



## The application of SPECT/CT scintigraphy with MIBI-Tc<sup>99m</sup> in the diagnosis of thyroid nodules — a preliminary report

Zastosowanie badania SPECT/CT z MIBI-Tc<sup>99m</sup> w diagnostyce zmian guzkowych w tarczycy — doniesienie wstępne

**Maria H. Listewnik<sup>1</sup>, Bożena Birkenfeld<sup>1</sup>, Hanna Piwowarska-Bilska<sup>1</sup>, Katarzyna Cichoń-Bańkowska<sup>1</sup>, Lidia Iglińska-Wagner<sup>2</sup>, Wanda Watrak<sup>4</sup>, Wiesława Smolira<sup>3</sup>, Piotr Zorga<sup>1</sup>, Krystyna Niedziałkowska<sup>1</sup>, Bogumiła Elbl<sup>1</sup>, Marek Sawrymowicz<sup>1</sup>**

<sup>1</sup>Department of Nuclear Medicine, Pomeranian Medical University, Szczecin, Poland

<sup>2</sup>Harbour Independent Public Health Care Institution, Out-patients Thyroid Clinic, Szczecin, Poland

<sup>3</sup>Non-Public Health Care Institution „Smol-Med”, Stargard Szczeciński, Poland

<sup>4</sup>Independent Public Integrated Voivodeship Hospital, Out-patients Thyroid Clinic, Szczecin, Poland

### Abstract

**Introduction:** Thyroid cancer diagnosis is based mainly on fine needle aspiration biopsy (FNAB) performed under ultrasonography guidance. Questions arise in cases of an inconclusive FNAB result — when there is no clear evidential data to support the existence of a malignant lesion or when there are any other reasons which make the decision process difficult, such as the patient's age or coexisting diseases. To clarify this issue the patient should be encouraged to undergo surgery treatment or to be followed up. Thyroid scintigraphy with an oncophilic tracer such as MIBI-Tc<sup>99m</sup> may be helpful.

**Material and methods:** The study comprised a group of 12 patients, aged 54–75 (av. 63.5) years, who, in 2009, underwent planar and SPECT/CT thyroid scintigraphy with MIBI-Tc<sup>99m</sup> using washout method. The tumour/background ratio in early and delayed images was calculated and the wash-out ratio was estimated. Patients with increased focal lesion uptake were operated on and the lesions were histopathologically verified.

**Results:** Abnormal scintigraphy results were obtained in 8 patients (10 lesions) and normal results in 4 patients (5 lesions). Out of 15 studies, in 13 cases the washout from the lesion was observed within 2 hours. It was noticed that the images obtained with SPECT/CT washout method were clearer and easier to read in comparison to planar studies.

Three patients with an abnormal results underwent surgery and had benign histopathology results after the operation, in 3 patients the observation is being confirmed without any increase in malignancy suspicions, and 2 were lost for observation.

**Conclusions:** Our preliminary results do support the use of MIBI-Tc<sup>99m</sup> in the evaluation of indeterminate thyroid nodules. To validate the hypothesis that MIBI-Tc<sup>99m</sup> may be used to exclude malignancy in lesions indeterminate by FNAB we propose to use SPECT-CT derived images and standardized evaluation criteria. (*Pol J Endocrinol* 2010; 61 (5): 422–426)

**Key words:** Technetium-99m-sestamibi, thyroid nodules, SPECT/CT

### Streszczenie

**Wstęp:** Niediagnostyczne badania cytologiczne (FNAB, *fine needle aspiration biopsy*) guzków tarczycy lub inne przyczyny utrudniające podjęcie decyzji o leczeniu operacyjnym tarczycy, takie jak wiek pacjenta lub zawansowanie choroby towarzyszące, stanowią poważną przyczynę w ostatecznym wyborze postępowania, szczególnie jeżeli nie ma jednoznacznych danych wskazujących na obecność zmiany nowotworowej. Dodatkowym sposobem wyjaśnienia charakteru zmiany jest badanie radioizotopowe z MIBI-Tc<sup>99m</sup>. Gromadzenie MIBI jest interpretowane jako sygnał zwiększający ryzyko złośliwości, zwłaszcza gdy utrzymuje się przez dłuższy czas. W pracy postanowiono ocenić przydatność badania scyntygraficznego SPECT/CT z MIBI-Tc<sup>99m</sup> metodą wymywania w relacji do wyników badania histopatologicznego.

