Comparison of double phase Tc-99m MIBI and Tc-99m Tetrofosmin scintimammography for characterization of breast lesions: Visual and quantitative analyses

I. J. KIM[1, 2], S. J. KIM,[1, 2*], Y. K. KIM[1, 2]

[1]*Department of Nuclear Medicine, Pusan National University School of Medicine e-growthkim@daum.net;* [2]*Medical Research Institute, Pusan National University School of Medicine, Busan, Republic of Korea, 602-739*

Received March 6, 2008

The aim of the current study was to compare the diagnostic reliability of visual and quantitative indices of double phase Tc-99m MIBI scintimammography (M-SMM) and Tc-99m Tetrofosmin scintimammography (TF-SMM) for detection of breast cancer. Double phase M-SMM and TF-SMM (early; 10 minutes, delayed; hour) were performed after injection of 925 MBq of radiotracers in 75 highly suspected breast cancer patients (malignant:49, benign:26). For visual analysis, five scoring methods were used. For quantitative analysis, early, delayed lesions to non-lesion ratios (L/Ns), and washout rate (%, WR) were calculated. When over grade of visual grade was used as cut-off value in the detection of primary breast cancer, M-SMM and TF-SMM showed similar diagnostic accuracies. The optimal quantitative indices of M-SMM for the detection of breast cancer were 2.06 for early L/N and 1.72 for delayed L/N. Those of TF-SMM were 3.13 for early, and 2.56 for delayed image. Visual and quantitative analyses showed similar results. However, delayed L/N of M-SMM was superior to that of TF-SMM for the detection of breast cancer. In conclusion, the double phase M-SMM and TF-SMM showed favorable diagnostic accuracy in differentiating benign from malignant breast lesions, visually and quantitatively. The optimal visual interpretation grades for the detection of primary breast cancer of double phase M-SMM and TF-SMM were grade and 5. The optimal quantitative indices of M-SMM for the detection of breast cancer were 2.06 for early L/N and 1.72 for delayed L/N. Those of TF-SMM were 3.13 for early, and 2.56 for delayed image.

Key words: breast cancer; Tc-99m MIBI; Tc-99m Tetrofosmin

Breast cancer continues to be major public health problem in the Republic of Korea and Western countries. The American Cancer Society estimates that in 2008, 182,460 new cases of breast cancer will be diagnosed in female and breast cancer expected to account for 15 of all female cancer deaths [1].

A realistic strategy for the reduction of breast cancer mortality rates is to detect the disease while it is still in an early stage. Routine physical examination and mammography remain the methods of choice in screening for breast cancer. Mammography has been proven in randomized controlled trials to be sensitive screening tool for the detection of early breast cancer [2]. However, its utility for differentiating benign from malignant lesions is limited, with rate of histological confirmation of just 10-35% in biopsies [3]. To improve diagnostic accuracy, new methods are being studied as alternatives to mammography.

The scintimamography (SMM) using several radiopharmaceuticals have been proposed to improve the specificity of conventional mammography. Among numerous radiopharmaceuticals, the use of Tc-99m MIBI is currently mainstay, although its mechanism of uptake in breast cancer cells is still being investigated. After being reported to accumulate in tumors, Tc-99m MIBI has been widely used in tumor studies and is known to be useful in the detection of various primary tumors and metastases [4–10]. The Tc-99m MIBI SMM (M-SMM) has been known to be useful for diagnosis of primary breast cancer [11–13].

Tc-99m Tetrofomsin, lipophilic anionic radiopharmaceutical, has also been shown to have accumulated in various tumors [14–17]. Tc-99m Tetrofosmin does not require boiling and therefore could reduce radiation exposure to health care

* Corresponding author

providers during preparation. It also clears rapidly from the blood pool, liver and lungs, and so provides better quality of images. No other study had been published of the use of Tc-99m Tetrofosmin for comparison of visual and quantitative analyses of double phase M-SMM and TF-SMM for the detection of primary breast cancer. In this study, we compared the visual and quantitative indices for the detection of breast cancer using receiver operating characteristic (ROC) analysis of double phase M-SMM and TF-SMM.

