Scintimammography (SMM) in Breast Cancer Patients

JIRAPORN MANGKHARAK, M.D.*

Abstract

The author retrospectively reviewed the scintimammography (SMM) using ^{201}Tl and/or ^{99m}Tc-MIBI in 45 breast cancer patients. 36 cases with 37 intact breast masses and another 9 cases with previous excision of the masses were studied. The sensitivity for the detection of the primary breast cancer was 92 per cent and that of ipsilateral axillary lymph node metastasis was only 48 per cent. SMM is helpful for the diagnosis of breast cancer and differentiating malignant from benign masses, thus improving the accuracy of routine mammography. In postoperative cases SMM is helpful to detect palpable local tumor recurrence and axillary node metastasis but it is not accurate enough for assessing the extent of microscopic tumor involvement locally and also distant metastasis. Thus, it is not recommended to use SMM alone for staging of breast cancer.

Key word : Scintimammography, Breast Cancer, Thallium-201, Technetium-99m MIBI

The incidence of breast cancer in the United States is growing and it is estimated that about 12 per cent of all women will be given a diagnosis of breast cancer and 3.5 per cent will die of the disease(1). In Thailand, breast cancer is the second most common cancer found in Thai women, which is second to cervical cancer(2). There are many kinds of investigations being used to diagnose this condition such as mammography, sonography, radionuclide scans and PET studies, CT, as well as MRI. Despite various modalities of imaging, the patients sometimes still need cytological diagnosis to confirm the nature of the lesions before definite surgery is performed. Each particular breast imaging has its own advantages and disadvantages. Mammography provides acceptable sensitivity in the identification of carcinoma occuring in fatty breasts, while it is not reliable in detecting malignant lesions in dense breasts. In addition, its specificity for the diagnosis is low(3-5). The radionuclide method is one of the modalities that has been used to pick up breast cancer. A number of radiopharmaceuticals were used in the past including ^{32}P, ^{42}K,^{86}Rb, ^{131}Cs, ^{87m}Sr,^{197}Hg-chlormeridrin, ^{67}Ga-citrate, ^{201}Bi-citrate, ^{99m}Tc pertechnetate, ^{131}I-human serum albumin, ^{192}Hg Cl_2, ^{99m}

* Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Tc-diphosphonate, and ^{99m}Tc-polyphosphate[6]. Among these agents, ^{67}Ga-citrate, ^{99m}Tc pertechnetate, and ^{99m}Tc diphosphonate compounds were studied widely more than other tracers[6-8]. However, the results were not so attractive that the radionuclide breast scan was not appreciated for routine use and the major role of radionuclide studies in the past mainly dealt with bone scintigraphy for detection of bone metastases rather than breast imaging to detect a primary lesion itself[6,9].

Since Hisada et al[10] reported thallium-201 (^{201}Tl) uptake in two cases of breast cancer, many studies have been conducted to evaluate the usefulness of this agent in detection of breast cancer, and also in the differentiation of benign and malignant breast masses[11-14].

Apart from ^{201}Tl, ^{99m}Tc-methoxyisobutylisonitrile (^{99m}Tc-MIBI or sestamibi) is another radiopharmaceutical which has been mainly used for myocardial perfusion imaging. It was first used for tumor imaging by Muller et al[15] and Hassen et al[16] and was subsequently found to concentrate on various malignancies, including carcinoma of the breast[17]. Then, more and more studies have been reported by using this radiopharmaceutical to diagnose breast cancer.

The aim of the current study is to evaluate the role of radionuclide breast scanning called scintimammography (SMM) using ^{201}Tl and/or ^{99m}Tc-MIBI in the detection of primary breast cancer, ipsilateral axillary node metastasis as well as distant metastasis in high-risk breast cancer patients.

MATERIAL AND METHOD

PATIENTS

Forty-five female patients, aged 28-73 yr (mean= 51.3 ± 10.8) were totally conducted in the study. All were histologically proved to have breast cancer. The patients were divided into two groups.

