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Metastatic Axillary Lymph Node Technetium-99m-MIBI Imaging in Primary Breast Cancer

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Technetium-99m-MIBI scintimammography has been shown to be useful in the detection of primary breast cancer. The purpose of this study was to evaluate the potential role of scintimammography in detecting axillary lymph node involvement in patients undergoing scintimammography to detect primary breast cancer. **Methods:** A group of 100 women with breast cancer who were scheduled for a Level I-II axillary dissection were prospectively studied. Scintimammography was performed in all patients before histopathologic confirmation of breast cancer. Two lateral (prone imaging) views and one anterior (supine) planar thoracic view were obtained 10–15 min after the injection of 25–30 mCi ^{99m}Tc-MIBI (10 min/view) by using a special breast positioning device (foam cushion) placed over the imaging table. Both of the axilla were included in the field-of-view. Two experienced blinded observers reviewed all cases both from films and from the computer screen with contrast adjustment when needed. The site of intravenous injection of ^{99m}Tc-MIBI was known to the interpreters in order to avoid reading any false-positive uptake in the axilla ipsilateral to the injection site. **Results:** A total of 52 patients had no axillary lymph node involvement (611 negative nodes) while 48 patients had at least one axillary lymph node with metastatic involvement (180/502 positive nodes). The sensitivity of scintimammography in detecting metastatic axillary lymph node involvement was 79.2% (38/48), and the specificity was 84.6% (44/52). The positive and the negative predictive values were 82.6% (38/46) and 81.5% (44/54), respectively. **Conclusion:** This study shows that scintimammography has good diagnostic accuracy for detecting axillary lymph node involvement in patients with breast cancer. This information should be added to the result of standard scintimammography, which requires very minor modifications in order to simultaneously evaluate both of the axilla.

Key Words: technetium-99m-MIBI; breast cancer; axillary lymph nodes

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Mammography currently represents the best imaging modality for the early detection and diagnosis of breast cancer (*1–7*). Although numerous advances and improvements in mammography have occurred, this technique is not without some drawbacks (*8–12*). Therefore, other methods to investigate the breast have been studied. These include ultrasound, MRI, CAT, digital mammography, PET and SPECT (*13–15*). Most of these methods have been developed primarily to improve the detection and diagnosis of a breast mass but not to detect metastatic axillary lymph node involvement. Since axillary lymph node involvement has been shown to be one of the most important prognostic factors for determining survival in patients with newly diagnosed primary breast cancer, almost every patient with invasive, and many with noninvasive, cancer will undergo an axillary dissection once the breast cancer diagnosis has been made. Although axillary dissection provides important staging and prognostic information and identifies patient subgroups for adjuvant therapy, its positive influence for breast cancer patients is controversial. It is accompanied by non-negligible morbidity including arm edema, lymphostasis and subsequent infections of the ipsilateral extremity (*16*).

A noninvasive technique to detect breast cancer that has metastasized to the axillary lymph nodes could permit better selection of patients for axillary dissection. Different radionuclide imaging procedures such as axillary lymphoscintigraphy, immunolymphoscintigraphy, lymphoscintigraphy with an intraoperative gamma probe and fluorine-18-fluorodeoxyglucose (FDG) PET have been proposed to assess metastatic involvement of axillary lymph nodes (*17–22*). More recently, ^{99m}Tc-MIBI scintimammography has been introduced to detect and evaluate patients with primary breast cancer (*23–32*). Preliminary data showed that this technique was useful not only in the detection of the primary breast cancer but also in the evaluation of metastatic axillary lymph node involvement (*26,33*). The purpose of this study was to evaluate the diagnostic accuracy of ^{99m}Tc-MIBI imaging to detect axillary lymph node involvement in patients at the time of ^{99m}Tc-MIBI scintimammography for primary breast cancer.

MATERIALS AND METHODS

Patients

One hundred women (mean age 59 ± 13 yr; mean weight 65 ± 15 kg) who were referred consecutively to the breast cancer clinic of Hôtel-Dieu de Montréal were prospectively studied. Before their enrollment in this study, patients had met the following three major criteria of inclusion: (1) a ^{99m}Tc-MIBI scintimammography was performed before the histopathologic confirmation of the presence of breast cancer, (2) there was a proven invasive type of breast cancer either from fine-needle aspiration cytology and/or excisional biopsy performed after scintimammography and (3) an axillary dissection was performed as part of the standard clinical staging. All patients gave informed written consent as part of the research protocol approved by our hospital's Institutional Review Board for Human Experimentation.

