

Is There a Clinical Role for Scintimammography in Breast Cancer Diagnosis?

Scintimammography is the functional imaging study of the breast with single-photon radiopharmaceuticals, such as ^{99m}Tc -sestamibi or ^{99m}Tc -tetrofosmin. In 1994, Khalkhali et al. (1) reported the first series with a relatively large number of patients on the clinical application of scintimammography. In their group of 59 patients, in whom an abnormal mammogram and physical examination warranted biopsy or fine-needle cytology of the breast, the sensitivity of scintimammography was 95.8%, specificity was 86.8%, positive predictive value was 82.1%, and negative predictive value was 97.1%. On the basis of these results, the authors concluded that scintimam-

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mammography is very sensitive and able to improve the specificity of mammography—so potentially useful to reduce the high rates of negative biopsies performed. After this investigation, numerous studies have been published about the clinical usefulness of scintimammography. The aggregated overall summary estimates of a recent meta-analysis selecting 64 unique studies (2), with data on 5,340 patients, including 5,354 breast lesions, were sensitivity, 85.2%; specificity, 86.6%; negative predictive value, 81.8%; positive predictive value, 88.2%; and accuracy, 85.9%. It is worth noting that 80% of the studies yielded sensitivity and specificity values of $>80\%$, and nearly half of them were values of $>90\%$. Moreover, in $>5,660$ cases re-

ported until now, the sensitivity and specificity of ^{99m}Tc -sestamibi scintimammography in detecting primary breast cancer were 83.8% and 86.4%, respectively (3).

Despite these very encouraging results suggesting that scintimammography could be a useful adjunct to mammography, the precise role of this technique in the algorithm of breast cancer diagnosis and its specific clinical indications are still being debated and are not definitively assessed.

In this issue of *The Journal of Nuclear Medicine*, Mathieu et al. (4) present the results of their investigations on the impact of scintimammography in a daily practice, using this technique as a second-line procedure in patients without a definitive diagnosis after the first-line examinations, including palpation, mammography, ultrasound, and fine-needle aspiration. Therefore, this study evaluated a difficult patient population, in which scintimammography determined a management modification in 49% of cases, analyzed in 4 different groups according to the clinical question.

When we look at the scintigraphic protocol, both planar and tomographic acquisitions were performed, with the sensitivity of SPECT results significantly higher than that of planar images—in particular, in the detection rate of smaller lesions (4). This issue is of the utmost importance: the ability to visualize small breast cancers is crucial for the development and acceptance of scintimammography, because other breast imaging modalities (mammography, MRI) permit an early detection of small lesions. On the other hand, it is well known that planar scintimammography has a low sensitivity for nonpalpable and ≤ 1 cm cancers, as indicated by several reports. In particular, in a multicentric study on 420 patients, Scopinaro et al.

(5) reported a sensitivity of 62% for nonpalpable tumors and of 46% for ones ≤ 1 cm, whereas the values for palpable and >1 cm cancers were 98% and 96%, respectively.

Therefore, increasing the sensitivity of planar scintimammography for small-sized tumors is clinically very relevant, and the role of SPECT in this task could be significant. Until now, some discordant results have been reported in the studies comparing tomographic and planar imaging in primary breast cancer diagnosis. These findings are primarily attributed to the fact that high-quality SPECT can be obtained only with the patient in the supine position and the arms up; prone SPECT is limited by geometric constraints of the patient, imaging table, and gantry (6), and the lower values are reported in the studies in which tomographic images are performed using this technique. In a group of 63 patients with 67 mammographically suspicious breast abnormalities (7), we observed a sensitivity of 93% for supine SPECT and of 86% for planar imaging, whereas accuracy was 91% and 88%, respectively. Moreover, in breast lesions ≤ 1 cm, supine SPECT yielded a significantly higher sensitivity than planar images both in T1b and nonpalpable breast cancers, without any decrease in specificity (8), thus indicating that SPECT acquisition is mandatory if scintimammography is performed for imaging small lesions. These clinical data are confirmed by a breast phantom study demonstrating that a better detection of small-sized lesions is achieved with tomographic images than with planar images (9). Moreover, from a technical point of view, these authors suggest that SPECT should be reconstructed using iterative algorithms instead of backprojection methods, and a $128 \times$

Received Jul. 7, 2005; revision accepted Jul. 11, 2005.

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128 matrix is preferable to a 64×64 one. Also, in a study including 113 patients, Tiling et al. (10) have reported that SPECT with iterative reconstruction is superior to filtered backprojection, showing both higher sensitivity and specificity.

The main drawback of SPECT is that, despite its better contrast resolution, it can be difficult to obtain a precise definition of the sites of radiopharmaceutical uptake, whereas prone lateral planar views provide natural landmarks of breast contours, which are useful for the localization of lesions. This limitation can be overcome by the recent availability of hybrid SPECT/CT systems, which allow—through the coregistration of SPECT and CT images—the precise correlation of functional and anatomic data on the same image. The first clinical applications of this new technology in breast imaging indicate that SPECT/CT can increase the accuracy of SPECT by a more accurate anatomic assessment of the sites of abnormal activity (11).

