VIA MEDICA

ISSN 1506–9680

Evaluation of nuclear medicine tests for the diagnosis of breast carcinoma

Philip C. Grammaticos
Nuclear Medicine Department, AHEPA Hospital of Thessaloniki, Greece

[Received 3 V 2002; Accepted 21 X 2002]

Abstract

In this paper, we evaluate nuclear medicine tests used for the diagnosis of breast carcinoma. Breast carcinoma is the most common carcinoma in women in Europe and its early diagnosis and treatment is important for the overall survival of the patients. Scintimammography technique, indications, contraindications and diagnostic procedures for the identification of the sentinel node and the axillary nodes infiltrated by tumour are described. Also, the use of the radiopharmaceuticals, radioactive thallium chloride-201, methylene diphosphonate labelled with technetium-99m, somatostatin receptors labelled with indium-111, diagnostic procedures with the PET camera, the labelled antibodies to CEA with technetium-99m and also the importance of the MRI and the US techniques are mentioned. These tests have greater diagnostic accuracy as compared to X-ray mammography, clinical examination, MRI and the US technique. Tumour markers in vitro are recommended for the follow-up of metastatic breast carcinoma.

Key words: breast carcinoma, scintimammography, lymphoscintigraphy, ^{99m}Tc-sestamibi, ^{99m}Tc-tetrophosmin

Introduction

Breast carcinoma (BC) is the most common carcinoma in women in Europe [1]. Nuclear Medicine (NM) has an important contribution both to the diagnosis and to the differential diagnosis of BC. It is known that the correct initial diagnosis permits progress to a successful treatment of BC. Unfortunately, at present, the correct diagnostic and therapeutic procedures are a matter of discussion. Questions like these that follow arise: Are X-ray mammography and physical examination enough to diagnose BC? What is the place of scintimammography (SM), sentinel node (SN) scintiscan, magnetic resonance imaging (MRI), ultrasound (US) for the diagnosis of BC? What are the future prospects of using whole body scintiscans imaging somatostatin receptors? Can tumour markers and positron emission tomography (PET) procedures contribute to the diagnosis of BC? How shall we reduce the discomfort of performing some of the diagnostic procedures? And the most important question of all: Can we increase the survival of patients suffering from BC?

In the present paper, we will discuss the contribution of NM in the early diagnosis of BC compared to other diagnostic techniques. While describing and supporting our points of view, we will take into consideration the opinions of others, published during the last seven years.

From the total range of NM techniques, we will describe the following: a) SM; b) the search for SN; c) the routine bone scan d) the PET test e) specific whole body scintiscan; f) the MRI test and g) tumour markers as in vitro tests.

Correspondence to: Prof. Philip C. Grammaticos
51 Hermou str.
546 23 Thessaloniki, Greece
Tel./fax: (+3031) 022 91 33
e-mail: fgrammat@med.auth.gr

Scintimammography

Scintimammography is the imaging of breast tumours by a special technique of NM. The first description of the SM technique was in 1987. Since then, considerable progress has been made. The most commonly used radiopharmaceuticals with a SPET camera are: a) exakis-2-methoxy-isobutil-isonitril labelled with ^{99m}Tc (^{99m}Tc-MIBI or sestamibi); b) tetrophosmin labelled with ^{99m}Tc (^{99m}Tc-tetrophosmin or myoview); c) radioactive thallium chloride-201 (^{201}TlCl) and d) methoxy-phosphonic technetium-99m (^{99m}Tc-MDP). The first two of the above mentioned radiopharmaceuticals are taken up by the cancer cells of the breast, 4–8 times more than from normal cells [1]. This takes place because cancer cells have an increased function in their mitochondria which means that they accept larger quantities of the two first radiopharmaceuticals [2, 3]. Cancer cells have increased turnover of potassium and so they take up larger quantities of thallium-201. Cancer cells also have increased turnover for phosphate and thus take up larger quantities of ^{99m}Tc-MDP. In contrast, benign tumours (adenomas, cysts, some chronic inflammatory lesions) are very slightly imaged or not at all by the above radiopharmaceuticals.

According to some writers, malignant tumours of the breast are better imaged in the late images while adenomas and inflammatory tumours are better seen in the early images. In order to

evaluate the latter finding, the difference in the intensity of the images should be clear and the images should be acquired under similar conditions [4]. The duration of acquisition for early images may vary from 5 to 10 min [5].

