# Breast Management in Women with Newly Diagnosed Breast Cancer

Nate L. Jones, MD[a], Shelley L. Galvin, MA[b], Ashley Case, MD[c]
[a]Mountain Area Health Education Center, Department of Obstetrics and Gynecology
[b]Mountain Area Health Education Center, Center for Research
[c]HOPE: A Women's Cancer Center

**Abstract**

**Objectives**: Breast-specific gamma imaging is a functional imaging modality that complements mammography and ultrasound in the detection of breast cancer. We sought to determine how often BSGI identified occult cancer and its impact on surgical management.
**Methods**: An institutional review board approved retrospective review was performed among all patients with newly diagnosed breast cancer in whom BSGI was performed as part of the preoperative work-up. Women underwent intravenous injection of 25-30 mCi of technetium-99m (99mTc) sestamibi and were imaged in mediolateral oblique, craniocaudal, and axillary projections using a high-resolution, small field-of-view gamma camera. Images were classified as positive (focal radiotracer uptake) or negative (no uptake or physiologic distribution) and compared with biopsy and surgical pathology.
**Results**: A total of 105 patients with biopsy-proven breast cancer underwent breast-specific gamma imaging between July 2011 and July 2012. Breast-specific gamma imaging confirmed the presence and location of known cancer in 104 lesions for true positive rate of 99%. One pathology proven lesion was not seen with breast-specific gamma imaging for a false negative rate of 0.7%. 35 patients (33%) had a positive study at a site remote from their known cancer; biopsy proved benign pathology in 12 (34%), and additional occult cancer in 23 (66%). Contralateral breast cancer was confirmed in 6 patients. Breast-specific gamma imaging findings along with additional biopsies and/or imaging changed surgical management in 39 patients (37.1%) resulting in 15 mastectomies, 3 wider excisions or quadrectomy, 11 neoadjuvant chemotherapy, 6 contralateral surgery, and 4 additional lumpectomies.
**Conclusions**: Additional or more extensive malignancy was detected in 22% of newly diagnosed breast cancer patients who underwent pre-operative breast-specific gamma imaging. Surgical management changed in 37%. Breast-specific gamma imaging plays an important role in the surgical and clinical management in women with breast cancer.

**Key Words**: Breast-specific gamma imaging; breast cancer; surgical management

## Introduction

Breast-specific gamma imaging (BSGI) is a functional imaging modality that complements mammography and ultrasound in the detection of breast cancer. While mammography is used universally for screening, the sensitivity ranges from 66-85%[1] and decreases to less than 60% in young women and women with dense breasts.[2-3] Additional imaging modalities including BSGI and magnetic resonance imaging (MRI) have been employed to aid in early diagnosis and help guide management of breast cancer. The goal of management is to provide breast conservation therapy (BCT) when possible while achieving adequate surgical margins and acceptable cosmesis. In conjunction with mammogram, BSGI and MRI provide additional information about tumor characteristics that improve sensitivity and may aid in the preoperative management of newly diagnosed breast cancer.

BSGI is a functional imaging modality, in contrast to mammography and ultrasonography which are anatomic imaging modalities. As such, BSGI relies on the physiologic difference in mitochondrial density between normal tissue and hyperproliferative tissue. An intravenous Tc-Sestamibi radioactive tracer is injected that binds to mitochondria throughout the body. A high-

resolution gamma camera then obtains images of the breast. Neoplastic tissue with greater mitochondrial density and greater tracer uptake is highlighted, while benign tissue appears normal, regardless of breast density.[4-5]

Multiple studies have shown that MRI and BSGI are equally sensitive in detecting breast cancer; however, BSGI appears to have greater specificity.[6-8] Additionally BSGI is more cost effective, may be used in patients with renal failure or claustrophobia, requires fewer images, and produces immediate images that are easily interpreted.[9] As with most new technologies, questions and concerns remain about these potential benefits vis-à-vis costs: expenses and availability of new equipment and radiopharmaceutical tools, and radiotracer dosing and exposure for both patients and technicians.[10]

We sought to determine how often BSGI identified occult cancer in women with newly diagnosed breast cancer and how it impacted their surgical and preoperative management.

