Comparison of ^{99m}Tc-Methoxyisobutyl Isonitrile and ^{201}Tl Scintigraphy for Detection of Residual Thyroid Cancer After ^{131}I Ablative Therapy

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In this study, we compared ^{99m}Tc-methoxyisobutyl isonitrile (MIBI) with ^{201}Tl scintigraphy for the detection of residual thyroid cancer not found by ^{131}I scans in patients with increased risk of recurrence after ^{131}I therapy. **Methods:** ^{201}Tl and MIBI scans were obtained in 54 patients with negative ^{131}I scans 3–25 y (median 7.9 y) after the first postsurgical ^{131}I therapy. Serum thyroglobulin (Tg) levels were measured while patients were receiving thyroid hormone and again 6 wk after withdrawal of hormone therapy. **Results:** The overall results were the same for both ^{201}Tl and MIBI imaging, with a sensitivity of 19 of 36 (53%), specificity of 17 of 17 (100%) and accuracy of 36 of 54 (69%). Planar images missed residual cancer in high cervical lymph nodes adjacent to salivary gland activity, in small nodes (<1 cm) deep in the neck or chest and with diffuse pulmonary micrometastases. Serum Tg was elevated in 24 of 36 (67%) patients with residual cancer; ^{201}Tl detected tumor sites in 13 of 24 (54%) of these patients, and MIBI detected tumor sites in 14 of 24 (58%) of these patients. Of the12 patients who had residual cancer and false-negative serum Tg levels, 6 had true-positive ^{201}Tl and 5 had true-positive MIBI scans. **Conclusion:** ^{201}Tl and MIBI planar imaging yield the same high specificity and positive predictive value for residual thyroid cancer in patients with high-risk profiles and negative radioiodide scans. Both imaging agents detected residual cancer in more than half of the patients in whom conventional staging techniques did not reliably detect either the presence or the extent of residual thyroid cancer and changed the management in patients with surgically resectable cancer.

Key Words: thyroid carcinoma; ^{99m}Tc-methoxyisobutyl isonitrile; ^{201}Tl; serum thyroglobulin

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Thyroid cancer recurs after radioiodide ablation of all residual functional neoplasms in more than 50% of patients who have metastasis at the time of initial therapy and in about 25% of patients who do not have detectable metastasis at that time (*1–3*). Factors associated with an increased rate of recurrence at 10–20 y even after ablation of thyroid remnants include: age greater than 45 y at time of diagnosis, primary tumor size larger than 3 cm, biologic variants (tall cell, insular and Hürthle cell), bilateral neck or mediastinal nodal involvement, extrathyroidal invasion other than lymph nodes, vascular invasion and distant metastases. ^{201}Tl-chloride scintigraphy has been reported to show considerable clinical use for follow-up of patients with differentiated thyroid cancer (*4–9*). ^{201}Tl imaging has been found to be most useful after thyroidectomy and ^{131}I ablative therapy in patients with rising or elevated levels of serum thyroglobulin (Tg) and negative ^{131}I scans (*10,11*). However, Tg production by thyroid neoplasms is quite variable and may depend on circulating levels of thyroid-stimulating hormone (TSH) (*10,11*). Thus, low serum Tg levels during thyroid replacement do not exclude the presence of well-differentiated metastatic thyroid cancer (*6–8, 12–19*). Furthermore, 8%–10% of hypothyroid patients with verified cancer and positive ^{201}Tl scans have low serum Tg levels (*6–8,15*).

^{99m}Tc-methoxyisobutyl isonitrile (MIBI) has shown promise as a substitute for ^{201}Tl for the scintigraphic detection of a variety of malignant neoplasms (*11*). MIBI imaging has been shown to be superior to ^{201}Tl imaging in detecting metastatic lesions in patients with Hürthle cell thyroid carcinoma after total thyroidectomy (*20,21*). MIBI and ^{201}Tl scintigraphy have shown similar results in the evaluation of primary thyroid neoplasms (*22*). Also, in a series of 34 patients (*23*), there was no significant difference observed in detection of residual cancer by MIBI compared with ^{201}Tl for both pre- and postablative scans. In addition, both agents showed similar results in a retrospective study of 27 patients with known metastases from differentiated thyroid cancer who had undergone postoperative radioiodide ablative therapy (*24*).