Technetium-99m-MIBI Scintimammography

All patients had the same ^{99m}Tc-MIBI breast and axilla imaging protocol. There was no specific patient preparation. MIBI (Cardiolite, DuPont Merck Pharmaceutical Co., N. Billerica, MA) was labeled as previously reported (*34*), and its labeling efficiency was always more than 95%. Patients were injected with 20–30 mCi (740-1100 MBq) according to their respective body weight (0.3 mCi/kg). The injection was given as a bolus into an antecubital vein through a plastic cannula in the arm on the opposite side of the known or suspected breast lesion to avoid any false-positive uptake in the axillary lymph nodes ipsilateral to the injection side. For patients with suspected lesions in both breasts, the injection of ^{99m}Tc-MIBI was given in a pedal vein. The syringe containing the radioactivity was always flushed with 10-cc normal saline solution.

Technetium-99m-MIBI scintimammography was performed using a rectangular single-detector gamma camera with a parallel-hole, high-resolution collimator interfaced to a computer. The energy peak was centered at 140 keV with a 10% window. Planar images (three views) were obtained 10–15 min postinjection. A preset data acquisition time (10 min/view) was used for each view. The first two images (right and left lateral thoracic views) were obtained while the patient was in a prone position on a special breast positioning device installed over the imaging table. The device consists of a foam cushion with a lateral semicircular aperture in which the breast was carefully positioned by an experienced technologist before imaging. The cushion allowed the breast to be pending and minimizes the distance between the breast and the detector. Special care was taken to ascertain that both the imaged breast and axilla were in contact with the collimator surface. Patients' arms were extended on each side of their heads. The opposite breast was not seen, and imaging the pending breast while the patient was prone provided optimal separation of the thoracic and abdominal organs, particularly the myocardium and liver in the lateral projections. The breast and axilla were centered in the field-of-view, which extended from the neck to the upper level of the abdomen.

A third image, which consisted of an anterior thoracic view including both of the axilla with the patient supine, was obtained after the initial lateral views of both breasts. When possible, the arms were raised and the hands placed behind the patient's head. This projection was used mainly to locate the primary tumor, especially those in the inner breast quadrants, and to visualize both axilla. The entire imaging procedure took approximately 40 min and all images were recorded on a computer.

Data Analysis

All scintimammograms were analyzed by two independent, experienced nuclear medicine physicians who were blinded to the clinical status, physical examination, radiologic mammogram and histopathologic results. However, the side of the intravenous injection of ^{99m}Tc-MIBI (and thus, indirectly, the side of the suspected breast lesion) was specified before the readings in order to avoid false-positive axillary lymph node uptake secondary to extravasation of the radiopharmaceutical at the injection site and any subsequent drainage through local and regional lymphatic vessels. Two different types of displays were available for the data analysis: hard copy of the analog film and direct reading from the computer screen with adjustments for contrast using a logarithmic scale.

Disagreements were resolved by consensus with a third experienced observer used as a referee. Readers were asked to determine if the study was positive or negative for metastatic involvement of axillary lymph nodes (contralateral to the side of radiotracer injection). A positive study for axillary lymph node involvement was defined as one or more focalized areas of increased uptake in the axilla compared to the surrounding normal tissues. Only uptake in the deep region of the axilla was considered as a positive node for metastatic involvement compared to the superficial uptake, which corresponded to either sudation or skin folds or sometimes to thyroid activity. If more than one focus of uptake was detected, the observers were asked to report the number of different foci. For each study, semiquantitative analysis was used to determine the relative degree of diagnostic certainty: 0 = definitely normal, 1 = probably normal, 2 = equivocal, 3 = probably abnormal and 4 = definitely abnormal. For the purpose of this study, Grades 0 and 1 were considered as being normal (negative for metastasis) whereas Grades 3 and 4 were considered as being positive for metastatic disease. Equivocal cases (Grade 2) were analyzed separately.

