



International prospective evaluation of scintimammography with ^{99m}Tc sestamibi

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Abstract

Background: The purpose of this study is to evaluate the efficacy of scintimammography with ^{99m}Tc-Sestamibi for the diagnosis of breast cancer.

Methods: This was a multicenter prospective cohort clinical trial. A total of 1,734 women were enrolled of whom 1,243 had complete data upon study completion.

Results: The mean \pm standard error age of the patients is 56 ± 12 years (with a range of 19 to 94). Mammographic results were classified by the Breast Imaging Reporting and Data System (BIRADS) as 199 (16%) BIRADS 5, 149 (12%) BIRADS 4, 199 (16%) BIRADS 3, and 696 (56%) BIRADS 2 or 1. Scintimammography was positive for 322 (26%) of the patients and negative for 921 (76%). Histopathology showed malignancy for 201 (16%) of the patients. Sensitivity and specificity of scintimammography was estimated 93% and 87% respectively. A positive predictive value (PPV) of 58% with a negative predictive value of 98% were calculated.

Conclusions: The present study suggests that scintimammography with ^{99m}Tc-Sestamibi is highly accurate for the detection of breast cancer. © 2003 Excerpta Medica, Inc. All rights reserved.

Keywords: Scintimammography; Mammography; ^{99m}Tc; Sestamibi; Breast cancer; Breast imaging

Breast cancer is the most common cancer among women, excluding nonmelanoma skin cancer. Currently, approximately 3 million women in the United States are living with the disease, including 2 million who have already been diagnosed, and another 1 million who do not yet know they have the disease [1].

The American Cancer Society (ACS) estimates for 2001 include 192,200 new cases of invasive breast cancer being diagnosed in the United States. In addition, ductal carcinoma in situ will be responsible for 39,900 new cases this year. In 2001, it is estimated that 1,500 men will be diag-

nosed with breast cancer. Year 2001 estimates include nearly 40,600 deaths occurring from breast cancer in the United States alone—this includes approximately 40,200 women and 400 men [1].

According to the National Breast Cancer Coalition (NBCC), breast cancer is the leading cause of cancer death among women between the ages of 20 and 59 in the United States, and the leading cause of cancer death among women worldwide. One of 8 women will develop breast cancer some time during her life—that means one new diagnosis every 2 minutes. Every 13 minutes, a woman will die of breast cancer [2].

All women, regardless of family history, are at risk for breast cancer. In fact, in 90% of cases, there is no family history of the disease. Regardless of age, African-American

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women have the highest breast cancer mortality rates. According to the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program (1995 to 1997), if current rates stay the same, a woman's chance of developing breast cancer is as follows [3]: by age 30, 1 of 2,000 women; by age 40, 1 of 233 women; by age 50, 1 of 53 women; by age 60, 1 of 22 women; by age 70, 1 of 13 women; by age 80, 1 of 9 women; during her lifetime, 1 of 8 women,

The minimum diameter for a breast cancer tumor to be detected by mammography is 3 to 4 mm. The time required for a breast cancer tumor cell to progress to 3 mm is 5 to 6 years. However, mammography is not infallible, and it does not detect all breast cancers. Given that a 3 mm tumor is less likely to be detected in a young woman with dense breast tissue along with the fact that at least 15% of breast cancers are diagnosed in women between 40 and 49 years and 5% in women younger than 40, the probability of a minimal breast cancer to be diagnosed in a young woman by mammography alone is significantly reduced.

On the other hand, 10% of breast cancers are not mammographically visible at all ages and any breast tissue density. The most rare lobular and inflammatory forms of breast cancer are not as easily detected by mammograms. It is therefore imperative that other diagnostic techniques are used to screen or follow up these patients.

At this point in time it is imperative to introduce, test and implement methods that will enable us to provide an accurate and efficient assessment of women requiring definitive diagnosis without compromising their safety and outcome. Scintimammography could address this need and play an important role in improving our efficiency and accuracy of diagnosing and treating breast cancer.

Scintimammography is a diagnostic technique that has been adapted primarily from cardiology to the evaluation of breast lesions. The biological principle of this technique is simply based on the fact that certain radiopharmaceuticals are absorbed at higher rates by malignant cells when compared with normal cells. This is due to the cationic lipophilic properties of the radiopharmaceuticals used. The increased permeability of the membrane allows them to permeate and adhere in the cytoplasm, with the negatively charged mitochondria. The increased vascularity of malignant cells is an important factor in the increased absorption [4–6]. The procedure involves the intravenous injection of the radiopharmaceutical and subsequent imaging of the breast. Increased uptake ratios of the area of interest (lesion) compared with normal breast tissue of the ipsilateral and contralateral breast or to the myocardium are considered to be suspicious and further diagnostic assessment with histopathological examination of biopsy specimens is indicated [7–9]. On the other hand, when no increased uptake is detected, the likelihood of malignant disease is low [10–13].