**Material i metody:** W 2009 roku wykonano u 12 chorych w wieku 54–75 (śr. 63,5) lat badania scyntygraficzne tarczycy planarne oraz SPECT/CT z MIBI-Tc<sup>99m</sup>, poprzedzone o badanie wymywania. Wyliczono wskaźniki wymywania i wskaźniki guz/tło w obrazach wczesnych i późnych. Chorzy ze wzmożonym wychwytem znacznika byli operowani i badani histopatologicznie.

**Wyniki:** Wzmożone gromadzenie MIBI-Tc<sup>99m</sup> obserwowano u 8 pacjentów (10 zmian), a brak gromadzenia (prawidłowy wynik) u 4 (5 zmian). Na 15 badań w 13 przypadkach zaobserwowano wymywanie się radiofarmaceutyku ze zmiany, które sugeruje łagodny charakter zmiany. Operowano trzech chorych ze zmianami gromadzącymi MIBI-Tc<sup>99m</sup> w badaniu scyntygraficznym, niemniej wynik badania histopatologicznego był we wszystkich przypadkach prawidłowy. Zaobserwowano, że interpretacja obrazów tarczycy SPECT/CT z MIBI-Tc<sup>99m</sup> uzyskiwanych metodą wymywania jest łatwiejsza i czytelniejsza niż w badaniu planarnym. U 3 z pozostałych 5 chorych dane kliniczne nie zwiększają obecnie podejrzania raka, u 2 nie kontynuowano obserwacji.

**Wnioski:** Ocena scyntygraficzna tarczycy wykonywana z zastosowaniem SPECT/CT z MIBI-Tc<sup>99m</sup> metodą wymywania może być pomocna w diagnostyce różnicowej guzków tarczycy. (*Endokrynol Pol* 2010; 61 (5): 422–426)

**Słowa kluczowe:** Sestamibi znakowane technetem 99, guzki tarczycy, SPECT/CT



Maria. H. Listewnik M.D., Department of Nuclear Medicine, Pomeranian Medical University, 71-252 Szczecin, Unii Lubelskiej St. 1, tel.: +48 91 425 34 48, fax: +48 91 425 34 43, e-mail: marlist@fiber.net.pl

## Introduction

Thyroid cancer diagnosis is based mainly on fine needle aspiration biopsy (FNAB) performed under ultrasonography guidance [1]. In cases of an inconclusive FNAB result, when there is no clear evidential data to support the existence of a malignant lesion, or due to any other reasons such as the patient's age or coexisting diseases, which make the decision process difficult, the question arises whether the patient should be followed up or should be encouraged to undergo surgery treatment.

The utility of nuclear medicine techniques in resolving these questions seems to be underestimated by endocrinology departments in Poland. Obviously the most common form of imaging modality is ultrasonography examination, which is mostly employed in diagnosis and therapeutic decisions in patients with nontoxic nodular goiter. Sometimes, however, conventional thyroid gland scintigraphy is used when endocrinologists and nuclear medicine specialists look for possible hyperfunctioning nodules which exhibit diminished malignancy risk [2]. Additional methods, such as scintigraphy with MIBI-Tc<sup>99m</sup>, are rarely used in everyday practice. This oncophilic tracer is mainly used in previously diagnosed thyroid malignancy but not in cases of benign thyroid goiter [3–11].

Recent publications which highlight the usefulness of MIBI-Tc<sup>99m</sup> in the decision process and the emergence of new hybrid equipment encouraged us to conduct the study [12, 13] to raise the question of whether MIBI-Tc<sup>99</sup> might be the useful in future in differential diagnosis of thyroid nodules. First, we wanted to evaluate the delayed SPECT images.

## Material and methods

Three specialists trained in endocrinology referred patients, in whom indications for thyroid surgery were not clear, to our nuclear medicine department. These included patients with non-diagnostic or inconclusive FNAB, advanced age, the presence of concomitant disorders, the presence of many nodules, or patients who were reluctant to undergo surgery as a method of treatment.

The study comprised 12 patients (14 F, 1 M) aged an average of 63.5 (54–75) years. Nine of them suffered from nodular goiter, two had Hashimoto thyroiditis and one had toxic nodular goiter. In all patients, an ultrasonography examination and a subsequent FNAB was performed in 2009. All had normal thyroid function, and one patient was treated with antithyroid drugs due to a toxic nodular goiter. Two suffered from recurrent goiter and had had previous subtotal thyroidectomy. FNAB in seven cases was normal, in two cases it revealed follicular tumour, non-diagnostic results were obtained in

two cases, and suspicious cells in one case. The relative contraindications to surgery were: advanced age, lung cancer in one case, arterial hypertension in two cases, and diabetes in one case. Two patients had diagnosed rheumatoid arthritis (one with systemic lupus erythematosus). In ultrasonography examination, lesion diameter was usually more than 10 mm (the biggest lesion diameter was 19 mm). There were many nodules present in five cases, three patients had microcalcifications on sonography, in two patients there was a palpable lymph node, and one patient had a "cold" nodule in scintigraphy. Ten out of twelve refused surgery as the treatment method.

