New Method for Breast Cancer Detection using TC-99M Sestamibi Scintimammography

Monita Yuen-Green MD, Richard Wasnich MD, Susan Caindec-Ranchez CNMT, James Davis PhD*

The combination of breast examination and radiographic mammography (XRMM) are the established methods for breast cancer detection. However, XRMM lacks sensitivity and specificity in women with dense breasts, leading to false positive findings in 80% and false negative findings in 10% to 15% of the cases.

Tc-99m Sestamibi (MIBI) scintimammography (SMM) is a new breast-imaging technique. This study shows that SMM has a positive predictive value of 83% and negative predictive value of 93%, which is similar to that reported by others. This supports other published reports that SMM is a potential excellent complimentary imaging technique to XRMM in improving the accuracy of breast cancer detection.

Introduction

Breast carcinoma is an important public health problem in the United States. One in eight women will be diagnosed with breast cancer, and one woman in 25 will die of the disease. Early detection is known to improve survival. Currently, the most effective means to detect breast cancer is XR mammography. However, XRMM lacks sensitivity and specificity in women with dense breasts, leading to a low positive predictive value (11% to 30%) which results in major costs including unnecessary biopsies, anxiety and residual scarring.[1,2] The false negative rate for XR mammography has been reported to vary from 10% to 15%, which may lead to delays in biopsy and diagnosis.[3] Therefore, major endeavors are justified to improve both the positive and negative predictive values of screening and diagnostic techniques.

Tc-99m Sestamibi (MIBI) scintimammography is a noninvasive imaging technique for screening and diagnosis of breast cancer. The uptake of MIBI in the breast is independent of the presence of dense breasts seen on XR mammography. Preliminary data show that this imaging technique has high sensitivity 95.8% to 100%, specificity 85% to 86.8%, positive predictive value 82.1%, and most important, high negative predictive value 97.1%.[3-4] Other investigational breast imaging techniques, such as magnetic resonance imaging (MRI) showed a sensitivity of 94% and specificity of 37%, while breast echography had a sensitivity of 49.2%.[5-6] Positron emission tomography (PET), another nuclear medicine imaging not currently available in Hawaii, has been shown to have a sensitivity of 80% for breast cancer detection.[7] Tc-99m MIBI scintimammography has been reported in recent studies to have a remarkable potential in selecting those patients who would benefit most from breast biopsy and reduce the number of negative biopsies.[3]

Methods

Patient population

Eighteen women (mean age of 53.9± 10.8 years) were enrolled in the study with informed consent. Each patient was examined by an investigator in the supine and upright positions and had XR mammography before enrollment into the study. Study inclusion criteria consisted of either a palpable breast mass and/or an abnormal XR mammography for which biopsies were recommended.

Mammography

Mammography was performed in standard craniocaudal and mediolateral oblique projections using a dedicated mammography unit. Additional views using cone compression and magnification were performed as indicated. The mammographic results were collected at the time of the initial interpretation with full knowledge of available clinical information and the patients' previous mammograms. All images were evaluated by two experienced radiologists. Any disagreement was resolved by consensus.

Scintimammography

Each patient received 20 mCi (740MBq) Tc-99m MIBI (Cardiolite, DuPont Pharma, Billerica, Mass) intravenously in the arm contralateral to the breast with the abnormality. Breast scintigraphy was performed using a single-head gamma camera (ADAC Genesis), equipped with a high resolution collimator. The spectrometer was centered at 140 keV with a 10% window. Patients were imaged in the prone position, which allowed the breast being imaged to be freely dependent of the imaging table. Each breast was imaged separately in order to exclude activity in the opposite breast.

Three standard planar images of the breasts and chest were acquired with a 128x128 matrix for 10 minutes per view. A 10-minute lateral image of the breast with the suspected lesion began 5 minutes post-injection. The patient was then repositioned with the contralateral breast dependent, and another lateral image was acquired. A final 10-minute anterior chest image was obtained in the

*Hawaii Nuclear Medicine Consultants
401 Kamakee Street
Honolulu, HI 96814-4224
Tel: (808) 592-2643
Fax: (808) 592-2638

supine position with the patient's arms raised for visualization of both axillae.