## Methods

An institutional review board approved retrospective review was conducted using inpatient and outpatient medical records of all patients with newly diagnosed breast cancer for whom BSGI was performed as part of the preoperative work-up. Women underwent intravenous injection of 25-30 mCi of technetium-99m (99mTc) sestamibi and were imaged in mediolateral oblique, craniocaudal, and axillary projections using a high-resolution, small field-of-view gamma camera. Images were classified as positive (focal radiotracer uptake) or negative (no uptake or physiologic distribution) and compared with biopsy and surgical pathology.

## Results

Of the 271 BSGI scans performed from July 2011 to June 2012, a total of 105 patients already had biopsy-proven new diagnosis of breast cancer and comprised our study sample. The mean age was 59.9 years (range 25-87). Patient medical history and presenting problems are outlined in Table 1. The majority presented with unilateral lesions detected primarily with breast ultrasound.

**Table 1. Patient Characteristics, N = 105**

| **Medical History** | **N (%)** |
|---|---|
| Personal history of breast cancer | 7 (6.7) |
| Personal history of endometrial, uterine or ovarian cancer | 2 (2.0) |
| Any Personal History | 9 (8.7) |
| Family history of breast cancer – 1st degree relative | 19 (18.1) |
| Family history of breast cancer – 2nd degree relative | 21 (20.0) |
| Family history of ovarian cancer – 1st degree relative | 2 (1.9) |
| Family history of ovarian cancer – 2nd degree relative | 4 (3.8) |
| Any Family History | 21 (20.0) |
| Any Personal and Family History | 8 (7.6) |
| **Presenting Problem** | |
| Lesions | |
| Right | 40 (38.1) |
| Left | 65 (61.9) |
| Palpable mass | 25 (23.8) |
| Dense breasts | 16 (15.2) |
| Abnormal mammogram (Birads 4-6) | 22 (20.9) |
| Abnormal US (Birads 4-6) | 86 (82.0) |

Tumor characteristics are presented in Table 2. The mean tumor size was 2.0 cm (range 0.1-9.0 cm). Largest tumor size was used in the event that multiple lesions were present; 7 (6.7%) women had two tumors and 1 (1%) had three. Ductal carcinoma in situ (DCIS), the abnormal cells inside a milk duct in the breast, was not included when calculating tumor size. There were 68 (64.8%) patients with invasive ductal cancer, 10 (9.5%) with invasive lobular, 3 (2.9%) with mixed ductal and lobular, 10 (9.5%) with DCIS, 4 (3.8%) others, and 10 (9.5%) unknown. Slightly more than half of the patients had negative nodes, and tumors were more often estrogen- and progesterone-receptor positive and human epidermal growth factor receptor 2 or HER-2/neu negative.

