SPECT-CT in breast cancer

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SUMMARY

The most important prognostic factors for breast cancer are the size of primary tumor and axillary lymph node status. Role of scintimammography with the cationic lipophilic 99mTc-Tetrofosmin and 99mTc-Sestamibi in preoperative evaluation and post-treatment follow-up of patients with breast cancer is well known. The added diagnostic value of SPECT-CT has recently been investigated. Scintigraphy provides a description of function or process whereas CT depicts the precise localization and type of morphological changes that have occurred in the lesions. Combined SPECT-CT imaging enables to localize positive primary tumors and/or loco-regional lymph nodes; to evaluate effect of neoadjuvant chemotherapy in locally advanced and non-operable breast tumors. SPECT-CT studies are useful in post-therapeutic follow-up of patients to visualize suspicious local recurrence, lymphadenopathy and disease extension. CT part of the study can increase the specificity of SPECT by more accurate anatomical assessment of the sites of abnormal activity with unclear character such as radiation pulmonitis, postoperative parenchymal changes, fibrocystic changes etc. According to the results reported in literature, all the axillary metastatic nodes that were false negative on SPECT image were non-palpable, small lesion size (<10 mm) with partial metastatic involvement or micrometastases in most cases. Lymphatic mapping of SLNs is now routinely done in breast cancer patients for correct N-staging. SPECT-CT has been used for clear depiction of the SLNs to provide the useful information for intraoperative gamma-probe detection in cases that are difficult to interpret planar images, in cases with unusual drainage or in cases of nonvisualization. SPECT-CT scintimammogarphy is preferable in terms of physical characteristic, execution time and cost-effectiveness, thus suggesting wider application of this procedure. SPECT-CT is a potential new tool for LN localization and radioguided surgery in the coming years.

Key words: *Breast Neoplasms; Positron-Emission Tomography and Computed Tomography; Radionuclide Imaging; Lymph Nodes*

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Breast cancer is the commonest malignancy in women with over 600 000 new cases worldwide each year. In the EC the disease represents about 24% of all cancer cases. More than 3000 new cases are discovered every year in Bulgaria (1).

The most important prognostic factor for breast cancer are the size of primary tumor and axillary lymph node status (2, 3).

Diagnostic imaging has gained a major role in the management of patients with breast cancer. Among the various imaging techniques used to assess primary or recurrent breast cancer, radionuclide imaging modalities such as planar scintimammography, SPECT and PET can provide an accurate assessment of the presence and extend of disease as well as unique information about tumor biological characteristics such as the rate of proliferation and metabolic activity (4, 5).

Scintimammography is not screening procedure, but it could be useful as a complementary test when the first–line examinations, including palpation, mammography, ultrasound and fine-needle aspiration are no diagnostic (6, 7).

Role of scintimammography with the cationic lipophilic 99mTc-Sestamibi/ 99mTc-Tetrofosmin and in preoperative evaluation and post-treatment follow-up of patients with breast cancer is well known (8-12). The uptake of these two radiotracers is favoured by increased blood flow and capillary permeability and elevated metabolic activity of neoplastic cells. It is strictly depend on cell membrane and mitochondrial potential and also on the expression of p-glycoprotein (13). 99mTc-Tetrofosmin predominantly accumulates in the cytosol and mitochondria, while 99mTc-Sestamibi accumulates only in the mitochondria in proliferative malignant cells (5).

Obwegeser et al reported data after performing a comparison between 99mTc-Sestamibi and 99mTc-Tetrofosmin to evaluate suspicious breast lesions. They demonstrated that these two radiotracers had similar diagnostic value in both planar and SPECT images (14). Analysing the published results of a meta-analysis selecting 64 unique studies (15), with data on 5340 patients, including 5354 breast lesions, sensitivity, was 85.2%; specificity - 86.6% respectively; negative predictive value - 81.8%; positive predictive value - 88.2% and accuracy - 85.9%. Other authors reported results in more than 5660 cases, the sensitivity and specificity of 99mTc-sestamibi scintimammography in detecting primary breast cancer were 83.8% and 86.4%, respectively (16). SPECT has proved more sensitive than planar imaging in various clinical settings because of better special resolution in particular, in the detection rate of smaller lesions (6, 17). This issue is of the most 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 (6, 18). On the other hand, it is well known that planar scintimammography has a low sensitivity for nonpalpable and less than 1 cm cancers, as indicated by several reports (17, 18). In a multicentric study on 420 patients, Scopinaro et al. (19) 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.

