CONCLUSION

Most physiological activity in FDG whole-body PET scans for tumor staging is visualized consistently. The brain, lung, liver, bone marrow and urinary system are consistently seen. Cardiac activity is inconsistent and related to the switch from FDG to free fatty acid metabolism (*12*). The most striking and irregular FDG uptake pattern is associated with various muscle groups that are exercised just before FDG injection. Because "hot" muscle groups can interfere with the diagnostic quality of a scan, care should be taken, particularly in the neck region, to rest the patient comfortably before injection. Lastly, knowing the muscle groups that have strong FDG accumulation will be extremely helpful in differentiating activity from pathological lesions.

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Thyroglobulin Determination, Neck Ultrasonography and Iodine-131 Whole-Body Scintigraphy in Differentiated Thyroid Carcinoma

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The long-term prognosis of patients with differentiated thyroid carcinoma depends on the early diagnosis and treatment of metastases and local recurrences. We evaluated serum thyroglobulin measurements, neck ultrasonography with ultrasound-guided biopsy and ^{131}I whole-body scintigraphy in the follow-up of 359 patients after surgical thyroidectomy and radioiodine ablation of the thyroid remnant. **Methods:** Serum thyroglobulin levels were determined and considered abnormal when the values were >5 ng/ml. Ultrasonography over the entire neck region and fine-needle aspiration biopsy of the mass or enlarged lymph nodes were carried out using 5- and 7.5-MHz transducers and 23-gauge needles. Whole-body scintigraphy was performed after administration of 185 MBq (5 mCi) ^{131}I. **Results:** Increased levels of thyroglobulin (ranging from 12 to >600 ng/ml) were measured in 40 of 55 (73%) patients with metastases or local recurrences. Ultrasonography revealed occult neck masses that were not detected by other methods. Neck ultrasonography and ultrasound-guided biopsy were positive for malignancy in 23 patients. Thyroglobulin levels were undetectable in 12 (52%) of these patients and ^{131}I whole-body scintigraphy was negative in 19 (83%) of them. **Conclusion:** The combined use of three diagnostic modalities (measurement of serum thyroglobulin, neck ultrasonography with ultrasound-guided biopsy for detecting recurrences of carcinoma in the neck region and ^{131}I whole-body scintigraphy) appears to give the best results in the follows-up patients with differentiated thyroid carcinoma.

Key Words: thyroid carcinoma; thyroglobulin; neck ultrasonography; iodine-131; whole-body scintigraphy

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Iodine-131 whole-body scintigraphy and serum thyroglobulin measurements are considered to be the most effective methods in the follow-up of patients with differentiated thyroid carcinoma who have undergone surgical thyroidectomy and radioiodine ablation of the thyroid remnant. Both diagnostic procedures, however, have some disadvantages. The major drawback of ^{131}I whole-body scintigraphy is the necessity to withdraw thyroid hormone suppression therapy, with the subsequent onset of hypothyroidism and its physical and psychological effects (*1*). Also, highly specific radioiodine scintigraphy may give false-negative results (*2*).

Numerous studies have shown that the determination of serum thyroglobulin levels is a suitable procedure for the follow-up of patients with thyroid carcinoma (*3–9*). The method's most important advantage is the detection of metastases or recurrences in patients who are on thyroid suppression therapy. It is still, however, controversial whether thyroid hormone

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therapy should be suspended. Some investigators have suggested that the withdrawal of thyroid therapy might not be necessary (*7,10–12*), but most reports have demonstrated that elevated levels of serum thyroid stimulating hormone (TSH) enhance serum thyroglobulin levels, primarily in patients with metastases. Therefore, thyroglobulin usually is measured during the suspension of suppression therapy (*9,13–15*). It has been reported that serum thyroglobulin is not sufficiently sensitive in detecting neck lymph node metastases and is inferior to whole-body scintigraphy (*14,16*). False-negative scintigraphic findings in patients with local metastases also have been demonstrated (*17*). Evidence of focal ^{131}I uptake in the thyroid bed after thyroidectomy usually is considered a normal finding consistent with the presence of thyroid remnants and obviates the need for further search of possible recurrence (*16*).

In this study, we used ultrasonography to detect tumor lesions limited to the neck region and ultrasound-guided biopsy to determine whether the neck mass represents malignant disease or benign tissue proliferation. Also, we evaluated the combined utility of thyroglobulin measurements, neck ultrasonography and ^{131}I whole-body scintigraphy in the follow-up of patients with differentiated thyroid carcinoma after surgical thyroidectomy and radioiodine ablation of the thyroid remnant.

MATERIALS AND METHODS

Patients

The study included 359 patients with differentiated thyroid carcinoma who were treated and underwent follow-up for a few months to more than 10 yr. The patient population consisted of 282 (79%) females and 77 (21%) males ranging in age on initial presentation from 10 to 85 yr. All patients had undergone surgical thyroidectomy and subsequent radioiodine ablation of the thyroid remnant. Histologically, 235 patients (65.5%) had papillary carcinoma, and 124 (34.5%) had follicular carcinoma. They were under treatment with L-thyroxine at a dose sufficient to suppress TSH and to maintain the euthyroid state. The presence or absence of metastatic or recurrent disease was assessed clinically, by radiographs, thyroglobulin determination, neck ultrasonography with ultrasound-guided biopsy, ^{131}I whole-body scintigraphy and, when necessary, by CT and bone scintigraphy.

