^{99m}Tc-Sestamibi and ^{131}I Whole-Body Scintigraphy and Initial Serum Thyroglobulin in the Management of Differentiated Thyroid Carcinoma

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^{99m}Tc-sestamibi whole-body scanning has been used in the postoperative assessment of differentiated thyroid carcinoma together with ^{131}I whole-body scanning and serum thyroglobulin (Tg) estimation. This study compared ^{99m}Tc-sestamibi whole-body scanning with ^{131}I whole-body scanning in the context of initial serum Tg levels of patients after total or near-total thyroidectomy who were taken off thyroxine suppression therapy and who had no ^{131}I ablation before surgery. **Methods:** A prospective study of 360 patients was undertaken. ^{99m}Tc-sestamibi whole-body scintigraphy was performed at least 5 wk after thyroidectomy and was followed by ^{131}I whole-body scanning. The patients had no thyroxine suppression for 5 wk, and Tg was measured thereafter. Radiologic studies (chest radiography, CT, MRI, sonography, and bone scanning) and histopathologic examinations were performed to clarify the presence of metastases with positive uptake on either ^{99m}Tc-sestamibi scans or ^{131}I whole-body scans. Positive scans were defined as those with the presence of thyroid remnants, lymph node disease, or metastases. **Results:** Two hundred fifty-nine (71.9%) of the 360 patients had initial serum Tg levels < 30 ng/mL (group 1), whereas 101 (28.1%) had initial serum Tg levels ≥ 30 ng/mL (group 2). Of the 259 group 1 patients, 82 had positive ^{99m}Tc-sestamibi scans and 113 had positive ^{131}I scans; 71.7% of patients with positive ^{131}I scans also had positive ^{99m}Tc-sestamibi scans, and 98.8% of patients with positive ^{99m}Tc-sestamibi scans also had positive ^{131}I scans. Of the 101 group 2 patients, 81 had positive ^{99m}Tc-sestamibi scans and 97 had positive ^{131}I scans; 83.5% of patients with positive ^{131}I scans also had positive ^{99m}Tc-sestamibi scans, and all patients with positive ^{99m}Tc-sestamibi scans also had positive ^{131}I scans. Of those with initial serum Tg levels ≥ 30 ng/mL (group 2), 27.2% had thyroid remnants and 68.8% had lymph node disease or metastases. ^{131}I scanning detects more thyroid remnants and lung metastases than does ^{99m}Tc-sestamibi scanning. **Conclusion:** Our findings suggest that, compared with ^{131}I scanning, ^{99m}Tc-sestamibi scanning is less sensitive in detecting thyroid remnants and lung metastases but appears to be more useful in the detection of lymph node disease before initial ^{131}I treatment.

Key Words: thyroid cancer; radioiodine; whole-body scintigraphy

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Patients with well-differentiated thyroid cancer are followed up after thyroidectomy by serial serum thyroglobulin (Tg) estimation and ^{131}I whole-body scanning. The use of ^{131}I requires the suspension of thyroxine (L-3,5,3′,5′-tetraiodothyronine) therapy for 4–6 wk (in the case in which synthetic thyroid-stimulating hormone [TSH] is not readily available), a higher radiation exposure, a longer scanning procedure, and poorer image quality. Thus, there has been interest in the use of ^{99m}Tc-sestamibi in the follow-up assessment of thyroid cancer metastases.

^{99m}Tc-sestamibi is a myocardial perfusion imaging agent. Studies have shown that this lipophilic cationic agent localizes largely within the mitochondria (*1*). It has been reported to localize in lung carcinoma (*2*), thyroid carcinoma (*3*), and osteogenic sarcoma (*4*). ^{99m}Tc-sestamibi has been used, like ^{201}Tl, to localize parathyroid tumors (*5*) and thyroid cancer metastases.

In this article, we report on the follow-up of patients with near-total or total thyroidectomy for thyroid carcinoma who had radioiodine whole-body scanning, ^{99m}Tc-sestamibi whole-body scanning, and serum Tg estimation. Other studies included sonography, radiography, CT, MRI, and bone scanning when clinically indicated. Radiologic studies (radiography, CT, and MRI) and histopathologic examinations were performed whenever necessary to clarify the presence of metastases with positive uptake on ^{99m}Tc-sestamibi scans or ^{131}I whole-body scans.