Statistical Analysis

Data were expressed as mean ± 1 s.d. Sensitivity was defined as the number of true-positive cases divided by the sum of the true-positive plus the false-negative studies. Specificity was the number of true-negative cases divided by the sum of true-negative plus false-positive studies. Positive and negative predictive values were defined as the number of true-positive cases divided by the sum of true-positive plus false-positive and the number of true-negative divided by the sum of true-negative plus false-negative cases, respectively.

RESULTS

Patient Population

All patients had a proven primary breast cancer with the following histopathologic diagnosis: infiltrating ductal carcinoma (n = 86), infiltrating lobular carcinoma (n = 7), medullary carcinoma (n = 2), cribriform carcinoma (n = 2), tubular carcinoma (n = 2) and lymphoma (n = 1). Level I-II axillary lymph node dissection was performed in all patients. Histopathologic examination revealed metastatic node involvement in 48 patients. A total of 502 nodes were removed, and 180 showed metastatic disease. Fifty-two patients did not have axillary lymph node metastatic involvement. A total of 611 negative nodes were removed.

Technetium-99m-MIBI Imaging

The sensitivity of ^{99m}Tc-MIBI imaging for detecting patients with metastatic axillary lymph node involvement was 79.2% (38/48 patients) while the specificity of ^{99m}Tc-MIBI imaging to exclude metastatic disease was 84.6% (44/52 patients). The positive and the negative predictive values were 82.6% (38/46) and 81.5% (44/54), respectively (Figs. 1–3). There were no equivocal (Grade 2) cases on semiquantitative analysis. All cases were judged to be either definitely or probably normal or abnormal. A summary of the correlation between ^{99m}Tc-MIBI axillary uptake and histologic evidence of metastatic axillary lymph node involvement is shown in Table 1.

The distribution of patients by considering the number of histologically positive nodes per patient in those with true-positive studies (n = 38) is shown in Figure 4. Although 35 patients had two or more histologically positive lymph nodes, ^{99m}Tc-MIBI imaging detected only one focus of increased uptake in the axilla in 29 patients (29/35, 82.8%). In the other nine patients, more than one area of increased axillary uptake was seen. Thus, there was no direct correlation between the number of metastatic lymph nodes and the number of axillary foci of increased uptake on ^{99m}Tc-MIBI imaging. Three patients with only one histologically positive node were correctly identified on ^{99m}Tc-MIBI imaging.

The distribution of patients by considering the number of histologically positive lymph nodes per patient in those having a false-negative study is shown in Figure 5. Six patients out of the 10 with a false-negative ^{99m}Tc-MIBI study had only one metastatic axillary lymph node on histopathologic examination, while two patients had two positive nodes, one had three and a fourth patient had four positive nodes. No patient with more than four metastatic axillary lymph nodes was missed by ^{99m}Tc-MIBI imaging. The axillary nodes that were missed were either micrometastases (involvement less than 2-mm) or clandestine metastases (involvement of small emboli of tumor cells in the sinuses of axillary nodes).

Eight studies were false-positive for the presence of metastatic axillary lymph node involvement. Histopathologic results showed a sarcoidosic lymphadenitis in one patient and a nonspecific chronic inflammatory reaction in two patients while, in the remaining five patients, histopathologic examination did not show any significant abnormality.

The diagnostic certainty for the 38 true-positive cases was as follows: 31 were read as definitely abnormal (81.6%) and seven as probably abnormal (18.4%). For the 10 false-negative cases, six were probably normal (60%) and four were definitely normal (40%). There were 44 true-negative studies: 38 were definitely normal (86.4%) and six were probably normal (13.6%). Six of the eight (75.0%) false-positive studies were interpreted as being probably abnormal and two were definitely abnormal (25.0%).

FIGURE 1. Normal ^{99m}Tc-MIBI imaging of the left axilla. There is no abnormal focus of increased uptake in the axilla. This patient had a nonpalpable 4-mm breast cancer of the upper portion of the breast without metastatic involvement of the axillary lymph nodes (17 negative nodes). Note the mild to moderate and superficial ^{99m}Tc-MIBI increased uptake corresponding to cutaneous activity (arrow).