The use of dedicated high-resolution cameras with a small field-of-view (20x16 cm or 20x20 cm) might play a role in the future both in the assessment of multicentricity and in the detection of the unknown primary breast tumors, the small (<1 cm) nonpalpable lesions with deep location, because of their excellent spatial resolution (20,21). Scintimammography performed on dedicated high-resolution cameras 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 (21, 22). Conners A.L et al, 2012 reported data selected from a database of over 3 000 examinations with 99mTc-Sestamibi performed on a dual-head cadmium-zinc-telluride (CZT) gamma camera mounted on a modified mammographic gantry. Median sensitivity was 100%, specificity – 88% and accuracy – 94% for imaging of breast malignancies (23).

Currently a further forward step has made with the introduction of fusion SPECT-CT techniques into the field. In 2004 the first combined clinical SPECT-CT system, the Symbia T2 (Siemens Medical Solutions), was launched comprising a dual-slice Emotion CT and dual-head Symbia S scintillation camera. This is the first commercial design that incorporated a fully-clinical CT system (24). This design, now named the Symbia TruePoint SPECT/CT, is also available with 6-slice and 16-slice Emotion CT systems (24).

This technology provides hybrid images of two independent modalities, a functional scintigraphic technique and an anatomical procedure, yielding a superior imaging study. Scintigraphy is based on the use of single photon emitting tracers such as 99mTc-Sestamibi or 99mTc-Tetrofosmin providing a description of function or processes, whereas computed tomography (CT), depicts the precise localization and type of morphological changes that have occurred in the lesions (24, 25).

The SPECT studies of the SPECT-CT procedure is performed using the routine acquisition protocols for the dual-head gamma camera (26). This machine is equipped with collimators for the specific radioisotope in use such as low-energy high-resolution collimators for ^{99m}Tc, high-energy collimators for ^{131}I etc. CT images are obtained immediately following the scintigraphic part of the combinative studies. For the low-dose CT devices, the acquisition parameters include settings at 130 kV, 17-70 mA, 256x256 image matrix, 3-5 mm slice thickness. For diagnostic CT acquisitions the settings are 130 kV, 80-300 mA, 512x512 image matrix, 1-5 mm slice thickness. Data are reconstructed using filtered back-projection software and filters, provided by the manufacturer (25, 26).

The first clinical application of this new technology indicates that SPECT-CT can increase the accuracy of SPECT by more accurate anatomic assessment of the sites of abnormal activity on the same image (27). Scillaci O. et al have studied 53 patients with mammographically suspicious lesions proved histologically and have observed that SPECT/CT scintimammography using a hybrid device is able to detect breast cancer, showing a sensitivity higher than that of planar images, especially for small cancers (28). The overall sensitivity of planar imaging was 73% (42.9% for lesions <10mm, 91.3% for those >10mm), while the sensitivity of SPECT-CT was 89.2% (71.4% for lesions <10mm, 100% for those >10mm) with equal specificity (93.8%).

We have performed SPECT-CT scintimammography in 73 women (age 34-80 years) with histologically proven breast cancer at our department for the period 2009-2011. Fourteen out of them were studied before operation; 59 patients were investigated after therapy due to some clinical and laboratory indices suspicious for the recurrent disease. 99mTc-Tetrofosmin 740-925 MBq per dose was administered i.v. All women underwent early SPECT-CT scintimammography 10-15 min after tracer application; in some pts late scanning 120 min was carried out. Double-head SPECT-CT camera Symbia T2, Siemens with low-dose CT scanning was used. SPECT-CT data were compared to the clinical status, radiological results and histological findings. Our results were as follow:

A. Pre-treatment SPECT-CT images was true positive in all 14 pts with primary cancer. In 1 case the breast tumor of the first and adenosis of the second breast were scanned (Figure 1).

