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Technetium-99m-MIBI Scintimammography in Palpable and Nonpalpable Breast Lesions

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The aim of this study was to determine the diagnostic accuracy of ^{99m}Tc-MIBI scintimammography in patients with palpable and nonpalpable breast cancer. **Methods:** One hundred and forty patients with a clinically palpable breast mass and/or suspicious mammographic finding had prone scintimammography after the intravenous injection of 740 MBq ^{99m}Tc-MIBI within 5 days before open biopsy or surgery. All patients had mammography within 2 mo before the scintimammography. The mammography was read as probably benign, probably malignant or indeterminate. The scintimammography was read as positive or negative for breast cancer. The scintigraphic studies were correlated with mammographic findings and with histopathology. **Results:** Histopathological studies showed that the mean tumor size for 61 palpable tumors was 2.57 cm with a range of 1–6 cm, and for 24 nonpalpable tumors the mean size was 1.34 cm with a range of 0.5–3 cm. Mammography had an overall sensitivity of 91.58% and a specificity of 42.87%; the sensitivity was 90.16% and 95.45% and specificity was 57.14% and 32.14% for palpable and nonpalpable tumors, respectively. Eight cases were considered indeterminate. Scintimammography was true-positive for 71 breast cancers, true-negative for 47, false-positive for 8 and false-negative for 14. The overall sensitivity was 83.5% and the specificity 85.4%. In the patients with palpable masses, sensitivity was 95.1% and specificity 75%; in those with nonpalpable lesions, sensitivity was only 54.2% and specificity, 93.5%. Among 18 cases of palpable abnormalities with probably benign mammography, six had true-positive scintimammography. Of eight patients with indeterminate mammography, one was true-positive on scintimammography. **Conclusion:** Scintimammography is an accurate and clinically useful tool for evaluating patients with palpable breast abnormalities when mammography is negative and in the cases of indeterminate mammography. A significant improvement in lesion detectability is necessary in nonpalpable breast abnormalities.

Key Words: scintimammography; breast cancer; technetium-99m-MIBI

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Breast cancer is the most frequently diagnosed malignancy in Israeli women, accounting for 31% of all female malignancies. Almost 2000 new cases were diagnosed in 1992, and the annual incidence is 80/100,000. In the U.S., the incidence of breast

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TABLE 1
Scintimammography, Histopathology and Lesion Size

Findings; AS	No. of patients	PLP (AS)	NPLP (AS)	Pathological lesion size <1	≥1–1.5≤	>1.5
True-positive; 2.41 (0.8–6.0)	71	58 (2.6)	13 (1.45)	1	18	52*
Infiltrating ductal carcinoma	64	53	11	1	16	47
Intraductal carcinoma	2	—	2	—	—	2*
Infiltrating lobular carcinoma	1	1	—	—	1	—
Mixed infiltrating lobular and ductal carcinoma	1	1	—	—	—	1
Poorly differentiated carcinoma with squamous differentiation	1	1	—	—	—	1
Invasive papillary carcinoma	1	1	—	—	—	1
Malignant fibrous hystiocytoma	1	1	—	—	—	1
True-negative	47	18	29	—	6	—
Fibrocystic disease	19	8	11	—	—	—
Fibroadenoma	6	2	4	—	6	—
Sclerosing adenosis	4	2	2	—	—	—
Fibrosis	2	—	2	—	—	—
Radial scar	1	—	1	—	—	—
Normal breast tissue	15	5	10	—	—	—
False-positive	8	6	2	—	2	—
Fibrocystic disease	3	2	1	—	—	—
Scarring (3 yr after lumpectomy followed by irradiation)	1	1	—	—	—	—
Foreign body reaction (3 wk after open biopsy)	1	1	—	—	—	—
Fibroadenoma	1	1	—	—	1	—
Severe mastitis with multiple abscesses	1	1	—	—	—	—
Benign angiomyoepithelioma	1	1	—	—	1	—
False-negative; 1.36 (0.5–3.0)	14	3 (2.0)	11 (1.22)	3	5	6†
Infiltrating ductal carcinoma	5	1	4	1	3	1
Intraductal carcinoma	6	1	5	1	1	4†
Infiltrating tubular carcinoma	2	—	2	1	1	
Infiltrating lobular carcinoma	1	1	—	—	—	1

