 % CI 3.13–6.85), negative likelihood ratio 0.08 (95 % CI 0.05–0.14), and diagnostic odds ratio 56.67 (95 % CI 26.68–120.34). The area under the SROC was 0.9552 and the Q* point was 0.8977. The pooled sensitivities for detecting subcentimetre cancer and DCIS were 84 % (95 % CI 80–88 %) and 88 % (95 % CI 81–92 %), respectively. Among patients with normal mammography, 4 % were diagnosed with breast cancer by BSGI, and among those with mammography suggestive of malignancy or new biopsy-proven breast cancer, 6 % were diagnosed with additional cancers in the breast by BSGI.
Conclusion BSGI had a high diagnostic performance as an excellent adjunct modality to mammography for detecting breast cancer. The ability to identify subcentimetre cancer and DCIS was also high.

Keywords Breast neoplasm · Breast-specific gamma imaging · Mammography · Meta-analysis

Introduction

Mammography is used as a standard breast cancer screening method because of its high sensitivity in most cases and because it leads to reduced mortality [1]. However, it has some significant limitations. As breast tissue density increases, the sensitivity of mammography deceases. Rosenberg et al. [2] found that the sensitivity in nondense breasts was 85 %, but was only 68 % in dense breasts. Breast density is strongly associated with the risk of developing breast cancer [3, 4]. Furthermore, patients with dense breasts are often young, and in this patient group breast cancers tend to be aggressive. So it is very important to find an effective modality as an adjunct to mammography.

Breast-specific gamma imaging (BSGI), also called molecular breast imaging, is a nuclear medicine breast imaging technique that uses a high resolution, small field-of-view breast-specific gamma camera. It has been significantly improved within recent years. BSGI is a functional imaging examination rather than an anatomic modality like mammography. It produces imaging based

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on two physiological mechanisms. One is that BSGI uses the radiopharmaceutical ^{99m}Tc sestamibi or ^{99m}Tc tetrofosmin, which specifically binds to mitochondria in cells. The density of mitochondria is a marker of cellular proliferative activity. Therefore, in the cancer cells there is a higher uptake of radiotracer than in the surrounding normal tissue [5]. The other mechanism involves neoangiogenesis in the cancer tissue, which leads to increasing pharmaceutical delivery to the lesions [6]. Therefore, in contrast to mammography, the sensitivity of BSGI is not influenced by the density of the breast tissue, implants, architectural distortion, or scars from prior surgery or radiation. In addition, in comparison to the conventional gamma camera, the dedicated gamma camera has greater intrinsic spatial resolution and accessibility to the posterior and medial areas of the breast, less radiation scatter from nearby organs on imaging, a minimal distance between the breast and the detector, and a lower amount of breast tissue between the lesion and the detector through mild compression and imaging in the positions comparable to mammography [7–9]. As a result, BSGI has better sensitivity than traditional planar scintimammography, especially in detecting subcentimetre or nonpalpable breast cancer.

More and more studies have now investigated the potential of BSGI for detecting breast cancer. Its sensitivity ranges from 85 % to 100 % and its specificity ranges from 60 % to 95 %. To our knowledge, there is no meta-analysis of the performance of BSGI. So we performed this analysis to evaluate the diagnostic performance of BSGI as an adjunct modality to mammography for detecting breast cancer.

Materials and methods

Search strategy

We searched MEDLINE (1984 to August 2012) and EMBASE (1994 to August 2012) with the language restriction of English to identify studies evaluating the diagnostic performance of BSGI in the detection of breast cancer. The search terms used were “breast cancer” OR “breast neoplasm” OR “breast carcinoma” OR “breast tumor”; “molecular breast imaging” OR “MBI” OR “breast-specific gamma imaging” OR “BSGI” OR “scintimammography” OR “high-resolution gamma camera”; “mammography”; and “sensitivity” OR “specificity”. Corresponding medical subject headings were also used. In addition, reference lists from all relevant articles were searched to identify additional studies. At first there were no restrictions as to publication form in order to achieve a highly sensitive search. However, in the end conference abstracts were excluded because of the limited data presented.

Study selection

Eligible studies were required to fulfil the following inclusion criteria.

(a) Patients had to have at least one of the following indications for BSGI: clinical abnormality such as a palpable mass, breast pain or bloody nipple discharge with normal mammography; suspicious mammography findings such as indeterminate asymmetry or calcifications; dense breast tissue, surgical scar or architectural distortion which was difficult to evaluate by mammography; personal history of breast cancer or a high-risk lesion; family history or other high-risk factors for breast cancer; and mammography suggestive of malignancy or new biopsy-proven breast cancer for further examination.
(b) To avoid selection bias, one study had to involve at least ten patients.
(c) If overlapping patient cohorts were presented among multiple studies, only the largest or the latest study was included.
(d) The BSGI camera used just a single detector. Dual-head dedicated breast gamma cameras were excluded.

Reviews and conference abstracts were excluded. For evaluating diagnostic performance, a 2 × 2 table for true-positive, false-negative, false-positive and true-negative values for identifying breast cancer was derived from the data provided, and histopathological assessment and/or clinical and imaging follow-up was used as the reference standard. When evaluating the potential as an adjunct to mammography, the study to be selected had to include data comparing BSGI with mammography.

Two authors (Yu Sun and Wei Wei) independently screened titles and abstracts of the relevant articles based on the inclusion criteria. When an article fulfilled the criteria, the full text was reviewed. Any disagreement was resolved by a third author.

Data extraction and quality assessment

Two authors (Yu Sun and Wei Wei) independently read the eligible papers, and recorded the first author’s name, publication year, original country, number of patients and lesions, patient age, study design and reference standard. The methodological quality of the study was estimated using the quality assessment of diagnostic accuracy studies (QUADAS) tool [10]. For each item there are three grades: “yes”, “unclear” and “no” with scores of 1 for “yes” and 0 for “unclear” or “no”. There are 14 items in the QUADAS. Items 1 (representative spectrum) and 2 (selection criteria) are about the variability of the studies, items 8 (index test execution), 9 (reference standard execution) and 13 (interpretable results reported) are about the

quality of the reporting, and the remaining items are about the bias of the studies. The rate of response "yes" for each question was calculated. If there were different opinions, then the problem was discussed by a third author.

Statistical analysis

A bivariate analysis was used to determine the per-lesion sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and diagnostic odds ratio (DOR) with corresponding 95 % confidence intervals (CIs) [11]. Atypical lesions were grouped with benign lesions. We evaluated only the ability of BSGI to detect breast cancer. Heterogeneity was evaluated by Q and I^2 statistics. If the P value for a Q statistic was less than 0.1 or the I^2 statistic was greater than 50 %, we deemed that there was statistically significant heterogeneity [12]. Then we pooled studies using a random effects model [13], and otherwise used a fixed effect model [14]. Although no absolute cut-off was used, an effective diagnostic test should have a PLR greater than 5.0 and a NLR less than 0.2 [15, 16]. DOR is the ratio of the odds of positivity in patients with disease relative to that in patients without disease. It is a single indicator of test performance [17]. The higher the DOR value, the better the diagnostic performance of the test.

The sensitivity and specificity of each study were used to plot a summary receiver operating characteristic (SROC) curve [18, 19]. Q* indexes (the point on the SROC curve where sensitivity and specificity are equal) were calculated. The higher the Q* value, the better the diagnostic test performance [18]. Deek's test was performed to assess publication bias [20]. A P value less than 0.05 indicates the existence of publication bias. We also pooled the per-lesion sensitivity of BSGI for identifying subcentimetre cancer and ductal carcinoma in situ (DCIS).

Two ratios were defined as follows: the ratio of the number of patients with cancer detected by BSGI only rather than by mammography relative to the total number of patients with normal mammography; and the ratio of the number of patients with multicentric, multifocal or bilateral cancers detected by BSGI only rather than mammography relative to the total number of patients with mammography suggestive of malignancy or new

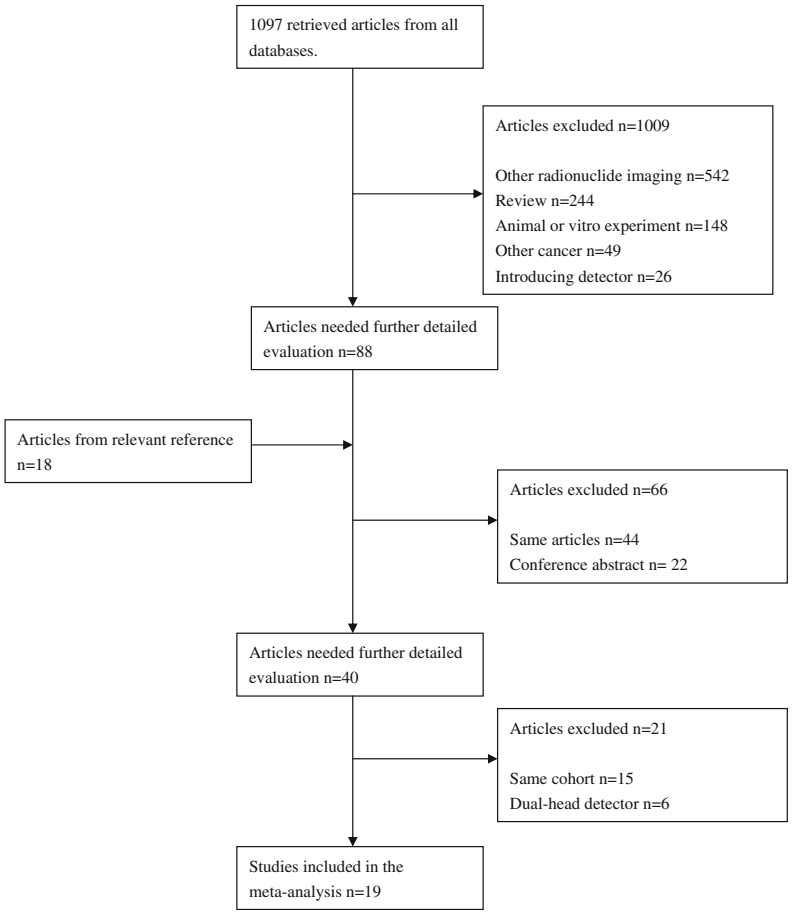

Fig. 1 Flow diagram of the study selection procedure for the meta-analysis

Table 1 Characteristics of the studies

Reference	Year	Country	No. of patients	No. of lesions	Age (years), mean (range)	Design	Reference standard	QUADAS score
[21]	2004	USA	37	37	54 (34–80)	Prospective	Histopathology or mammography	11
[22]	2005	USA	94	94	55 (36–78)	Prospective	Histopathology or imaging and clinical follow-up	12
[23]	2006	Italy	29	29	(27–77)	Prospective	Histopathology or imaging and clinical follow-up	12
[24]	2007	USA	20	22	55 (34–76)	Retrospective	Histopathology	11
[25]	2007	USA	99	114	59 (18–86)	Unclear	Histopathology	13
[26]	2008	USA	146	167	53.1 (32–98)	Retrospective	Histopathology	13
[27]	2008	USA	149	245	Unclear	Unclear	Histopathology or imaging and clinical follow-up	12
[28]	2008	USA	176	182	53 (27–86)	Retrospective	Histopathology or imaging and clinical follow-up	11
[29]	2009	USA	138	163	55 (30–81)	Retrospective	Histopathology	11
[30]	2009	USA	82	100	53 (33–83)	Retrospective	Histopathology	12
[31]	2010	USA	159	213	54 (29–93)	Retrospective	Histopathology or imaging and clinical follow-up	11
[32]	2011	USA	100	100	Unclear	Unclear	Histopathology	11
[33]	2012	USA	416	416	Unclear	Retrospective	Histopathology or imaging and clinical follow-up	12
[34]	2012	USA	329	329	Unclear	Retrospective	Histopathology or imaging and clinical follow-up	12
[35]	2012	USA	18	18	51	Prospective	Histopathology	12
[36]	2012	Italy	467	554	57 (26–81)	Prospective	Histopathology	13
[37]	2012	Italy	33	33	56.8 (41–81)	Retrospective	Histopathology	12
[38]	2012	Korea	471	474	49.63±10.43	Retrospective	Histopathology or imaging and clinical follow-up	12
[39]	2012	Korea	121	228	45±8.1	Retrospective	Histopathology	13

biopsy-proven breast cancer. The values were also recalculated from relevant studies.

All analyses were executed using Meta-DiSc, version 1.4 (XI Cochrane Colloquium, Barcelona, Spain) and Stata, version 12.0 (Stata Corporation, College Station, TX).

Results

Literature search

The retrieval strategy and application of the eligibility criteria detailed above resulted in the selection of 40 articles

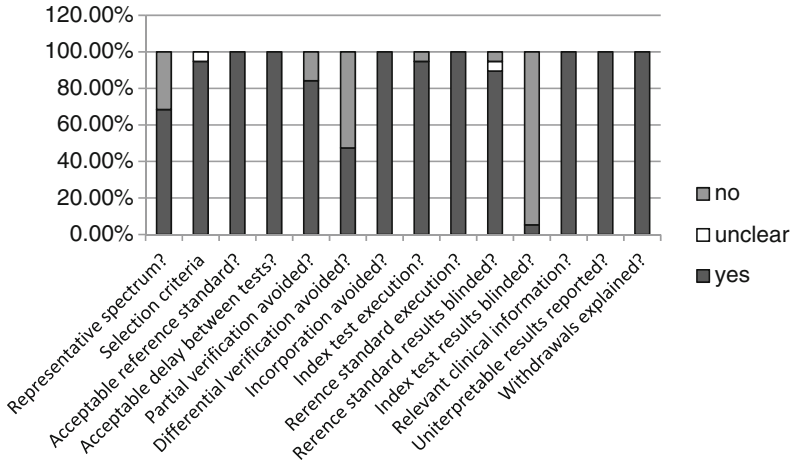

Fig. 2 Study design characteristics based on the QUADAS tool

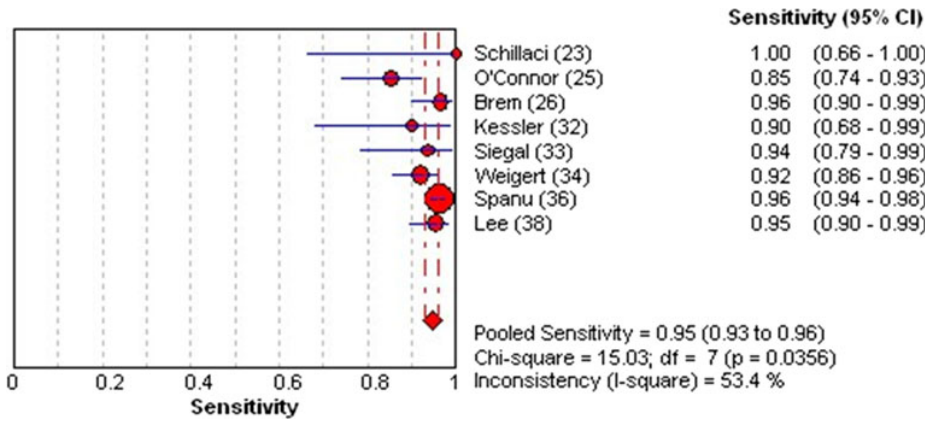

Fig. 3 Forest plot of sensitivity of BSGI for detecting breast cancer

from 11 institutions. Six articles were excluded because a dual-head detector had been used. Another 15 articles were excluded because that they did not have the data needed or they were not the largest or latest studies in their institution on the aspects analysed in this study. Finally 19 studies were eligible for our meta-analysis [21–39](Fig. 1).

Study characteristics and quality assessments

The 19 studies published between 2004 and 2012 shown Table 1 were selected for analysis. Eight studies including 2,183 lesions were evaluated for diagnostic value [23, 25, 26, 32–34, 36, 38]. Five studies including 276 lesions were evaluated for sensitivity in detecting subcentimetre lesions [26, 27, 36, 37, 39]. Six studies including 161 lesions were evaluated for sensitivity in detecting DCIS [24, 29, 33, 35, 37, 39]. In five studies in which 350 patients with normal mammography were also examined by BSGI, 47 patients were proven to have breast cancer [21, 22, 28, 34, 36]. In five studies, 904 patients with mammography suggestive of malignancy or new biopsy-proven breast cancer were also examined by BSGI, and 64 patients were found to have multicentric, multifocal or bilateral breast cancer [25, 29–31, 36]. The studies used ^{99m}Tc sestamibi or ^{99m}Tc tetrofosmin as radiopharmaceutical.

The QUADAS tool was used to assess the quality of studies (Fig. 2). For six studies the response was "yes" to 11 of 14 items [21, 24, 28, 29, 31, 32]. For nine studies the response was "yes" to 12 of 14 items [22, 23, 27, 30, 33–35, 37, 38]. For four studies the response was "yes" to 13 of 14 items [25, 26, 36, 39]. For Items 1 and 2, 68 % and 95 % of the responses were "yes". For items 8, 9 and 13, 95 %, 100 % and 100 % of the responses, respectively, were "yes". For the remaining items which assessed bias, the rates for the response "yes" were relatively high, except for item 11 (index test results blinded). In 18 studies, the results of reference standard were interpreted with knowledge of the index test results, and for 95 % of the studies the response to question 11 was "no".

