Mammography and ^{99m}Tc-MIBI Scintimammography in Suspected Breast Cancer*

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The aim of this work has been to evaluate whether a diagnostic protocol based on the joint use of mammography and ^{99m}Tc-methoxyisobutyl isonitrile (MIBI) scintimammography is capable of reducing the number of biopsies required in patients with suspected breast cancer. **Methods:** We performed prone scintimammography in 90 patients with suspected breast cancer, involving 97 lesions. In all patients, the diagnosis was established by way of biopsy. On mammography, we evaluated the degree of suspicion of malignancy and the size of the lesion (smaller or larger than 1 cm in diameter). **Results:** The results of only 41 of the biopsies indicated malignancy. On mammography, 20 lesions (of which 1 was breast cancer) were considered to be of low suspicion of malignancy, 31 (of which 4 were breast cancer) as indeterminate and 46 (of which 36 were breast cancer) as high. Fourteen lesions (2 low probability, 2 indeterminate and 10 high) were smaller than 1 cm, whereas 83 (18 low probability, 29 indeterminate and 36 high) were larger. The sensitivity, specificity, positive predictive value and negative predictive value of scintimammography were 85%, 79%, 74% and 88%, respectively. Scintimammography was positive in all cases of breast cancer that initially had a low or indeterminate suspicion of malignancy according to mammography, as well as in 30 cases of breast cancer that initially were highly suspicious. Six false-negative scintimammography studies were obtained in lesions with a high suspicion of malignancy. **Conclusion:** We propose a diagnostic protocol with a biopsy performed on lesions that have a high suspicion of malignancy as well as those with low or indeterminate suspicion that are smaller than 1 cm or with positive scintimammography results. This would have reduced the total number of biopsies performed by 34%. More importantly, there would have been a 65% reduction in number of biopsies performed in the low and indeterminate mammographic suspicion groups. All 41 cases of breast cancer would have been detected.

Key Words: ^{99m}Tc-MIBI scintimammography; mammography; breast cancer diagnostic protocol

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Breast and lung cancers are the most common neoplasms in women. In the U.S., breast cancer comprises some 32% of the cancers diagnosed in the female population, with 183,000 new cases detected in 1995, leading to 46,000 deaths (*1*). In the European Union the data are similar, with approximately 135,000 new cases detected every year, resulting in 58,000 deaths (*2*). In Spain, a country that, like others in Southern Europe, had significantly low rates of breast cancer in a European context, deaths from breast cancer have gradually increased in recent decades, with the current incidence of breast cancer approximately equal to the European Union average (*3,4*).

Mammography is the diagnostic method with the greatest usefulness, both in screening and in diagnosing breast cancer. However, although mammography is a highly sensitive technique in the diagnosis of breast cancer, it is frequently incapable of differentiating malignant lesions from a benign ones (*5*). Most published studies have obtained a positive predictive value (PPV) for mammography that ranges between 10% and 40% (*6–10*). This PPV causes a large number of breast biopsies to be performed on benign lesions, resulting in a high financial cost and possibly making subsequent mammographic evaluation more difficult (*10*). Furthermore, in young studies, fibrocystic disease, dense breasts or evaluation after biopsy, surgery or radiotherapy, the sensitivity of mammography is much lower and the diagnosis of the cancer is occasionally impossible (*11*). Bearing all these limitations in mind, the importance of a complementary diagnostic procedure that allows the PPV of mammography to be enhanced and that completes the study of patients who are difficult to evaluate by way of mammography becomes clear.

^{99m}Tc-methoxyisobutyl isonitrile (MIBI) is a tracer that is widely used as a myocardial perfusion agent. In 1987, Müller et al. (*12*) observed, by accident, the uptake of this radiopharmaceutical in the lung metastasis of a thyroid carcinoma. In 1989, Hassan et al. (*13*) studied a group of 19 patients with suspected lung neoplasms and detected 10 of the 13 cancers present by ^{99m}Tc-MIBI scintigraphy. Since these pioneering works, a broad experience has been amassed in the usefulness of ^{99m}Tc-MIBI scintigraphy in the evaluation of different types of neoplasms, fundamentally in gliomas, bone tumors, lung cancer, thyroid cancer and others (*14,15*). Although the first articles on ^{99m}Tc-MIBI uptake in breast cancer appeared in 1992 (*16,17*), it was the research of Waxman et al. (*18*) and Khalkhali et al. (*19,20*) that

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generated the clinical interest in evaluating breast cancer with this radiopharmaceutical. Since then, various authors have studied the possible usefulness of ^{99m}Tc-MIBI scintimammography in the evaluation of breast cancer (*21–24*).