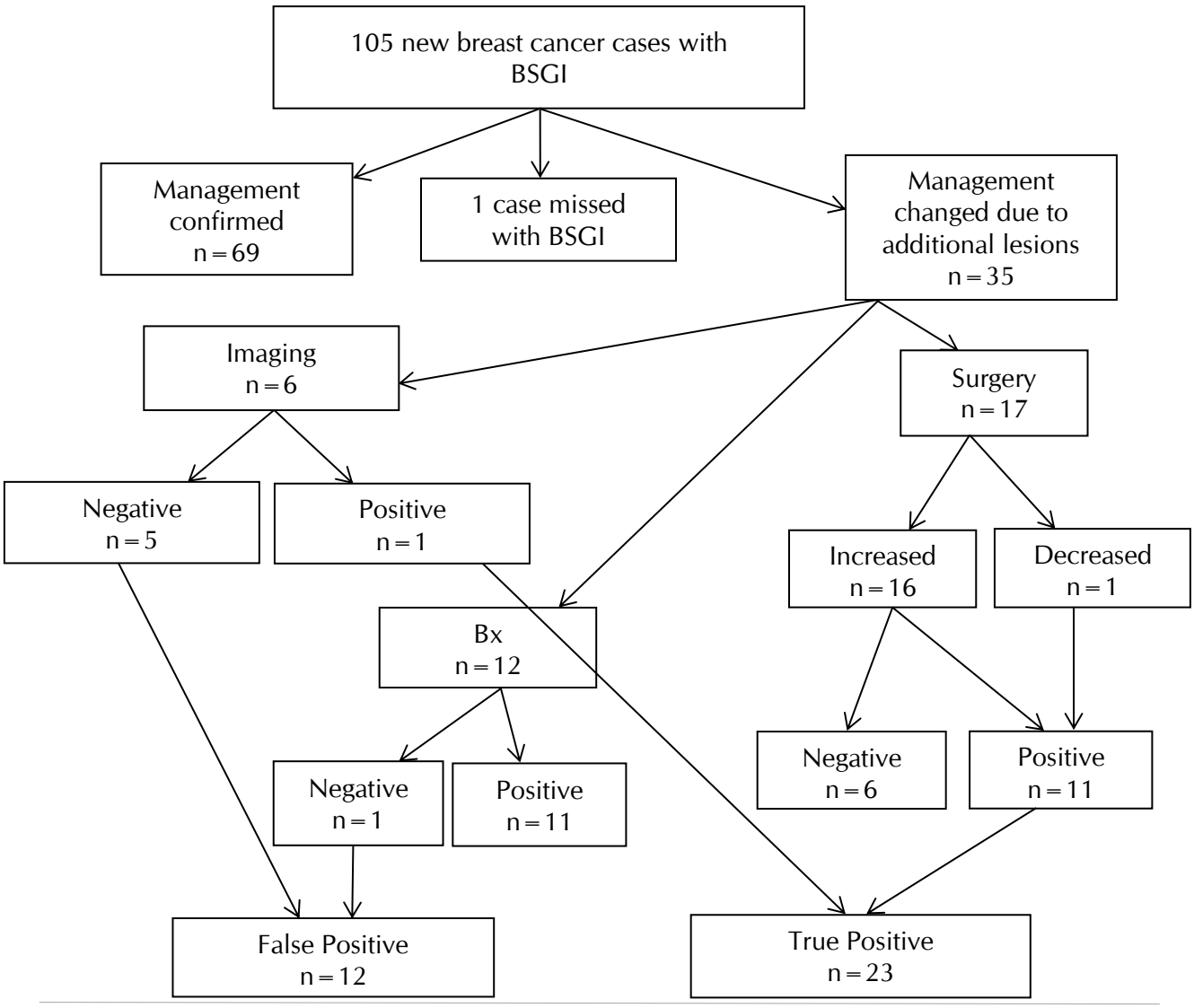
**Table 2. Tumor Characteristics, N = 105**

| Characteristic | N (%) |
|---|---|
| Pathology | |
| Invasive ductal | 68 (64.8) |
| Invasive lobular | 10 (9.5) |
| Ductal carcinoma in situ (DCIS) | 10 (9.5) |
| Mixed | 3 (2.9) |
| Other | 4 (3.8) |
| Unknown | 10 (9.5) |
| Tumor size, cm | |
| < 0.5 | 6 (5.7) |
| 0.5-0.9 | 6 (5.7) |
| 1-1.9 | 50 (47.6) |
| 2-4.9 | 23 (21.9) |
| > 5 | 5 (4.8) |
| Unknown | 15 (14.3) |
| Nodal status | |
| Positive | 41 (39.0) |
| Negative | 43 (41.0) |
| Unknown | 22 (20.0) |
| Estrogen Receptor status | |
| Positive | 78 (74.3) |
| Negative | 20 (19.0) |
| Unknown | 7 (6.7) |
| Progesterone Receptor status | |
| Positive | 65 (61.9) |
| Negative | 33 (31.4) |
| Unknown | 7 (6.7) |
| Human epidermal growth factor receptor 2 | |
| HER-2/neu status | 12 (11.4) |
| Positive | 75 (71.4) |
| Negative | 1 (1.0) |
| Equivocal | 17 (16.2) |
| Unknown | |
| Characteristic | N (%) |
| Lymphovascular Invasion status | |
| Positive | 17 (16.2) |
| Negative | 72 (68.6) |
| Suspicious | 1 (1.0) |
| Unknown | 15 (14.3) |

