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Technetium-99m-Sestamibi Scintigraphy Compared with Thallium-201 in Evaluation of Thyroid Tumors

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Technetium-99m methoxyisobutylisonitrile (MIBI) is a myocardial perfusion imaging agent that has been reported to effectively localize in various tumors (e.g., lung and thyroid carcinomas and osteogenic sarcoma). To determine its usefulness in thyroid tumors, we compared ^{99m}Tc-MIBI with ^{201}Tl imaging. **Method:** We evaluated 25 patients with thyroid tumors (papillary carcinoma in 11, follicular carcinoma in 2, follicular adenoma in 7, adenomatous goiter in 5). Fifteen metastatic lesions from differentiated thyroid carcinomas were also evaluated. Early (10 min after injection) and delayed images (120 min after injection) were obtained for both ^{99m}Tc-MIBI and ^{201}Tl scintigraphy. **Results:** The early images showed very similar findings for both ^{99m}Tc-MIBI and ^{201}Tl. However, the delayed images showed that malignant tumors tended to retain more tracer agent than benign nodules. Marked retention was in 61.5% (8 of 13) of ^{201}Tl images and 53.8% (7 of 13) of ^{99m}Tc-MIBI images. For metastatic lesions from thyroid carcinomas, the findings for ^{99m}Tc-MIBI imaging were nearly identical to those for ^{201}Tl imaging. A slight difference in clarity was seen that may have been due to the effect of the ^{99m}Tc. **Conclusion:** Although ^{99m}Tc-MIBI scintigraphy does not have particularly good results in differentiating malignant from benign thyroid tumors, it may be useful in evaluating metastases or predicting recurrence because of its better imaging characteristics.

Key Words: technetium-99m-sestamibi; thallium-201; thyroid tumors

J Nucl Med 1996; 37:901–904

Technetium-99m-methoxyisobutylisonitrile (MIBI) was introduced as a myocardial perfusion agent in 1989 (*1,2*). Like ^{201}Tl, ^{99m}Tc-MIBI has been reported to accumulate in benign and malignant lesions, such as lung (*3,4*), brain (*5,6*) and parathyroid tumors (*7,8*) and bone lesions (*9*).

In thyroid tumors, ^{201}Tl scintigraphy has been used to differentiate benign from malignant nodules (*10–12*) and to locate metastatic or recurrent lesions in follow-up studies (*13–15*). Delayed scanning was reported to be useful in differentiating malignant from benign tumors, but the results were not very satisfactory.

Recently, Maublant et al. (*16*) reported that accumulation of ^{99m}Tc-MIBI was more useful in distinguishing normal from malignant cells than ^{201}Tl in an in vitro study. In the present report, we evaluate the usefulness of ^{99m}Tc-MIBI in differentiating malignancies in thyroid tumors and detecting metastatic or recurrent thyroid cancers.

Received Jul. 14, 1995; revision accepted Dec. 13, 1995.

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MATERIALS AND METHODS

We studied 25 patients with primary thyroid tumor (21 women, 4 men; mean age 53.3 yr, range 29–75 yr) and 15 with metastatic or recurrent lesions from thyroid cancer (11 women, 4 men; mean age 58.8 yr, range 30–78 yr). Of the 25 patients with primary thyroid tumors, papillary carcinoma occurred in 11, follicular carcinoma in 2, follicular adenoma in 7 and adenomatous goiter in 5. In these patients, all but one tumor consisted mainly of a solid mass; the remaining adenomatous goiter had had small cystic components. Of the 15 patients with metastatic lesions from thyroid cancer, papillary carcinoma occurred in 13 (10 from the lymph nodes, 3 from the lungs) follicular carcinoma in 2 (both from bone).