The purpose of this study was to compare the abilities of MIBI and ^{201}Tl scintigraphy to detect residual cancer in high-risk patients who had negative or equivocal radioiodide scans after one or more postoperative ^{131}I therapies for differentiated thyroid cancer.

MATERIALS AND METHODS

Patient Population

We retrospectively evaluated our 5-y experience with 63 consecutive post-thyroidectomy patients with differentiated thyroid cancer

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who had received at least one postoperative ^{131}I therapy (2590–5550 MBq, 70–150 mCi). Each of these patients underwent planar MIBI and ^{201}Tl imaging after a negative or equivocal 74- to 111-MBq (2–3 mCi) ^{131}I total-body scan. The results of 9 patients were excluded, because 3 patients with negative paired scans had been followed up less than 3 y post-thyroidectomy and 6 patients had moved to other regions of the country and were no longer followed up on at this medical center. The results for the 54 remaining patients are the subject of this article. Patient age at the time of initial thyroid surgery ranged from 18 to 84 y (median 47 y). Thirty of the patients were younger than 45 y but had one or more factors associated with increased risk of recurrence.

In 43 patients, the ^{201}Tl and the MIBI scans were obtained immediately after an ^{131}I scan. For these patients, l-thyroxine (Synthroid; Knoll Pharmaceutical Co., Mt. Olive, NJ) was stopped 6 wk and triiodothyronine (Cytomel; Smith Kline Beecham, St. Louis, MO) was stopped 2 wk before imaging, and at the time of imaging, all had serum TSH concentrations higher than 50 μIU/mL (normal 0.4–3.5 μIU/mL). Three of the 43 patients had had previous negative ^{201}Tl and MIBI scans while taking thyroid hormone therapy, despite elevated serum Tg levels. These 3 patients were reimaged when they were hypothyroid 6 wk after thyroid hormone was stopped and were found to have focal uptake of ^{201}Tl and MIBI. Eleven patients did not have their ^{201}Tl and MIBI scanning in conjunction with ^{131}I imaging; instead, the ^{201}Tl and MIBI scans were obtained within 1–3 mo of a negative ^{131}I scan while the patients were taking l-thyroxine.

Scintigraphy

Regional 10-min neck and chest and anterior and posterior total-body ^{131}I scans (Siemens MS 2, 6 cm/min with medium-energy ^{131}I collimators; Siemens Corp., Hoffman Estates, IL) were obtained 24 and 96 h after an oral dose of 74–111 MBq (2–3 mCi) sodium iodide. In all but 11 patients, ^{201}Tl imaging was done simultaneously with the 96-h ^{131}I imaging that occurred 10 min after a 74- to 111-MBq (2–3 mCi) intravenous dose of ^{201}Tl. A 10-min regional image of the neck and chest was obtained followed by anterior and posterior total-body scintigraphy. In the 11 patients who underwent ^{201}Tl and MIBI imaging while taking thyroid hormone, ^{201}Tl images were acquired within 30 min of a 74- to 111-MBq (2–3 mCi) intravenous dose of ^{201}Tl, and these scans were obtained using a high-resolution, low-energy collimator. A second set of such images was obtained on the same day after a 740- to 925-MBq (20–25 mCi) intravenous dose of MIBI (5-min regional neck and chest image and both anterior and posterior total-body scans at 12 cm/min).

Whenever the ^{131}I scan showed an abnormal focal collection of ^{131}I, the percentage uptake was obtained by placing a known ^{131}I standard (0.148–0.37 MBq, 0.004–0.01 mCi) in the field of view during the 10-min regional computer acquisition. A region of interest was drawn around each focus and the counts were compared with the known (0.148–0.37 MBq, 0.004–0.01 mCi) ^{131}I standard on the 10-min regional image. An ^{131}I scan showing only a faint or questionable focus just visible over background activity was considered to be negative if the background-corrected uptake at 24° was estimated to be less than 0.1%. Each ^{201}Tl and MIBI study was interpreted as positive, negative or equivocal by two experienced observers unaware of the patient's history and the results of the ^{131}I scintigraphy. The criterion for a positive ^{201}Tl or MIBI scan was a definite focus of abnormal localization that was clearly visible over adjacent background activity. A faint or questionable focus just visible over background activity was considered an equivocal or negative study. If there was disagreement, the study was interpreted by a third reader and was called positive or negative depending on that interpretation.

