Technetium-99m-Tetrofosmin Scintimammography in Suspected Breast Cancer Patients: A Comparison with Technetium-99m-MIBI

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Key Words

Technetium-99m-MIBI · Technetium-99m-tetrofosmin · Scintimammography · Breast cancer

Abstract

Objective: To investigate the diagnostic role of ^{99m}Tc-tetrofosmin in the detection of primary breast cancer and axillary lymph node metastasis and to compare the findings with those of ^{99m}Tc-MIBI. **Methods:** Forty-eight patients with clinically palpable masses or abnormal radiologic findings had ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin scintimammographies (SMMs) after intravenous injections of 925 MBq of radiopharmaceuticals. The SMMs were correlated with histopathologic findings. **Results:** Thirty-three patients were diagnosed with breast cancer and 15 patients with benign breast diseases. The number of true positive, true negative, false positive,

and false negative cases of ^{99m}Tc-tetrofosmin SMM were 31, 10, 5, and 2, respectively. The sensitivity, specificity, positive predictive value and negative predictive value of ^{99m}Tc-tetrofosmin SMM were 93.9, 66.7, 86.1 and 73.3%, respectively. The number of true positive, true negative, false positive, and false negative cases of ^{99m}Tc-MIBI SMM was 29, 10, 5, and 4, respectively. The sensitivity, specificity, positive predictive value, and negative predictive value of ^{99m}Tc-MIBI SMM were 87.8, 66.7, 85.3 and 73.3%, respectively. In assessment of axillary lymph node involvement, ^{99m}Tc tetrofosmin SMM demonstrated 31.8, 100, 100, and 42.3% sensitivity, specificity, positive and negative predictive values, respectively. The sensitivity and specificity of ^{99m}Tc-MIBI SMM was 22.7 and 100%. Positive and negative predictive values were 100 and 39.3%, respectively. One patient was false negative in both ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin SMMs with a tumor

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size of 0.5 cm. **Conclusion:** ^{99m}Tc -tetrofosmin and ^{99m}Tc -MIBI SMMs were noninvasive and useful in the detection of primary breast cancer and ^{99m}Tc tetrofosmin was comparable to ^{99m}Tc -MIBI in the detection of primary breast cancer. However, both radiopharmaceuticals had limited values in the assessment of axillary lymph node involvement.

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Introduction

Breast cancer accounts for the highest proportion of cancer-related deaths among women, and the incidence of this malignant disease is still increasing [1]. In consideration of this increasing incidence, early diagnosis is essential in providing appropriate treatment and the best prognosis for breast cancer patients. In addition to the physical examination of the breast, mammography is widely used as a screening method for the early detection of breast cancer. Although mammography is a useful screening method, its deficiency is low specificity in differentiating malignant from benign diseases, especially in patients with dense breast tissue or those who have received augmented mammoplasty, breast implants, or previous radiation treatment [2, 3]. Also mammography has a low positive predictive value of 15–30% for nonpalpable malignancy, and a positive predictive value of only 22% for palpable carcinoma [2]. The most exact method to differentiate malignancy is excision of the mass and analysis of the histopathologic tissue. The drawback, of course, is that excisional biopsy is an invasive method. An alternative precise method is needed to correctly detect malignancy in patients suspected of having breast cancer.

Scintimammography (SMM) using various radiopharmaceuticals was introduced to de-

tect primary breast cancer as a noninvasive method. Among the various radiopharmaceuticals, ^{99m}Tc -MIBI, developed as a myocardial perfusion-imaging agent, has been reported to have a very high sensitivity and specificity for the diagnosis of primary and recurrent breast cancer [4–9].

^{99m}Tc -tetrofosmin, a lipophilic anionic radiopharmaceutical, has also been shown to have accumulated in various tumors [10–13]. After the report of Rambaldi et al. [14] of increased ^{99m}Tc -tetrofosmin uptake in breast cancer patients who had undergone myocardial perfusion imaging, it was investigated in various tumors. With respect to cost, ^{99m}Tc -tetrofosmin and ^{99m}Tc -MIBI are similar. However, ^{99m}Tc -tetrofosmin does not require boiling and therefore may reduce radiation exposure to health care providers during preparation. It also clears rapidly from the blood pool, liver and lungs, and so provides better images. Some researchers have noted the high sensitivity and specificity of ^{99m}Tc -tetrofosmin SMM in the detection of primary breast cancer [15–22].

To our knowledge, however, there have been few comparative studies of ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin SMMs in the diagnosis of primary breast cancer and axillary lymph node metastasis in the same patient. In this study the diagnostic role of ^{99m}Tc -tetrofosmin SMM was investigated in the detection of primary breast cancer and axillary lymph node metastasis in suspected breast cancer patients as compared with that of ^{99m}Tc -MIBI.