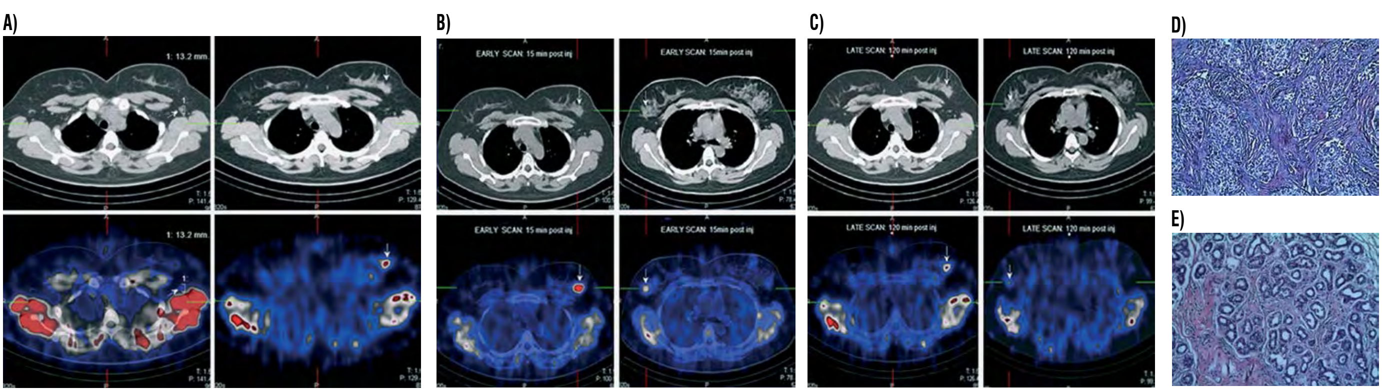

Figure 1. Pt (F,40yo) with carcinoma of the left breast. SPECT-CT images showed intensive focal tracer uptake in the left breast and left axillary lymphadenopathy (A). Early SPECT-CT imaging: intensive tracer uptake was also seen in the right breast (B) . Late SPECT-CT imaging showed tracer uptake only in the left breast (C). After surgery carcinoma of the left breast (D) and adaenosis of the right breast (E) were proven by histology (H+E)

SPECT-CT showed precise N-staging and M-staging in patients with disease extension: for precise topography of secondary lesions: axillary lymph node metastases and/or osteolytic bone lesions were visualized in 9/14 pts (Figure 2).

B. Post-treatment SPECT-CT was negative in 12/59 cases. Local relapse was diagnosed in 9/59 pts; metastatic lesions – in 12/59 pts; tumor persistence – in 1/59 case (Figure 3, Figure 4).

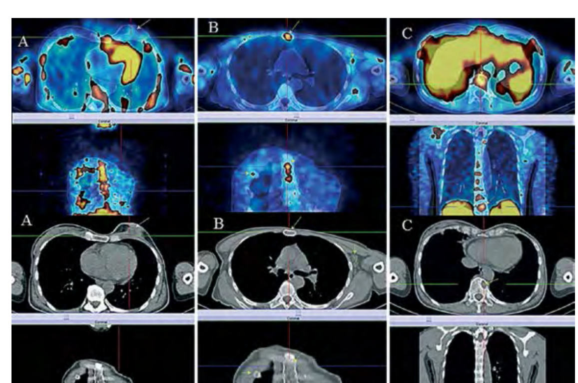

Figure 2. Locally advanced cancer of the left breast (A) with multiple bone lesions (B) and axillary lymphadenopathy (C)