The amount of radiation to the patient from one dose of 20 mCi of Tc-99m MIBI would be 0.13 rad to the breasts (compared with mean radiation dose of 0.16 rad by standard 2 view XR mammogram, plus 0.08 rad per additional view). The estimated amount of total body radiation from one dose of Tc-99m MIBI is 0.33 rad, which is roughly equivalent to that of radiographic imaging of the lumbosacral spine.

All images were evaluated for abnormal Tc-99m MIBI uptake by two nuclear medicine physicians blinded to the patients' clinical presentation and mammographic results. Any disagreement was resolved by consensus.

Data analysis

XRMM results were classified into three categories: normal, 0, benign or very low suspicious, 1, suspicious, 2. Categories 0 to 1 are classified as negative while category 2 is classified as positive interpretation for cancer. Similarly, SMM results were classified into 3 categories by visual scoring: normal, 0, benign, 1, and suspicious, 2. Categories 0 to 1 are classified as negative while category 2 is classified as positive interpretation for cancer. Results of XRMM and SMM were correlated with excisional biopsy in 20 lesions and core-needle biopsy in one lesion. Statistical analysis was performed based on the comparison of the proportions as paired samples.[8]

Results

Eighteen women with 21 lesions were studied (mean age of 53.9±10.8 years): There were 9 palpable masses and 15 abnormal XR mammographic lesions. Four of the 15 abnormal XR mammographic lesions were palpable. Pathology results were obtained by excisional biopsies in 20 lesions and core-needle biopsy in one within one month after XR mammogram and scintimammogram.

There were 6 malignant primary breast cancer lesions and 15 benign lesions. Three of the 6 malignant lesions were palpable. The size of malignant lesions on pathology ranged from 0.1 cm to 1.8 cm measured in the largest diameter with the mean size of 1.1 ± 0.6 cm. Scintimammogram correctly detected 5 of 6 malignant lesions, whereas XR mammogram detected only 4 of 6. Scintimammogram identified 14 of 15 benign lesions correctly while XR mammogram identified only 4 of 15. Twelve patients had 15 benign lesions and only one patient had a false positive SMM result. By contrast, 11 had false positive results by XRMM (Table 1).

The sensitivity of SMM in this study is 83% compared with 67% for XRMM ($p>0.75$). The specificity of SMM is 93% compared with 27% for XRMM ($p<0.005$) (Fig 1). The positive predictive value of SMM is 86% compared with 27% for XRMM. The negative predictive value of SMM is 93% compared with 67% for XRMM (Fig 2).

Table 1.—Results of Radiographic Mammography (XRMM) and Scintimammography (SMM).

EXAM	TP	FP	FN	TN
XRMM	4	11	2	4
SMM	5	1	1	14

PE = Physical examination; XR = radiographic mammography; SMM = scintimammography; TP = true positive; FP = false positive; FN = false negative; TN = true negative.

Discussion

Approximately 175,000 women in the United States are diagnosed as having breast cancer each year, representing 32% of all women diagnosed with cancer. Breast cancer also is causing more than 150,000 hospitalizations and 44,000 deaths annually in the U.S. Efforts to reduce morbidity and mortality from breast cancer have focused on a combination of breast self-examination, clinical

Fig 1.—Comparison of the sensitivity and specificity of scintimammography (SMM) and radiographic mammography (XRMM).

