

SCINTIMAMMOGRAPHY WITH ^{99m}Tc SESTAMIBI IN BREAST CANCER

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Summary. Physical breast examination and mammography are currently the most recognized and most frequently used screening tools for detection of breast cancer. Breast mammography has some limitations. Scintimammography using ^{99m}Tc sestamibi has been shown to have the potential to reduce the number of false negative mammography findings and also has a comparable diagnostic accuracy in patients with radiologically dense breasts and those with non-dense breasts. The aim of this study was to investigate the contribution of scintimammography with ^{99m}Tc sestamibi in the diagnosis of breast cancer. Fortytwo women (median age 46 years, range 21-78 years) with clinical and/or mammographic and/or cytological suspicion of breast cancer were investigated. All of them underwent clinical investigation, ultrasonography, mammography, and level of tumor markers - CA15.3 and CEA, fine needle aspiration cytology (FNA) and scintimammography before the surgery. The final diagnosis was determined by histopathological examination. A dose of 740 MBq of ^{99m}Tc sestamibi for scintimammography was injected into a foot vein. Imaging was performed 10 minutes after injection. The results of scintimammography were compared with histopathology. The histopathological findings were malignant in 33 (78.6%) and benign in 9 (21.4%) cases. Scintimammography showed true positive findings in 31 (73.8%) cases with breast cancer. Scintimammography was negative in 2 cases with breast cancer (1 - invasive ductal carcinoma, 2 - invasive lobular carcinoma). True negative findings with no focally increased uptake were found in 8 (88.9%) cases with benign conditions. Scintimammography was suspicious for malignancy in 1 (11.1%) case with benign lesions (pathohistology - fibroadenoma). The diagnostic positive predictive value, negative predictive value, sensitivity specificity and accuracy of ^{99m}Tc sestamibi scintimammography were 93.9%, 80%, 93.9%, 88.9 and 92.9%, respectively. ^{99m}Tc sestamibi imaging had high sensitivity and accuracy in the diagnosis of breast cancer. It could provide reliable information in confirming the diagnosis in patients with clinically suspected breast cancer.

Key words: Scintimammography, sestamibi, breast cancer

Introduction

It is already known that breast cancer is the most common malignancy in women (1). Out of the total number of female patients in our hospital, suffering from cancer during the period 1993-2000, 20.5% were related to breast cancer. During this period the total number of breast cancer patients increased by 9.9% at the end of the period observed (2). The incidence of breast cancer is increasing. In the last three years, approximately 400 new cases of breast cancer each year have been registered in our hospital (covering the region with 800,000 inhabitants). Early detection of breast cancer lowers mortality and prolongs life expectancy.

Physical breast examination and mammography are currently the most recognized and the most frequently used screening tools for detection of breast cancer. These methods have been proved successful for early detection of breast cancer (1). Breast mammography has some limitations, especially in women with dense breast tissue, or in those who underwent partial mastectomy

and post-surgical scars are present, or in those who underwent radiotherapy or chemotherapy. Considering the 85% sensitivity associated with combined mammography and physical examination and low positive predictive value of 20-30% for diagnoses of breast cancer, there is a critical need for the use of other complementary imaging procedures such as scintimammography (3). The aim of this study was to investigate the contribution of scintimammography with ^{99m}Tc sestamibi to the diagnosis of breast cancer.

Patients and Methods

The study population consisted of 42 women (5 with non-palpable and 37 with palpable breast lesions), who were referred to our Department with clinical and/or mammographic and/or cytological suspicion for breast cancer. The median age of the patients was 46 years, range 21-78 years. Before inclusion in the study each patient underwent a physical breast examination, mam-

mography, ultrasonography of breasts, level of tumor markers - CA15.3 and CEA, fine needle aspiration cytology (FNA). The inclusion criterion was a non-pregnant woman with suspicious lesions for breast cancer.

The final diagnosis was determined by histopathological examination.

Scintimammography

Scintimammography was performed using one-head gamma camera equipped with a high-resolution collimator. The energy pick was centered at 140 KeV with a 10% window. Images were acquired on matrix 128x128. Each image was acquired for 10 minutes and 3 minutes with a marker. The distance between the breast and the detector was kept minimal.