*One patient with extensive diffuse intraductal carcinoma.
†Three patients with extensive diffuse intraductal carcinoma.
AS = average size in cm; PLP = palpable lesions; NPLP = nonpalpable lesions.

cancer increased by 55% to 110/100,000 during the period 1950–1991 (*1*). Early diagnosis is the most significant factor influencing survival (*2,3*). This is best achieved by self-examination and annual clinical examination and mammography screening. Already in 1951, Leborgne defined radiological characteristics of tumors of the breast and predicted a role the mammography would play in the screening of asymptomatic women (*4*). It is well known that the sensitivity of mammography is fairly high in the fatty breast of older women and lower in dense breasts (*5,6*). The low specificity of mammography is the main reason for the low cancer yield (25%) in breast biopsies (*7*).

Technetium-99m-MIBI scintimammography is a recently developed imaging procedure with a target-to-nontarget ratio that allows good visualization of the breast tumor. Published results show a good overall sensitivity of 84%–96% for the detection of breast carcinoma (*8–12*). When considering only the nonpalpable cases, the published results are conflicting and range from 27%–88% sensitivity (*11,13*). The aim of this study was to determine the diagnostic accuracy of this tool in patients referred before biopsy or surgery for suspected breast cancer. Special consideration was given to the correlation between the palpability and histological size of the lesions and the diagnostic accuracy of ^{99m}Tc-MIBI scintimammography.

MATERIALS AND METHODS

Patients

The study population included 140 consecutive patients (138 women, 2 men; age range 29–87 yr; mean 61.41 ± 12.23 yr) with a clinically palpable mass in the breast and/or suspicious mammographic finding. Eighty-five patients had palpable lesions and 55 had nonpalpable lesions. Patients were enrolled for the study prospectively on referral for a scintimammography by the department of surgery. Physical examination of the breast was done by an experienced breast surgeon. All patients had a mammography within 2 mo before the scintimammography.

Mammography

The mammography was performed in craniocaudal and mediolateral oblique projections using a dedicated mammography unit. An experienced radiologist, who was informed about the patient's history, clinical presentation, physical examination and the results of any previous mammograms, interpreted all studies. The results were rated as: 1 = most probably benign; 2 = most probably malignant; and 3 = indeterminate.

The criteria for benign lesions were sharp margins, low density and, if calcified, these were coarse calcifications. The criteria for malignant lesions were poorly defined margins, spicular margins, high density and small, thin, multiple calcifications with a desmoplastic reaction surrounding the lesion. The criteria for indeterminate mammography were dense breast tissue or parenchymal nodes and asymmetry or microcalcifications less than five per square centimeter.

Scintimammography

A kit for preparation of ^{99m}Tc-MIBI was used and 740 MBq of the radiopharmaceutical agent was slowly injected intravenously into the arm contralateral to the breast with the suspected lesion. Imaging commenced at 10–20 min after injection using a gamma

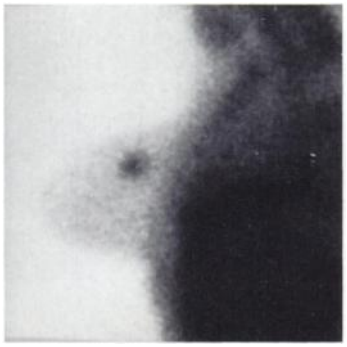

FIGURE 1. Left lateral prone view showing well-defined pathological concentration of ^{99m}Tc-MIBI in an infiltrating duct carcinoma measuring 1.9 × 2.6 × 3.1 cm.

FIGURE 2. Left lateral prone view in a 27-yr-old patient with a palpable mass in the breast. An image was read as negative for malignancy and consistent with severe fibrocystic changes, which were confirmed on biopsy.

camera with a single, rectangular detector and low-energy, general-purpose collimator. The energy peak was centered at 140 keV with a 10% window. Data were recorded on a 256 × 256 matrix. Every planar image was acquired for 7 min. The total picture count was at least 3000 kilocounts. An anterior view in the supine position and lateral and 30° posterior oblique views of both breasts in the prone position were obtained in all patients. For the lateral and oblique views, the patient lay prone on a foam cushion with semicircular apertures in which the breasts were freely dependent at the time of imaging (*14*). While the lateral view was being obtained, the opposite aperture was filled by foam cushions so that all activity in the contralateral breast was excluded from the field of view. In all views, the arms were raised and axillary regions were included in the field of view.