Of the 105 cases, BSGI identified an additional 35 lesions representing a total of 140 lesions. BSGI correctly confirmed the presence and location of lesions in 99% of known cancer cases (104 of 105). Of the 35 new lesions identified, 23 were eventually confirmed cancer (65.7%). This represents a lesion-specific true positive rate of 91% (127 of 140). BSGI identified 12 new lesions that were ultimately benign representing a false positive rate of 8.5% (12 of 140). One pathology proven lesion was not seen with BSGI for a false negative rate of 0.7% (1 of 140). Contralateral breast cancer was confirmed in 6 patients.

Of the 105 scans performed, BSGI confirmed location of known cancer in 104 patients (see Figure 1). In 11 patients, BSGI suggested greater extent of disease, and follow up imaging and/or biopsies deemed these patients candidates for neoadjuvant chemotherapy rather than surgery. BSGI also identified 35 additional suspicious areas not identified on prior imaging or physical exam. Six patients underwent additional imaging resulting in one positive study that required mastectomy. Twelve patients underwent additional biopsies resulting in 11 additional malignant lesions requiring change to surgical management. Seventeen patients had additional or more extensive surgery performed based on BSGI findings alone, 11 of which were confirmed malignant lesions. In total, additional surgery was performed on 29 patients and additional cancer was found in 23 patients.

**Figure I. BSGI Diagnosis of Lesions, N = 140 and Effect on Management, N = 105**



BSGI findings contributed to change in preoperative management in 46 patients (43%). Based on these findings, BSGI contributed to change in surgical management in 40 patients (38%). The need for more extensive surgery resulted in 16 mastectomies, three wider excisions or quadrectomy, four additional lumpectomies, and six contralateral surgeries. The need for less surgery based on disease burden resulted in 11 patients electing for neoadjuvant chemotherapy. In women with newly diagnosed cancer who underwent BSGI as part of their preoperative evaluation, 23 of 105 (22%) were found to have additional cancer that was not detected by prior imaging or physical exam (see Table 3).

**Table 3. Pathology of Additional Lesions Identified by BSGI, N = 35**

| Pathology | N (%) |
|---|---|
| Invasive ductal | 14 (40.0) |
| Invasive lobular | 4 (11.4) |
| Ductal carcinoma in situ (DCIS) | 2 (5.7) |
| Mixed | 1 (2.9) |
| Lobular carcinoma in situ (LCIS) | 1 (2.9) |
| Other | 1 (2.9) |
| Negative | 12 (34.3) |

## Discussion

While mammography remains the gold standard for breast cancer detection, adjuvant imaging modalities are emerging to address the limitations of mammography in regards to its sensitivity and specificity. Dense breast tissue is especially difficult to evaluate with mammography. In women with dense breasts, studies have shown that ultrasound improves breast cancer detection when used in conjunction with mammography.[11-12] The specificity of ultrasound, however, remains low resulting in unnecessary interventions and added cost to the system. MRI has been shown to have sensitivity ranging from 88-99%,[1-2,13-14] although its specificity is highly variable in the literature ranging from 37-83%.[15-19]

BSGI has been shown to have equal sensitivity to MRI but with improved specificity ranging from 59-71%.[13-14] BSGI is specifically unaffected by dense breast tissue. Few studies have addressed the impact of BSGI on the surgical management of patients with newly diagnosed breast cancer.

We specifically addressed the lesion-specific true positive of BSGI in our study which was 91%, comparable to prior studies addressing patient-specific true positives.[4,6] In 11 patients, BSGI confirmed extensive disease suggested by prior imaging and changed planned management to neoadjuvant therapy rather than surgery. In 35 patients, additional lesions were identified that were not seen on prior imaging which changed pre-operative management for all 35 patients. After additional work-up surgical management was subsequently changed in 29 patients and 23 additional malignant lesions were identified, representing 22% of our patient population. Other studies using BSGI have found new cancer in 9-11% of their patients.[4-6] Those studies also found that 18-22% of patients had a positive BSGI at a site remote from their known cancer, compared to 33% in our study. Finally, their false positive rates of 7% and 10% were comparable to our rate of 8%.

