** EANM Disclaimer*
Authoritative source: Dr. Richard Wolf, LL.M. Partner (legal advisor)
Please note that this guideline has not been updated since 2003 and, therefore, may not reflect the current knowledge and practice in the field of oncology. EANM is providing this guideline on an 'as is' basis for general information purposes only and does not accept any responsibility for the accuracy, completeness, currency, relevance, reliability or suitability of the information contained therein.

BREAST SCINTIGRAPHY
PROCEDURE GUIDELINES FOR TUMOUR IMAGING

Emilio Bombardieri[1], Cumali Aktolun[2], Richard P. Baum[3], Angelica Bishof-Delaloye[4], John Buscombe[5], Jean François Chatal[6], Lorenzo Maffioli[7], Roy Moncayo[8], Luc Mortelmans[9], Sven N. Reske[10]

[1]Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano, Italy
[2]University, Kocaeli, Turkey
[3]PET Center, Bad Berka, Germany
[4]CHUV, Lausanne, Switzerland
[5]Royal Free Hospital, London, UK
[6]CHR, Nantes Cedex, France
[7]Ospedale "A. Manzoni", Lecco, Italy
[8]University of Innsbruck, Austria
[9]University UZ Gasthuisberg, Louvain, Belgium
[10]University of Ulm, Germany

Under the auspices of the Oncology Committee of the European Association of Nuclear Medicine

Key words: Breast Scintigraphy – Scintimammography - Tumour Imaging – Procedure Guidelines - Indications

Referees: Bender H., (*Department of Nuclear Medicine, University of Bonn, Germany*); de Jong M., (*Department of Nuclear Medicine, University Hospital, Rotterdam, The Netherlands*); Lassmann M., (*Klinik Nuklearmedizin University Wuerzburg, Germany*); Maccauro M., (*Division of Nuclear Medicine, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano,* Italy); Mather S.J., (*Department of Nuclear Medicine, St. Bartholomew's Hospital, London, UK*); Maublant M., (*Department of Nuclear Medicine, Centre Jean Perrin, Clermont-Ferrand, France*); Palmedo H., (*Department of Nuclear Medicine, University of Bonn, Germany*); Prats-Rivera E., (*Department of Nuclear Medicine, Hospital Clinico Universitario, Zaragoza, Spain*); Quirce Pisano R., (*Department of Nuclear Medicine, Hospital Universitario Marques de Valdecilla, Santander, Spain*).

Aim

The aim of this document is to provide general information about breast scintigraphy in patients with known or suspected breast cancer. This guideline does not include all the existing procedures for scintimammography. It describes only the ^{99m}Tc-SestaMIBI (2-methoxyisobutiylisonitrile) and the ^{99m}Tc-Tetrofosmin (1,2-bis bis(2-ethoxy-ethylphosphine)ethane) breast scintigraphy protocols used in the current clinical routine. The guideline should therefore not be taken as exclusive of other nuclear medicine procedures useful to obtain comparable results. It is important to remember that the resources and the facilities available for patient care may vary from one country to another and from one medical institution to another. The present guide has been prepared for nuclear medicine physicians and intends to offer assistance in optimising the diagnostic information that can be obtained from scintimammography. The corresponding guidelines of the Society of Nuclear Medicine (SNM) have been taken into consideration and partially integrated with the present text. The same has been done with the most relevant literature on this topic, and the final result has been discussed by a group of distinguished experts.

Background

Breast scintigraphy is a non-invasive diagnostic tool that produces planar and tomographic images and gives general information on tumour cell viability and cellularity. A variety of radiopharmaceuticals have been used for this technique. The widely used tracer for breast scintigraphy are lipophilic cation analogues, such as ^{99m}Tc-SestaMIBI, which has been the first radiopharmaceutical registered for this purpose in U.S.A) and ^{99m}Tc-Tetrofosmin. Other radiopharmaceuticals, including ^{201}Tl-chloride and ^{99m}Tc-MDP, have also been proposed in the study of breast cancer. ^{99m}Tc-SestaMIBI and ^{99m}Tc-Tetrofosmin are small cationic complexes of technetium, which are accumulated in the myocardium and in various neoplasms. Their mechanism of uptake has been described. They are markers of cellular transmembrane electrical potentials and they concentrate most markedly in mitochondria. The uptake is related to increased energy-dependent metabolism and cell proliferation. Recent papers have demonstrated that its cellular accumulation is reduced when multidrug resistance proteins are overexpressed.