The current study evaluates the accuracy and clinical utility of scintimammography in a multicenter observational

prospective study. Patients are enrolled from seven breast diagnostic centers in Canada. The objective of the present study was to evaluate the validity and reliability of scintimammography as an imaging agent in the diagnosis of breast cancer.

Methods

This is a prospective observational cohort study in which 1,500 women were submitted to adjunct scintimammography and 300 were evaluated without scintimammography according to the established routine protocol at the institution where they are referred.

The enrolled women were referred for evaluation to the breast clinics of the Montreal General Hospital, Hôpital Hotel Dieu, Hôpital Sacré-Coeur, Hôpital Notre Dame, Hôpital St. Luc, Hôpital Joliette, and Brandon Hospital Manitoba. Patients less than 18 years of age, with an invasive evaluation of the breast within last 30 days, pregnant, or not consenting to study participation were excluded from the study.

Scintimammography was performed according to a standardized protocol. The patients were injected intravenously with 20 mCi to 30 mCi of ^{99m}Tc Technetium [MIBI]₆ where MIBI is 2-methoxy isobutyl isonitrite or Sestamibi, in the antecubital fossa of the arm opposite to the breast with the lesion or suspicious finding. In cases of suspected bilateral disease, the injection was through the dorsalis pedis vein. The radiopharmaceutical injection was followed by 10-minute planar images, at 5 minutes after injection. The patient was placed in prone position on a specialized imaging table, with a special plastic cushion that enables the examined breast to hang freely through an opening. This allows the acquisition of images without chest wall interference. The breast under examination was imaged without compression. Analogue and digital images were obtained using a low energy all-purpose collimator and software zoom (on the digital images). Lateral images were acquired in the prone position. Finally anterior supine images were taken, which allow for a better view of axillary lymph nodes. For the supine imaging the patient's arms were raised above the head and a 10-minute acquisition was made on a 128 × 128 matrix.

It has been established that myocardial cells have an increased uptake of ^{99m}Tc Technetium labeled sestamibi. In contrast, normal breast tissue has shown no activity with these radioisotopes. An area of interest where a lesion is suspected in the breast or axilla was compared with the myocardium (positive control) and normal breast tissue (negative control). The myocardium is easily visualized in all left breast images.

Validity of a diagnostic procedure is a measure of how close the test result corresponds to the diagnostic gold standard for the particular disease. The validity of scintimammography was evaluated by all psychometric measures

Table 1
Scintimammography results compared with pathological analysis of the specimens excised

	Malignant disease		
	Yes	No	Total
Scintimammography			
Positive	186 (58%)	136 (42%)	322 (26%)
Negative	15 (2%)	906 (98%)	921 (74%)
Total	201 (16%)	1042 (84%)	1243 (100%)

of accuracy, sensitivity, and specificity, and positive and negative predictive value. The gold standard in this assessment was the histopathological result.

Results

A total of 1,822 patients were recruited from seven Canadian centers of whom 1,734 women were submitted to scintimammography. All data were entered and managed using software that was developed for the study. Until the end of the study complete data was collected for 1,243 patients. For the remaining 491 patients histopathology results were pending. The mean ± SE age of the patients is 56 ± 12 years with a range between 19 and 94.

There were 503 (40%) of the women in the sample who

Table 2
Psychometric properties

Parameter	Estimate (%)	95% CI
Sensitivity	93	81.3–96.6
Specificity	87	84.4–90.6
Positive predictive value	58	41.4–60.3
Negative predictive value	98	96.9–99.5
Accuracy	88	85.1–90.8

CI = confidence interval.

were postmenopausal and 69 (6%) who were perimenopausal. Breast density was graded as dense for 381 (30%), normal for 970 (78%), and fatty for 381 (30%).

Of the 1,243 women in the study 417 (33%) had a palpable mass upon physical examination. The mammographic results were classified as 199 (16%) BIRADS 5, 149 (12%) BIRADS 4, 199 (16%) BIRADS 3, and the remaining 696 (56%) BIRADS 2 or 1. The scintimammography results were positive for 322 (26%) of the patients and negative for 921 (74%). The histopathology showed malignant breast disease for 201 (16%) of the patients in the sample.