The aims of this study were (a) to confirm in our own environment the usefulness of ^{99m}Tc-MIBI scintimammography and, fundamentally, (b) to determine whether a diagnostic protocol based on the joint use of mammography and scintimammography is capable of reducing the number of biopsies required in patients with suspected breast cancer.

MATERIALS AND METHODS

We retrospectively studied 90 women (age range 28–83 y, average age 55 y) with mammographic suspicion of breast cancer using ^{99m}Tc-MIBI scintimammography and in whom a breast biopsy was subsequently performed. As inclusion criteria, we considered women older than 21 y who were neither pregnant (a) nor lactating (b) in whom mammography had been performed previously, with a maximum interval of 3 wk, and (c) in whom an excisional biopsy of the lesion was performed no more than 6 wk after the scintigraphy. In those instances when the patient underwent fine needle biopsy of the suspected lesion, we waited at least 1 wk before performing scintimammography. The total number of lesions subjected to biopsy was 97, and in all patients the breast biopsy was indicated on the basis of the mammographic findings. Sixty-six lesions were detected by palpation, whereas in the other 31 lesions, the palpation was normal.

Mammography was performed in all patients in craniocaudal and mediolateral oblique views. When necessary, additional projections or coned compressions were obtained or magnification techniques used. For all patients, the mammograms were evaluated according to the probability of malignancy, with the studies divided into three groups representing low, indeterminate or high probability of malignancy. Similarly, the size of the lesion was determined and classified in two groups according to whether the size was smaller or larger than 1 cm. In those patients in whom mammography did not allow us to evaluate the size of the lesion, 7 with dense breast tissue and 1 with microcalcifications, we classified the lesions as being larger or smaller than 1 cm depending on whether they were palpated.

The labeling and quality controls of ^{99m}Tc-MIBI were performed according the manufacturer's instructions (DuPont Radiopharmaceuticals, Billerica, MA). The radiopharmaceutical was injected into the arm on the contralateral side of the affected breast. When there were clinical and/or mammographic suspicions of a bilateral pathology, the injection was made in the dorsal vein of the foot.

Prone breast scintigraphy was performed with a special table using the technique described by Khalkhali et al. (*19,20*). The injected dose of ^{99m}Tc-MIBI was 740 MBq, and planar image acquisition began 10 min after radiopharmaceutical administration. The same imaging sequence was performed in all patients, beginning with the lateral view of the breast with the suspected abnormality, followed by the lateral view of the contralateral breast and the anterior view of both breasts. Image acquisition time was 10 min, using a high-resolution collimator and a 256 × 256 matrix.

All focal or multifocal uptake of ^{99m}Tc-MIBI higher than the background uptake of the breast was considered a positive result. Diffuse breast uptake was not considered to be suggestive of malignancy. In all patients, the final diagnosis was established by biopsy results.

The study was approved by the Research Ethics Committee of the Zaragoza University Teaching Hospital, and all patients gave informed consent for scintimammography to be performed.

RESULTS

Excisional biopsy results identified cancer in 41 lesions (42%) and a benign pathology in 56 lesions (58%). The final diagnoses were infiltrating ductal carcinoma (n = 34), infiltrating lobular carcinoma (n = 3), ductal carcinoma in situ (n = 3), papillary carcinoma (n = 1), fibrocystic disease (n = 45) and fibroadenoma (n = 11).