Clinical indications

Although at present mammography should be considered the main diagnostic imaging technique to study breast cancer, breast scintigraphy has a role in the following indications:

- detection of breast cancer when mammography is doubtful, inadequate or indeterminate. In particular, it may serve as a complementary procedure in patients with doubtful microcalcifications or parenchymal distortions, in the presence of scar tissue in the breast following surgery or biopsy, in mammographically dense breast tissue, and in breasts with implants;
- assistance in identifying multicentric, multifocal or bilateral breast cancer in patients with a diagnosis of breast cancer;
- study of multidrug resistance;
- evaluation and prediction of tumour response to chemotherapy for breast carcinoma.

Precautions

- Pregnancy (suspected or confirmed). In the case of a diagnostic procedure in a patient who is known or suspected to be pregnant, a clinical decision is necessary to consider the benefits against the possible harm of carrying out any procedure.
- Breastfeeding (when possible, breastfeeding should be interrupted for 24 hours following administration of the radiopharmaceutical).

Although some protocols include checking of the patient's menstrual cycle, no clear influence of this factor on breast scintigraphy has been reported.

Pre-examination procedures

1) Patient preparation

No special preparation for the test is required.

The technologist or physician should give the patient a thorough explanation of the test.

The patient should remove all clothing and jewellery above the waist immediately prior to the examination.

2) Pre-injection

Clinical evaluation by the nuclear medicine physician

The nuclear medicine physician should perform an accurate breast physical examination to evaluate the abnormalities under study. Also the locoregional lymph nodes should be explored.

In addition, the physician should consider any information that can be useful for the interpretation of the scintigraphic images, including:

- menstrual cycle of the patient (even if no clear influence of this factor on breast scintigraphy has been demonstrated);
- recent mammography (mandatory), up to 4 weeks previously;
- recent ultrasonography (optional), up to 4 weeks previously;
- other possible previous clinical images.

In particular, all the following information should be evaluated and checked, as these situations are causes of false positive results:

- recent breast surgery or any invasive diagnostic procedures such as cyst aspiration or fine-needle aspiration (scintigraphy should be delayed at least 2 weeks), core or excisional biopsy (scintigraphy should be delayed 4 to 6 weeks) and breast surgery or radiation therapy (scintigraphy should be delayed at least 2 months);
- recent chemotherapy.

3) Tracer injection, dosage and administration

Tracer should be administered by intravenous injection in an arm vein contralateral to the breast with the suspected abnormality. If the disease is bilateral, the injection is ideally administered in a dorsal vein of the foot. A butterfly can be adopted to ensure correct venous access before drug administration. Perivenous extravasation may lead to visualisation of non-pathological lymph nodes in the related lymph node basins. The injection should be followed by flushing with 5-10 ml of saline.

With regard to the injected activity of radiopharmaceuticals. The activity of radiopharmaceutical to be administered should be determined after taking account of the European Atomic Energy Community Treaty, and in particular article 31, which has been adopted by the Council of the European Union (Directive 97/43/EURATOM). This Directive supplements Directive 96/29/EURATOM and guarantees health protection of individuals with respect to the dangers of ionising radiation in the context of medical exposures. According to this Directive, Member States are required to bring into force such regulations as may be necessary to comply with the Directive. One of the criteria is the designation of Diagnostic Reference Levels (DRL) for radiopharmaceuticals; these are defined as *levels of activity for groups of standard-sized patients and for broadly defined types of equipment.* It is expected that these levels will not to be exceeded for standard procedures when good and normal practice regarding diagnostic and technical performance is applied.

For the aforementioned reasons the following activity for SestaMIBI and Tetrofosmin should be considered only as a general indication, based on the data of the literature and the current experience. However, it should be noted that in each country nuclear medicine physicians should respect the DRLs and the rules stated by the local law.

The SestaMIBI or Tetrofosmin activity required for good imaging should range between 740 and 1110 MBq (20-30 mCi). Injection of activities greater than local DRLs should be justified. The organs which receive the largest radiation doses are gall bladder and kidneys (see Table).

Physiological ^{99m}Tc-SestaMIBI or ^{99m}Tc-Tetrofosmin distribution

Evident concentration of the ^{99m}Tc-SestaMIBI can be seen *in vivo* in several organs. In particular, normal tracer uptake is evident in the salivary glands, thyroid, myocardium, liver, gallbladder, small and large intestine, kidneys, bladder, choroid plexuses and skeletal muscles. At five minutes post-injection about 8% of the injected dose of ^{99m}Tc-SestaMIBI remains in circulation. The effective half-life of clearance is approx. 3 hours for the heart and approx. 30 minutes for the liver.