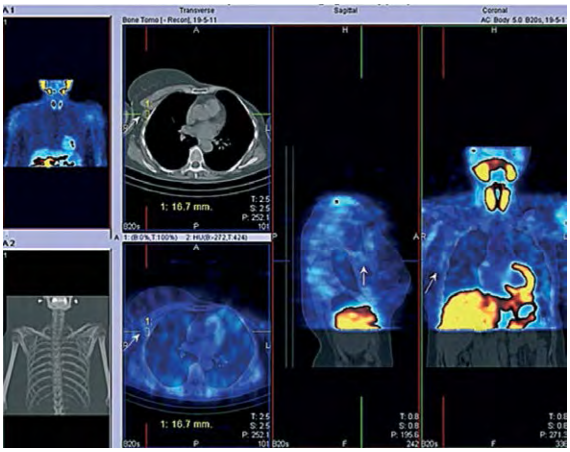

Figure 3. Carcinoma of the left breast after radical mastectomy and radiation therapy with elevated level of CA 15-3. Fusion SPECT-CT images 2 enlarged metastatic lymph nodes in the contralataral axilla with intensive tracer accumulation– progression of the disease

Also SPECT images were positive in 9/59 pts with benign fibrocystic changes and mastopathy; in 2 pts with postoperative parenchymal changes; in 3 pts with postradiation pulmonitis.

SPECT images were negative in 2 pts with fibroadenomas; in 3 – with lymphocele, in 4 pts with CT lymphadenopathy due to iatrogenic interventions. W**e** can summarize that the main indications for SPECT-CT scintimammography with 99mTc-Tetrofosmin are as follows:

1. Diagnosis of malignant diseases
   - Limited role only in selected cases**:** to depict non-palpable lesion for correct biopsy; in small lesion <10 mm with negative planar image.
2. Staging of malignant diseases:
   - Pre-treatment correct N-staging and M-staging of locally advanced carcinomas
3. Follow-up of patients after the final treatment:
   - For early determination of recurrence in cases with abnormal clinical and laboratory indices
   - For precise topography of metastatic foci in patients with disease extension
   - For differential diagnosis of proliferative tumoral tissue from fibrosis and inflammation
   - For differential diagnosis of malignant from benign lesions and physiological uptake

C. Planning in radiotherapy to target precise tumor volume delineation (Figure 4).

The breast cancer gives metastases in over 90% of cases mainly in lymphatic way. The sentinel lymphadenectomy has been shown as an attractive technique in multiple studies, carried out as a part of on-going effort to find a less invasive and still adequate method for axillary staging (No or N1) in the cases with early breast cancer. The first node draining the lymphatic flow from primary tumor site is defined as “Sentinel Lymph Node - SLN”. The method of selective biopsy of SLN is based on the hypothesis that at the absence of metastatic lesions, other lymph nodes are not involved. But if the metastatic growth is found in it, then a radical axillary dissection is mandatory due to a possibility of infiltrating of the neighboring lymph nodes (29, 30).