Thyroglobulin Determination

In the 43 patients who underwent sequential ^{131}I, ^{201}Tl and MIBI scanning, serum Tg concentration (Smith Kline Bioscience Labs, St. Louis, MO) was obtained during suppressive therapy and again after cessation of thyroid hormone therapy, that is, at least 6 wk for l-thyroxine and 2 wk for triiodothyronine. After l-thyroxine administration was stopped, 25 μg triiodothyronine was routinely administered orally twice a day for 4 wk. A low-iodide diet was started the same day that triiodothyronine was stopped, 2 wk before ^{131}I imaging. The 11 patients who underwent ^{201}Tl and MIBI scanning while on hormone replacement therapy had Tg determinations obtained in the suppressed state and at the time of their previous ^{131}I scan.

Disease Confirmation

Thirty-six patients were shown to have residual thyroid cancer on further investigations: 18 patients had histopathologic confirmation of metastatic neoplasm and 18 patients without histopathology had negative pretherapy but positive post-therapy ^{131}I scans after additional radioiodide therapy. Eighteen patients have had no evidence of thyroid cancer after 4–15 y (median 8.6 y) of clinical follow-up. Specifically none of the 18 patients have shown a clinical indication of recurrence on physical examination or an elevation of serum Tg concentration. Also, a subset of 8 of these patients showed no evidence of persistent or recurrent neoplasm when studied with ^{18}F-fluorodeoxyglucose (FDG) PET imaging. A serum Tg < 4 ng/mL in a euthyroid state and a Tg < 10 ng/mL in a hypothyroid state were considered to indicate a low likelihood of residual disease.

Statistics

The following formulas were used: sensitivity = TP/(TP + FN); specificity = TN/(TN + FP); accuracy = TP + TN/(TP + FP + TN + FN); predictive value of positive test = TP/(TP + FP); predictive value of a negative test = TN/(TN + FN); where T = true, F = false, P = positive and N = negative.

RESULTS

The scintigraphic results for the 54 patients with confirmation of disease state by biopsy or adequate follow-up are

TABLE 1
Results of ^{201}Tl and MIBI Imaging (n = 54)*

	^{201}Tl			MIBI		
Cancer	Positive	Negative	Total	Positive	Negative	Total
Present	19	17	36	19	17	36
Absent	0	18	18	0	18	18
Total	19	35	54	19	35	54

*These data include the second "hypothyroid" scan results in 3 patients who initially had negative ^{201}Tl and MIBI scans obtained while suppressed (thyroid-stimulating hormone < 0.05 μIU/mL).

MIBI = methoxyisobutyl isonitrile.

Sensitivity = 53%; specificity = 100%; accuracy = 69%; positive predictive value = 100%; negative predictive value = 51%.

