Comparison of Technetium-99m-Sestamibi Scintimammography with Contrast-Enhanced MRI for Diagnosis of Breast Lesions

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Scintimammography using ^{99m}Tc-sestamibi and contrast-enhanced MRI were performed to determine the diagnostic accuracy of either method in the diagnostic workup of patients suspicious for breast tumors. **Methods:** Fifty-six patients (42 with indeterminate mammograms) underwent preoperative prone planar scintimammography and pre- and postcontrast-enhanced MRI. Visually determined signal increase after application of Gd-DTPA was compared with visually scored sestamibi uptake, and the diagnoses of both methods were correlated with the final histopathologic results. **Results:** Overall sensitivity and specificity of scintimammography for diagnosing breast cancer were 88% and 83%, respectively. In the subgroup of patients with indeterminate mammograms, sensitivity was 79% and specificity was 83%. MRI readings provided a higher sensitivity (91% with respect to all patients and 89% with respect to patients with indeterminate mammograms), but a considerably lower specificity (52% in both groups) due to contrast-enhancement in different benign lesions. **Conclusion:** Due to its considerably higher specificity, scintimammography rather than MRI may be suitable to reduce the number of breast biopsies which yield benign results. Thus, this method may be suggested as the preferable tool in the diagnostic workup of patients with indeterminate mammographic findings.

Key Words: breast cancer; technetium-99m-sestamibi; scintimammography; contrast-enhanced MRI

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Breast cancer is the most commonly diagnosed cancer after skin cancer and the second leading cause of cancer death among women in the United States. The annual incidence rates have increased approximately 52% from 1950 to 1990, with a dramatic increase of 32% reported between 1980 and 1987 (*1–3*). The incidence of tumors less than 3 cm in diameter has increased more rapidly than that of tumors 3 cm or larger, which may have resulted from more efficient screening methods (*4,5*). On the other hand, survival rates have improved among cases diagnosed over this time period (*5*). Therefore, a primary diagnostic aim is to optimize the common screening methods or to develop new modalities to detect carcinomas in an early stage, thereby reducing death rates.

Routine physical examinations and mammography, although the most common methods for early cancer detection, still have diagnostic limitations. Due to its high sensitivity and availability, mammography is the method of choice in screening asymptomatic women (*6–10*). However, mammography has major problems in additional assessment of patients with dense breast tissue, unclear microcalcifications or opacities and in differentiating between scar and recurrency (*7,8*). The positive predictive value of mammography (carcinomas diagnosed per number of recommended biopsies) is low (*6,9,10*). MRI, although unreliable in tissue characterization based on different relaxation times (*11–14*), has gained wide interest in breast cancer diagnosis after the development and use of the paramagnetic contrast agent Gd-DTPA. Although the positive predictive value and specificity of MRI have been reported as lower than that of conventional mammography (*11,15–19*), contrast-enhanced MRI enables further evaluation of indeterminate mammographic findings in particular cases.

Recent articles on nuclear medicine techniques, specifically scintigraphy using ^{99m}Tc-sestamibi, report promising results in the diagnosis of breast carcinomas. Technetium-99m-sestamibi scintimammography has been reported to have a high sensitivity, ranging from 84%–96% (*20–29*), for the detection of breast carcinoma.

The major goal of this study was to assess the value of scintimammography using ^{99m}Tc-sestamibi, particularly in patients with indeterminate findings from previously performed mammography. Further aims were to compare sestamibi uptake with the contrast behavior in contrast-enhanced MRI and to define the diagnostic accuracy of both methods.

MATERIALS AND METHODS

Patients

Fifty-six women (age range 22–80 yr; mean age 53 yr; 26 postmenopausal) underwent ^{99m}Tc-sestamibi scintimammography and Gd-enhanced MRI between September 1994 and August 1995. All patients had abnormal physical examination and/or mammographic findings that warranted excisional biopsy or more extended surgery. Sestamibi scans and Gd-enhanced MRI were performed on the same day within 2 wk after mammography. For a more refined assessment, the patients were subdivided according to the likelihood of malignancy determined by mammography. There were 14 patients with mammograms suspicious for malignancy (11 with palpable, 3 with nonpalpable lesions) and 42 patients with indeterminate mammograms (32 with palpable, 10 with nonpalpable lesions). All patients with suspicious mammograms had spiculated masses (four patients with additional clustered microcalcifications) with a diameter ranging from 0.5 to 6 cm. The explanations for indeterminate mammographies were dense fibroglandular breast (n = 8), unclear opacities or asymmetrial

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densities (n = 21) and unclear microcalcifications (n = 13). All 56 patients underwent open-excisional biopsy within 1 wk after MRI and scintigraphy. In 12 patients, additional mastectomy was performed. In the case of nonpalpable lesions (n = 13), needle localization was used before surgical biopsy. Mammograms from the surgical specimen were obtained in 10 patients with indeterminate microcalcifications.