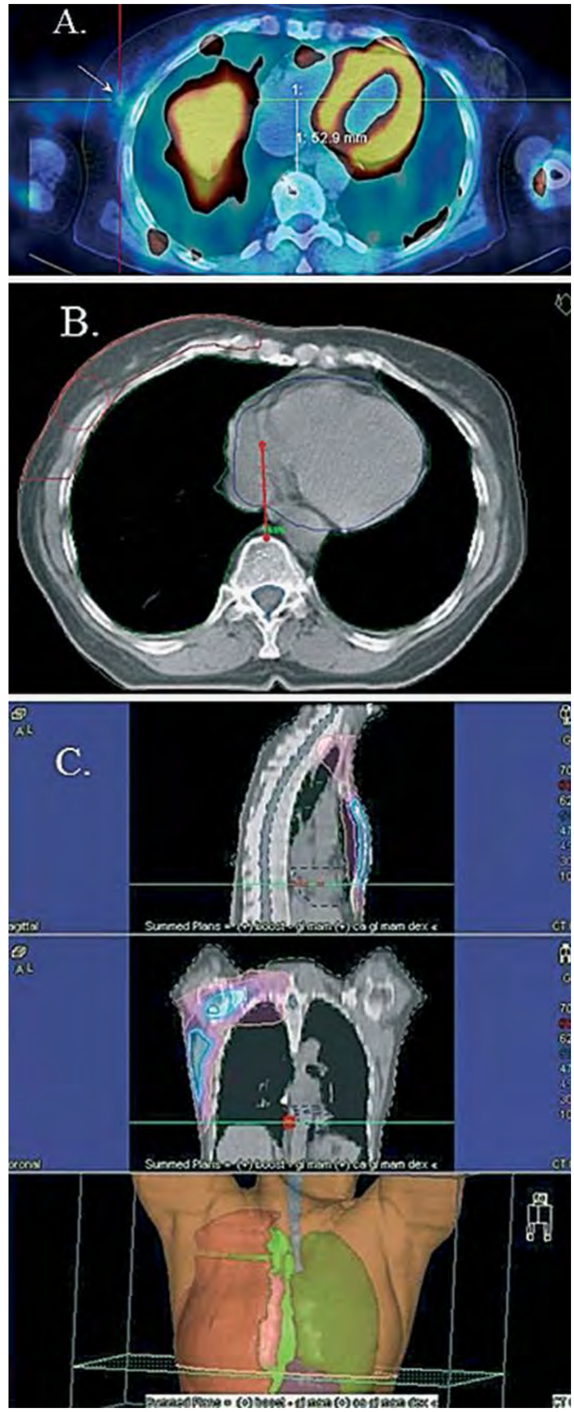

Figure 4. Carcinoma of the right breast after 6 courses FEC and quadrantectomy and right axillary lymph node dissection, pT4N3cM0 (skin infiltration). SPECT-CT images showed residual tumoral tissue, clinical CT data for supraclavicular enlarged lymph nodes (A,B). EBRT planning with overdose of 66Gy (C)

Lymphatic mapping and radioguided SLN Biopsy are accepted standard-of-care in management of breast cancer predominantly in the early stages of the disease as it is significantly contributes to the assessment of metastatic involvement of regional lymph nodes and identify lymphatic drainage to atypical locations (31, 32).

Introduction of SPECT-CT technique results in clear depiction of SLNs providing a useful topographic map for surgeons. In the region of the chest fusion images correlate the site of 99mTc-colloid uptake in the SLNs to important anatomical landmarks thus better guiding the surgeon to perform SLNB. There are three levels of axillary lymph nodes depending on their location relative to the *pectoralis minor muscle* (34).

SPECT-CT accurately characterizes the number, size, depth and regional location of SLNs in breast cancer patients (35).

This new technique is very important to image no visible on the planar scanning SLNs. SLNs are visible on conventional lymphoscintigraphy in 72-94% of the patients and these numbers improved to 89-100% by adding SPECT-CT because of its better contrast and resolution (36).

According to the data of *Renato A.Valdes Olmos et al* (37) depending on the injection technique (peri-tumoral or peri-areolar) SPECT-CT can determinate:

- the exact intercostal space where internal mammary SN is located
- SLN location in the subclavicular or supraclavicular fossa
- SLN between the pectoralis muscles – interpectoralis LNs
- SLN within the breast parenchyma – intramammary LNs
- SLN close to the injection site non-visible on the planar lymphoscintigraphy
- Two SLNs from one to another when depicted as one on planar image

Furthermore, SPECT-CT improved SLN detection in obese patients with breast cancer (35*)*.

We have presented some SPECT-CT cases studied in our department of nuclear medicine for imaging of SLNs (Figure 5, Figure 6).