As regards ^{99m}Tc-Tetrofosmin, less than 5% of the injected dose remained in blood by 10 minutes post-injection ad taken up predominantly in muscles. The effective half-life of clearance is 4 hours for the heart and 30 minutes for the liver.

A faint homogeneous uptake of both radiopharmaceuticals in the breast or axilla is normal. Physiological tracer uptake may be observed in the nipples.

Radiation dosimetry

The estimated adsorbed radiation dose to various organs in healthy subjects following administration of Technetium-MIBI is given in the following Table. The data are quoted from ICRP no. 80.

	Absorbed dose per unit activity administered (mGy/MBq)	
Organ	Adult	15 years
Adrenals	0.0075	0.0099
Bladder	0.011	0.014
Bone surfaces	0.0082	0.010
Brain	0.0052	0.0071
Breast	0.0038	0.0053
Gall bladder	0.039	0.045
Stomach	0.0065	0.0090
Small Intestine	0.015	0.018
Colon	0.024	0.031
Heart	0.0063	0.0082
Kidneys	0.036	0.043
Liver	0.011	0.014
Lungs	0.0046	0.0064
Muscles	0.0029	0.0037
Oesophagus	0.0041	0.0057
Ovaries	0.0091	0.012
Pancreas	0.0077	0.010
Salivary glands	0.014	0.017
Skin	0.0031	0.0041
Red marrow	0.0055	0.0071
Spleen	0.0065	0.0086
Testes	0.0038	0.0050
Thymus	0.0041	0.0057
Thyroid	0.0053	0.0079
Uterus	0.0078	0.010
Remaining organs	0.0031	0.0039
Effective dose (mSv/MBq)	**0.0085**	**0.011**

The estimated adsorbed radiation dose to various organs in healthy subjects following administration of Technetium-Tetrofosmin is given in the following Table. The data are quoted from ICRP no. 80.

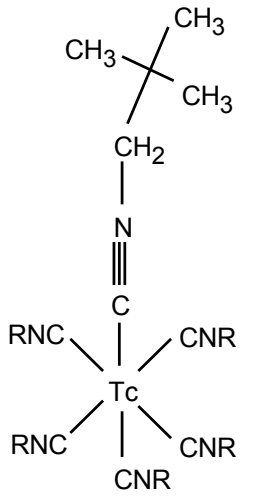
	Absorbed dose per unit activity administered (mGy/MBq)	
Organ	Adult	15 years

Adrenals	0,0033	0,0043
Bladder	0,0260	0,0330
Bone surfaces	0,0048	0,0058
Brain	0,0005	0,0006
Breast	0,0010	0,0013
Gall bladder	0,0270	0,0310
Stomach	0,0035	0,0047
Small Intestine	0,0110	0,0140
Colon	0,0180	0,0230
Heart	0,0048	0,0061
Kidneys	0,0110	0,0130
Liver	0,0033	0,0042
Lungs	0,0022	0,0029
Muscles	0,0041	0,0050
Oesophagus	0,0024	0,0030
Ovaries	0,0076	0,0095
Pancreas	0,0039	0,0051
Salivary glands	0,0093	0,0110
Skin	0,0014	0,0017
Red marrow	0,0029	0,0035
Spleen	0,0030	0,0039
Testes	0,0029	0,0039
Thymus	0,0024	0,0030
Thyroid	0,0048	0,0071
Uterus	0,0076	0,0093
Remaining organs	0,0041	0,0051
Effective dose (mSv/MBq)	**0,0070**	**0,0082**

Radiopharmaceuticals [^{99m}Tc]-SestaMIBI

Description

SestaMIBI is commercially available as Cardiolite. It is supplied as a vial containing, in a lyophilised form the Cu (I) salt of tetrakis (2-methoxy isobutylisonitrile), stannous reducing agent and excipients.



$R=CH_2C(CH_3)_2OCH_3$

Tc-MIBI (Cardiolite)

Preparation

^{99m}Tc-SestaMIBI is prepared by addition of the required amount of sodium [^{99m}Tc] pertechnetate diluted in sterile physiological saline to the vial and heating at 100 °C for 10 minutes according to the manufacturer instructions.

Quality control

The radioactive concentration should be determined by measuring the activity of the vial in a calibrated ionisation chamber. Radiochemical purity may be confirmed using a TLC method. (Solid phase Baker-Flex Aluminium oxide plate, mobile phase Ethanol >95% Rf SestaMIBI 1.0, unbound Tc-99m 0.0). Labelling efficiency should be >90%.

