Molecular Breast Imaging (MBI)

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1. Introduction

For more than 2 decades both planar and SPECT scintimammographic methods have been investigated for their ability to image breast malignancies or pre-malignant conditions using several radiopharmaceuticals, including ^{99m}Tc Sestamibi. However, until recently scintimammography was not implemented in the diagnostic work-up of patients with (suspicion of) breast cancer due to its limited sensitivity for non palpable, small breast tumours, attributed to the limited resolution and sensitivity of conventional gamma cameras. Some studies report an increase in sensitivity using SPECT, but the sensitivity for sub-centimetre lesions remains limited. Moreover, correlation of SPECT images with mammographic findings is difficult. Since the introduction of breast-dedicated molecular imaging systems the clinical accuracy has improved leading to an increasing clinical relevance.

This chapter is dedicated to molecular breast imaging using a breast-dedicated gamma camera and single-photon emitting tracers like ^{99m}Tc-sestambi or ^{99m}Tc-tetrofosmin, markers of increased metabolic function. Uptake of both tracers is dependent on the perfusion and metabolic status of the cell. Both parameters are generally increased in malignant tumours. ^{99m}Tc-sestambi is the preferred agent for this indication, due to the higher extraction rate as compared to ^{99m}Tc-tetrofosmin.

2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

3. Indications

BSGI can be used as a substitute for breast MRI. At the moment the most important and generally accepted indications are:

A. Preoperative evaluation in patients with recently detected breast malignancy

a. Detecting multifocal, multicentric or bilateral disease in patients scheduled for breast conservation therapy.
b. Evaluating the extent of disease in patients scheduled for breast conservation therapy.

B. Evaluation of indeterminate breast abnormalities or symptoms, especially in patients with technically difficult breast imaging (radiopaque tissue, implants etc.)

a. Discrepancies between clinical and radiological findings
b. Evaluation of BI-RADS 3 lesions when patient reassurance is warranted
c. Evaluation of (bloody) nipple discharge with normal or indeterminate radiological findings

Other indications:
C. Detection of occult primary breast malignancy in patients presenting with regional lymph node metastases
D. Assessment of response to neo-adjuvant chemotherapy.
E. Follow-up after breast intervention (surgery, radiotherapy, biopsy): differentiation between scar tissue and malignancy/tumour recurrence

4. Relation to other diagnostic procedures

- At present, BSGI cannot replace mammography and ultrasound, but is complementary to these modalities, comparable to breast MRI.
- Breast MRI has a high sensitivity for detecting breast cancer, determining tumour size, multifocality and pre-malign lesions. It can be used for problem solving when indeterminate lesions are found on mammography and ultrasound. However, the specificity of breast MRI is relatively low; up to two third lesions may be benign.
- MRI is contraindicated in the first three months of pregnancy. At later stages MRI may be performed, but administration of gadolinium is contraindicated due to the unknown effect on the foetus. Therefore, MRI for breast pathology is of little use during pregnancy.
- In most clinical trials, BSGI has a comparable sensitivity to breast MRI for both invasive ductal type carcinoma and invasive lobular type carcinoma, but with a lower rate of false positives, thus better specificity. The role of BSGI in detection of ductal carcinoma in situ (DCIS) is unclear due to the variable sensitivity rates found. The costs of BSGI are lower than of breast MRI. A disadvantage is the added radiation exposure, although the radiation dose to the breast is lower than that of mammography.
- Positron Emission Mammography (PEM) has a comparable accuracy to BSGI. However, the FDG avidity of lobular carcinoma is relatively low and both the radiation dose and the costs of PEM are higher than those of mammoscintigraphy.
- Dedicated breast Positron Emission Tomography (DbPET) is performed on a breast-dedicated PET scanner which is primarily used for characterisation of known breast malignancies and response evaluation. This modality has a better spatial resolution than BSGI and more accurate image quantification, but is more expensive.
- At the moment there is no role for BSGI in general screening programmes due to the relatively high total body radiation dose. BSGI could play a role however, in screening high-risk patients (especially patients with radiation-susceptible breast tissue as in BRCA 1/2 mutations).
- An BSGI-guided needle biopsy system is available. It is compatible with the Dilon breast gamma camera. This biopsy method can be used in patients with radiologically occult breast lesions. An initial evaluation showed high accuracy and high patient acceptance of this system.

5. Medical information necessary for planning

- Relevant clinical information should be available, especially signs, symptoms and the location of palpable masses.
- Relevant imaging studies (recent mammography, ultrasound and/or MRI) should be available for correlation.

- Date of last menses. BSGI should be performed between day 2 and day 12 of the patient's cycle if applicable.
- Date of breast interventions. BSGI should be performed prior to interventional procedures. If performed after such procedures, it should be conducted within the first 72 h after biopsy or otherwise 4-6 weeks later to avoid false positive results at the biopsy site. Fine needle aspiration (FNA) does not seem to cause a relevant tissue reaction.