A dose of 740 MBq of ^{99m}Tc sestamibi was injected into a foot vein followed by 10ml saline flush. The patient was placed in a prone position on an imaging couch designed in our Department that allowed the breast to be freely dependent of the imaging couch and with lead between breasts. Prone imaging of a single dependent breast provided maximum separation of the breast tissue from the chest wall, myocardium and liver, as well as elimination of the risk of inadvertently superimposing the image of the opposition breast.

Imaging was performed 10 minutes after injection beginning with the affected breast. Lateral views of breasts and axillae were acquired with the patient lying prone. Anterior view of the breasts and both axillae was performed with a patient in supine position with her arms raised behind her head. Delay scintigraphy in prone position (lateral view) was done 60 minutes after injection.

Two independent, experienced nuclear medicine physicians analyzed all scintimammograms. Focal accumulation of sestamibi uptake in the breast on early and delay scintigrams was interpreted to represent malignancy.

All patients underwent surgical treatment. The results of scintimammography were compared with histopathology.

Statistical analysis

Sensitivity was defined as true positives (TP)/TP+false negatives (FN), specificity as true negative (TN)/TN+false positive (FP), positive predictive values (PPV) as TP/(TP+FP), negative predicative values (NPV) as TN/(TN+FN), and accuracy as (TN+FP)/overall patients.

Results

Table 1 summarizes the ^{99m}Tc sestamibi scintimammography results and histopathological diagnoses of 42 patients. The histopathological findings were malignant in 33 (78.6%) cases and benign in 8 (21.4%) cases. The median histopathological tumour size was 22mm (range from 8mm to 38mm) in all the cases.

Scintimammography was positive in 32 cases (76.2%), and negative in 10 cases (23.8%). There were 31 true-positive results (73.8%), with histopathological

diagnoses positive for malignancy. Among all lesions with true-positive results confirmed on pathohistology findings, scintimammography demonstrated focal areas of increased ^{99m}Tc uptake that corresponded to breast carcinoma (Figure 1). Scintimammography suggested malignancy in 21 (95.5%) cases with invasive ductal carcinoma, in 3 (75%) cases with invasive lobular carcinoma, in all cases - 2 with ductal carcinoma in situ, and in all cases - 5 with mixtae carcinoma.

Table 1. Histopathological findings and findings of ^{99m}Tc scintimammography

Histopathological findings	Number	Scintimammography	
		Positive	Negative
Malignant findings	33	31	2
Invasive ductal carcinoma	22	21	1
Invasive lobular carcinoma	4	3	1
Ductal carcinoma <i>in situ</i>	2	2	0
Carcinoma mixtae	5	5	0
Benign findings	9	1	8
Fibroadenoma	5	1	4
Fibrocystic mastopathy	2	0	2
Benign phyllodes tumor	1	0	1
Sclerosing adenosis	1	0	1

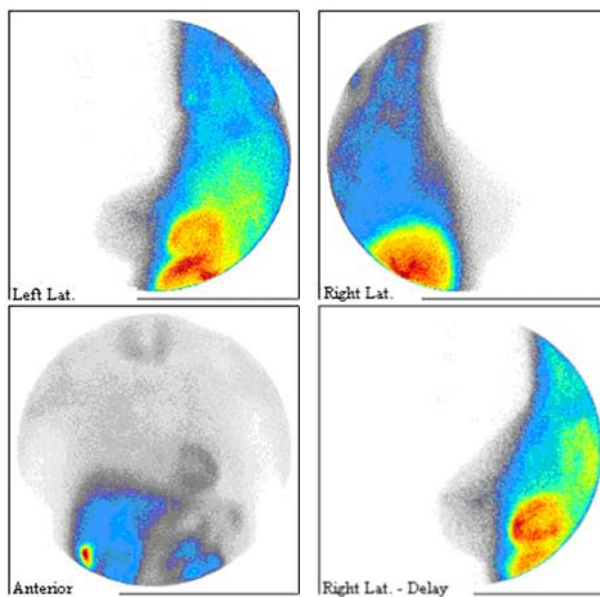


Fig. 1. ^{99m}Tc scintimammography in malignant breast lesion

True-negative results were found in 8 patients (88.9%). In this group, scintimammography were with no focally increased uptake (Figure 2). Histopathological exam was negative for malignancy in all cases.

