Comparison between ^{99m}Tc -Methoxyisobutyl Isonitrile and ^{99m}Tc -Methylenediphosphonate Scintimammography for Detection of Breast Carcinoma

Shao-Liang Chen^a Wenguan Liu^a Ying Mao^a Weimin Zhu^a Zhifeng Yao^a
Xiaoguang Sun^a Yan Xiu^a Yiqing Yin^b Junxue Chen^b

^aDepartment of Nuclear Medicine, Institute of Nuclear Medicine, and ^bDepartment of Surgery, Shongshan Hospital, Fudan University, Shanghai, China

Key Words

Breast cancer · Scintimammography ·

^{99m}Tc -Methoxyisobutyl isonitrile ·

^{99m}Tc -Methylenediphosphonate

Abstract

Objective: The goal of the study was to assess the values of scintimammography with ^{99m}Tc -methoxyisobutyl isonitrile (^{99m}Tc -MIBI) and ^{99m}Tc -methylenediphosphonate (^{99m}Tc -MDP) in detecting breast cancer. **Methods:** A total of 35 women with clinical findings of suspicious breast lesions were studied with both ^{99m}Tc -MIBI and ^{99m}Tc -MDP scintimammography. All patients underwent surgery within 1 week, and the results of the histopathological diagnosis were obtained. **Results:** Eighteen of 35 abnormalities of the breast were pathologically confirmed as primary breast cancer and 17 as benign lesions. In this group of patients, the sensitivity, specificity and accuracy of ^{99m}Tc -MIBI scintimammography were 77.8, 88.2 and 82.9%, respectively, while those of ^{99m}Tc -MDP scintimammography were 72.2, 88.2 and 80.8%, respectively. There was no significant difference between the results of ^{99m}Tc -MIBI and ^{99m}Tc -MDP scintimammography. **Conclusion:** This study demonstrated a high diagnostic accuracy of both ^{99m}Tc -MIBI and ^{99m}Tc -MDP scintimammography in detecting breast cancer.

Both radiopharmaceuticals can be used as an adjunct method for the noninvasive assessment of breast cancer prior to surgery. However, ^{99m}Tc -MDP is less expensive and more readily available than ^{99m}Tc -MIBI.

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Introduction

Technetium-99m methoxyisobutyl isonitrile (^{99m}Tc -MIBI) is routinely used as a myocardial perfusion imaging agent, and like thallium-201, it has tumor-imaging capability [1]. The mechanism of uptake of ^{99m}Tc -MIBI in tumors is not fully understood, but it appears to be partially attributable to the uptake of the tracer into mitochondria, especially in malignant cells. Technetium-99m methylenediphosphonate (^{99m}Tc -MDP) is routinely used as a bone-imaging agent because it has a high concentration in the bone, rapid blood clearance, low radiation dose to the patient and is easy to prepare. Incidental findings of breast cancer have been observed on bone images obtained with ^{99m}Tc -MDP [2]. Since ^{99m}Tc -MIBI and ^{99m}Tc -MDP have been used to image breast cancer [1, 2], the question that arises is whether one radiopharmaceutical is better than the other for the noninvasive detection of breast cancer. For this purpose, visual and semiquantitative comparisons between uptakes of ^{99m}Tc -MIBI and ^{99m}Tc -MDP in breast cancer were performed.

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Prof. Shao-Liang Chen
Institute of Nuclear Medicine, Department of Nuclear Medicine
Medical College of Fudan University
Shanghai 200032 (China)
E-Mail slchen@shmu-edu.cn

Subjects and Methods

Subjects

Each patient had a physical breast examination by a surgeon in the supine and upright positions. There were 38 palpable breast masses in the 35 patients. All patients underwent surgery within 1 week after scintimammography, and the results of the histopathological diagnosis were obtained. The mean age of the patients was 47.3 ± 12.1 years (range 27–80 years). Radionuclide single-photon emission computed tomographic (SPECT) images were obtained from 35 consecutive female patients with suspicious breast lesions on clinical examination after intravenous injection of ^{99m}Tc -MIBI or ^{99m}Tc -MDP. The two SPECT studies were performed within an interval of 2–3 days (mean 2.1 days) of each other.