Indications: SM is recommended to women, older than 21, not pregnant, not lactating, with a clinically palpable nodular mass in their breast and a doubtful X-ray mammography [6]. Also, SM is recommended in order to discern the existence of local cancerous lymph nodes when the tumour markers in vitro are positive, even if we do not palpate a tumour and in order to choose the best treatment schedule and to follow up the efficacy of treatment. The above mentioned indications for applying SM are reinforced in the case where the woman examined has a family history of breast carcinoma or is a carrier of the BCL2 genetic index [7]. The patient should be thoroughly informed about the kind and importance of the examination and agree to undergo it [6].

Scientimammography is not recommended in the case of preexisting partial mastectomy because false positive signs due to surgery may appear. Also, SM is not indicated in the case of a thin needle biopsy performed within the previous week because the local haemorrhage from the puncture can result in a false negative image. Finally, SM is not recommended after scintigraphy with some other radionuclide if 10 halflives of this radiopharmaceutical have not elapsed. Otherwise we may have false positive findings [6].

The technique of SM is as follows [4]: about 740 MBq (660––1110 MBq) of ^{99m}Tc-sestamibi is injected intravenously. A specially adapted bed is used so that the breast, when the patient is in prone position, hangs downwards and thus the image of the heart and liver are separated (Fig. 1). Early images are acquired at 10–15 min post injection. The breast is scintiscanned in supine, lateral and oblique positions. At 45–60 min post injection the so-called late image is acquired. The radiopharmaceutical is prepared by the radiophysicist or a trained technologist under the radiophysicist's supervision, as follows: the stable substance in powder is contained in a sterilised vial with a capacity of about 20 ml. A solution of the radionuclide $Na_2{}^{99m}TcO_4$ is added to the vial and the whole is warmed in a waterbath. In the end, the purity of the complex radiopharmaceutical should not be less than 90%. This is tested by chromatography. Otherwise, the whole is rejected.

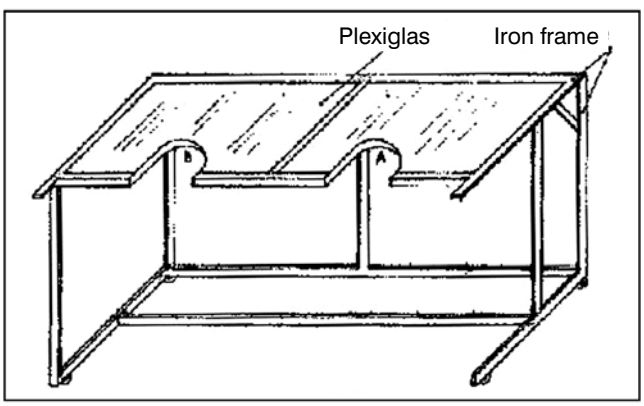

Figure 1. The examination bed as specifically modified for scintimammography. The lying level is from plexiglass and all the rest of the bed consists of a metal frame.

The above used radiopharmaceuticals are normally retained, mainly in the myocardium, the liver, the spleen, the thyroid and the salivary glands, while they are excreted mainly through the liver and the biliary system.

When SM is done not by the planar but by the tomographic γ-camera, SPET and by the use of the radiopharmaceutical ^{99m}Tc-sestamibi, the sensitivity of the test is increased by 30%, without an increase in its specificity [8]. The accuracy of the diagnosis with the above mentioned radiopharmaceutical and the planar camera is slightly higher than that of the X-ray mammography, regarding tumours located inside the breast [9]. The above technique is characterised by diagnostic accuracy, specificity and sensitivity higher than 95% [11]; in multicellular breast cystic adenomas it is often false positive [10]. It is worth mentioning that the cancerous tumour of patients undergoing chemotherapy, after about 3 months of chemotherapy, absorbs almost half of the radiopharmaceutical, compared to that before chemotherapy; however, this finding has no significant impact on the response of breast cancer to chemotherapy [11].