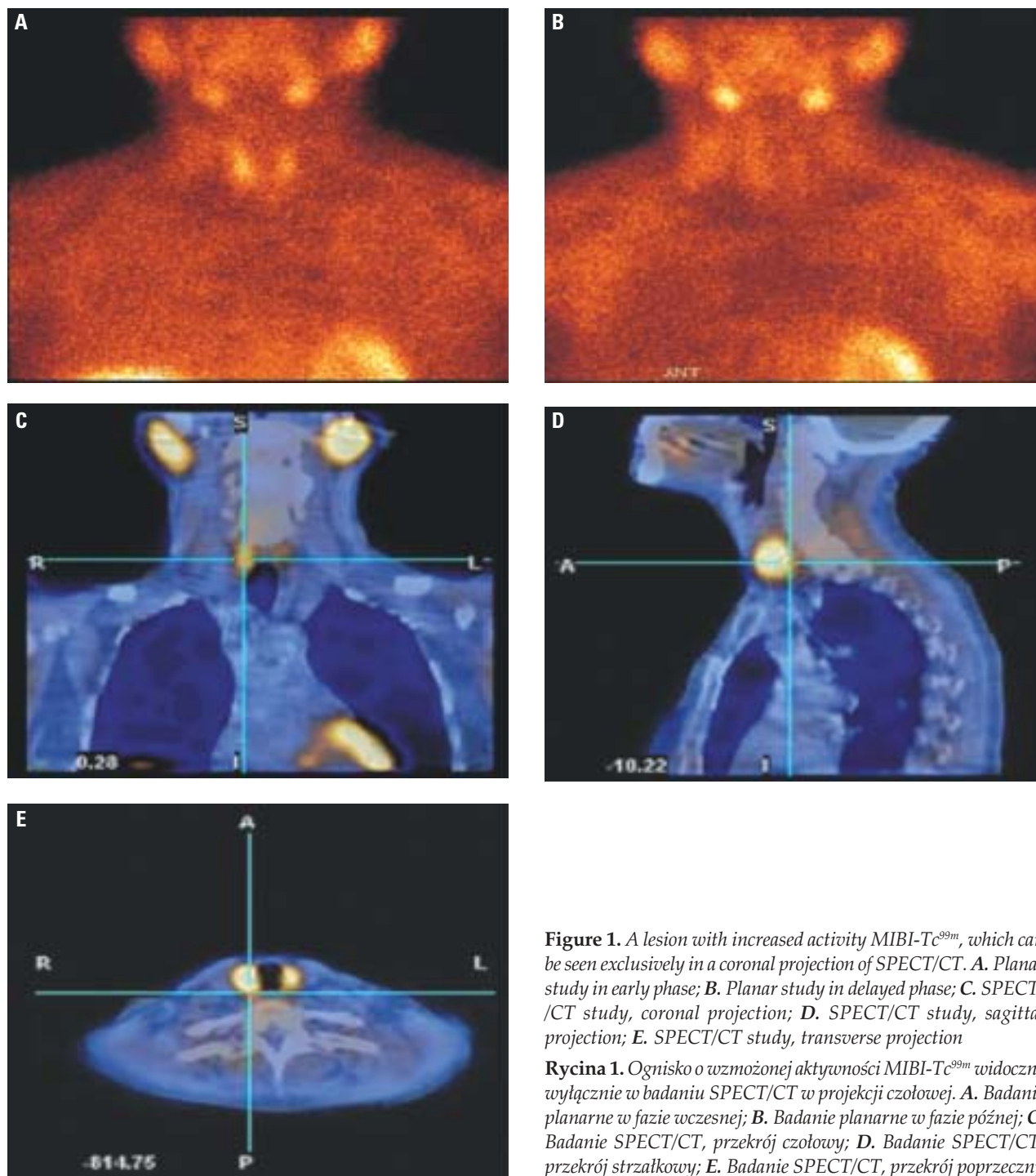
### Acquisition protocol

The patients were given an intravenous injection of 700–800MBq MIBI (Hexakis 2-Methoxy Isobutyl Isonitrile) labelled with Tc<sup>99m</sup>. Five minutes later, planar and then SPECT/CT acquisition was performed with a SPECT/CT gamma camera Infinia Hawkeye 4 with Xeleris clinical software. The patient was in the supine position with her/his arm down during two phases of the study. Two hours after the tracer injection, the same procedure was repeated as a delayed phase. During the two hours between both acquisitions the patient was encouraged to drink fluids to clear the background.