Special precautions

The preparation may be diluted with sterile physiological saline if required. The radiopharmaceutical should be used within 6 hours of preparation.

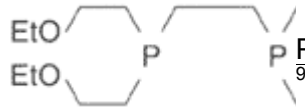
Extensive adsorption of the radiopharmaceutical to some vials and syringes has been observed.

Radiopharmaceuticals [^{99m}Tc]-Tetrofosmin

Description

Tetrofosmin is commercially available as Myoview. It is supplied as a vial containing, in a lyophilised form 0,23 mg of Tetrofosmin (1,2-bis bis(2-ethoxy-ethylphosphine)ethane), with stannous chloride de-hydrated, di-sodium-sulpho-salicylate and sodium-di-gluconate and other excipients.

Structure of Tetrofosmin



Preparation

^{99m}Tc-Tetrofosmin is prepared by addition of the required amount of sodium [^{99m}Tc] pertechnetate diluted in sterile physiological saline to the vial, according to the manufacturers instructions.

Quality control

The radioactive concentration should be determined by measuring the activity of the vial in a calibrated ionisation chamber. Radiochemical purity may be confirmed using a ITLC/SG method. Use a 35:65 v/v mixture of acetone and dichloromethane a Gelman ITLC/SG strip (2cm x 20cm). After deposition, free ^{99m}Tc-pertechnetate runs to the top piece, technetium Tc-99m-tetrofosmin runs to the center piece, and any hydrophilic complex impurities remain at the origin of the strip. Labelling efficiency should be >90%.

Gamma camera quality control

A strict quality control programme should be routinely performed according to the rules of each country, as stated in the 97/43/Council Directives EURATOM.

Image acquisition

1) Instrumentation

- A single- or multiple-head gamma camera is needed to acquire planar and/or tomographic (SPECT) images.
- The gamma camera should be equipped with a low-energy, high-resolution collimator.
- An imaging table (mattress) with specially designed breast cutouts to allow the breast to be fully dependent or with a foam cushion with a lateral semicircular aperture is required.
- The energy window for image collection should be 10% (±5%) centred over the 140 keV photopeak of ^{99m}Tc.

2) Acquisition modality

- Lateral views in prone position and anterior view in supine position must be acquired in all circumstances. The detector should touch the patient's side to improve the resolution. Prone lateral breast images should be acquired with the patient lying prone with her head resting on her arms on a breast scintigraphy mattress. This projection allows excellent separation of the deep breast structures from the myocardium or liver. The contralateral breast should be compressed against the table to prevent cross-talk of activity. The axilla must be included in the lateral and anterior views in all circumstances: the arms should be raised to provide clear imaging of the axilla.
- Planar images should be acquired 5-10 minutes after injection for 10 minutes each, using a 256x256 or larger matrix. Electronic magnification can be used to optimise pixel size and to exclude internal organ activity.
- The images must be acquired in the following sequence:
  1) prone lateral scintigraphy of the breast with the suspected lesion;
  2) prone lateral scintigraphy of the contralateral breast;
  3) supine (or upright) anterior scintigraphy.

Optional images

1) SPECT images (360°, 120 steps, 20 seconds per step).
2) Prone posterior oblique scintigraphy (30°).
3) Images with markers over the nipple or breast lesion(s).
4) In order to evaluate multidrug resistance, delayed images (1 hour after injection) should be collected in the same conditions.

Image processing

No particular processing procedure is needed for planar images. Only masking of the high activities from internal organs is necessary.

A logarithmic scale to enhance low-count areas instead of a linear scale is preferable for image display.

When SPECT is performed one should take into account the different types of gamma camera and software available. Careful choice of image processing parameters should be adopted in order to optimize the imaging quality.

Interpretation criteria

To evaluate breast scintigraphy the following items should be taken into consideration:

- clinical issue raised in the request for scintimammographic imaging
- clinical history of the patient
- anatomical localisation of the uptake according to other imaging data
- intensity and characteristics of tracer uptake. Focal uptake is suspicious for malignancy, while diffuse and moderate accumulation is often related to benign disease. It should be remembered that the nipples frequently show physiological tracer uptake. Any focal deep uptake in the axilla is suggestive of axillary

involvement. Note that a linear and superficial axillary uptake on the lateral views usually corresponds to uptake in skin folds.
- clinical correlation with any other data from previous clinical, biochemical and morphological examinations
- causes of false negative results (lesion size, incorrect patient positioning, chemo- or radiotherapy, physiological uptakes masking cancer lesions, etc.)
- causes of false positive results (artefacts, uptake in benign processes, post-therapy uptakes).