Patients and methods

Patients. Seventy five patients with palpable breast masses on physical examination and/or suspicious mammographic findings were included in this study. Patients with either palpable breast mass or suspicious mammographic finding which required core needle biopsy were referred to the double phase M-SMM and TF-SMM. The patients mean age was 46.9±9.5. All patients had mammography and comprehensive physical examination by an experienced breast surgeon before double phase SMMs. Among 49 malignant breast diseases, 30 patients had palpable breast lesions and 19 had nonpalpable lesions. Among 26 benign diseases, 11 patients had palpable and 15 had nonpalpable lesions. The time interval between double phase M-SMM and TF-SMM was 7.1±3.1 days. Pathologic results were obtained by operation in 49 patients and in 26 patients by core needle biopsy and compared with the results of double phase SMMs. The Joint Ethical Committee of the Pusan National University Hospital Review Board approved this study. Informed written consents to participate in the double phase SMM studies were obtained from all patients.

Double phase Tc-99m MIBI and Tc-99m Tetrofosmin SMM. Double phase SMMs were performed in early (10 minutes) and delayed (3 hours) phases after intravenous injection of 925 MBq of Tc-99m MIBI (Cardiolite™; DuPont Pharma, Billerica, MA) and Tc-99m Tetrofosmin (Myoview™; Amersham Health; UK) on separate day in the antecubital vein contralateral to the affected breast or dorsalis pedis vein. Patients were laid in prone position on foam cushion designed for breast imaging overlying the imaging table, which permitted the breast to hang freely. Planar images with matrix size of 128×128 pixels and 1.5 zoom factor were acquired with dual headed gamma camera (Vertex, ADAC, Milpitas, CA, USA) equipped with low energy high resolution (LEHR) collimators. The energy discriminator was centered on 140 keV photopeak of Tc-99m with symmetric 20% window. For the lateral planar images (15 minutes acquisition, total 8,500,000 counts in both of Tc-99m MIBI and Tc-99m Tetrofosmin), layer of 2.5 thick and 10×5 rectangular lead was interposed in the foam cushion to avoid artifacts from the contralateral breast. After acquisition of both lateral images, planar anterior chest image including both breasts and axilla (7 minutes acquisition, total 4,500,000 counts in both of Tc-99m MIBI and Tc-99m Tetrofosmin) was also acquired in supine position. The supine position with raised arms was used for better depiction of both axillary regions.

Visual analysis of Double Phase M-SMM and TF-SMM. Two-experienced nuclear physicians who were not familiar with the patients clinical informations like the history, physical examinations, or radiological findings interpreted the M-SMM and TF-SMM individually on workstation connected to gamma camera with adjustments for contrast. The qualitative interpretation grades were as follows. Grade 1: no abnormal increased uptake in both early and delayed images. Grade 2: mildly increased uptake in the early image without retention in the delayed image. Grade 3: mildly increased uptake in the early image with retention in the delayed image. Grade 4: definite focal increased uptake in the early image without retention in the delayed image. Grade 5: definite focal increased uptake in the early image with retention in the delayed image. For analysis of axillary lymph node status, any clearly increased focal tracer accumulation in the axillary region was interpreted as lymphatic metastasis.

Calculation of quantitative indices. For quantitative analysis, ROIs (region of interest, mean pixel size; 78) were drawn around the tumor and to the area of normal breast tissue in the same breast, and lesion to non-lesion ratios (L/N) of early and delayed M-SMM and TF-SMM were determined. In case of visual grade 1, L/N considered to be because of absent of radiopharmaceutical uptake. The washout rate (%, WR) was determined by the following formula: (Early L/N-Delayed L/N) /Early L/N 100.

Statistical analysis. All numerical results are reported as mean values with SDs. Student t-test was used for statistical comparison of quantitative indices between malignant and benign breast disease groups. The MedCal software (Mariakerke, Belgium) was used to determine optimal visual interpretation grade and cut-off value of quantitative indices for the detection of primary breast cancer. The sensitivities and specificities of M-SMM and TF-SMM according to visual interpretation criteria and quantitative indices were obtained and the standard errors (SE), 95 confidence intervals (CI) and area under curves (AUCs) were also calculated. The comparison of diagnostic performances of visual and quantitative analyses were examined through use of AUC in receiver operating characteristic curve (ROC) analysis. Statistical significance was defined as $p<0.05$.