The lesion with focally increased activity in scintigraphy was processed. The region of interest (ROI) was manually drawn on the lesion (T). Then, the selected region was projected and pasted to the background (B), situated outside of the thyroid in early and delayed studies for every patient. Subsequently, average ROI counts on the lesion in the early phase were divided by average ROI counts on the background in 10 minutes (tumour to background ratio in 10 minutes-TBR10). Analogically, the same procedure was repeated in a delayed study (tumour to background ratio in 120 minutes-TBR120). Washout was calculated as a ratio (T10-T120dc)/T10 where dc means decay correction exponential.

The protocol used for the planar study was as follows: matrix 256 × 256, zoom 2 with anterior view of the neck, time acquisition as needed to acquire 700,000 counts. The protocol used for the SPECT study was as follows: matrix 128 × 128, 20 sec/projection, zoom 2, tomo mode H. Immediately after SPECT acquisition, the CT scans (140 kV, 2.5 mA) were acquired.

As well as the nuclear medicine study, an ultrasonography examination was performed for correlation with scintigraphic findings. Patient documentation was collected and analyzed and the patients were encouraged to contact the department. Patients with increased focal lesion uptake were referred to surgery if possible or continued further follow-up.



**Figure 1.** A lesion with increased activity MIBI-Tc<sup>99m</sup>, which can be seen exclusively in a coronal projection of SPECT/CT. **A.** Planar study in early phase; **B.** Planar study in delayed phase; **C.** SPECT/CT study, coronal projection; **D.** SPECT/CT study, sagittal projection; **E.** SPECT/CT study, transverse projection

**Rycina 1.** Ognisko o wzmożonej aktywności MIBI-Tc<sup>99m</sup> widoczne wyłącznie w badaniu SPECT/CT w projekcji czołowej. **A.** Badanie planarne w fazie wczesnej; **B.** Badanie planarne w fazie późnej; **C.** Badanie SPECT/CT, przekrój czołowy; **D.** Badanie SPECT/CT, przekrój strzałkowy; **E.** Badanie SPECT/CT, przekrój poprzeczny

## Results

Positive results (increased tracer uptake) in thyroid lesions were obtained in 8 patients, (10 lesions) and negative results (normal uptake), which suggested a diagnosis of benign lesion, in 4 patients (5 lesions). TBR10 varied from 2.07 to 3.14; TBR120 was found to be 0.37–15.42.

Washout ratios in two cases were below zero, which means that the activity in the lesion increased over time

(−0.08 and −0.7, respectively). In the remaining cases, washout ratio ranged from 0.08 to 0.76, which means that MIBI-Tc<sup>99m</sup> was pumped out from cells. It was noticed that the images obtained with the SPECT/CT washout method were clearer and easier to read than were those obtained from planar examination (Fig. 1A–E).

Three patients with positive results underwent surgery and all had benign histopathology results after the operation. One patient with a toxic nodular goiter accepted radioiodine treatment as an alternative method

to surgery after negative results of the MIBI-Tc<sup>99m</sup> examination. Two patients with an increased tracer accumulation are continuing follow-up because one does not agree to surgery and the other has contra-indications for surgery.

## Discussion

A clinician who is about to decide whether to recommend a patient with thyroid nodule for thyroid surgery treatment may encounter various obstacles that can influence the final decision. They may be medical reasons such as: inconclusive or non-diagnostic FNAB results, advanced patient age, or coexisting diseases or it may be the patient who disagrees to undergoing surgery. Patients nowadays have many more sources of information and they ask physicians for more detailed data to legitimate radical treatment like thyroid surgery. During the last decade great progress concerning technical possibilities has been made, which may influence the diagnostic process per se.

In everyday practice, a traditional thyroid scan is two-dimensional. Three-dimensional SPECT projections are also becoming widespread. Moreover, it is possible to co-register function (SPECT) and structure (CT) in one SPECT/CT device [12]. Usually, the power of the hybrid equipment is used for "major" indications such as neuroendocrine tumours or parathyroid gland localization, but one has to bear in mind that in some clinical situations fusion imaging may be of great value in the differential diagnosis process of thyroid nodules [13–16].

