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Breast-specific gamma imaging as an adjunct modality for the diagnosis of invasive breast cancer with correlation to tumour size and grade

[1]R V TADWALKAR, MD, [1]J A RAPELYEA, MD, [1]J TORRENTE, MD, [1]L R RECHTMAN, MA, [2]C B TEAL, MD, [2]A P McSWAIN, MD, [1]C DONNELLY, BS, [1]A B KIDWELL, BS, [1]C M COFFEY, BS and [1]R F BREM, MD

[1]*Breast Imaging and Interventional Center, Department of Radiology, The George Washington University, Washington, DC, USA and* [2]*Department of Surgery, The George Washington University, Medical Faculty Associates, Washington, DC, USA*

Objectives: The purpose of this study was to determine the sensitivity of breast-specific gamma imaging (BSGI) in the detection of invasive breast cancers and to characterise the sensitivity of BSGI based on tumour size and pathological grade.
Methods: 139 women with invasive carcinoma who underwent BSGI were retrospectively reviewed. Patients were injected in the antecubital vein with 20–30 mCi (925–1110 MBq) of technetium-99m sestamibi. Images were obtained with a high-resolution, breast-specific gamma camera (Dilon 6800) and were categorised based on radiotracer uptake as normal, normal with heterogeneous uptake, probably abnormal and abnormal. For a positive examination, the region of the area of increased uptake had to correlate with the laterality and location of the biopsy-proven cancer.
Results: 149 invasive cancers in 139 patients with a mean size of 1.8 cm (0.2–8.5 cm) were included. 146 were identified with BSGI (98.0%). All cancers which measured $\geq$0.7 cm (n=123) as well as all cancers grade 2 or higher (n=102), regardless of tumour size, were identified with BSGI (100%). There were 6 cancers that were pathological grade 1 and measured less than 7 mm, of which 50% (3/6) were identified with BSGI. The overall sensitivity of BSGI for the detection of invasive breast cancer is 98.0%. The sensitivity for subcentimetre cancers is 88.5% (23/26).
Conclusion: BSGI has a high sensitivity for the detection of invasive breast cancer. Our results demonstrate that BSGI detected all invasive breast cancers pathological grade 2 and higher regardless of size and all cancers which measured 7 mm or greater regardless of grade. BSGI can reliably detect invasive breast cancers and is a useful adjunct imaging modality for the diagnosis of breast cancer.

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Mammography has remained the modality of choice for breast cancer screening. Nevertheless, it is an imperfect examination with a sensitivity of 78–85% that declines to 68% in women with dense breasts [1–6]. The limitations of mammography have resulted in the development of adjunct imaging modalities to improve breast cancer detection. Most frequently, ultrasound is used in conjunction with mammography as an adjunct imaging modality for breast cancer diagnosis, particularly in women with dense breasts [2].

Mammography and ultrasound are both anatomical approaches for the diagnosis of breast cancer. Nuclear medicine techniques that utilise physiological properties of tumours are increasingly being used. A meta-analysis of scintimammographic studies using a traditional, general purpose gamma camera demonstrated an average sensitivity of 84% for breast cancer detection, although many of the cancers included in these studies were palpable and larger [7]. However, scintimammography with a general purpose gamma camera is limited in the detection of non-palpable cancers and cancers less than 1 cm in size because of intrinsic resolution limitations [8–11]. Another limitation is the inability of a general purpose gamma camera to image in positions comparable to those obtained with mammography, limiting the ability to correlate between these two modalities.

To overcome the limitations of a traditional gamma camera for the detection of breast cancer, a high-resolution, small-field-of-view gamma camera was developed that allows for the reliable detection of cancers smaller than 1 cm [12]. This technique is referred to as breast-specific gamma imaging (BSGI). Studies with BSGI have demonstrated reliable detection of cancers, both invasive and ductal carcinoma *in situ* (DCIS), as small as 1 mm [13]. Furthermore, the BSGI camera allows for imaging in positions comparable to mammography, which allows for more direct correlation of mammographic imaging and BSGI [14].

An early study using prototype BSGI cameras reported an improvement in the sensitivity for detecting breast cancer when compared with a traditional gamma camera

Address correspondence to: Dr Rachel Brem, Director, Breast Imaging and Interventional Center, The George Washington University, 2150 Pennsylvania Avenue, NW, Washington, DC 20037, USA. E-mail: rbrem@mfa.gwu.edu

[15]. One study of high-risk women with normal clinical breast examination and a BIRADS 1 or 2 mammogram demonstrated that BSGI was able to locate occult carcinomas in 13.5% of patients [16]. A recent report demonstrated that BSGI has a sensitivity of 96.4% for invasive carcinoma and 90.9% in DCIS [13, 17].