According to a paper by colleagues from 7 European countries, who have studied 195 palpable and 58 non-palpable nodular breast lesions, when the images were being examined by nuclear medicine practitioners, the general sensitivity of SM was 91% [7]. Similar sensitivity was noticed between breast cancer of the ducts and of the gland lobes parenchyma. Tumours with a diameter of 1 cm to 1.5 cm had a sensitivity of 74%. When the tumour had a diameter of more than 1.5 cm, sensitivity increased to 95% [6]. Generally speaking, breast tumours with a diameter of less than 1 cm are not evaluated. The specificity of diagnosis with SM, which depends on the kind and the size of the lesion as well as on the evaluation of the positive findings in the scintiscan image, ranges from 70–81% [6]. In general, according to multi-centre studies in Europe, Canada and the USA, SM sensitivity regarding palpable breast lesions reaches 95% [6, 12]. The above figures show that the positive "warm" images of lesions in palpable breast tumours with a diameter bigger than 1.5 cm can distinguish carcinomas from benign lesions, up to a percentage of 95%. On the whole, SM is more trustworthy when a lesion is diagnosed as non-cancerous. The above mentioned refer to studies where the radiopharmaceutical ^{99m}Tc-sestamibi was used.

As regards the other radiopharmaceutical used in SM, that is ^{99m}Tc-myoview or tetrophosmin, cancerous cells absorb it in the same manner as ^{99m}Tc-sestamibi but this radiopharmaceutical is retained for a shorter period of time by the chromosomes. ^{99m}Tc-myoview SM has a sensitivity and specificity in the diagnosis of BC higher than 90% [13–16]. A negative scintimammogram with ^{99m}Tc-sestamibi in a woman with a left mastectomy for breast carcinoma is shown in Figure 2. Another scintimammogram positive for breast carcinoma is shown in Figure 3.

Compared to other diagnostic techniques, SM can detect a cancerous lesion in the breast in the case where the X-ray mammography gives doubtful results, to a percentage of 61%. For the X-ray mammography, the specificity is only 42%. In the case of a concrete tumour not palpated not shown in the X-ray mammography but having microcalcifications, a fine needle biopsy and the surgical removal of the lesion are recommended [1]. In such a case, SM is not recommended since it cannot trace lesions like the minute infiltrating duct carcinoma which may be the cause of the above case [1].

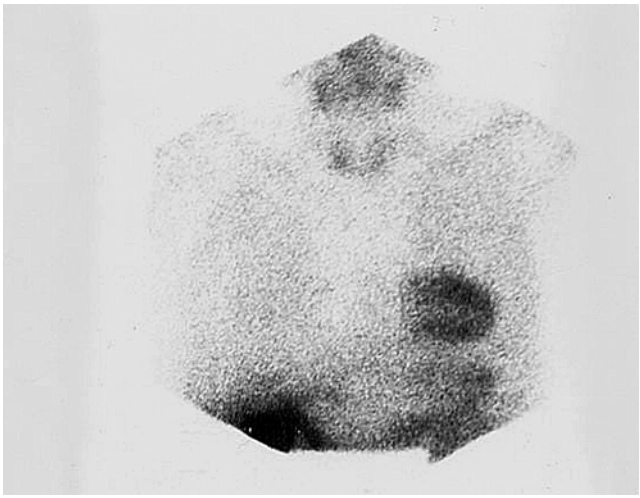

Figure 2. A 53-year-old patient with breast carcinoma and left mastectomy a year ago. Because of pain in her right breast, she had an X-ray mammography with a doubtful result. Scintimammography with ^{99m}Tc-sestamibi followed which was clearly negative. The patient is well 3 years later.

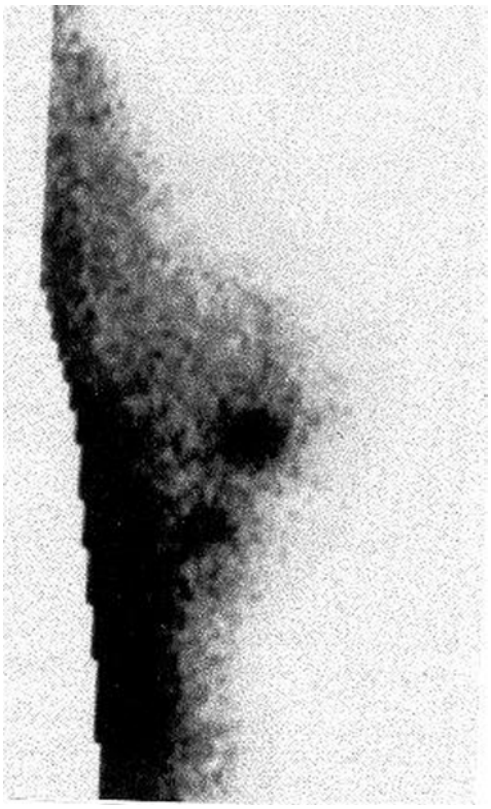

Figure 3. In the scintimammography performed with ^{99m}Tc-sestamibi, two breast lesions due to ductal carcinoma are seen at the lower part of the right breast. Microcalcifications were seen in the X-ray mammography.