In conventional nuclear medicine, MIBI-Tc<sup>99m</sup> is a well established tumour-seeking agent. Its value has been shown in many publications [17–23]. MIBI-Tc<sup>99m</sup> has good characteristics for *in vivo* tumour imaging, which has been proven in many experimental culture studies [17]. An experimental study by Crane proved that the highest uptake was at the periphery of the tumour while the centre of the tumour showed less retention. It is understandable because the centre of the tumour is often acellular and may be filled with necrotic debris.

MIBI-Tc<sup>99m</sup> exhibits a complicated tumour uptake due to the biochemical characteristics of MIBI-Tc<sup>99m</sup> itself (positive cationic charge and lipophilicity) and due to features of the tissue characteristic (local blood flow, transcapillary exchange, interstitial transport, the number of mitochondria). The tracer is actively taken up by mitochondria and passively transferred across the cell membrane [17, 18]. In the last few years the relationship between multidrug-resistant (MDR1) phenotype and MIBI-Tc<sup>99m</sup> scanning has been intensively investigated in many oncological fields [19–23]. Some publi-

cations [20–22] reveal an attempt to quantify the tumour by background ratio and/or washout rate. This interest is shared by authors of papers dealing with the application of MIBI-Tc<sup>99m</sup> scintigraphy in the assessment of thyroid nodules [2–6].

In clinical practice, the dilemma between a wait-and-see attitude and surgery as the best method of treatment may be insolvable. The group of patients described in the present study may serve as an example. When there are such factors as advanced age, chronic diseases which make the risk of operation higher, inconclusive FNAB results, the presence of many nodules which are not large, and strengthened by patients' reluctance to undergo surgery, there is a need for an additional technique. From this perspective, negative MIBI-Tc<sup>99m</sup> may be crucial in the process of excluding malignancy. It brings important input, both for clinicians and patients. Such support we gained, however, only in four patients from the investigated group. Thus we intended to analyze the washout of the radiopharmaceutical from the nodule by SPECT/CT imaging.

SPECT/CT is a new tool which helps to visualize abnormal thyroid lesions better. It also provides nuclear medicine practitioners with much more data to analyse and interpret than they would obtain from a planar study. However, it may also lead to false positive conclusions (which might have happened in our group). Only for three out of the eight patients did we have pathology evaluations, done postoperatively, and in all cases they were benign. Also, for three of the five remaining MIBI-positive cases, for whom the data from the follow up were available, it did not increase the suspicion of malignancy.

The problem is that there is no experience with assessing MIBI-Tc<sup>99m</sup> SPECT/CT imaging with quantitative methods. As a result, there may be some discordance between medical centres in the interpretation of the data. In literature, timing and calculating the tumour/background and washout ratios (the latter less often) differs from study to study. For example, Sharma compared the region of increased uptake with the second region of interest, which was drawn just below the nodule for background activity 30 minutes after injection [24]. Other authors calculated activity after 10 minutes or used different protocols for the tumour/background ratio. There is a need for standardization of image interpretation across the literature. This opinion is expressed by Hurtado-López in one of the last issues of *Nuklearmedizin* [25]

## Conclusions

We consider that the majority of our patients could be considered to have benign thyroid nodules on the ba-

sis of the good MIBI washout. Our preliminary results support the use of MIBI-Tc<sup>99m</sup> in the evaluation of indeterminate thyroid nodules. To validate the hypothesis that MIBI-Tc<sup>99m</sup> can be used to exclude malignancy in lesions indeterminate by FNAB, we propose the use of SPECT-CT derived images and standardized evaluation criteria.