The purpose of this study was to investigate the sensitivity of BSGI for invasive breast cancers in the largest reported series to date and to correlate BSGI sensitivity based on tumour pathological size and grade.

Materials and methods

Data collection and statistical analysis

From November 2004 to June 2007, 139 consecutive women with biopsy-proven invasive carcinoma who underwent BSGI were retrospectively reviewed. The mean patient age was 52.8 years (range 29–83 years, standard deviation (SD) 11.8 years, median 51 years). Indications for BSGI examination included evaluation for additional lesions in women with biopsy-proven cancer, indeterminate palpable breast findings during mammographic or physical examination, and women defined as high risk by the Breast Cancer Risk Assessment Profile [18].

The sensitivity of BSGI in detecting invasive breast cancer was calculated (Microsoft Excel, 2003, Redmond, WA; Online Clinical Calculator, 2007, Division of General Internal Medicine, Medical College of Wisconsin, Milwaukee, WA; available at: http://www.intmed.mcw.edu/clincalc/bayes.html). Tumour size, as determined by pathology, and the Scarff–Bloom–Richardson three-point grading system for tumour grade were noted and correlated to BSGI findings.

Breast-specific gamma imaging

A high-resolution, small-field-of-view breast-specific gamma camera (Dilon 6800; Dilon Technologies, Newport News, VA) was used (Figure 1). Patients were injected intravenously with 20–30 mCi (925–1110 MBq) of technetium-99m sestamibi (Cardinal Health, Charlotte, NC) in the antecubital vein. Injection was performed in the contralateral arm for patients with a suspicious breast finding prior to the BSGI examination. This was done in an effort to lessen the uncertainty of increased axillary radiotracer uptake secondary to extravasation of radiotracer during the injection, even though a recent report suggested the ability to differentiate metastatic nodes from nodes with increased radiotracer uptake due to extravasation [19]. Pedal vein injection was not performed because of strong patient preference. Imaging began immediately after injection of the radiotracer. Mediolateral (MLO) and craniocaudal (CC) views were obtained at 7–10 min per image with the patient seated for a minimum of 100 000 counts.

Additional views were obtained as deemed necessary for clinical evaluation by the interpreting radiologist. Studies were interpreted by one of two breast imagers with at least 7 years' experience in interpretation of BSGI. The radiologists were blind to pathology results and

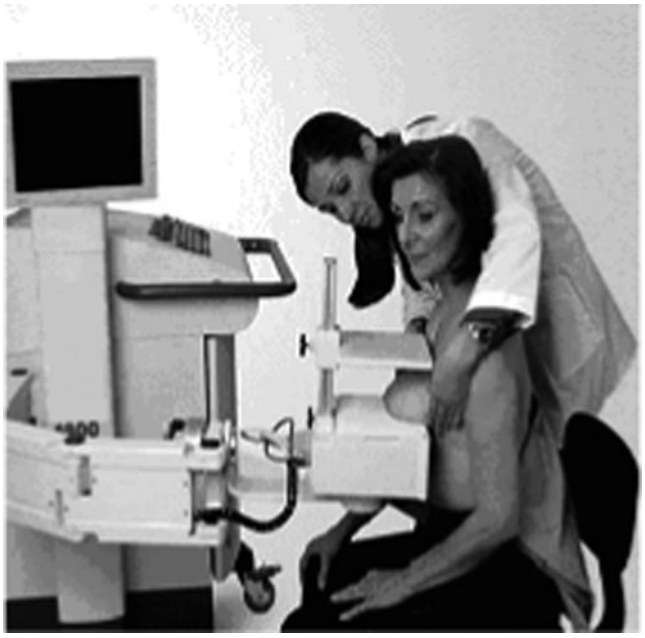

Figure 1. Breast-specific gamma imaging camera (Dilon 6800; Dilon Technologies, Newport News, VA).