Data Analysis

All scans were read by two nuclear medicine physicians blinded to the patient's history, clinical presentation, physical examination, mammography result and histopathology findings as positive or negative for carcinoma. Any disagreement was resolved by consensus. Scintimammography was considered positive if a well-defined focally increased uptake in breast tissue was demonstrated in at least one view. Uniform distribution of the tracer or symmetrical nonhomogeneity was interpreted as negative. In all cases, final diagnosis was established by excisional biopsy performed within 5 days of the scintimammography.

RESULTS

The results of the scintimammography, palpability and histological diagnosis and size of the lesion are presented in Table 1. Of the 140 patients, 85 had malignancies; 61 of them were palpable and 24 were nonpalpable. The results of scintimammography were divided into true-positive, true-negative, false-positive and false-negative.

True-Positive

The most frequent malignancy in this group was infiltrating duct carcinoma (64 of 71 patients) (Fig. 1). Of these, 19 also had an intralesional intraductal carcinoma. Two intraductal carcinomas were correctly diagnosed, both were large, extensive, multifocal tumors. Despite their large size, both were nonpalpable, possibly because of the diffuse nature of this tumor. Other lesions successfully detected by scintimammography were (one patient each) infiltrating lobular carcinoma, mixed infiltrating lobular and ductal carcinoma, poorly differentiated carcinoma with squamous differentiation, invasive papillary carcinoma and malignant fibrous histiocytoma (in a male patient). Fifty-eight of the 71 detected tumors were palpable. The average histological size of the detected tumors was 2.41 cm (range 0.8–6 cm) in the greatest dimension.

True-Negative

Nineteen of 47 patients had fibrocystic disease on histopathology (Fig. 2); of the remainder, 6 had fibroadenomas, 4 sclerosing adenosis, 2 fibrosis and 15 had normal breast tissue.

False-Positive

Of eight patients in this group, three had fibrocystic disease, three had focal inflammatory reaction, one had a benign angiomyoepithelioma and one had fibroadenoma. In one of the patients with inflammatory reaction, an accumulation of the radiopharmaceutical agent was demonstrated in a postlumpectomy scar (surgery had been performed 3 yr previously and was followed by radiation) (Fig. 3). The others were a patient with foreign body reaction at 3 mo after open biopsy, and a male patient with severe mastitis and multiple abscesses. The appearance of the inflammatory lesions was more diffuse and poorly defined compared to the cancerous lesions.

False-Negative

Of the 14 patients in this group, five had infiltrating duct carcinoma, two had infiltrating tubular carcinoma, one had infiltrating lobular carcinoma and six had intraductal carcinoma. Of these 14 false-negative cancers, 11 were nonpalpable. The average histological size of undetected tumors was 1.36 cm (range 0.5–3.0 cm) in the greatest dimension. The tumor location for 14 false-negative scans were: seven upper lateral, three lower lateral, one upper medial and three lower medial.

The sensitivity of scintimammography for tumors smaller than 1 cm in the greatest dimension was 25%, between 1 and 1.5 cm was 78% and for tumors larger than 1.5 cm it was 94%. The smallest detected tumor was 0.8 cm.

The sensitivity of mammography was 90.16% for palpable lesions and 95.45% for nonpalpable lesions. Sensitivity of mammography was calculated from 132 patients (eight indeter-

FIGURE 3. Left lateral prone view showing pathological concentration of the ^{99m}Tc-MIBI in the scar area of the left breast. The superficial concentration visualized in the axillary region represents intensive perspiration. The patient had a lumpectomy followed by irradiation 3 yr before this study. Fat necrosis, hyalinization and extensive calcifications were found in the biopsy specimen. No tumoral cells were found.

TABLE 2
Scintimammography Versus Mammography

	Scintimammography			Mammography		
	Total	Palpable	Nonpalpable	Total	Palpable	Nonpalpable
Total	140	85	55	132	82	50
True-positive	71	58	13	76	55	21
True-negative	47	18	29	21	12	9
False-positive	8	6	2	28	9	19
False-negative	14	3	11	7	6	1
Sensitivity	83.53	95.08	54.17	91.58	90.16	95.45
Specificity	85.45	75.00	93.55	42.86	57.14	32.14
Accuracy	84.29	89.41	76.36	73.48	81.71	60.00
Positive predictive value	89.87	90.62	86.70	73.08	85.94	52.50
Negative predictive value	77.05	85.71	72.50	75.00	66.66	90.00

minate mammographies were not included) (Table 2). There were seven false-negative studies, six of which were palpable and one was nonpalpable. Of them, six were infiltrating duct carcinoma and one was infiltrating lobular carcinoma. Scintimammography was positive in six of these seven cases. The average histological size of mammographically undetected tumors was 2.2 cm (range 1.3–3.0 cm) in the greatest dimension.

