Original Article

Application of Breast Scintigraphy for Patients with Suspicious (Breast Imaging-Reporting and Data System IV) Breast Lesions

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Abstract

Background: The surgery for a breast imaging-reporting and data system (BIRADS) IV lesions needs imaging or pathology supporting data. The roll of breast scintigraphy for this purpose is unclear.

Materials and Methods: In a prospective design, 16 patients with 25 BIRADS IV lesions who were scheduled for surgery were included. Before the surgery, breast scintigraphy was done using a nondedicated dual head gamma camera in the prone position employing a shaped foam pad providing imaging at breast pendulous position. Twenty mCi $^{99\ m}$Tc methoxy-isobutyl-isonitrile was injected and two 15 and 60-min delayed imaging were done (anterior, bilateral, and single photon emission computed tomography [SPECT] projections). Pathology reports were collected and tumor to nontumor uptake ratio (T/NT) was analyzed, accordingly.

Results: Out of all lesions, 12 were malignant (invasive ductal and lobular carcinoma ductal carcinoma *in situ*). At 15 min, T/NT was insignificantly higher in the malignant compared to benign lesions (22.8 ± 23.9 vs. 10.1 ± 10.1; $P = 0.109$). The optimal T/NT cutoff for discrimination of malignant and benign lesions was 20. Only 1 out of 13 benign lesions presented uptake >20 (7.7%; false-positive rate; $P = 0.047$). The diagnostic accuracy, sensitivity, and specificity for T/NT calculated at 0.68, 0.42, and 0.92, respectively. The T/NT at 60 min remained unchanged for either benign or malignant lesions (22.3 ± 30.2 vs. 11.7 ± 17.1; $P = 0.296$).

Conclusions: Breast scintigraphy with general purpose gamma camera employing SPECT imaging may assist the selection of BIRADS IV lesions in need for surgery. All uptake positive cases should undergo surgery and decision for uptake negative cases should be made based on other data.

Keywords: Breast neoplasms, diagnostic imaging, gamma cameras, technetium Tc 99 m

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Introduction

The breast surgeon encounters a critical question to operate or not operate a patient with a breast imaging-reporting and data system (BIRADS) IV breast lesion.[1] Clinical history, imaging, and pathology from the needle, core, or vacuum biopsies may classify high and low risk lesions. The major conflict rise when there is discrepancy of pathology benign or border line report with clinical data (e.g., remarkable family history) or imaging (e.g., an ultrasonography reporting BIRADS IV but with an infiltrative component). The dilemma when the

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pathology is nonmalignant and the imaging is BIRADS IV, known as discordant lesion, could be solved by close follow-up or surgery.[2] An alternative method would be the use of other imaging techniques. Using tumor agents, nuclear medicine may provide certain light into the problem.

It has been reported that methoxy-isobutyl-isonitrile (MIBI) accumulates in malignant tumors.[3] Before the advent of 18F-fluorodeoxyglucose, MIBI played a remarkable roll as tumor agent, overwhelmed latterly by the former. For breast lesions, however, the application of MIBI imaging, known as breast specific imaging (BSI), may yet assist proper selection of patients' high risk for malignancy.[4] Dedicated mamoscintigraphy cameras with high spatial resolution were developed for this purpose[5] and are integrated into clinical breast screening protocols.[6] General purpose gamma cameras have remarkable drawback for BSI. Historically, the spatial resolution of general purpose gamma cameras was considered low for sub-centimeter lesions. Furthermore, the flat bed of these cameras is unsuitable and unfitted for breast imaging. Considering that single photon emission computed tomography (SPECT) imaging definitely provide added remarkable data into many traditional nuclear medicine images, we suspected whether SPECT may provide such improvement for BSI with general purpose gamma cameras which are more available than dedicated mamoscintigraphy cameras. Furthermore, we believe that the spatial resolution of general purpose gamma cameras has significantly improved in recent years, so that the sub-centimeter lesions may become visualized employing SPECT image acquisition.

To assess the capability of SPECT imaging by a general purpose gamma camera, in the current study, the optimal threshold for tracer accumulation in malignant versus. nonmalignant breast BIRADS IV lesions was studied. For SPECT imaging by a general purpose gamma camera, a molded foam pad was used to provide hanging breast at prone position.