categorised the studies based on radiotracer uptake as normal (no increased radiotracer uptake), normal with heterogeneous uptake (scattered uptake without focal increased radiotracer uptake), probably abnormal (heterogeneous uptake with one or more areas of more focal radiotracer uptake) and abnormal (definitive focus of increased radiotracer uptake). For analysis, the results were grouped into two categories: negative (normal and normal with heterogeneous uptake) and positive (probably abnormal and abnormal). The laterality and quadrant of the focal area of increased radiotracer uptake were noted and compared with the laterality and location of the biopsy-proven invasive cancer. If the cancer was in the same quadrant of the breast as well as in the same area of the breast from the nipple (anterior, mid or posterior), the findings were considered concordant. If the pathology report did not indicate the quadrant of the breast but the laterality was consistent, the BSGI and pathological findings were considered concordant. For this study, if the BSGI was performed as part of the patient's clinical evaluation, the BSGI report in the patient's medical record was used and the studies were not reinterpreted. Patients who met the criteria for entry but were part of other clinical trials and thus did not have a BSGI report in their record had their images reinterpreted by one of the two radiologists (R.F.B., J.A.R.) with the radiologists unaware of the pathological findings.

This study was approved by the Institutional Review Board and was in compliance with the Health Insurance Portability and Accountability Act.

Results

There were 149 invasive cancers identified in 139 patients. There was a single cancer in 128 patients, 2 cancers in 7 patients and multifocal cancer in 4 patients.

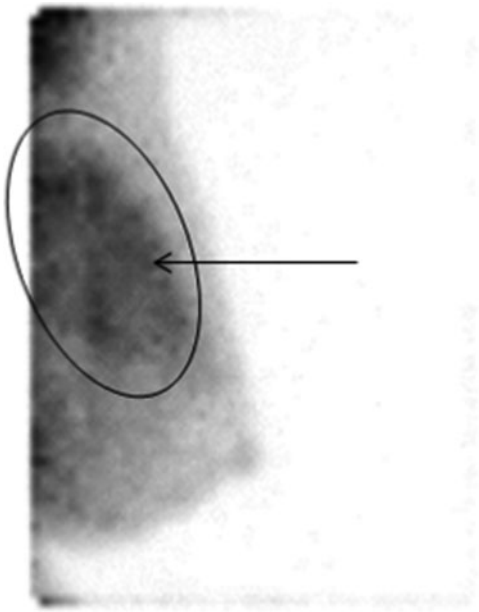

Figure 2. A 32-year-old woman with diffuse infiltrating ductal carcinoma of the left breast visualised clearly by breast-specific gamma imaging in the medial–lateral view: 2.5 cm; grade 2 of 3.

For each of these multifocal cases, only lesions with associated tumour sizes, as determined pathologically, were included. There were 126 infiltrating ductal carcinomas (84.6%) (Figure 2), 9 infiltrating lobular carcinomas (6.0%), 7 mixed infiltrating ductal and infiltrating lobular carcinomas (4.7%) (Figure 3), 2 mucinous carcinomas (1.3%), 2 tubulolobular carcinomas (1.3%), 1 infiltrating tubular carcinoma (0.7%), 1 infiltrating papillary carcinoma (0.7%), and 1 medullary carcinoma (0.7%) (Table 1). The four patients with multifocal cancers all had infiltrating ductal carcinomas (Figure 4).

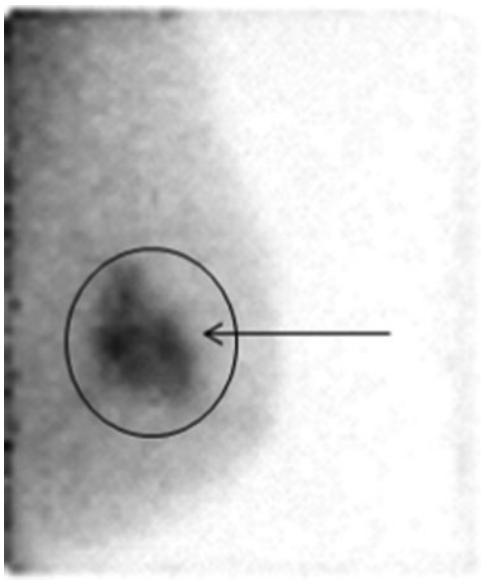

Figure 3. Medial–lateral oblique view showing infiltrating lobular carcinoma in the upper right breast of a 54-year-old woman: 6 cm; grade 2 of 3.