If supine SPECT represents an easy-to-perform technique to improve the sensitivity of breast scintigraphy, other options should be considered. Until now, scintimammography has been usually performed with standard γ -cameras that are large, bulky, and not specifically designed for breast imaging. Dedicated small-field-of-view high-resolution cameras can allow greater flexibility in patient positioning (it is possible to acquire the scintigraphic images in the same mammographic views) and breast compression, increasing the target-to-background ratio. In fact, the detector can be placed directly against the chest and a mild compression reduces breast thickness and improves the camera's sensitivity. Moreover, by design, the breast cameras are also able to provide better intrinsic and extrinsic spatial resolution than conventional cameras, with an enhancement in contrast resolution of small lesions (12). Using a dedicated camera for breast imaging, a sensitivity of 86% has been recently achieved in detecting malignant lesions that are <1 cm, together with the visualization

of all cancers that are >1 cm and some additional tumor lesions not seen on mammography (13).

What are the potential specific clinical applications of scintimammography? Scintimammography is not a screening procedure, but it could be useful as a complementary test when the first-line examinations are nondiagnostic, as indicated by Mathieu et al. (4). In a multicenter trial enrolling 1,734 women, scintimammography sensitivity and specificity in the group of patients with equivocal mammography (Breast Imaging Reporting and Data System [BI-RADS] categories III and IV) were 88% and 91%, respectively (14). In this study, the inclusion of scintigraphy in the algorithm of breast cancer diagnosis caused a reduction of 62% in the number of unnecessary biopsies and an 86% reduction in missed cancers. The most important finding of these data is the capacity of scintimammography to significantly increase the detection rate of breast cancer in a patient population with a low prevalence of disease.

Because radiopharmaceuticals' uptake is independent of the breast density, and the accuracy of scintimammography is similar for fatty and dense breasts (15), scintigraphy is indicated for patients with a palpable mass not detected on mammography because of dense breast tissue—in particular, when the other diagnostic tests are inconclusive. Furthermore, scintimammography is particularly useful in patients with doubtful microcalcifications or parenchymal distortions, in the presence of scar tissue after surgery or biopsy and in breasts with implants (16). It's well known that mammography is less accurate in evaluating breasts that have been previously submitted to surgery, biopsy, radiation therapy, or chemotherapy. Patients who have a scar within the breast due to these iatrogenic interventions are often difficult for mammographic interpretation, whereas scintimammography is not affected by these morphologic changes. Nevertheless, it is worth noting that Mathieu et al. (4) have reported the highest rate of false-positive

scintigraphic results in the group of patients studied for suspected recurrence after treatment. Moreover, in the false-positive cases, the mean time interval between therapy and scintigraphy was shorter than that in the rest of the patients. This aspect should be considered when performing scintimammography early after surgery or radiation therapy, which may cause inflammatory changes, whose presence demonstrated the decisive factor for increased tracer uptake by benign breast lesions in a recent targeted analysis of false scintigraphic diagnoses (17). Therefore, to avoid false-positive findings in patients being evaluated for suspected local relapse, scintimammography should be performed after an adequate time interval from treatment. However, as suggested by Mathieu et al. (4), the development of a scoring system might also be of value to increase the specificity of SPECT in this subset of patients, because ^{99m}Tc -sestamibi uptake was faint in all their false-positive cases.

Finally, the possible role of scintimammography in the identification of multifocal-multicentric breast cancer and in the detection of the possible primary breast tumor in patients with metastatic axillary lymph-node involvement must be considered. The detection of multicentric lesions is of the utmost importance, because it can alter the surgical management of the patient (i.e., total mastectomy instead of quadrantectomy). It has been reported that scintimammography is able to assess the presence of multifocal-multicentric disease, as to detect bilateral breast cancers, with higher sensitivity when compared with mammography or ultrasound (18). However, because of the limited data available in this specific application, together with the low sensitivity of scintimammography in visualizing small additional malignant lesions (19), this potential indication deserves further studies in a larger series; moreover, the good performance of MRI in this field should be considered (20). In patients with

axillary lymph-node metastases attributed to adenocarcinoma, but negative mammography and ultrasound, scintimammography may be useful for detecting the possible primary tumor in the breast. Nevertheless, also for this application, until now there has been insufficient evidence for recommending breast scintigraphy. The use of dedicated high-resolution cameras might play a role in the future both in the assessment of multicentricity and in the detection of the unknown primary breast tumors, because of their excellent spatial resolution; moreover, a comparison with MRI in these specific indications is desirable.

In conclusion, the article of Mathieu et al. (4) substantiates the clinical utility of scintimammography as a complementary test in breast cancer diagnosis when other imaging methods are inconclusive. Their study also highlights the role of SPECT with the patient in supine position for increasing the scintigraphic sensitivity, with an important impact on patient management. Therefore, paraphrasing the title of a *JNM* Newsline article published 10 y ago (21), scintimammography is not the magic bullet for breast cancer diagnosis, but neither only a false promise. Nevertheless, probably only the development and large availability of dedicated high-resolution cameras will allow scintimammography in some

precise clinical applications to readily become routine.

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