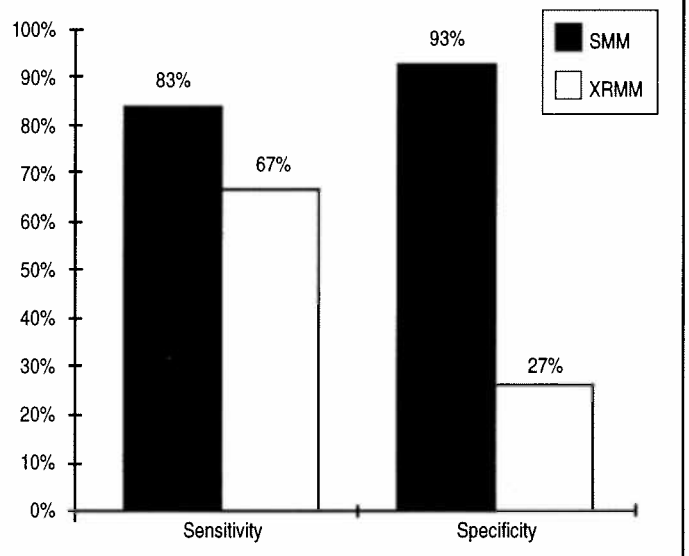
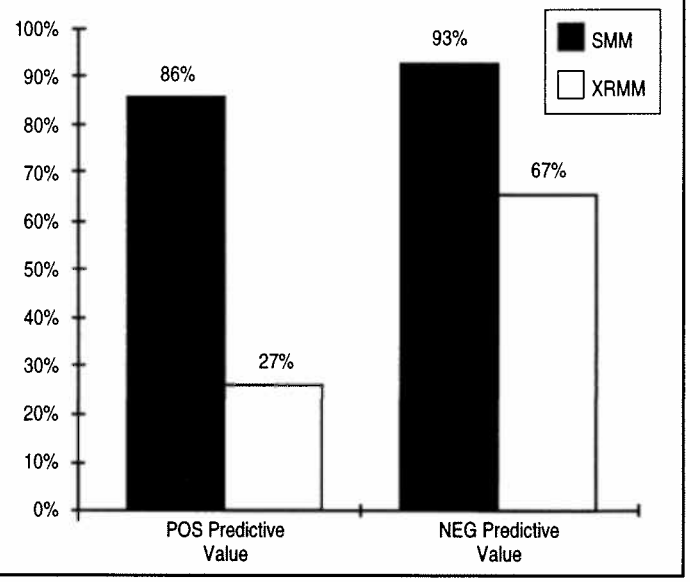


Fig 2.—Comparison of the positive and negative predictive values of scintimammography (SMM) and radiographic mammography (XRMM).



breast examination, and mammography. However, 11% to 30% of women with breast cancer have benign-appearing mammograms.[1,9] This indicates the importance of physical examination and the need for the development of an effective alternative imaging technique for this subset of patients.

Of those women who are referred for breast biopsy, only one in five is a true positive, and therefore, has a malignant breast tumor. The incidence of benign breast biopsy is even higher in younger women, about 16.4 benign to one malignant biopsy in the 35 to 39 age group, and 9.5 to one in the 40 to 44 age group. The high benign biopsy rates in these younger women probably reflect the high incidence of fibrocystic disease in women of this age group.[10] Recent studies have shown that in the subset of patients with radiodense breasts, surgical or radiotherapy scars, or breast prosthesis, SMM is an excellent complimentary imaging technique to XRMM in improving the accuracy of breast cancer detection.[11]

Tc-99m Sestamibi (MIBI) is an FDA-approved radio-pharmaceutical that has been used mainly in myocardial perfusion studies for the detection of coronary artery disease. It also has been used for other tumor imaging, including brain, bone, thyroid, parathyroid and lung. It is not metabolized, and it is excreted into the biliary system within one hour.

The exact mechanism of cellular uptake of Tc-99m MIBI by carcinomas is unknown but recent data suggest it is concentrated in the mitochondria. Laboratory studies also have shown that MIBI uptake may be impeded by the presence of p-glycoprotein, a membrane transporter on cell surfaces, found in multidrug-resistant cancers.[12] This may lead to false-negative readings on SMM. On the other hand, SMM may have the potential to determine multidrug resistant tumor and help in the chemotherapy management of breast cancer patients.

The one false negative case in our study is a woman who had a surgical biopsy for a palpable breast mass. The pathology showed intraductal adenocarcinoma that was missed by XRMM. Her SMM was done about two weeks after her surgical biopsy showing minimal uptake which was classified as benign inflammatory reaction after biopsy. Her mastectomy specimen showed a single 0.1 x 0.1 cm residual tumor focus. Other investigators have reported low sensitivity of SMM for the detection of breast lesions less than 6 mm.[13] A larger scale multi-center trial is underway to validate the accuracy of SMM.