Data synthesis

In eight studies the diagnostic performance of BSGI was evaluated [23, 25, 26, 32–34, 36, 38]. All the patients in these eight studies had histopathology or imaging and clinical follow-up, and all these studies provided true-positive, false-

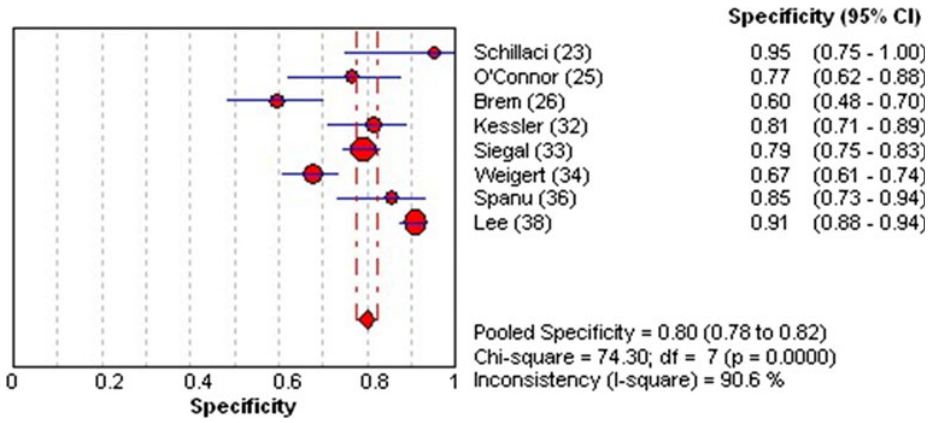

Fig. 4 Forest plot of specificity of BSGI for detecting breast cancer

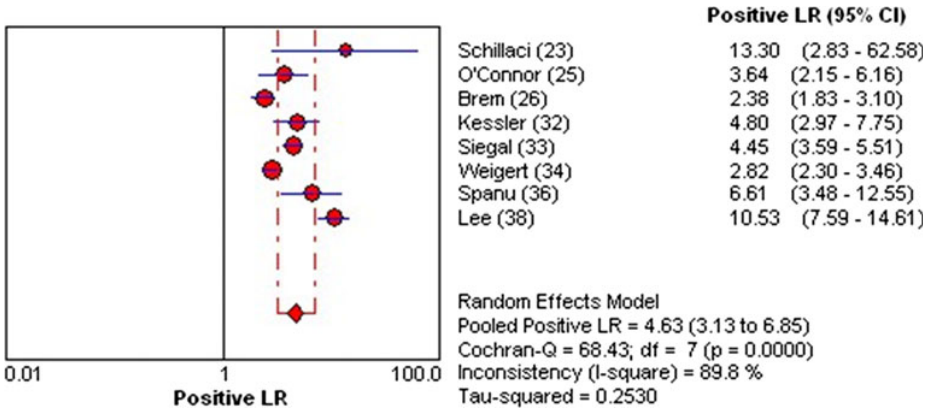

Fig. 5 Forest plot of PLR of BSGI for detecting breast cancer

negative, false-positive and true-negative values for BSGI. Because the heterogeneity was significant, a random effects model was used. The result showed a pooled sensitivity and specificity of BSGI of 95 % (95 % CI 93–96 %) and 80 % (95 % CI 78–82 %), respectively (Figs. 3 and 4). The pooled PLR was 4.63 (95 % CI 3.13–6.85), and the NLR was 0.08 (95 % CI 0.05–0.14; Figs. 5 and 6). The pooled DOR was 56.67 (95 % CI 26.68–120.34; Fig. 7). The area under the SROC curve was 0.9552, and the summary point Q* was 0.8977 (Fig. 8). Publication bias in the literature was evaluated using Deek's test. The result was $T=-0.3$, $P=0.775$, indicating that there was no publication bias (Fig. 9).

In five studies the sensitivity of BSGI for detecting subcentimetre breast cancer was evaluated [26, 27, 36, 37, 39]. Because the heterogeneity was significant ($Q=19.39$, $P=0.0007$, $I^2=79.4$ %), a random effects model was used. The pooled sensitivity was 84 % (95 % CI 80–88 %; Fig. 10).

In six studies the sensitivity of BSGI for detecting DCIS was evaluated [24, 29, 33, 35, 37, 39]. Because there was no heterogeneity ($Q=8.86$, $P=0.1146$, $I^2=43.6$ %), a fixed effects model was used. The pooled sensitivity was 88 % (95 % CI 81–92 %) (Fig. 11).

In five studies patients with normal mammography were also examined by BSGI [21, 22, 28, 34, 36]. The rates of newly diagnosed breast cancer were recorded. Because the heterogeneity was significant ($Q=123.74$, $P=0.000$, $I^2=96.8$ %), a random effects model was used. The pooled rate was 18 % (95 % CI 6–30 %) (Fig. 12). The rate of newly diagnosed breast cancer found in the study by Spanu et al. [36] was much higher than in the other studies. If this study by Spanu et al. was omitted, the heterogeneity decreased ($Q=8.36$, $P=0.039$, $I^2=64.1$ %) the pooled rate was 4 % (95 % CI 1–8 %; Fig. 13).

In five studies patients with mammography suggestive of malignancy or new biopsy-proven breast cancer were also examined by BSGI [25, 29–31, 36]. The rates of multicentric, multifocal, and bilateral cancer were recorded. Because there was no heterogeneity ($Q=6.61$, $P=0.158$, $I^2=39.5$ %), a fixed effects model was used. The pooled rate was 6 % (95 % CI 5–8 %; Fig. 14).

Discussion

The results of this meta-analysis indicated that BSGI has an excellent diagnostic performance as an adjunct modality to mammography for identifying breast cancer with high sensitivity and moderate specificity. The overall PLR was 4.63

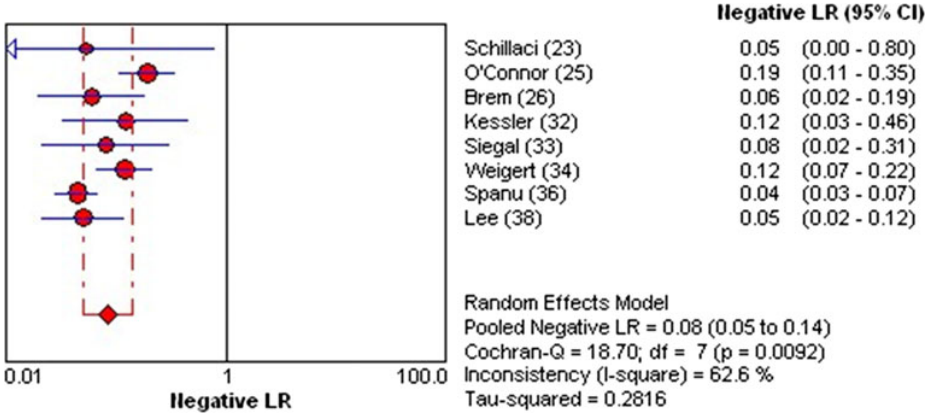

Fig. 6 Forest plot of NLR of BSGI for detecting breast cancer

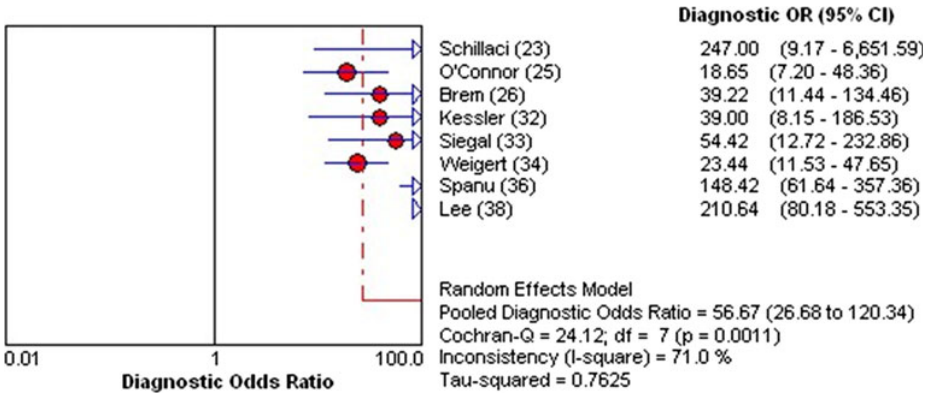

Fig. 7 Forest plot of DOR of BSGI for detecting breast cancer

and the NLR was 0.08. This means that the likelihood of a positive BSGI result in patients with breast cancer is 4.63 times higher than in patients without the disease, and if BSGI is negative, the probability that the patient has breast cancer is 8 %. The overall DOR was 56.67. This means that the odds ratio of BSGI positivity in a patient with breast cancer relative to the odds of positivity without the disease is 56.67. The area under the curve of the SROC was 0.9552 and point Q* was 0.8977. This reveals the discriminatory power of BSGI for detecting breast lesions.

Fibrocystic changes, fibroadenoma and benign breast tissue were the most common false-positive lesions detected by BSGI [23, 25, 26, 32, 33, 36, 38, 39]. Most of the false-negative lesions were subcentimetre invasive ductal carcinoma and DCIS [26, 33, 36–39]. Just a few studies reported the poison of the false-negative lesions [25, 26, 33, 36]. Lesions located deep in the breast close to the chest wall were not readily shown by BSGI. Improving detector and breast positioning techniques may reduce the false-negative rate.

Tumor diameter is an independent prognostic indicator. With increasing diameter of the breast cancer from less than 20 mm to more than 50 mm, the 5-year survival rate decreased from 96.3 % to 82.2 % in patients with node-negative disease [40]. So it is important to find an effective examination technique for detecting small cancer to achieve early detection and early treatment. In our analysis, BSGI showed a sensitivity for detecting subcentimetre breast cancer of 84 %, and the smallest carcinoma identified by BSGI was 1 mm [26, 33]. Mammography is the standard screening

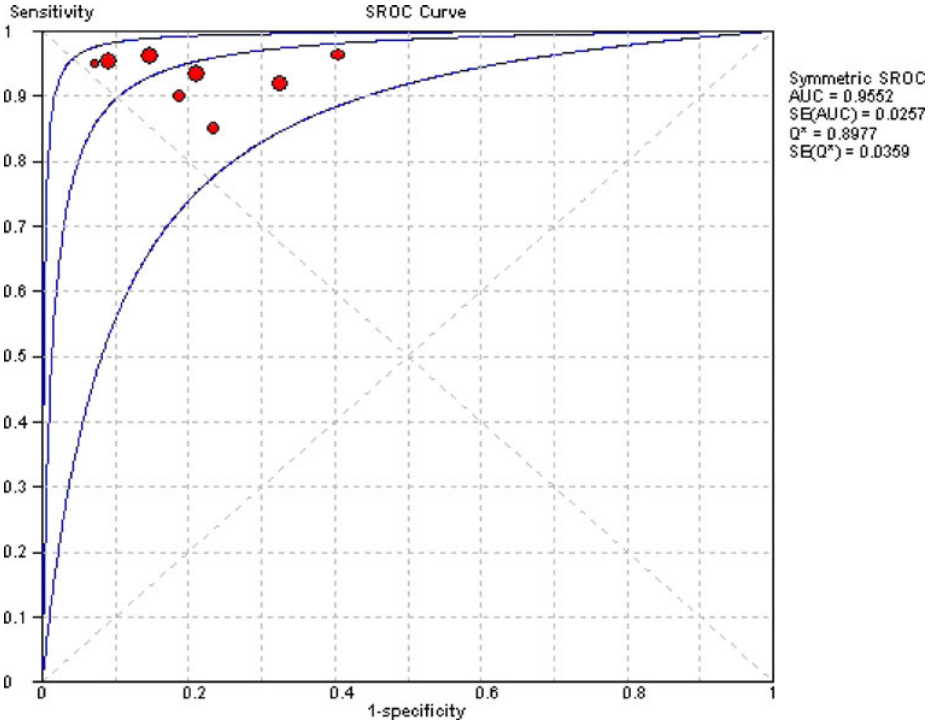

Fig. 8 SROC and Q* index of BSGI for detecting breast cancer

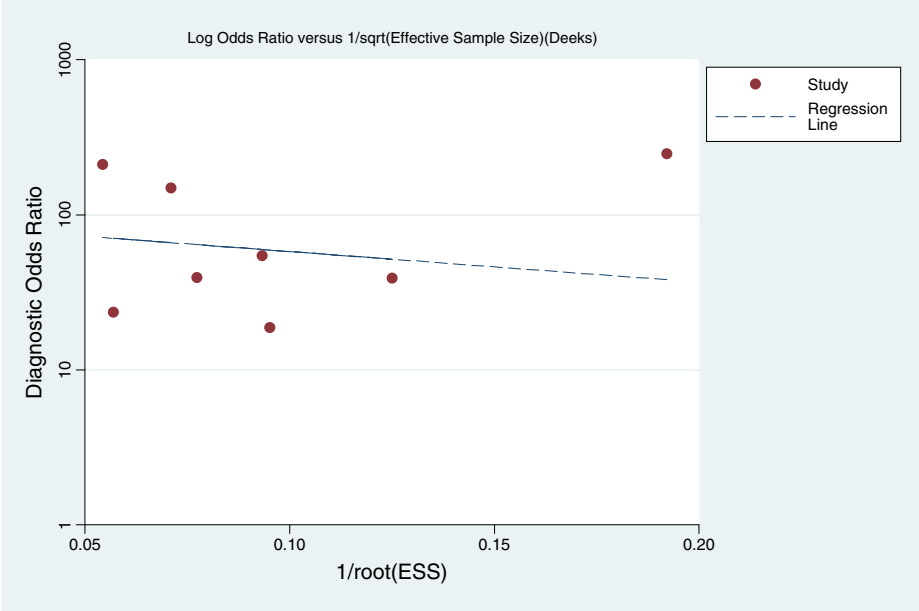

Fig. 9 Deek's test plot of the studies evaluating the diagnostic performance of BSGI

tool for the diagnosis of DCIS [41, 42]. Most of these lesions show microcalcification [43, 44], but not all DCIS show microcalcification. The sensitivity of mammography in detecting DCIS ranges from 27 % to 82 % [24, 45, 46]. Based on our analysis, the pooled sensitivity of BSGI for detecting DCIS was higher than that of mammography at 88 %.

BSGI has also shown other particular advantages in the detection of breast cancer. Invasive lobular carcinoma (ILC) spreads through diffuse infiltration of single rows of malignant cells. It does not readily form a discrete mass because of its incohesive histological growth pattern [47]. The low rates of suspicious calcification and opacity on mammography lead to difficulties in detecting ILC [48]. The sensitivity of mammography for identifying ILC ranges from 34 % to 81 % [46, 48–50]. Brem et al. [50] found that the sensitivity of BSGI in detecting ILC was 93 %, which is higher than that of mammography. Women with atypical lesions, such as atypical ductal hyperplasia and lobular neoplasia, are at high risk of breast cancer. Ling et al. [51] reviewed 15 patients in whom the most aggressive pathology on surgical excision was atypical ductal hyperplasia or lobular neoplasia. The sensitivity of BSGI for the detection of atypical breast lesions was 100 %. BSGI was also used to evaluate the response to neoadjuvant chemotherapy or hormone therapy. Spanu et al. [52] assessed 15 patients with locally advanced breast cancer treated by neoadjuvant chemotherapy or hormone therapy. BSGI correctly classified all patients. Two patients had minimal residual disease after treatment, which was not accurately evaluated by clinical examination and other imaging modalities. However, BSGI was able to accurately monitor tumour response. Therefore BSGI could help in the planning of appropriate surgical treatment. The number of patients examined using BSGI is limited. Further studies with a large number of patients are needed to assess the use of BSGI for evaluation of breast cancer.

The results of our analysis revealed that BSGI showed breast cancer in 4 % of patients with normal mammography (BI-RADS categories 1–3), and BSGI showed multicentric, multifocal and bilateral cancers in 6 % of patients with

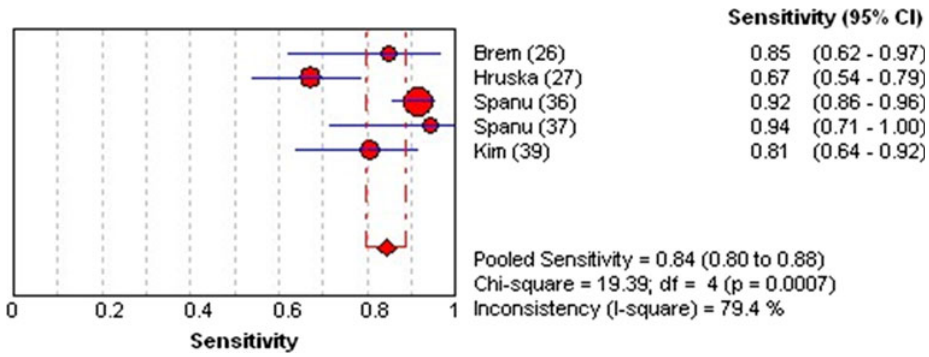

Fig. 10 Forest plot of sensitivity of BSGI for detecting subcentimetre breast cancer

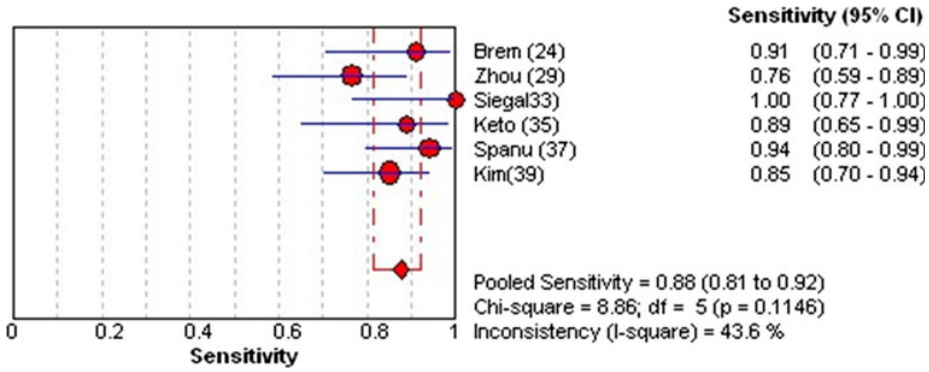

Fig. 11 Forest plot of sensitivity of BSGI for detecting DCIS

mammography suggestive of malignancy (BI-RADS categories 4 or 5) or new biopsy-proven breast cancer. These new findings could greatly help are vital for both in planning the surgical strategy and in prognosis. The need for a second surgical procedure or a high risk of local recurrence may occur with preoperatively undetectable additional cancers.