Results

Histopathologic results. The pathologic results were obtained from operations in 49 patients and core needle biopsy in 26 patients. The pathological diagnosis was malignant breast diseases in 49 patients and benign breast diseases in 26 patients, yielding breast cancer prevalence in this series of 65.3%. Among the malignant breast diseases, invasive ductal carcinoma was the most common (44 pts). The other pathologic results were ductal carcinomas-in-situ, invasive tubular carcinoma, mucinous carcinoma, medullary carci-

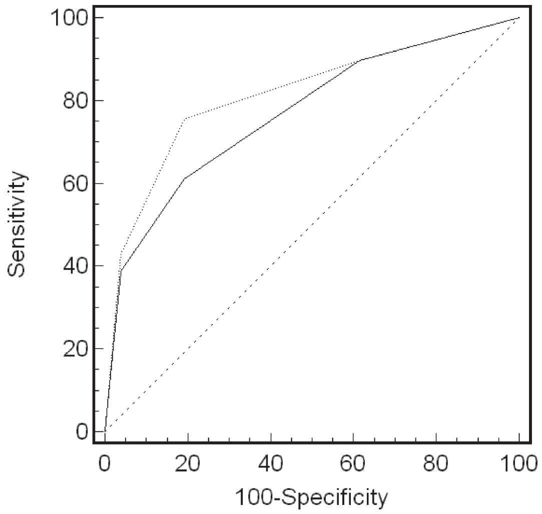

Figure 1. ROC comparison of M-SMM and TF-SMM for the detection of primary breast cancer (Line; M-SMM, Dotted line; TF-SMM).

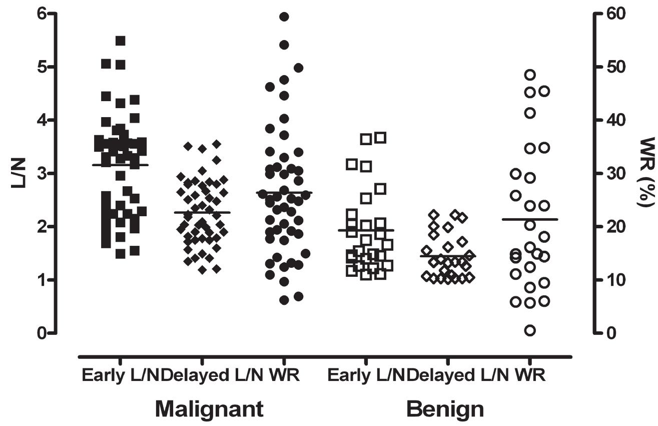

Figure 2. Quantitative indices of double phase M-SMM between malignant and benign breast diseases.

noma. The benign breast diseases included 16 fibrocystic diseases, fibroadenomas, mastitis, and tubular adenoma. Disagreed visual analyses were cases and all of them were consensused by the readers.

Axillary lymph node assessment. Axillary lymph node dissection was performed in patients with confirmed malignancy of the breast. Thirty-two patients had axillary lymph node metastasis and 17 had no axillary lymph node metastasis. The diagnostic accuracy of M-SMM and TF-SMM for the detection of axillary lymph node involvement was compared with histopathologic results. The true positive, true negative, false positive, and false negative of M-SMM and TF-SMM were 22, 15, 2, and 10 patients respectively. The sensitivity, specificity, and accuracy of M-SMM and TF-SMM for the evaluation of axillary lymph node involvement were 68.7%, 88.2%, and 75.5%, respectively.