Reporting

The nuclear medicine physician should record all information regarding the patient, type of examination, date, radiopharmaceutical (administered activity and route), concise patient history, all correlated data from previous diagnostic studies, and the clinical question.

The report to the referring physician should describe:
- the absence or presence of focal increased tracer uptake in the breast
- the absence or presence of focal increased tracer uptake in the axilla
- comparative analysis: the findings should be related to previous information or results from other clinical or instrumental evaluations
- interpretation: a clear diagnosis of benign/malignant disease should be made if possible, accompanied – when appropriate – by a differential diagnosis
- comments on factors that may limit the accuracy of scintigraphy are sometimes important (size of the lesions, artefacts, etc.)
- in case the conclusive impression should require additional diagnostic examination or an adequate follow-up, this must be recommended.

Sources of error
- small lesion size (lesions <1 cm may be missed)
- extravasation following tracer injection in the contralateral arm, as this may result in areas of abnormal uptake in the axillary region
- couch scatter
- patient motion; wrong patient positioning: the breast must be fully dependent, and the detector must be as close as possible to the patient
- if both breasts are dependent, cross-talk of activity may result in a false positive result in the contralateral breast
- local pathological or physiological uptakes masking or confounding cancer lesions
- interfering cytostatic treatments that decrease tumour uptake
- post-surgery uptakes
- post-radiotherapy uptakes.

Issues requiring further clarification
- Breast scintigraphy is not considered today a routinarily application for primary breast cancer diagnosis or axillary staging in patients with breast masses. Further study is needed to determine the characteristics of the population most likely to benefit from breast scintigraphy as a complimentary diagnostic modality.
- Recent results from clinical studies indicate that the benefits of conventional SPECT compared with those of planar breast scintigraphy are still debatable and no consensus has been reached for the diagnosis of breast disease. However SPECT is superior for the assessment of axillary involvement. Recently some authors have published interesting dedicated breast approaches using pinhole and other collimator configurations and demonstrated that these application-specific imaging can provide improved images of breast and axillary lesions. These methods are very promising and should be validated with further clinical evaluations.

- ^{201}Tl and ^{99m}Tc-MDP have been used for breast scintigraphy in few studies. Their clinical usefulness and that of other single photon emitting radiopharmaceuticals for breast scintigraphy have not been established.
- Among the oncology applications, breast cancer represents one of the most extensively studied disease with FDG-PET. FDG-PET has been performed for diagnosis, staging and restaging of invasive breast cancer and for monitoring the responsiveness to therapy. At present, the results of FDG-PET in detection of primary breast cancer are mixed and inconclusive. Very interesting data have been obtained in staging axillary lymph nodes. Results demonstrating the superiority of FDG-PET over anatomic imaging modalities in detection of distant metastases, recurrences and monitoring therapies are well documented. At present these applications have been accepted by the physicians and the scientific community.
- Scintimammography with ^{99m}Tc-SestaMIBI or ^{99m}Tc-Tetrofosmin can be used in evaluating multidrug resistance (MDR). An increased washout from the tumour seems to be related to overexpression of multidrug resistance proteins. The adequate criteria for objective measurement of this parameter have not yet been defined.

Disclaimer

The European Association has written and approved guidelines to promote the use of nuclear medicine procedures with high quality. These general recommendations cannot be applied to all patients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures and exclusive of other procedures reasonably directed to obtaining the same results. The spectrum of patients seen in a specialised practice setting may be different than the spectrum usually seen in a more general setting. The appropriateness of a procedure will depend in part on the prevalence of disease in the patient population. In addition, resource available for patient care may vary greatly from one European country or one medical facility to another. For these reasons, guidelines cannot be rigidly applied.

Acknowledgements: the Authors thanks Ms. Annaluisa De Simone Sorrentino and Ms. Marije de Jager for their valuable editorial assistance.

Essential References

Allen MW, Hendi P, Bassett L, Phelps ME, Gambhir SS. A study on the cost effectiveness of sestamibi scintimammography for screening women with dense breasts for breast cancer. Breast Cancer Res Treat 1999; 55: 243-258.