There were 2 false negative results – scintimammograms without focal areas of increased uptake that suggested benign lesions with histopathological findings positive for malignancy. Of these 2 lesions one was invasive ductal carcinoma and the other was invasive lobular carcinoma. One false positive result was also found (11.1%). Despite a focal area of increased uptake on scintimammogram, the histopathological diagnosis was fibroadenoma.

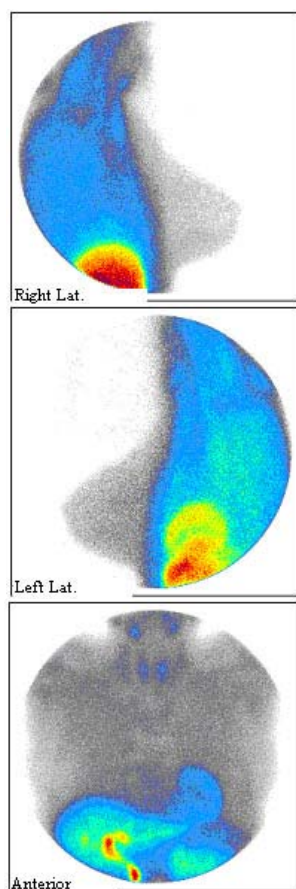


Fig. 2. ^{99m}Tc sestamibi scintimammography in benign breast lesion

The results in this group indicate a sensitivity of 93.9%, a specificity of 88.9%, a positive predictive value of 93.9%, a negative predictive value of 80%, and an accuracy of 92.9% for ^{99m}Tc sestamibi scintimammography used in detecting breast cancer.

Discussion

Detection of breast carcinoma and avoiding unnecessary operative biopsies of benign lesions are the main challenges in the diagnosis of breast lesions. The diagnostic work-up of patients with breast lesions should be performed using the triple assessment consisting of physical examination, mammography, ultrasonography and needle biopsy (fine needle aspiration biopsy or core biopsy) that has been reported to have excellent sensitivity and specificity (4). But each of these techniques has some limitation. Mammography is currently the "gold standard" for the detection and diagnosis of breast cancer. Unfortunately, the sensitivity and specificity of mammography are limited, especially in younger and premenopausal patients. Scintimammography using ^{99m}Tc sestamibi is being established as a second line diagnostic test for the detection of breast cancer in patients with suspected lesions in the breast (5, 6). Taillefer in a meta-analysis of the literature showed that the sensitivity and specificity of scintimammography ranged between 83%

and 95%, and 77% and 96%, respectively (7). The current sensitivity and specificity rates for scintimammography with ^{99m}Tc sestamibi depend on a number of factors, including lesion size and site. Scintimammography shows an excellent sensitivity and specificity in cases with palpable breast lesions, as demonstrated in our findings, as well as in other studies (1, 7, 8).

Khalkhali et al. in multicentre trials enrolled 673 women, and demonstrated that ^{99m}Tc sestamibi breast imaging can make a significant contribution to the diagnosis of breast cancer. A low sensitivity of scintimammography was observed in nonpalpable lesions less than 1cm in size. The sensitivity of scintimammography appeared not to be affected by age but by size of lesions (9). Lumahl et al. showed that the sensitivity of scintimammography was strictly related to the size of the lesions, reaching 100% in patients with breast cancer of 8mm or more (10). In our study all 5 cases with nonpalpable invasive ductal carcinoma were positive on scintimammography. The reason for this may be the small number of patients and the size of lesions – two lesions were under 1cm (8mm and 9mm) and three lesions were above 1cm (11mm and two times 12mm).

Scintimammography was positive in two cases with ductal carcinoma *in situ*. In both cases mammography showed only microcalcifications and ultrasonography showed mild hypoechogenic nodules. Microcalcification without density or mass is a common finding in mammography in ductal carcinoma *in situ*. Cwikla et al. in a series of 15 patients with ductal carcinoma *in situ* showed scintimammography encouraging results with 80% sensitivity (11). Therefore, scintimammography has the role in the diagnosis of ductal carcinoma *in situ*.