Materials and Methods

From Cancer Institute Tehran University of Medical Science (Tehran, Iran), 16 women were included who had 25 BIRADS IV lesions on sonography. The surgery was planned based on overall clinical and imaging data as well as core needle biopsy available in a portion of patients. In our practice, BIRADS IVa breast lesions which the patient is discussed and unwilling to present for follow-up sessions are surgically excised. Furthermore, the lesions in an ipsilateral or contralateral breast of patients with another lesion with operation indication are surgically excised. Furthermore, certain BIRADS IVa lesion is considered not safe for conservative follow-ups including large fibroadenoma. Patients with previous history of breast surgery, recurrence, and chemotherapy were not included. Patients had no vacuum or core biopsy or fine-needle aspiration within 2 weeks before SPECT. The written consent forms were collected for radiation risk and imaging procedures. The protocol of the study was approved by the Institutional Research Ethics Committee. For the imaging, 20 mCi 99 mTC MIBI (pars isotope co, Tehran, Iran) was injected intravenously. Fifteen and 60 min after injection, anterior and bilateral in addition to SPECT projections were acquired. SPECT was done using a dual-head gamma camera with general purpose low energy collimation (AnyScan, Mediso, Budapest, Hungary) with the following specifications: 64 projections, 64 × 64 matrix sixe, and 20 s projection times. The patients lie down on a foam pad cut for the position of hanging breasts so that the image was acquired in prone and pendulous breast position. Images were processed and a region of interest (ROI) was placed over the tumor. The tumor location was centered and an isocontour ROI was automatically generated and borders placed at 10%–50% count variation points. The threshold for placement of the tumor limits was changed from 10% incrementing to 50% to delineate the perceived tumor contours. Another ROI was generated in the deep region of breasts anterior to the muscle. The tumor to nontumor uptake ratio (T/NT) was calculated as the ratio of the tumor count to the mean of nontumor ROI. Then, patients were operated and followed for the pathology after the surgery. The lesions were categorized for malignant and nonmalignant lesions corresponding to the pathology report. The T/NT was compared between the groups using *t*-test. Receiver operating curve for T/NT values to diagnose malignant lesions was drawn. Accordingly, T/NT was analyzed for the optimal threshold for categorization of malignant/nonmalignant lesion employing the shortest distance on the receiver operating characteristic (ROC) curve. Furthermore, a subgroup analysis was done for evaluation of correlation of the T/NT with the Ki-67 (categorized at 14%) and estrogen receptor (ER) status.

Before the operation, if the mass was not palpable the radiologic-guided wire localization was performed. All of the breast masses, including palpable or untouchable ones were excised. The technique of the surgery was selected based on the type of prior pathology, clinical and radiologic findings. For benign masses simple excision and for suspicious or malignant lesions, the appropriate oncoplastic surgery technique was employed. Patients were followed to collect their pathology report.

Data analyses were done using the IBM SPSS statistics (vs26; Endicott, NY, US). The quantitative data were compared using the independent sample *t*-test. Cross-tabulation analysis was done by the Chi-squared test. ROC curve analysis was done, and area under the ROC curves was considered as accuracies. To assess the change of values of T/NT from 15 to 60, general linear model was designed to perform the repeated measure analysis.

Results

Sixteen patients mean aged 50.6 ± 12.1 with 25 BIRADS 4 breast lesions (12 malignant and 13 benign) were recruited. These patients where scheduled for at least lumpectomy