Scintimammography results were positive in 35 cases of breast cancer (35 true-positive [TP]), and 6 cases had no ^{99m}Tc-MIBI uptake (6 false-negative [FN]). In the benign lesions, scintimammography results were positive in 12 cases (12 false-positive [FP]) and normal in 44 (44 true-negative [TN]). The sensitivity and specificity of ^{99m}Tc-MIBI scintimammography were 85% and 79%, respectively, with a PPV of 74% and a negative predictive value (NPV) of 88% (Table 1). Of the 12 FP results, 7 were fibroadenomas and 5 were fibrocystic disease. The 7 fibroadenomas detected by scintimammography measured more than 1 cm in length, with 4 of them exceeding 3 cm in diameter. The FN results were produced by 4 tumors <1 cm in length (3 ductal carcinomas in situ and 1 infiltrating ductal carcinoma of 0.4 cm) and 2 infiltrating ductal carcinomas 1.2 and 1.4 cm in diameter, respectively.

The size of the mammographic alterations was <1 cm in 14 lesions and >1 cm in 83. We found a good correlation between the size of the lesion as determined by mammography and histopathology ($\kappa = 0.76$). The smallest and largest lesions studied measured 0.4 and 8 cm in diameter, respectively. In lesions smaller than 1 cm, scintimammography was positive in only 2 examinations (2 cases of cancer) and normal in 12 (8 benign lesions and 4 cases of cancer). The small number of lesions that were <1 cm limits the value of the statistical analysis in this subset. In lesions larger than 1 cm, scintimammography was positive in 45 examinations (33 TP, 12 FP) and negative in 38 (36 TN, 2 FN), which supposes a sensitivity of 94%, a specificity of 75%, a PPV of 73% and an NPV of 95% (Table 1).

Mammograms were interpreted as revealing a low suspicion of malignancy in 20 examinations, an indeterminate suspicion in 31 and a high suspicion in 46 (Table 2). In the 20 lesions with a low suspicion of malignancy, the biopsy results indicated only 1 case of cancer, that is to say, 5% of

TABLE 1
Results of ^{99m}Tc-MIBI Scintigraphy

	No. of lesions	Sensitivity	Specificity	PPV	NPV
Total	97	85%	79%	74%	88%
Lesions >1 cm	83	94%	75%	73%	95%

PPV = positive predictive value; NPV = negative predictive value.

TABLE 2
Definitive Diagnostic Results of ^{99m}Tc-MIBI Scintigraphy and Lesion Size According to Mammographic Degrees of Malignancy

Probability of malignancy according to mammography	Diagnosis	Scintimammography		Lesion size	
		+	−	<1 cm	>1 cm
Low (n = 20)	Infiltrating lobular carcinoma	1			1
	Fibrocystic disease	1	13	2	12
	Fibroadenoma	2	3		5
Indeterminate (n = 31)	Infiltrating ductal carcinoma	3			3
	Infiltrating lobular carcinoma	1			1
	Fibrocystic disease	2	21	2	21
	Fibroadenoma	4			4
High (n = 46)	Infiltrating ductal carcinoma	28	3	3	28
	Ductal carcinoma in situ		3	3	
	Infiltrating lobular carcinoma	1			1
	Papillar carcinoma	1			1
	Fibrocystic disease	2	6	4	4
	Fibroadenoma	1	1		2

the lesions included in this group. Scintimammography was positive in 4 lesions in this group (1 cancer, 1 fibrocystic disease and 2 fibroadenomas) and negative in 16 (13 fibrocystic disease and 3 fibroadenomas). Only 2 cases of fibrocystic diseases were <1 cm (Table 2).

Of the 31 lesions evaluated by mammography with an indeterminate probability of malignancy, the biopsy demonstrated 4 cases of cancer, that is to say, 13% of the lesions included in this group, with all of these presenting anomalous ^{99m}Tc-MIBI uptake (Fig. 1). In the 27 cases of benign lesions, the scintimammography was positive in 6 (4 fibroadenomas and 2 fibrocystic diseases) and negative in 21 (21 fibrocystic diseases) (Fig. 2). In a manner analogous to that of the low probability group, only 2 lesions with an indeterminate probability of malignancy, namely two cases of fibrocystic disease, had a size smaller than 1 cm (Table 2).