The use of BSGI can also reduce the rate of unnecessary biopsies. In the study by Kessler et al. [32], there were 93 mammographies in patients with BI-RADS category 4, and the positive biopsy rate was 14 %. Before the biopsy they all had BSGI and the results showed 67 lesions were negative. If they carried out biopsy according to the BSGI, 65 lesions would avoid unnecessary biopsies and only 2 lesions with cancer were not biopsied. So if BI-RADS category 4 lesions negative on BSGI were excluded from biopsy, the positive biopsy rate would have been 42.3 %. The American College of Radiology suggest that the positive biopsy rate should be 25–40 % [32]. In patients with undetermined mammography (BI-RADS category 0), BSGI can correctly categorize

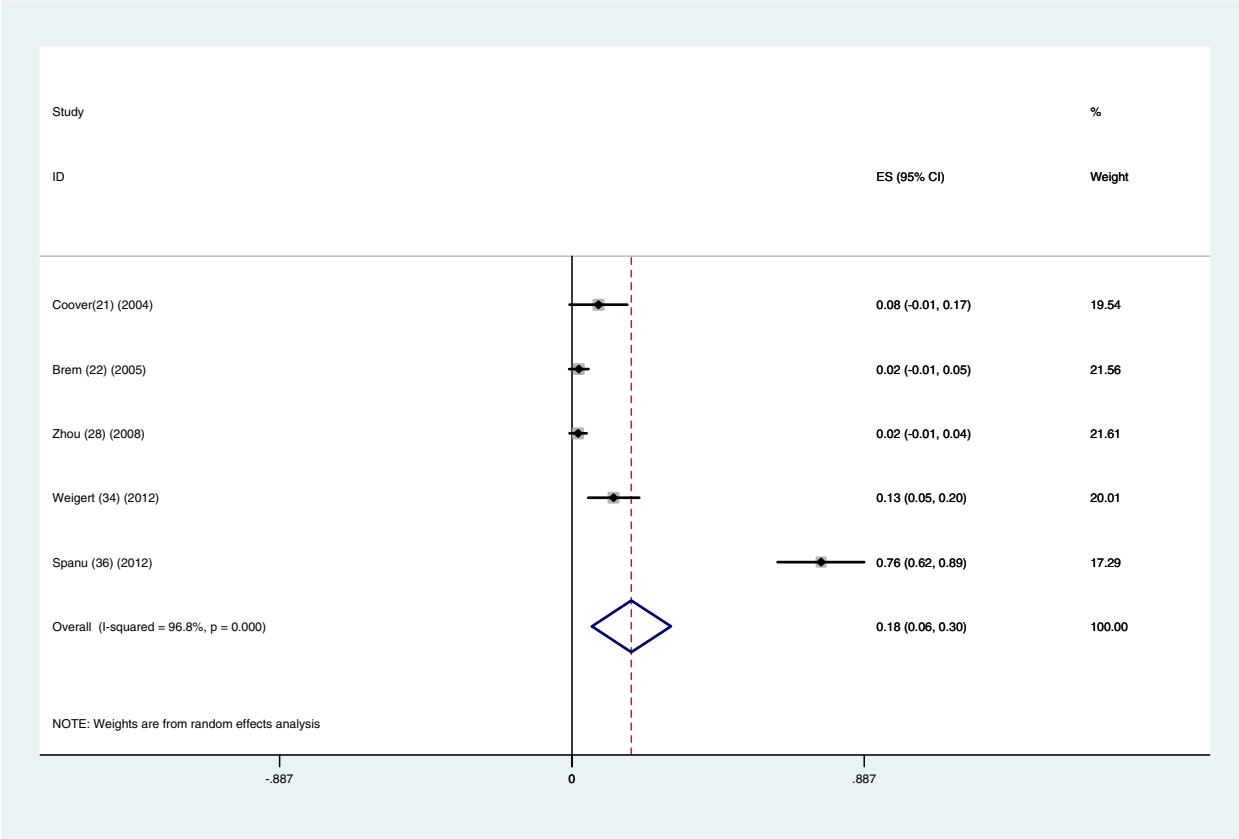

Fig. 12 Pooled proportion of patients with normal mammography in whom breast cancer was detected by BSGI

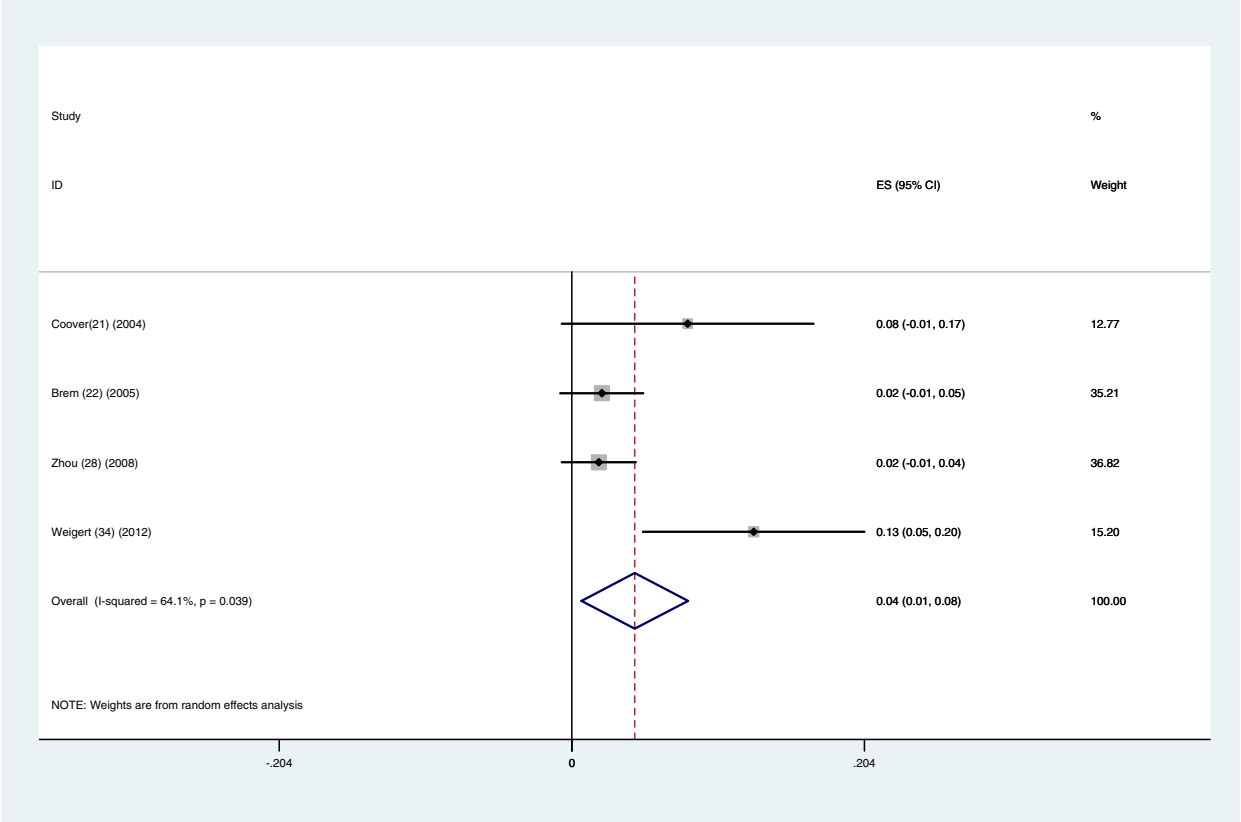

Fig. 13 Pooled proportion of patients with normal mammography in whom breast cancer was detected by BSGI after omitting the study by Spanu et al. [36]

the lesions. In the study by Weigert et al. [32], 119 patients were BI-RADS category 0 on mammography. However, 90 patients were correctly categorized by BSGI, in 15 of whom the lesion was malignant and in 75 benign.

Our analysis showed BSGI to have a high diagnostic performance. However, BSGI is considered just as an adjunct rather than as an alternative to mammography. First, mammography screening has been proved to reduce mortality in breast cancer [1], but there is no such study concerning the use of BSGI. Second, the radiation exposure from BSGI is higher than that from mammography, which suggests that BSGI is not suitable for screening breast cancer [53]. So it is better to use BSGI as a complement to mammography.

In order to reduce breast thickness and limit movement artefacts, BSGI uses light pain-free compression forces of 15 lb in contrast to 35–45 lb in standard mammography [54]. O'Connor et al. [25] evaluated the tolerability of patients using a pain score (on a scale of 0 to 10, with 0 indicating no pain). The average pain score for BSGI was 0.8±1.5, and that for mammography was in the range 3.8–4.7 [55]. So BSGI is more comfortable than mammography.

MRI is an established adjunct physiological breast imaging modality. Two studies [24, 56] comparing BSGI with MRI indicated comparable sensitivity and improved specificity of breast cancer diagnosis by BSGI over MRI. In addition, BSGI is performed in a sitting position as against a prone position inside a small chamber in MRI, which makes patients uncomfortable especially those with claustrophobia or an endomorphic body habitus. In MRI the administration of gadolinium causes renal complications which is not an issue with BSGI. Patients with other MRI contraindications such as ferromagnetic implanted devices can also undergo BSGI. Furthermore, the cost of BSGI is lower than that of MRI. Zhou et al. [28] reported the total costs of BSGI, MRI and mammography in their institution were $1,259, $3,400 and $340, respectively. Compared with the four to ten images obtained with BSGI, hundreds images can be obtained with MRI. So the interpretation time for BSGI is shorter. Another advantage of BSGI is the use of the same position as used in mammography, leading to the possibility to compare directly corresponding images from the two modalities.

BSGI is being developed into a standardized diagnostic modality. Clinical and research indications of BSGI have been listed by the Society of Nuclear Medicine [57], and include evaluation of patients with recently detected breast

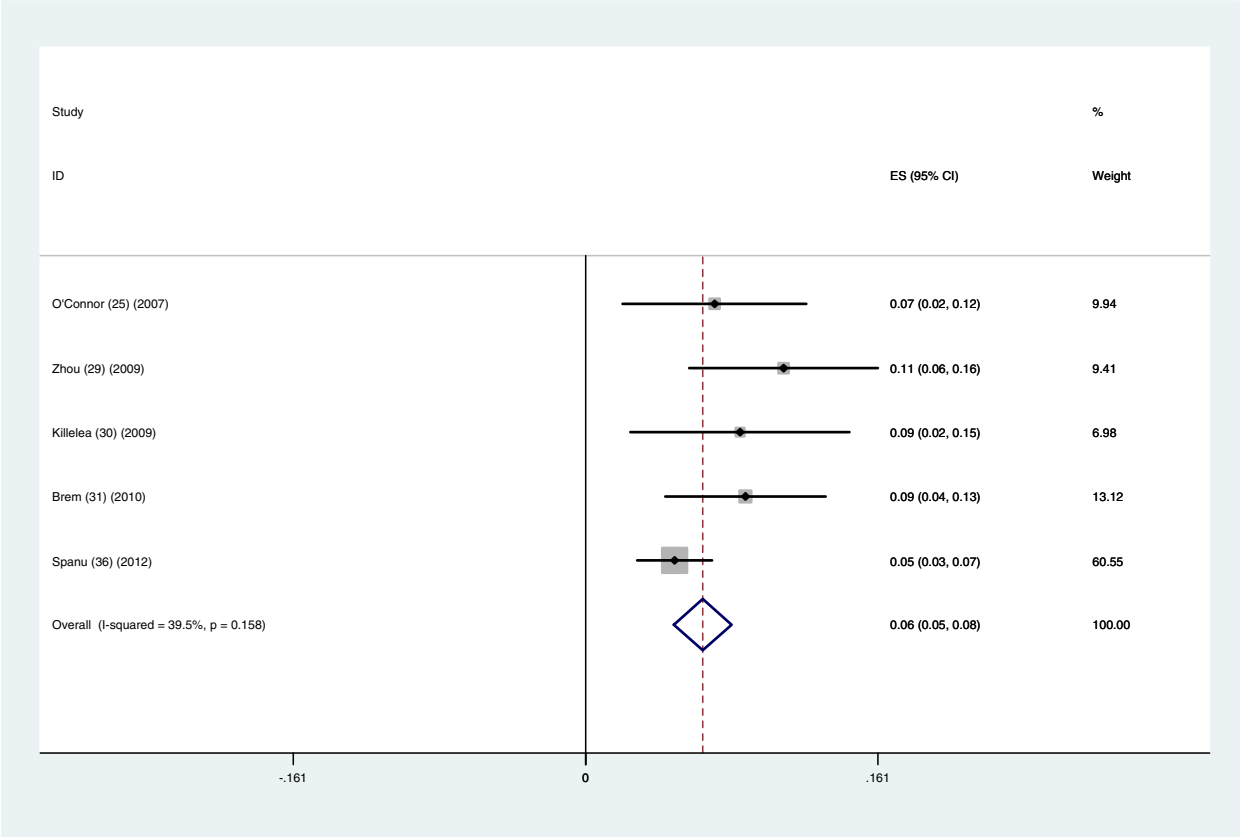

Fig. 14 Pooled proportion of patients with mammography highly suggestive of malignancy or new biopsy-proven breast cancer in whom additional cancers were detected by BSGI

malignancy, patients at high risk of breast malignancy, patients with indeterminate breast abnormalities and remaining diagnostic concerns, patients with technically difficult breast imaging, patients with MRI contraindications and patients who require monitoring of neoadjuvant tumour response. Conners et al. [58] have provided a detailed lexicon for BSGI. The lexicon can been used to regularize BSGI reports. The study [58] also showed that for newly trained radiologists with experience in breast imaging, BSGI studies can be quickly interpreted and the interobserver agreement is high.

In spite of the advantages of BSGI described above, it also has weaknesses, such as its limited ability to detect axillary lymph nodes and to guide biopsy, and relatively high dose of radionuclide. However, researchers from various institutions are developing this technique to overcome these limitations. Concerning the limitation of BSGI in detecting axillary lymph node metastasis of breast cancer, Spanu et al. [59] found that the sensitivity of BSGI in the detection of axillary lymph node metastasis in 76 breast cancer patients was just 25 %. Fewer than three nonpalpable or metastatic nodes could not be detected by BSGI. Jones et al. [60] developed a new method to detect nodes by BSGI. They suggested that the axilla of the patient should be positioned as close as possible to the camera face and the arm hung over the camera at an angle of 90°. A lead apron should be placed across the shoulder and upper arm of the axilla to avoid artefacts from the nearby organs. They have applied this method in the clinic and found it to be a good approach, but there are as yet no detailed data on sensitivity and specificity. Further studies are needed to evaluate this technique.

Some new BSGI-guided biopsy procedures have been suggested. Coover et al. [21] described a detailed method to localize the lesion using an open biopsy paddle with a dedicated breast camera. Welch et al. [61] developed a small dedicated gamma camera-guided stereotactic breast biopsy system. These methods are very useful when the lesion is not detected by palpation or mammography and is shown only by BSGI.

The most important disadvantage is the radiation dose from ^{99m}Tc sestamibi and ^{99m}Tc tetrofosmin. According to the US Food and Drug Administration drug safety sheet and all the studies to date, 740–1,110 MBq (20–30 mCi) of ^{99m}Tc is recommended for breast imaging, which is equivalent to 6.29–9.44 mSv [56]. However, the radiation dose to the breast from a screening mammogram is 0.7–1.0 mSv

[62]. Many institutions are engaged in decreasing breast uptake of tracer. Hruska et al. of the Mayo Clinic [63, 64] have put forward two dose-reduction methods: optimized collimation, widened energy window. They used a dual-head camera with low-dose BSGI performed with 148 MBq ^{99m}Tc sestamibi and obtained images with quality matching that of standard BSGI performed with 740 MBq dose in phantoms [63]. They also found that an administered dose from BSGI using the above methods of 296 MBq ^{99m}Tc sestamibi was possible in patients [64]. The approaches to solve the disadvantages of BSGI are still new. More studies are required to confirm the clinical usefulness of these methods.

Our meta-analysis had several limitations. BSGI is a new technique for identifying breast cancer. The details of the BSGI protocols, such as the camera, the dose of radionuclide and breast position, and the ability of radiologists, are different between institutions. These could all have affected the estimates of diagnostic accuracy which might have been the reasons for the heterogeneity found. This was not analysed because the number of studies included was limited and insufficient. Large and well-designed studies of BSGI are still needed.

Conclusion

BSGI will gradually become a normal procedure in the future. Current evidence suggests that BSGI is an extremely useful adjunct to mammography for its ability to identify breast cancer with a high diagnostic performance. It also has a high sensitivity for detecting subcentimetre cancer and DCIS. BSGI also has some weaknesses including its limited ability to detect axillary lymph nodes and to guide biopsy, and relatively high dose of radionuclide. Many new techniques to solve these problems have been proposed. Studies with a large number of patients are needed in the future to further improve BSGI.

Conflicts of interest None.

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The Breast Journal

ORIGINAL ARTICLE

Breast Molecular Imaging: A Retrospective Review of One Institutions Experience with this Modality and Analysis of its Potential Role in Breast Imaging Decision Making

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■ **Abstract:** Breast Molecular Imaging (or Breast-Specific Gamma Imaging) has been previously shown to be both sensitive and specific for the detection of breast cancer. The purpose of our study was to retrospectively review all cases of Breast Molecular Imaging (BMI) performed at our institution to determine BMI's potential role in Breast Imaging decision making. A total of 416 cases of BMI from January 2007 to November 2009 were analyzed and the following data were collected: indication for examination, BIRADS assignment after BMI, biopsy outcomes, sensitivity and specificity of the modality and patient follow-up. Fifty-six percent of cases were ordered for an indeterminate asymmetry or focal asymmetry, 14% for evaluation of calcifications, and less than 10% each for the remainder of the indications including palpable lumps with negative imaging, evaluation of extent of disease in patients with known breast cancer and screening of high risk patients who could not undergo MRI. BMI was also shown to be helpful in evaluation of lesions that were difficult to biopsy or for patients that desired further testing rather than biopsy or short term follow-up of abnormalities. Seventy percent of BMI cases performed completed the diagnostic evaluation with BIRADS 1 or BIRADS 2 designations. Only 14% of cases ultimately resulted in biopsy. Contra-lateral findings were discovered in 10% of patients, more than half of which were occult malignancies or high-risk lesions. Of the lesions for which biopsy was recommended, 43% were malignant and 15% were high-risk lesions. Sensitivity of the test at our institution was 93% and specificity 78.9%. Our results show that BMI is both a sensitive and specific test which is useful as an adjunct to standard breast imaging modalities for problem solving in indeterminate cases. ■

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

Breast cancer is the second leading cause of cancer deaths in women and the leading cause of new cancer cases in women in 2009. A total of 192,370 new cases were diagnosed in 2009 (1). The standard evaluation of abnormalities, either clinical findings or abnormalities on screening mammogram, includes compression and magnification mammography, breast ultrasound, which provide anatomic information, and increasingly breast MRI, which can provide both physiologic and anatomic information. Another available modality for physiologic analysis of the breast is Breast Molecular Imaging (BMI), also called Scintimammography or Breast-Specific Gamma Imaging (BSGI) when dedicated high resolution, small field-of-view breast imaging gamma cameras are used.

Breast Molecular Imaging has previously been shown to be a useful adjunctive tool in the evaluation of suspicious clinical, mammographic and ultrasound abnormalities, as well as for patients with known breast cancers for evaluation of extent of disease. The Society of Nuclear Medicine lists many potential clinical and research indications for this examination in its Guideline for Breast Scintigraphy with Breast-Specific Gamma Cameras. These include, but are not limited to, evaluation of patients with recently detected breast malignancy, patients at high risk for breast malignancy, patients with indeterminate breast abnormalities or remaining diagnostic concerns, patients with

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technically difficult breast imaging and patients for whom Breast MRI would be indicated, but is unsafe or difficult to perform (2).

Previous studies have shown high sensitivity and good specificity for this modality. The largest study, by Sampalis et al. in 2003 with 1734 cases, demonstrated a sensitivity of 93% and a specificity of 87% (3). More recent studies by Brem et al. and Zhou et al. have shown sensitivities ranging from 89 to 100% and specificities from 59.5% to 85% (4–9). A previous study by Hruska et al. stratified sensitivities by lesion size, showing that sensitivity of BMI is quite high for lesions above 6 mm, 97% for larger lesions greater than 10 mm, and 91% for lesions 6–10 mm, but does drop, as expected, in lesions less than 5 mm in size, 69% (10). A prior study by Brem et al. has also shown BMI to have equal sensitivity to MRI (8), demonstrating a potential role for BMI as a viable alternative test to MRI.