from February 2019 to Jan 2020 at Cancer institute (Tehran University of Medical Sciences). The characteristics of the lesions are presented in Table 1. According to permanent pathology 12 lesions were malignant (ductal carcinoma *in situ* 3, invasive ductal carcinoma 8, and invasive lobular carcinoma 1) and 13 were benign (fibroadenoma 5, complex fibroadenoma 2, intraductal papilloma 1, sclerosing adenosis 1, usual ductal hyperplasia 2, complex adenosis 1, and fat necrosis 1). The benign tumors were insignificantly larger than malignant tumors (18.3 ± 10.4 vs. 11.2 ± 5.5; $P = 0.058$). Patients were consented then imaged with MIBI at the nuclear medicine department. The quality of the images was good [Figure 1]. Visual assessment indicated 17 MIBI tepid and 8 MIBI avid lesions. Four out of 13 benign (30.8%) and 4 out of 12 malignant (33.3%) lesions were MIBI avid. Visual MIBI uptake did not discriminate benign and malignant lesions ($P = 0.891$). At 15 min, T/NT was 10.1 ± 10.1 and 22.8 ± 23.9 in benign and malignant lesions, respectively; and at 60 min 11.7 ± 17.1 (for benign lesions) and 22.3 ± 30.2 (for malignant lesions), respectively. ROC curve analysis indicated accuracy of 0.62 and 0.56 for T/NT at 15 and 60 min, respectively. Differences of T/NT were not significant between malignant and benign lesions either at 15 ($P = 0.109$) or 60 min ($P = 0.296$). The uptake pattern in benign and malignant tumors was similar from 15 to 60 min [Figure 2]. After categorization of T/NT uptake into 2 low and high uptake group with an optimal cutoff at 20, 12 out of 13 benign lesions (92.3%; $P = 0.047$) had low uptake indicating only a false-positive result, but 7 out of 12 (58.3%) of malignant lesions also presented in low uptake category (false-negative cases). The diagnostic performance of visual and quantitative analyses is presented in Table 2. The accuracy of lesions classification into positive and negative MIBI uptake had low accuracy (68%) and sensitivity (42%) to classify the malignant or benign nature of the lesions, but the specificity was optimal at 92%. Regarding the size-related MIBI uptake in malignant lesions, 2 out of 6 subcentimetric and 3 out of 6 larger malignant lesions presented >20 T/NT uptake at 15 min. Out of 12 malignant lesions, 11 were positive ER, 5 had high and 6 low T/NT at 15 min. Similarly, in 9 patients with available Ki67 evaluations (cancers excluding DCIS), 5 (55.6%) patients had high Ki67 index (≥14%), two of them presented T/NT >20 at 15 min.

Table 1: The specifications of the breast lesions

Tumor characteristics	Statistics
Size (sonography) mm	14.9 (9.0)
Size (pathology) mm	17.0 (11.0)
BIRADS	
IVa	11 (44.0)
IVb	12 (48.0)
IVc	2 (8.0)
Side	
Left	17 (68.0)
Right	8 (32.0)
Estrogen receptor	
Not determined	13 (benign)
Negative	1 (9.1)
Positive	10 (90.9)
Progesterone receptor	
Not determined	13 (benign)
Negative	1 (9.1)
Positive	10 (90.9)
Human epidermal growth factor receptor	
Not determined	16 (benign and DCIS)
Negative	8 (88.9)
Positive	1 (11.1)
Ki67	16.1 (11.7)
Grade	
1	2 (16.6)
2	8 (66.6)
3	1 (8.3)
Not determined†	1 (8.3)
Lymphovascular invasion‡	17
Negative	1
Positive	7

†Due to pathology register technical error, ‡In DCI cases. Data are mean (SD) or *n* (%). SD: Standard deviation, DCIS: Ductal carcinoma *in situ*, BIRADS: Breast imaging-reporting and data system; DCI: Ductal carcinoma *in situ*

Discussions

The benign lesions presented with low MIBI uptake according to quantitative analysis. Less than 10% of benign tumors showed high T/NT uptake ratio more than 20 with only a falsely positive result in an active but benign lesion. This could be used as a specific measure for detection of lesions in need for surgery. Nevertheless, the sensitivity of the method for the detection of malignant lesions was low and overall accuracy of the scan was not optimal for discrimination