Acquisition Protocols

Scintimammography. Planar scans, with a matrix size of 256 × 256 pixels, were acquired with a dual-head camera equipped with low-energy, high-resolution collimators (LEHR). Patients laid on a special positioning device installed over the table with their arms above their head in a prone position to achieve better separation of the deep breast structures from the myocardium and liver. Five minutes after intravenous injection of 740 MBq ^{99m}Tc-sestamibi in an antecubital vein contralateral to the breast with the suspected abnormality, 10-min lateral images of both breasts were acquired simultaneously with minimum distance between breasts and detectors.

MRI. MRI was also performed in the prone position using a superconducting system at a field strength of 1.5 Tesla. We used a dedicated surface coil to enable simultaneous imaging of both breasts. Data were acquired before, immediately and approximately 5 min after intravenous injection of Gd-DTPA, a paramagnetic contrast agent (0.1 mmole/kg body weight). T1-weighted, gradient-echo sequences with a flip angle of 50° (FLASH 3D 50), a repetition time (TR) of 40 msec and an echo time (TE) of 14 msec were used. Twenty-four continuous transverse slices were obtained in an acquisition time of 5.3 min per sequence.

Image Readings

Scintigraphy. Sestamibi uptake was evaluated visually using scoring categories as described below:

1. Normal (homogeneous not higher than background activity) or equivocal (inhomogeneous without any delineable focus).
2. Focal, low intense (lower than uptake of the upper chest in lateral projection).
3. Focal, medium intense (comparable to uptake of the upper chest in lateral projection).
4. Focal, high intense (higher than uptake of the upper chest in lateral projection).

MRI. The signal increase after application of Gd-DTPA (all lesions being hypointense compared to fat tissue in precontrast MRI), which represents the major criterion for malignancy, was scored visually according to the following criteria:

1. No enhancement (unchanged signal intensity before and after Gd-DTPA).
2. Low enhancement (signal intensity after Gd-DTPA lower compared to fat but higher compared to precontrast MRI).
3. Medium enhancement (lesion isointense compared to fat after Gd-DTPA).
4. High enhancement (lesion being hyperintense compared to fat after Gd-DTPA).

TABLE 1
Scintimammography: Correlation between Technetium-99m-Sestamibi Uptake and Final Diagnosis (n = 56)

Final diagnosis	Sestamibi uptake			
	Normal/ Equivocal	Focal low	Focal medium	Focal high
Carcinoma	4	4	12	13
Fibroadenoma	4	1	–	–
Fibrocystic disease	14	1	–	–
Papillomatosis	–	1	–	–
Chronic inflammation	–	–	1	–
Scar	1	–	–	–

In addition to Gd uptake, lesion morphology after enhancement was considered. The contrast dynamics were also assesed in cases with high or medium enhancement after comparison of signal intensity between the first and second postcontrast measurement.

Image Interpretation and Analysis

Scintigraphically, every focal sestamibi uptake was considered as pathologic and suspicious for malignancy. In the initial MRI readings, every Gd-enhancement was diagnosed as positive, because, according to strict criteria, a definitive exclusion of carcinoma is not possible in cases of contrast-enhancement. After taking into account lesion morphology after Gd-enhancement and Gd dynamics, we differentiated MRI diagnoses in three groups: suspicious for malignancy, indeterminate and probably benign. A MRI study was considered suspicious if solitary or multiple foci with spiculated or irregular borders and a high or medium, but rapid signal increase were observed. Furthermore, well-circumscribed lesions with a high and rapid enhancement were considered suspicious. Any patient without Gd-enhancement, with diffuse/micronodular low or medium, but delayed enhancement of breast parenchyma and with well-defined, low-enhancing lesions was classified as probably benign. Each other constellation was judged as indeterminate.

