11. Khalkhali I, Cutrone JA, Mena IC, et al. Scintimammography: the complementary role of Tc-99m sestamibi prone breast imaging for the diagnosis of breast carcinoma. *Radiology* 1995;196:421–426.
12. 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.
13. Waxman A, Nagarai N, Kovalevsky M, et al. Detection of primary breast malignancy with Tc-99m methoxyisobutylisonitrile (MIBI) in patients with non-palpable primary malignancies: the importance of lesion size [Abstract]. *J Nucl Med* 1995;36:194P.
14. Khalkhali I, Mena I, Jouanne E, et al. Prone scintimammography in patients with suspicion of carcinoma of the breast. *J Am Coll Surg* 1994;178:491–497.
15. Hisada K, Tonami N, Miyamae T, et al. Clinical evaluation of tumor imaging with Tl-201 chloride. *Radiology* 1978;129:497–500.
16. Waxman AD, Ramanna L, Memsic LD, et al. Thallium scintigraphy in the evaluation of mass abnormalities of the breast. *J Nucl Med* 1993;34:18–23.
17. Muller ST, Reiners C, Pass M, et al. Technetium-99m MIBI and thallium-201 uptake in bronchial carcinoma [Abstract]. *Eur J Nucl Med* 1989;33:84.
18. Delmon-Moingeon I, Piwnica-Worms D, Van den Abbeele AD, et al. Uptake of the cation hexakis (2-methoxy isonitrile) ^{99m}Tc by human carcinoma cell lines in vitro. *Cancer Res* 1990;50:2198–2202.
19. Maffioli L, Agresti R, Chiti A, et al. Prone scintimammography in patients with non-palpable breast lesions. *Anticancer Res* 1996;16:1269–1273.
20. Tiling R, Pechmann M, Sommer H, et al. Does SPECT improve the diagnostic accuracy of planar scintimammography with sestamibi? [Abstract] *J Nucl Med* 1996;37:252P.
21. Ryu JS, Choi YY, Yang S-O, et al. Technetium-99m-sestamibi imaging in the evaluation of breast cancer and axillary lymphadenopathy: comparison of planar and SPECT imaging [Abstract]. *J Nucl Med* 1996;37:252P.

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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TABLE 1
Characteristics of 25 Subject Patients

Age (yr)	Sex	Stage	p(T/N)1	p(T/N)4	p(%R)	t(T/N)1	t(T/N)4	t(%R)	Response
72	F	L	1.37	1.41	97.16	2.03	1.87	108.56	CR
47	M	L	1.38	1.41	97.87	1.96	1.86	105.38	CR
63	M	L	1.64	1.68	97.62	2.37	2.56	92.58	CR
46	M	E	1.97	1.59	123.90	3.13	4.34	72.12	CR
46	M	E	1.97	1.84	107.07	3.13	2.32	134.91	CR
52	M	E	2.53	1.14	221.93	2.46	1.89	130.16	CR
53	M	E	1.18	1.16	101.72	4.15	3.40	122.06	CR
68	F	L	1.34	1.90	70.53	2.74	2.89	94.81	PR
49	M	L	1.51	1.80	83.89	2.14	2.23	95.96	PR
54	M	L	1.68	1.56	107.69	2.45	2.34	104.70	PR
56	M	L	1.68	1.66	101.20	2.54	2.40	105.83	PR
65	M	L	1.80	1.91	94.24	2.48	2.44	101.64	PR
48	F	E	1.18	1.09	108.26	2.01	3.36	59.82	PR
58	M	E	2.01	1.92	104.69	2.50	2.57	97.28	PR
68	M	E	1.28	1.37	93.43	1.91	1.76	108.52	PR
73	M	E	1.39	1.38	100.72	2.71	2.98	90.94	PR
78	M	E	1.50	1.16	129.31	1.99	1.85	107.57	PR
53	M	L	1.22	1.20	101.67	1.55	1.23	126.02	NC
66	M	L	1.77	1.20	147.5	1.93	1.87	103.21	NC
48	F	L	1.27	1.04	122.12	1.62	1.04	155.77	NC
68	F	L	1.95	1.58	123.42	2.11	1.82	115.93	NC
70	F	L	1.10	1.13	97.35	1.51	1.91	79.06	NC
48	M	E	1.40	1.38	101.45	2.08	2.24	92.86	NC
52	M	E	1.04	1.90	54.74	1.14	1.28	89.06	NC
71	M	E	1.23	1.23	100.00	1.27	1.90	66.84	PD