Breast Molecular Imaging has been in routine use at Lahey Clinic since January of 2007 during which time over 400 BMI examinations have been performed. Over that time we have noted many potential uses for BMI as a helpful adjunctive tool in our Breast Imaging department. By analyzing our clinic's experience with this modality, this study hopes to demonstrate the potential options for BMI use in breast imaging decision making and patient care.

MATERIALS AND METHODS

A total of 416 patients underwent Breast Molecular Imaging at our institution from January 2007 to November of 2009. Indications and reason for ordering of the test were reviewed. Patients were injected intravenously with 25 mCi of Tc-99m sestamibi and imaging was performed after 5–10 minutes. The CC and MLO views of both breasts were obtained with a high-resolution, small field-of-view, breast-specific gamma camera (Dilon 6800 Gamma Camera; Dilon Technologies, Newport News, VA). Additional projections, such as 90° lateral or exaggerated CCL views were obtained at the discretion of the interpreting physician. All images were interpreted by either a physician who is a member of both the nuclear medicine and breast imaging sections or by a nuclear medicine physician in conjunction with a member of the breast imaging section. BIRADS categories were assigned for each breast as follows: BIRADS 1 or 2 were assigned to cases with homogenous uptake of radiopharmaceutical throughout the breasts or patchy or diffusely increased uptake of mild to moderate intensity. BIRADS 3 was assigned for patchy, mild to moderate uptake with corresponding probably benign BIRAD 3 features on mammogram. BIRADS 4 was assigned for small areas of focal uptake of variable intensity and BIRADS 5 for well defined areas of intense uptake. Outcomes of all 416 cases were then further reviewed, including any further diagnostic testing performed, any biopsy results, and any available follow-up of each patient over time.

RESULTS

Indications

The stated indications given for BMI were reviewed and analyzed (Fig. 1). Reason for BMI order were as follows: 56% for evaluation of an indeterminate asymmetry, 14% for evaluation of indeterminate calcifications, 6% for further evaluation of a mass, 7% for evaluation of a palpable finding with negative mammogram and ultrasound, 3% for breast pain with negative mammogram and ultrasound, 5% for evaluation of a change in a surgical scar, 2% or less each for the remaining indications, evaluation of patients with dense breast tissue, known family history of breast cancer, architectural distortion and further evaluation in patients with known personal history of breast cancer or a high-risk lesion.

A total of 229 patients, or 56% of the study population, underwent BMI for evaluation of an asymmetry/ies. Types of diagnostic dilemmas involving asymmetries referred for BMI included: asymmetry seen in only one view, asymmetry seen in two views with a negative ultrasound or multifocal asymmetries that were difficult to characterize in two views for ultrasound evaluation or biopsy. All cases were considered to be of relatively low suspicion. An example of a case where BMI was used for evaluation of an asymmetry with negative ultrasound is seen in Figure 2. BMI was negative and the patient returned to routine screening.

A total of 60 patients, or 14% of the study population, underwent BMI for evaluation of calcifications. Approximately half (48%) were for bilateral, multifocal groups of calcifications without a single more suspicious group. Eight percent were for focal groupings only seen in one view. Twenty-six percent were for low suspicion focal groupings of calcifications, performed when patients or clinicians desired more

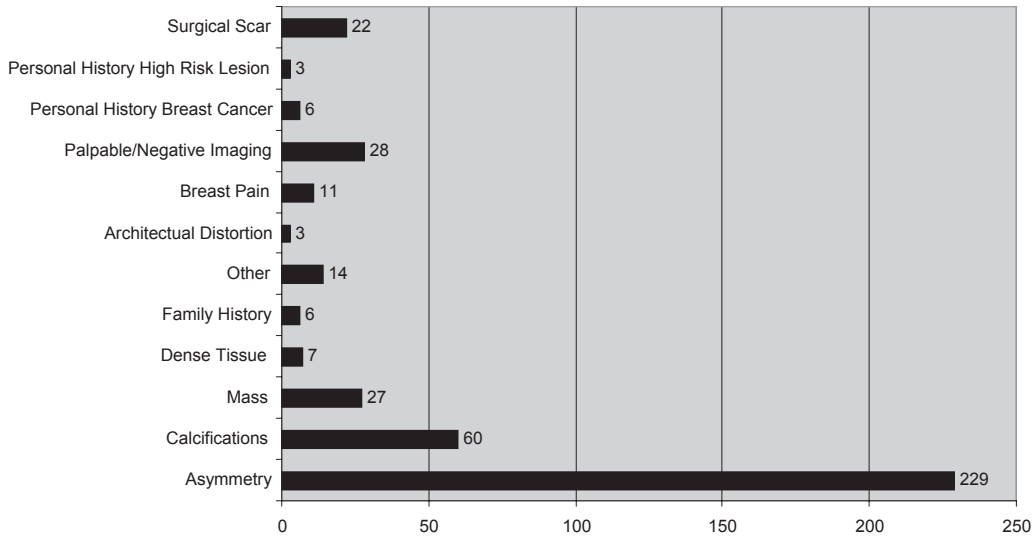

Figure 1. Distribution of indications for BMI at Lahey Clinic in 416 BMI cases since January 2007.

immediate testing options to help alleviate the anxiety of a 6 month follow-up with BIRADS 3 calcifications. Eighteen percent of cases were performed when biopsy was difficult to perform or attempted and failed.

BIRADS Categories

Two hundred and eighty-nine of the 416 patients undergoing BMI (70%) were assigned a negative or benign BIRADS category, which most often completed the diagnostic evaluation in these patients. If any lesions remained suspicious despite a negative BMI, the lesion was biopsied or further evaluated with other imaging. One hundred and twenty-seven cases had further imaging or follow-up recommended. Eighty-four cases (20%) were assigned BIRADS 0 and further testing was recommended, the majority of those patients then went on to MRI (59%) and the remainder nearly equally split between ultrasound or further mammographic imaging. Only 17 cases (4%) were assigned a BIRADS 3 and followed in 6 months with mammogram or ultrasound, and only 25 patients (6%) were suspicious, BIRADS 4 and 5. One case was in a known cancer and was assigned a BIRADS 6. Contralateral findings were discovered in 10% of patients, 40% of these contralateral findings had biopsy recommended due to suspicious appearance on BMI or appearance on further imaging obtained after BMI.

Biopsy and Pathology

Of the 416 BMI cases performed, 68 cases, 14%, resulted in biopsy. The types of biopsies performed were 21% MRI guided, 39% ultrasound guided, 36% stereotactic guided, and 4% surgical biopsies. Of cases biopsied, 43% were malignant, 15% were high risk (atypical ductal or lobular hyperplasia, lobular carcinoma in situ, flat epithelial atypia and papilloma) and 42% benign. For contralateral suspicious lesions incidentally found on BMI and biopsied, the majority (64%) were malignant or high-risk lesions. An example of an incidental contralateral malignancy discovered by BMI is shown in Figure 3.

Fifteen of the 29 cancers identified were invasive ductal or lobular carcinoma and 14 were ductal carcinoma in situ (DCIS) (Table 1). Four cases each of high and low grade DCIS were identified and two cases of intermediate grade. High-risk lesion types biopsied are also shown, the majority of the cases comprised of atypical ductal hyperplasia and papillomas (Table 1). Lesion size detected on BMI and excised ranged from 0.1 to 8 cm (both the largest and smallest were DCIS). The average size was 1.6 cm.

Twenty-nine benign lesions were read as positive and suspicious on BMI and biopsied, the pathology mainly consisting of benign breast tissue, fibrocystic tissue and fibroadenomas (Table 2). Figure 4 is an example of a patient with a palpable lump who initially refused biopsy and thus BMI was recommended. As there was indeed some focal uptake in the region of the palpable lump and small mass on ultrasound, biopsy was performed which demonstrated a fibroadenoma.

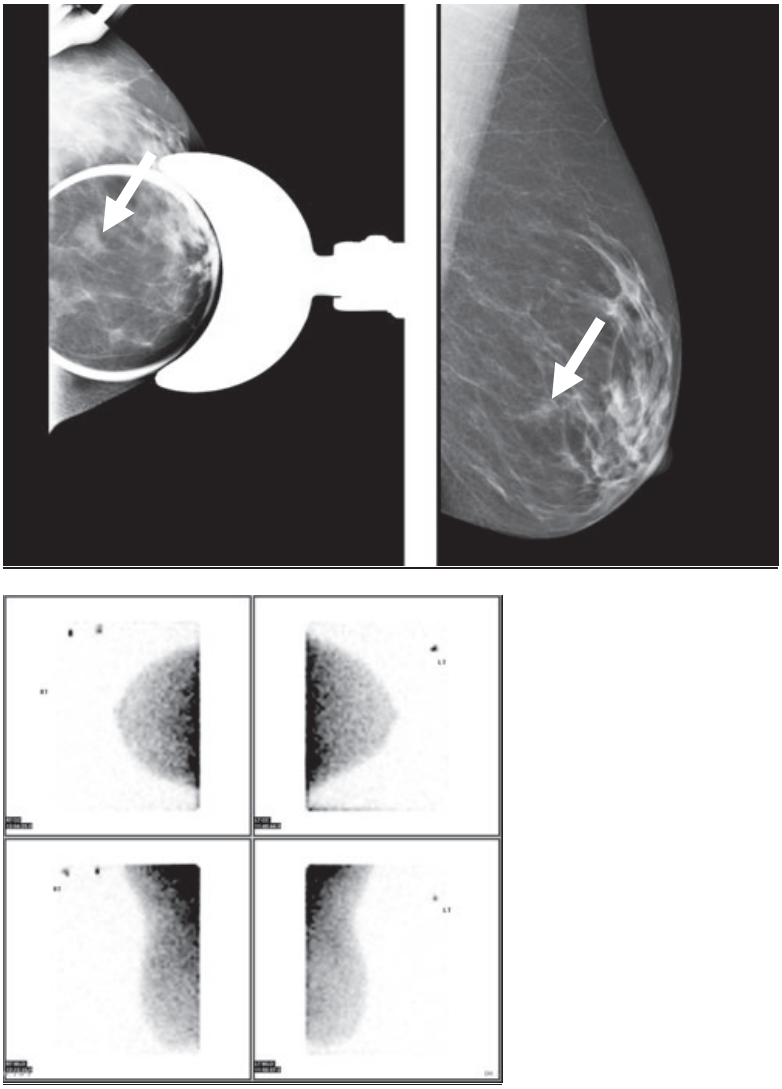

Figure 2. Spot compression craniocaudal view and ML view of a patient with a mammographic asymmetry for which BMI was ordered. Ultrasound was negative and is not shown. BMI was negative and is shown above.

Follow-up

To assess for potential false negatives, we examined patient records of all patients with negative or benign BMI BIRADS designations to determine if any of these patients were biopsied despite reassuring BMI results. Of those that were biopsied we identified those with malignant pathology. We also assessed records of patients with benign or negative BMI's from the time of this BMI to present day (April 2010) to determine if any diagnosis of cancer was made in these patients at any point after their BMI.

We discovered two potential false negative cases, both with BMI's read as negative. In the first case, the mammogram contained a suspicious focal asymmetry biopsied despite negative BMI and shown to represent a 6 mm invasive ductal carcinoma. This mass had also been seen on ultrasound and BMI had been performed to evaluate multiple groups of bilateral calcifications to assess for need for additional biopsy sites (patient unable to undergo MRI due to abnormal laboratory data). In the second case, a patient with negative BMI had calcifications which were biopsied anyway showing 3 mm focus of invasive ductal carcinoma. Final pathology at surgery showed no invasive cancer and only rare foci of DCIS.

As BMI cases included in this study ranged from January of 2007 to November of 2009, our follow-up ranged from 5 months to over 3 years in some patients. In this follow-up of all cases of benign or negative BMI's, two other cases were identified. In the first case, a patient was found to have developed cancer approximately 2 years after their initial BMI,

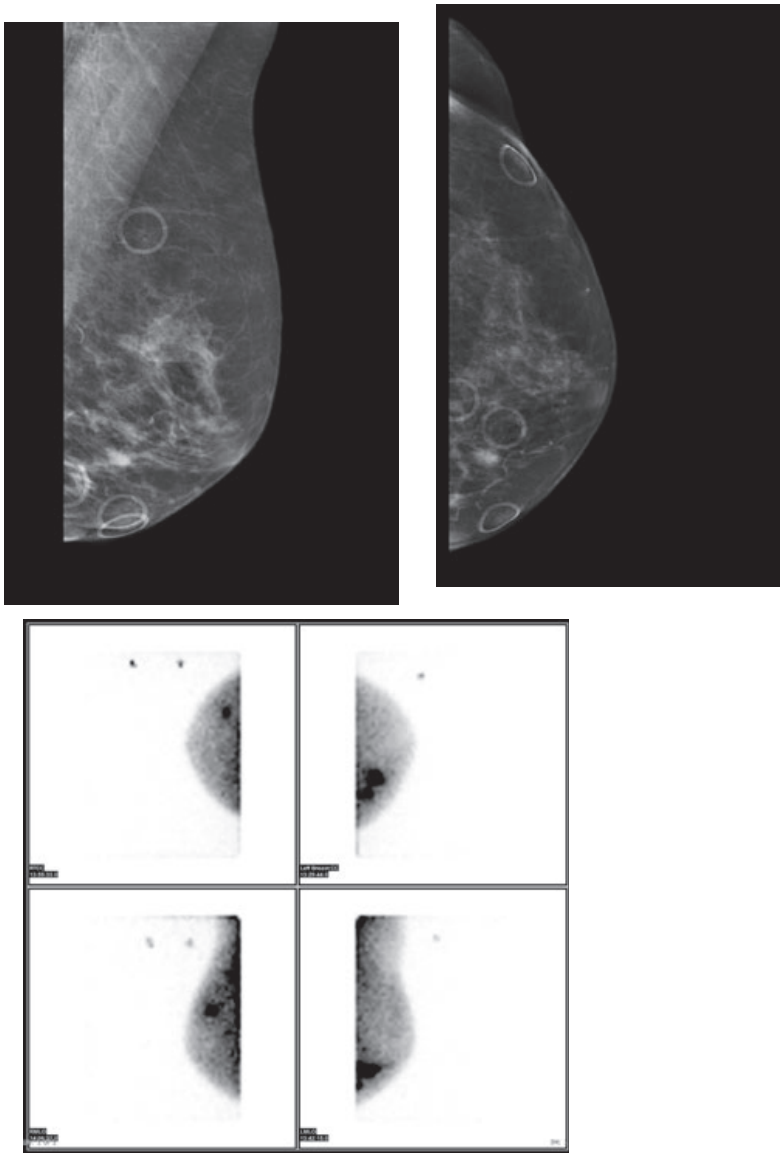

Figure 3. Example of BMI performed for evaluation of left breast focal asymmetry in the lower inner quadrant for which ultrasound evaluation was negative (not shown). BMI imaging shown demonstrates intense uptake corresponding to the focal asymmetry on mammogram in the left lower inner quadrant as well as an incidental contralateral focus of moderately intense uptake in the upper outer quadrant of the right breast. MRI was also performed (not shown) to assist in biopsy guidance. Pathology on the left was invasive ductal carcinoma. Pathology on the right was DCIS.

however, a second BMI performed at that time prior to biopsy of that cancer was positive, so this malignancy probably developed during that 2-year period and this was not considered a miss or false negative. A second patient was diagnosed with cancer 13 months after negative BMI; however, these were new calcifications and pathology of biopsy demonstrated only tiny focus of DCIS, with no additional DCIS found at lumpectomy.

DISCUSSION

Breast Molecular Imaging has been shown in this study as well as in multiple prior studies to be a useful tool with very good sensitivity and specificity for the evaluation of clinical or mammographic findings. In our experience, sensitivity of this test was 93% and specificity 78.9%. This is comparable with results that others have seen (3–10). Only two false negative cases were identified in the 416 examinations performed. One of these appears to be a true false negative case, where a 6-mm lesion seen on ultrasound and mammogram did not demonstrate increased radiotracer uptake on BMI. The lesion was middle depth within the breast tissue, its location appears to have been included within the imaged area on BMI; thus, the reason for absence of significant radiotracer uptake within this lesion is unclear. Cases such as this

Table 1. Pathology of Malignant and High-Risk Lesions After Biopsy of Suspicious BMI Finding

Malignant and high risk lesions	# Cases
Invasive ductal carcinoma	15
DCIS, high	4
DCIS, intermediate	2
DCIS, low	4
Invasive Lobular Carcinoma	4
ADH	4
ALH	0
Flat epithelial atypia	0
Papilloma	5
LCIS	1

Table 2. Pathology of Benign Lesions After Biopsy of Suspicious BMI Finding

Pathology of benign lesions	# Cases
Benign breast tissue	13
Usual ductal hyperplasia	1
Fat necrosis	2
Scar tissue	1
Fibroadenoma	4
Fibrocystic tissue	7
Gynecomastia	1

demonstrates the need for further research in this modality, and suggest that a negative BMI should not replace biopsy for findings on mammogram or ultrasound that are truly suspicious. The second case was a negative BMI of calcifications which were ultimately biopsied and found to contain a 3 mm focus of invasive ductal carcinoma. Although small malignancies can be identified with BMI, this finding suggests what other studies have also shown, that sensitivity may decreased with lesion size.