Thirty-six (78%) of the 46 lesions with a high mammographic probability of malignancy were diagnosed as cancer. Scintimammography was positive in 30 of these lesions (Fig. 3) and normal in 6. In 4 of the normal studies and in 2 of the positive, the lesion was <1 cm. Of the 10 benign lesions in this group, scintimammography was normal in 7 (1 fibroadenoma and 6 fibrocystic disease) and pathologic in 3 (1 fibroadenoma and 2 fibrocystic diseases). In 4 of the lesions with fibrocystic disease with normal scintimammography results, the lesion was <1 cm (Table 2).

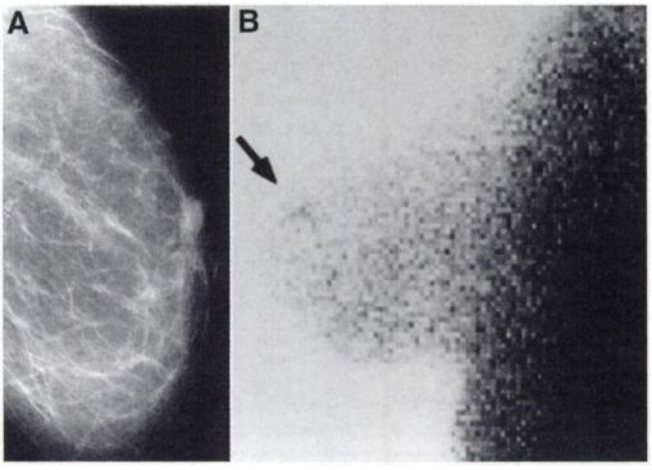

FIGURE 1. (A) Mammogram shows high-density, irregular mass with ill-defined, fuzzy margins and indeterminate suspicion of malignancy. (B) Left lateral prone ^{99m}Tc-MIBI scintimammogram shows focal area of radiopharmaceutical uptake (arrow). Excisional biopsy results indicated infiltrating ductal carcinoma.

DISCUSSION

In the last few years, several studies have investigated the usefulness of ^{99m}Tc-MIBI scintimammography in the evaluation of patients with suspected breast cancer (*19–24*). The overall results of these studies are, in general, good, with a sensitivity between 84% (*25*) and 94% (*26*) and a specificity between 72% (*18*) and 94% (*27*). In this study the sensitivity is 85%, which is similar to that obtained by other authors such as Kao et al. (*25*), Palmedo et al. (*23*) or Villanueva-Meyer et al. (*24*).

Of the 6 FN results in this series, 4 were lesions <1 cm in diameter and 2 were >1 cm. FN results have been attributed to lesion size <1 cm, to overexpression on the part of the tumoral cells of the multidrug resistance (MDR) gene or to tumors with minimal desmoplastic reaction (*24*).

The specificity of scintimammography in this study was 79%, lower than that obtained by Taillefer et al. (*27*) and Khalkhali et al. (*26*), but similar to that obtained by Palmedo et al. (*23*), Jimenez et al. (*21*) or the Multicenter Clinical Test performed in the U.S. (*28*). The 12 FP results were 5 cases of fibrocystic disease and 7 fibroadenomas. Considered as possible causes of the FP results are hyperproliferative breast disorders, especially hyperplasia associated with atypia (*29*), and juvenile adenomas with high mitotic activity or local inflammation (*23*). Khalkhali et al. (*30*) associated lesions with hypercellularity to FP results. In the evaluation of FP results caused by fibroadenomas, and in