p(T/N)1 and p(T/N)4 = planar tumor-to-normal lung ratio at 1 and 4 hr; p(%R) = percent retention calculated from planar images; t(T/N)1 and t(T/N)4 = tomographic tumor-to-normal lung ratio at 1 and 4 hr; t(%R) = percent retention calculated from tomographic images; L = limited stage; E = extensive stage; CR = complete response; PR = partial response; NC = no change; PD = progressive disease.

Differences in T/NL and %R among the three groups were analyzed using ANOVA.

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 response, partial response, no change and progressive disease according to the change of tumor size on chest radiograph and CT images. If there was no change or an increase in tumor size on chest radiograph, we omitted CT imaging. According to the WHO criteria (*5*), definitions of complete remission, partial remission, no change and progressive disease were as follows: complete remission = disappearance of all known disease; partial remission = 50% or more decrease in total tumor load; no change = < 50% decrease or < 25% increase in total tumor load; and progressive disease = > 25% increase in total tumor load or appearance of new lesions.

RESULTS

Among 25 patients, 7 showed complete remission, 10 showed partial remission, 7 showed no change and 1 showed progressive disease (Table 1). No change and progressive disease were grouped as no response for statistical analysis. There was no statistical difference of age and sex between three groups.

Table 2 shows the comparison of uptakes and retention of ^{99m}Tc-MIBI according to the response to chemotherapy (complete remission, partial remission and no remission). T/NL of planar images showed no statistically significant difference between groups, while T/NL of tomographic images was significantly different between groups ($p = 0.001$ on 1 hr image; $p = 0.014$ on 4 hr image). However, a considerable overlap was noted between groups. Percent retention between 1 and 4 hr was not different between groups either on planar or tomographic images. Figures 1 and 2 were cases illustrating patients with complete remission and no change, respectively.

DISCUSSION

Technetium-99m-MIBI uptake is related to the chemotherapy response in patients with SCLC. In other words, SCLC patients with higher uptakes of ^{99m}Tc-MIBI were more likely to respond to chemotherapy than those with lower uptakes.

Factors related to ^{99m}Tc-MIBI uptake in tumors are blood flow, tissue viability, vascular permeability, tumor necrosis, metabolic demand and mitochondrial activity of the tumor, and Pgp or multidrug resistance associated protein (MRP) expression in tumor tissue (*6*). Among them, Pgp or MRP expression is clearly associated with multidrug resistance. Blood flow to the tumor could be related to the response to chemotherapy. Higher blood flow to the tumor, which is related to higher uptake of ^{99m}Tc-MIBI in tumor (*7*), might render the tumor

TABLE 2
Comparison of Technetium-99m MIBI Uptakes According to Response To Chemotherapy

Parameters	Response to chemotherapy			p value
	CR (n = 7)	PR (n = 10)	NR (n = 8)	
p(T/N)1	1.72 ± 0.47	1.54 ± 0.26	1.37 ± 0.32	0.176
p(T/N)4	1.46 ± 0.26	1.58 ± 0.31	1.33 ± 0.28	0.233
p(%R)	121.04 ± 45.48	99.40 ± 15.67	106.03 ± 26.90	0.353
t(T/N)1	2.75 ± 0.78	2.35 ± 0.31	1.65 ± 0.36	0.001
t(T/N)4	2.61 ± 0.94	2.48 ± 0.50	1.66 ± 0.42	0.014
t(%R)	109.40 ± 22.10	96.71 ± 14.25	103.59 ± 28.43	0.500

See table 1 for abbreviations.