Group I : Scintimammography was achieved preoperatively in 36 patients with 37 palpable breast masses (one patient had two lesions). The age ranged from 28 to 73 years old (mean = 52.1 ± 11.1).

Group II : Scintimammography was performed on 9 patients whose primary tumors were previously removed by undergoing either mastectomy or excision of the masses. The patients were aged from 35 to 63 years old (mean = 48.1 ± 9.0). This imaging was undertaken in addition to the routine bone scan which was primarily the investigation of choice to seek for any distant bony metastasis.

METHOD

Patient preparation:

The patients were advised to have a light diet before the imaging procedure to reduce the splanchnic blood flow to the abdominal region.

Imaging technique:

All the patients were imaged with the same technique. About 2-3 mCi of ^{201}Tl and / or 15-20 mCi of ^{99m}Tc-MIBI were / was injected intravenously into the arm opposite to the breast lesion followed by saline flushing to eliminate the retention of the radiotracer along the injected vein. 13 patients were studied by both agents while 28 and 4 patients were studied by ^{201}Tl and ^{99m}Tc-MIBI alone respectively.

Ten minutes later the images were taken while the patient was supine on the imaging table with her arms raised during the scanning. Multiple planar images including anterior, and both anterior oblique views with also placing a marker on the breast mass in another anterior image were obtained using a large-field-of-view gamma camera provided with a low-energy, general purpose collimator. The peak energy was centered at 69-80 KeV for ^{201}Tl and 140 KeV for ^{99m}Tc-MIBI with 20 per cent window . The acquisition was achieved on 128x 128 matrix with a preset count of 700 Kcounts for ^{201}Tl and 1000 Kcounts for ^{99m}Tc-MIBI in the anterior and the anterior oblique images for the ipsilateral side with the same preset time for the contralateral oblique scan. In the second group both anterior and posterior whole-body images were also acquired at the rate of 12.5 cm/min.

Data Analysis

All images were recorded in the computer for the analysis. The scans were interpreted blindly without knowledge of the clinical and histological information. Regions of interest were drawn over areas of the breast masses as well as the corresponding regions of the contralateral breast tissue. The target-to-background ratio more than 1.17 (mean + 3SD = 1.05 + 0.12) was called positive[18].

RESULTS

All patients in the study were histologically proved to have carcinoma of the breast.

Thirty-one patients in the first group subsequently underwent modified radical mastectomy while the remainder presenting with advanced tumor had only incisional biopsy or fine needle aspiration. There were 31 invasive ductal carcinoma, which was the most common histologic type of breast cancer, two invasive apocrine carcinoma, two intraductal carcinoma, one containing mixed type of invasive ductal and intraductal component.

In group I patients, there were totally 37 masses detected in 36 patients. 19 lesions were detected on the right side while 18 were on the left. The size of the breast masses varied from 1.5x1.8x 2.2 cm to more than ten cm (4 cases) in maximum diameter. The primary breast tumors were categorized according to the TNM classification. These included 18 T2, 10 T3 and 9 T3 lesions. The location of the masses was defined as a diagram shown in Fig. 1. About one-third of them were located in the upper inner quadrant which was the most common location in this study.

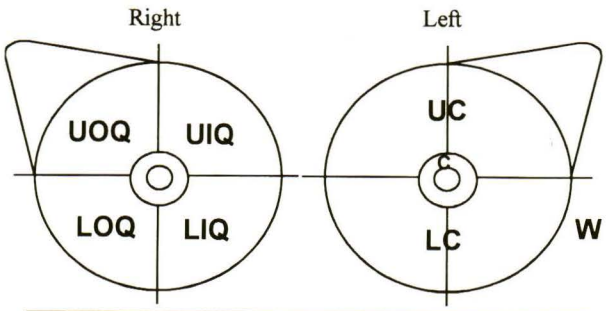


Fig. 1. Diagram classifying regions of the breast mass.