Scintimammograhy was studied using ^{99m}Tc-sestamibi in 22 palpable and 5 non palpable breast carcinoma patients in comparison with the X-ray mammography and MRI. SM was proven to have a significantly better specificity in palpable (75%, 25% and 50% respectively) and in non-palpable tumours (62%, 10% and 15% respectively) [17].

Scintimammograhy results using ^{99m}Tc-tetrophosmine were found to be similar to the above with very good diagnostic acurracy [13, 14, 17].

The diagnosis of the sentinel node and the axillary lymph nodes infiltrated by tumour — lymphoscintigraphy

There has been a tendency, in recent years, to limit the extent of surgical operations in cases of breast carcinoma [18]. These operations aim at radically removing the carcinoma without affecting the healthy tissues. According to this point of view, the early diagnosis of the initial cancerous lesion and the nearby lymph nodes where the lesion has probably spread, is extremely useful. Through a special technique, NM traces the lymph nodes that are possibly infiltrated by carcinoma and during the operation points out the positions where metastatic cancerous tissue exists [19]. By tracing the SN, we specify the primary line of lymph flow from the tumour. The SN may be affected by metastases. The test shows the existence of SN but not whether it contains metastatic cells. If, during the histological examination that will follow the removal of the lymph node, no metastasis is found, the surgeon might avoid the total removal of the axillar lymph nodes. Before or after the operation, this technique can find non-palpable cancerous lesions of BC and thus facilitate their surgical removal [19]. This test is based on the fact that radiopharmaceuticals of a certain molecular size that are injected around or inside the initial breast carcinoma, are trapped in the SN. The radiopharmaceutical is injected before, during or after the operation. We examine the lymph nodes that absorbed the radiopharmaceutical and/or the initial tumour in two different ways: a) With a special cylindrical probe for surface measurements. This probe is sterilised and used even inside the operating-theatre (counting probe) and b) Applying a scintiscan after 10–20 min, 2 h, 6 h even after 24 h, depending on the surgeon's will and injecting a higher dose of radioactivity respectively.

We use as radiopharmaceuticals: a) macroaggregates of human albumin with a molecular diameter of 10–150 μm (Macrotec, Amersham-Sorin Co) labelled with ^{99m}Tc which more often are injected inside the lesion; b) colloid particles of human albumin with a diameter of 0.2–1.0 μm (Albures, Amersham-Sorin Co) labelled also with ^{99m}Tc in a volume of 0.2 ml, that are injected outside but near the tumour in order to get trapped in the SN; c) sulphur colloid also labelled with radioactive technetium, usually injected outside the tumour. The above mentioned radiopharmaceuticals are administered in a dose of 11 MBq for each primary tumour.

We believe that the two latter radiopharmaceuticals that have a smaller molecular diameter can be injected simultaneously both around and inside the tumour. Several variations of this technique exist, especially in the case of more than one infusion in the area around the tumour. We usually perform scintiscan images immediately after the injection of the radiopharmaceutical in supine and front lateral position so as to examine the axillary area too. The head of the γ-camera is placed as close to the patient's body as possible, while an anatomic marker of ^{57}Co is placed on her skin. This marker may be solid or liquid containing ^{57}Co. As a linear anatomic marker we may use a thin flexible tube containing the

same radiopharmaceutical. Thus, the limits of the breast under investigation become visible especially in the lateral position [20]. The lateral images are useful for tracing the depth of SN but also of the initial tumour [19]. The above scintiscan is repeated after 45 min — 3 h. This late image shows the initial tumour and the SN better, since it has less background (bg) radiation of the surrounding tissues.

The predominant technique of breast lymphoscintigraphy, which coincides with our observations, refers to the injection of 0.4 ml of the radiopharmaceutical with 70 MBq, divided into 4 equal doses, in the periphery of the primary tumour [5, 21]. The hypodermic injection is not recommended. If surgical removal of the tumour has preceded long before, the above injection is done in the walls of the surgically created cavity. The position of the injection, as well as the position of the SN, might be at a depth of 1 to 7 cm; so, in non-palpable lesions we might get help from an ultrasound test in order to locate its position. For lymposcintigraphy, a special bed is not recommended. The patient is lying in supine and lateral position and images are acquired at 10 min, 2 h or even 24 h. The actual surgical operation usually takes place 24 h after the injection of the radiopharmaceutical [19].