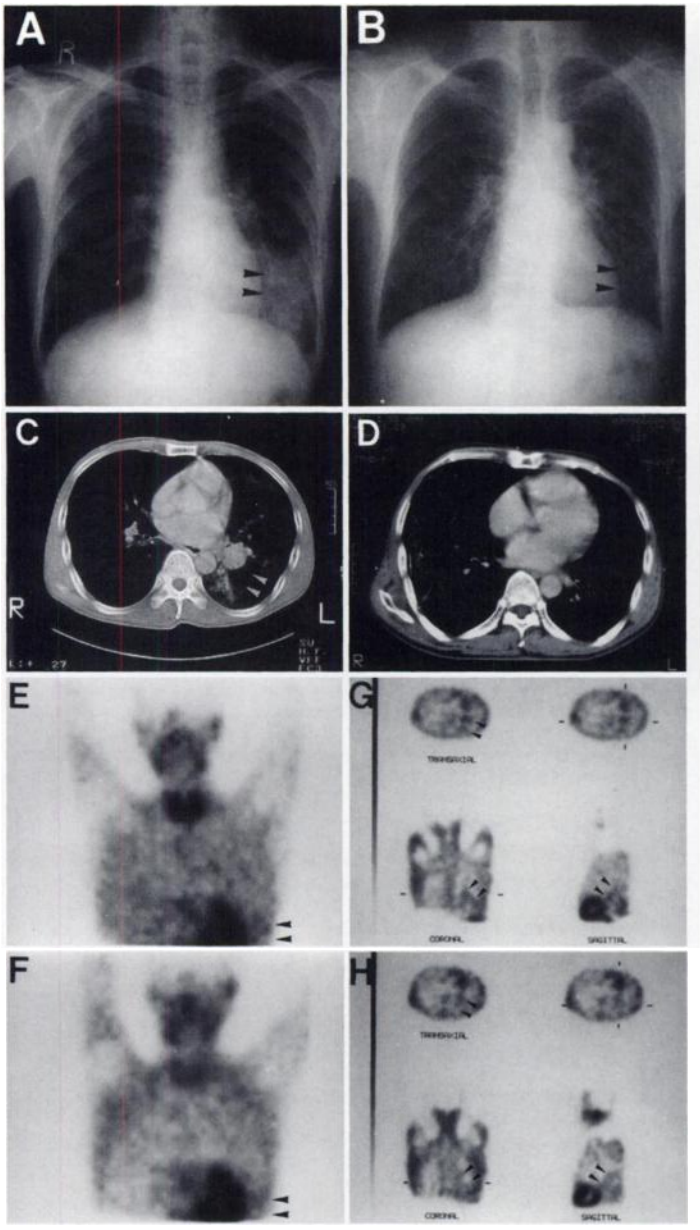

FIGURE 1. Complete response. A tumor mass in the left lower lung (black arrow heads, (A) was completely resolved after three courses of VAP chemotherapy (black arrowheads, (B). CT images before (C) and after (D) chemotherapy show disappearance of tumors (white arrowheads). Both 1 hr (E) and 4 hr (F) ^{99m}Tc-MIBI planar images show hot uptakes in the left lower lung (black arrowheads). One hour (G) and 4 hr (H) tomographic images of ^{99m}Tc-MIBI show hot uptakes in the tumor (small black arrowheads). Apparent washout of ^{99m}Tc-MIBI is noted in both planar and tomographic images.