Allen MW, Hendi P, Schwimmer J, Bassett L, Gambhir SS. Decision analysis for the cost effectiveness of sestamibi scintimammography in minimizing unnecessary biopsies. Q J Nucl Med 2000; 44: 168-185.

Alonso O, Delgado L, Nunez M et al Predictive value of 99m-Tc-sestamibi scintigraphy in the evaluation of doxorubicin based chemotherapy response in patients with advanced breast cancer. Nucl Med Comm 2002; 23: 765-771

Arslan N, Ozturk E, Ilgan S, et al. 99mTc-MIBI scintimammography in the evaluation of breast lesions and axillary involvement: a comparison with mammography and histopathological diagnosis. Nucl Med Commun 1999; 20: 317-325.

Bombardieri E, Crippa F. PET imaging in breast cancer. Q J Nucl Med 2001; 45: 245-56.

Buck A, Schirrmeister H, Kuhn T, Shen C, Kalker T, Kotzerke J, Dankerl A, Glatting G, Reske S, Mattfeldt T. FDG uptake in breast cancer: correlation with biological and clinical prognostic parameters. Eur J Nucl Med Mol Imaging 2002; 29: 1317-23.

Buscombe JR, Cwikla JB, Holloway B, Hilson AJ. Prediction of the usefulness of combined mammography and scintimammography in suspected primary breast cancer using ROC curves. J Nucl Med 2001; 42: 3-8.

Cwikla JB, Buscombe JR, Kolasinska AD, Parbhoo SP, Thakrar DS, Hilson AJ. Correlation between uptake of Tc-99m sestaMIBI and prognostic factors of breast cancer. Anticancer Res 1999; 19: 2299-2304.

Cwikla JB, Kolasinska A, Buscombe JR, Hilson AJ. Tc-99m MIBI in suspected recurrent breast cancer. Cancer Biother Radiopharm 2000;15: 367-372

Danforth DN jr, Aloj L, Carrasquillo JA, Bacharach SL, Chow C, Zujewski J, Whatley M, Galen B, Merino M, Neumann RD. The role of 18F-FDG-PET in the local/regional evaluation of women with breast cancer. Breast Cancer Res Treat 2002; 75: 135-46.

Danielsson R, Reihner E, Grabowska A, Bone B. The role of scintimammography with 99mTc-sestamibi as a complementary diagnostic technique in the detection of breast cancer. Acta Radiol 2000; 41: 441-445.

Del Vecchio S, Ciarmiello A, Pace L, et al. Fractional retention of technetium-99m-sestamibi as an index of p-glycoprotein expression in untreated breast cancer patients. J Nucl Med 1997; 38: 1348-1351.

Derebek E, Balci P, Alanyali H, et al. Detection of bilateral multifocal breast cancer using Tc-99m sestamibi imaging. The role of delayed imaging. Clin Nucl Med 1999; 24: 590-593.

Diggles L, Mena I, Khalkhali I. Technical aspects of prone dependent-breast scintimammography. J Nucl Med Tech 1994; 22: 165-170.

Eur J Surg Oncol 2002, 28:108-112

Fujii H, Nakamura K, Kubo A, et al. Preoperative evaluation of the chemosensitivity of breast cancer by means of double phase 99mTc-MIBI scintimammography. Ann Nucl Med 1998; 12: 307-312.

Fuster D, Vinolas N, Mallafre C, Pavia J, Martin F, Pons F. Tetrofosmin as predictor of tumour response. Q J NUcl Med 2003; 47: 58-62.

Greco C, Crippa F, Agresti R, Seregni E, Gerali A, Giovanazzi R, Micheli A, Asero S, Ferraris C, Gennaro M, Bombardieri E, Cascinelli N. Axillary lymph node staging in breast cancer by 2-fluoro-2-deoxy-D-glucose positron emission tomography: clinical evaluation and alternative management. J Natl Cancer Inst 2001; 93: 630-5.

Higley B, Smith FW, Smith T, et al. Technetium-99m-1,2-bis[bis(2-ethoxyethyl) phosphino] ethane: human biodistribution, dosimetry and safety of a new myocardial perfusion imaging agent. J Nucl Med. 1993;34:30-38.

Horne T, Pappo I, Cohen-Pour M, Baumer M, Orda R. 99Tc(m)-tetrofosmin scintimammography for detecting breast cancer: a comparative study with 99Tc(m)-MIBI. Nucl Med Commun. 2001 Jul;22(7):807-11.

Horne T, Pappo I, Cohenpour M, Mindlin L, Orda R. 99Tc-MIBI scintimammography for the detection of breast malignancies: the contribution of the count ratio to specificity. Nucl Med Commun 1999; 20: 511-516.