Of 37 primary breast lesions, 34 (92%) showed positive uptake of the radiotracer; the smallest mass was 1.1x1.9x2.5 cm in diameter. False-negative SMM results were found in three patients whose masses were 1.5x1.8x2.2, 2.2x2.5x 2.5, and 3x3.5x4 cm in size and were all located in the inner quadrant. Two masses were on the right and the other one was on the left. There were two invasive ductal carcinoma and one intraductal carcinoma. A false negative SMM result is shown in Fig. 2 which demonstrated no definite accumulation in the breast lesion. The findings of the scans using both ^{201}Tl and ^{99m}Tc-MIBI were similar and the results were concordant in all. The pathological and/ or clinical results revealed evidence of ipsilateral axillary lymph node metastasis in 27 cases. Of these, SMM could pick up only 13 cases (48.1%). The results are summarized in Table 1 and Fig. 3 demonstrates uptake of the tracers in both the primary tumors and the ipsilateral axillary lymph nodes.

In group II, 5 patients had a modified radical mastectomy (MRM) performed one to two years before SMM and the others had had previous excisional biopsy done recently. Only two revealed recurrent palpable mass lesions at the same side of operation and showed thallium uptake (Fig. 4). Another two cases had ipsilateral enlarged axillary lymph nodes and only one demonstrated thallium accumulation (Fig. 5).

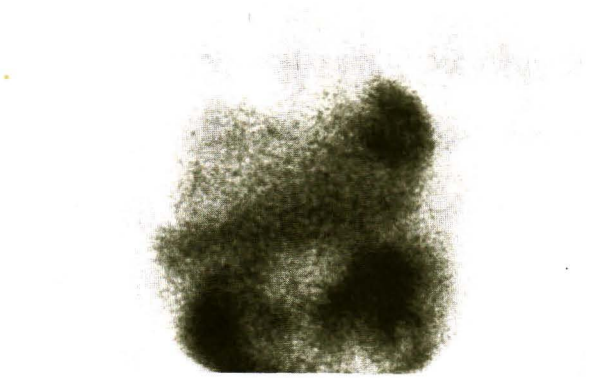


Fig. 2. False-negative SMM result in a 49 year-old patient with a small right breast mass.

Table 1. The results of SMM to detect ipsilateral axillary lymph node metastases as compared to the histological and/or clinical findings.

	Positive LN metastasis	Negative LN metastasis
Positive scan	13	0
Negative scan	14	9

Sensitivity = 13/27 = 48.1%
Specificity = 9/9 = 100%

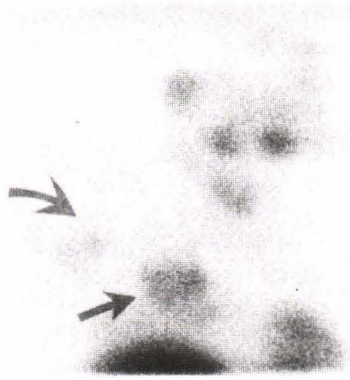


Fig. 3. Positive SMM result in both primary tumor on the right breast (straight arrow) and ipsilateral axillary lymph nodes (curved arrow).

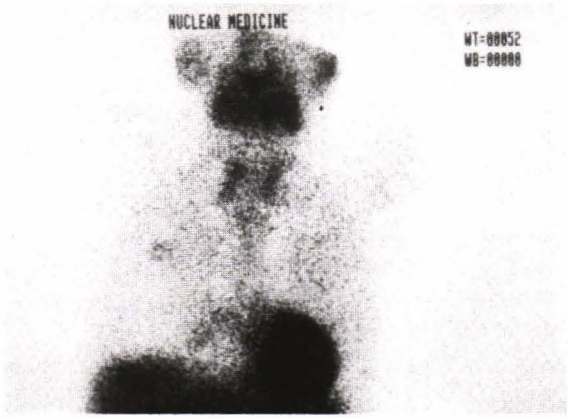


Fig. 4. Positive SMM result in recurrent breast cancer S/P right MRM.