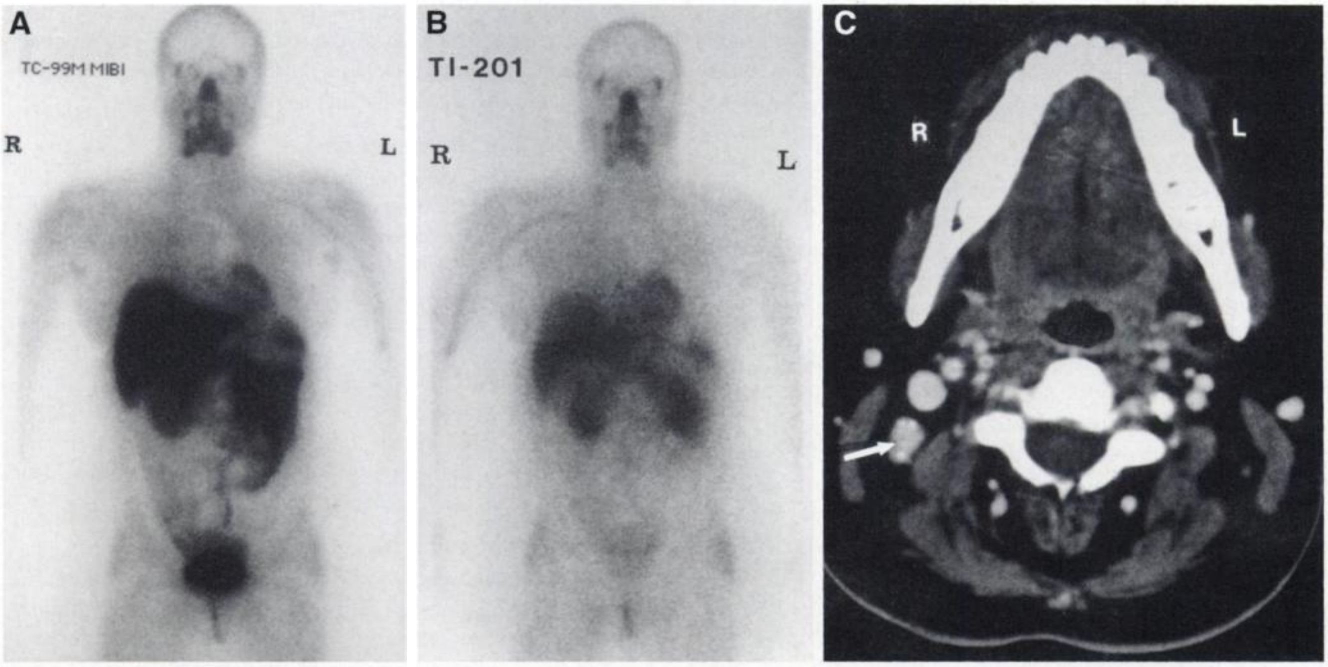

FIGURE 1. This 42-y-old man had three negative ^{131}I scans (1, 2 and 4 y after 5476 MBq [148 mCi] postoperative ^{131}I therapy) for multifocal papillary thyroid cancer and 24 positive lymph nodes. False-negative methoxyisobutyl isonitrile (MIBI) (A) and ^{201}Tl total-body (B) scans (slight asymmetric uptake in region of salivary glands). (C) CT scan shows 1- to 2-cm calcified right cervical lymph node (arrow) containing metastatic cancer.

summarized in Table 1. Both ^{201}Tl and MIBI scans yielded 19 true-positive, 17 false-negative and 18 true-negative results; neither produced any false-positive results. Two of the patients with true-positive ^{201}Tl scans had false-negative MIBI scans and 2 patients with false-negative ^{201}Tl scans had true-positive MIBI scans. The sensitivity, specificity and accuracy for both MIBI and ^{201}Tl imaging in the 54 patients were 53%, 100% and 69%, respectively, with a positive predictive value of 100% and a negative predictive value of 51%.

Among the 17 patients with false-negative MIBI and ^{201}Tl studies, 14 had residual cancer in the thyroid bed or metastatic cancer in the cervical lymph nodes, mediastinal lymph nodes or in both. Nine of these 14 patients (64%) had small lesions (<1 cm) deep in the neck or chest that were detected either by FDG PET or CT scans before surgical