The ^{99m}Tc -MIBI and ^{99m}Tc -MDP were prepared according to the manufacturer's instructions and administered in random order on different days. The patients received a mean dose of 740 MBq (20 mCi) of ^{99m}Tc -MIBI or ^{99m}Tc -MDP. The radiopharmaceuticals were intravenously injected as a bolus in the arm contralateral to the breast with the abnormality. The equipment consisted of a large field of view gamma camera (Elsint, Apex SP-6) fitted with a low-energy high-resolution collimator. Patients were imaged in the prone position using a special table overlay that allowed the breast being imaged to depend freely from the imaging table. The arms were raised with the hands placed behind the patient's head when possible. The radionuclide images, from scintimammography, were acquired for 10–20 min 2 h after injection of the radiopharmaceutical. Three planar images of right and left lateral prone and anterior supine views were also obtained.

Data Analysis

All images were stored in the computer for further analysis. The images were classified as positive (focal abnormal accumulation at the tumor site) or negative (no abnormal focus of activity at the lesion site) by at least two nuclear medicine physicians blinded to the clinical findings. Scintimammographic results of ^{99m}Tc -MIBI and ^{99m}Tc -MDP were compared with surgical histopathological diagnoses.

For semiquantitative analysis, regions of interest were drawn on the tumor and normal tissue of the breast, and the ratio of tumor to normal tissue was computed. Results were expressed as the mean $\pm$ SD. Statistical analysis was accomplished by use of the χ^2 test. Sensitivity was defined as the number of true-positive cases divided by the sum of the true-positive + the false-negative studies. Specificity was the number of the true-negative divided by the sum of true-negative + false-positive studies. Positive and negative predictive values were defined as the number of true-positive cases divided by the sum of true-positive + false-positive and the number of true-negative divided by the sum of true-negative + false-negative cases, respectively.

Results

No side effects or discomfort were observed. There was complete agreement among the observers in evaluating the scintimammograms.

Table 1. Final diagnosis based on histology

Histological diagnosis	Cases
<i>Benign</i>	
Fibrocystic disease	8
Fibroadenomas	4
Cysts	2
Mammitis	2
Accessory mammae	1
Subtotal	17
<i>Malignant</i>	
Infiltrating carcinoma	15
Tubular carcinoma	1
Mixed ductal and lobular carcinoma	1
Adenocarcinoma	1
Subtotal	18
Total	35

Histology

The final diagnosis was based on histology. There were 18 primary breast cancers (4 different histological types) and 17 benign breast lesions (5 different histological diagnoses). Seven of the 18 primary breast cancers had nodal metastases and 11 had no metastases. The smallest tumor size, as measured by the surgeon during operation, was $1 \times 1 \times 0.5$ cm; the largest tumor was $9.5 \times 9.0 \times 0.5$ cm. Table 1 summarizes the final diagnoses based on histology.

Scintimammography

The results of ^{99m}Tc -MIBI and ^{99m}Tc -MDP scintimammography compared with histological diagnoses are summarized in tables 2 and 3, respectively. Representative images for ^{99m}Tc -MIBI and ^{99m}Tc -MDP are shown in figures 1 and 2, respectively.

Malignant Tumors

Of the 18 patients with malignant diseases, there were 14 lesions detected with ^{99m}Tc -MIBI. These were the true-positive findings of ^{99m}Tc -MIBI. The pathological confirmation is as follows: 12 lesions were characterized as infiltrating ductal carcinoma, 1 as adenocarcinoma, another as mixed ductal and lobular carcinoma. Only 13 lesions, however, were found with ^{99m}Tc -MDP. One infiltrating carcinoma could not be visualized using ^{99m}Tc -MDP. With ^{99m}Tc -MIBI, 4 studies were proved to be false-negative results by pathological findings of surgical biopsy specimens. Three patients with infiltrating ductal carcinoma and 1 patient with tubular mammitis were confirmed.