Visual assessment of M-SMM and TF-SMM. ROC analyses were performed to determine the optimal visual grade for the detection of malignant breast disease. Figure demonstrated the ROC comparison of M-SMM and TF-SMM for the detection of primary breast cancer. The optimal visual grades were grade and in both of double phase M-SMM and TF-SMM. When over grade of visual grade was used as cut-off value in the defection of primary breast cancer with M-SMM, the sensitivity and specificity were 61.2% and 80.8%, respectively. The positive and negative predictive values were 85.7% and 52.5%, respectively. The AUC was 0.769 (95% CI, 0.657-0.858) and SE was 0.054. With the TF-SMM, the sensitivity and specificity were 75.5% and 80.8%, respectively. The positive and negative predictive values were 88.1% and 63.6%, respectively. The AUC was 0.814 (95% CI, 0.707-0.894) and SE was 0.048. However, no statistical differences were found between M-SMM and TF-SMM for the detection of primary breast cancer with visual assessment (difference between area; 0.045, SE; 0.030, 95% CI; -0.014-0.104, p=0.134).

Comparison of quantitative indices between malignant and benign diseases. Figure showed the results of quantitative indices of double phase M-SMM between malignant and benign breast diseases. Early L/N of malignant breast disease was significantly higher than that of benign one (3.15±0.94 vs 1.93±0.76, p=<0.0001). Also, delayed L/N of malignant breast disease was significantly higher than that of benign one (2.26±0.61 vs 1.44±0.40, p<0.0001). However, WR revealed no statistical differences (26.3±12.1 vs 21.4±13.6, p=0.1078). Figure showed the results of TF-SMM. Early L/N of malignant breast disease was significantly higher than that of benign one (3.49±1.17 vs 2.15±0.46, p=0.0001). Also, delayed L/N of malignant breast disease was significantly higher than that of benign one (2.54±0.76 vs 1.91±0.42, p=0.0002). However, WR also revealed no statistical differences (25.6±11.73 vs 23.7±9.8, p>0.05).

Quantitative analysis of double phase M-SMM and TF-SMM. ROC analyses were performed to determine the optimal cut-off values of early and delayed L/Ns of M-SMM and TF-SMM for the detection malignant breast disease. With the M-SMM, the optimal L/N ratios were 2.06 for early, and 1.72 for delayed image. When early L/N 2.06 was used as cut off point, the sensitivity and specificity of M-SMM were 85.7% and 73.1%, respectively. The positive and negative predictive values were 85.7% and 73.1%, respectively. The AUC was 0.850 (95% CI, 0.748-0.922) and SE was 0.043. With delayed L/N 1.72 was used as cut-off value, the sensitivity and specificity were 81.6% and 76.9%, respectively. The positive and negative predictive values were 87% and 69%, respectively. The AUC was 0.869 (95% CI, 0.771-0.936) and SE was 0.040.

With the TF-SMM, the optimal L/N ratios were 3.13 for early, and 2.56 for delayed image. When early L/N 3.13 was used as cut off point, the sensitivity and specificity of TF-SMM were 61.2% and 96.2%, respectively. The positive and negative predictive values were 96.8% and 56.8%, respectively. The AUC was 0.809 (95% CI, 0.702-0.890) and SE was 0.049. With delayed L/N 2.56 was used as cut-off value, the sensitivity and specificity were 46.9% and 96.2%, respectively. The positive and negative predictive values were 95.8% and 49%, respectively. The AUC was 0.741 (95% CI, 0.627-0.835) and SE was 0.057.

Comparison of quantitative analysis of M-SMM and TF-SMM for detection of breast cancer. There were no statistical differences between quantitative analysis of early image of M-SMM and TF-SMM (difference between area; 0.041, SE; 0.044, 95% CI; -0.046-0.128, p=0.359). However, delayed L/N of M-SMM was superior to delayed L/N ratio of TF-SMM for the detection of breast cancer (difference between area; 0.128, SE; 0.053, 95% CI; 0.024-0.232, p=0.016).