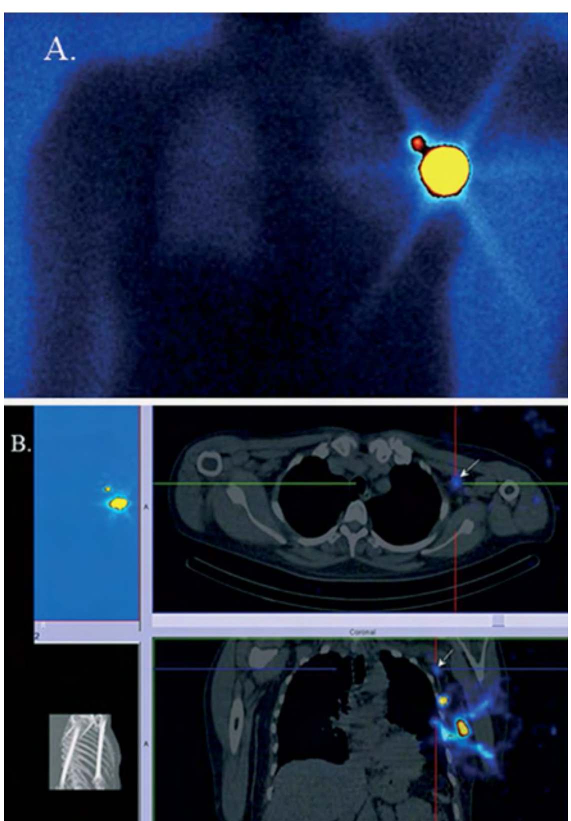

Figure 5. Pt with carcinoma of the left breast. Planar lymphoscintigrapgy showed 1 axillary SLN (A). SPECT-CT images showed 1 additional SLN on the II axillary level (B)

A)

B)

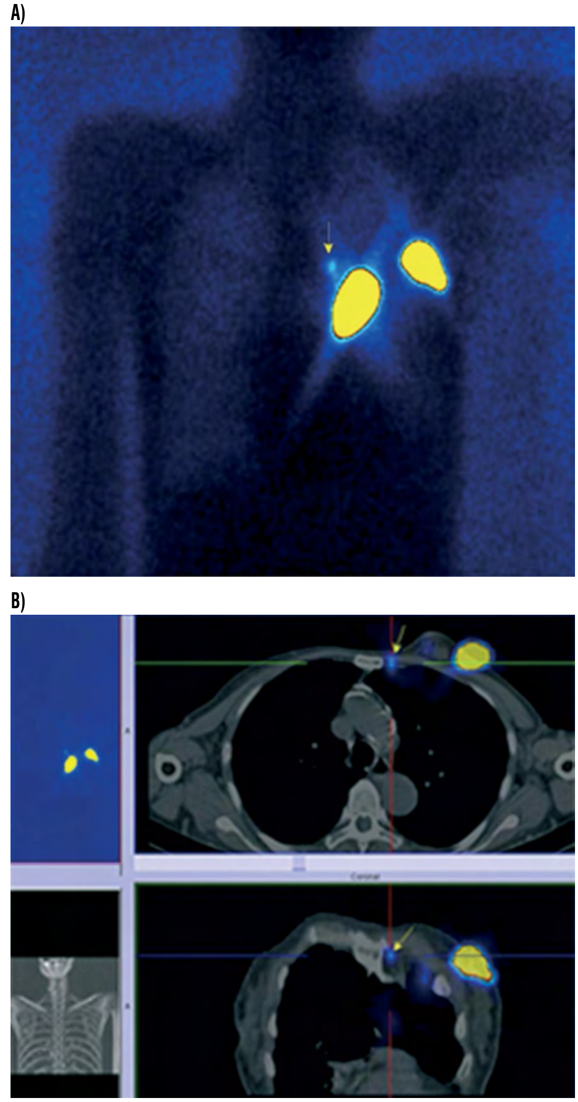

Figure 6. Pt with carcinoma of the left breast. Planar image showed 1 parasternal SLN (A). SPECT-CT images showed correct intercostal location of this internal SLN (B)

In conclusion combined SPECT-CT studies have grown in the past years due to the almost simultaneous acquisition of transmission and emission information, thus obtaining optimal fusion in a very short time.