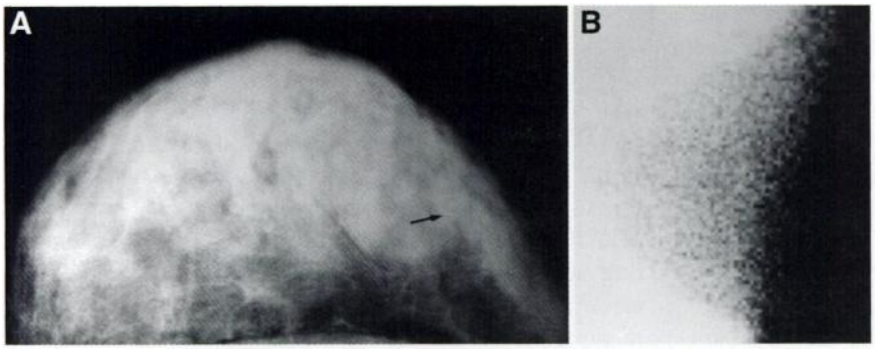

FIGURE 2. (A) Craniocaudal mammogram of extremely dense breast tissue shows grouped punctuate calcifications (arrow). Mammogram was interpreted as revealing indeterminate suspicion of malignancy. (B) ^{99m}Tc-MIBI scintimammogram shows normal results. Excisional biopsy results diagnosed cystic disease.

addition to the causes cited above, consideration must be given to the size of the lesion. In this study, 4 fibroadenomas that were >3 cm in diameter had ^{99m}Tc-MIBI uptake. Other causes that contributed to the relatively low specificity in our series are the selection of the patients to be studied and the interpretation criteria followed when classifying a scintimammogram as positive. A series with a high prevalence of benign lesions, primarily with hyperproliferative breast disorders such as fibrocystic disease or large fibroadenomas, will have a higher proportion of FP results. In this series, 58% of the lesions were benign. The prevalence of cancer in the different series using scintimammography varies, ranging from 41% to 84%, according to Waxman (*29*). In this study, we included lesions with all degrees of mammographic suspicion of malignancy, not just those with a high degree of suspicion. As result, only 42% of the lesions were diagnosed as breast cancer. Furthermore, and with the aim of detecting the largest possible number of cancers, in this study, all focal or multifocal breast uptake of radiopharmaceutical was considered to be positive, independent of the intensity of its uptake.

Mammography is a diagnostic technique of unquestionable usefulness in screening for breast cancer except for the fact that, on many occasions, a diagnosis of cancer cannot be discounted with any certainty because it is not capable of distinguishing between benign and malignant lesions. Furthermore, there is also a large interobserver variability in its interpretation (*31,32*). Because the PPV of mammography is approximately 10%–40% (*6–10*), a large number of biopsies must be performed on benign lesions. The sensitivity of mammography to detect breast cancer ranges between 85% and 90%, with dense breast tissue being the main cause of FN results (*11,33*). Fibrocystic disease or studies performed after biopsy, surgery or radiotherapy could also limit its sensitivity (*11*).

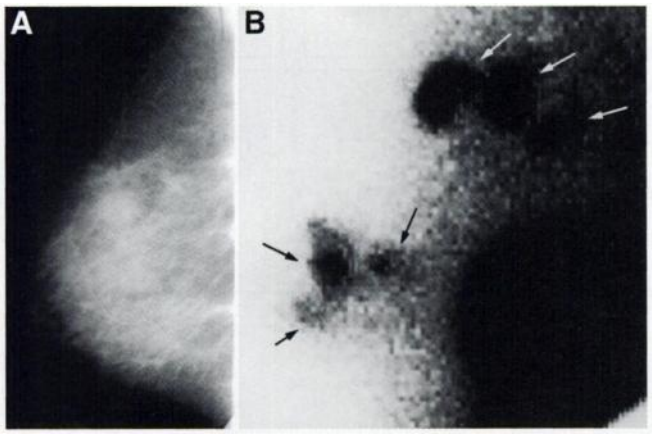

FIGURE 3. (A) Mammogram shows mass with spiculated margins and architectural distortion and, probably, a satellite node. Nipple retraction is visible. Suspicion of breast carcinoma was high. (B) Left lateral prone ^{99m}Tc-MIBI scintimammogram shows multifocal breast cancer (black arrows) with axillary involvement (white arrows). Excisional biopsy results indicated multifocal infiltrating ductal carcinoma with axillary involvement.