MATERIALS AND METHODS

Since 1990, ^{99m}Tc-sestimibi whole-body scanning was performed on patients referred to our department for the diagnosis or treatment of thyroid cancer. All patients with well-differentiated thyroid cancer had ^{99m}Tc-sestamibi scintigraphy performed 1 wk before ^{131}I whole-body scanning. The patients had stopped thyroxine replacement for about 5 wk before ^{131}I scanning. All thyroidectomies were done at least 5 wk before ^{99m}Tc-sestamibi whole-body scanning.

On arrival in the department, before any scanning procedure was initiated, a blood sample was taken from each patient for measurement of serum Tg, anti-Tg antibody, serum free thyroxine, and TSH. Tg was assayed using the immunoradiometric assay (double-antibody competitive radioimmunoassay; RSR Ltd., Cardiff, UK) with a functional assay sensitivity of 2 ng/mL Tg and a normal

range of up to 50 ng/mL in regular blood donors. The anti-Tg antibody levels give an indication of the reliability of the assay results (*6,7*). The anti-Tg antibody assay is based on ^{125}I-labeled autoantigens (RSR). In this study, for patients who recently underwent surgery, we used a Tg level of 30 ng/mL (on the basis of our previous experience with 300 patients) to discriminate those with remnant thyroid tissue from those with nodal or metastatic disease.

Patients were injected intravenously with 555 MBq (15 mCi) ^{99m}Tc-sestamibi (Cardiolite; Dupont Pharmaceuticals Co., Billerica, MA). Whole-body scans and spot views were obtained 20–30 min later. Scanning was done on a dual-head γ camera (ADAC Laboratories, Milpitas, CA) with a low-energy, high-resolution, parallel-hole collimator.

The following week, the patients were given ^{131}I (185–370 MBq for diagnostic scans, 1110 MBq for low-risk outpatient ablative therapy, and 3,700–11,100 MBq for patients with known metastases). Whole-body scans and spot views were obtained 72 h later using a γ camera equipped with a high-energy, general-purpose collimator. Patients who were given >1110 MBq ^{131}I were admitted for isolation and were discharged only when it was confirmed that whole-body retention of ^{131}I was below the regulatory limit. All patients were given instructions regarding avoidance of iodine-rich foodstuffs and medications for 3 d before the ^{131}I dose and up to 3 d afterward. Follow-up of the patients included clinical history and physical examination, chest radiography, and, when indicated, sonography of the neck, bone scanning, MRI, and CT of organ systems. Serum free thyroxine, TSH, Tg, and anti-Tg antibody levels were also measured during follow-ups. All patients had elevated TSH and low serum free thyroxine before ^{131}I studies were performed.

RESULTS

This study included 368 patients (105 males, 263 females; age range, 11–83 y; mean age, 47.2 y). Follow-up of these patients ranged from 1 to 8 y. Of the 368 post-total thyroidectomy or near-total thyroidectomy patients, only 360 had both ^{131}I whole-body scanning and ^{99m}Tc-sestamibi scanning done. Two hundred eighty-seven (79.7%) of the 360 patients had papillary carcinoma, and the other 73 had follicular carcinoma (20.3%).

The patients were categorized into 2 groups for analysis: those with levels of initial serum Tg < 30 ng/mL (group 1; n = 259) and those with initial serum Tg ≥ 30 ng/mL (group 2; n = 101). Twenty-five percent (90/360) of all patients had anti-Tg antibodies above the normal range (i.e., >0.3 U/mL). The ^{99m}Tc-sestamibi whole-body scans were broadly classified into normal and abnormal scans as were the ^{131}I whole-body scans. Normal or negative scans are those that reveal no thyroid remnants, lymph node disease, or metastases. Scans were otherwise classified as abnormal or positive. Foci of uptake in the thyroid bed were generally considered as thyroid remnants, although the possibility of abnormal tissue could not be totally excluded, whereas uptake elsewhere in the neck was considered lymph node disease. Clinical examination and other imaging modalities were used to confirm lymph node metastases.

The results are tabulated in 2 contingency tables (Tables 1 and 2). Table 3 indicates the findings according to organ sites. Figures 1–3 are the corresponding ^{131}I and ^{99m}Tc-sestamibi whole-body scintigraphic findings in 3 patients.