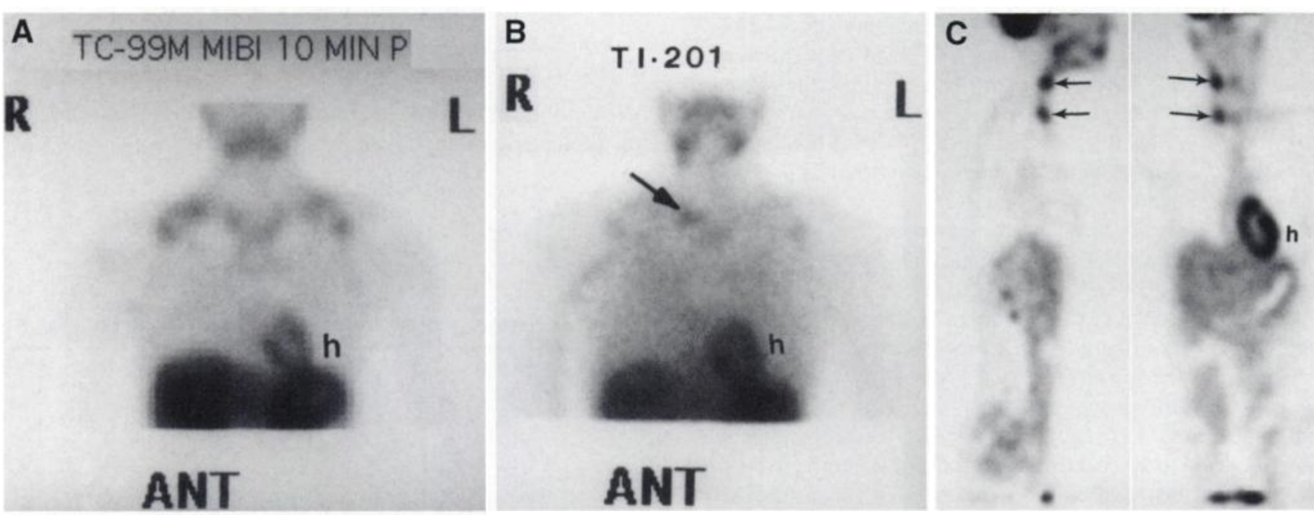

FIGURE 2. This 22-y-old woman underwent thyroidectomy and lymph node resection (two positive nodes) for tall cell variant of papillary carcinoma. ^{131}I scan was negative 1 y after 6993 MBq (189 mCi) ^{131}I therapy. (A) Methoxyisobutyl isonitrile (MIBI) scan is false-negative. (B) True-positive ^{201}Tl scan shows focal uptake in right retroclavicular region (arrow) plus asymmetric uptake in upper neck (salivary glands). (C) Total-body FDG PET scan shows two discrete foci in right neck (arrows) caused by surgical positive lymph nodes. ANT = anterior; h = heart.

resection. Four of these 14 patients (28%) had residual neoplasm in cervical lymph nodes that were obscured by normal physiologic activity in adjacent salivary glands (Fig. 1). One patient had a false-negative MIBI scan (Fig. 2A) due to superimposition of the tumor site with normal tracer uptake in the overlying proximal clavicle; this 2-cm residual cancer was identified correctly on the ^{201}Tl scan (Fig. 2B) and was surgically excised.

Three of the 17 patients with false-negative studies had diffuse micrometastatic lung lesions that were not discernible even retrospectively on the ^{201}Tl or MIBI studies as tracer uptake higher than the normal residual lung background activity at the time of imaging (10–40 min after tracer injection). Two additional patients who had true-positive scans indicating residual metastatic lesions in the neck and mediastinum also had micrometastatic lung lesions that were missed (false-negative sites) on both MIBI and ^{201}Tl images (Fig. 3). Another patient with diffuse bone and lung metastases also had false-negative ^{201}Tl and MIBI image patterns in the lungs and in both femora, but a large (2 cm) lesion in the distal right femur and along the right hip prosthesis were visualized by both agents (Fig. 4A). The femoral and lung micrometastases did show ^{131}I uptake on the 9-d post-therapy scan (Fig. 4B).

The correlation of serum Tg levels with the results of ^{201}Tl and MIBI imaging is given in Table 2. Twenty-four patients with residual cancer had elevated Tg levels: 13 had true-positive ^{201}Tl scans, 14 had true-positive MIBI scans, 11 had false-negative ^{201}Tl scans, 10 had false-negative MIBI scans and there were no false-positive scans. Thus, residual sites of cancer were detected in 54% (^{201}Tl) and 58% (MIBI) of patients with elevated serum Tg levels and negative ^{131}I scans.