Two patients in the first group and six in the second group had bone metastases demonstrated by bone scan. Four cases in the latter group also had evidence of metastases in one or more of the following organs ie. brain, liver, and lungs. Nevertheless, ^{201}Tl and/ or ^{99m}Tc-MIBI whole-body scan revealed uptake only in some areas of these metastases (Fig. 6).

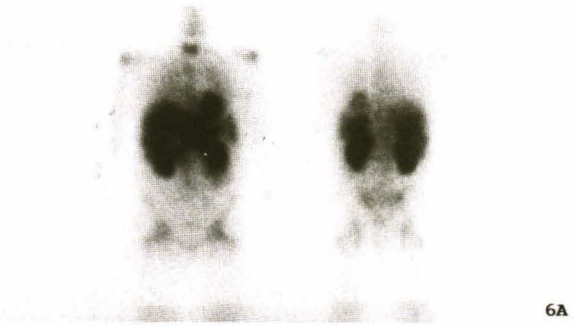
DISCUSSION

The rationale for screening of breast cancer was generally based on physical examination and mammography. However, mammography lacks adequate specificity and, therefore, has low positive

Fig. 5. Positive ^{201}Tl-SMM finding in the recurrent tumor of the right axillary node. Anterior (above) and right anterior oblique views (below) of ^{201}Tl-SMM revealed focal thallium uptake in the right axilla but not in the breast regions.

predictive value which is about 15-30 per cent for detection of breast cancer[3]. Furthermore, Bird et al found 77 of 320 carcinomas diagnosed by pathology were missed by mammography, thus reflecting a false-negative rate of 24 per cent which is quite high[4].

SMM has been widely studied to provide additional information in these settings to give better accuracy of the diagnosis. Among various radiotracers, ^{201}Tl and ^{99m}Tc-MIBI are generally accepted as most impressive agents, eventhough Piccolo et al recently reported an excellent result of ^{99m}Tc-MDP SMM to diagnose primary breast cancer[19]. The uptake of ^{201}Tl in the tumor cells depends on the ATPase sodium potassium transport system[20]. On the other hand, the uptake mechanism of ^{99m}Tc-MIBI is not clearly understood and it has been suggested that ^{99m}Tc-MIBI could bind to the cytosol in the tumor cells[20] and 90 per cent of the tracer activity is concentrated in the mitochondria[21]. The cationic charge and lipophilicity of ^{99m}Tc-MIBI, the mitochondrial and plasma



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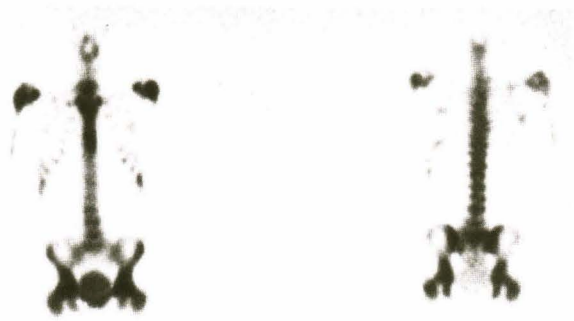

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Fig. 6. Breast cancer with multiple bone metastases. ^{201}Tl whole-body image (A) was far less impressive for the evaluation of bone metastases as compared to ^{99m}Tc-MDP scan (B).

membrane potentials of tumor cells, and the cellular mitochondrial content may play a significant role in the tumor uptake of this agent[22,23]. Furthermore, the uptake of ^{99m}Tc-MIBI in the tumor cells also appears to be an invivo marker of P-glycoprotein activity which is associated with multi-drug resistance[24,25].