While examined retrospectively on a relatively small sample of women at one site, the inclusion of BSGI with women with newly diagnosed breast cancer was beneficial in our pre-operative management planning. Further study is warranted due to the limitations of generalizability from our study and to conduct formal cost-benefit analyses.

## References


1. Rosenberg RD, Hunt WC, Williamson MR, Gilliland FD, Wiest PW, Kelsey CA, Key CR, Linver MN. Effects of age, breast density, ethnicity, and estrogen replacement therapy on screening mammographic sensitivity and cancer stage at diagnosis: review of 183,134 screening mammograms in Albuquerque, New Mexico. Radiology. 1998 Nov;209(2):511-8. PubMed PMID: 9807581.
2. Morrow M, Freedman G. A clinical oncology perspective on the use of breast MR. Magn Reson Imaging Clin N Am. 2006 Aug;14(3):363-78, vi. Review. PubMed PMID: 17098177.
3. Pisano ED, Gatsonis C, Hendrick E, Yaffe M, Baum JK, Acharyya S, Conant EF, Fajardo LL, Bassett L, D'Orsi C, Jong R, Rebner M; Digital Mammographic Imaging Screening Trial (DMIST) Investigators Group. Diagnostic performance of digital versus film mammography for breast-cancer screening. N Engl J Med. 2005 Oct 27;353(17):1773-83. Epub 2005 Sep 16. Erratum in: N Engl J Med. 2006 Oct 26;355(17):1840. PubMed PMID: 16169887.
4. Killelea BK, Gillego A, Kirstein LJ, Asad J, Shpilko M, Shah A, Feldman S, Boolbol SK. George Peters Award: How does breast-specific gamma imaging affect the management of patients with newly diagnosed breast cancer? Am J Surg. 2009 Oct;198(4):470-4. doi: 10.1016/j.amjsurg.2009.06.016. PubMed PMID: 19800450.
5. Brem RF, Schoonjans JM, Kieper DA, Majewski S, Goodman S, Civelek C. High-resolution scintimammography: a pilot study. J Nucl Med. 2002 Jul;43(7):909-15. PubMed PMID: 12097461.
6. Zhou M, Johnson N, Gruner S, Ecklund GW, Meunier P, Bryn S, Glissmeyer M, Steinbock K. Clinical utility of breast-specific gamma imaging for evaluating disease extent in the newly diagnosed breast cancer patient. Am J Surg. 2009 Feb;197(2):159-63. doi: 10.1016/j.amjsurg.2008.10.002. PubMed PMID: 19185109.
7. Brem RF, Fishman M, Rapelyea JA. Detection of ductal carcinoma in situ with mammography, breast specific gamma imaging, and magnetic resonance imaging: a comparative study. Acad Radiol. 2007 Aug;14(8):945-50. PubMed PMID: 17659240.
8. Brem RF, Ioffe M, Rapelyea JA, Yost KG, Weigert JM, Bertrand ML, Stern LH. Invasive lobular carcinoma: detection with mammography, sonography, MRI, and breast-specific gamma imaging. AJR Am J Roentgenol. 2009 Feb;192(2):379-83. doi: 10.2214/AJR.07.3827. PubMed PMID: 19155397.
9. Jones EA, Phan TD, Blanchard DA, Miley A. Breast-specific gamma-imaging: molecular imaging of the breast using 99mTc-sestamibi and a small-field-of-view gamma-camera. J Nucl Med Technol. 2009 Dec;37(4):201-5. doi: 10.2967/jnmt.109.063537. Epub 2009 Nov 13. PubMed PMID: 19914975.
10. Imaging Technology News [Internet]. Arlington Heights, IL: Scranton Gillette Communications; c2012 [updated 2012 Jul 25; cited 2016 Apr 16]. Pros and cons of molecular breast imaging tools: a comparison of BSGI, MBI and PEM; [about 6 screens]. Available from: http://www.itnonline.com/article/pros-and-cons-molecular-breast-imaging-tools#sthash.x9DjKejS.dpuf.
11. Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. Radiology. 2002 Oct;225(1):165-75. PubMed PMID: 12355001.
12. Berg WA, Blume JD, Cormack JB, Mendelson EB, Lehrer D, Böhm-Vélez M, Pisano ED, Jong RA, Evans WP, Morton MJ, Mahoney MC, Larsen LH, Barr RG, Farria DM, Marques HS, Boparai K; ACRIN 6666 Investigators. Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA. 2008 May 14;299(18):2151-63. doi: 10.1001/jama.299.18.2151. Erratum in: JAMA. 2010 Apr 21;303(15):1482. PubMed PMID: 18477782; PubMed Central PMCID: PMC2718688.