In our study scintimammography was false negative in one case with invasive lobular carcinoma and in one case with invasive ductal carcinoma. In both cases the lesions were palpable, located in the medial part of the breast, which is further away from a detector. These patients had fairly large breasts and the size of lesions was 13mm and 15mm. The false negative findings in scintimammography were rare in invasive ductal carcinoma (one case, 4.5%) compared to invasive lobular carcinoma (25% false negative rate). False negative results in invasive lobular carcinoma have also been reported in some other series (1). The diagnosis of invasive lobular carcinoma is not always easy by mammography or FNA, which both often result in indeterminate or benign findings. Therefore, it is reasonable to believe that location, size and histological structure of these lesions may explain the false negative results.

Maunda et al. have shown that in regions with high incidence of benign breast disease scintimammography with ^{99m}Tc sestamibi is a valuable technique for screening to evaluate compared to mammography and having very high inter-observer agreement. (8). In fibroadenoma, the finding in mammography is often typical but may be confused with invasive lobular carcinoma often presenting with a density without a speculated outline. The cytodiagnosis of fibroadenoma is sometimes difficult,

and suspicious or atypical findings are not rare. In the present study, scintimammography showed false positive results in one case (11.1%) of fibroadenoma, but we had a small number of benign lesions in the breast. Other authors also reported positive scintimammography findings in fibroadenoma (1,4) Increased ^{99m}Tc sestamibi uptake has been reported in "metabolically active cells" of an in-vivo cell-line culture of normal tissue (12). The histological results suggested that the "hypercellularity" of a breast lesion with or without atypia could accumulate ^{99m}Tc sestamibi, which results in false positive findings.

The 88.9% specificity and 80% negative predictive value observed in the present study are somewhat lower than those obtained in previous studies (1). A small number of benign lesions in the breast result in low

NPV and low specificity. The reason for this is selection of patients.

Another potential application of ^{99m}Tc sestamibi scintimammography is the detection of axillary lymph-node involvement in a patient with known primary breast cancer (13). Scintimammography with ^{99m}Tc sestamibi has also been used in a study to monitor the response of locally advanced breast cancer to neoadjuvant therapy (14).

Conclusion

^{99m}Tc sestamibi imaging had high sensitivity and accuracy in the diagnosis of breast cancer. It could provide reliable information in confirming the diagnosis in patients with clinically suspected breast cancer.

References

1. Tiling R, Linke R, Kesler M, Unth M, Sommer H, Brinkbaumer K, Becker I, Hohn K. Scintimammography using ^{99m}Tc sestamibi – use and limitations. *Nuklearmedizin* 2002; 41:148-156.
2. Jungić S, Jakovljević B, Rakita I, Vranjes Z, Kecman G, Jotanović G. Malignant disease in Clinical Center Banja Luka in the period 1993-2000. II Congress of War Medicine 2001.
3. Buscombe J, Hill J, Parbhoo S. Scintimammography, a guide to good practice. Gibbs Associates Limited 1998.
4. Leidenius MHK, Leppanen EA, Tykka HT, von Smitten KAJ. The role of ^{99m}Tc sestamibi scintimammography in combination with the triple assessment of primary breast cancer. *EJSO* 2002; 28: 108-112.
5. Prats E, Bazo J, Meroa J, herranz R, carril J. ^{99m}Tc MIBI scintimammography as a complement of the mammography in patients with suspected breast cancer. A multicentre experience. *Breast* 2001; 10:109-116.
6. Alonso O, Massardo T, Delgado LB, Horvath J, Kabasakal L, Llams-Olier A et al. Is ^{99m}Tc sestamibi scintimammography complementary to conventional mammography for detecting breast cancer in patients with palpable masses? *J Nucl Med* 2001; 42:1614-1621.
7. Taillefer R. The role of ^{99m}Tc sestamibi and other conventional radiopharmaceuticals in breast diagnosis. *Semin Nucl Med* 1999; 29:16-40.
8. Maunda KY, Chande H, Mselle TFA, Bomanji JB. ^{99m}Tc sestamibi scintimammography in the diagnosis of palpable breast masses. *Nucl Med Commun* 2003; 24:141-144.
9. Khalkhali I, Villanueva-Mayer J, Edelli SL, et al. Diagnostic accuracy of ^{99m}Tc sestamibi breast imaging: multicentre trial results. *J Nucl Med* 2000; 41:1973-1979.
10. Lumachi F, Zucchetto P, Marzola MC, Ferretti G, Povolato M, Paris MK, Brandes AA, Bui F. Positive predictive value of ^{99m}Tc sestamibi scintimammography in patients with non-palpable, mammographically detected, suspicious, breast lesions. *Nucl Med Commun* 2002; 23:1073-1078.
11. Cwika JB, Buscombe JR, Parbhoo SP, T. Davidson, B. Holloway A.J.W. Hilson. Detection of DCIS using ^{99m}Tc MIBI scintimammography. *Eur J Cancer* 2000; 36 (suppl 5): A126.
12. Maublant JC, Zhang Z, Rapp M. In vitro uptake of ^{99m}Tc tetroxine in carcinoma cell lines and normal cell lines: Comparison with ^{99m}Tc sestamibi and ^{201}Tl thallium. *J Nucl Med* 1993; 34:1949-1952.
13. Arslan N, Ozutka E, Ilgan S ar at. ^{99m}Tc 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.
14. Buscombe JR. Monitoring therapy in breast cancer. *Nucl Med Commun* 2002; 23:619-624.