Materials and Methods

Study Population

This study, conducted from January 1999 to August 1999, included 48 patients who exhibited palpable breast masses or who had abnormal radiologic findings. Forty-four patients had palpable breast masses and 4 patients had nonpalpable breast masses. Thirty-

Table 1. Histopathologic results of patients

	Number
Benign	
Fibroadenoma	7
Fibrocystic disease	6
Chronic mastitis	2
Malignant	
Invasive ductal carcinoma	27
Ductal carcinoma in situ	6
Total	33

two patients had either a mammography or a breast ultrasound performed. Sixteen patients had both a mammography and a breast ultrasound performed. All patients had ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin SMMs and pathological results were obtained from surgery in 33 patients and fine needle aspiration biopsy (FNAB) in 15. The SMM method was explained to the patients and/or their family members. The study was approved by the ethics committee of the university hospital and informed consent was obtained from all patients.

^{99m}Tc -MIBI and ^{99m}Tc -Tetrofosmin SMMs

^{99m}Tc -MIBI SMM was performed 10 min after intravenous injection of 925 MBq of ^{99m}Tc -MIBI in the arm contralateral to the affected breast or foot dorsal vein. Patients lay in a prone position on a foam cushion designed for breast imaging overlying the imaging table, which permitted the breast to hang freely. Planar images with a matrix size of 128×128 pixels and 1.5 zoom factor were acquired with a dual-headed gamma camera (VertexTM, ADAC, Milpitas, Calif., USA) equipped with low-energy high-resolution collimators. The energy discriminator was centered on 140 keV photopeak of ^{99m}Tc with a 20% window. Ten minutes after injection of ^{99m}Tc -MIBI, 15 min of both lateral breast images were acquired. After acquisition of both lateral chest images, a planar anterior chest image including both breasts and axilla was also acquired in a supine position. The supine position with raised arms was used for better depiction of both axillary regions. ^{99m}Tc -tetrofosmin SMM was performed within 2 weeks after ^{99m}Tc -MIBI SMM completion. In 43 patients, ^{99m}Tc -tetrofosmin SMMs were obtained as dynamic 80 frames (1 min/frame) after intravenous

injection of 925 MBq of ^{99m}Tc -tetrofosmin. In 4 patients, the ^{99m}Tc -tetrofosmin SMM was acquired in the same fashion as ^{99m}Tc -MIBI.

Interpretation of ^{99m}Tc -MIBI and ^{99m}Tc -Tetrofosmin SMMs

Two experienced nuclear medicine physicians who did not know the patients' clinical information and radiologic findings interpreted the SMMs individually on a workstation connected with a gamma camera. Malignant breast diseases were determined to exist if focal increased uptake of ^{99m}Tc -MIBI was noted in the breast. Diffuse or diffuse/symmetrical uptakes in both breasts were defined as benign breast diseases. A third nuclear medicine physician interpreted discordant results of the SMMs. For the interpretation of dynamic ^{99m}Tc -tetrofosmin SMM, all frames were summed into one image on the workstation. A gray color scale was used for the interpretation of both radiopharmaceuticals.

Statistical Analysis

The sensitivity, specificity, positive and negative predictive values of ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin SMMs in the detection of primary breast cancer and axillary lymph node involvement were obtained in the usual fashion. The comparison of diagnostic sensitivity and specificity between ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin was made by χ^2 test and Fisher's exact test. Statistical significance was defined as $p < 0.05$.

Results

Histopathologic Diagnosis

The patient's mean age was 46.6 ± 9.1 years with a distribution of 28–70 years of age. Pathologic results were obtained during surgery in 33 patients and FNAB in 15 patients. Histopathologic results of patients are summarized in table 1. Malignant breast diseases were diagnosed in 33 patients and benign breast diseases in 15 patients. Among the malignant breast diseases, invasive ductal carcinoma was most common (27, 81.8%). The other pathologic results were 6 ductal carcinomas in situ. The benign breast diseases revealed a distribution of 6 fibrocystic diseases (74%), 7 fibroadenomas, and 2 cases of

Table 2. Detection of breast cancer using ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin

	TP	FP	TN	FN	Sens	Spec	Accur	PPV	NPV
^{99m}Tc -MIBI	29	5	10	4	87.8	66.7	81.3	85.3	71.4
^{99m}Tc -tetrofosmin	31	5	10	2	93.9	66.7	85.4	86.1	83.3

TP = True positive; FP = false positive; TN = true negative; FN = false negative; Sens = sensitivity (%); Spec = specificity (%); Accur = accuracy (%); PPV = positive predictive value (%); NPV = negative predictive value.