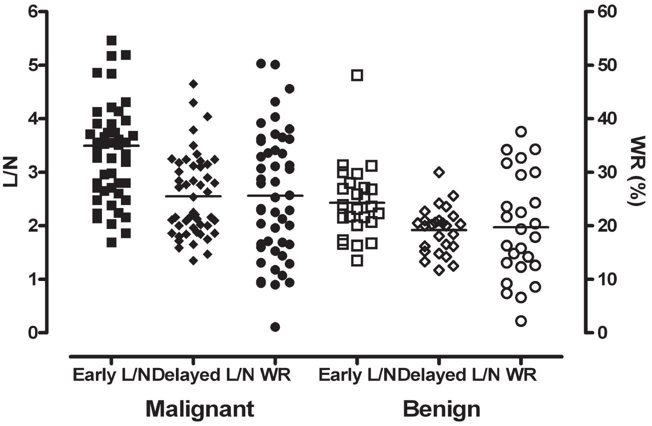

Figure 3. Quantitative indices of double phase TF-SMM between malignant and benign breast diseases.

Discussion

Detection of malignant disease and avoiding unnecessary operative biopsies of benign lesions are the main challenges in the detection of palpable breast masses and mammographic abnormalities. Mammography is the principal complementary imaging modality for the diagnosis of breast cancer. It is of fundamental importance for early detection of less advanced lesions that has become increasingly frequent as result of its use. However, although mammography is highly sensitive technique, it is frequently incapable of differentiating malignant lesions from benign ones, especially in patients with dense breast tissue or those who have received augmented mammoplasty, or previous radiation therapy. Therefore, most mammographic abnormalities require biopsies, which result in large number of non-malignant specimens.

To overcome the limitations of mammography, there has been growing interest in the employment of radiopharmaceutical products. Among these radiotracers, Tc-99m MIBI and Tc-99m Tetrofosmin have given the most interesting results. SMM with these radiopharmaceuticals is especially indicated in patients with dense breast or mastopathy or with mammary implants in which mammography is indeterminate or less effective, as well as in those with low or intermediate mammographic suspicion of malignancy, contributing to reduce the number of unnecessary biopsies [22–24].

The major findings of this study are that the optimal visual interpretation grades of M-SMM and TF-SMM for the detection of primary breast cancer were grade and grade 5. Using these grades as cut-off value, visual assessment of M-SMM and TF-SMM revealed similar diagnostic efficacies for the detection of primary breast cancer. The optimal quantitative indices of M-SMM were 2.06 for early L/N and 1.72 for delayed L/N. Also, the optimal quantitative indices of TF-SMM were 3.13 for early L/N and 2.56 for delayed L/N, which were higher values than those of M-SMM. ROC comparison revealed no statistical differences between M-SMM and TF-SMM early L/Ns for differentiation of malignant breast diseases. However, the delayed L/N of M-SMM was superior to that of the TF-SMM for breast cancer detection.

Comparative study has demonstrated that Tc-99m MIBI and Tc-99m Tetrofosmin give similar results in breast cancer detection, thus they can be used indifferently [25].

Interestingly, current study exhibited similar diagnostic efficacy for the detection of primary breast cancer of visual and quantitative analyses of M-SMM and TF-SMM. However, the cut-off values of early and delayed L/Ns of TF-SMM were higher than those of M-SMM. Favorable pharmacokinetic properties of Tc-99m Tetrofosmin may give rise to these results [26]. It clears rapidly from blood pool, liver and lungs, and so provides better images with higher tumor/background ratio. Faster hepatic clearance could be an advantage in the evaluation of tumors located in breast or lung near the liver, determining lower background. Also, Tc-99m Tetrofosmin does not require boiling and may reduce radiation exposure to health care providers during preparation.

To date, there was no report of comparative visual and quantitative study of double phase M-SMM and TF-SMM for the evaluation of breast cancer. Using Tc-99m MIBI, some studies of double phase SMM for the detection of breast cancer has been reported [27–29]. Also, double phase TF-SMM study was performed recently [30]. The reason for performing early and delayed imaging was to differentiate between benign and malignant diseases more accurately. They presumed that the radiopharmaceutical uptake by malignant tumors might persist on delayed images in contrast to that of benign lesions, which would fade away.