The indications for BMI performed at our institution are broad, but are in keeping with the recent examples of clinical and research indications stated in the Society of Nuclear Medicine Guideline for Breast Scintigraphy with Breast-Specific Gamma Cameras (2). At our institution, BMI has been most commonly used for evaluation of diagnostic dilemmas with mammographic asymmetries (seen in only one view, negative ultrasound or multifocal). BMI has also been used at our institution in the evaluation of diagnostic dilemmas with calcifications (to pinpoint best location for biopsy in cases with multifocal groups of suspicious calcifications or to localize a group of calcifications seen in only view). These asymmetries and calcifications are either lesions that are difficult to biopsy or

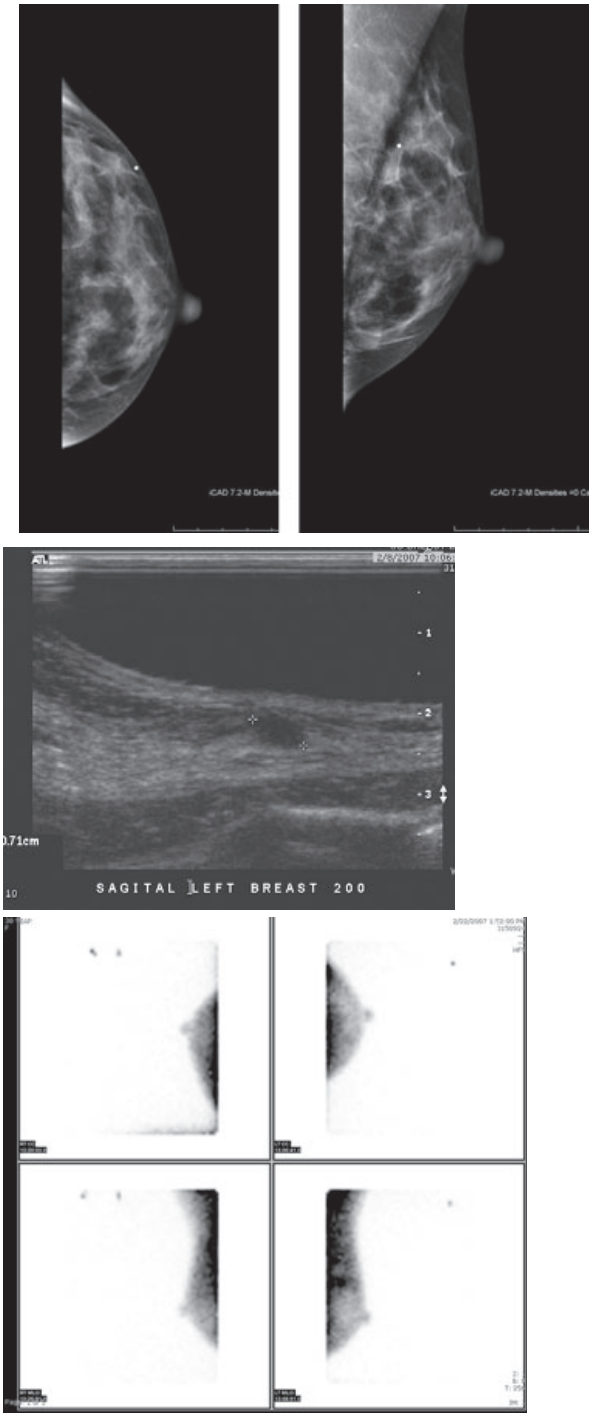

Figure 4. Patient with a palpable lump in the left upper outer quadrant (indicated by BB marker on the CC and MLO mammogram views). Patient refused biopsy. Small hypoechoic mass was seen on ultrasound. As there was indeed some focal uptake on BMI in the region of the palpable lump and small mass on ultrasound, biopsy was performed which demonstrated a fibroadenoma.

patient desires not to have biopsied, or are considered not sufficiently suspicious to recommend biopsy, but either the patient, clinician or radiologist prefer obtaining more information sooner than 6 month follow-up. Another use was in the evaluation of palpable findings with negative mammogram and ultrasound. BMI can be used an additional tool in all of these cases to ease physician and patient minds without the cost, time, and discomfort of an MRI. In fact, 70% of ordered cases end the diagnostic evaluation, and only 14% result in biopsy. In addition, when biopsy was recommended from BMI, the majority of biopsies were performed with ultrasound and stereotactic guidance, rather than with MRI guidance. Finally, BMI can also be used as a screening tool in high risk women for whom MRI is contraindicated. At least one malignancy not seen on screening MRI was discovered by BMI at our institution in this population of patients.

For those cases that did lead to biopsy, more than half of the biopsied lesions turned out to be malignant or high-risk lesions needing further surgery. BMI also led to the discovery of occult/contralateral lesions in 10% of our cases, more than half of which ended up being malignant or high-risk lesions. Malignant lesions identified on BMI included both DCIS (high, intermediate, and low grade) and invasive ductal and lobular carcinoma. BMI was able to detect a large range in size of lesions, of note 11 of 30 biopsied lesions were under 1 cm in size, with foci of malignancy as small as 0.1 cm on final pathology.

As part of our study, we also followed all BMI cases given a negative, benign or probably benign BIRADS category (306 cases). Our follow-up ranges from 5 months for those studies most recently performed, to over 3 years. To the best of our knowledge, only two malignancies have subsequently developed/been diagnosed in these 306 patients. The first case was over 2 years after the original BMI and had a positive BMI at that time so, was likely an interval cancer which developed after the original BMI. The second case was a tiny focus of DCIS discovered at biopsy 13 months after the original BMI this also may have developed during that time period or may simply have been too small for detection at the time of the patient's BMI study.

Future research may include imaging appearance on BMI of benign versus malignant lesions, or imaging appearance of DCIS versus invasive cancers. This could include quantitative analysis of uptake in different types of lesions in addition to lesion morphology. In addition, further long-term follow-up of negative or benign BMI cases would be helpful in further evaluating for any potential false negative cases.

CONCLUSION

Breast Molecular Imaging, although still not widely available or routinely used, is both sensitive and specific for the identification of breast malignancy. This study is an example of how BMI has been utilized in our institution and how it can be a useful tool in diagnostic dilemmas in the breast imaging population.

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Clinical utility of breast-specific gamma imaging for evaluating disease extent in the newly diagnosed breast cancer patient

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KEYWORDS:
Breast-specific gamma imaging;
BSGI;
Preoperative breast cancer staging;
Breast imaging;
Magnetic resonance imaging

Abstract

BACKGROUND: Breast-specific gamma imaging (BSGI) is a functional imaging modality that has comparable sensitivity but superior specificity compared with magnetic resonance imaging, yielding fewer false-positive results and thereby improving clinical management of the newly diagnosed breast cancer patient.

METHODS: A retrospective review was performed from 2 community-based breast imaging centers of newly diagnosed breast cancer patients in whom BSGI was performed as part of the imaging work-up.

RESULTS: A total of 138 patients (69 invasive ductal carcinoma, 20 invasive lobular carcinoma, 32 ductal carcinoma in situ, and 17 mixtures of invasive ductal carcinoma, invasive lobular carcinoma, or ductal carcinoma in situ and other) were reviewed. Twenty-five patients (18.1%) had a positive BSGI study at a site remote from their known cancer or more extensive disease than detected from previous imaging. Fifteen patients (10.9%) were positive for a synchronous or more extensive malignancy in the same or contralateral breast. Five patients had benign findings on pathology, 5 benign on ultrasound follow-up (false-positive rate, 7.2%). Findings converted 7 patients to mastectomy, 1 patient to neoadjuvant chemotherapy, and 7 patients were found to have previously undetected contralateral cancer. The positive predictive value for BSGI was 92.9%.

CONCLUSIONS: BSGI detected additional or more extensive malignancy in the same or contralateral breast in 10.9% of newly diagnosed breast cancer patients. Only 7.2% incurred an additional work-up. BSGI provides accurate evaluation of remaining breast tissue in newly diagnosed breast cancer patients with few false-positive readings.

Surgical management of breast cancer is becoming more complex as the pendulum swings from the Halstedian radical mastectomy to minimally invasive procedures such as exploration of transcutaneous ablation of tumors without resection. At the same time as surgical excisions have become less invasive, so to have radiation treatment fields. Whole-breast irradiation has given way to partial breast irradiation. In this current treatment milieu, complete and accurate imaging evaluation of the breast tissue becomes critical. Defining the extent of disease within the ipsilateral breast is essential in planning treatment fields. The presence of contralateral disease can alter planned therapy.

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Women with newly diagnosed breast cancer are at risk of harboring more extensive disease than can be detected by mammography and/or ultrasonography. Estimates of multifocal and multicentric disease very widely. Depending on the specific criteria used, estimates may range from 7% to 63%.[1–4] Being able to accurately determine the extent of disease preoperatively can decrease additional surgeries, decrease future local recurrences, and may result in a better outcome.[5,6]

With demands for improved imaging to assist with more complex treatment planning, magnetic resonance imaging (MRI) with gadolinium enhancement has gained immense popularity. MRI of the breast offers high sensitivity for additional lesions and provides morphologic detail of anatomy and the extent of disease. Sensitivity is reported at 93% to 100% in the preoperative setting.[5,7–9] Unfortunately, the advantage of superior sensitivity often is countermanded by the low specificity of MRI (range, 65%–79%).[8] In recent prospective studies, the false-positive rate in the setting of newly diagnosed breast cancer causes an inordinate number of additional follow-up imaging studies with up to 89% of patients with a positive MRI undergoing additional imaging and/or biopsies. Unfortunately, only about 20% will be true positives.[5,10]

The advent of high-resolution, small field-of-view, breast-specific nuclear scanners has brought resurgence in gamma breast imaging. We review here our experience with breast-specific gamma imaging (BSGI) in newly diagnosed breast cancer patients.

Materials and Methods

Patients

This was a retrospective review of 138 patients who were referred for BSGI at 2 separate community breast imaging centers. Patients were included for analysis if they had a new biopsy-proven breast cancer, were undergoing BSGI for preoperative evaluation, and complete data were available for analysis. The Legacy Health System Institutional Review Board approval was obtained for review of the data.

Imaging

Patients were injected with 25 to 30 mCi (925–1,110 MBq) of technetium-99m sestamibi into an arm vein contralateral to the breast of interest. A dorsalis pedis vein was used if no suitable arm vein was found. Imaging was begun immediately after injection of the isotope. Craniocaudal and mediolateral views were performed of both breasts with approximately 10 minutes per view (total time, 40 min). Images were obtained with a high-resolution, small field-of-view, breast-specific gamma camera (Dilon 6800 Gamma Camera; Dilon Technologies, Newport News, VA).

Image evaluation

All images were interpreted by 1 of 7 dedicated breast radiologists. The images were classified as either negative, no further work-up recommended; or positive, further work-up such as additional imaging or biopsy recommended.

Data collection and analysis

Data were collected retrospectively and stored in a Microsoft Excel 2003 program (Microsoft Corporation, Redmond, WA). Statistical analysis was performed with Microsoft Excel.

Results

Between December 2006 and December 2007, there were 649 BSGI performed and 138 patients who met the study criteria were reviewed. The mean age of the patients was 55 years (range, 30–81 y). The distribution of pre-BSGI biopsy pathology were invasive ductal carcinoma (IDC), 69 (50.4%); invasive lobular carcinoma (ILC), 20 (14.5%); ductal carcinoma in situ (DCIS), 32 (23.2%); and mixed (combination of IDC, ILC, or DCIS and other malignant pathology), 17 (12.3%).

Twenty-five (18.1%) of the patients had a positive BSGI remote from their known focus of cancer (Table 1). Ten

Table 1

Preoperative biopsy pathology	N (%)	Mean age, y (range)	Positive BSGI at sight remote from known cancer (%)	False-positive results (%)	Additional cancer found (%)
Total patients	138 (100)	55 (30–81)	25 (18.1)	10 (7.2)	15* (10.9)
IDC	69 (50.4)	55 (30–79)	13 (9.4)	4 (3.0)	9 (6.5)
ILC	20 (14.5)	61 (38–81)	4 (3.0)	1 (.7)	3 (2.2)
DCIS	32 (23.2)	53 (31–70)	2 (1.4)	1 (.7)	1 (.7)
Mixed	17 (12.3)	56 (40–80)	6 (4.3)	4 (3.0)	2 (1.4)

Mixed = combination of IDC, ILC, or DCIS and other malignant pathology.

*One patient with additional positive BSGI findings confirmed on ultrasound (BI-RADS 5) elected for neoadjuvant chemotherapy before pathologic confirmation and had complete response of known cancer site and no cancer at additional BSGI site.

(7.2%) patients were false positives. Four of the 11 patients underwent an additional biopsy that was benign, 5 patients underwent additional ultrasound, and 1 patient was converted to mastectomy with benign pathology at the suspicious site.

Fourteen (10.1%) patients had false-negative BSGI results. These patients had negative BSGI results in the known tumor bed, however, on final surgical pathology, residual tumor remained. Most residual tumor findings were DCIS (N = 8), ranging in size from microscopic to 1.5 cm. The remaining residual tumor findings included 5 IDC (size, .5–.8 cm) and 1 intraductal papillary carcinoma (1.3 cm).

Fifteen patients (10.9%) were discovered to have a synchronous cancer remote from their known focus. Eight (5.8%) of these foci were in the ipsilateral breast; the remainder (7; 5.1%) were in the contralateral breast. Clinical management was altered in all 8 patients with additional ipsilateral cancer. Six patients were converted to mastectomy after BSGI detected their multifocal or multicentric disease. One had a positive lymph node confirmed on needle biopsy after a positive BSGI and elected to undergo neoadjuvant chemotherapy. One patient with additional positive BSGI and a concordant suspicious follow-up ultrasound (Breast Imaging Reporting and Data System [BI-RADS] 5) refused additional needle biopsy and elected to undergo neoadjuvant chemotherapy and a bilateral mastectomy. At surgery she had complete pathologic response of the original biopsy-proven cancer with no residual tumor found at the positive BSGI/ultrasound site. The histology of the additional cancers found included 7 (5.1%) IDC, 5 (3.6%) ILC, 2 (1.4%) DCIS, and 1 complete response.

The positive predictive value of BSGI for detecting synchronous tumor or extensive disease in the preoperative setting for this group of patients was 92.9%.

Comments

There is currently an abundance of literature evaluating the role of MRI in preoperative breast cancer evaluation.[8,11] Most of these are retrospective reviews. Although they all agree on the value of MRI and focus on its high sensitivity, the issue of specificity is not addressed directly. Tremendous advances have been made in the past 2 decades in the performance and interpretation of breast MRI. The American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS) has brought uniformity to the interpretation of breast MRI examinations. Detection is based on enhancement characteristics of lesions after gadolinium injection. The best results are achieved with the use of a dedicated double breast coil. Enhancement is based on vascularity, permeability of vessels, and the interstitial space of tumor, and is reported in enhancement curves.[11] Benign and malignant probabilities are predicted on the basis of contrast enhancement and washout characteristics. Morphologic detail also is assessed in establishing a differential diagnosis. The role for breast MRI in preoperative breast cancer staging, although actively researched and widely available, remains controversial.[8] There are no published guidelines for the use of MRI in the preoperative work-up of breast cancer patients and practices vary widely between institutions. In general, physicians advocate MRI in patients at high risk for breast cancer, young patients, or those with very dense breast. MRI, however, is recommended by the American Cancer Society as a screening tool for high-risk patients (BRCA mutation, lifetime risk ≥20%–25% as defined by BRCAPRO).[12]

There has been a recent resurgence in gamma imaging of the breast with the development of a high-resolution, small field-of-view gamma camera. Gamma breast imaging provides physiologic data in breast cancer imaging via 2 mechanisms. First, the radioactive tracer sestamibi is distributed evenly throughout the circulatory system. Because malignant tumors induce neoangiogenesis to support their hyperproliferation, pharmaceutical delivery to these lesions is enhanced.[13] Second, sestamibi specifically binds mitochondria within cells. Because cancer cells have a higher cytoplasmic mitochondrial density than benign tumor cells and cells in the surrounding breast tissue, they retain more of the radiopharmaceutical.[14] These 2 mechanisms make gamma breast imaging highly sensitive and specific.[15] The development of a high-resolution, small field-of-view dedicated breast gamma imaging system (BSGI) has overcome the 2 major limitations of gamma breast imaging (tumor localization and detection of subcentimeter lesions) that previously prevented its wide adoption. BSGI is not affected by breast density similar to MRI and can obtain equivalent if not better sensitivity with much improved specificity.[15–18] Any patient who is a candidate for MRI can undergo BSGI as an alternative.

There are 2 recently published prospective studies on the impact of preoperative breast MRI on newly diagnosed breast cancer patients.[5,10] Bilimoria et al[5] reported on 155 patients with newly diagnosed breast cancer undergoing preoperative breast MRI. Of 124 additional suspicious lesions detected, 65 underwent further imaging, and 41 additional biopsies, for a total of 15 patients with a beneficial change in surgical management. The false-positive rate was 78%.[5] Lehman et al[10] reported on 969 patients with newly diagnosed unilateral breast cancer undergoing MRI of the contralateral breast. They found 135 lesions that were recommended for biopsy, 121 underwent biopsy, and 30 were confirmed cancer, with 91 (75%) unnecessary biopsies. The number of unnecessary follow-up imaging studies as a result of MRI findings was not reported. The calculated negative predictive value was excellent at 99%, but the positive predictive value was a disappointing 21%. BSGI compares very favorably in our series of 138 patients undergoing preoperative BSGI showing 25 additional lesions, 6 underwent additional imaging and 18 had additional biopsies (1 went directly to mastectomy), for a total of 14 additional cancers found (Table 2). Our false-positive rate was 7.2%,

Table 2

Study	n	Patients with additional positive imaging (%)	Additional cancer found (%)	Positive predictive value
Zhou et al (this study)	138	25 (18.1)	15 (10.9)	92.9%
Bilimoria et al[5]	155	73 (47.1)	9 (5.8)	N/A
Lehman et al[10]	969	135* (13.9)	30* (3.1)	21%

N/A = not applicable.
*Looked at additional cancer in the contralateral breast only.

with a positive predictive value of 92.9%. These results are congruent with findings by Brem et al[17] comparing BSGI with MRI in a group of 23 patients. They found no statistically significant difference in sensitivity, but the specificity between BSGI and MRI was 71% and 25%, respectively.

With the increasing cost of health care and increasing demand on health care providers to be fiscally responsible, BSGI represents a cost-effective alternative to MRI. At our institution BSGI is about a third of the cost of MRI ($1,260 vs $3,400).[18]

The shortfalls of our study are that it was a retrospective review and, as a result, subject to some inherent bias. We also had a relatively small sample size. The high-resolution BSGI system is a new technology and with all new technologies there can be a lack of standardization. We grouped our BSGI results as either positive or negative. To reference our results more closely with others, a grading system similar to the ACR BI-RADS system for mammography and breast ultrasound would be desirable. A grading system has been described by Brem et al,[19] but has not been universally adopted.

Reporting of lesion size can be more challenging with BSGI. This is because BSGI is a purely physiologic and not an anatomic imaging modality. The edges often are not as crisply defined and not as easily measured. We recommend that surgeons review the gamma images to get a visual assessment of tumor extent. Some patients (not included in this analysis) were converted from mastectomy to lumpectomy after a review of the BSGI images, which showed less disease than indicated by MRI. An important advantage of the small field-of-view BSGI system is that images are obtained with comparable craniocaudal and mediolateral oblique positioning to mammographic positioning. This advantage greatly simplifies establishing concordance and correlation of mammographic lesions with focal BSGI abnormalities.