DISCUSSION

The axillary lymph node chains are the major regional drainage sites for the breast. Presently, in patients with proven breast cancer or in whom a breast lesion is suspected, axillary lymph node status is determined either clinically or pathologically. So far, imaging modalities have played a very limited clinical role in this condition. The clinical evaluation of lymph node status, however, is frequently inaccurate. Among patients with clinically palpable lymph nodes thought to be positive for metastatic involvement, 38% would not have lymph node metastases on histologic review (*35*). Conversely, among patients with clinically negative axillary lymph nodes, up to 39% may have histologically positive nodes. Axillary dissection provides very important staging and prognostic information and remains the best procedure to evaluate axillary lymph node status in patients with primary breast cancer. However, this surgical procedure is associated with a certain degree of morbidity. Sometimes, surgeons may be reluctant to perform an axillary dissection in certain types of patients (very obese or elderly patients, for example) who are more prone to complications. An imaging procedure able to detect the presence or absence of axillary metastases would be useful in such clinical situations.

Scintimammography using ^{99m}Tc-MIBI has been recently introduced to evaluate patients with suspected or proven primary breast cancer. Some preliminary studies performed in a relatively limited number of patients have shown that ^{99m}Tc-MIBI breast imaging can also be used to detect metastatic axillary lymph nodes (*26,33*). Our study, performed in 100 patients with proven primary breast cancer, axillary dissection

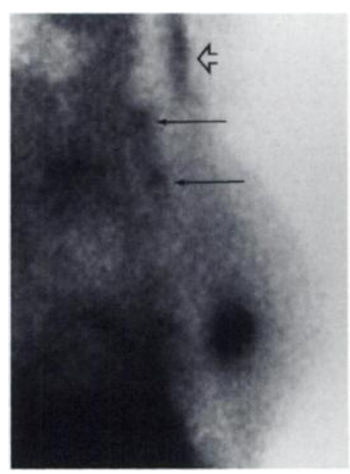

FIGURE 2. This patient had a primary carcinoma of the right breast (dense focus of increased uptake) with metastatic axillary lymph node involvement (4 of 20 removed nodes were histologically positive). Two more well-delineated foci of increased uptake are seen in the right axilla (arrows). Note the superficial activity (arrowhead), which should not be misinterpreted as a positive metastatic lymph node.

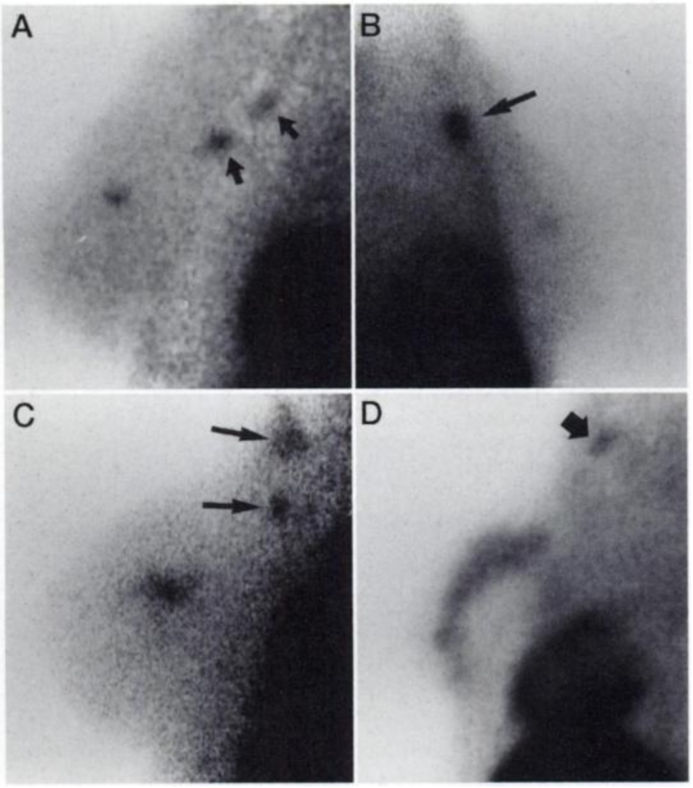

FIGURE 3. Technetium-99m-MIBI breast and axilla imaging from four patients with proven infiltrating ductal carcinoma of the breast and metastatic involvement of the ipsilateral axillary lymph nodes (arrows). (A) Left breast cancer with two metastatic nodes along the lymphatic chain. (B) Right primary breast cancer (inner and upper quadrant) with a focus of significantly increased uptake in the axilla. Three small metastatic nodes were found. (C) Patient with a large cancer of the left breast with multiple foci of increased ^{99m}Tc-MIBI uptake in the ipsilateral axilla. Seven out of 20 nodes were found to be metastatic on histopathologic study. (D) Patient with a left breast prosthesis and overlying primary breast carcinoma. One focus of increased uptake was detected in the left axilla. Two lymphatic nodes were histologically positive for metastatic involvement.