Table 1. Percentage and number of invasive cancers characterised by pathological subtype

Type	Number of cases	Percentage
Infiltrating ductal carcinoma	126	84.6%
Infiltrating lobular carcinoma	9	6.0%
Mixed infiltrating ductal and infiltrating lobular carcinoma	7	4.7%
Mucinous carcinoma	2	1.3%
Tubulolobular carcinoma	2	1.3%
Infiltrating tubular carcinoma	1	0.7%
Infiltrating papillary carcinoma	1	0.7%
Medullary carcinoma	1	0.7%

Pathological cancer sizes were available for 126 out of the 149 cancers. The mean cancer size was 1.80 cm (range 0.2–8.5 cm, SD 1.33 cm, median 1.45 cm). Individual tumour grades using the Scarff–Bloom–Richardson grading system were available for 120 out of 149 total cancers. The mean tumour grade was 2.28 (range 1–3, SD 0.71, median 2).

Of the 149 lesions, 146 were identified with BSGI for a sensitivity of 98.0% for BSGI detection of invasive breast cancer.

3 of 149 cancers (2%) were not identified with BSGI. All three were grade 1 infiltrating duct carcinomas, and all were 0.7 cm or less (0.7, 0.7 and 0.4 cm). All cancers that were grade 2 or 3, regardless of size, and all cancers that were larger than 0.7 cm, regardless of grade, were identified by BSGI.

The sensitivity of BSGI for invasive ductal carcinoma was 97.6% (123/126) with 100% sensitivity for the remaining pathological subtypes of cancer (Table 2).

4 of 149 (2.7%) infiltrating ductal carcinomas were multifocal. BSGI correctly identified all cases of multifocal breast cancer.

The sensitivity for cancers greater than 0.7 cm was 100% (105/105), whereas cancers less than or equal to

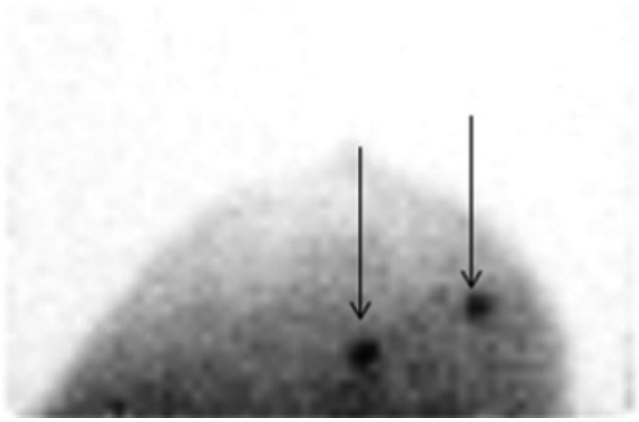

Figure 4. Craniocaudal view of a 48-year-old woman with multifocal infiltrating ductal carcinoma of the left breast seen as separate areas of increased radiotracer uptake: 1.2 and 1.0 cm; grade 3 of 3.

Table 2. Sensitivity of breast-specific gamma imaging by pathological subtype of cancer

Type	Percentage
Infiltrating ductal carcinoma	97.6%
Infiltrating lobular carcinoma	100%
Mixed infiltrating ductal and infiltrating lobular carcinoma	100%
Mucinous carcinoma	100%
Tubulolobular carcinoma	100%
Infiltrating tubular carcinoma	100%
Infiltrating papillary carcinoma	100%
Medullary carcinoma	100%

0.7 cm demonstrated a sensitivity of 88.5% (21/24) (Table 3). Cancers which were pathologically grade 2 and 3 had a sensitivity of 100% (102/102) regardless of cancer size, whereas grade 1 cancers had a sensitivity of 83.3% (15/18) (Table 4). Of the 6 cancers that were grade 1 and less than or equal to 7 mm, BSGI demonstrated 3 of the 6, to give a sensitivity of 50%.

Discussion

The use of physiological imaging as an adjunct imaging modality for breast cancer detection can improve breast cancer detection. The purpose of this study was to evaluate the sensitivity of BSGI in the diagnosis of invasive breast cancer and to correlate these findings with pathological cancer size and grade. Our study demonstrates that BSGI has a high sensitivity (98%) for the detection of all invasive breast cancers. Interestingly, BSGI detected invasive cancers with some dependency upon tumour size and grade. All cancers of grade 2 or 3 were detected, regardless of size and as small as 2 mm. Furthermore, all cancers, whether they were grade 1, 2 or 3, were detected with BSGI if they were 7 mm or larger. The only cancers not detected were 3/6 grade 1 cancers that were 7 mm or less. The reason these three grade 1, subcentimetre cancers were not identified with BSGI is not known. However, it is likely that the biology of these cancers resulted in their non-visualisation with BSGI. It is of note that the three cancers which were not detected with BSGI were all low-grade, small cancers; cancers which are probably of the least clinical significance. As BSGI is increasingly being integrated in clinical practice, it is noteworthy that all of those cancers that are likely to be of the greatest clinical significance, that is, higher grade cancers, were identified with BSGI.