The sensitivity and the specificity of ^{201}Tl SMM in the detection of primary breast cancer in the previous reports varied from 80-96 per cent and 91-96 per cent respectively,[12-14] while those of ^{99m}Tc-MIBI SMM were 83-94 per cent and 88-100 respectively[26-31]. However, there are very few studies comparing the results of SMM using these two agents which demonstrated that ^{99m}Tc-MIBI had superior sensitivity than ^{201}Tl for this cancer detection[17,32]. ^{99m}Tc-MIBI is generally more attractive than ^{201}Tl because ^{99m}Tc is more widely available, cheaper, and also provides better physical characteristics as well as less radiation to the patients due to shorter half life. Nevertheless, an interesting advantage of imaging using ^{201}Tl is that it can be performed on the same day with another ^{99m}Tc study such as whole-body bone scan while the imaging using ^{99m}Tc-MIBI can not. In the current study, the images obtained by using the two tracers were not significantly different resulting in the same sensitivity, about 92 per cent for detection of primary breast cancer.

Concerning the size of the lesions, many investigators found higher sensitivity for detecting palpable than nonpalpable malignant lesions[29-31]. Villanueva-Meyer J et al found the smallest breast cancer detected by SMM was 0.5 cm in diameter[31]. In addition, Waxman et al[12] and Cimitan et al[14] agreed that the sensitivity of ^{201}Tl SMM to detect the mass lesions larger than 1.5 cm was very high. Although the false negative SMM results are more likely to occur in the small non-palpable malignant lesions, these could occur in some palpable ones. As in this study, Kao et al reported the false negative SMM finding in the mass as big as 7x4x3 cm in diameter and concluded that the likelihood of ^{99m}Tc-MIBI uptake was not related to the tumor size alone[26].

Furthermore, the technique of imaging and interpretation also play an important role for the sensitivity of detection. A good gamma camera equipped with a high-resolution collimator should be used for planar imaging while SPECT (Single Photon Emission Computed Tomography) did not render a significant improvement over planar images and was shown to be of little help in only certain cases, particularly the small nonpalpable lesions[29,30]. To enhance the accuracy of the interpretation some investigators calculated the tumor uptake ratio for the quantitative analysis [14,18,28-30,33] and some used prone position for imaging as first introduced by Khalkhali et al[27]. Prone SMM was claimed to be more favorable than the supine position because of excellent separation of deep breast structures from the myocardium in the left breast and excellent separation of the right breast from the liver[29]. However, this probably provides less benefit in Asian women who generally have less breast tissue relative to Western women.

False positive SMM findings have been described in certain benign breast disorders eg. fibroadenoma, fibrocystic disease, inflammatory lesions, hemangioma[14,18,28-30].

The SMM in group II demonstrated positive accumulation of ^{201}Tl in two recurrent palpable masses in the breasts status post MRM but did not reveal any focal abnormal uptake of the tracer at the pathologic breast with previous inadequate surgery done before. Thus, SMM is not useful for the evaluation of microscopic tumors which could be present at the surrounding tissues of the areas of previously excised masses.

For the evaluation of axillary lymph node metastasis, we found the lower sensitivity of SMM, about 48 per cent, compared with that of primary breast carcinoma. Previous researchers reported a wide range of the sensitivity from 27-84 per cent [12,14,26,28,29]. However, the number of the patients in each of these series was still small.

The role of ^{201}Tl and ^{99m}Tc-MIBI for the staging of breast cancer has not been evaluated fairly. Bone metastases demonstrated by whole-body bone scan are much more impressive than those revealed by ^{201}Tl or ^{99m}Tc-MIBI scan. Thus, ^{99m}Tc-MDP bone scan is still preferred for the routine evaluation of the bone metastases in these patients.

However, SMM has some benefits in terms of prognostic stratification[18,33,34]. Scopinaro et al studied ^{99m}Tc-MIBI uptake and angiogenesis which is the most reliable marker of breast cancer invasiveness. They quantitatively assessed the angiogenesis by staining of endothelial cells for factor VIII with standard immunoperoxidase technique and counted the number of microvessels in the areas of highest vascularization. They found that all the node-positive patients showed a positive ^{99m}Tc-MIBI uptake of the primary tumor and had higher microvessel density while all the node-negative patients showed negative scan and had lower microvessel density. So they suggest that ^{99m}Tc-MIBI is a marker of breast cancer invasiveness because its uptake is related to angiogenesis[34].