Let us point out that in surgical practice, when the palpable breast carcinoma has a diameter of less than 1 cm, the feasibility to cause metastases in the SN is less than 5%. As a result, the surgical cleansing of the axillary area might not be necessary [18]. In order to determine cancer metastases surely in SN we use the above technique. This technique has also been successfully applied in melanomas [18]. If a further biopsy of the SN is negative, we do not proceed to sugical cleansing of the axillary area [18]. Provided that SN shows no metastases by this technique, the fine needle biopsy in the suspected lymph nodes is avoided [18]. What is more, the radionuclide technique determines the stage of the cancer so as to plan the therapeutic procedure better.

Before the application of the radionuclide technique mentioned in order to trace SN, the surgeons used an infusion of a blue pigment in or around the primary tumour and searched for lymph nodes retaining the pigment, during surgical intervention. The latter technique is successful in only 60–70% of cases [18, 19]. Some disadvantages of the blue pigment technique are: a) the fact that it can be used only during surgery and not before or after surgery; b) it is difficult to find a possibly suspicious or metastatic lymph node; c) it is unpleasant for the surgeon to use the pigment; d) the surgeon does not know if he has removed all the lymph nodes that contain the pigment; as a result, he is obliged to search as much as possible by making several search incisions. In contrast, when using the radiopharmaceutical technique that was previously described, the technique can be applied before, during and after surgery; in this way, we avoid all the above mentioned disadvantages and increase the percentage of a successful diagnosis of the SN to 97% [19]. According to other researchers [21], the positive and the negative values of the radionuclide technique are 100% and 96% respectively. Based on these results, certain surgical clinics do not proceed to axillary diagnostic lymphadenectomy when the patient is in stage T1 and the SN technique is negative [20]. Some believe the same about stage T2, when the primary tumour is small [21].

Not finding an affected SN via the radiopharmaceutical technique clinically means that, in such a case, the 10-year survival, compared to the one if the patient had 1–3 metastatic lymph nodes, is increased by about 15% [20]. In case the SN is histologically negative, yet accompanied by: a) a primary cancerous tumour bigger than 1 cm b) a tumour that is histologically extremely malignant c) when micrometastases are found via immunohistochemical techniques d) when via the chain reaction of the reverse transpeptidase-polymerase, special cancerous genes are found, then despite the negative SN, an international research team recommends supplementary or additional chemotherapy with or without tamoxifen. This treatment is believed to increase the survival expectancy of 10 years by around 7% [22, 23]. This percentage is not big. Of course, the above special histopathological examinations for the tracing of micrometastases in the lymph nodes are conducted only in very few laboratories; as a result, most surgeons are based on the diameter of the primary tumour (> 1 cm) and the degree of histological malignancy of the cancer in relation to the existence of oestrogen receptors and the NM tests in order to choose the best therapeutic process. The whole issue is still under research [22].

Diagnostic procedures with ^{201}TICl and ^{99m}Tc-MDP

The relevant scintiscans are not used today, since these radiopharmaceuticals have been replaced, because of lower diagnostic acurracy, by the ^{99m}Tc-sestamibi and ^{99m}Tc-tetrophosmin mentioned above. During the usual bone scintiscan which is performed with ^{99m}Tc-MDP and which is usually recommended to women with breast carcinoma, it is better to acquire images of the breast area in supine and lateral positions and during about 2 h from the time of the infection, so as to obtain better information regarding the evolution of breast carcinoma or its response to treatment.

Diagnostic procedures with the PET camera

The diagnostic procedures with a PET camera are performed by using positron emitting radiopharmaceuticals such as H_2O [15], 18F-d-glucose etc. A comparative study, with the SPET camera and ^{99m}Tc-sestamibi on the one hand and PET camera with 18F-d-glucose on the other, showed equal sensitivity and specificity in the diagnosis of primary breast carcinomas. However, as regards the diagnosis of metastatic infiltration of the axillary lymph nodes, the PET technique was better since it diagnosed 100% of the cases, compared to 92% that the SPET technique diagnosed [24]. The smallest lymph node depicted had a diameter of 1.2 cm. We mention that although clinical examination and radiological mammogram have a diagnostic accuracy of 73% and 70% respectively, examination with the PET technique shows specificity and sensitivity that exceed 90% [25]. The PET camera can trace more small lymph nodes with a diameter of around 1 cm. We believe that the PET technique will turn out to have even higher specificity in diagnosis in the future [26]. The PET technique has more advantages compared to the functional MRI (fMRI) technique because it can better examine the whole body metastases. Besides, it has a significantly higher sensitivity and specificity as regards the whole body bone scintiscan [27].