Table 3. Sensitivity of breast-specific gamma imaging in the detection of invasive cancers by largest pathological size

Size (cm)	Percentage
>7.1	100%
5.1–7.0	100%
3.1–5.0	100%
1.1–3.0	100%
0.81–1.0	100%
0.61–0.8	77.8%
0.41–0.6	100%
0.21–0.4	75%
<0.2	100%

Table 4. Sensitivity of breast-specific gamma imaging in the detection of invasive cancers by tumour grade

Grade	Percentage
3	100%
2	100%
1	83.3%

MRI is used as an adjunct imaging modality for the detection of invasive breast cancer. Kuhl et al [20] have demonstrated that MRI has a sensitivity of 92% for the detection of DCIS. This is comparable to the recent report of the sensitivity of BSGI for the detection of DCIS, which demonstrated a sensitivity of 91% [17]. The similarity in the detection of DCIS with both MRI and BSGI suggests that these two physiological-based approaches are comparable in sensitivity [21]. Similarly, this study demonstrated comparable sensitivity of BSGI to MRI for the diagnosis of invasive breast cancer [22]. It is important to note that MRI is performed without ionising radiation and BSGI uses a low-dose radiotracer that has safely been used in medical imaging for decades with ongoing studies aimed at further decreasing the dose. Nevertheless, there are advantages to imaging with BSGI. Patients imaged with BSGI are comfortably seated as compared with prone in the MRI scanner, and there is no concern with claustrophobic patients with BSGI. Additionally, the BSGI examination generates 4–10 images as compared with 1000 images obtained with breast MRI. Although there has not been a formal study comparing the time for radiologist interpretation of MRI and BSGI examinations, it has been our experience that interpretation of BSGI examinations requires far less time for interpretation than breast MRI examinations. Further, nephrogenic systemic fibrosis is not an issue with BSGI.

Although this study did not address the cost of BSGI, nor was it a comparison with MRI, the cost of a BSGI examination is typically half that of a breast MRI examination. Additional studies investigating the cost-effectiveness of MRI and BSGI are needed to better define and compare BSGI and MRI.

Our study demonstrated that the four multifocal infiltrating ductal carcinomas were correctly identified with BSGI. This concurs with recent reports indicating that BSGI can detect additional foci of occult cancers in women with one known cancer [13, 22, 23].

BSGI was able to diagnose all pathological subtypes of invasive breast cancer with 97.6% sensitivity and all other subtypes of breast cancer with 100% sensitivity. The three cancers not detected by BSGI were all invasive ductal carcinoma. However, this is likely to be the result of the preponderance of this pathological type of invasive cancer both in our study and in clinical practice. The limited number of other pathological subtypes of invasive breast cancer that were not of ductal origin is a limitation of this study, and is undoubtedly the cause for the 100% sensitivity of invasive breast cancer not of ductal origin. Furthermore, a recent report describing the sensitivity of BSGI in the detection of invasive lobular carcinoma involving 28 biopsy-proven cancers reported a 93%, and not 100% sensitivity [24]. Additional larger

studies are needed to more definitively identify the sensitivity of BSGI in the detection of invasive breast cancer that is not of ductal origin.

There are limitations to this study. First, it is a retrospective study. It would be optimal to design and undertake a prospective trial evaluating the sensitivity of BSGI in the diagnosis of invasive breast cancer. However, a retrospective approach to study new modalities for the diagnosis of breast cancer has been used in evaluating other emerging imaging modalities. Prospective trials investigating BSGI are underway and should further our understanding of the use of BSGI as an adjunct imaging modality for the diagnosis of breast cancer. Additionally, indications for study patients' referrals for BSGI were varied and could therefore introduce bias. Nevertheless, this study, which is the largest to date evaluating invasive breast cancer with BSGI, has demonstrated the high sensitivity of BSGI in the diagnosis of all subtypes, sizes and grades of invasive breast cancer and even with its limitations increases our understanding of BSGI in the diagnosis of breast cancer.

Conclusion

Our study demonstrated that BSGI has a very high sensitivity for all sizes and grades of invasive breast cancer. In fact, all breast cancers which were grade 2 or 3 and which measured 8 mm or greater were detected with BSGI and only a subset of invasive breast cancers that were less than 8 mm and grade 1 were not seen with BSGI. Therefore, BSGI is a highly reliable imaging modality for the detection of clinically significant invasive breast cancers.

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