All patients underwent both ^{99m}Tc-MIBI and ^{201}Tl scintigraphy within 5 days. The ^{99m}Tc-MIBI was prepared by adding 740 MBq of [^{99m}Tc]pertechnetate in 5 ml saline solution to a freeze-dried kit. In the 25 patients with primary thyroid tumor, 74 MBq ^{201}Tl was injected, and 185 MBq ^{99m}Tc-MIBI was administered intravenously. In the 15 patients with metastatic lesions, 111 MBq ^{201}Tl was injected, and 740 MBq ^{99m}Tc-MIBI was administered intravenously. At follow-up study, thyroid suppression therapy (thyroxine medication) was not stopped before the studies, and ^{131}I studies were not performed in all patients.

Static images were obtained 10 min (early image) and 120 min (delayed image) after injection in patients with primary thyroid tumors. Whole-body and static images (early and delayed images) were obtained in patients with metastatic lesions. Imaging was performed with a gamma camera with a high-resolution collimator.

Accumulation of both ^{99m}Tc-MIBI and ^{201}Tl in primary thyroid tumors was classified as high (uptake in tumor was higher than that in normal thyroid tissue); iso (uptake in tumor was almost equal to that of normal thyroid tissue); or low (uptake in tumor was lower than that in normal thyroid tissue).

A semiquantitative method for assessing uptake was used, whereby uptake was measured in rectangular (10 mm × 10 mm) regions of interest (ROIs) over tumor and normal thyroid tissue. Tumor uptake of ^{99m}Tc-MIBI and ^{201}Tl was expressed as the

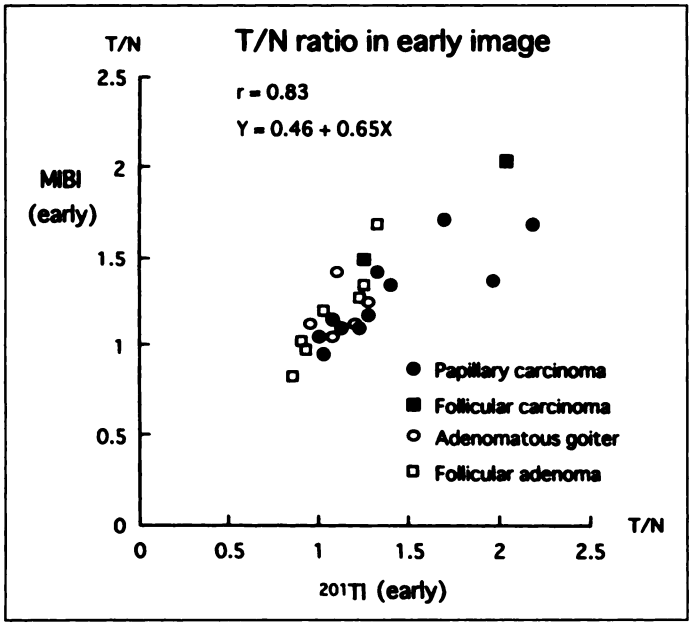

FIGURE 1. Correlation between ^{99m}Tc-MIBI and ^{201}Tl T/N ratios on early images from 25 patients with thyroid tumor.