SPECT-CT study represents an easy-to-perform technique to improve sensitivity of scintimammography and lymphoscintigraphy because of their excellent spatial resolution.

SPECT-CT scintimammography is preferable in terms of physical characteristic, execution time and cost-effectiveness, thus suggesting wider application of this procedure.

SPECT-CT is a potential new tool for LN localization and radioguided surgery in the coming years especially in patients with extra-axillary SLN location and non-visualization.

Conflict of interest

We declare no conflicts of interest.

REFERENCES

1 Valerianova Z., Vukov Dimitrova N. Cancer Incidence in Bulgaria for 2009.2011, v.XX

2 Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status and survival in 24740 breast cancer cases. *Cancer*. 1989;63:181-7.

3 Saez RA, NcGuire WL, Clark GM. Prognostic factors in breast cancer. *Semin Surg Oncol*. 1989;5:102-10.

4 Benard F, Turcotte E. Imaging in breast cancer: Single-photon computed tomography and positron-emission tomography. *Breast Cancer Res*. 2005;7:153-62.

5 Madeddu G, Spanu A. Use of tomographic nuclear medicine procedures, SPECT and pinhole SPECT, with cationic lipophilic radiotracers for evaluation of axillary lymph node status in breast cancer patients. *Eur L Nucl Med Imaging*. 2004;31(Suppl.1):S23-S34.

6 Mathieu I, Mazy S,Willemart B, Destine M, Mazy G, Lonneux M. Inconclusive triple diagnosis in breast cancer imaging: is there a place for scintimammography? *J Nucl Med.* 2005;46(10):1574-81.

7 Wang HC, Chen DR, Kao CH, Lin CC, Lee CC. Detecting breast cancer in mammographically dense breasts: comparing technetium-99m tetrofosmin mammoscintigraphy and ultrasonography. *Cancer Invest*. 2002;20:932–8.

8 Moretti JL, Azaloux H, Boisseron D. Primary breast cancer imaging with technetium-99m sestamibi and its relation with P-glycoprotein overexpression. *Eur J Nucl Med*. 1996;23:980-6.

9 Schillaci O, Buscombe JR. Breast scintigraphy today: indications and limitations. *Eur J Nucl Med Mol Imaging*. 2004;31(suppl 1):S35–S45.

10 Sergieva BS, Timcheva KV, Hadjiolov ND. ^{99m}Tc -MIBI scintigraphy as a functional method for Multi Drug Resistance (MDR) evaluation in breast cancer patients. *J BUON*. 2006;11(1):61–8.

11 Spanu A, Farris A, Schillaci O. The usefulness of 99mTc tetrofosmin scintigraphy in patients with breast cancer recurrences. *Nucl Med Commun.* 2003;24:145–54.

12 Bongers V, Perre C, de Hooge P. The use of scintimammography for detecting the recurrence of loco-regional breast cancer: histopathologically proven results. *Nucl Med Commun*. 2004;25:145–9.

13 Vergote J, Moretti JL, De Vries EGE. Comparison of the kinetics of active efflux of 99mTc-MIBI in cells with P-glycoprotein-mediated and multidrug-resistance protein-associated multidrug-resistance phenotypes. *Eur J Biochem*. 1998;252:140-6.

14 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;26:1553-9.

15 Liberman M, Sampalis F, Mulder DS, Sampalis JS. Breast cancer diagnosis by scintimammography: a meta-analysis and review of the literature. *Breast Cancer Res Treat.* 2003;80:115–26.

16 Taillefer R. Clinical applications of 99mTc-sestamibi scintimammography. *Semin Nucl Med.* 2005;35:100–15.

17 Spanu A, Schillaci O, Madeddu G. ^{99m}Tc labelled cationic lipophilic complexes in malignant and benign tumors: the role of SPET and pinhole-SPET in breast cancer, differentiated thyroid carcinoma and hyperparathyroidism. *Q J Nucl Med Imaging*. 2005;49:145-69.