TABLE 1
Patients with Serum Tg Level <30 ng/mL

^{131}I whole-body findings	^{99m}Tc-sestamibi findings		
	Normal	Abnormal	Total
Normal	145	1	146
Abnormal	32	81	113
Total	177	82	259

Of the 259 group 1 patients, 82 had positive ^{99m}Tc-sestamibi scans and 113 had positive ^{131}I scans; 71.7% of patients with positive ^{131}I scans also had positive ^{99m}Tc-sestamibi scans, and 98.8% of patients with positive ^{99m}Tc-sestamibi scans also had positive ^{131}I scans. Of the 101 group 2 patients, 81 had positive ^{99m}Tc-sestamibi scans and 97 had positive ^{131}I scans; 83.5% of patients with positive ^{131}I scans also had positive ^{99m}Tc-sestamibi scans, and all positive ^{99m}Tc-sestamibi scans were also positive ^{131}I scans.

Of those with initial serum Tg ≥ 30 ng/mL (group 2), 27.2% had scan evidence of thyroid remnants and 68.8% had lymph node disease or metastases. Table 3 shows that ^{131}I scanning detects more thyroid remnants and lung metastases than does ^{99m}Tc-sestamibi scanning.

DISCUSSION

Nemec et al. (*8*) found that thyroid cancer scintigraphy using ^{99m}Tc-sestamibi has a very high sensitivity and specificity in detecting bone and lung metastases. Our study is a larger follow-up study (n = 360) after a previous study on a small number of patients (n = 31) showed ^{99m}Tc-sestamibi scanning to have sensitivity comparable with ^{131}I whole-body scanning (*9*). In this larger series of patients, it appears that ^{131}I whole-body scintigraphy detects more abnormalities than does ^{99m}Tc-sestamibi whole-body scintigraphy. Considering both groups of patients, ^{99m}Tc-sestamibi scans concur with 71.7%–83.5% of abnormal ^{131}I scans, whereas 98.8%–100% of abnormal ^{99m}Tc-sestamibi scans will also be abnormal on ^{131}I scans.

Among the 32 patients who had negative ^{99m}Tc-sestamibi results but had positive results on the ^{131}I whole-body scans, 29 patients had residual thyroid remnants, 2 had bone metastases, and 1 had lung metastases.

TABLE 2
Patients with Serum Tg Level ≥30 ng/mL

^{131}I whole-body findings	^{99m}Tc-sestamibi findings		
	Normal	Abnormal	Total
Normal	4	0	4
Abnormal	16	81	97
Total	20	81	101

TABLE 3
Comparison of ^{131}I and ^{99m}Tc-Sestamibi Whole-Body Scanning

	^{131}I whole-body scans		^{99m}Tc-sestamibi whole-body scans	
Scan interpretation	n	%	n	%
No abnormality	150	41.7	197	54.7
Residual thyroid tissue	142	39.4	90	25.0
Lymph nodes	35	9.7	37	10.3
Lungs	36	10.0	23	6.4
Bones	17	4.7	17	4.7
Indeterminate uptakes*	1	0.3	7	1.9

*Indeterminate uptakes refers to generally faint uptakes of equivocal significance.

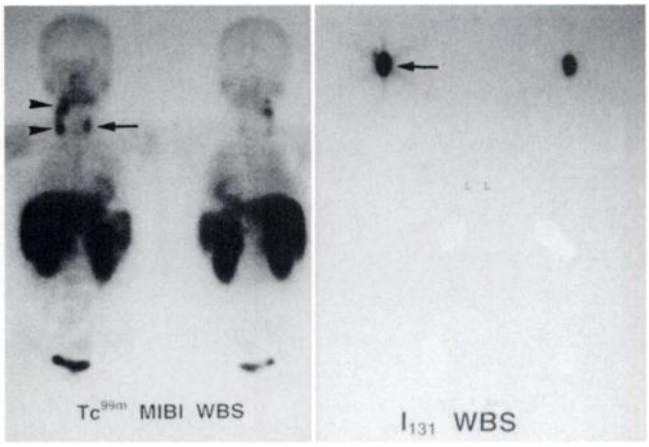

FIGURE 1. Images show that lymph node disease (arrowheads) is more evident on ^{99m}Tc-sestamibi scan than on ^{131}I scan. This finding may be attributed to preferential uptake by left thyroid remnant (arrows). MIBI = 2-methoxyisobutyl isonitrile; WBS = whole-body scan.