Scintigraphic and MRI readings were performed by two independent, experienced nuclear medicine physicians and radiologists who were blinded to the results of previous investigations and to the histopathologic outcome. Disagreements concerning the visual scoring of three sestamibi patients and four Gd-enhancement patients were resolved by consensus, with a third observer as a referee. Discrepancies in diagnoses (positive compared with negative in scintigraphy, suspicious/indeterminate/probably benign in MRI) did not occur.

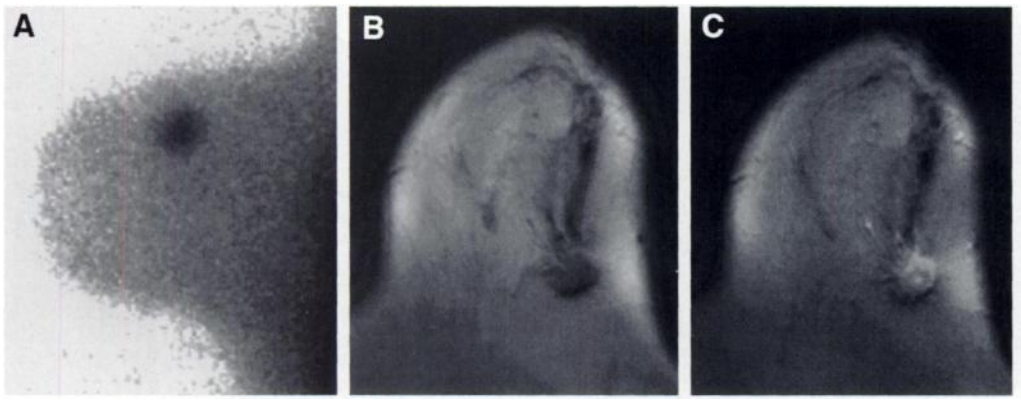

FIGURE 1. Ductal invasive breast carcinoma (pT1c). Previous mammography showed a spiculated lesion suspicious for carcinoma. (A) Scintimammography confirmed the lesion as malignant by revealing focal high sestamibi uptake. (B) Precontrast MRI showed an irregular, poorly marginated, hypointense mass. (C) After application of Gd-DTPA, marked contrast-enhancement was assessed.

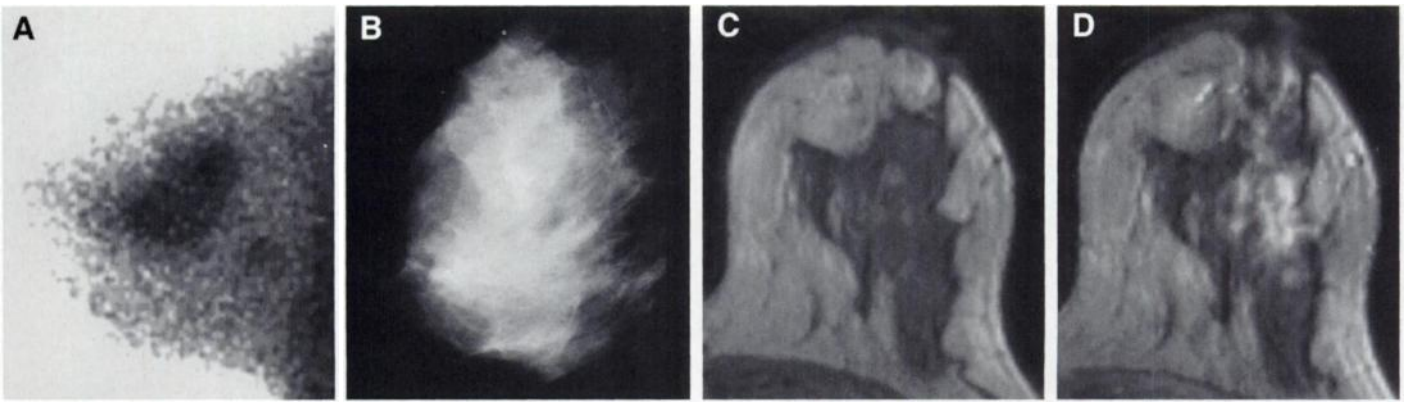

FIGURE 2. Multifocal ductal invasive breast carcinoma (pT2). (A) Scintimammography was positive and detected two foci of increased sestamibi uptake in accordance to the histological proven multifocal carcinoma. (B) Previous mammography could not evaluate the palpable mass due to dense breast tissue. (C, D) MRI delineated a focal lesion with irregular borders and clear contrast-enhancement suggesting findings suspicious for carcinoma.