Table 3. Detection of axillary lymph node metastasis using ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin SMMs

	TP	FP	TN	FN	Sens	Spec	PPV	NPV
^{99m}Tc -MIBI	5	0	11	17	22.7	100	100	39.3
^{99m}Tc -tetrofosmin	7	0	11	15	93.9	66.7	100	42.3

Sens, Spec, Accur, PPV, and NPV in percent.

chronic mastitis. The minimum tumor size was 0.5 cm; the maximum was 7 cm with a mean of 2.5 cm.

Diagnostic Accuracy of ^{99m}Tc -MIBI and ^{99m}Tc -Tetrofosmin SMMs in the Detection of Primary Breast Cancer

The ^{99m}Tc -MIBI SMM revealed 29 true positives, 5 false positives, 4 false negatives, and 10 true negatives (table 2). The sensitivity, specificity, accuracy, positive and negative predictive values in the detection of primary breast cancer were 87.8, 66.7, 81.3, 85.3, and 71.4%, respectively. The ^{99m}Tc -tetrofosmin SMM revealed 31 true positives, 5 false positives, 2 false negatives, and 10 true negatives. The sensitivity, specificity, accuracy, positive and negative predictive values in the detection of primary breast cancer were 93.9, 66.7, 85.4, 86.1, and 83.3%, respectively.

Diagnostic Accuracy of ^{99m}Tc -MIBI and ^{99m}Tc -SMMs in the Detection of Axillary Lymph Node Involvement

The pathologic results of 33 patients suspected of having breast cancer who had received axillary dissection were compared to ascertain the diagnostic accuracy of ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin SMMs in the detection of axillary lymph node involvement. The true positives, true negatives, false positives and false negatives of ^{99m}Tc -MIBI were 5, 11, 0 and 17 patients, respectively (table 3). The sensitivity and specificity of ^{99m}Tc -MIBI SMM in axillary lymph node involvement were 22.7 and 100%. Positive and negative predictive values were 100 and 39.3%, respectively. The true positives, true negative, false positives and false negatives of ^{99m}Tc -tetrofosmin SMM were 7, 11, 0 and 15 patients, respectively. The sensitivity, specificity, positive and negative predictive values

Fig. 1. ^{99m}Tc -tetrofosmin SMM (**A**) missed the primary breast cancer. However, ^{99m}Tc -MIBI SMM (**B**) correctly detected the primary breast cancer (arrow). The tumor size was 1 cm and the pathologic result was ductal carcinoma in situ.

of ^{99m}Tc -MIBI SMM in axillary lymph node involvement was 31.8, 100, 100, and 42.3%, respectively.

Discordant Results between ^{99m}Tc -MIBI and ^{99m}Tc -Tetrofosmin SMMs

One patient showed true positive in ^{99m}Tc -MIBI but false negative in ^{99m}Tc -tetrofosmin and the pathologic result was ductal carcinoma in situ with a size of 1.5 cm (fig. 1). In contrast, 2 patients were found to be true positive in ^{99m}Tc -tetrofosmin but false negative in ^{99m}Tc -MIBI and the pathologic results were invasive ductal carcinoma with a size of 1 cm (fig. 2). However, in 15 patients with benign breast diseases, there were no discordant findings between ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin SMMs.

Discussion

The significance of this study is the comparison of ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin in the same clinically suspected breast cancer patients. We have found that ^{99m}Tc -tetrofosmin is equal to ^{99m}Tc -MIBI in terms of diagnostic efficacy of primary breast cancer. In previous studies, thallium-201 and ^{99m}Tc -MIBI were used in most of the studies. According to Cimitan et al. [23] and Lee et al. [24] thallium-201 showed high sensitivity and specificity in the diagnosis of primary breast cancer. However, thallium-201 has a low energy level and relatively long half-life and therefore provides low quality images and high radiation exposure to patients. In contrast, ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin have short half-lives and therefore provides better images with less radiation exposure to patients.

^{99m}Tc -MIBI has been shown to have a very high sensitivity and specificity in the detec-

Fig. 2. Case of invasive ductal carcinoma 1 cm in size. ^{99m}Tc -MIBI SMM (**A**) showed no abnormal finding but ^{99m}Tc -tetrofosmin SMM (**B**) correctly detected the primary breast cancer (arrow).

tion of primary breast cancer [4–9]. Nevertheless, it requires a process of boiling and cooling before injection in patients, and has the risk of radiation exposure during that time. However, tetrofosmin (Myoview) does not require boiling and therefore can be prepared at room temperature.