18 Schillaci O. Is There a Clinical Role for Scintimammography in Breast Cancer Diagnosis? *J Nucl Med*. 2005;46:1571-3.

19 Scopinaro F, Schillaci O, Ussof W. A threecenter study on the diagnostic accuracy of 99mTc-MIBI scintimammography. *Anticancer Res.* 1997;17:1631–4.

20 Hruska C, Boughey J, Philips SW, et al. *Am J Surg*. 2008;(4):470-6.

21 Williams MB, Judy PG, Gunn BSS, Majewski SA. Dual-Modality Breast Tomosynthesis. *Radiology*. 2010;255(1):191-8.

22 Goldsmith S, Parsons W,Guiberteau M, et al. SNM Practice Guideline for Breast Scintigraphy with Breast-Specific –Camera. *J Nucl Med Technol*. 2010;38:219-24.

23 Conners AL, Hruska CB, Tortorelli CL, et al. Lexicon for standardized interpretation of gamma camera molecular breast imaging: observer agreement and diagnostic accuracy. *Eur J Nucl Med Mol Imaging*. 2012;39:971-82.

24 Beyer T, Freudenberg LS, Townsend DW, Czernin J. The future of hybrid imaging —part 1: hybrid imaging technologies and SPECT/CT. *Insights Imaging*. 2011;2:161–9.

25 Schafers KP, Stegger L. Combined imaging of molecular function and morphology with PET-CT and SPECT-CT: Image and motion correction. *Basic Res Cardiol*. 2008;103:191-9.

26 Nunez R, Erwin WD, Wendt III RE, et al. Acquisition Parameters for Oncologic Imaging with a New SPECT/Multislice CT Scanner. *Mol Imaging Biol*. 2010;12:110-38.

27 Schillaci O, Danieli R, Manni C, Simonetti G. Is SPECT-CT with hybrid camera useful to improve scintigraphic imaging interpretation? *Nucl Med Commun*. 2004;25:705-10.

28 Scillaci O, Danieli R, Filippi L, et al. Scintimammography with a Hybrid SPECT/CT Imaging System. *Anticancer Res*. 2007;27:557-62.

29 Veronesi U, Paganelli G, Viale G. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med*. 2003;349:546-53.

30 Naik AN, Fey J, Gemignani M, et al. The Risk of Axillary Relapse After Sentinel Lymph Node Biopsy for Breast Cancer Is Comparable With That of Axillary Lymph Node Dissection A Follow-up Study of 4008 Procedures. *Ann Surg*. 2004;240:462–71.

31 Luini1 G, Gatti B, Ballardini S, Zurrida V, Galimberti P, Veronesi U. Development of axillary surgery in breast cancer. *Ann Oncol*. 2005;16:259–62.

32 Sergieva S, Alexandrova E, Baichev G, Ganchev G, Tzonevska A, Bogkova D. Lymphoscintigraphy and immunohistochemistry for the assessment of sentinel lymph nodes in patients with breast cancer. *Hell J Nucl Med*. 2002;2:127-9.

33 Gang Cheng G, Kurita S, Torigian DA, Alavi A. Current status of sentinel lymph-node biopsy in patients with breast cancer. *Eur J Nucl Med Mol Imaging*. 2011;38:562–75.

34 Van der Ploeg IM, Nieweng OE, Kroon BB, et al. The yield of SPECT-CT for anatomical mapping in patients with breast cancer. *Eur J Nucl Med Mol Imaging*. 2009;36:903-6.

35 Mariani G, Bruselli L, Kuwert T, et al. *Eur J Med Mol Imaging*. 2010;37:1959-85.

36 Van der Ploeg IM, Valdes Olmos RA, Kroon BBR, Nieweg OE. The hybrid SPECT-CT as an additional lymphatic mapping tool in patients with breast cancer. *World J Surg*. 2008;32:1930-4.

37 Valdes Olmos RA, Vidal-Sicart S, Nieweg OE. *Eur J Nucl Med Mol Imaging*. 2009;36:1-5.