6. Radiopharmaceutical

Tracer:	^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin
Nuclide:	Technetium-99m (140 KeV)
Activity:	200-600 MBq (depending on camera system)
Administration:	intravenously in the contra lateral arm (or in one of the feet)

7. Radiation safety

a. Pregnancy

The external dose to the foetus ranges from 0,012-0,0044 mGy/MBq for ^{99m}Tc-sestamibi and from 0,0096-0,0036 mGy/MBq for ^{99m}Tc-tetrofosmin, depending on the stage of gestation. Nevertheless, the investigation should be postponed if possible. BSGI should only be done if, not doing the investigation poses a greater risk to the mother than the radiation risk to the foetus and if no alternative modality is available (MRI is of little use during pregnancy, see paragraph 3.). In such cases consider reducing the amount of activity to be administered (ICRP-84, ICRP-106).

One should realise however that the possibility of obtaining non-interpretable images is high due to the physiological glandular response to hormonal influences.

b. Lactation

According to ICRP 106 there is no need to interrupt breastfeeding, but due to possible free ^{99m}Tc pertechnetate it is advisable to interrupt the feeding for 4 h.

c. Radiation exposure

The effective dose depends on the amount of activity administered (0,009 mSv/MBq for ^{99m}Tc-sestamibi and 0,008 mSv/MBq for ^{99m}Tc-tetrofosmin, ICRP-80). The radiation dose to the breast is 4-10 times lower than for mammography. Radiation exposure to hospital staff and to relatives of patients is limited, and no special precautions are needed.

8. Patient preparation/essentials for procedure

No special preparation is required.

9. Acquisition and processing

a. Patient positioning: the patient is seated during the entire procedure. The breast is fixed onto the detector using the fixation plate, though it is not compressed. For lesions close to the chest wall minimal fixation / immobilisation is recommended in the cranio-caudal view.

b. Imaging: Imaging should begin 5-10 min post injection. Acquisition time per view depends on the system used and the administered activity (for example 8-10 min with a singlehead system using 600MBq). Planar images are acquired in 2 standard views, similar to the standard mammography views, for each breast:

- caudal with the detector under the breast comparable to the cranio-caudal mammography view
- 45° lateral oblique with the detector at the lateral side of the breast comparable to the medio-lateral oblique mammography view

If required additional images may be acquired: CCA view ('Cleopatra', axillary cranio-caudal view), 90° lateral or medial view, antero-posterior view (axilla).

c. Processing: For interpretation of the images a viewing system should be available which enables the adjustment of the image contrast and simultaneous display of the mammographic and scintigraphic images. Use of a linear grey scale or linear monochromatic colour scale is preferred.

10. Interpretation

- The images should be correlated to radiological as well as clinical findings.
- Tracer distribution is homogenous in the normal, healthy breast. Uptake is low in both fibro-glandular tissue and fatty tissue of the breast.
- Focal accumulation seen in only one view could be a result of summation; focal activity should be visible in at least two views to be interpreted as a real focal lesion. However, mildly active sub-centimetre lesions are not always visible in two directions.
- Focally increased uptake is suggestive of invasive cancer. The intensity of uptake at cancer sites is highly variable and is dependent on both tumour characteristics and attenuation.
- Patchy uptake is suggestive of lobular type carcinoma or DCIS (especially when there is a wedge shape or ductal pattern). However, patchy uptake can also be caused by mastopathy, inflammation or, in case of known breast cancer, regional tissue reaction (desmoplastic reaction surrounding the malignant lesion).
- Benign conditions which often show (mild to moderately) increased uptake include fibrocystic mastopathy (usually patchy, but can also have focal components), adenosis, mastitis/inflammation, fibroadenoma (often no uptake is seen), duct ectasia with hyperplasia, reactive lymph nodes.
- In pre-menstrual women, uptake in fibroglandular tissue may be increased in the second phase of the menstrual cycle. This reflects the physiological glandular response to hormonal influences and increases the difficulty of image interpretation.
- Mild to moderate bilateral and symmetrical patchy uptake which matches the pattern of fibroglandular tissue of the breasts as seen on the mammogram, is usually benign.
- Recent biopsy may cause false positive results due to tissue reaction.
- Uptake in thoracic wall musculature and axilla musculature is relatively high. Scatter from this area may cause false positive results.
- Imaging the posterior portion of the breast, adjacent to the chest wall is difficult. Lesions in this area may be missed as they often lie outside the field of view.
- One should be aware of the fact that small, mildly active lesions in the upper medial quadrant of the breast may be missed due to attenuation because of the relatively large distance to the detector in both standard views.
- Late images can lead to false negative results because of an increased wash-out from malignant tumours with the MDR-1 phenotype, expressing MRP.
- Increased uptake in an axillary lymph node in the presence of malignancy in the ipsilateral breast is suggestive of lymph node metastasis.

11. Report

The report should state the location (quadrant), diameter and characteristics such as boundaries (ill defined or sharp), uptake pattern (focal or patchy, linear/ductal or wedge form), symmetry, correlation with substrates on the mammogram and correlation with the distribution of the fibroglandular tissue seen on the mammogram.

The report should indicate the most likely diagnosis and recommend appropriate further management (additional imaging studies, routine interval imaging, short-term follow-up, or biopsy) using BI-RADS classification.

The BI-RADS classification for molecular breast imaging is still under development. The classification published by the Society for Nuclear Medicine (SNM) is applicable, but one should realise that this classification is currently too simplistic and will be extended in the coming years. Most importantly, the SNM BI-RADS classification does not take enough account of the radiological findings and scintigraphic uptake patterns and characteristics. The actual rate of malignancy in the BI-RADS categories may differ from the radiological BI-RADS classification and has still to be investigated.

12. Literature

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