ICRP Publication 80 Radiation dose to patients from radiopharmaceuticals. Annals of ICRP 1998 28: 3; Pergamon Press, Oxford

Imbriaco M, Del Vecchio S, Riccardi A, et al. Scintimammography with 99mTc-MIBI versus dynamic MRI for non-invasive characterization of breast masses. Eur J Nucl Med 2001; 28: 56-63.

Jain D. Technetium-99m labeled myocardial perfusion imaging agents. Semin Nucl Med. July 1999:29:221-236.

Kao CH, Tsai SC, Liu TJ, Ho YJ, Wang JJ, Ho ST, ChangLai SP. P-glycoprotein and multidrug resistance-related protein expressions in relation to technetium-99m methoxyisobutylisonitrile scintimammography findings. Cancer Res 2001; 61: 1412-1414.

Khalkhali I, Baum JK, Villanueva-Meyer J et al 99mTc-sestamibi breast imaging for the examination of patients with dense and fatty breasts: multicenter study Radiology 2002;222:149-155

Khalkhali I, Diggles LE, Taillefer R, Vandestreek PR, Peller PJ, Abdel-Nabi HH. Procedure guideline for breast scintigraphy. Society of Nuclear Medicine. J Nucl Med 1999; 40: 1233-1235.

Khalkhali I, Itti E Functional breast imaging using the single photon technique Nucl Med Commun 2002; 23:609-611

Khalkhali I, Villanueva-Meyer J, Edell SL, et al. Diagnostic accuracy of 99mTc-sestamibi breast imaging: multicenter trial results. J Nucl Med 2000; 41: 1973-1979.

Leidenius MH, Leppanen EA,Tykka HT et al The role of Tc99m-sestamibi scintigraphy in combination with the triple assessment of primary breast cancer

Leung JW New modalities in breast imaging: digital mammography, positron emission tomography, and sestamibi scintimammography Radiol Clin Noth 2002;40:467-482

Lumachi F, Ferretti G, Povolato M, et al. Usefulness of 99m-Tc-sestamibi scintimammography in suspected breast cancer and in axillary lymph node metastases detection. Eur J Surg Oncol 2001; 27: 256-259.

Maffioli L, Agresti R, Chiti A, et al. Prone scintimammography in patients with non-palpable breast lesions. Anticancer Res 1996; 16: 1269-1274.

Maffioli L, Steens J, Pauwels EJ, Bombardieri E. Application of Tc-99m SestaMIBI in oncology. Tumori 1996; 82:12-21.

Mankoff DA, Dunnwald LK, Gralow JR, Ellis GK, Drucker MJ, Livingston RB. Monitoring the response of patients with locally advanced breast carcinoma to neoadjuvant chemotherapy using [technetium 99m]-sestamibi scintimammography. Cancer 1999; 85: 2410-2423.

Marian T, Szabo G, Goda K, et al. In vivo and in vitro multitracer analyses of P-glycoprotein expression-related multidrug resistance. Eur J Nucl Med Mol Imaging 2003; 30: 1147-54.

Mlikotic A, Mishkin FS. Visualization of the right atrial appendage during sestamibi scintigraphy. Clin Nucl Med 2000; 25: 848-849.

Munch G, Neverve J, Matsunari I, Schroter G, Schwaiger M. Myocardial technetium-99m-tetro- fosimin and technetium-99m-sestamibi kinetics in normal subjects and patients with coronary artery disease. J Nuc/ Med. 1997;38:428-432.

Obwegeser R, Berghammer P, Rodrigues M, et al. A head-to-head comparison between technetium-99m-tetrofosmin and technetium-99m-MIBI scintigraphy to evaluate suspicious breast lesions. Eur J Nucl Med 1999;26: 1553-1559.

Palmedo H, Biersack HJ, La Storia S, Maublant J, Prats E, Stegner HE, Bourgeois P, Hustinx R, Hilson AjW,Bischof Delaloye A Scintimamography with technetium-99m methoxyisobutylisonitrile: results of a prospective European multicentric trial Eur J Nucl Med 1998; 25: 375-385

Palmedo H, Schomburg A, Grunwald F, et al. Scintimammography with Tc-99m MIBI in patients with suspicion of primary breast cancer. Nucl Med Biol 1996; 23: 681-684.