Despite the limitations of mammography and the good results obtained with ^{99m}Tc-MIBI scintimammography, Waxman (*29*) indicated that this technique cannot be considered as a screening test. Its sensitivity in lesions <1 cm is very low, and as the results of this study show, 6% of breast neoplasms >1 cm are not detected. In the light of this finding, we concentrated the objective of this study on answering the following questions: What role could ^{99m}Tc-MIBI scintimammography play in the study of breast cancer and, more specifically, could scintimammography be used jointly with mammography as a diagnostic protocol aimed at reducing the number of biopsies performed on benign lesions after mammographic indication?

Although there are a considerable number of articles devoted to the usefulness of ^{99m}Tc-MIBI scintimammography in the study of breast cancer; very few studies evaluated mammography and scintimammography jointly. Tabuenca et al. (*34*) presented the results obtained in a group of 28 patients with mammographic criteria for malignancy, evaluating whether the inclusion of scintimammography could reduce the number of biopsies performed on benign lesions. The sensitivity and NPV of their study was 100%, and the inclusion of scintimammography would reduce the number of unnecessary biopsies by 30%.

Having confirmed the usefulness of ^{99m}Tc-MIBI scintimammography in the study of breast cancer, we believe the possible inclusion of scintimammography in a diagnostic protocol of breast cancer must be supported by a joint evaluation of the results obtained both by mammography and by scintimammography. In our mammography studies, we determined both the degree of suspicion of malignancy

of the lesion and its size. The size was established according to the results of the mammogram, with mammography considered more objective than palpation and less dependent on the size of the breast or the depth of the lesion being studied. We divided the lesions into two groups according to their diameter, either smaller or larger than 1 cm, with this size considered as an acceptable limit for its detection by scintimammography. The low sensitivity of scintimammography in lesions <1 cm in diameter caused us to reject its use in this size lesion.

The American College of Radiology (ACR) classifies mammography results into five categories according to their suspicion of malignancy (*35*), ranging from 1 (normal) to 5 (high suspicion of malignancy). The suspicions of malignancy in this study are covered by three of these categories: probably benign, category 3; indeterminate probability of malignancy, category 4; and high suspicion of malignancy, category 5. The incidence of breast cancer in categories 3, 4 and 5 is 2%, 10% and 82%, respectively (*30*). When we take into account that roughly 700,000 biopsies are performed every year in the U.S., at an estimated cost of $1555–$3000 per biopsy, we can get some idea of the financial impact of a new diagnostic procedure performed to determine which lesions should undergo biopsy.

Like the ACR classification, mammograms in this series were evaluated as having a low, indeterminate or high probability of malignancy. The incidence of breast cancer in these groups was 5%, 13% and 78%, respectively, similar to those obtained in categories 3, 4 and 5, according to the above-mentioned ACR classification.

Although with the qualification that this study contains a limited number of patients, the diagnostic protocol we propose (Fig. 4) clearly differentiates between those lesions with a high mammographic suspicion of malignancy and those with a low or indeterminate probability of malignancy. In the former lesions, of which 78% were breast cancer, a breast biopsy must be performed and as soon as possible. With these lesions, scintimammography would be indicated only when there is a suspicion of multicenter or bilateral cancer, in the study of axillary extension, in postchemotherapy control or in the evaluation of MDR.

In lesions with a low or indeterminate mammographic probability of malignancy and with a diameter >1 cm, the inclusion of ^{99m}Tc-MIBI scintimammography may have important consequences in reducing the number of biopsies. After examination with ^{99m}Tc-MIBI, the biopsy of mammographically visualized lesions would be performed only on lesions with positive scintimammography results, whereas lesions with negative scintimammography results, clinical follow-up and routine mammography would be indicated.