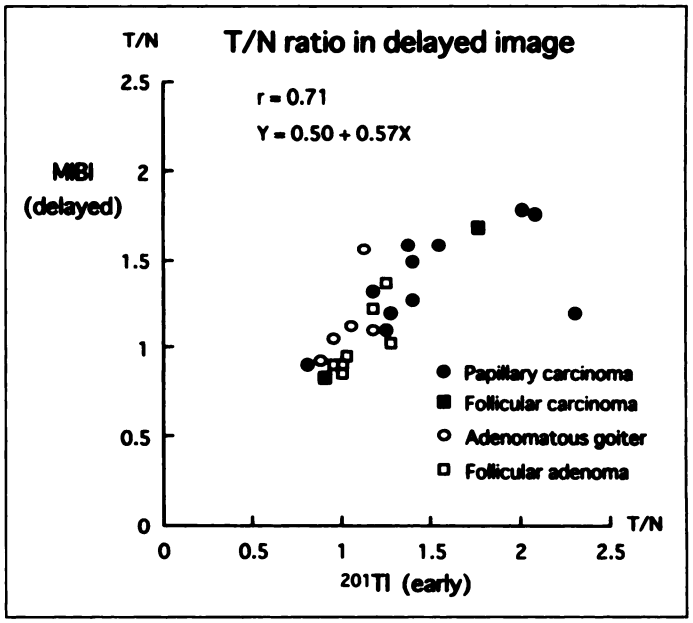

FIGURE 2. Correlation between ^{99m}Tc-MIBI and ^{201}Tl T/N ratios on delayed images from 25 patients with thyroid tumor.

tumor-to-normal thyroid tissue activity ratio (T/N ratio), or the ratio of activity in the ROI of the tumor to the activity of the ROI that was positioned on the normal thyroid tissue.

For metastatic lesions from thyroid carcinomas, only those 1 cm in diameter or larger were evaluated. Both ^{99m}Tc-MIBI and ^{201}Tl accumulations in metastatic lesions were classified as positive (accumulation was clearly depicted); equivocal (accumulation was ambiguously depicted); or negative (accumulation was not depicted).

RESULTS

Primary Tumors

Figure 1 shows the correlation between the ^{99m}Tc-MIBI and ^{201}Tl T/N ratios on the early images from 25 patients with thyroid tumors (correlation coefficient $r = 0.83$; $p < 0.001$; slope of computed regression line 0.65). Figure 1 reveals a relative linear relationship between the T/N ratios of ^{99m}Tc-MIBI and ^{201}Tl images.

Figure 2 shows the correlation between ^{99m}Tc-MIBI and ^{201}Tl T/N ratios on the delayed images from the same patients (correlation coefficient $r = 0.71$; $p < 0.001$; slope of computed regression line 0.57). On the delayed images, the relationship between the T/N ratios of ^{99m}Tc-MIBI and ^{201}Tl was not as linear as on the early images.

Table 1 details the scintigraphic findings in 25 patients with primary thyroid tumors. All 11 papillary carcinomas showed iso or high accumulation of both ^{201}Tl and ^{99m}Tc-MIBI on the early images. The delayed images revealed a high accumulation of ^{201}Tl (7 of 11 tumors), nearly identical to that for ^{99m}Tc-MIBI (6 of 11 tumors) (Fig. 3).

On early imaging of the two follicular carcinomas, one had a high accumulation of both ^{201}Tl and ^{99m}Tc-MIBI, and the second had a nearly identical accumulation of both ^{201}Tl and ^{99m}Tc-MIBI. On delayed imaging, the first tumor had a high accumulation, but the second had washed out both tracers.

Of the seven follicular adenomas, two revealed relatively low accumulation, four had iso accumulation and one had high accumulation in both early images compared with normal thyroid tissue. On delayed imaging, the same two tumors revealed low accumulation, only three revealed iso accumulation and two had relatively high accumulation compared with normal thyroid tissue.

In the five patients with adenomatous goiter, two low and three iso accumulations were seen on the early images of both ^{201}Tl and ^{99m}Tc-MIBI. On the delayed images, the same two tumors revealed low accumulation, and two had iso accumulation. The remaining tumor showed high accumulation in one part of the adenomatous nodules on both images. In all 25 primary thyroid tumors, ^{201}Tl and ^{99m}Tc-MIBI images had nearly identical findings, but ^{99m}Tc-MIBI images were slightly clearer than ^{201}Tl images.