The major drawback of the current study is lack of SPECT acquisition of M-SMM and TF-SMM. SPECT has proved more sensitive than planar imaging in various clinical circumstances, but until now has not been employed in the diagnosis of breast cancer with M-SMM and TF-SMM.

In conclusion, double phase M-SMM and TF-SMM showed favorable diagnostic accuracy in differentiating benign from malignant breast lesions, visually and quantitatively. The optimal visual interpretation grades for the detection of primary breast cancer of double phase M-SMM and TF-SMM were grade and 5. The optimal quantitative indices of M-SMM for the detection of breast cancer were 2.06 for early L/N and 1.72 for delayed L/N. Those of TF-SMM were 3.13 for early, and 2.56 for delayed image. Visual and quantitative analyses showed similar results. However, delayed L/N of M-SMM was superior to that of TF-SMM for the detection of breast cancer. These findings deserve further investigation on larger number of patients to be performed to allow better validation of the differentiation malignant from benign breast lesions using double phase M-SMM and TF-SMM.

References

[1] JEMAL A, SIEGEL R, WARD et al. Cancer statistics, 2008. CA Cancer CLin 2008; 58: 71–96.

[2] NYSTROM L, ANDERSSON I, BJURSTAM et al. Long-term effects of mammography screening: updated overview of the Swedish randomized trails. Lancet 2002; 359; 909–919.

[3] KERLIKOWSKE K, ICHIKAWA L, MIGLIORETTI DL. et al. Longitudinal measurement of clinical mammographic breast density to improve estimation of breast cancer risk. Natl Cancer Inst 2007; 99: 386–395.

[4] FONTI R, SALVATORE B, QUARANTELLI et al. ^{18}F-FDG PET/CT, ^{99m}Tc-MIBI, and MRI in evaluation of patients with multiple myeloma. Nucl Med 2008; 49: 195–200.

[5] RONGA G, VENTRONI G, MONTESANO T et al. Sensitivity of ^{99m}Tc-methoxyisobutylisonitrile scan in patients with metastatic differentiated thyroid cancer. J Nucl Med Mol Imaging 2007; 51: 364–371.

[6] PEER FI, PUI MH, MOSAM et al. ^{99m}Tc-MIBI imaging of cutaneous AIDS-associated Kaposi's sarcoma. Int Dermatol 2007; 46: 166–171.

[7] LO CY, LANG BH, CHAN WF et al. prospective evaluation of preoperative localization by technetium-99m sestamibi scintigraphy and ultrasonography in primary hyperparathyroidism. Am Surg 2007; 193: 155–159.

[8] HURTADO-LOPEZ LM, MARTINEZ-DUNCKER C. Preoperative evaluation of thyroid nodules with 18FDG-PET/CT or MIBI scan ?. Surgery 2007; 141: 1166–1174.

[9] LEE BJ, WANG SG, GOH EK et al. Usefulness of technetium-99m methoxyisobutylisonitrile single-photon emission computed tomography and computed tomography in the evaluation of cervical lymph node metastasis. Laryngol Otol. 2005; 119: 882–887.

[10] SHINOURA N, YAMADA R, TAKAHASHi et al. Use of Tc-99 MIBI SPECT for characterization of metastatic brain tumors: implications for surgery. Clin Nucl Med. 2006; 31: 538–540.

[11] PRATS E, RAZOLA P, SAINZ JM et al. Scintimammography with ^{99m}Tc-MIBI in the clinical practice: repercussion on the clinical management of the patient. Rev Esp Med Nucl. 2007; 26: 153–159.

[12] FLIPPI L, PULCINI A, REMEDIANI et al. Usefulness of scintimammography with Tc-99m MIBI in clinical practice. Clin Nucl Med. 2006; 31: 761–763.

[13] MATHIEU I, MAZY S, WILLEMART et al. Inconclusive triple diagnosis in breast cancer imaging: is there place for scintimammography? Nucl Med. 2005; 46: 1574–1581.

[14] FATTORI B, GROSSO M, NACCI et al. The role of ^{99m}Tc-tetrofosmin scintigraphy for staging patients with laryngeal cancer. Cancer Biother Radiopharm. 200520: 27–35.