The overall specificity of mammography in this study was 42.8%; 57.14% for palpable lesions and 32.14% for nonpalpable lesions.

Of eight indeterminate mammographies, one was an infiltrating duct carcinoma, one was intraductal carcinoma and six were negative for cancer. Scintimammography was positive in the case of infiltrating duct carcinoma (Table 3).

DISCUSSION

Garfinkel et al. (*3*) have reported an increase in the overall incidence of breast cancer, with almost no change in mortality from 1980 to 1990. The increase in incidence was largely accounted for by detecting tumors smaller than 2 cm in the greatest dimension and carcinomas in situ. This improvement in small cancer detection coincides with the greater use of mammography in screening asymptomatic patients. Yet mammography has an overall sensitivity of 85%, with a significantly lower lesion detectability in dense breasts. Mammography also has a well-recognized low positive predictive value (*7*). The latter is the main reason for the low yield of cancers (25%) among the total number of biopsies performed.

The use of scintimammography with ^{201}Tl-chloride was reported by Hisada et al. (*15*). Waxman et al. (*16*) found that ^{201}Tl scintimammography had a sensitivity of 96% in 47 patients with palpable breast masses. The smallest detected lesion was 1.3 cm. No palpable malignancies were included in this study. Muller et al. (*17*) reported tumor imaging with ^{99m}Tc-MIBI. This radiopharmaceutical, with its cationic charge and lipophilicity, is passively transferred across the cell membrane and concentrated in the mitochondria, making it a good marker of viable tumor tissue (*18*).

We decided to use a low-energy, general-purpose collimator instead of a high-resolution collimator used by other groups. There is a loss of resolution FWHN of 0.7 mm and 1.1 mm at 5 and 10 cm distances, respectively, by using a general-purpose collimator. On other hand, there is a 1.6 increase in the sensitivity by using a general-purpose collimator. Seven minutes acquisition with a general-purpose collimator would result in an increase of 16% of counts compared to 10 min with a high-resolution collimator. Dealing with the detection of hot lesions, the 1 mm loss of resolution is, in our view, well compensated by higher counts. Shortening the acquisition time makes the study more comfortable for patients and reduces the possibility of movement artifacts.

This study on the efficacy of ^{99m}Tc-MIBI scintimammography for the detection of breast tumors demonstrated that sensitivity strongly depended on palpability and histological size of the tumor. We found that 95% of 61 palpable tumors were detected compared with only 54% of 24 nonpalpable tumors. The sensitivity strongly correlated with histological size with poor sensitivity of 25% for lesions smaller than 1 cm, 78% for lesions ranged between 1 and 1.5 cm and high sensitivity of 94% for lesions larger than 1.5 cm (Table 4). In 1995, Khalkhali et al. (*10,11*) published their results of breast cancer detection with ^{99m}Tc-MIBI scintimammography. In their first study, 21 of the 106 lesions examined were nonpalpable and only three of the 21 were cancerous. Two (66%) were

TABLE 3
Indeterminate Mammography

Patient no.	Dense breast	Scintigraphy	Pathology		
			Malignancy	Histopathology	Size
1	Y	Negative	Negative	Fibrocystic changes	—
2	—	Negative	Negative	Fibrocystic changes	—
3	—	Positive	Positive	Inf. duct ca	2
4	—	Negative	Negative	Fibroadenoma; fibrocystic changes	—
5	—	Negative	Negative	Fibrocystic changes	—
6	Y	Negative	Negative	Fibroadenoma; fibrocystic changes	—
7	—	Negative	Negative	Fibrocystic changes	—
8	—	Negative	Positive	Extensive intraductal carcinoma	*

*Extensive diffuse intraductal carcinoma, impossible to evaluate size accurately.