Thirty patients did not have elevated serum Tg levels (4 of

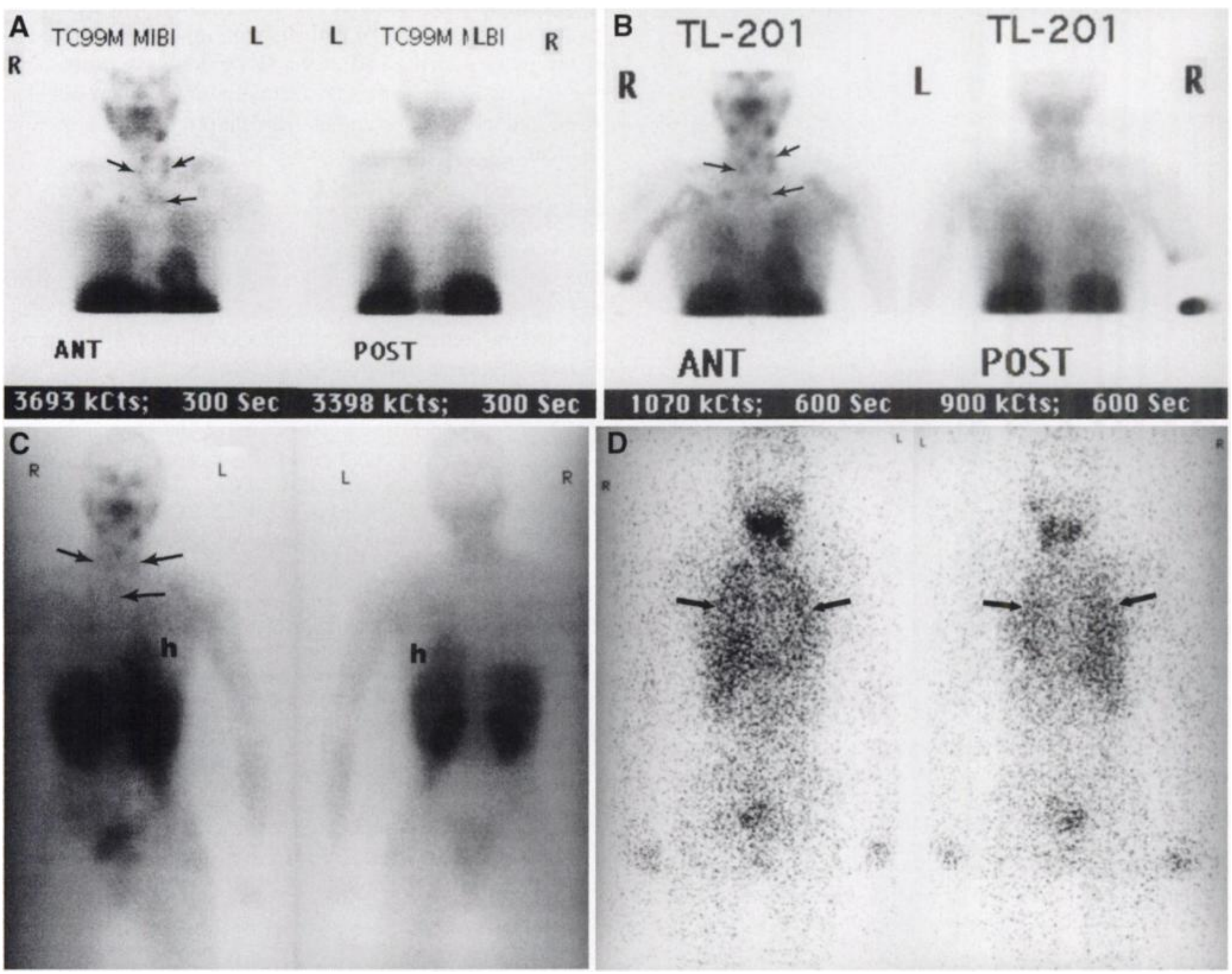

FIGURE 3. This 17-y-old female received 5180 MBq (140 mCi) postoperative ^{131}I therapy for papillary thyroid cancer with invasion of adjacent soft tissue and lymph nodes. Follow-up ^{131}I scan was negative 1 y later. Methoxyisobutyl isonitrile (MIBI) (A) and ^{201}Tl (B) images (10-min postinjection) show multiple abnormal foci in neck and upper mediastinum (arrows) and diffuse lung blood-pool activity. (C) Total-body ^{201}Tl scan obtained 30 min later shows no evidence of abnormal lung localization (false-negative in lung). (D) Total-body scan obtained 13 d after 7400 MBq (200 mCi) ^{131}I therapy reveals diffuse micrometastatic lung uptake (arrows). ANT = anterior; POST = posterior; h = heart.