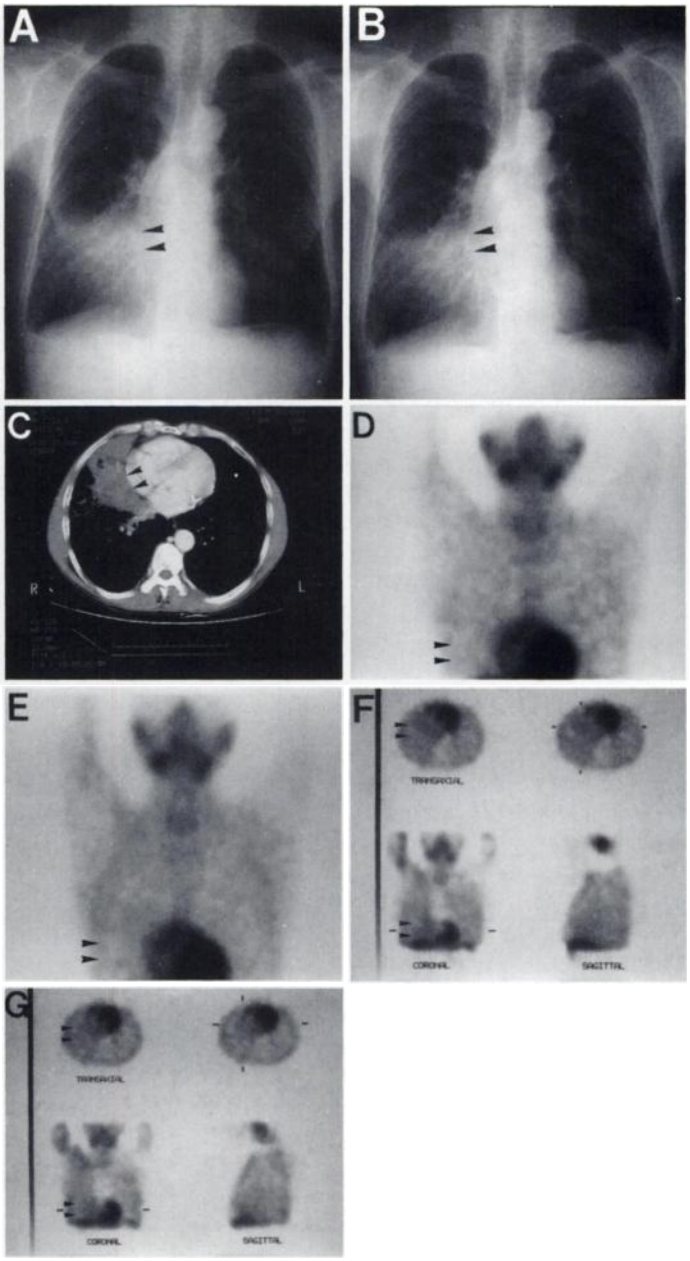

FIGURE 2. No response. A tumor mass in the right middle lung (black arrowheads, (A) was not resolved after three courses of VAP chemotherapy (black arrowheads, (B). CT shows a tumor lesion in the right middle lung (black arrowheads, (C). Technetium-99m-MIBI planar and tomographic imagings were done before chemotherapy. One hour (D) and 4 hr (E) planar images of anterior chest show no uptake in the tumor mass (black arrowheads). One hour (F) and 4 hr (G) tomographic images of ^{99m}Tc-MIBI SPECT show only faint uptake in the tumor mass (small black arrowheads).

cells to have more chance to be exposed to chemotherapeutic agents. Factors associated with multidrug resistance are ATP binding cassette transporters such as Pgp or MRP, altered topoisomerase II, enhanced glutathione transferances and detoxification mechanisms, enhanced DNA repair and low levels of cytochrome p450 reductase (*8*). Among them, only Pgp and MRP expressions were reported to be related to ^{99m}Tc-MIBI uptake (*3,9*). Moretti et al. (*4*) first reported that absence of ^{99m}Tc-MIBI uptake in SCLC was associated with failure of chemotherapy. They underwent both ^{99m}Tc-MIBI and ^{111}In-octreotide scintigraphies and showed positive uptake of ^{111}In-octreotide and negative uptake of ^{99m}Tc-MIBI. Similar results could be obtained if we use both ^{201}Tl and ^{99m}Tc-MIBI (*10*).