The SMM of the one false positive case in this study showed a slight degree of focal uptake. This patient had no palpable mass but an abnormal XRMM indicating suspicious subareolar microcalcification. The biopsy result showed fibrocystic disease with benign ductal adenosis. Others have reported false-positive SMM results in highly proliferative conditions such as fibroadenoma and fibrocystic disease.[3] Semiquantitative evaluation of MIBI uptake using region of interest technique may enhance the specificity of SMM for detecting breast cancer.[14]

SMM is a promising new imaging technique with preliminary data indicating improved accuracy for the detection of breast cancer. This new imaging technique has the potential to decrease the number of benign biopsies, thereby substantially reduce physical and psychological scarring, costs, and morbidity of unnecessary biopsies, thereby, benefiting both patients and third-party payers. It also may make mammographic screening more cost-effective, especially among women under 50.[15]

Conclusion

The combination of breast examination and XR mammography (XRMM) is the established method for breast cancer detection. XRMM remains the procedure of choice in screening; however, it has a number of critical limitations leading to false positive findings in 73% and false negative findings in 33% of our study.

Breast scintigraphy (SMM) is a noninvasive nuclear medicine imaging procedure with preliminary data indicating high accuracy for the detection of breast cancer. SMM has the potential to reduce the large number of breast biopsies performed for benign, non-neoplastic conditions. In our small study sample, SMM appears to be both more sensitive (83% versus 67%) and specific (93% versus 27%) than XRMM. Further studies are warranted to determine the role of SMM as a breast cancer detection tool and to define the subgroups of women who would benefit most from this test.

References

1. Sickles EA. Periodic mammographic follow-up of probably benign lesions: results in 3,184 consecutive cases. *Radiology.* 1991; 179:463-468.
2. Robertson CL. A private breast imaging practice: medical audit of 25,788 screening and 1,077 diagnostic examinations. *Radiology.* 1993; 187:75-79.
3. Khalkhali I. Prone scintimammography in patients with suspicion of breast cancer. *J Am Coll Surg.* 1994; 178:491-497.
4. Waxman AD. Thallium scintigraphy in the evaluation of mass abnormalities of the breast. *J Nucl Med.* 1993; 39:18-23.
5. Harms SE. MR imaging of the breast with rotating delivery of excitation of resonance: clinical experience with pathologic correlation. *Radiology.* 1993; 187:493-501.
6. Catarzi S. A multicenter study for the evaluation of the diagnostic efficiency of mammography and echography in nonpalpable breast neoplasms. *Radiol Med* (Torino). 1992; 84:664.
7. Tsen Y. The application of positron emission tomographic imaging with fluoro-2- deoxy-D-glucose to the evaluation of breast disease. *Surgery.* 1992; 216:27-34.
8. Snedecor GW, Cochran WG. *Statistical methods.* 7th ed. The Iowa State University Press, 1980.
9. Sienko DG. Mammography use and outcomes in a community. *Cancer.* 1993; 71:1801-1809.
10. Baker LH. Breast cancer detection demonstration project: five-year summary report. *CA Cancer.* 1982; 32:194-225.
11. Khalkhali I. The usefulness of scintimammography in patients with dense breasts on mammogram. *J Nucl Med.*1995; 36:208
12. Bender H. Detection of multi-drug resistance with Tc-99m sestamibi. *J Nucl Med.*1995; 36:529
13. Waxman A. Detection of primary breast malignancy with Tc-99m MIBI in patients with non-palpable primary malignancies. *J Nucl Med.*1995; 36:877.
14. Tiling R. Integrated diagnosis of breast tumors: semiquantitative Tc-99m MIBI imaging versus dynamic MRI. *J Nucl Med.*1995; 36:205.
15. Miller AB. The costs and benefits of breast cancer screening. *An J Prev Med.* 1993; 175-180.