and histopathologic correlation, confirms the relatively good diagnostic accuracy of this procedure to evaluate axillary lymph node status with a sensitivity of 79.2%, a specificity of 84.6%, a positive predictive value of 82.6% and a negative predictive value of 81.5%. No patients with more than four histologically proven metastatic axillary lymph nodes have been missed by ^{99m}Tc-MIBI imaging. Six patients out of the 10 false-negative ^{99m}Tc-MIBI studies had only one metastatic axillary lymph node. Three out of the eight patients with false-positive studies had axillary nodes with an inflammatory reaction, which can explain the presence of positive ^{99m}Tc-MIBI uptake. The diagnostic certainty gradation showed that there is a high level of confidence in the final diagnosis of ^{99m}Tc-MIBI axilla imaging with 81.6% of true-positive cases read as being definitely abnormal, and 86.4% of true-negative studies as being definitely normal.

As with any other diagnostic procedure, technical considerations for ^{99m}Tc-MIBI breast and axilla imaging are important for obtaining satisfactory results. As previously reported, 20–30 mCi ^{99m}Tc-MIBI intravenously was used, in addition to a relatively lengthy acquisition time (10 min/view), in order to provide images with high count density. This is especially important for this procedure, given the relatively low absolute ^{99m}Tc-MIBI uptake in both primary breast cancer and metastatic axillary lymph nodes (*36*). The breast and the axilla must also be as close as possible to the detector surface. This is facilitated by using the foam cushion and putting patients in the prone position. In some patients, slight anterior oblique projections may also be useful. Direct reading from the computer screen, with appropriate adjustments for contrast, was found to be the most critical part of the study especially when organs or tissues adjacent to the target lesion showed a significant ^{99m}Tc-MIBI uptake.

In this study, only planar imaging was used. Although SPECT imaging provides a better contrast resolution than planar studies, accurate localization of the lesion sometimes can be more difficult to obtain given the low absolute activity in the lesions. A previous study (*37*), using a standard gamma camera, showed that the sensitivity for detecting breast cancer and axillary metastases was similar for planar and SPECT imaging, but the specificity was decreased with SPECT compared to planar acquisition. Recent advances in detector technology, with potential improvement in spatial resolution, possibly could increase the sensitivity and more precisely delineate the metastatic axillary lymph nodes. Also, in our study, ^{99m}Tc-MIBI imaging detected only one focus of increased uptake in the axilla in 76.3% of patients who had two or more histologically positive lymph nodes. This is not a surprising finding since most of the lymph nodes have a small volume, a relatively low absolute uptake and are close to each other.

Given a sensitivity of 79.2% and a specificity of 84.6% for ^{99m}Tc-MIBI imaging in detection of axillary metastases, the clinical value of this procedure might be questioned. A sensitivity in the order of 80% is probably too low to use ^{99m}Tc-MIBI imaging on a routine basis to avoid unnecessary axillary dissection since 20% of the patients with metastatic involvement would be missed. However, a positive axillary ^{99m}Tc-MIBI uptake might have a more important clinical significance. In a patient with breast carcinoma who is reluctant, or in whom the surgeon is reluctant, to proceed to an axillary dissection for medical or technical reasons (such as obesity, systemic disease or age), an increased ^{99m}Tc-MIBI uptake in the axilla with a specificity of approximately 85% certainly represents a good indication for performing the axillary dissection and convincing both the patient and the surgeon. A negative study in these circumstances may also be useful. It may help avoid an axillary

TABLE 1
Correlation Between Technetium-99m-MIBI Axillary Uptake and Histologic Evidence of Metastatic Axillary Lymph Node Involvement

