

The Society of Black Academic Surgeons

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.

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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 transcuteaneous 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.

Presented at the 17th annual meeting of the Society of Black Academic Surgeons, April 17–20, 2008, Cleveland, OH.

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Manuscript received May 25, 2008; revised manuscript October 6, 2008

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 vary 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 differ-

ential 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 $\geq 20\%$ – 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 al⁵ 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 al¹⁰ 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 al¹⁷ 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, how-

ever, 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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