Fig. 1. The same patient's scintimammography with ^{99m}Tc -MDP and ^{99m}Tc -MIBI. Both ^{99m}Tc -MDP and ^{99m}Tc -MIBI visualized the breast tumor.

Fig. 2. The same patient's scintimammography with ^{99m}Tc -MDP and ^{99m}Tc -MIBI. ^{99m}Tc -MDP was false-negative.

For ^{99m}Tc -MDP scintimammography, 5 studies had false-negative findings.

Benign Tumors

Of the 17 patients with benign diseases, 15 lesions were detected with both ^{99m}Tc -MIBI and ^{99m}Tc -MDP. The classifications using pathological findings were as follows: 7 lesions as fibrocystic disease, 4 as fibroadenoma, 2 as cysts, 1 as mastitis and 1 as accessory mamma. There were 2 breast lesions with focal areas of increased uptake both on ^{99m}Tc -MIBI and ^{99m}Tc -MDP scintimammography that were finally proved to be benign on pathology. One patient had fibrocystic disease and one acute mammitis.

Comparison of ^{99m}Tc -MIBI and ^{99m}Tc -MDP

Visual evaluation of the scintimammography studies revealed excellent agreement between ^{99m}Tc -MIBI and ^{99m}Tc -MDP except in 1 patient for whom ^{99m}Tc -MIBI was positive while that of ^{99m}Tc -MDP was negative. The patient underwent surgery and the final histopathological diagnosis was infiltrating carcinoma. The comparison of ^{99m}Tc -MIBI and ^{99m}Tc -MDP scintimammography is shown in table 4. The activity ratios of primary breast tumor to normal breast tissue in ^{99m}Tc -MIBI and ^{99m}Tc -MDP were 1.82 ± 0.71 and 1.60 ± 0.59 , respectively. There was no significant difference between them ($p > 0.05$).

Table 2. Comparison of results of ^{99m}Tc -MIBI scintimammography with histological diagnosis

^{99m}Tc -MIBI scintimammography	Histological diagnosis		
	malignant	benign	total
Positive	14 (77.8)	2 (11.8)	16
Negative	4 (22.2)	15 (88.2)	19
Sum	18	17	35

$\chi^2 = 14.91$, $p = 0.00011$. Figures in parentheses are percentages.

Table 4. Comparison of results of ^{99m}Tc -MIBI and ^{99m}Tc -MDP scintimammography

^{99m}Tc -MIBI scintimammography	^{99m}Tc -MDP scintimammography		
	positive	negative	total
Positive	15	1	16
Negative	0	19	19
Sum	15	20	35

$\chi^2 = 30.28$, $p = 0.000002$.

The sensitivity, specificity and accuracy of ^{99m}Tc -MIBI scintimammography were 77.8, 88.2 and 82.9%, respectively, while those of ^{99m}Tc -MDP were 72.2, 88.2 and 80.9%, respectively. The positive and negative predictive values of ^{99m}Tc -MIBI and ^{99m}Tc -MDP were 87.5 and 78.9%, while those of ^{99m}Tc -MDP were 86.7 and 75%, respectively (table 5).