^{99m}Tc-MIBI uptake (n = 100)	Patients with negative nodes (n = 52)	Patients with positive nodes (n = 48) number of positive nodes per patient			
		n = 1	n = 2	n = 3	n ≥ 4
Positive (n = 46)	8 (15.4%)	3 (33.3%)	6 (75.0%)	9 (90.0%)	20 (95.2%)
Negative (n = 54)	44 (84.6%)	6 (66.7%)	2 (25.0%)	1 (10.0%)	1 (4.8%)

Sensitivity: 79.2% (38/48); positive predictive value: 82.6% (38/46).
Specificity: 84.6% (44/52); negative predictive value: 81.5% (44/54).

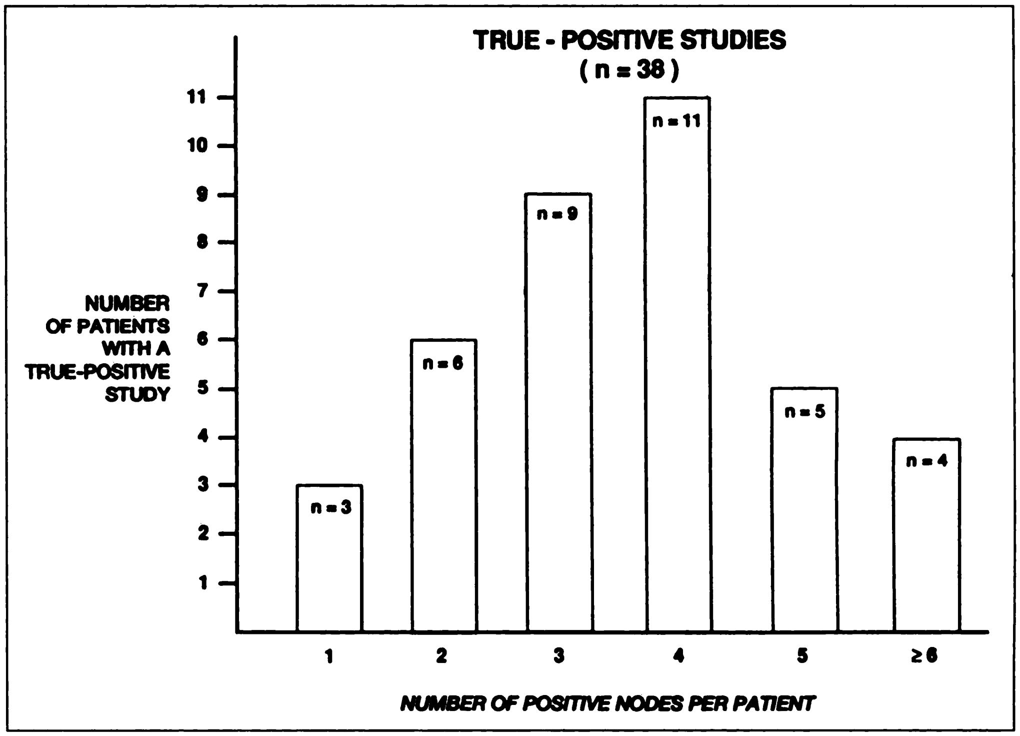

FIGURE 4. Distribution of patients according to the number of histologically positive axillary nodes per patient in those with true-positive studies.

dissection with its short-term and long-term complications. A positive ^{99m}Tc-MIBI axillary uptake for lymph node metastases may increase diagnostic confidence that a lesion in the breast will correspond to a primary carcinoma.

Technetium-99m-MIBI imaging of the axilla is easy to perform, and the information is concomitantly obtained from a standard ^{99m}Tc-MIBI scintimammography without significant modification. The only difference is to make sure that the complete axillary region is included in the field-of-view. Other imaging parameters remain the same, and contrast adjustment is also important for breast imaging. Although the clinical role of axillary lymph node imaging is not yet clearly defined, the information on the axillae status should be part of the report of a scintimammography. It would be interesting to compare the results of ^{99m}Tc-MIBI axillary node imaging to those obtained with lymphoscintigraphy and an intraoperative gamma probe, which is another new and promising diagnostic radionuclide procedure, to obtain lymphatic mapping and sentinel node biopsy (*38*).