The development of Multi-Drug Resistance (MDR) is a major limitation in chemotherapy. MDR which has been associated with the 170 kDa p-glycoprotein (P-gp)[25] is believed to be a factor contributing to the failure of some tumor response to antineoplastic agents such as doxorubicin and paclitaxel[35]. Recently ^{99m}Tc-MIBI was found to be a substrate for P-gp by Piwnica-Worms et al[22] and thus MIBI uptake may provide additional information about the P-gp status of tumor cells. Varrella et al used ^{99m}Tc-MIBI SMM for monitoring tumor response in patients with advanced breast cancer and concluded that the mammographic evidence of tumor associated with lack of MIBI uptake suggests the onset of the MDR phenomenon leading to the change of therapeutic regimen[36].

SUMMARY

In summary, physical examination and mammography are still recommended for the screening of breast cancer but ^{201}Tl or ^{99m}Tc-MIBI scintimammography can provide additional information and thus increase accuracy of the mammographic results. Both agents provide similar images and give high sensitivity for detection of primary breast cancer, which is slightly higher in palpable lesions than nonpalpable ones. SMM has also good specificity for differentiating malignant and benign masses. However, SMM is relatively less sensitive for diagnosing ipsilateral axillary node metastasis and it is not an accurate way to evaluate the extent of distant metastases, especially bone metastases. In addition, more and more studies about the ^{99m}Tc-MIBI imaging in breast cancer have been conducted to evaluate its role for the development of MDR and therapeutic planning.

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การตรวจเต้านมทางเวชศาสตร์นิวเคลียร์ในผู้ป่วยมะเร็งเต้านม

*จิราพร มังครักษ์, พ.บ.**

ได้ทำการศึกษาการตรวจเต้านมทางเวชศาสตร์นิวเคลียร์ (scintimammography) โดยใช้สารธัลเลี่ยม-201 (^{201}Tl) และ/หรือ เทคนีเชียม-99 เอ็ม เอ็มไอบีไอ (^{99m}Tc-MIBI) ในผู้ป่วยหญิงที่เป็นมะเร็งเต้านมจำนวน 45 ราย โดยผู้ป่วย 36 ราย มีก้อนที่เต้านมขณะตรวจและยังไม่ได้รับการผ่าตัด ผู้ป่วยอีก 9 ราย ได้รับการผ่าตัดเอาก้อนที่เต้านมออกไปแล้ว ความไวในการตรวจพบมะเร็งเต้านมคิดเป็นร้อยละ 92 และ ความไวในการตรวจพบการแพร่กระจายของมะเร็งเต้านมไปยังต่อมน้ำเหลืองที่รักแร้ข้างเดียวกันคิดเป็นร้อยละ 48 การถ่ายภาพเต้านมด้วยสารเภสัชรังสีดังกล่าว มีประโยชน์ช่วยวินิจฉัยมะเร็งเต้านม และช่วยให้การตรวจเอกซเรย์เต้านม (mammography) มีความแม่นยำในการวินิจฉัยโรคเพิ่มขึ้น นอกจากนั้นยังมีประโยชน์ในการวินิจฉัย การกลับเป็นใหม่ของมะเร็งหลังการรักษา การวินิจฉัยและการแพร่กระจายของมะเร็งเต้านม ไปยังต่อมน้ำเหลืองที่รักแร้ แต่ประโยชน์น้อยในการพิจารณาการแพร่กระจายของมะเร็งเต้านมไปยังส่วนอื่นๆ เช่น ตับ หรือกระดูก

คำสำคัญ : การตรวจเต้านมทางเวชศาสตร์นิวเคลียร์, มะเร็งเต้านม, ธัลเลี่ยม-201, เทคนีเชียม-99 เอ็ม เอ็มไอบีไอ

* สาขาวิชาเวชศาสตร์นิวเคลียร์, ภาควิชารังสีวิทยา, คณะแพทยศาสตร์ศิริราชพยาบาล, มหาวิทยาลัยมหิดล, กรุงเทพมหานคร 10700