## References

- Cooper DS, Doherty GM, Haugen BR. Revised management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009; 19: 1167–1214.
- Polyzos SA, Kita M, Efstathiadou Z et al. The use of demographic, ultrasonographic and scintigraphic data in the diagnostic approach of thyroid nodules. *Exp Clin Endocrinol Diabetes* 2009; 117: 159–64.
- Hurtado-López LM, Martínez-Duncker C. Negative MIBI thyroid scans exclude differentiated and medullary thyroid cancer in 100% of patients with hypofunctioning thyroid nodules. *Eur J Nucl Med Mol Imaging* 2007; 34: 1701–1703.
- Theissen P, Schmidt M, Ivanova T. MIBI scintigraphy in hypofunctioning thyroid nodules—can it predict the dignity of the lesion? *Nuklearmedizin* 2009; 48: 144–152.
- Mezosi E, Laszlo Bajnok L, Gyory F et al. The role of technetium-99m methoxyisobutylisonitrile scintigraphy in the differential diagnosis of cold thyroid nodules. *Eur J Nucl Med* 1999; 26: 798–803.
- Giovanella L, Suriano S, Maffioli M et al. (99m)Tc-sestamibi scanning in thyroid nodules with nondiagnostic cytology. *Head Neck* 2010; 32: 607–611.
- Boi F, Lai ML, Deias C, et al. The usefulness of 99mTc-SestaMIBI scan in the diagnostic evaluation of thyroid nodules with oncocyctic cytology. *Eur J Endocrinol* 2003; 149: 493–498.
- Sathekge MM, Mageza RB, Muthuphei MN et al. Evaluation of thyroid nodules with technetium-99m MIBI and technetium-99m pertechnetate. *Head and Neck* 2001; 23: 305–310.
- Sundram FX, Mack P. Evaluation of thyroid nodules for malignancy using 99Tcm-sestamibi. *Nucl Med. Commun* 1995; 16: 687–693.
- Erdi TY, Ozker K, Kabasakal L et al. Correlation of technetium-99m MIBI and thallium-201 retention in solitary cold thyroid nodules with postoperative histopathology. *Eur J Nucl Med* 2000; 27: 713–720.
- Koray D, Ozlem K., Cem Y. et al. A comparison of radionuclide thyroid angiography, 99mTc-MIBI scintigraphy and power Doppler ultrasonography in the differential diagnosis of solitary cold thyroid nodules. *Eur J Nucl Med Mol Imaging* 2003; 30: 642–650.
- Townsend DW. Multimodality imaging of structure and function. *Phys Med Biol* 2008; 53: R1-R39.
- Neumann DR, Obuchowski NA, DiFilippo FP. Preoperative 123I/99mTc Sestamibi Subtraction SPECT and SPECT/CT in Primary Hyperparathyroidism. *J Nucl Med* 2008; 49: 2012–2017.
- Krausz Y, Keidar Z, Kagan I et al. SPECT/CT hybrid imaging with 111In-pentetreotide in assessment of neuroendocrine tumours. *Clin Endocrinol (Oxf)* 2003; 59: 565–573.
- Hindiè E, Ugur Ö, Fuster D et al. 2009 EANM parathyroid guidelines. *Eur J Nucl Med Mol Imaging* 2009; 36: 1201–1216.
- Spanu A, Solinas ME, Chessa F. et al. SPECT/CT in the follow-up differentiated thyroid carcinoma: incremental value versus planar imaging. *J Nucl Med* 2009; 50: 184–190.
- 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.
- Crane P, Ontohank D, Retos C et al. Technetium-99m-sestamibi retention in the c-neu oncomouse: an in vivo model for breast tumour imaging [Abstract]. *J Nucl Med* 1994; 35: 21P.
- Del Vecchio S, Ciarmiello A, Potena MI et al. In vivo detection of multidrug-resistant (MDR1) phenotype by technetium-99m sestamibi scan in untreated breast cancer patients. *Eur J Nucl Med* 1997; 24: 150–159.
- Kim SW, Park S-S, Ahn SJ. et al. Identification of angiogenesis in primary breast carcinoma according to the image analysis. *Breast Cancer Res Treat* 2002; 74: 121–129.
- Fuster D, Munoz M, Pavia J et al. Quantified 99m-Tc MIBI scintigraphy for predicting chemotherapy response in breast cancer patients: factors that influence the level of 99m-Tc MIBI uptake. *Nucl Med Commun* 2002; 23: 31–38.
- Taki J, Sumiya H, Asada N et al. Assessment of P-glycoprotein in patients with malignant bone and soft-tissue tumors using technetium-99-MIBI scintigraphy. *J Nucl Med* 1998; 39: 1179–1184.
- Cayre A, Cachin F, Maublant J et al. Single static view 99mTc-sestamibi predicts response to neoadjuvant chemotherapy and is related to MDR expression. *Inter J Oncology* 2002; 20: 1049–1055.
- Sharma R, Mondal A, Shankar LR et al. Differentiation of malignant and benign solitary thyroid nodules using 30- and 120- minute Tc99m MIBI scans. *Clin Nucl Med* 2004; 29: 534–537.
- Hurtado-López LM, Martínez-Duncker C. Comment on: Nuklearmedizin. MIBI scan negative or positive. 2009; 48: 144–152.