If we were to apply this diagnostic protocol to these patients, of the 97 lesions being studied, it would have been necessary to perform a biopsy only on 64 lesions (46 cases of high probability of malignancy, 4 of low or indeterminate probability with a lesion size <1 cm and 14 of low or indeterminate probability with positive scintimammography results), representing a 34% reduction in the total number of biopsies. Bearing in mind that, as Khalkhali et al. (*30*) indicated, the contribution of nuclear medicine to the study of breast cancer is to reduce the number of biopsies on

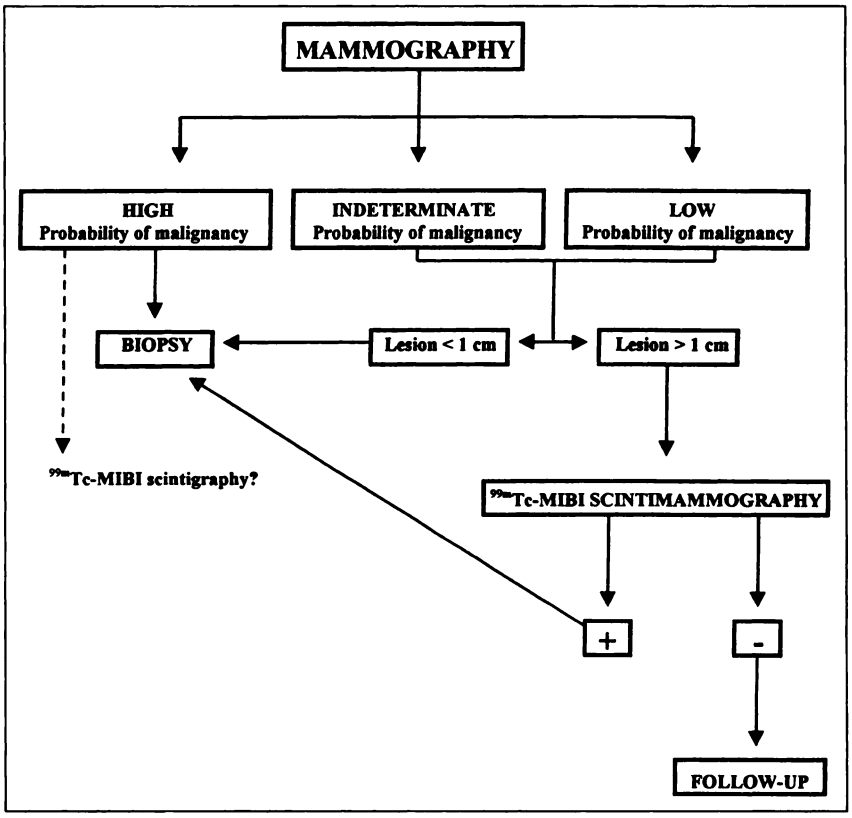

FIGURE 4. Mammography-^{99m}Tc scintimammography diagnostic protocol in patients with mammographic suspicion of breast cancer.

lesions with a low or medium probability of malignancy, if the proposed protocol were applied to these types of lesions (n = 51), 18 biopsies would have been performed after ^{99m}Tc-MIBI scintimammography, representing a 65% reduction in the number of biopsies performed on these lesions. Logically, the application of this mixed mammography-scintimammography diagnostic protocol would be acceptable only if, apart from helping to reduce the number of biopsies, it detected all cases of cancer. In this series, the application of this protocol would have detected all 41 cases of breast cancer. Of course, these results must be considered in the context of a limited group of patients, such that prospective larger studies will be necessary to confirm these initial findings.

In our opinion, the results obtained from the joint evaluation of mammography and ^{99m}Tc-MIBI scintimammography reflect the complementary roles of these two diagnostic procedures. All FN scintimammography results were obtained in lesions with a high suspicion of malignancy, which, on mammography, manifested themselves as grouped microcalcifications in a small space. Other authors have indicated how this type of lesion could be the cause of FN results in scintimammography (*19,21*). By contrast, conditions that are difficult to evaluate by mammography, such as dense breast tissue, areas of architectural distortion or asymmetric breast tissue, are, generally, easily evaluated by scintimammography.

CONCLUSION

We suggest that ^{99m}Tc-MIBI scintimammography, used as a complementary technique to mammography, is a useful test in the examination of patients with suspected breast cancer. The adoption of a joint mammography-scintimammography diagnostic protocol could considerably reduce the number of biopsies performed in patients with lesions of low or indeterminate mammographic suspicion of malignancy. Larger series will be necessary to determine the definitive value of this protocol, which has been drawn up to select those patients with suspected breast cancer in whom a biopsy of the lesion should be performed.

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