[15] FILIPPI L, SCHILLACI O, SANTONI et al. Usefulness of SPECT/CT with hybrid camera for the functional anatomical mapping of primary brain tumors by [Tc99m] tetrofosmin. Cancer Biother Radiopharm. 2006; 21: 41–48.

[16] SHARMA R, CHAKRAVARTY KL, TRIPATHI et al. Role of ^{99m}Tc-Tetrofosmin delayed scintigraphy and color Doppler sonography in characterization of solitary thyroid nodules. Nucl Med Commun. 2007 28: 847–851.

[17] ALEXIOU GA, FOTOPOULOS AD, PAPADOPOULOS et al. Evaluation of brain tumor recurrence by ^{99m}Tc-tetrofosmin SPECT: prospective pilot study. Ann Nucl Med. 2007; 21: 293–298.

[18] SPANU A, CHESSA F, BATTISTA MELONI et al. Scintimammography with high resolution dedicated breast camera and mammography in multifocal, multicentric and bilateral breast cancer detection: comparative study. J Nucl Med Mol Imaging. 2008 Apr 25. [Epub ahead of print]

[19] SPANU A, COTTU P, MANCA et al. Scintimammography with dedicated breast camera in unifocal and multifocal/multicentric primary breast cancer detection: comparative study with SPECT. Int Oncol. 2007; 31: 369–377.

[20] JAUKOVIC LDJ, AJDINOVIC BZ, JANKOVIC ZD et al. Technetium-99m-tetrofosmin in diagnosis of breast cancer and axillary lymph node involvement. Nucl Med Rev Cent East Eur 2006; 9: 30–36.

[21] SCHILLACI O, DANIELI R, ROMANO et al. Scintimammography for the detection of breast cancer. Expert Rev Med Devices. 2005; 2: 191–196.

[22] CUTRONE JA, KHALKHALI I, YOSPUR LS et al. Tc-99m sestamibi scintimammography for the evaluation of breast masses in patients with radiographically dense breasts. Breast 1999; 5: 383–388.

[23] KHALKHALI I, VILLANUEVA-MEYER J, EDELL SJ et al. Diagnostic accuracy of ^{99m}Tc-Sestamibi breast imaging: multicenter trial results. Nucl Med 2000; 41: 1973–1979.

[24] POLAN RL, KLEIN BD, RICHMAN RH. Scintimammography in patients with minimal mammographic or clinical findings. Radiographics 2001; 21: 641–653.

[25] OBWEGESER R, BERGHMMER P, RODRIGUES M et al. head to head comparison between technetium-99m-tetrofosmin and technetium-99m-MIBI scintigraphy to evaluate suspicious breast lesions. Eur Nucl Med 1999; 26: 1553–1559.

[26] HIGLEY B, SMITH FW, GEMMELL HG et al. Technetium-99m-1, 2-bis[bis(2-ethoxyethyl) phosphinol] ethane: human biodistribution, dosimetry and safety of new myocardial perfusion imaging agent. Nucl Med 1993; 34: 30–38.

[27] KIM SJ, BAE YT, LEE JS et al. Diagnostic performances of double-phase Tc-99m MIBI scintimammography in patients with indeterminate ultrasound findings: visual and quantitative analyses. Ann Nucl Med 2007; 21: 145–150.
[28] KIM SJ, KIM IJ, BAE YT et al. Incremental diagnostic value of quantitative analysis of double phase Tc-99m MIBI scintimammography for the detection of primary breast cancer additive to visual analysis. Breast Cancer Res Treat. 2004; 83: 129–38.
[29] KIM SJ, KIM IJ, BAE YT et al. Comparison of Early and Delayed Quantified Indices of Double-Phase ^{99m}Tc MIBI Scintimammography in the Detection of Primary Breast Cancer. Acta Radiologica 2005; 46: 148–154.
[30] LEE JS, KIM SJ, KIM IJ et al. Characterization of breast lesion using double phase Tc-99m Tetrofosmin scintimammography: Comparison of visual and quantitative analyses. Eur Radiol 2006; 57: 76–80.