^{99m}Tc -tetrofosmin has been used in primary breast cancer detection after first being reported by Rambaldi et al. [14–22]. Fenlon et al. [15] reported 95.2% sensitivity, 91.3% specificity, 90.9% positive predictive and 95.4% negative predictive values of ^{99m}Tc -tetrofosmin SMM in the detection of primary breast cancer. In a study of Batista et al. [17], ^{99m}Tc -tetrofosmin SMMs were all true positive in 7 patients of pathologically diagnosed malignant diseases. In 2 patients with benign breast diseases, ^{99m}Tc -tetrofosmin SMMs revealed no definite abnormal increased uptake and they concluded ^{99m}Tc -tetrofosmin SMM might be used in differentiating palpable breast masses. Schillaci et al. [18] also re-

ported on the high sensitivity and specificity of ^{99m}Tc -tetrofosmin SMM in 54 patients.

There were 5 false positives with ^{99m}Tc -MIBI in our study and all of them were also false positives with ^{99m}Tc -tetrofosmin. Of these, 4 patients were diagnosed as having fibroadenomas and 1 chronic mastitis. There were also 4 false negatives with ^{99m}Tc -MIBI. For 2 of them, ^{99m}Tc -tetrofosmin SMMs also showed false negatives. The tumor sizes were 0.5 and 1 cm, but in the other 2 patients, ^{99m}Tc -tetrofosmin could correctly diagnose breast cancer with a size of 1 cm. In this study, 1 patient with a small breast cancer (0.5 cm) showed false negative results with ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin. We are aware that both radiopharmaceuticals have limited diagnostic value when the size of the breast cancer is small; indeed the most important factor affecting the diagnostic accuracy of SMM is tumor size. We used surgery and FNAB as gold standards for the diagnosis of breast cancer. FNAB was performed in most

of the benign breast disease patients. ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin SMMs showed 5 false positives. The false negatives of ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin were 4 and 2, respectively in patients with malignant breast diseases diagnosed by surgery. Thus, gold standard methods we used had no influence on the diagnostic differences between these two radiopharmaceuticals.

With regard to axillary lymph node metastases, this study showed a very low sensitivity of 22.7% for ^{99m}Tc -MIBI, 31.8% for ^{99m}Tc -tetrofosmin and a high specificity of 100% for both radiopharmaceuticals. In contrast to our results, Taillefer et al. [25] reported 79.2% sensitivity and 84.6% specificity in the diagnosis of axillary lymph node involvement of ^{99m}Tc -MIBI in a study of 100 patients and Danielsson et al. [26] reported 67% sensitivity and 80% specificity for ^{99m}Tc -MIBI planar images in 58 patients. Using ^{99m}Tc -tetrofosmin, other researchers reported 57, 72 and 91.6% sensitivity and 100% specificity in the diagnosis of axillary lymph node metastasis [20–21, 27]. The low sensitivity in the detection of axillary lymph node metastasis may be due to a patient's characteristics or the patient's position during image acquisition. However, patients were placed in a supine position with raised arms for both axillary regions.

In a study similar to ours, Akcay et al. [28] performed both ^{99m}Tc -MIBI and ^{99m}Tc -tetrofosmin SMMs in the same patients. They reported that the sensitivity, specificity and accuracy of ^{99m}Tc -MIBI were 90, 90, and 91%, respectively, and those of ^{99m}Tc -tetrofosmin were 93, 100 and 94%, respectively, and that ^{99m}Tc -tetrofosmin was more accurate than ^{99m}Tc -MIBI in the detection of primary breast cancer [28]. According to our study, however, the sensitivity, specificity and accuracy were not statistically different and showed similar results. We assume that some

factors might affect the results, and the effect of patient characteristics and number of patients cannot be excluded.

The exact mechanism of tumor uptake of ^{99m}Tc -tetrofosmin has not been clarified, but the mechanism might be similar to that of ^{99m}Tc -MIBI. It might be suggested that lipophilicity, anionic property, cellular mitochondrial contents, difference of membrane potential, increased blood flow to the tumor and increased capillary permeability may all have important roles in tumoral uptakes of ^{99m}Tc -MIBI.

Conclusion

^{99m}Tc -tetrofosmin is a convenient and noninvasive method and is useful for the detection of primary breast cancer. Moreover, the diagnostic accuracy of ^{99m}Tc -tetrofosmin for primary breast cancer was comparable to that of ^{99m}Tc -MIBI. However, both radiopharmaceuticals had limited value in the assessment of axillary lymph node involvement.

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