Discussion

Carcinoma of the breast is one of the most common invasive malignancies in Chinese women, and its incidence is increasing. Much work has been done to improve the early detection of breast cancer as this reduces mortality and allows surgical therapy. Currently, self-examination, physical examination of the breast by a physician and mammography are the main methods available for successful screening procedures of early breast cancer. The sensitivity of self-examination is extremely low. Sometimes even experienced physicians have difficulty in accurately differentiating benign from malignant lesions. Equally, mammography has low sensitivity, specificity and predictive values. Specificity and positive predictive

Table 3. Comparison of results of ^{99m}Tc -MDP scintimammography with histological diagnosis

^{99m}Tc -MDP scintimammography	Histological diagnosis		
	malignant	benign	total
Positive	13 (72.2)	2 (11.8)	15
Negative	5 (27.8)	15 (88.2)	20
Sum	18	17	35

$\chi^2 = 12.68$, $p = 0.00037$. Figures in parentheses are percentages.

Table 5. Sensitivity, specificity, predictive values and accuracy of ^{99m}Tc -MIBI and ^{99m}Tc -MDP scintimammography

	^{99m}Tc -MIBI	^{99m}Tc -MDP
Malignant	14 TP, 4 FN	13 TP, 5 FN
Benign	15 TN, 2 FP	15 TN, 2 FP
Sensitivity	77.8%	72.2%
Specificity	88.2%	88.2%
Positive predictive value	87.5%	86.7%
Negative predictive value	78.9%	75.0%
Accuracy	82.9%	80.0%

FP = False-positive; FN = false-negative; TP = true-positive; TN = true-negative.

values of nonpalpable cancers are only 10–35% and the positive predictive value for palpable carcinoma is only 22% [3–5]. Abnormalities detected by physical breast examination or mammography frequently require biopsy of the breast with the consequent physical and psychological side effects. It would be helpful to use a noninvasive technique with a high specificity, thus reducing the need for biopsies.

^{99m}Tc -MIBI, a radiopharmaceutical used for myocardial perfusion, is also used for tumor imaging [6–10]. Tumor imaging with ^{99m}Tc -MIBI was first reported in 1987 [11]. Although the exact mechanism of ^{99m}Tc -MIBI cellular uptake by cancer cells is not really known [12], ^{99m}Tc -MIBI imaging has been used in various cancers such as lung carcinoma, osteosarcoma and brain tumors as well as benign tumors such as thyroid or parathyroid adenomas [13, 14]. In 1992, Campeau et al. [15] reported the uptake of ^{99m}Tc -MIBI in an unsuspected breast tumor. The ^{99m}Tc -MIBI has good characteristics for in vivo tumor imaging because of the more favorable emission characteristics of ^{99m}Tc .

There are many reports regarding the possible clinical use of ^{99m}Tc -MIBI scintimammography [16–19]. A sensitivity between 86 and 94% and a specificity of 53–94% have been reported by different authors [7, 13, 20, 21]. False-negative results have mainly been related to lesion size. False-positive results can occur in highly cellular lesions such as fibrocystic disease with pronounced epithelial hyperplasia or in fibroadenomas with accompanying hyperplasia [7]. The accumulation of ^{99m}Tc -MIBI in breast cancer is probably an indicator of cell proliferation [1]. A relationship between ^{99m}Tc -MIBI uptake and chemoresistance in human breast cancer has also been observed [7, 22], suggesting a possible role of ^{99m}Tc -MIBI scintimammography as a diagnostic tool prior to chemotherapy.

Compared to ^{99m}Tc -MIBI, ^{99m}Tc -MDP is more readily available and less expensive. The ^{99m}Tc -MDP scintimammography can represent the first phase of a bone scan. It

may form part of a routine study in the staging and follow-up of patients with breast cancer. In a group of 400 patients selected for having a high pretest probability of cancer because of abnormal clinical findings, a 92% sensitivity and specificity in the diagnosis of breast cancer was calculated [23], which is fairly consistent with the results of this study.

Conclusion

This study showed that ^{99m}Tc -MIBI and ^{99m}Tc -MDP scintimammographies have a high diagnostic accuracy in detecting breast cancer. Scintimammography is a simple, cost-effective and noninvasive method for assessing breast cancer before surgery. However, ^{99m}Tc -MDP is less expensive and more readily available than ^{99m}Tc -MIBI.

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