Diagnostic procedures with somatostatine receptors labelled with radioactive Indium-111

We refer to the radioactive octreotide: ^{111}In-Octreotide, which is intravenously injected at a dose of about 220 MBq and the scintiscan is performed at 4 and at 24 hours post injection. This radiopharmaceutical gives better results than using as a radiopharmaceutical ^{201}TlCl[28], but not better than ^{99m}Tc-sestamibi[26]. Finally, it is 3–4 times more expensive than ^{99m}Tc-sestamibi.

Diagnostic procedures with MRI and with US

This diagnostic procedure of the MRI has the disadvantage of being difficult to perform on a large number of patients because the relevant apparatus is not often available. It is considered to have the same sensitivity but significantly less specificity compared to SM performed with the ^{99m}Tc-sestamibi [29–31].

As for the use of US in the detection of BC, in a total of 353 female patients, US detected 70%, while SM 96% of all BC cases [32]. US is more often recommended for disinguishing solid from cystic masses of BC [33].

Diagnostic procedures with labelled antibodies to CEA (CEA-Ab-^{99m}Tc)

This test can locate cancerous breast lesions or whole body metastases but does not seem to have significantly higher specificity as regards SM performed with the ^{99m}Tc radiopharmaceuticals, since its specificity reaches only 63% [34, 35].

Dosimetry

In the usual X-ray mammography, the image acquired is considered to give to the person examined 1.4 mGy in average, while the lateral image gives 1.7 mGy [36]. From the 111 MBq ^{201}TlCl administered for the performance of SM, a nurseling that breastfeeds, absorbs a dose of up to 1.6 mSv [36, 37]. This dose is significant, since the yearly allowed dose limit per adult is 1 mSv. Generally, a dose higher than 74–111 MBq of ^{201}TlCl should not be administered to an adult, because this radionuclide is absorbed by the genital organs and in higher doses harms them seriously. However, SM performed with the ^{99m}Tc radiopharmaceuticals, the scintigraphic procedure for identifying the SN and lymphoscintigraphy emit smaller and permitted doses of radioactivity to the adult patients [38, 39]. Children of up to 1 year old that breast feed, absorb up to 0.9 mSv [38].

The techniques for tracing SN and lymphoscintigraphy emit a minimum absorbed dose to the patient and, consequently, no special measures of radiation protection are required [8].

The *in vitro* tumour markers for the diagnosis of breast carcinoma

We refer to serum tests with radionuclides or not in patients for tracing special anticancerous antibodies or antibodies against the cancer-embryonic antigen (CEA). These antibodies are traced using radioactive iodine — 125 which, in contrast to iodine-131, has a low γ radiation (35 keV) and longer half-life (60 days); for these reasons, it is ideal for in vitro measurements of serum samples. The relevant radioimmunological techniques are the RIA and IRMA techniques that differ since the IRMA technique is more sensitive because it uses a double antibody in order to distinguish the substance examined [37].

The tumour markers do not apply in the diagnosis of breast carcinoma at initial stages I and II. They are used mainly for diagnosis in cases of wholebody metastases. In fact, we study the changes of these markers during therapy so as to estimate their diagnostic importance. Consequently, tumour markers are useful as relative signs of improvement or aggravation of the metastatic disease. Their sensitivity in the diagnosis of cancer does not exceed 70–75% [40, 41].

Apart from RIA and IRMA tests, there are also non-radionuclidic tests by immunoenzymatic or fluorinometric or other corresponding techniques (ELISA, LIA etc). These techniques are obviously less sensitive and specific as compared to the radionuclidic ones because they are based on photometry or fluorometry of many relevant molecules, whereas radionuclides label and examine each molecule and measure the radioactivity they emit.

The most sensitive markers for breast carcinoma are: CA 15–3 (with two anticancerous antigens of the breast), TPA (tissue specific antigen) and CEA. At stages III and IV of breast carcinoma, these markers have a greater sensitivity in the diagnosis of whole body metastases compared to SM [41]. It is believed that CEA increases 3.9 months before the clinical finding of breast carcinoma metastases [42]. However, we should bear in mind the great sensitivity of the known γ-glutamyl-transferase that significantly increases in the case of liver metastases of any cause [43].