13. Brem RF, Floerke AC, Rapelyea JA, Teal C, Kelly T, Mathur V. Breast-specific gamma imaging as an adjunct imaging modality for the diagnosis of breast cancer. Radiology. 2008 Jun;247(3):651-7. doi: 10.1148/radiol.2473061678. Erratum in: Radiology. 2009 Apr;251(1):308. PubMed PMID: 18487533.
14. Brem RF, Petrovitch I, Rapelyea JA, Young H, Teal C, Kelly T. Breast-specific gamma imaging with 99mTc-Sestamibi and magnetic resonance imaging in the diagnosis of breast cancer--a comparative study. Breast J. 2007 Sep-Oct;13(5):465-9. PubMed PMID: 17760667.
15. Bluemke DA, Gatsonis CA, Chen MH, *et al*. Magnetic resonance imaging of the breast prior to biopsy. *JAMA* 2004;292:2735–42.
16. Drew PJ, Turnbull LW, Chatterjee S, et al. Prospective comparison of standard triple assessment and dynamic magnetic resonance imaging of the breast for the evaluation of symptomatic breast lesions. *Ann Surg* 1999; 230:680–5.
17. Fischer U, Kopka L, Grabbe E. Breast carcinoma: effect of preoperative contrast-enhanced MR imaging on the therapeutic approach. *Radiol* 1999; 213:881–8.
18. Kuhl CK, Mielcareck P, Klaschik S, et al. Dynamic breast MR imaging: are signal intensity time course data useful for differential diagnosis of enhancing lesions? *Radiol* 1999; 211:101-10.
19. Teifke A, Hlawatsch A, Beier T, et al. Undetected malignancies of the breast: dynamic contrast-enhanced MR imaging at 1.0 T. *Radiol* 2002; 224:881–8.

**Acknowledgements:** The authors would like to thank the other surgeons at HOPE, David Hetzel, MD, Blair Harkness, MD and Tim Vanderkwaak, MD, for the inclusion of their surgical cases in this review and their thoughtful comments on the conduct of this project.

**Disclosure:** None of the authors have any conflicts of interest to disclose.
**Financial Support:** None
**Authors' Contributions:**

Nate L. Jones, MD, Principal Investigator: All aspects of the study from conceptualization and design through presentation and manuscript.

Shelley L. Galvin, MA, Co –Investigator: Data collection, management and analyses; presentation and manuscript.

Ashley Case, MD, Senior Investigator: Conceptualization, design, interpretation, and manuscript.

**Previous Presentation:**

Jones NL, Galvin SL, Vanderkwaak T, Hetzel D, Harkness B, Case A. The role of breast-specific gamma imaging on preoperative and surgical management in women with newly diagnosed breast cancer. Poster session presented at: 44th Annual Society of Gynecologic Oncology Meeting on Women's Cancer; 2013 March; Los Angeles, CA.

**Corresponding Author:** Shelley L. Galvin, MA
MAHEC Center for Research 119 Hendersonville Rd. Asheville, NC 28803
Office: (828)771-550; Fax: (828) 251-0024; Cell (828) 772-8829
Email: Shelley.Galvin@mahec.net