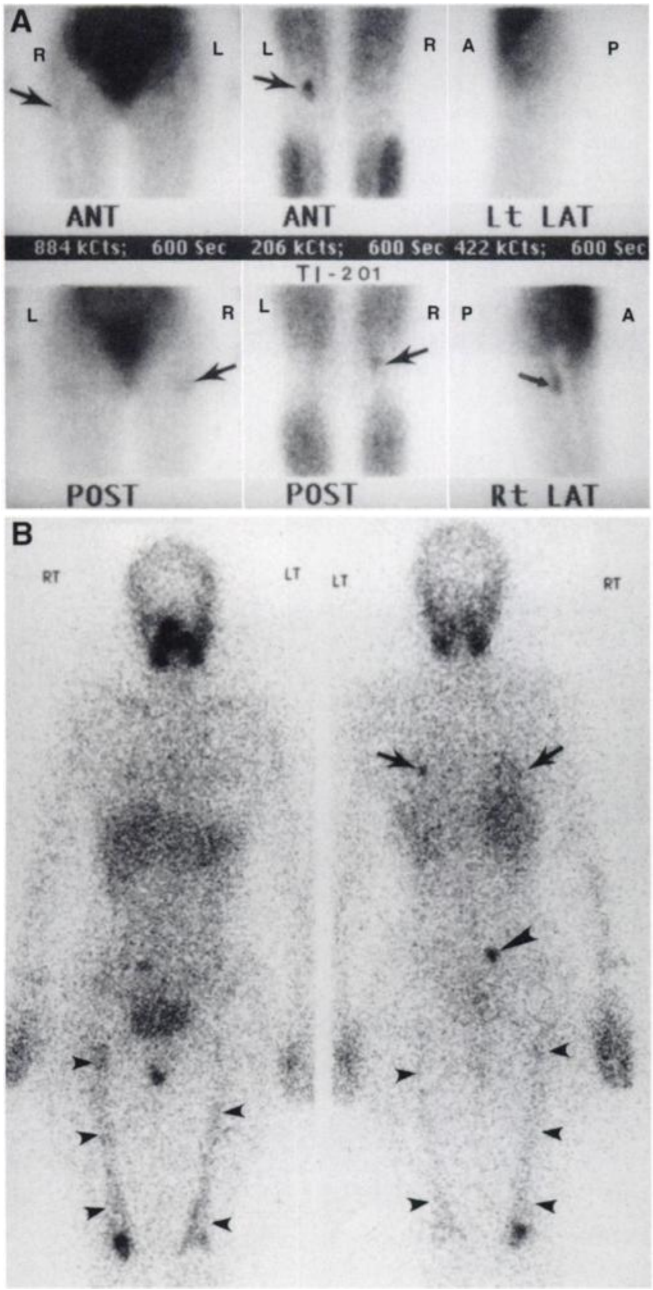

FIGURE 4. This 56-y-old woman had rising serum Tg 3 y after surgery and ^{131}I therapy for pathologic right hip fracture due to metastatic papillary thyroid cancer. (A) ^{201}Tl regional images show abnormal localization along right hip prosthesis (arrow) and discrete focus in distal right femur (arrow) but no uptake in bilateral diffuse femoral bone (arrowheads, B) and lower lung (arrows, B) micrometastases shown on 9-d postoperative ^{131}I (12,210 MBq, 330 mCi) therapy scan (B). (Posterior pelvis focus [arrowhead] is thought to be due to urine contamination.) A = anterior; P = posterior; ANT = anterior; Lt = left; LAT = lateral; POST = posterior; Rt = right.

these patients had elevated serum Tg antibody titers). Eighteen of the 30 patients (60%) did not have residual cancer, and 12 (40%) were found to have residual thyroid cancer. Six of the 12 patients had true-positive ^{201}Tl scans and 5 had true-positive MIBI scans (Table 2). Among the remaining patients without elevated serum Tg levels, 18 had true-negative ^{201}Tl and MIBI scans, 6 had false-negative ^{201}Tl scans and 7 had false-negative MIBI scans. There were no false-positive scans. Thus, 18 of 30 patients (60%) without an elevated serum Tg and a negative ^{201}Tl or MIBI scan did not have residual cancer (true-negative). However, 6 of 30 patients (20%) without elevated serum Tg had residual cancer that was detected by ^{201}Tl (3 of the 6 had elevated Tg antibody titers) and 5 of 30 patients (17%) had residual cancer that was detected by MIBI (2 of 5 had elevated Tg antibody titers) that was surgically resectable. The 6 patients with false-negative ^{201}Tl scans had small lymph nodes (<1 cm) in the neck (4 patients) and upper mediastinum (2 patients) that were later detected on follow-up FDG PET scans and were surgically excised (3 patients) or that were detected on post-therapy ^{131}I scans (3 patients) and were confirmed by CT scans. In summary, in high-risk patients, ^{201}Tl and MIBI scans detected residual cancer in more than 50% of patients with elevated serum Tg levels but in only 20% of patients with low Tg levels, and 3 of the latter patients had elevated Tg antibody titers. The presence of Tg antibodies artifactually lowers the serum Tg levels and may also be an independent prognostic factor for residual or recurrent neoplasm (*25*).