Metastatic or Recurrent Lesions from Thyroid Carcinomas

Table 2 shows the scintigraphic findings in patients with metastatic lesions from thyroid carcinomas. In 10 patients with metastatic lymph nodes, 29 were over 1 cm in diameter. Of

TABLE 1
Scintigraphic Results for Thyroid Tumors

		Scintigraphic appearance			T/N ratio	
		Low	Iso	High	Mean	(s.d.)
Papillary carcinoma (n = 11)						
^{201}Tl	Early	0	8	3	1.39	0.41
^{99m}Tc-MIBI	Early	0	8	3	1.27	0.25
^{201}Tl	Delayed	0	4	7	1.52	0.44
^{99m}Tc-MIBI	Delayed	0	5	6	1.39	0.29
Follicular carcinoma (n = 2)						
^{201}Tl	Early	0	1	1	1.66	0.57
^{99m}Tc-MIBI	Early	0	1	1	1.77	0.38
^{201}Tl	Delayed	1	0	1	1.34	0.57
^{99m}Tc-MIBI	Delayed	1	0	1	1.27	0.58
Follicular adenoma (n = 7)						
^{201}Tl	Early	2	4	1	1.10	0.21
^{99m}Tc-MIBI	Early	2	4	1	1.21	0.29
^{201}Tl	Delayed	2	3	2	1.07	0.18
^{99m}Tc-MIBI	Delayed	2	3	2	1.03	0.20
Adenomatous goiter (n = 5)						
^{201}Tl	Early	2	3	0	1.11	0.11
^{99m}Tc-MIBI	Early	2	3	0	1.20	0.14
^{201}Tl	Delayed	2	2	1	1.10	0.13
^{99m}Tc-MIBI	Delayed	2	2	1	1.14	0.26

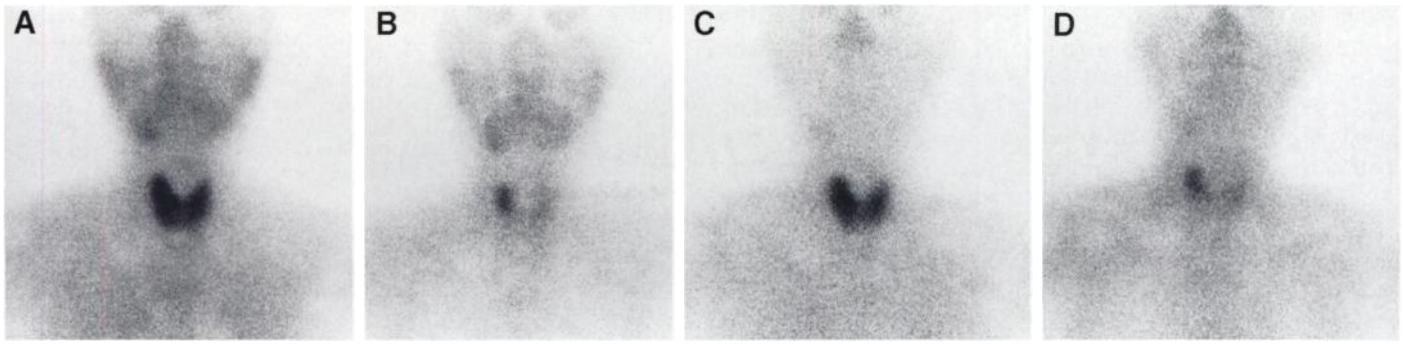

FIGURE 3. (A) Early ^{99m}Tc-MIBI image in a patient with papillary carcinoma in the right lobe of the thyroid. Accumulation in the tumor was nearly identical to normal thyroid tissue. (B) Delayed ^{99m}Tc-MIBI image in the same patient showing a high accumulation in the tumor but low accumulation in normal thyroid tissue. (C) Early ^{201}Tl image in the same patient. Accumulation in the tumor was nearly equal to that in the normal thyroid tissue. (D) Delayed ^{201}Tl image in the same patient. The tumor had high accumulation, and the normal thyroid tissue had low accumulation. Findings were nearly identical for both ^{99m}Tc-MIBI and ^{201}Tl scintigraphy, but ^{99m}Tc-MIBI images were slightly clearer.

these 29 lymph nodes, 25 were clearly depicted (positive) (Fig. 4), and 4 were equivocal or had no depiction (equivocal or negative) on both ^{201}Tl and ^{99m}Tc-MIBI images. Of these four less clearly depicted metastatic lymph nodes, three were in the submandibular regions below the mandibular angle, and one was the paratracheal lymph node just below the thyroid gland.