TABLE 4
Nonpalpable Cancers

Patient no.	Pathological size (cm)	Positive scintigraphy	Mammography		Intraductal ca in situ	Inf. duct ca	Tubular ca
			Positive	Indeterminate			
1	*	—	—	Yes	Yes	—	—
2	*	Yes	Yes	—	Yes	—	—
3	*	—	Yes	—	Yes	—	—
4	*	Yes	Yes	—	Yes	—	—
5	0.50	—	Yes	—	Yes	—	—
6	0.70	—	Yes	—	—	Yes	—
7	0.80	Yes	Yes	—	—	Yes	—
8	0.90	—	Yes	—	—	—	Yes
9	1.00	—	Yes	—	—	Yes	—
10	1.00	Yes	Yes	—	—	Yes	—
11	1.00	Yes	Yes	—	—	Yes	—
12	1.10	Yes	Yes	—	—	Yes	—
13	1.10	Yes	Yes	—	—	Yes	—
14	1.20	—	Yes	—	—	—	Yes
15	1.20	Yes	Yes	—	—	Yes	—
16	1.20	—	Yes	—	—	Yes	—
17	1.30	Yes	Yes	—	—	Yes	—
18	1.50	—	Yes	—	Yes	—	—
19	1.50	Yes	Yes	—	—	Yes	—
20	2.00	—	Yes	—	—	Yes	—
21	2.00	Yes	Yes	—	—	Yes	—
22	2.00	Yes	—	Yes	—	Yes	—
23	2.00	—	Yes	—	Yes	—	—
24	3.00	Yes	Yes	—	Yes	—	—
Total		13	22	2	8	14	2

*Extensive diffuse intraductal carcinoma, impossible to evaluate a size accurately.

correctly identified by the authors (*10*). In their second paper, the total number of lesions studied was 153, and 40 of these were nonpalpable. Nine of the nonpalpable lesions proved to be malignant (*11*). The sensitivity of the detection of nonpalpable lesions in this latter publication improved to 88%. In our study, 55 patients of our total population of 140 had nonpalpable lesions, and of this group 24 were cancerous. The difference in the number of cancerous nonpalpable cases between the studies of Khalkhali et al., three cases in his first paper (*10*) and nine cases in his second paper (*11*), and this study, 24 cases, is evident. Waxman et al. (*13*) showed a sensitivity of 27% detecting six of 22 nonpalpable tumors studied with ^{99m}Tc-MIBI. The largest size of the missed tumors was 1.5 cm. Maffioli et al. (*19*), in the study of 14 nonpalpable breast tumors, showed a sensitivity of 50% with specificity of 90%. When correlated with histological size, the sensitivity was 33% and 62% for lesions smaller and larger than 1 cm, respectively.

In 14 false-negative scintimammography cases, mammography was positive for malignancy in 11 and suggestive of benign disease in three. On biopsy, six were malignant intraductal tumors and eight infiltrating carcinoma.

To improve small-lesion detection and location by scintimammography, SPECT with ^{99m}Tc-MIBI was used. Tiling et al. (*20*) found no increase in sensitivity between planar and SPECT studies performed in the same patients. Ryu et al. (*21*) found no improvement in sensitivity and a decrease in specificity by using SPECT.

Of the eight false-positive lesions on scintimammography, five also were read as probably malignant on mammography. Of 18 probably benign mammographies in patients with palpable findings, scintigraphy was true-positive in six of seven tumors found in this group. Of eight indeterminate mammographies, two were proven to be breast cancers, one of them was positive on scintigraphy. Of the 28 false-positive mammographies, 23 were true-negative on scintimammography.

Based on the results in our 140 patients, 85 of them with breast cancer, scintimammography improved the diagnostic accuracy in cases of palpable findings with probably benign mammographies and in the indeterminate cases. In nonpalpable cases, the sensitivity of scintimammography was unsatisfactory.

CONCLUSION

This study showed that the ^{99m}Tc-MIBI scintimammography is a valuable complementary tool in palpable breast lesions. For nonpalpable lesions, this study indicates the need for improving detection capability. The development of new, dedicated instrumentation could help overcome this drawback.