RESULTS

Thirty-three of 56 patients had a histopathologically proven carcinoma (24 invasive ductal, 2 intraductal, 7 invasive lobular) with the following postoperative primary tumor stages (according to the TNM classification): 2 carcinoma in situ, 1 pT1a, 5 pT1b, 11 pT1c, 10 pT2, 1 pT3 and 3 pT4.

The size of carcinomas ranged from 5 mm to 6 cm in diameter, with a mean diameter of 21 mm. The remaining 23 patients had different benign lesions, including 5 fibroadenomas, 15 fibrocystic diseases, 1 papillomatosis, 1 chronic inflammation and 1 postoperative scar.

Scintimammography revealed that 29/33 carcinomas showed focal sestamibi accumulation with varying intensities (Table 1). Representative examples for a focal high uptake in carcinomas are shown in Figures 1 and 2. Two invasive lobular (diameter 0.5 and 2.5 cm) and two invasive ductal (diameter 0.5 cm and one cutaneous infiltration with a diameter of 1.5 cm) carcinomas had normal or equivocal sestamibi uptake and therefore could not be differentiated from normal glandular parenchyma. The smallest carcinoma (0.5 cm diameter) was detected scintigraphically as an area of focal, medium intense sestamibi uptake.

Four of the 23 patients with benign lesions showed focal sestamibi uptake. The one patient with chronic inflammation demonstrated focal sestamibi uptake with medium intensity. Three other patients with fibroadenoma, fibrocystic disease and papillomatosis revealed focal, low intense sestamibi accumulation. All other patients with benign abnormalities showed normal ($n = 12$) or equivocal ($n = 7$) uptake of the radiopharmaceutical (Fig. 3).

The sensitivity and specificity of visual scintigraphic readings for diagnosing breast carcinoma were 88% and 83%, respectively. The positive and negative predictive values were 88% and 83%, respectively.

Consideration of only the subpopulation with indeterminate mammograms (Fig. 2) results in a lower number of true-positive and an unchanged number of false-negative diagnoses (sensitivity 79%, specificity 83%).

With MRI, 24/33 carcinomas showed a high increase of signal intensity after the injection of Gd-DTPA (Figs. 1 and 2). Three of four sestamibi-negative carcinomas failed to demonstrate positive Gd-enhancement in MRI and were diagnosed as false-negative (Table 2). The one carcinoma missed by scintigraphy but correctly diagnosed by MRI with Gd-enhancement of medium intensity was lobular invasive with a diameter of 2.5 cm. However, MRI showed a high number of benign lesions with low (9/23), medium (7/23) or high signal increase (5/23) after contrast application (Fig. 3). Due to these results, it was impossible to differentiate the enhancing lesions from malignancies or to exclude malignancy, if only the presence of Gd-uptake was considered as a criterion for malignancy.

Including the margins of enhancement and the Gd dynamics as diagnostic criteria, 25 (24 carcinomas and 1 chronic inflammation) clearly enhancing lesions with spiculated or irregular borders were diagnosed as suspicious for carcinoma. Sixteen lesions (six carcinomas, three fibroadenomas, six fibrocystic diseases and one papillomatosis) were classified as indeterminate, and lesions in 15 additional patients (including three nonenhanced carcinomas) were judged to be probably benign. When combining all suspicious and indeterminate diagnoses as positive, the sensitivity of modified MRI readings was 91%, but the specificity was low (52%). In the subgroup of patients with indeterminate mammograms, modified MRI readings showed a sensitivity of 89%, with specificity remaining at 52%.