In order to better evaluate and possibly enhance the clinical potential of ^{99m}Tc-MIBI axillary imaging in patients with primary breast cancer, the next research step would be to directly compare, in a prospective blinded study (using histopathologic correlation as the gold standard), the results of

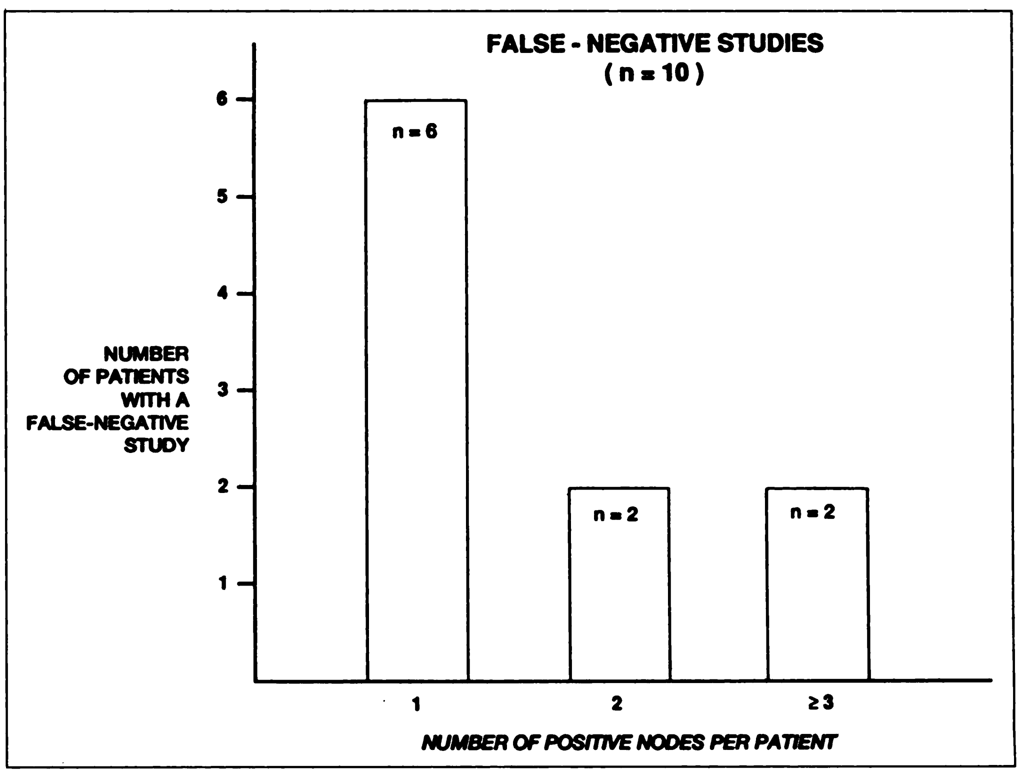

FIGURE 5. Distribution of patients according to the number of histologically positive axillary nodes per patient in those with a false-negative ^{99m}Tc-MIBI study.

^{99m}Tc-MIBI axillary imaging and those of the clinical physical examination of the axilla (also using a diagnostic certainty grading system). It is likely that the overall combination of the results of both a physical examination and ^{99m}Tc-MIBI imaging of the axilla would improve their respective diagnostic accuracy. This addition of two noninvasive procedures, such as clinical and scintigraphic axillary evaluation, could be advantageous for patients with primary breast cancer. A direct comparison with other radiopharmaceuticals such as ^{99m}Tc-methyldiphosphonate, ^{99m}Tc-tetrofosmin or ^{18}F-FDG would also be interesting.

CONCLUSION

This study confirmed the results of some previous preliminary reports and demonstrated good diagnostic accuracy for ^{99m}Tc-MIBI axillary imaging to detect lymph node metastases from primary breast cancer. The information on axillary nodes was simply derived from a slightly modified standard ^{99m}Tc-MIBI scintimammography (with the inclusion of the entire axillary region in the field-of-view) and was obtained as concomitant data to those of the breast lesion. Technological improvements may also contribute to a more widespread clinical use of ^{99m}Tc-MIBI breast and axillary imaging in patients with known or suspected primary breast cancer.

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