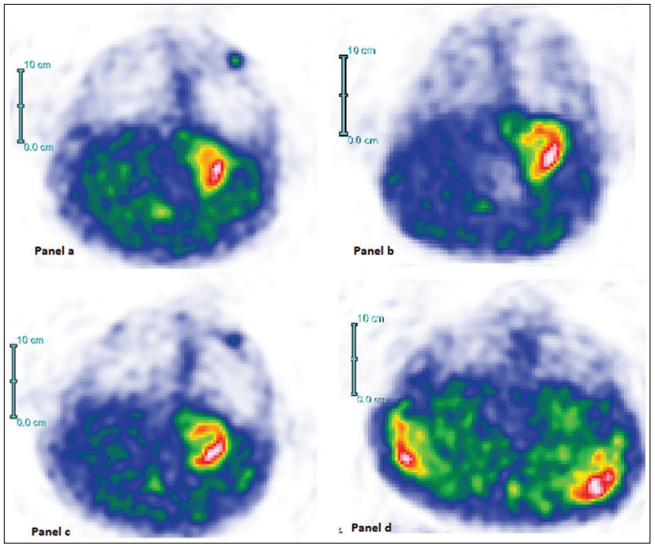

Figure 1: The transaxial image of breast from 4 different patients. Typical positive uptake in a malignant tumor (a), negative uptake in malignant tumors (b) which was a frequent finding, positive uptake in benign tumor (c) which was the unique false negative result, and a typical negative uptake in a benign tumor (d)

Table 2: Diagnostic performance of single photon-emission computed tomography imaging with general purpose gamma camera of breast imaging-reporting and data system IV breast lesions using ^{99m}Tc methoxy-isobutyl-isonitrile

Pathology	Benign	Malignant	Sensitivity	Specificity	PPV	NPP	Accuracy
Visual							
Negative	9	8	0.33	0.69	0.50	0.53	0.52
Positive	4	4					
Quantitative							
Negative	12	7	0.42	0.92	0.83	0.63	0.68
Positive	1	5					
Total	13	12					

Both visual (i.e. visualization of discrete MIBI avid tumor on SPECT images) and quantitative analyses (i.e. tumoral to nontumoral MIB uptake at cutoff level of 20 at 15 min) are presented for discrimination between benign from malignant lesions. SPECT: Single photon-emission computed tomography, MIBI: Methoxy-isobutyl-isonitrile, NPV: Negative predictive value, and PPV: Positive predictive value

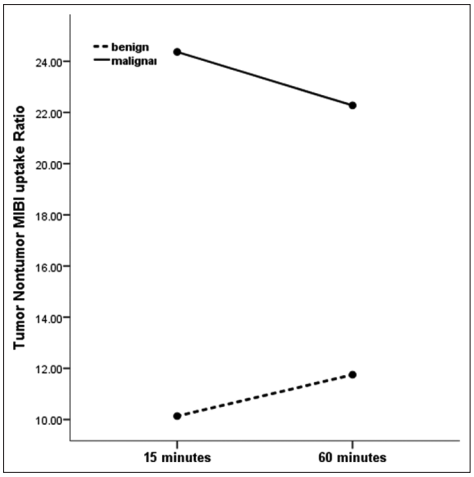

Figure 2: Tumor to nontumor methoxy-isobutyl-isonitrile uptake at 15 and 60-min delayed images in patients with benign and malignant tumors. Tumor to nontumor of the malignant tumors was significantly higher than those for benign lesions

between malignancy and benignity. The positive scans may play a role to support the surgeon and patient to proceed for surgery of BIRADS IV lesions. On the other hand, due to high uptake of a benign lesion out of 13, the unnecessary surgery of benign lesions would be very infrequent in this way. This conclusion is consistent with the finding of Zhou *et al*.[7] reporting a false-positive rate of about 7% employing dedicated mamoscintigraphy camera. The decision for surgery of a low uptake lesion should be made based on other imaging and clinical data. In the current study, the quantitative assessment of MIBI uptake was superior to visual interpretation which accuracy was very low.

In the current study, we used SPECT imaging which is a rather new application in the field of BSI. The dedicated cameras for breast scintigraphy provide with high sensitivity and spatial resolution.[8] In general, reports of the diagnostic accuracy of BSI with dedicated mamoscintigraphy camera infer high sensitivity and rather low specificity for the BSI.[9-15] A recent meta-analyses reported better diagnostic performance for breast-specific gamma camera imaging compared to MRI.[16] The nonindex detected benign lesions may be higher by MRI leading to better positive predictive value for BSI.[17] The drawbacks comprise high cost and unavailability. The imaging with dedicated devices is done in a position similar to mammography (MG) and the images perfectly correspond to the MG images. The nature of these images is planar and the spatial comparability with ultrasonography and MRI images are low. The use of planar images with general purpose cameras is hindered; the quality of the images is low, spatial resolution is suboptimal, and the positioning of the breasts is not feasible. The SPECT acquisition, increases the spatial resolution and increases the power to discriminate tumor from nontumoral tissue. Furthermore, employing the SPECT method, the positioning of the breast in hanging positions would become practical which is also used in certain dedicated breast PET scanners. The prone breast images provide the advantage of comparability with MRI images.