Initial Tg levels determined after total thyroidectomy or near-total thyroidectomy with patients off thyroxine and before ^{131}I administration for therapy or scanning showed that 71.9% (259/360) of patients had initial levels < 30 ng/mL (group 1) and, conversely, 28.1% (101/360) had initial levels ≥ 30 ng/mL (group 2). Ozata et al. (*10*) reported that in patients who had total or near-total thyroidectomy and ^{131}I ablation and were monitored for up to 18 y, only 10.5% (6/57 patients) (off thyroxine) had Tg levels > 10 ng/mL. Comparison with our findings suggests that with ^{131}I ablation and long-term thyroxine suppression, the level of Tg (when off thyroxine) tends to fall.

Considering patients with thyroid remnants, lymph node disease, or metastases detected on either ^{131}I or ^{99m}Tc-sestamibi scans, initial Tg levels were elevated at ≥30 ng/mL in 46.0% (97/211) and were <30 ng/mL in 54.0% (114/211). In patients whose scans were negative for thyroid remnants, lymph node disease, or metastases, only 2.7% (4/149) had an initial serum Tg ≥ 30 ng/mL

Conversely, in patients with initial Tg levels < 30 ng/mL, 44.0% (114/259) had scan evidence (using ^{131}I or ^{99m}Tc-sestamibi) of thyroid remnants, lymph node disease, or metastases. Of these 114 patients with abnormal ^{131}I scans, 92% of the abnormalities were associated with thyroid remnants, whereas the remaining 8% were associated with nodal disease or distant metastases.

Filesi et al. (*11*) reported that, in their series of patients, 66.7% of patients with metastases had their first Tg levels > 60 ng/mL. Our findings are somewhat lower: 46% of patients with thyroid remnants or metastases had elevated initial serum Tg levels ≥ 30 ng/mL. They also reported that the first ^{131}I whole-body scan detected metastases in 47.8% of patients with Tg values of <60 ng/mL. We found that 44.0% of patients with Tg levels < 30 ng/mL have scan evidence of thyroid remnants, lymph node disease, or metastases. However, although they found that 61.3% of patients with the first whole-body scan negative for metastases had Tg levels > 60 ng/mL, we found that only 2.7% of scan-negative subjects had initial serum Tg levels ≥ 30 ng/mL. This finding may be associated with the possibility that, in their study, 61.3% included those with thyroid remnants.

Lubin et al. (*12*) showed that all their patients who were scan-positive on ^{131}I had a Tg value of >10 ng/mL. Our results suggest that if the cutoff Tg level of 30 ng/mL were used, approximately half of all patients with positive scans for thyroid remnants, lymph node disease, or metastases would have initial serum Tg levels < 30 ng/mL.

As Schlumberger and Baudin (*13*) and others reported (*14–17*), in 80% of patients with Tg levels >40 ng/mL after L-thyroxine withdrawal, an ^{131}I whole-body scan performed with 3700 MBq revealed uptake in the thyroid bed or lymph nodes or at distant sites. We found that 96% (97/101) of patients with initial serum Tg levels ≥ 30 ng/mL (without thyroxine) had scan evidence of thyroid remnants, lymph

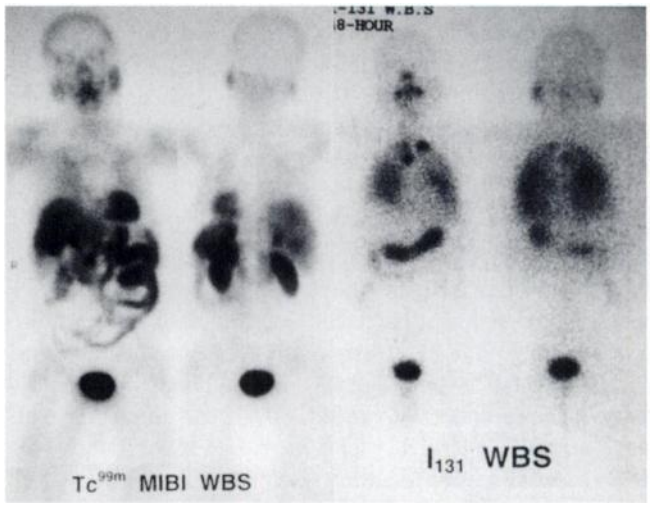

FIGURE 2. Images show lung uptake and superior mediastinal uptake on ^{131}I scan but no definite uptake on ^{99m}Tc-sestamibi scan. MIBI = 2-methoxyisobutyl isonitrile; WBS = whole-body scan.