Palmedo H, Hensel J, Reinhardt M, von Mallek D, Matthies A, Biersack HJ. Breast cancer imaging with PET and SPECT agents: an in vivo comparison. Nucl Med Biol 2002; 29: 809-15.

Paz A, Melloul M, Cytron S, Koren R, Ohana G, Michalevich D, Gal R, Wolloch Y. The value of early and double phase 99Tcm-sestamibi scintimammography in the diagnosis of breast cancer. Nucl Med Commun 2000; 21:341-348.

Peller P, Khedkar N, Martinez C. Breast tumor scintigraphy. J Nucl Med Tech 1996; 24: 198-203.

Rem RF, Schoonjans JM, Kieper DA et al High-resolution scintimammography: a pilot study J Nucl Med 2002;43:909.915

Rodrigues M, Chehne F, Kalinowska W, Berghammer P, Zielinski C, Sinzinger H. Uptake of 99mTc-MIBI and 99mTc-tetrofosmin into malignant versus nonmalignant breast cell lines. J Nucl Med 2000; 41: 1495-1499.

Schillaci O, Scopinaro F, Spanu A, Donnetti M, Danieli R, Di Luzio E, Madeddu G, David V. Detection of axillary lymph node metastases in breast cancer with Tc-99m tetrofosmin scintigraphy. Int J Oncol. 2002 Mar;20(3):483-7.

Spanu A, Schillaci O, Meloni GB, Porcu A, Cottu P, Nuvoli S, Falchi A, Chessa F, Solinas ME, Madeddu G. The usefulness of 99mTc-tetrofosmin SPECT scintimammography in the detection of small size primary breast carcinomas. Int J Oncol. 2002 Oct;21(4):831-40.

Spanu A, Dettori G, Nuvoli S, et al. 99mTc-Tetrofosmin SPET in the detection of both primary breast cancer and axillary lymph node metastasis. Eur J Nucl Med 2001; 28: 1781-94.

Sun SS, Hsieh JF, Tsai SC, Ho YJ, Kao CH. Expression of drug resistance protein related to Tc-99m MIBI breast imaging. Anticancer Res 2000; 20: 2021-2025

Sun SS, Hsieh JF, Tsai SC, Ho YJ, Lee JK, Kao CH. Expression of mediated P-glycoprotein multidrug resistance related to Tc-99m MIBI scintimammography results. Cancer Lett 2000; 153: 95-100.

Taillefer R, Robidoux A, Lambert R, et al. Technetium-99m-sestamibi prone scintimammography to detect primary breast cancer and axillary lymph node involvement. J Nucl Med 1995; 36: 1758-1765.

Taillefer R. The role of 99mTc-sestamibi and other conventional radiopharmaceuticals in breast cancer diagnosis. Semin Nucl Med 1999; 29: 16-40.

Tiling R, Sommer H, Pechmann M, et al. Comparison of technetium-99m SestaMIBI scintimammography with contrast-enhanced MRI for diagnosis of breast lesions. J Nucl Med 1997; 38: 58-62.

Tiling R, Tatsch K, Sommer H, et al. Technetium-99m sestamibi scintimammography for the detection of breast carcinoma: comparison between planar and SPECT imaging. J Nucl Med 1998; 39: 849-56.

Tornai MP, Bowsher JE, Jaszczak RJ, Pieper BC, Greer KL, Hardenbergh PH, Coleman RE. Mammotomography with pinhole incomplete circular orbit SPECT. J Nucl Med 2003; 44: 583-93.

Vargas HI, Agbunag RV, Kalinowski A, et al The clinical utility of Tc-99m sestamibi scintimammography in detecting multicentric breast cancer Am Surg 2001; 67:1204-1208

Villanueva-Meyer J, Leonard MH, Briscoe E, et al. Mammoscintigraphy with technetium-99m SestaMIBI in suspected breast cancer. J Nucl Med 1996; 37: 926-930.

Wang HC, Sun SS, Kao A et al Comparison of technetium-99m methoxyisobutitylisonitrile scintimammography ultrasonography in the diagnosis of breast cancer patients with mammographically dense breast Cancer Invest 2002; 20: 318-323.

Wu D, Gambhir SS. Positron emission tomography in diagnosis and management invasive breast cancer: current status and future perspectives. Clin Breast Cancer 2003; 4: S55-63.

Yang MD, Sun SS, Kao CH, Lin CC, Lee CC. Usefulness of technetium-99m tetrofosmin scintimammography to detect breast cancer in mammographically dense breasts. Cancer Invest. 2002; 20: 518-23.

Guidelines issued date: September 2, 2003