Conclusions

BSGI shows promise in the preoperative evaluation of newly diagnosed breast cancer patients. A review of the literature shows that BSGI is at least equivalent to MRI in sensitivity, with greater specificity. In this study BSGI was able to detect previously occult synchronous breast cancers in the range reported for MRI. The false-positive rate, however, is improved dramatically, with a significant decrease in unnecessary additional work-ups. It is also a cost-effective tool. As BSGI becomes more widely adopted, an ACR BI-RADS–type system needs to be established. Larger prospective studies of BSGI in the preoperative setting should be performed. This study would suggest that BSGI is a more appropriate imaging modality for use in the newly diagnosed breast cancer patient compared with MRI. It affords accurate detection of additional lesions, defines extent of disease with far fewer false-positives, and has a lower cost.

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Results of a Multicenter Patient Registry to Determine the Clinical Impact of Breast-Specific Gamma Imaging, a Molecular Breast Imaging Technique

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OBJECTIVE. Molecular breast imaging techniques, such as breast-specific gamma imaging, are increasingly being used as adjunctive diagnostic technologies to mammography and ultrasound. This multicenter clinical patient registry was designed to quantify the impact of this modality on the management of the breast patient population in clinical practice and to identify the subgroups of patients benefiting from its use.

MATERIALS AND METHODS. There were 1042 patients included in this analysis, and breast-specific gamma imaging typically was recommended when the patient had at least two of the following indications: equivocal or negative mammogram or sonogram and an unresolved clinical concern; personal history of breast cancer or current cancer diagnosis; palpable masses negative on mammographic and sonographic examination; radiodense breast tissue; or high risk for breast cancer. Pathologic analysis or follow-up imaging, if biopsy was not conducted, was used as the reference standard, and lesions were classified as positive (i.e., malignant or high risk) in 250 cases and as negative (i.e., benign) in 792 cases.

RESULTS. Breast-specific gamma imaging was positive in 408 patients (227 malignant or high-risk lesions requiring additional intervention), negative in 634 patients (23 with malignant or high-risk lesions), and indeterminate in 69 patients (all benign lesions). Breast-specific gamma imaging had an overall sensitivity of 91% and specificity of 77%.

CONCLUSION. Breast-specific gamma imaging significantly contributed to the detection of malignant or high-risk lesions in patients with negative or indeterminate mammographic findings, and it provided improved management when compared with ultrasound.

Keywords: breast cancer, breast-specific gamma imaging, mammography, ultrasound

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WEB
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Mammography and ultrasound are common anatomic imaging procedures used to detect breast cancer. Although screening mammography, especially when combined with ultrasound, has shown the ability to detect nonpalpable breast cancer, these modalities still suffer from some significant limitations. According to the results of the American College of Radiology Imaging Network 6666 clinical trial, which evaluated the addition of ultrasound in high-risk patients with dense breasts and negative screening mammograms, when combined, these technologies provided a positive predictive value of only 11.2% and a missed breast cancer in eight of the 40 (sensitivity, 80%) participants with malignant lesions [1]. In recent years, molecular imaging technologies have been developed to address these limitations.

Breast-specific gamma imaging, also referred to as molecular breast imaging, scintimammography, or mammoscintigraphy, is a nuclear medicine breast imaging technique that has been significantly improved within recent years with the invention of breast-optimized gamma camera designs. Before this development such studies were generally conducted with standard large-FOV gamma cameras. Nearly 100 peer-reviewed papers dating back more than 15 years have documented the experience of this imaging technique using ^{99m}Tc-methoxyisobutylisonitrile (sestamibi), and several studies comparing standard and optimized camera designs have provided evidence that the breast-optimized designs improve the clinical accuracy of this procedure, especially in sensitivity for subcentimeter lesions [2–5]. Clinical evidence proving the increased lesion sensitivity of breast-specific gamma imaging over scintimammography is now available [6–8]. In addition, there have been several publications indicating that the sensitivity and specificity for breast-specific gamma imaging are both around 89–96% and 65–90%, respectively

[9–12]. Although alternate pharmaceuticals are available and others are under investigation, sestamibi is currently the only U.S. Food and Drug Administration–approved single-gamma emission isotope approved for breast imaging.

There are several clinical indications for breast-specific gamma imaging proposed in the medical literature and provided in guidelines from the Society of Nuclear Medicine [13]. This clinical patient registry was designed to examine the overall performance of breast-specific gamma imaging and the impact of breast-specific gamma imaging on patient management in clinical practice.

Materials and Methods

Institutional review board approval was obtained for a retrospective review of patient data. Before analysis, all patient-identifying markers were removed. Each institution maintained a clinical registry of patients undergoing breast-specific gamma imaging. All imaging modalities, including breast-specific gamma imaging, digital mammography, ultrasound, and MRI, were conducted as deemed clinically necessary by either the referring physician or radiologist.

All patients had at least one (the majority of patients had two or more) of the following indications for recommending the breast-specific gamma imaging procedure: equivocal mammography or ultrasound findings; personal history of breast cancer; family history or other factors establishing high risk for developing breast cancer; recent positive mammogram; clinical finding such as palpable mass, breast pain, or bloody nipple discharge; and radiodense breast tissue difficult to image on mammogram.

Breast-specific gamma imaging was conducted using 555–925 MBq of ^{99m}Tc-sestamibi and a gamma camera (model 6800, Dilon Technologies) (Fig. 1). Imaging began 3–10 minutes after injection with a minimum of two views of each breast, including craniocaudal and medial lateral oblique. Additional views including, but not limited to, rolled craniocaudal views, 90° lateral, were conducted as deemed clinically necessary, and the imaging time for each projection ranged from 5 to 10 minutes depending on institutional protocol.

The interpreting radiologist had access to all studies and patient history at the time of interpretation. Breast-specific gamma imaging examinations were interpreted in a scoring system similar to that of the BI-RADS classification for mammography: 1, normal study with no focal abnormality; 2, broad heterogeneous distribution consistent with benign breast tissue changes; 3, regional heterogeneous distribution or patchy distribution without focal abnormality, lacking evidence of malignancy but insufficient to rule out malignant processes; 4, low-to-medium intensity focal abnormality suggesting the possibility of malignancy; and 5, high focal intensity suggesting high possibility of malignancy.

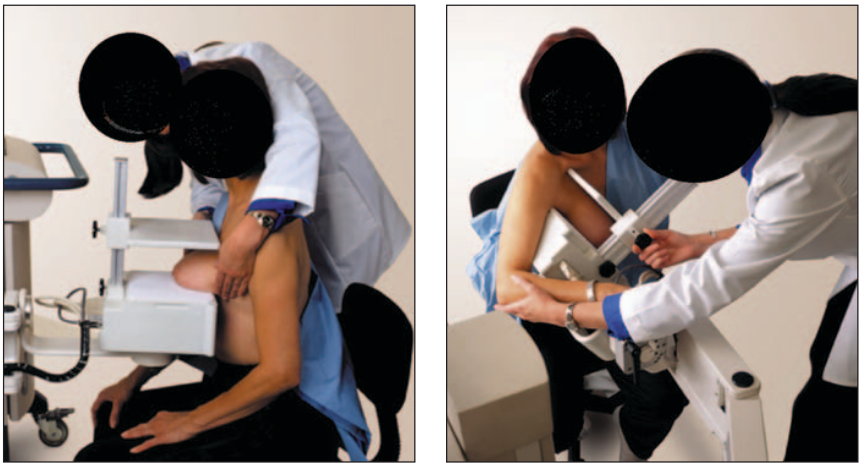


Fig. 1—Patient being positioned for breast-specific gamma imaging.
A and **B**, Photographs show patient being positioned in craniocaudal (**A**) and mediolateral oblique (**B**) views.

Biopsy was performed when deemed necessary by the radiologist. Imaging-guided biopsies were typically performed using ultrasound, stereotactic x-ray, or MRI; however, more recently, a stereotactic breast-specific gamma imaging–guided biopsy system has become available. In addition, follow-up imaging was conducted on an interval deemed clinically necessary. Biopsy or follow-up imaging, if biopsy was not conducted, was used as the reference standard. Biopsy results were classified as positive (i.e., malignancy or high-risk lesions, such as atypical ductal hyperplasia, atypical lobular hyperplasia, and lobular carcinoma in situ) or negative (i.e., benign conditions not requiring additional intervention). Imaging studies were classified as positive (BI-RADS category 4 or 5), negative (BI-RADS category 1 or 2), or indeterminate (BI-RADS category 0 or 3). For the purposes of statistical preparation, all indeterminate findings were classified as negative, having resulted in no definitive change of management.

Because this scoring system was used in a clinical setting, the interpreting radiologist used all imaging studies, patient history, and other available information while interpreting each study and determining the management pathway: additional imaging, biopsy, short-term follow-up, or return to annual screening. Information regarding the case, such as patient's risk factors, clinical concern, clinical history, BI-RADS rating of all imaging studies, biopsy results, and follow-up imaging, could be recorded in a spreadsheet (Excel, Microsoft). To be included in the overall analysis, each patient required a minimum of breast-specific gamma imaging findings and pathology or follow-up imaging results recorded in the patient registry. To measure the impact of breast-specific gamma imaging in patient management, the dataset of patients with breast-specific gamma imaging and biopsy or follow-up imaging used in the overall analysis was further reduced to include only those patients with results of both mammography and ultrasound recorded in the registry.

The typical methods for statistical analysis of medical tests assumes that all imaging studies are either positive or negative and thus can be sorted into one of the four statistical expressions used: true-positive, true-negative, false-positive, or false-negative. However, according to the American College of Radiology BI-RADS Atlas [14], mammograms (and each subsequent diagnostic imaging modality: diagnostic mammography, ultrasound, and MRI) are interpreted on the basis of a six-category reporting system. Similarly, in clinical practice and according to several authors, it is common to use a similar rating system for reading breast-specific gamma imaging. Each category and the management recommendations provided by the American College of Radiology [14] are as follows: BI-RADS category 1, negative (return to annual screening); BI-RADS category 2, benign findings (return to annual screening); BI-RADS category 3, likely benign (less than 2% chance of malignancy; 6-month follow-up imaging is recommended); BI-RADS category 4, possibility of malignancy (biopsy should be considered); BI-RADS category 5, 95% probability malignancy likely (intervention required); and BI-RADS category 0, ad-

ditional imaging or information is required to make proper management decisions. Working from these BI-RADS classifications, there are essentially three management routes for the diagnostic breast patient: follow-up imaging at 6- or 12-month intervals, biopsy, or additional imaging.

In addition, it is typical to analyze the performance of a breast imaging modality using biopsy or follow-up imaging as the reference standard and to classify the findings as positive (biopsy-proved cancer) or as negative (no evidence of malignancy). However, in clinical practice, there are a number of benign lesions that typically undergo additional interventional procedures either because of the possibility of upgrading the lesion at excision or because they are sometimes associated with malignant processes. Therefore, there are three possible clinical classifications for needle biopsy results: benign, no additional intervention required; high risk, additional intervention needed to clarify diagnosis; and malignant, additional intervention needed to treat.

To understand the clinical impact of adjunctive imaging modalities, such as breast-specific gamma imaging and ultrasound, on the population undergoing mammography, these management routes and biopsy results need to be considered in the quantification. Given that mammography is typically the primary imaging modality, the registry data were divided into three classifications: negative or likely benign findings resulting in follow-up imaging at an established time interval, indeterminate findings leading to additional imaging, or positive findings indicating the potential need for biopsy.

To quantify and compare the impact of breast-specific gamma imaging and ultrasound on patient management, the results from adjunctive imaging procedures can be sorted into one of three categories as they relate to the mammogram: concordant, no change in management (same finding as mammography or a BI-RADS category 0 result); or discordant, correct change in management (improving cancer detection or eliminating intervention for a benign lesion) or incorrect change in management (misdiagnosis or delay in cancer detection or indicating the need for intervention on a benign lesion).

Because all of these patients had a mammogram indicating follow-up imaging as the proper management pathway, the adjunctive imaging studies were recommended because of some additional clinical factors impeding the clinician's confidence in the mammogram. As part of the patient registry, the interpreting physicians were asked to choose from the following reasons for recommending the additional diagnostic examinations for each patient: questionable findings on mammography, palpable mass, dense breasts (limiting the utility of mammography), or physician referral.

TABLE 1: Overall Performance of Each Imaging Modality for 329 Patients

Performance Parameter	Imaging Modality		
	Mammogram	Ultrasound	Breast-Specific Gamma Imaging
Sensitivity	74	84	92
Specificity	79	62	70
Positive predictive value	71	60	68
Negative predictive value	82	85	93

Note—Data are percentages.

Results

A total of 2004 patients were entered into the patient registry at four institutions. There were 962 patients who did not undergo biopsy and who lacked the required 6 months of follow-up imaging at the time of this analysis. The other 1042 patients underwent pathologic analysis ($n = 642$) or follow-up imaging ($n = 400$) and were included in this study. Pathologic analysis or follow-up imaging resulted in 250 positive and 792 negative findings. Breast-specific gamma imaging was positive in 408 patients, 227 of whom had a malignant or high-risk lesion. Breast-specific gamma imaging was negative in 634 patients, and 611 of these lesions were negative on biopsy or follow-up imaging. Breast-specific gamma imaging was indeterminate in 69 lesions, all of which were benign. Breast-specific gamma imaging had an overall sensitivity, specificity, positive predictive value, and negative predictive value of 91%, 77%, 57%, and 96%, respectively.

Mammography and ultrasound findings were reported for 329 patients, and the results from each of the modalities are compared in Table 1. When categorized by age, there were 42 patients younger than 45 years, 99 patients 46–55 years old, 97 patients 56–65 years old, and 91 patients older than 65 years. In this group of patients, 48 (14.6%) had one indication for breast-specific gamma imaging, whereas 222 (67.5%) had two indications and 59 (17.9%) had three or more indications. Overall, breast-specific gamma imaging provided a statistically significant improvement in sensitivity and negative predictive value ($p < 0.000001$, McNemar test).

Although Table 1 provides an overall comparison of the clinical performance of the three modalities, in practice, mammography is the primary screening and diagnostic imaging modality for the majority of patients, whereas ultrasound and breast-specific gamma imaging are adjunctive imaging procedures used when the results of mammography are not sufficient to identify the proper management pathway (i.e., return to screening, short-term follow-up, or biopsy). In Table 2 and the following sections, patients are subcategorized by their mammographic findings to compare the effectiveness of breast-specific gamma imaging and ultrasound in their role as adjunctive imaging modalities to contribute toward the management of patients. The majority of patients (38%) were referred because of questionable findings in mammography. These findings included nonspecific asymmetric changes, vague calcifications, potential findings obscured by overlaying breast tissue, or discordant results between multiple imaging studies, such as screen and diagnostic mammography or diagnostic mammography and ultrasound. Another 20% of patients were reported to have breast density sufficient to impede the interpretation of mammogram, and 11% had a palpable mass that was negative on mammography. The remaining 31% of patents were either referred for additional imaging studies by the primary physician (11%) or had no specific reason provided for the additional imaging (20%).

Patients With BI-RADS Categories 1–3 Mammogram

There were 71 patients who had negative or likely benign findings on mammogram (BI-RADS categories 1, 2, or 3) who were referred for additional sonographic and breast-specific gamma imaging studies. The majority of these patients (85%) had either heterogeneously dense breast tissue or very dense breast tissue, which can impede the sensitivity of mammography. Thirty-six patients (51%) were reported as either high risk as determined by the clinician, very high risk (two first-order relatives with breast cancer before the age of 50 or *BRCA* positive), or had a personal history of breast cancer. There were 35 patients without reported risk factors.

There were 53 benign, six high-risk, and 12 malignant lesions in this population. Ultrasound resulted in no change for 44 patients; 38 patients had studies concordant with mammog-

TABLE 2: Breast-Specific Gamma Imaging Compared With Ultrasound in the Management of Patients

Mammography Results	Ultrasound	Breast-Specific Gamma Imaging
Negative mammogram (BI-RADS categories 1–3)		
Concordant	38	41
BI-RADS category 0		
Malignant or high-risk lesions	2	0
Benign	4	1
Discordant (BI-RADS category 4 or 5)		
Malignant or high risk	11	15
Benign	16	14
Positive mammogram (BI-RADS category 4 or 5)		
Concordant	121	117
BI-RADS category 0		
Malignant or high risk	1	0
Benign	2	1
Discordant (BI-RADS categories 1–3)		
Malignant or high risk	6	8
Benign	9	13
Indeterminate mammogram (BI-RADS category 0)		
Concordant	48	10
BI-RADS categories 1–3		
Malignant or high risk	3	0
Benign	30	75
BI-RADS category 4 or 5		
Malignant or high risk	10	17
Benign	28	17

Note—Data are number of examination results.

raphy and six patients had BI-RADS category 0 findings. Ultrasound was discordant (positive) in 27 patients, resulting in 16 benign, three high-risk, and eight malignant lesions. The breast-specific gamma imaging resulted in no change for 42 patients (41 concordant with the mammogram and one BI-RADS category 0 result). Breast-specific gamma imaging yielded 29 discordant (positive) examinations (14 benign, six high-risk, and nine malignant lesions).

Although both breast-specific gamma imaging and ultrasound improved the management of this patient group, breast-specific gamma imaging was positive in nine malignant lesions, whereas ultrasound was positive in eight. In addition, breast-specific gamma imaging was positive in three high-risk lesions (all atypical ductal hyperplasia at needle biopsy), two of which were classified as BI-RADS category 0 and one as BI-RADS category 3 by ultrasound. Breast-specific gamma imaging was positive in fewer benign lesions (14 vs 16 by ultrasound) (Table 2).

Patients With BI-RADS Category 4 or 5 Mammogram

There were 139 patients with positive findings on mammography (41 benign, two high-risk, and 96 malignant lesions). Ultrasound provided no change in management for 124 patients. It was concordant in 121 lesions (30 benign, two high-risk, and 89 malignant), and three patients had a BI-RADS category 0 ultrasound (two benign and one malignant lesion). Ultrasound was discordant (negative) in 15 patients (nine benign and six malignant lesions). Breast-specific gamma imaging resulted in no change for 118 patients. For 117 patients, breast-specific gamma imaging was concordant with mammography (27 benign, 89 malignant, and one high-risk lesion), whereas one patient with benign findings had a BI-RADS category 0 breast-specific gamma imaging. Twenty-one breast-specific gamma imaging studies resulted in discordant (negative) findings (13 benign, seven malignant, and one high-risk lesion).

Breast-specific gamma imaging was negative in seven malignant and one high-risk lesion, whereas ultrasound was negative in six malignant and two high-risk lesions. Breast-specific gamma imaging was true-negative in 13 patients, whereas ultrasound was true-negative in nine patients (Table 2).