In conclusion, in the diagnosis of the first stages of breast carcinoma, the search for SN can be performed with lymphoscintigraphy and SM is recommended to support operation planning [44]. These tests have a greater diagnostic accuracy compared to X-ray mammography, clinical examination and MRI. Tumour markers in vitro are recommended for the follow-up of metastatic breast carcinoma.

References

1. Jensen OM, Esteve J, Moller H et al. Cancer in the European Community and its member states. Eur J Cancer 1990; 26: 1197–1256.
2. Grammaticos PC, Nuclear Medicine — Applications in 15 Medical Disciplines. 4th edition, Thessaloniki: Ziti, 1996: 211–220: 269–272.
3. Arbab AS, Koizumi K, Toyama K et al. Uptake of technetium-99m-tetrofosmin, technetium-99m-MIBI and thallium-201 in tumor cell lines. J Nucl Med 1996; 37: 1551–1556.
4. Gerassimou G, Costopoulos I, Fahantidis E et al. Search for lymph node metastases in the breast area using a special scintillation detector and lymphoscintigraphy. Hell J Nucl Med 1998; 1: 19–21.
5. Clarke EA, Notghi A, Harding LK. Can reduced imaging times be used for scintimammography? Nucl Med Commun 1999; 20: 883–886.
6. Palmedo H, Biersack HJ, Lastoria S, et al. Scintimammography with technetium-99m methoxyiso-butylisonitrile: results of a prospective European multicentre trial. Eur J Nucl Med 1998; 25: 375–385.
7. Buscombe JR, Cwikla DS, Thakrar DS et al. Scintigraphic imaging of breast cancer: Review Nucl Med Commun 1997; 18: 698–709.
8. Taillefer R, Robidoux A, Lambert R, et al. Tc-99m MIBI prone scintimammography to detect primary breast cancer and axillary lymph node involvement. J Nucl Med 1995; 36: 1758–1765.