SCINTIMAMOGRAFIJA ^{99m}Tc SESTAMIBIJEM KOD KARCINOMA DOJKE

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Kratak sadržaj: Najčešće korištene i poznate skrining metode za otkrivanje karcinoma dojke danas su klinički pregled dojki i mamografija. Mamografija ima izvjesna ograničenja. Utvrđeno je da scintimamografija sa ^{99m}Tc sestamibijem ima mogućnosti da smanji broj lažno negativnih nalaza mamografije kao i da ima istu dijagnostičku tačnost kod bolesnica sa mamografski detektovanim veoma gustim dojkama kao i kod onih kod kojih dojke na mamografiji nisu guste. Cilj ove studije je da utvrdi doprinos scintimamografije sa ^{99m}Tc sestamibijem u dijagnostici karcinoma dojke. U studiju su uključene četrdest dve (42) žene (srednje životne dobi od 46 godina, starosti 21-78 godina) sa kliničkom i/ili mamografskom i/ili citološkom sumnjom da imaju karcinom dojke. Sve one su podvrgnute kliničkom pregledu, ehotomografiji dojki, mamografiji, određivanju vrijednosti tumor markera—CA 15.3 i CEA, punkciji čvora u dojci i

scintimamografiji prije upućivanja na operativni zahvat. Konačna dijagnoza je postavljena histopatološkim pregledom. Doza od 740 MBq ^{99m}Tc sestamibija za scintimamografiju je inicirana u venu na stopalu. Slikanje je započeto 10 minuta nakon injiciranja. Rezultati scintimamografije su upoređivani sa histopatološkim nalazom.

Histopatološki nalaz je pokazao malignu leziju u 33 (78,6%) i benignu u 9 (21,4%) slučajeva. Scintimamografija je bila tačno pozitivna u 31 (73,8%) slučaju karcinoma dojke. Scintimamografija je bila negativna u 2 slučaja karcinoma dojke (1-invazivni duktalni karcinom i 2-invazivni lobularni karcinom). Tačno negativan nalaz karakteriziran izostankom lokaliziranog nakupljanja radiofarmaka u dojci je nađen u 8 (88,9%) slučajeva sa benignom lezijom. Scintimamografija je pokazala sumnju na malignitet u 1 (11,1%) slučaju benigne lezije (patohistološki nalaz-fibroadenom). Pozitivna prediktivna vrijednost, negativna prediktivna vrijednost, senzitivnost, specifičnost i tačnost ^{99m}Tc sestamibi scintimamografije je bila 93,9%, 80%, 93,9%, 88,9% i 92,9%.

^{99m}Tc sestamibi scintimamografija ima veliku senzitivnost i tačnost u dijagnostici karcinoma dojke. Ona može obezbjediti pouzdane podatke u potvrđivanju dijagnoze kod bolesnika sa kliničkom sumnjom na karcinom dojke.

Ključne reči: Scintimamografija, sestamibi, karcinom dojke