In three patients with lung metastases, nine metastatic nodules were estimated to be over 1 cm in diameter by CT. Six of seven of these nodules were clearly depicted on both ^{201}Tl and ^{99m}Tc-MIBI scintigrams. Accumulation was unclear in two of three images for both ^{201}Tl and ^{99m}Tc-MIBI. These findings were nearly identical, but ^{99m}Tc-MIBI images were slightly clearer than ^{201}Tl images.

In two patients with metastatic bone tumors, metastases of cervical vertebrae and the left eighth rib were evaluated. Both metastases were clearly depicted on both images, but a high accumulation ^{201}Tl in the liver and small intestine and ^{99m}Tc-MIBI in the liver/biliary system and small intestine hid the lower thoracic/lumbar vertebral regions.

DISCUSSION

Technetium-99m-MIBI is a superior myocardial perfusion agent (*1,2*). It is a lipophilic cationic agent whose myocardial distribution is proportional to regional blood flow. It has been reported that ^{99m}Tc-MIBI accumulates within the mitochondria and cytoplasma of cells on the basis of the electrical potentials generated across the membrane bilayers (*17*), whereas ^{201}Tl mostly follows the potassium pathway through the ATPase-dependent Na^+/K^+ pump (*18,19*).

Recently, ^{99m}Tc-MIBI has been reported to accumulate in benign and malignant lesions, such as lung (*3,4*), brain (*5,6*), carcinoid (*20*) and parathyroid tumors (*7,8*) and bone lesions (*9*). In thyroid tumors, this tracer is reported to accumulate in recurrent Hurthle cell carcinoma (*21*) and primary thyroid lymphoma (*22*).

In thyroid tumors, ^{201}Tl has been used to differentiate benign from malignant nodules (*10–12*) and to find metastatic or recurrent lesions during follow-up studies (*13–15*). Delayed imaging has been reported to be useful in differentiating malignant tumor from benign tumor, but the results were not very satisfactory. Like ^{201}Tl, ^{99m}Tc-MIBI does not require stopping thyroid medications before beginning the study. We think that ^{99m}Tc-MIBI scintigraphy is advantageous over ^{131}I scintigraphy in that it requires no preparation before study.

In the present study, ^{99m}Tc-MIBI images were very similar to ^{201}Tl images. In papillary carcinoma, 6 (54.5%) of 11 tumors showed marked retention of ^{99m}Tc-MIBI, and 7 (63.6%) of 11 tumors showed marked retention of ^{201}Tl on the delayed image. In differentiating malignant from benign thyroid nodules, El-Desouki et al. (*11*) and Ochi et al. (*12*) reported a sensitivity of over 90% (for tracer retention in tumors on the delayed images) for ^{201}Tl, but Koizumi et al. (*10*) reported a 74% sensitivity in 246 thyroid nodules. We think that these results are dependent on tumor size to some degree. In the present study, one of two follicular carcinomas showed marked accumulation on both early and delayed images, whereas the other showed high accumulation on the early image only and no accumulation on the delayed image for both ^{99m}Tc-MIBI and ^{201}Tl. In well-differentiated follicular carcinomas, neoplastic follicles are similar to those of histologically normal thyroid tissue. We agree with Ochi et al. (*12*) that differentiation of well-differen-

TABLE 2
Scintigraphic Results in Metastatic Lesions (> 1cm) from Thyroid Carcinomas

	Positive	Equivocal	Negative
LN (n = 29) in ten patients			
^{201}Tl	25	1	3
^{99m}Tc-MIBI	25	2	2
Lung metastases (n = 9) in three patients			
^{201}Tl	6	3	0
^{99m}Tc-MIBI	7	2	0
Bone metastases (n = 2) in two patients			
^{201}Tl	2	0	0
^{99m}Tc-MIBI	2	0	0

LN = lymph node.