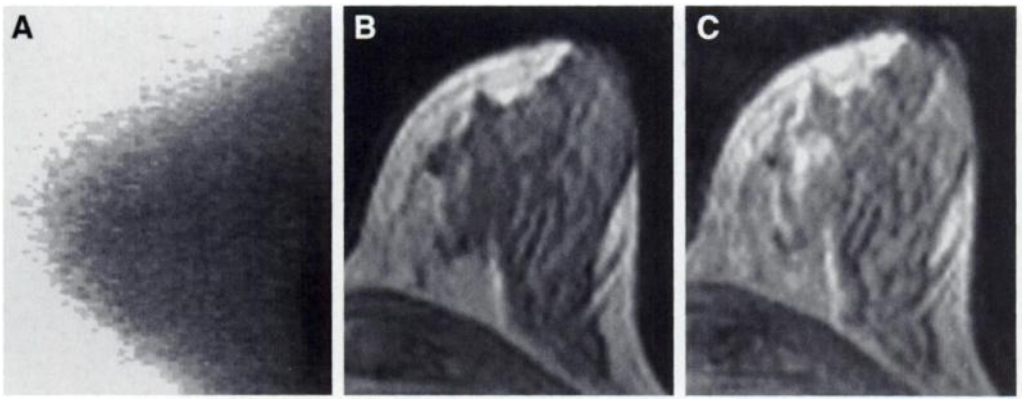

FIGURE 3. Proliferating fibrocystic disease. Previous mammographic readings were indeterminate due to dense fibroglandular parenchyma. (A) In scintimammography, no focal accumulation of sestamibi was observed. (B, C) MRI showed an irregular lesion with a high Gd-enhancement so MRI diagnosis was false-positive.

TABLE 2
MRI: Correlation between Signal Increase after Application of Contrast Medium (Gd Uptake) and Final Diagnosis (n = 56)

Final diagnosis	No.	Gd uptake Low	Medium	High
Carcinoma	3	2	4	24
Fibroadenoma	1	–	2	2
Fibrocystic disease	1	8	4	2
Papillomatosis	–	–	1	–
Chronic inflammation	–	–	–	1
Scar	–	1	–	–

DISCUSSION

Mammography, a method with excellent resolution and high sensitivity, remains the procedure of choice in screening for breast cancer (*6*). However, due to a positive predictive value of less than 35% in the United States (*9,10*), other diagnostic modalities are desirable to reduce the number of biopsies yielding benign results. MRI has gained wide interest in breast cancer diagnosis and demonstrates a high negative predictive value, but the reported positive predictive values were not higher compared to conventional mammography (*11,15–19, 30*). In addition, the expense and lack of availability of MRI may limit its use as a routine diagnostic method for breast cancer. These limitations of MRI for breast cancer diagnosis have led to investigations into other modalities.

Recent publications have reported favorable sensitivity and specificity results, 84%–96% and 72%–94%, respectively, for ^{99m}Tc-sestamibi scintigraphy in the diagnosis of breast cancer (*20,22–29*). The reported results for the scintigraphic studies focused mainly on a preselected patient population with suspicious palpable or mammographic lesions. Therefore, in this study, we considered the entire patient population, as well as a subpopulation of patients that had indeterminate results from previous mammographies. This subpopulation is the patient group that can determine the value of scintimammography in the future.

The scintigraphic results for specificity (83%) were the same for the entire patient population and the subpopulation and were comparable to those values previously reported (*20,23,24,26, 28*). Sensitivity results, however, were lower in the subpopulation (79%) than in the overall population (88%), as well as lower than reported values (*20,23,24,26,27*). The higher sensitivity values previously reported may have been overestimated due to the preselection of the patient population with abnormalities suspicious for carcinoma.

The high specificity values reported for ^{99m}Tc-sestamibi could not be achieved with MRI. The difference in these values may be explained by the mechanisms of Gd-DTPA uptake compared with that of sestamibi. Any contrast-enhancement of Gd-DTPA is commonly considered as the major criterion for malignancy in MRI (*31–35*). Gd-DTPA is known to distribute in the extracellular space and to accumulate in tissues with expanded interstitial space (*11,19,36*). Additionally, the uptake of Gd-DTPA has been reported to depend significantly on neovascularity (*14*). Any tumor greater than 3–4 mm, benign or maligant, can conceivably exhibit neovascularity, thereby increasing the number of false-positive results with Gd-DTPA. Futhermore, the degree of enhancement varies within benign abnormalities (e.g., fibroadenomas and fibrocystic changes), and the overlap between uptake values of benign and malignant lesions has been reported to be very high (*11,14,32*). In addition, several authors discovered that the early dynamic imaging characteristics of benign and malignant lesions may overlap (*16,18,32,37*). These characteristics of Gd-DTPA have led to controversial discussion regarding the use of uptake values and dynamics for differentiation between benign and malignant lesions. Taking this into consideration, the degree of Gd-DTPA enhancement was not quantitatively measured in this study but was visually scored. The kinetics were also visually estimated by comparing the first and the second postinjection measurements. The morphology of the lesions was evaluated as previously reported (*11,19,33,37*) to further improve specificity. The results of such image readings confirmed the high sensitivity of contrast-enhanced MRI, but they could not compete with the considerably higher specificity of scintimammography.