9. Cwikla JB, Buscombe JR, Parbhoo SP et al. Use of ^{99m}Tc-MIBI in the assessment of patients with suspected recurrent breast cancer. Nucl Med Commun 1998; 19: 649–655.
10. Lu G, Shih WJ, Huang HY, et al. ^{99m}Tc-MIBI mammoscintigraphy of breast masses: Early and delayed imaging. Nucl Med Commun 1995; 16: 150–156.
11. Cwikla JB, Buscombe JR, Barlow RV et al. The effect of chemotherapy on the uptake of technetium-99m sestamibi in breast cancer. Eur J Nucl Med 1997; 24: 1175–1178.
12. Khalkhali I, Villanueva-Meyer J, Edel SL et al. Diagnostic accuracy of ^{99m}Tc-MIBI breast imaging in breast cancer detection. J Nucl Med 1996; 7: 74 (Abstract).
13. Rambaldi PF, Mansi L, Procaccini E et al. Breast cancer detection with Tc-99m tetrofosmin. Clin Nucl Med 1995; 20: 703–705.
14. Adalet I, Demirkol MO, Muslumanoglu M et al. ^{99m}Tc-tetrofosmin scintigraphy in the evaluation of palpable breast masses. Nucl Med Commun 1997; 18: 118–121.
15. Schillaci O, Scopinaro F, Danieli R et al. Technetium-99m-tetrofosmin scintimammography in patients with suspicion of breast cancer. J Nucl Med 1996; 37: 255P (Abstract).
16. Palmedo H. Grunwald F, Bender H et al. Scintimammography with technetium-99m methoxyiso-butylisonitrile: comparison with mammography and magnetic resonance imaging. Eur J Nucl Med 1996; 23: 940–946.
17. Batista JF, Solano ME, Oliva JP et al. Usefulness of ^{99m}Tc-tetrofosmin scintimammography in palpable breast tumours. Nucl Med Commun 1997; 18: 338–340.
18. Costa A, Zurrida S. The future of breast cancer surgery. Oncology in Practice 1998; 3: 8–10.
19. Schneebaum S, Even-Sapir E, Cohen M et al. Clinical applications of gamma-detection probes-radioguided surgery. Eur J Nucl Med 1999, 26 (suppl): S26–S35.
20. Paganelli G. Sentinel node biopsy: role of nuclear medicine in conservative surgery of breast cancer. Eur J Nucl Med 1998; 25: 99–100.
21. Giuliano AE, Dale PS, Turner RR et al. Improved axillary staging of breast cancer with sentinel lymphadenectomy. Ann Surg 1995; 222: 394–401.
22. Van der Wall E. The sentinel node in breast cancer: implications for adjuvant treatment? Eur J Nucl Med 1999; 26: S17–S19.
23. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomized trials. Lancet 1998; 352: 930–942.
24. Palmedo H, Bender H, Grunwald F et al. Comparison of fluorine-18 flyorodeoxyglucose positron emission tomography and technetium-99m metho-xyisobutylisonitrile scintimammography in the detection of breast tumours. Eur J Nucl Med 1997; 24: 1138–1145.
25. Powe JE. Positron emission tomography (PET) scanning in breast cancer. Brit J Radiol 1997; 70: 668–670.
26. Chiti A, Agresti R, Maffioli L et al. Breast cancer staging using technetium-99m sestamibi and indium-111 pentetreotide single-photon emission tomography. Eur J Nucl Med 1997; 24: 192–196.
27. Lewanski CR, Kaplan GR, Potter J et al. Bone marrow involvement in breast cancer detected by positron emission tomography. J R Soc Med 1999; 92: 193–195.
28. Vural G, Unlu M, Atasever T et al. Comparison of indium-111 octreotide and thallium-201 scintigraphy in patients mammographically suspected of having breast cancer: preliminary results. Eur J Nucl Med 1997; 24: 312–315.
29. Tiling R, Khalkhali I, Sommer H et al. Limited value of scintimammography and contrast-enhanced MRI in the evaluation of microcalcification detected by mammography. Nucl Med Commun 1998; 19: 55–62.
30. Liu PF, Debatin JF, Caduff RF et al. Improved diagnostic accuracy in dynamic contrast enhanced MRI of the breast by combined quantitative and qualitative analysis. Brit J Radiol 1998; 71: 501–509.
31. 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.
32. Cwikla JB, Buscombe JR, Holloway B et al. Can scintimammography with ^{99m}Tc-MIBI identify multifocal and multicentric breast cancer? Nucl Med Commun 2001; 22: 1287–1293.
33. Ell PJ, Keeping abreast of time. Editorial. Eur J Nucl Med 1995; 22: 967–969.
34. Gulec SA, Serafini AN, Sfakianakis GN et al. CEA-scan in diagnosis and staging of breast cancer. J Nucl Med 1996; 37: 238P (Abstract).
35. Abdel-Nabi A, Rosner D, Erb D, et al. Evaluation of suspicious mammographic findings with CEA-scanTM and correlation with histopathological results. J Nucl Med 1996; 37: 238P (Abstract).
36. Burch A, Goodman DA. A pilot survey of radiation doses received in the United Kingdom Breast screening programme. Br J Radiol 1998; 71: 517–527.
37. Johnston RE, Muklerji SK, Perry R, et al. Radiation dose from breastfeeding following administration of thallium-201. J Nucl Med 1996; 37: 2079–2082.
38. Cremonesi M, Ferrari M, Sacco E et al. Radiation protection in radioguided surgery of breast cancer. Nucl Med Commun 1999; 20: 919–924.
39. International Commission on Radiological Protection. 1990. Recommendations of the International Commission on Radiological Protection. ICRP Publication 60. New York: Pergamon Press, 1991.
40. Gakis D. The radioimmunoassays *in vitro* and the main applications of tumour markers. Hell J Nucl Med 1998; 1: 21–29.
41. Mangkharak J, Patanachak C, Padhisuwan K et al. The evaluation of combined scintimammography and tumor markers in breast cancer patients. Anticancer Res 1997; 17 (3B): 1611–1614.
42. Barrenetxea G, Schneider J, Lliorente MF et al. Use of serum tumor markers for the diagnosis and follow-up of breast cancer. J Postgrad Med 1996; 42 (3): 68–71.
43. J Ritzke C, Stieber P, Untch M et al. Alkaline phosphatase isoenzymed in detection and follow up of breast cancer metastases. Anticancer Res 1998; 18 (2B): 1243–1249.
44. Keshtgar MRS, Waddington WA, Lakhani SR et al. The Sentinel Node in Surgical Oncology. Springer, Berlin 1999.