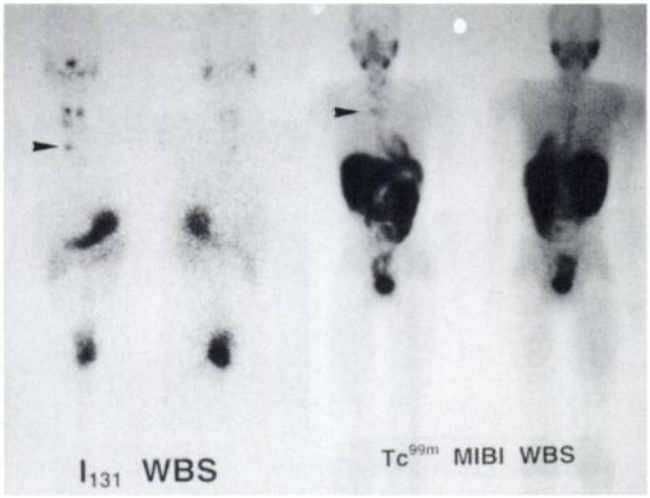

FIGURE 3. Images show correspondence between ^{131}I and ^{99m}Tc-sestamibi scans, although ^{131}I scan shows thyroid remnants and upper mediastinal disease (arrowheads) more clearly than does ^{99m}Tc-sestamibi scan. MIBI = 2-methoxyisobutyl isonitrile; WBS = whole-body scan.

nodes, or distant metastases. Further analysis showed that of this 96%, 27.2% had only residual thyroid tissue affected and 68.8% had lymph node disease and metastases (with or without concomitant thyroid residue).

Our observation during follow-up is that the level of serum Tg rises, on average, approximately 8 times when patients are off thyroxine than when they are on thyroxine suppression (TSH levels below normal and generally <0.1 mU/L or not detected). Eight (8/360) of these patients had surgery for hyperthyroidism. With a mean follow-up of 3 y, the thyroid peroxidase antibody levels before and after radioiodine therapy were still high (mean, 10.8 U/mL; normal, <0.3 U/mL).

Some divergence of opinion exists regarding the sensitivity of ^{99m}Tc-sestamibi scintigraphy in comparison with ^{131}I scintigraphy. Dadparvar et al. (*18*) found a poor sensitivity (36%) but a high specificity (89%) for ^{99m}Tc-sestamibi scanning compared with ^{131}I whole-body scanning. Other studies have noted comparable sensitivity of ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin whole-body scintigraphy compared with ^{131}I (*19–21*).

Our results also concur with the findings of others that ^{131}I is more sensitive in delineating residual thyroid tissue and lung metastases. Miyamoto et al. (*22*) reported that ^{131}I whole-body scanning detected lung metastases in more patients than did ^{99m}Tc-sestamibi (85% compared with 75%), although ^{99m}Tc-sestamibi detected lymph node metastases in more patients than did ^{131}I (100% compared with 41.7%).

One possible confounding factor in our study is the presence of anti-Tg antibody in 25% of our patients. This may affect the reliability of the serum Tg results and also reduces its clinical usefulness in follow-up and management. If ^{131}I therapy had been given previously, which is not the case with this study, the issue of radioresistance might be a confounding factor.

CONCLUSION

The level of 30 ng/mL for serum Tg was established on the basis of our previous experience. However, further studies should evaluate the issue of the discriminatory power of various levels of serum Tg in different contexts. Our findings suggest that, compared with ^{131}I scanning, ^{99m}Tc-sestamibi scanning is less sensitive in detecting thyroid remnants and lung metastases but it appears to be more useful in detecting lymph node disease before initial ^{131}I treatment.

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