In contrast to Gd-DTPA, the exact mechanisms of ^{99m}Tc-sestamibi uptake by tumor cells is not completely understood. Recent data suggest that the lipophilicity of the cationic tracer, the mitochondrial and plasma membrane potentials, as well as the mitochondrial content and an increase in blood flow and capillary permeability play an important role in the mechanism (*38–40*). When compared to the influence of the mitochondria, the effects of neovascularity seem to be less significant. Therefore, the lower number of false-positives in the scintigraphic findings compared to MRI could be explained.

Although scintigraphy shows fewer false-positives, the limitations of spatial resolution could be the explanation for the reported number of false-negatives. In this study, two carcinomas with diameters less than 5 mm were misdiagnosed scintigraphically. These data would support the previously mentioned limitation, but these tumors were also incorrectly diagnosed by MRI due to the lack of contrast enhancement. A 2.5-cm lesion, one well within the resolution of the imaging system, was not detected by scintigraphy but was positive with contrast-enhanced MRI.

Two of four carcinomas without sestamibi uptake were invasive lobular, suggesting that the detection of lobular carcinomas may be more difficult than ductal carcinomas. However, the number of patients studied at this time cannot allow definite statements about uptake by histologically different lesions.

CONCLUSION

Scintimammography using ^{99m}Tc-sestamibi, rather than contrast-enhanced MRI, may be used to further assess patients with indeterminate mammographic findings (e.g., dense fibroglandular breast and unclear microcalcifications or opacities). In these patients, the comparatively higher specificity of scintimammography compared to MRI and mammography could influence the therapeutic strategy and reduce the number of mammographically recommended surgical biopsies that yield benign results.

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Technetium-99m-MIBI Scintigraphy of Thyroid Nodules in an Endemic Goiter Area

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Technetium-99m-methoxyisobutylisonitrile (MIBI) was introduced for myocardial imaging as an alternative to ^{201}Tl. According to biodistribution studies, MIBI also accumulates in the thyroid gland. The aim of this study was to find out which thyroid nodules retain MIBI and whether preoperative evaluation of malignancy is possible. **Methods:** Single injection, dual-phase (30 min and 2 hr) thyroid scintigraphy with ^{99m}Tc-MIBI was performed on 62 patients who showed a cold nodule on previously performed ^{99m}Tc scintigraphy. MIBI scans were considered positive if there was a clear tracer retention in the late 120-min image compared to the early 30-min image. Sonographic examination and fine-needle aspiration biopsy, guided by ultrasonography, was also done on each patient. In the following days and weeks, all patients underwent surgery. **Results:** Histopathological diagnoses revealed a total of 12 thyroid carcinomas, five were MIBI positive and seven MIBI negative. Out of 27 patients with thyroid adenomas (nine microfollicular, ten follicular, eight oxyphilic), 18 were MIBI positive and nine MIBI negative. There was no MIBI retention on the scans of 22 patients with degenerative changes in the goiter and the one with Hashimoto's disease. **Conclusion:** These results indicate that MIBI accumulation and retention is not specific for thyroid malignancy. Indeed, all evidence points to the fact that a positive MIBI scan is more likely to indicate thyroid adenoma than a malignant tumor.

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Technetium-99m-methoxyisobutylisonitrile (MIBI), a cationic complex molecule, was primarily introduced for perfusion myocardial imaging. Over the years, MIBI scintigraphy has also become one of the most sensitive methods in the detection of parathyroid adenomas (*1,2*). Briele et al. (*3*) also detected thyroid cancer metastases with MIBI scintigraphy. Until recently, ^{201}Tl still played an important role in the follow-up of thyroid cancer as well as in the preoperative evaluation of thyroid nodules (*4*). In 1980, Harada et al. (*5*) examined 55 patients using ^{201}Tl as a preoperative evaluation of thyroid nodules. Scintigraphy visualized 13 of 16 thyroid carcinomas, but thyroid adenomas were also depicted by ^{201}Tl scintigram. Thus, ^{201}Tl could not differentiate conclusively between benign and malignant thyroid nodules. It is, therefore, valid to ask whether ^{99m}Tc-MIBI is more suitable for evaluation purposes in the preoperative clarification of hypofunctional goiter nodules. Furthermore, it would be advantageous to use ^{99m}Tc-MIBI instead of ^{201}Tl, as it requires a smaller radiation dose (*6*) and is more readily available. Moreover, MIBI can be kept in stock and is easily labeled with ^{99m}Tc, in contrast to ^{201}Tl.