The tumor-to-normal lung ratio on 1 hr tomographic image was best in prediction of response to chemotherapy followed by T/NL on 4 hr tomographic image. The tumor-to-normal lung ratio on planar images failed to differentiate response groups. SPECT offers advantages over planar imaging in the evaluation of tumoral uptake in the body because of increased contrast enhancement, which allows for precise anatomic localization of tumor. Therefore, use of tomographic imaging is recommended to evaluate or quantitate tumoral uptake of ^{99m}Tc-MIBI in lung cancer.

Although there is significant difference of ^{99m}Tc-MIBI uptake between responders and nonresponders, there was considerable overlap among subjects. So, the prediction of outcome in an individual patient might be difficult if the uptake was borderline. However, those patients who showed hot uptake (ratio > 3.0) responded well to chemotherapy (complete remis-

sion) while those who showed faint uptake (ratio < 1.7) did not respond to chemotherapy.

The time sequence of ^{99m}Tc-MIBI washout in Pgp expressed or not expressed tumor cells is not well known especially in vivo. Piwnica-Worms et al. (*11*) characterized multidrug resistance Pgp transport function with ^{99m}Tc-MIBI. They showed a rapid excretion of ^{99m}Tc-MIBI from Pgp expressed Chinese hamster V79 lung fibroblast cell lines in vitro. T1/2 was < 5 min. Although planar imagings were acquired earlier, (< 15 min) after injection of ^{99m}Tc-MIBI (*12*), tomographic imagings of lung tumors using ^{99m}Tc-MIBI were usually done at 1 hr and delayed imaging in 2–3 hr after injection (*13*). In this study, we measured the retention of ^{99m}Tc-MIBI between 1 and 4 hr, which might be too late. Late measurement could be one of the reasons why there was no relationship between %R and response to chemotherapy. Recently, Luker et al. (*14*) acquired images 30 min and 90 min after ^{99m}Tc-MIBI injection. They chose this time on the basis of known organ pharmacokinetics of ^{99m}Tc-MIBI (*15*). Yamamoto et al. (*16*) obtained early and delayed imagings at 15 min and 180 min after ^{99m}Tc-MIBI injection. They found that responders to chemotherapy showed higher T/NL on the early images and higher retention index.

One of the limitations of our study is lack of histopathological backup of P-glycoprotein in our histological specimens. Because we have only small bronchoscopic biopsy specimens, we could not do histopathologic assessment of Pgp in cellular level. Tumor markers were used to predict survival and monitor remission in SCLC patients (*17–19*). Serum neuron specific enolase was significantly related to extent of disease, to response duration and to prognosis. Serum lactic dehydrogenase was also a strong prognostic factor, and an increase in serum lactic dehydrogenase level is often a sign of progressing metastases especially in the liver and bone marrow (*17*). The response rate to chemotherapy was also correlated with serum levels of chromogranin A (*18*) and C-reactive protein (*19*). We did not correlate ^{99m}Tc-MIBI uptake with tumor markers that were known to be related to prognosis in SCLC patients. It would be worthwhile to compare ^{99m}Tc-MIBI uptake to tumor marker levels or changes.

CONCLUSION

This study reports the correlation between the degree of ^{99m}Tc-MIBI uptake in SCLC or its retention on delayed imaging with the response to chemotherapy in 25 patients. SCLC patients with higher uptake of ^{99m}Tc-MIBI are more likely to respond to chemotherapy than those with lower uptakes. However, there was considerable overlap of uptake among subjects. No significant correlation between the ^{99m}Tc-MIBI retention between 1 hr and 4 hr, and the response to chemotherapy was noted.