Meissnitzer and Meissnitzer[18] used planner imaging and reported high sensitivity and accuracy for it. The result of the current study employing SPECT imaging which theoretically provide better target to back ground and quantification measurements indicate low sensitivity for BSI with high false-negative rates by either visual or quantification assessments. The PPV was high in the study of Meissnitzer and Meissnitzer[18] similar to the current study, but they reported very low specificity. The low specificity with high PPV in the study by Meissnitzer infer the high malignancy rate in their sample. They included BIRADS IV and V lesions with about 73% malignancy rate. Different study population and inclusion criteria may justify the difference between the results of the two studies, at least partially. Nevertheless, in the current study, it is documented that the uptake of MIBI in malignant lesions is variable and only one third and less than half of malignant lesions were detectable by visual and quantitative methods, respectively. Reasonably, low malignancy rate in our study population compared with the study by Meissnitzer has dragged the cutoff up and may justify the high rate of false-negative findings. Finally, because there was no statistical difference between the uptakes value in benign and malignant lesions, one may conclude that our results are substantially different from those by Meissnitzer, but it should be considered that the value of the 15-min uptake in the malignant lesions was twofold of

that in the benign lesions, although insignificant possibly due to low sample size. Breast SPECT imaging was previously used by Ma *et al*.[19] at supine position. Nevertheless, they reported remarkably higher sensitivity (about 88%) but lower specificity (about 73%). Compared to the current study, they employed a different method for calculation/quantification. They reportedly drawn the ROIs around the "tumor and an area of normal breast tissue in the same breast on lateral images." After SPECT image process, it is unusual to draw ROIs on lateral images. The ROIs are usually drawn on 2 dimensional transverse images similar to the current study, and unusually on other 2 dimensional reconstructions (i.e., sagittal or coronal), or on 3 dimensional volume rendered reconstructions. Also, they imaged patients at supine position which flattens the breast and causes over implosion of breast tissue and activity with those of heart, chest, and abdominal wall; a fact that is evident in their Figure 2 panel B. It is also noteworthy, that the population of the study by Qingjie Ma *et al*. comprised more cancer cases (about 2/3 of the cases) compared to the current study affecting the accuracy of the test.

Interestingly, the uptake in the malignant lesions was high at 15 min after tracer injection, and rather stable late at 60 min. Many malignant tumors present gradual tracer uptake,[20] inconsistent with the stable MIBI accumulation in breast lesions in the current study. In benign lesion, the uptake was lower at 15 and similarly remained low at 60 min. The initial high uptake in malignant lesions documented in the current study and supported by Meissnitzer results may reflect high blood flow into and around the malignant lesions. In this context other nuclear medicine tracers including $^{99\ m}$Tc pertechnetate or $^{99\ m}$Tc medronate may play the same roll at blood flow and pool imaging phases, i.e., early to 15 min. This notion may contradict the essential/traditional fact that MIBI accumulates within malignant cells due to high mitochondria content of the neoplastic cells.[3] Urbano *et al*. suggested that MIBI accumulation in breast lesions may correlate with the expression of ER and presence of breast osteoblast-like cells in the tumor.[21] Suggestions have been done to predict bone metastasis propensity with MIBI uptake.[22] Furthermore, experiments with radio-guided biopsy from occult lesions have been done.[10]

Conclusion

MG is the essential screening and initial diagnosis imaging of breast cancer and breast sonography (US) play a remarkable complementary role; there are certain occasion in which there is no clear guide to decide between excisions or close follow-up.[23] Tadwalkar *et al*.[24] employing dedicated mamoscintigraphy camera reported sensitivity of more than 90 for BSI with MIBI which may add to the MG and US findings. Not only we cannot repeat the Tadwalkar's conclusion for general purpose gamma cameras but also we documented low sensitivity for the detection of malignant lesions. Employing quantification, due to low false-positive results, surgery is plausible for patients suspected for benign lesions according to other imaging but with high MIBI uptake.

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Conflicts of interest

The are no conflicts of interest.

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