Patients With BI-RADS Category 0 Mammogram

There were 119 patients in this category, with 102 benign, 15 malignant, and two high-risk lesions. Ultrasound provided no change in management for 48 patients (44 benign, three malignant, and one high-risk lesion). Ultrasound was negative in 33 cases (30 benign and three malignant lesions) and was positive in 38 cases (28 benign, nine malignant, and one high-risk lesion). Breast-specific gamma imaging resulted in no change in management in 10 cases, all benign. Thirty-four patients had positive breast-specific gamma imaging studies (17 benign, 15 malignant, and two high-risk lesions) and 75 had negative studies, all benign (Table 2).

For this group of patients, breast-specific gamma imaging was significantly more likely to contribute to patient management than ultrasound (109 vs 71 patients) and it was less likely to be negative in malignant lesions (three vs zero). In addition, breast-specific gamma imaging was less likely to be positive in benign lesions.

Overall Performance

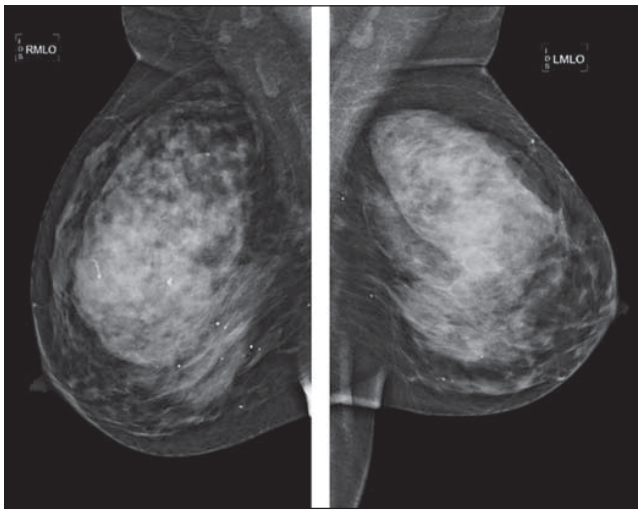
Table 3 provides a summary of the overall impact of breast-specific gamma imaging and ultrasound when these studies are discordant from the mammogram. Breast-specific gamma imaging indicated a change in management for a greater number of patients (156 vs 113) and was typically more effective than ultrasound overall with marked improvement in terms of specificity and positive predictive value.

Figure 2 is an example case of an asymptomatic patient with dense breasts. Bilateral breast ultrasound revealed bilateral areas of possible abnormality. Breast-specific gamma imaging was performed to determine which abnormalities should be biopsied. Breast-specific gamma imaging revealed no abnormalities. Biopsy of lesions were negative; thus, breast-specific gamma imaging was true-negative.

TABLE 3: Statistical Performance of Ultrasound and Breast-Specific Gamma Imaging When Discordant From Mammography

Performance Parameter	Ultrasound (*n* = 113 Patients)	Breast-Specific Gamma Imaging (*n* = 156 Patients)
Sensitivity	70 (50–85)	80 (64–90)
Specificity	47 (36–58)	76 (67–83)
Positive predictive value	32 (22–45)	53 (40–66)
Negative predictive value	81 (67–91)	92 (84–96)

Note—Data are percentage (95% CI).



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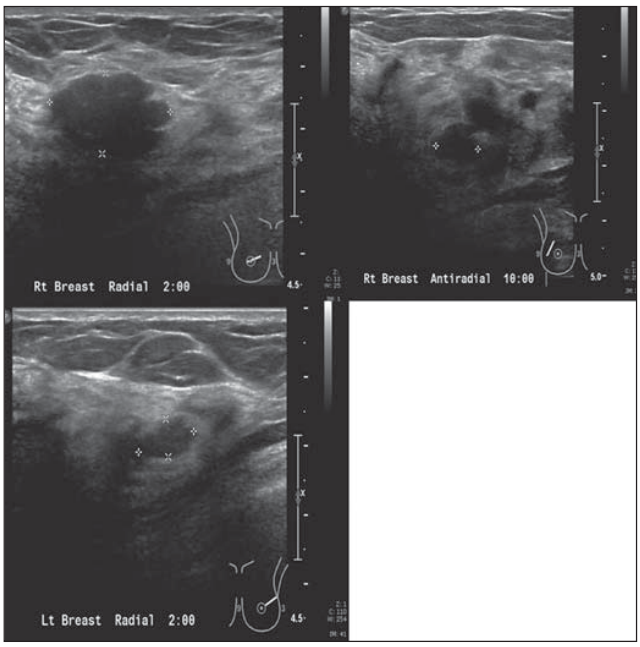

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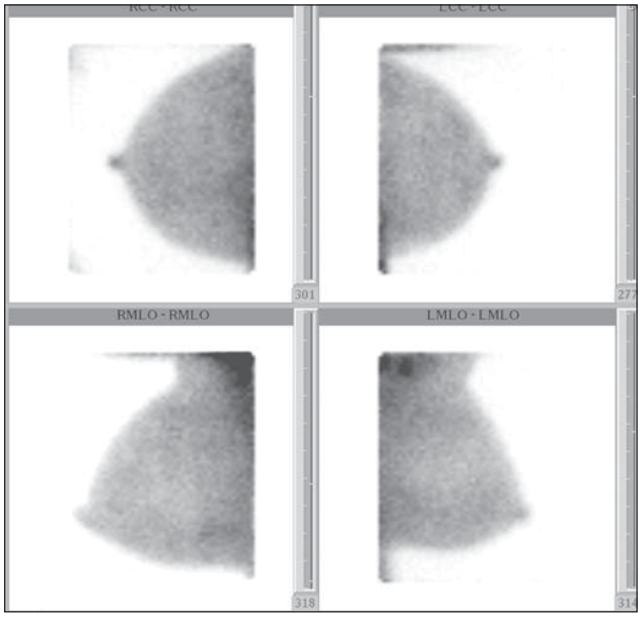

C

Fig. 2—53-year-old woman with difficult to manage clinical case (i.e., asymptomatic with dense breasts). **A–C,** Images are from mammogram (**A**), ultrasound (**B**), and breast-specific gamma imaging (**C**). RMLO = right mediolateral oblique, LMLO = left mediolateral oblique.

Discussion

The role of adjunctive imaging for breast diagnostic patients is to improve management when prior imaging studies have failed to provide conclusive confident results. For the purposes of quantifying the impact on management, if the findings of an adjunctive imaging study are concordant with the mammogram or if the adjunctive study results in a BI-RADS category 0 result or equivalent, then the study has resulted in no net change to management. However, if the adjunctive study is discordant, then it indicates that a change in management should be considered.

For patients with a negative mammogram and remaining diagnostic concern, only a positive finding from the adjunctive procedures indicates a change in management. In this group of patients, breast-specific gamma imaging and ultrasound were positive in 29 and 27 patients, respectively. Breast-specific gamma imaging was slightly more likely to be positive

in patients with malignant or high-risk lesions than ultrasound (15 vs 11) and slightly less likely to be positive in benign lesions (14 vs 16), although the improvements were not statistically significant ($p = 0.69$). The resulting positive predictive values for breast-specific gamma imaging and ultrasound were 52% and 41%, respectively ($p = 0.69$).

In patients with a positive finding on mammography, a negative finding by adjunctive imaging indicates a change in management. Breast-specific gamma imaging and ultrasound were negative in 21 and 15 patients, respectively. Ultrasound was less likely to be negative in malignant lesions than breast-specific gamma imaging (six vs eight), but breast-specific gamma imaging was more likely to be negative in benign lesions (13 vs nine); these differences were not statistically significant ($p = 1.0$). Because the need for biopsy has already been indicated by mammography, a negative adjunctive imaging procedure may contribute only by obviating biopsy. To maintain the standard of care, the false-negative rate of the imaging procedure must be equal to or greater than that provided by biopsy procedures (~ 3%) [9]. The false-negative rate for ultrasound and breast-specific gamma imaging was 6% and 8%, respectively, indicating that neither procedure had adequate performance to obviate biopsy when indicated by mammography. There may still be a role for these adjunctive imaging procedures in treatment planning, such as determining the extent of the primary lesion and detecting additional disease occult by mammography, but these roles are beyond the scope of this work.

Adjunctive imaging procedures play a greater role for patients who have a BI-RADS category 0 finding on mammography because the management pathway has not been defined. Discordant findings may be positive, indicating the need for biopsy, or negative, indicating either a return to screening or follow-up imaging at a later date. Breast-specific gamma imaging provided a change in management in a larger number of patients (109/119 [92%]) compared with ultrasound (71/119 [40%]). For patients with positive findings, breast-specific gamma imaging had a positive predictive value of 50% (17/34) compared with 26% (10/38) for ultrasound, which was a statistically significant improvement over ultrasound ($p < 0.0003$). Breast-specific gamma imaging also performed better than ultrasound in terms of false-negative rate (0% vs 9%; $p < 0.000001$) and it provided better accuracy than ultrasound (84% vs 56%).

As with all studies, there are some limitations to the data provided. First, this is a retrospective analysis without a control group. In addition, of the 2004 patients, 1042 were included in the overall statistical analysis; pathologic analysis was available for 642 patients, whereas 400 patients had negative follow-up imaging studies at a minimum of 6 months after enrollment. This length of follow-up provides limited evidence regarding the lack of malignant process; however, it should be noted that, of the 329 patients included in the comparison with ultrasound, 283 (86%) had pathologic confirmation of diagnosis. Finally, in nearly all cases, breast-specific gamma imaging was recommended after mammography and ultrasound failed to provide a confident diagnosis; thus, there is a selection bias toward patients with difficult to interpret or discordant mammographic and sonographic studies.

MRI was not evaluated in this study because most of the patients were not eligible for MRI because of insurance-related issues, personal choice, acute claustrophobia, or physical issues, such as ferromagnetic implants, pacemakers, excessive body habitus or weight exceeding the table limit, and breasts too large for the coil. In addition, MRI is not recommended in the workup of indeterminate lesions according to the 2005 guidelines established by the American Cancer Society.

In summary, for patients who had adjunctive imaging procedures with results discordant from those for mammography, breast-specific gamma imaging provided higher accuracy than ultrasound (77% vs 53%), and the group of patients with BI-RADS category 0 mammograms received the greatest benefit from the use of breast-specific gamma imaging. Pathology reports obtained from needle biopsy show the largest differences in detection between the two modalities are atypical ductal hyperplasia (breast-specific gamma imaging was positive in six cases and ultrasound was positive in four cases) and ductal carcinoma in situ (breast-specific gamma imaging was positive in 20 cases and ultrasound was positive in 13 cases).

The primary advantage of ultrasound is that it does not involve exposure to ionizing radiation. For a breast-specific gamma imaging examination, the patient undergoes an IV injection of ^{99m}Tc-sestamibi, a radiopharmaceutical common to nuclear medicine procedures. According to the U.S. Food and Drug Administration drug data sheet for sestamibi and all published literature to date, the recommended dose for breast imaging is 740–1110 MBq. A 740-MBq injection of sestamibi exposes the patient to a whole body effective dose of approximately 6 mSv [10]. This dose is comparable with or lower than that of other diagnostic imaging procedures, and the radiation dose to the breast tissue is lower than that for standard mammography [11]. According to the National Institutes of Health [12], an exposure of 6 mSv increases the lifetime risk of fatal cancer of less than one-tenth of a percent, from 25% to 25.024%. As with all medical procedures, the risks of performing the procedure must be considered along with the benefits. In this population of 329 patients, when the adjunctive imaging study results were discordant with those of mammography, breast-specific gamma imaging detected eight more malignant lesions than ultrasound. As a result, 2% of patients experienced a benefit from breast-specific gamma imaging; therefore, the benefit-to-risk ratio is 83:1.

In addition, it should be noted that the existing dose recommendation was established in the 1990s using the general nuclear medicine imaging systems. The newer position-sensitive photomultiplier and cadmium zinc telluride technologies used in the breast-optimized cameras have nearly identical photon sensitivity that is more than 3.5 times greater than the older systems [15, 16]. With this improvement, these advanced technologies should be capable of producing adequate clinical images using an injected dose of 148–296 MBq, resulting in whole-body radiation dose of 1.2–2.5 mSv. Several prospective studies are under way to determine the clinical impact of reducing the dose; however, using a dose of less than 740 MBq at this time is an off-label use of sestamibi without clinical literature to show comparable efficacy when using the lower dose.

In conclusion, breast-specific gamma imaging significantly contributed to the detection of malignant or high-risk lesions in patients with negative or indeterminate mammographic findings and it provided improved management of patients with indeterminate mammograms when compared with ultrasound. However, neither breast-specific gamma imaging nor ultrasound should be used to obviate biopsy in patients with suspicious findings in mammography. In addition, although breast-specific gamma imaging involves radiation exposure to the patient, the benefit of using breast-specific gamma imaging outweighs the risks by a factor of 82:1. Breast-specific gamma imaging is a useful diagnostic modality to augment mam-

mography in the management of patients with difficult to diagnose breast tissue and in cases where unresolved clinical concern remains after mammography.

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ORIGINAL ARTICLE

Usefulness of breast-specific gamma imaging as an adjunct modality in breast cancer patients with dense breast: a comparative study with MRI

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Abstract
Objective The aim of this study was to evaluate the adjunctive benefits of breast-specific gamma imaging (BSGI) versus magnetic resonance imaging (MRI) in breast cancer patients with dense breasts.
Methods This study included a total of 66 patients (44.1 ± 8.2 years) with dense breasts (breast density >50%) and already biopsy-confirmed breast cancer. All of the patients underwent BSGI and MRI as part of an adjunct modality before the initial therapy. Of 66 patients, the 97 undetermined breast lesions were newly detected and correlated with the biopsy results.
Results Twenty-six of the 97 breast lesions proved to be malignant tumors (invasive ductal cancer, $n = 16$; ductal carcinoma in situ, $n = 6$; mixed or other malignancies, $n = 4$); the remaining 71 lesions were diagnosed as benign tumors. The sensitivity and specificity of BSGI were 88.8% (confidence interval (CI), 69.8–97.6%) and 90.1% (CI, 80.7–95.9%), respectively, while the sensitivity and specificity of MRI were 92.3% (CI, 74.9–99.1%) and 39.4% (CI, 28.0–51.7%), respectively ($p < 0.0001$). MRI detected 43 false-positive breast lesions, 37 (86.0%) of which were correctly diagnosed as benign lesions using BSGI. In 12 malignant lesions <1 cm, the sensitivities of BSGI and MR imaging were 83.3% (CI, 51.6–97.9%) and 91.7% (CI, 61.5–99.8%), respectively.
Conclusion BSGI showed an equivocal sensitivity and a high specificity compared to MRI in the diagnosis of breast lesions. In addition, BSGI had a good sensitivity in discriminating breast cancers ≤1 cm. The results of this study suggest that BSGI could play a crucial role as an adjunctive imaging modality which can be used to evaluate breast cancer patients with dense breasts.

Keywords Breast cancer · Breast-specific gamma imaging · MRI · Dense breast · Tumor size

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Introduction

Breast cancer is one of the most common cancers in women and the incidence has increased over the past several decades [1]. Newly developed diagnostic methods and advanced therapies have improved the survival rate of patients with breast cancer and have increased the early detection rate of breast cancer. Mammography, which is based on an anatomical approach, is currently the standard screening modality for breast cancer. The sensitivity of mammography has been reported to be 78–85%, but the sensitivity is decreased to 42–68% in women with dense breasts [2, 3]. Thus, the ability of mammography to discriminate between breast lesions depends on the difference in density between lesions and normal breast tissues.

Magnetic resonance imaging (MRI) is an effective adjunct diagnostic tool in breast cancer patients, which can identify additional breast lesions and evaluate the extent of breast cancer using the anatomical and physiological nature of tumors. MRI is important because multifocal and multicentric lesions are common (49.1–63% of patients) [4, 5]. Although MRI has a higher sensitivity than mammography, the benefit of MRI is diminished by its low specificity. It

has been reported that MRI has a sensitivity of 85.7–99% in detecting breast cancer, but a specificity of 37–90.9% [6–8]. Additionally, only 24.8% of the suspected breast lesions which were newly detected by MRI were subsequently proved to be true-positive after biopsy [9].

Since 1994, ^{99m}Tc-sestamibi scintimammography (SM) utilizing a general purpose gamma camera with a high field of view has been used to evaluate breast cancer lesions [10]. SM discriminates between breast cancer and normal breast tissue based on the difference in radiotracer uptake. Breast cancer usually shows a higher uptake than normal breast tissue due to the increased vascularity and activity of mitochondria within the cells. The sensitivity and specificity of SM have been reported to be 84 and 86%, respectively [11]. In contrast to mammography, the sensitivity of SM is not affected by the density of breast tissue or structural distortions, such as augmentation or scars [12–14]. However, the sensitivity of SM for lesions <1 cm is low, with a yield of 35–60% [15, 16]. For this reason, breast-specific gamma imaging (BSGI) with a small field of view and a high resolution was developed, which yielded improved results in detecting lesions <1 cm [17, 18].

The purpose of this study was to evaluate the adjunctive benefits of BSGI compared to MRI in discriminating between breast lesions in breast cancer patients with dense breasts.

Materials and methods

Patients

Between March 2009 and March 2011, a total of 130 women with newly biopsy-confirmed breast cancer underwent BSGI and MRI as part of an adjunct modality to evaluate multifocality and multiplicity before the initial therapy. All of the patients studied adjunct modalities due to dense breast (breast density >50%) in whom conventional mammography using a senograph DS (GE Medical Systems, Milwaukee, WI, USA) was inadequately sensitive. Of 130 breast cancer patients, 66 patients (44.1 ± 8.2 years) with 97 undetermined breast lesions were enrolled in our study. All of the 97 undetermined breast lesions were newly detected on the adjunct modalities and diagnosed as malignant or benign lesions based on additional biopsy-confirmed pathologic evaluation. Already confirmed 66 primary breast cancers were excluded to evaluate the additional usefulness of BSGI in dense breast. The medical records were retrospectively reviewed and all results and data were obtained. Our institutional review board approved this retrospective study.

Breast-specific gamma imaging and image analysis

Patients were administered 925–1,110 MBq of ^{99m}Tc-sestamibi through the antecubital vein contralateral to the breast lesion. BSGI was performed 10 min after injection of the radioisotope. The patients were seated for the procedure, and craniocaudal and mediolateral oblique images were obtained of the breasts bilaterally using a high-resolution breast-specific gamma camera (6800 Gamma Camera; Dilon Technologies, Newport News, VA, USA). The acquisition time for each image was approximately 5 min and >100,000 counts per image were defined as the minimal range.

The lesions detected by BSGI were classified as positive and negative according to visual interpretation. Lesions lacking focal uptake and those with diffuse heterogeneous or minimal patchy uptake were interpreted as negative, while those which showed scattered patchy uptake with partly focal uptake or any other focal uptake lesions were interpreted as positive, as described in a previous study [17].