Of the 201 malignant lesions scintimammography correctly identified as positive 186 (93%). There were 1,042 women without a malignant lesion of which scintimammography correctly identified 906 (87%). From a total of 322 positive scintimammograms 186 (58%) were proven to be

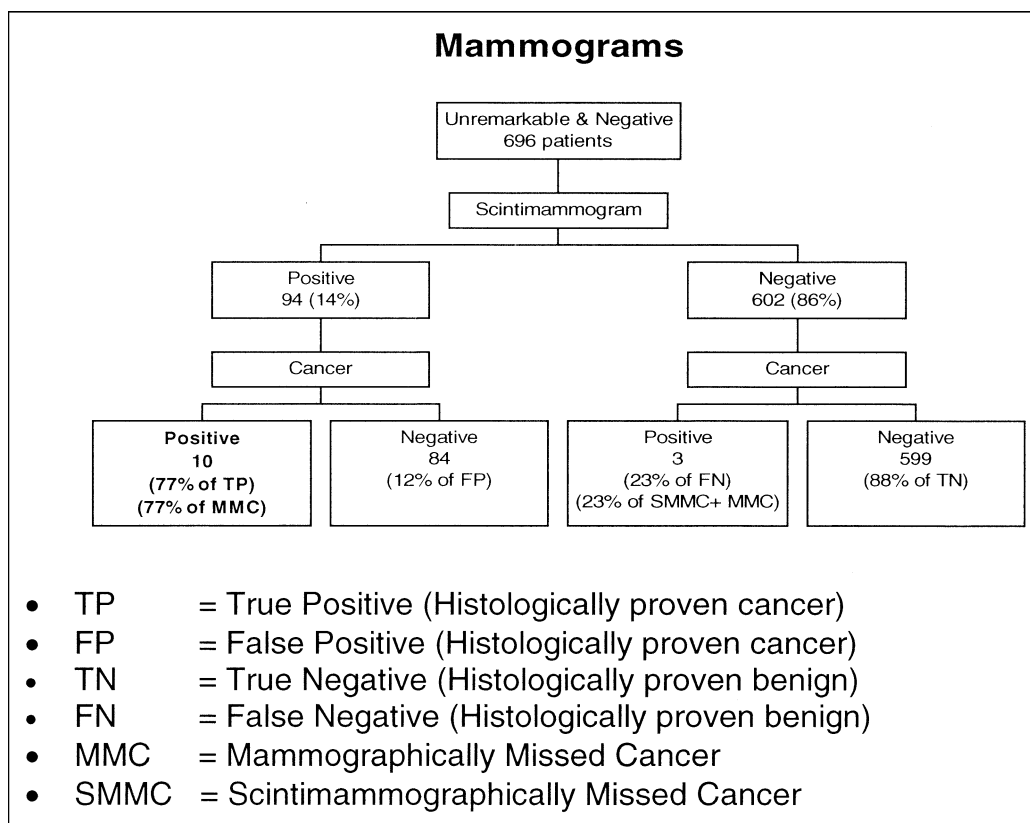


Fig. 1. BIRADS 1 and 2 mammograms versus scintimammograms versus tumor histopathology.