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REFERENCES

1. Ihde DC. Chemotherapy of lung cancer. *N Engl J Med* 1992;327:1434–1441.
2. Deuchars KL, Ling V. P-glycoprotein and multidrug resistance in cancer chemotherapy. *Semin Oncol* 1989;16:156–165.
3. Piwnica-Worms D, Chiu ML, Budding M, Kronauge JF, Kramer RA, Croop JM. Functional imaging of multidrug-resistant P-glycoprotein with an organotechnetium complex. *Cancer Res* 1993;53:977–984.
4. Moretti JL, Caglar M, Boaziz C, Caillat-Vigneron N, Morere JF. Sequential functional imaging with technetium-99m hexakis-2-methoxyisobutylisonitrile and indium-111 octreotide: can we predict the response to chemotherapy in small cell lung cancer? *Eur J Nucl Med* 1995;22:177–180.
5. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207–214.
6. Waxman AD. Thallium-201 and technetium-99m methoxyisobutyl isonitrile (MIBI) in nuclear oncology. In: Sandler MP, Coleman RE, Wackers FJT, Patton JA, Gottschalk A, Hoffer PB, eds. *Diagnostic nuclear medicine*, 3rd ed. Baltimore: Williams and Wilkins 1996:1261–1274.
7. Scopinaro F, Schillaci O, Scarpini M, et al. Technetium-99m sestamibi: an indicator of breast cancer invasiveness. *Eur J Nucl Med* 1994;21:984–987.
8. Harris AL, Hochhauser D. Mechanisms of multidrug resistance in cancer treatment. *Acta Oncologica* 1992;31:205–213.
9. Crankshaw C, Piwnica-Worms D. Tc-99m sestamibi may be a transport substrate of the human multidrug resistance-associated protein (MRP) [Abstract]. *J Nucl Med* 1996;37:247P.
10. Kapucu LO, Akyuz C, Vural G, et al. The value of MIBI scintigraphy in predicting the prognosis in pediatric patients with lymphoma [Abstract]. *J Nucl Med* 1996;37:139P.
11. Piwnica-Worms D, Rao VV, Kronauge JF, Croop JM. Characterization of multidrug-resistance P-glycoprotein transport function with an organotechnetium cation. *Biochemistry* 1995;34:12210–12220.
12. Hassan I, Sahweel C, Constantinides A, et al. Uptake and kinetics of Tc-99m hexakis 2-methoxy isobutyl isonitrile in benign and malignant lesions in the lungs. *Clin Nucl Med* 1989;14:333–340.
13. Lebouthillier G, Taillefer R, Lambert R, et al. Detection of primary lung cancer with Tc-99m MIBI [Abstract]. *J Nucl Med* 1989;34:140P.
14. Luker GD, Fracasso PM, Dobkin J, Piwnica-Worms D. Modulation of the multidrug-resistance P-glycoprotein: detection with technetium-99m-sestamibi in vivo. *J Nucl Med* 1997;38:369–372.
15. Wackers FJ, Berman D, Maddahi J, et al. Technetium-99m-hexakis 2-methoxy isobutilisonitrile: human biodistribution, dosimetry, safety and preliminary comparison to thallium-201 for myocardial perfusion imaging. *J Nucl Med* 1989;30:301–311.
16. Yamamoto Y, Nishiyama Y, Fukynaga K, Satoh K, Takashima H, Tanabe M. Evaluation of Tc-99m MIBI to predict chemotherapeutic response of patients with small cell lung cancer [Abstract]. *Ann Nucl Med* 1996;10(suppl):S137.
17. Jorgensen LG, Osterlind K, Hansen HH, Cooper EH. Serum neuron-specific enolase (S-NSE) in progressive small cell lung cancer (SCLC). *Br J Cancer* 1994;70:759–761.
18. Johnson PW, Joel SP, Love S, et al. Tumor markers for prediction of survival and monitoring of remission in small cell lung cancer. *Br J Cancer* 1993;67:760–766.
19. Arpin D, Trillet-Lenoir V, Lasset C, et al. Value of C-reactive protein determination in small cell lung cancer. *Bull Cancer* 1993;80:1063–1068.