MRI and image analysis

MRI was performed with the patient in the prone position, using a 3.0 Tesla (T) scanner (Achieva; Philips Medical Systems, Best, The Netherlands) using a 7-channel dedicated breast coil system. MRI was performed using the following procedure at supine position. An axial, fat-suppressed, fast-echo T_2-weighted image was obtained first, and then axial DWI with single-shot echo planar imaging (EPI) was performed. Dynamic pre-contrast-enhanced T1-weighted images in the axial plane were obtained using a 3-dimensional radiofrequency spoiled gradient echo sequence with a repetition time of 4.7 ms, an echo time of 2.3 ms, a flip angle of 10° and a field of view of 28–36 cm was acquired (150 slices with a thickness <2.0 mm and a matrix of ~320 × 320). After acquisition of native images, 0.1 ml/kg body weight of gadopentetate-dimeglumine (Gd-DTPA, Magnevist; Schering, Berlin, Germany) was administered as a bolus at a velocity of 2 ml/s, followed by 10 cc of saline. After a 32-s delay, all 7 cycles with a 77-s interval were acquired. The maximum intensity projection and subtraction images were obtained using post-processing after imaging studies.

The morphologic and kinetic analyses for breast lesions on MRI were interpreted according to the BI-RADS classification system, which was discussed in a previous study [7]. Briefly, breast lesions with scores of 1, 2 or 3 were defined as negative, while those with scores of 4 or 5 were classified as positive. The longest diameter of breast lesion was recorded on MRI**.** An experienced radiologist resolved the inter-examiner discordance by consensus. The lesions which were detected on the BSGI or MRI were considered to be the same lesion when they were located in the same

quadrant or distance from the nipple as mentioned on the previous study [17].

Statistical analysis

BSGI and MRI were compared in terms of per-lesion sensitivity, specificity, and the 95% exact confidence interval (CI). Significant differences between the individual parameters were examined using the McNemar test for a correlated proportion and the alpha value was defined as 0.05. The estimated differences in sensitivity and specificity between the individual parameters were examined using corresponding 95% CI and p values. Tumor sizes are presented as the mean ± standard deviation and analyzed using the independent t test. Statistical analysis was carried out using Analyse-It (v2.22 software add-in for Microsoft Excel; Analyse-it Software, Ltd, Leeds, UK).

Results

Malignant and benign lesions

Of the 97 undetermined breast lesions, 26 lesions proved to be malignant tumors and the remaining 71 lesions were diagnosed as benign tumors based on the biopsy-confirmed pathologic evaluation (Table 1). The 4 mixed or other malignancies were as follows: invasive lobular carcinoma ($n = 1$), intraductal carcinoma ($n = 2$) and lobular carcinoma in situ ($n = 1$). The 4 other benign lesions were as follows; periductal mastitis ($n = 2$), tubular adenoma with intraductal papilloma ($n = 1$) and atypical ductal hyperplasia ($n = 1$). The sizes of malignant and benign breast lesions were 12.7 ± 6.7 and 8.7 ± 5.2 mm, respectively ($p < 0.008$).

Of the 26 malignant breast lesions, 24 patients had additional breast cancers: 22 patients with 1 additional lesion (8 patients with contralateral breast cancer); 2 patients with 2 additional lesions (one patient had cancers of both breasts). BSGI and MRI correctly detected 23 and 24 lesions, respectively. Of the 71 benign lesions, BSGI finding were negative for malignancy in 64 lesions and MRI finding were benign in 28 lesions, respectively (Table 2). The time interval between BSGI and MRI was 1.0 ± 2.3 days. The positive predictive value (PPV) and negative predictive value (NPV) of BSGI was 76.7% (23/30) and 95.5% (64/67), respectively. MRI had a PPV of 35.8% (24/67) and a NPV of 93.3% (28/30). BSGI had significantly different results from MRI (Table 3).

Table 1 Pathology of breast lesions in breast cancer patients with dense breasts

	No. of cases
Malignancy	
Invasive ductal carcinoma	16
Ductal carcinoma in situ	6
Mixed or other malignancies	4
Benign	
Fibroadenoma	24
Fibrocyst	25
Adenosis	7
Fibrosis	4
Intraductal papilloma	7
Other benign lesions	4

False-positive/negative lesions

Of the 71 benign lesions, BSGI demonstrated 7 false-positive lesions with a mean size of 10.4 ± 2.8 mm. Of the false-positive lesions detected by BSGI, only one (a 15-mm intraductal papilloma) was correctly diagnosed by MRI. However, MRI detected 43 false-positive lesions with a mean size of 9.5 ± 5.6 mm (Table 4). Of the 43 false-positive lesions, 37 (86.0%) were correctly diagnosed as no uptake lesions by BSGI (Fig. 1). BSGI findings were false negative in 3 malignant lesions, including a 3.0-mm ductal carcinoma in situ (DCIS), a 20.0-mm DCIS and a 9.7-mm intraductal carcinoma. MRI correctly detected 2 false-negative lesions by BSGI. Two breast cancers, including a 3.0-mm DCIS and a 13.6-mm DCIS, were misdiagnosed by MRI.

Lesion size

The sensitivity and specificity of BSGI and MRI in tumor size are shown in the Table 5. Of the 28 breast lesions >1 cm, the sensitivity and specificity of BSGI were 92.9 and 78.6%, respectively, while the sensitivity and specificity of MRI were 92.9 and 21.4%, respectively (Table 6). The sizes of the malignant and benign breast masses of the 28 breast lesions were 17.4 ± 5.7 and 16.5 ± 7.3 mm, respectively ($p < 0.713$). Of the 69 breast lesions ≤1 cm, the sensitivity and specificity of BSGI were 83.3 and 93.0%, respectively, while the sensitivity and specificity of MRI were 91.7 and 43.9%, respectively (Table 7). The sizes of malignant and benign breast lesions of the 69

Table 2 Sensitivity and specificity of breast-specific gamma imaging and MRI in patients with dense breasts

	Sensitivity (95% CI)	Specificity (95% CI)
BSGI	88.8 (69.8–97.6)	90.1 (80.7–95.9)
MRI	92.3 (74.9–99.1)	39.4 (28.0–51.7)

BSGI breast-specific gamma imaging, *MRI* magnetic resonance imaging

Table 3 Cross-tabulations of breast-specific gamma imaging and MRI in patients with dense breasts

BSGI breast-specific gamma imaging, *MRI* magnetic resonance imaging

Imaging study	BSGI		Estimated difference in sensitivities (95% CI)	Exact McNemar *P* value
	Positive	Negative		
MRI			−0.381 (−0.418 to −0.283)	<0.0001
Positive	28	2		
Negative	39	28		

Table 4 Pathology of BSGI- and MRI-false-positive lesions

Histopathologic diagnosis	No. of cases[a] (%)	
	BSGI	MRI
Fibroadenoma	2/24 (8.3)	13/24 (54.2)
Fibrocyst	1/25 (4.0)	17/25 (68.0)
Adenosis	1/7 (14.3)	5/7 (71.4)
Fibrosis	1/4 (25.0)	1/4 (25.0)
Intraductal papilloma	2/7 (28.6)	4/7 (57.1)
Other benign lesion	0/4 (0)	3/4 (75.0)

BSGI breast-specific gamma imaging, *MRI* magnetic resonance imaging

[a] Data means number of detected lesions/total number of benign lesions

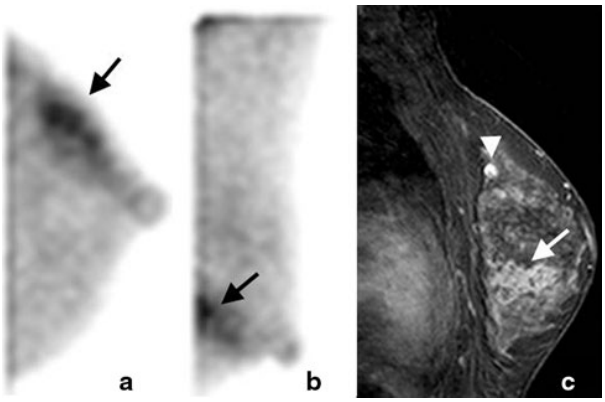

Fig. 1 Breast images of a 50-year-old woman with a known 5.1-cm ductal carcinoma in situ which proved to be a 0.8-cm fibroadenoma in the left breast. **a**, **b** Breast-specific gamma imaging demonstrates a left breast cancer lesion with intense uptake in the outer pericentral area (*arrow*). **c** Contrast-enhanced MRI demonstrates a left breast cancer lesion in the outer pericentral area (*arrow*) and a focal abnormal enhancement lesion in the upper outer quadrant of the left breast (*arrow head*), which was confirmed as a fibroadenoma

breast lesions were 7.3 ± 2.2 and 6.8 ± 1.6 mm, respectively ($p < 0.434$). Of 12 malignancies ≤1 cm, the smallest breast cancer was a 3.0-mm DCIS. MRI alone detected this smallest breast cancer, even though it was incorrectly diagnosed. BSGI and MRI correctly diagnosed the second smallest lesion which was a 5.3-mm IDC. BSGI detected the second smallest lesion of the DCIS which was 8.2 mm.

Discussion

The purpose of our study was to evaluate the adjunctive benefits of BSGI versus MRI in breast cancer patients with dense breasts (breast density >50%). BSGI, with a sensitivity and specificity of 88.8 and 90.1%, respectively, had a lower sensitivity and a higher specificity than MRI in discriminating multifocal or multicentric lesions in breast cancer patients with dense breasts ($p < 0.0001$). This result is similar to those of previous studies comparing BSGI with MRI [17, 19].

In discriminating breast lesions ≤1 cm, the sensitivity and specificity of BSGI were 83.3 and 93.0%, respectively, which were significantly different from MRI ($p < 0.0001$). Due to the small field of view and high resolution, BSGI had good results in breast cancer patients with dense breasts than SM, including breast lesions ≤1 cm. In addition, a 5.3-mm breast cancer lesion was detected by BSGI in our study. This result is consistent with those of previous studies which reported a sensitivity of 88.9% and the detection of 1-mm breast cancer lesions [11, 17, 18]. In breast lesions >1 cm, the sensitivity and specificity of BSGI were significantly different from MRI ($p < 0.0386$). However, BSGI had a tendency for improved sensitivity but decreased specificity compared to the group including all breast lesions.

In our study, MRI had a slightly high sensitivity (92.3%) than BSGI (88.8%), which is similar to the results of previous studies [8, 9, 20]. MRI is an excellent adjunct imaging modality for evaluating the extent of tumor and for detecting additional occult breast lesions, regardless of the location. However, MRI had a higher false-positive rate (60.6%) than BSGI (9.9%), though the NPV of MRI was 93.3%. Of 43 false-positive lesions on MRI, 37 (86.0%) were correctly diagnosed by BSGI (Fig. 2). We can reduce the number of unnecessary biopsies by using BSGI, which is concurrent with previous studies [9, 19, 21]. According to tumor type, MRI demonstrated a lower sensitivity in diagnosing DCIS than IDC (100 vs. 66.7%), which is similar to the results of a previous study [22]. However, BSGI had a sensitivity of 66.7% (4/6) in detecting of DCIS, but a sensitivity of 100% (16/16) in detecting IDC. This result is discordant with those of previous studies which reported to be 91–93.8% in the detection of DCIS [17, 23]. This difference could be attributed to the small-sized

Table 5 Sensitivity and specificity of BSGI and MRI in tumor size

BSGI breast-specific gamma imaging, *MRI* magnetic resonance imaging

[a] Data means number of detected lesions/total number of malignant lesions

Tumor size (cm)	BSGI ($n = 97$)		MRI ($n = 97$)	
	No. detected[a](%)	95% CI	No. detected[a](%)	95% CI
Malignant ≤1	10/12 (83.3)	51.6–97.9	11/12 (91.7)	61.5, 99.8
Malignant >1	13/14 (92.9)	66.1–99.8	13/14 (92.9)	66.1, 99.8
Benign ≤1	53/57 (93.0)	83.0–98.1	25/57 (43.9)	30.7, 57.6
Benign >1	11/14 (78.6)	49.2–95.3	3/14 (21.4)	4.7, 50.8

Table 6 Cross-tabulations of breast-specific gamma imaging and MRI in breast cancer patients with dense breasts (tumor size >1 cm)

Imaging study	BSGI		Estimated difference in sensitivities (95% CI)	Exact McNemar *P* value
	Positive	Negative		
MRI			0.286 (0.014–0.411)	<0.0386
Positive	14	10		
Negative	2	2		

BSGI breast-specific gamma imaging, *MRI* magnetic resonance imaging

Table 7 Cross-tabulations of breast-specific gamma imaging and MRI in breast cancer patients with dense breasts (tumor size ≤1 cm)

Imaging study	BSGI		Estimated difference in sensitivities (95% CI)	Exact McNemar *P* value
	Positive	Negative		
MRI			0.420 (0.320–0.420)	<0.0001
Positive	14	29		
Negative	0	26		

BSGI breast-specific gamma imaging, *MRI* magnetic resonance imaging

enrolled population of our study. Further studies with a larger sample size are needed to confirm our results.

Though we could not determine the significant differences between BSGI and mammography due to disparities in the number of enrolled lesions, BSGI had a tendency for higher sensitivity and lower specificity than mammography in breast cancer patients with dense breasts. Of the 62 breast cancer patients with dense breasts, 48 with 74 breast lesions were evaluated using mammography. Of the 74 breast lesions, 19 were proved to be malignancies and 55 lesions were confirmed as benign lesions. The sensitivity and specificity of mammography was 47.4% (95% CI, 24.4–71.1%) and 94.5% (95% CI, 84.9–98.9%), respectively. This result is similar to those of the previous studies of women with dense breasts [2, 3]. Furthermore, the mammographic finding of the other 14 patients included category 0 which needed additional imaging evaluation. Seven of the 14 patients had additional 7 biopsy-proved malignancies, of which both BSGI and MRI detected 6. Additional studies with a larger sample size are needed to compare the diagnostic values between BSGI and mammography in breast cancer patients with dense breasts.

The results of this study are subject to some limitations. First, this is a retrospective study. Second, this study analyzed a relatively small number of breast cancer patients with dense breasts. This could lead to bias and reduced statistical power. Third, we only enrolled breast cancer patients without the exclusion of the menstruation factor which may have impacted radiotracer uptake. Fourth, it was difficult to correct positional gap induced by the different postures between two adjuvant modalities though we used the same method as noted on the previous study [17]. Prospective studies with a larger patient group at multiple institutions are needed to verify the usefulness of BSGI as an adjunctive imaging modality.

BSGI has several benefits as an adjunct imaging modality and in addition has higher specificity than MRI, in breast lesions. Patients can undergo BSGI in a comfortable sitting position, while MRI can cause claustrophobia by placing them inside an MRI chamber. While BSGI requires several images for analysis, MRI requires hundreds of images for an accurate examination. Unlike MRI, BSGI is not impacted by breast density, breast distortion due to augmentation or scarring, it is unlimited by the use of metal implants [12–14]. The use of ^{99m}Tc-sestamibi did not cause any serious adverse events, but the intravenous administration of gadolinium on MRI can lead to adverse renal events.

BSGI has several limitations as a breast imaging modality. Patients are exposed to the radiation from BSGI study. Approximately 740–1,110 MBq of ^{99m}Tc-sestamibi was recommended and the effective dose equivalent for BSGI study is about 6.29–9.44 mSv [24]. It is about two–three times higher effective dose than that of annul radiation exposure from natural sources. Hence, BSGI might be recommended on patients with suspicious breast lesions or dense breasts in whom conventional mammography was inadequately sensitive. But, radiation dose can be reduced by using lower doses and longer acquisition times. As mentioned previously, BSGI can be affected by menstrual cycle. Therefore, the recommended period is between days 2 and 14 of cycle. BSGI finding can be false positive at the biopsy site. However, it can be reduced if BSGI is studied within the first 3 days after aspiration.

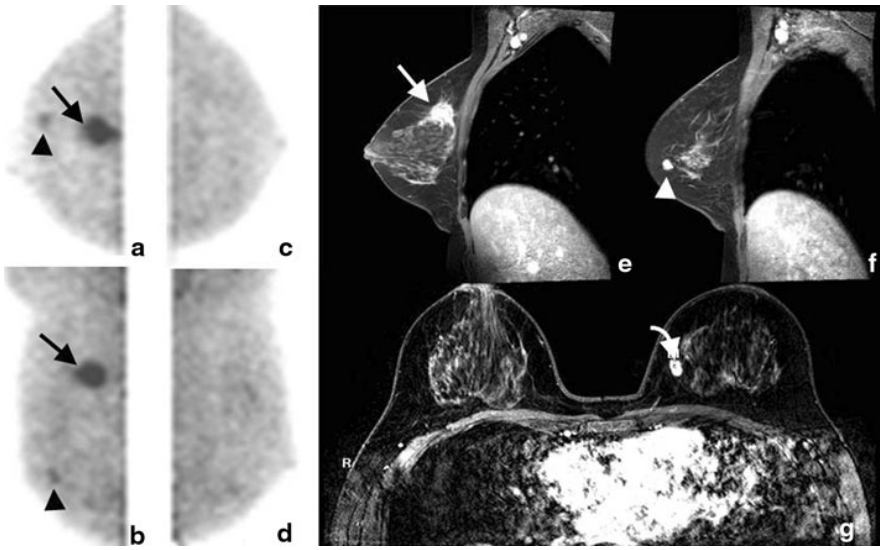

Fig. 2 Breast images of a 52-year-old woman with a known 2.23-cm invasive ductal cancer of the right breast; biopsies confirmed 0.95- and 1.06-cm fibroadenomas in the bilateral breasts, additionally. **a–d** Breast-specific gamma imaging demonstrated a known right breast cancer lesion with intense focal uptake in the upper pericentral area (*arrow*) and mild focal uptake in a lesion in the lower outer quadrant area (*arrow head*) of the right breast which was confirmed to be a 0.95-cm fibroadenoma. **e–g** Contrast-enhanced MRI demonstrated a known right breast cancer lesion in the upper pericentral area (*arrow*) and detected two abnormal enhancement lesions in the lower outer quadrant area (0.95 cm, *arrow heads*) of the right breast and lower inner portion (1.06 cm, *curved arrow*) of the left breast which were confirmed to be fibroadenomas

In summary, BSGI showed a borderline sensitivity but a higher specificity than MRI in diagnosing breast lesions. BSGI had a high sensitivity in discriminating breast cancers $\leq$1 cm. The results of this study suggest that BSGI may play a crucial role in discriminating breast lesions and can be used to evaluate newly diagnosed breast cancer patients with dense breasts.

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