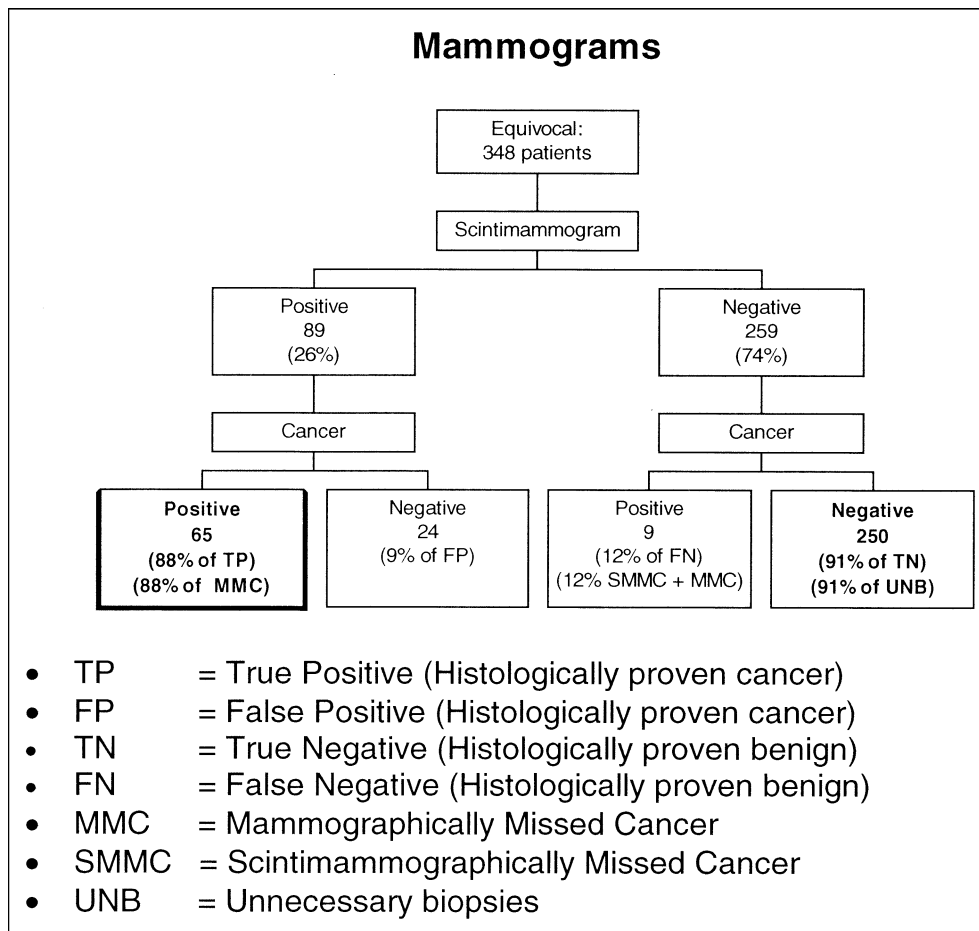


Fig. 2. BIRADS 3 and 4 mammograms versus scintimammograms versus tumor histopathology.

true positive. Of the 921 negative scintimammograms 906 (98%) were true negatives (Table 1). These data yield the following estimates of the psychometric properties of scintimammography: sensitivity: 93%, specificity 87%, positive predictive value 58%, negative predictive value 98%, and accuracy 88% (Table 2).

The mammographic, scintimammographic, and histopathological results are correlated in Figs. 1, 2, and 3. Among the 696 BIRADS 1 and 2 mammograms, 13 (2%) were histologically diagnosed as cancer and 683 (98%) as benign. Scintimammography accurately identified 10 (77%) of true positive and 599 (88%) of true negative for malignancy lesions. Scintimammography falsely detected 84 (2.3%) benign lesions as positive and 3 (23%) malignant lesions as negative.

Of the 348 BIRADS 3 and 4 mammograms, 74 (21%) were histologically diagnosed as cancer and 274 (79%) as benign. Scintimammography correctly diagnosed 65 (88%) of true positive and 250 (91%) of true negative for malignancy lesions. Scintimammography falsely detected 24 (8.8%) benign lesions as positive and 9 (12.2%) malignant lesions as negative.

There were 199 BIRADS 5 mammograms, of which 114 (57%) were histologically diagnosed as cancer and 85

(43%) as benign. Scintimammography accurately identified 111 (98%) of true positive and 57 (67%) of true negative for malignancy lesions. Scintimammography falsely detected 28 (33%) benign lesions as positive and 3 (2%) malignant lesions as negative.

Comments

During the last decade the validity of scintimammography as a diagnostic radioactive imaging agent for breast cancer has been evaluated in numerous studies. The majority of these studies enrolled patients from one center except for a multicenter (42 centers) trial conducted by Khalkali et al [14–17]. The number of recruited patients ranges from 35 to 558. The results of these studies have shown that the sensitivity of Sestamibi in detecting breast cancer ranges from 63% to 98% and the specificity in detecting lack of malignancy ranged from 72% to 100% [14]. These values varied according to the population and the subgroup of women studied. The overall consensus from these studies is that Sestamibi is a useful tool for the diagnosis of breast cancer [4,14–17]. These studies have mainly recruited patients with equivocal or vague screening or diagnostic mam-