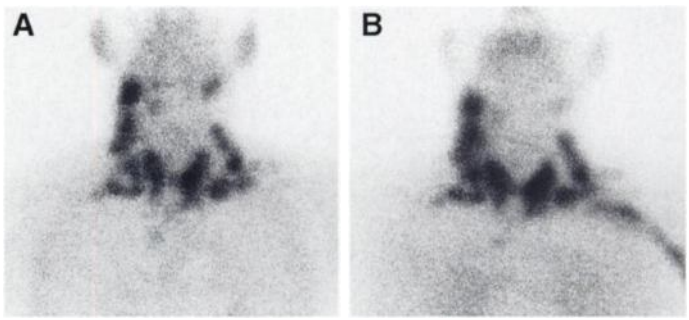

FIGURE 4. (A) Early ^{99m}Tc-MIBI image in a patient with papillary carcinoma with cervical lymphadenopathy showing several metastatic lymph nodes in the bilateral neck region and one in the upper mediastinum. (B) Early ^{201}Tl image in the same patient shows findings similar to those on the ^{99m}Tc-MIBI image. The ^{99m}Tc-MIBI image is clearer than the ^{201}Tl image, and one lymph node in the upper mediastinum is slightly clearer on the ^{99m}Tc-MIBI image than the ^{201}Tl image.

tiated follicular carcinoma may be beyond the scope of a scintigraphic study. For benign nodules (follicular adenoma and adenomatous goiter) in our series, 8 (66.7%) of 12 nodules had no marked retention of either ^{99m}Tc-MIBI or ^{201}Tl on the delayed images. Previously, benign thyroid nodules were reported to show no increased thallium activity in 92% (*11*) and 89.7% (*12*), but 58% showed no increased thallium activity on visual evaluation of 246 lesions (*10*). These results are disappointing compared with those for aspiration cytology, with a sensitivity of 65% to 98% and a specificity of 72% to 100% (*23,24*). However, critics point out that fine-needle biopsy has limitations according to the skill of aspirator, the expertise of the cytologist and the difficulty in differentiating some benign adenomas from malignancies (*23*). Therefore, ^{99m}Tc-MIBI or ^{201}Tl imaging should be used to supplement aspiration cytology in the differentiation of the thyroid tumors.

As for the evaluation of metastases or recurrences, ^{99m}Tc-MIBI and ^{201}Tl images and results were nearly identical. About 34 (85.0%) of 40 metastases or recurrences were clearly revealed on the early images for both ^{99m}Tc-MIBI and ^{201}Tl. These results are relatively satisfactory. The ^{99m}Tc-MIBI images were slightly clearer than those of ^{201}Tl. However, Brendel et al. (*13*) reported that ^{201}Tl imaging is not recommended as the only modality for follow-up studies in patients with well-differentiated thyroid carcinoma because the sensitivity of ^{201}Tl imaging for detecting tumor location is not 100%, and serum thyroglobulin measurements are more reliable in successful thyroid ablation. We share this opinion and recommend the combination of ^{99m}Tc-MIBI or ^{201}Tl imaging with thyroglobulin measurement during the follow-up period.

CONCLUSION

Technetium-99m-MIBI images were similar to ^{201}Tl images. In differentiating malignant from benign tumors in thyroid masses, both ^{99m}Tc-MIBI and ^{201}Tl were insufficient compared with aspiration cytology. However, these studies help with the diagnosis when the aspiration study results are unsatisfactory and when imaging reveals metastatic lymph nodes or strong accumulation on the delayed image. Technetium-99m-MIBI studies are also useful in follow-up evaluation of thyroid carcinoma because of the superior imaging characteristics of ^{99m}Tc-MIBI compared with ^{201}Tl.

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