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Technetium-99m-MIBI Uptake in Small Cell Lung Cancer

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Patients with small cell lung cancer (SCLC) often fail to respond to chemotherapy due to multidrug resistance (MDR). Technetium-99m-MIBI was reported to be a suitable transport substrate of P-glycoprotein, which is a cytoplasmic membrane protein encoded by the MDR gene. The purpose of this study was to evaluate whether or not the degree of MIBI uptake in SCLC or its retention on delayed imaging correlated with response to chemotherapy. **Methods:** Twenty-five patients (19 men, 6 women; mean age 59 ± 10 yr) with biopsy-proven SCLC had MIBI SPECT 3–7 days before starting chemotherapy. Imaging was acquired 1 and 4 hr after injection of 740 MBq MIBI using a single-head rotating gamma camera. Tumor-to-normal lung uptake ratio (T/NL) was measured. Percent retention (%R) was measured as: %R = 100 × (T/NL at 4 hr)/(T/NL at 1 hr). All patients received VAP chemotherapy (VP-16 100 mg/m^2, adriamycin 40 mg/m^2, cisplatin 25 mg/m^2) every 4 wk for at least three times. Response to chemotherapy was grouped as complete remission, partial remission and no remission according to the change of tumor size on chest radiograph and CT images. Differences in T/NL and %R among the three groups were analyzed using ANOVA. **Results:** T/NL of patients with complete remission (n = 7) and partial remission (n = 10) were significantly higher than that of no remission (n = 8) in 1 hr and 4 hr. T/NL at 1 hr in three groups were 2.75 ± 0.78, 2.35 ± 0.31 and 1.65 ± 0.36, respectively. T/NL at 4 hr in three groups was 2.61 ± 0.94, 2.48 ± 0.50 and 1.66 ± 0.42, respectively. However, %R was not different among three groups. Percent retention in three groups was 109.40 ± 22.10, 96.71 ± 14.25 and 103.59 ± 28.43, respectively. **Conclusion:** SCLC with a higher MIBI uptake was more likely to respond to chemotherapy than that with a lower uptake. However, there was a considerable overlap of MIBI uptake among subjects. No significant correlation between the MIBI retention between 1 hr and 4 hr, and the response to chemotherapy was noted.

Key Words: technetium-99m-MIBI; small cell lung cancer; chemotherapy

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Although patients with small cell lung cancer (SCLC) usually respond well to chemotherapy, failure of chemotherapy was observed in 15% of SCLC patients (*1*). Failure of chemotherapy can be induced by the presence of P-glycoprotein (Pgp), a 170-kDa cytoplasmic membrane protein encoded by the MDR1 gene, which pumps out cytotoxic drugs such as anthracyclines, vinca alkaloids, epipodophyllotoxins, colchicine and actinomycin D (*2*). Recently, it has been found that Pgp also recognizes ^{99m}Tc-MIBI as a suitable transport substrate (*3*). One case report in particular showed that absence of ^{99m}Tc-MIBI uptake was associated with failure of chemotherapy (*4*). We hypothesized that higher ^{99m}Tc-MIBI uptake was related to better response to chemotherapy in SCLC and vice versa. The purpose of this study was to evaluate whether or not the degree of ^{99m}Tc-MIBI uptake in SCLC or its retention on delayed imaging correlated with response to chemotherapy.

MATERIALS AND METHODS

Twenty-five patients (19 men, 6 women; mean age 59 ± 10 yr) with biopsy-proven SCLC were studied. They underwent ^{99m}Tc-MIBI planar and tomographic imagings 3–7 days before starting chemotherapy. Imaging was acquired 1 hr and 4 hr after injection of 740 MBq (20 mCi) ^{99m}Tc-MIBI. Planar images (64 × 64 or 128 × 128 matrices, 10^6 counts) of the chest were acquired in the anterior projection on a large field-of-view gamma camera equipped with a low-energy, high-resolution, parallel-hole collimator and peaked at 140 keV with a symmetric 20% window. A single-head rotating gamma camera was used to obtain SPECT images immediately after planar imaging. Sixty-four projections of 20 sec each over a 360° circular orbit were obtained. Standard filtered backprojection processing with uniformity correction, but without attenuation correction, was used to create one-pixel sections in the transaxial plane followed by reconstruction in the coronal and sagittal planes. The reconstruction algorithm using a Hamming-Hann filter was reviewed on a computer terminal and photographed in single-pixel slices. Region of interests (ROI) were localized to the tumor mass and normal lung. From them, the tumor-to-normal lung ratio (T/NL) was obtained. Percent retention (%R) was measured as: %R = 100 × (T/NL at 4 hr)/(T/NL at 1 hr).

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