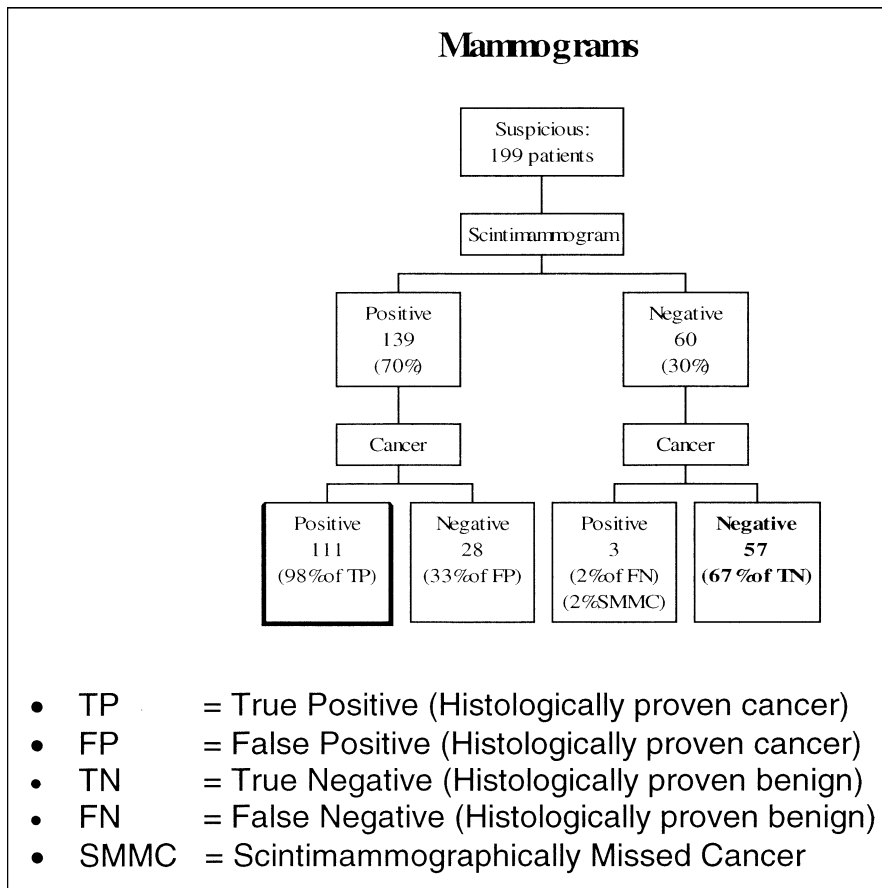


Fig. 3. BIRADS 5 mammograms versus scintimammograms versus tumor histopathology.

mammograms or palpable lesions that are not detected by mammograms. Therefore, high-risk patients predominate in the analyzed population, introducing an indirect negative selection bias. As a result, the high pretest probability of breast cancer will affect the potential utility of the test and the positive predictive value, which is of the utmost importance. To this date, a prospective study in which all eligible patients are tested with scintimammography has not been conducted. Such a study will allow the generalization of the results to all groups of women requiring diagnostic testing for breast cancer.

The estimates of sensitivity for scintimammography from our study are comparable with those reported by Lee [18], Khalkhali et al [14], Fenlon et al [15], and others. Other authors have reported somewhat lower sensitivity estimates. Tiling et al [16] reported a sensitivity of 79% and 88% in two series of women with equivocal mammograms. Similarly, Cwikla et al [18] reported a sensitivity of 89% in women with suspicious lesions. Our estimate of specificity was similar, although somewhat lower than those reported in the literature. Khalkhali et al [14] reported a specificity of 88% in women with mammographic findings or palpable mass. Higher estimates of specificity among women with a palpable mass have also been reported by Fenlon et al [15] and Palmedo et al [17]. Lower specificity estimates of 52%

and 49% were reported by Cwikla et al [18] and Tiling et al [16], respectively.

Figs. 1, 2, and 3 correlate the mammographic, scintimammographic and histopathological results. From this correlation it is clearly deduced that the implementation of scintimammography could reduce the amount of unnecessary biopsies from 1,042 to 136 (a reduction of 62.1%) and most important, the number of missed cancers from 87 to 12 (a reduction of 86%).

One observation that requires some attention at this point in time is the low positive predictive value. The estimate of 51% with confidence intervals between 41% and 60% may be considered as quite low. In fact these results would suggest at first review, that scintimammography does not provide any additional information over chance, assuming that we just toss a coin. This impression however, is not accurate for the following reasons:

First, the positive predictive value is affected by the prevalence of disease. In this sample the prevalence is 13%, which is low, but within the expected range given the method by which the sample was selected. Second, the positive predictive value is interpreted as the posttest probability of disease given a positive test result. In this sample the pretest probability of disease would be best estimated by the prevalence of disease, which is equal to 13%. A positive

scintimammography result would change the estimated probability to 51%, which is equivalent to a 400% change from the pretest value. Therefore a positive scintimammography result significantly increases our ability to predict the presence of malignant disease in this population.

Conclusions

The results of the present study demonstrate that the implementation of scintimammography as an adjunct diagnostic tool along with mammography and physical examination can significantly improve the diagnostic accuracy of breast cancer, reduce the number of unnecessary breast biopsies and most important substantially reduce the number of missed breast cancers. Scintimammography can produce significant benefits to both the patients and to the health care system. The results of the current study strongly support the implementation of scintimammography in the current methods and processes of breast cancer diagnosis and immediate implementation in the management of waiting lists as a triage tool

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