DISCUSSION

The results of planar regional and total-body imaging for detection of residual thyroid cancer were the same for MIBI and ^{201}Tl scintigraphy. This is consistent with published data reported by others (*23,24*). Both MIBI and ^{201}Tl scans yielded the same information except in 4 patients. Two patients had negative or equivocal ^{201}Tl scans when their MIBI images were true-positive and 2 patients had true-positive ^{201}Tl scans when their MIBI scans were negative.

TABLE 2
Results in Patients With and Without Elevated Serum Thyroglobulin (Tg)

	^{201}Tl			MIBI		
Cancer	Positive	Negative	Total	Positive	Negative	Total
With Elevated Serum Tg*†						
Present	13	11	24	14	10	24
Absent	0	0	0	0	0	0
Total	13	11	24	14	10	24
Without Elevated Serum Tg†						
Present	6	6	12	5	7	12
Absent	0	18	18	0	18	18
Total	6	24	30	5	25	30

*These data include second "hypothyroid" scan results in three patients who initially had negative ^{201}Tl and MIBI scans obtained while suppressed (thyroid-stimulating hormone < 0.05 μIU/mL).

†Tg > 4 ng/mL while on thyroid suppression or >10 ng/mL when hypothyroid.

MIBI = methoxyisobutyl isonitrile.

Most of the false-negative scans can be attributed in large part either to superimposition of sites of normal physiologic tracer localization with sites of residual cancer or to the small size of the tumor metastases. Because SPECT MIBI imaging was not performed in most patients, we cannot say whether SPECT imaging would have performed better than the planar technique. A study by Charkes et al. (*26*) reported increased lesion detection using ^{201}Tl SPECT compared with planar ^{201}Tl imaging. However, small diffuse pulmonary micrometastases usualy are not detected by SPECT imaging with either ^{201}Tl or MIBI (*27,28*).

High-quality MIBI images were obtained in about one half the time required for ^{201}Tl images. Previous work suggests that the optimal detection of residual thyroid cancer in most patients can be achieved by initiating image data acquisition within 10–30 min after injection of MIBI or ^{201}Tl (*10,29*). Sehweil et al. (*29*) have shown that the highest tumor-to-background ratios for ^{201}Tl are reached in most neoplasms between 10 and 20 min after intravenous injection of the tracer. Furthermore, most neoplasms showed variable ^{201}Tl washout, which may have reached 25% or more by 1–2 h after injection. Similar observations have also been reported for MIBI when it is used for the detection of various neoplasms (*10*).

Miyamoto et al. (*24*) reported that the abnormal MIBI localization that was observed in early images (10–30 min after tracer injection) was no longer present on delayed (3 h) images in 8 of 13 patients with known lung metastases from thyroid cancer and in 5 of 11 patients with bone metastases, but abnormal localization was still observed at 3 h in all 11 of their patients with lymph node metastases. In our series, none of the 5 patients with diffuse micrometastatic lung disease showed evidence of an early abnormal ^{201}Tl or MIBI lung pattern that could be differentiated from normal lung background activity (Fig. 3). Furthermore, in our experience, the amount of MIBI and ^{201}Tl localization compared with ^{131}I uptake can be quite variable even among different lesions in the same patient (Fig. 4).

CONCLUSION

The results of this study suggest that MIBI or ^{201}Tl imaging is useful for follow-up of high-risk patients who have negative radioiodide scans. More than half of the patients with an elevated serum Tg level had one or more surgically resectable sites detected. In patients whose ^{201}Tl and MIBI scans led to discovery of macroscopic tumor sites (i.e., when enlarged lymph nodes or recurrent neoplasm in the neck or mediastinum was confirmed by CT, MRI or sonography), the existence of a previously negative ^{131}I scan implied that this residual neoplasm was unlikely to respond to ^{131}I therapy, and surgical excision was indicated.

An attractive feature of using MIBI or ^{201}Tl imaging for thyroid cancer follow-up is that scintigraphy with these tracers can be performed without stopping thyroid hormone therapy. However, sufficient data are lacking on the relative sensitivity of MIBI or ^{201}Tl imaging during a suppressed versus nonsuppressed (elevated TSH) state. Three of our patients who converted from negative ^{201}Tl or MIBI scans to positive scans after induction of a hypothyroid state (although their concurrent ^{131}I scans were negative) suggest that improved sensitivity might be obtained with ^{201}Tl or MIBI scintigraphy during concurrent TSH stimulation. Further study of this potentially important factor as well as further study of SPECT compared with planar imaging is needed.

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