Thyroglobulin Measurements

Blood samples for measuring serum thyroglobulin were drawn from patients during suspension of suppression therapy at the time of ^{131}I whole-body scintigraphy. Only patients with negative anti-thyroglobulin antibody measurements were included in the study. In 98 patients, thyroglobulin also was measured during suppression therapy. The thyroglobulin levels were determined by radioimmunoassay using a commercial kit (Mallinckrodt Diagnostica, Byk Sangtec), with sensitivities in the range of 5–600 ng/ml. Serum thyroglobulin levels were considered abnormal when the values were above 5 ng/ml.

Neck Ultrasonography

Neck ultrasonography was performed on 116 patients at the time of ^{131}I whole-body scintigraphy with a real-time sonographic scanner using 5- and 7.5-MHz transducers. Scanning covered the entire neck to visualize the submandibular glands, the thyroid bed, the area deep to the clavicle, the superior mediastinum and areas lateral to the carotid artery and jugular vein.

Ultrasonography-guided fine-needle aspiration biopsies using 23-gauge needles were performed in 61 patients (53%) who had cervical lymphadenopathy or a mass in the thyroid bed. All specimens were processed by the May-Grünwald-Giemsa method, and examined by a cytopathologist.

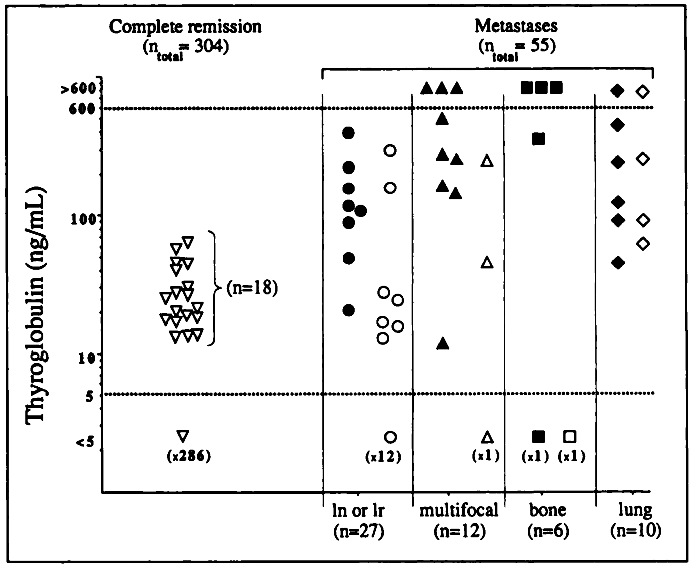

FIGURE 1. Thyroglobulin levels in patients in complete remission (▽) and in those with nonfunctional (○, △, □, ◇) and functional (●, ▲, ■, ◆) metastases in various organs: lymph node metastases (ln) or local recurrence (lr), multifocal metastases, bone metastases and lung metastases.

Whole-Body Scintigraphy

Iodine-131 whole-body scintigraphs were obtained routinely at 3, 6 and 12 mo during the first year after surgery and/or iodine therapy, and subsequently, at yearly intervals or less frequently. The patients were studied during suspension of thyroid hormone suppression therapy (30 days for T4 and 15 days for T3) and when serum TSH levels were more than 30 μU/ml. Scans 72–96 hr after oral administration of 185 MBq (5 mCi) of ^{131}I on an Anger camera with a high-energy collimator. Whole-body scintigraphy also was performed 5–7 days after a therapeutic dose of ^{131}I (varying from 1.85 to 7.40 GBq, 50–200 mCi). Iodine-131 scintigraphy was considered positive when increased focal activity was visually observed in regions that do not normally accumulate radioiodine.

RESULTS

According to the results of clinical, radiological, ultrasonography with ultrasound-guided biopsy or scintigraphic procedures, 304 patients were free of disease and 55 had metastases. Metastases were observed in the lungs (10 patients), bones (6 patients) and neck lymph nodes (22 patients). Five patients had local recurrence in the thyroid bed, and 12 patients had multifocal metastases with metastases in two or more organs (Fig. 1). Twenty-eight patients had functional metastases and 27 had nonfunctional ones.

Thyroglobulin Levels

Patients without Evidence of Neoplastic Tissue. Serum thyroglobulin concentrations were measured during suspension of suppression therapy in 304 patients without signs of metastases or recurrence (Fig. 1). In 286 (94%) patients, no recurrences or metastases were detected. Increased thyroglobulin levels, ranging from 13 to 63 ng/ml, were found in the remaining 18 patients (Fig. 1). Thyroglobulin was measured again during suppression therapy in 82 of 304 patients, including six of those with elevated thyroglobulin levels. All patients on suppression therapy had thyroglobulin levels under 5 ng/ml.

Patients with Metastases or Local Recurrence. Elevated thyroglobulin levels were found in 40 of 55 (73%) patients with distant metastases, neck lymph-node metastases, or local recurrence during suspension of suppression therapy (Table 1). Twenty-seven of 28 patients with metastases accumulating ^{131}I

TABLE 1
Comparison of Iodine-131 Whole-Body Scintigraphy and Serum Thyroglobulin Levels in Patients with Metastases

	WBS-positive				WBS-negative				
	Distant metastases		Local metastases		Distant metastases		Local metastases		
	Papillary	Follicular	Papillary	Follicular	Papillary	Follicular	Papillary	Folicular	Total
Tg >5 ng/ml	9	10	7	1	3	3	7	0	40
Tg < 5 ng/ml	1	0	0	0	0	2	10	2	15
Total	20		8		8		19		55

WBS = whole-body scintigraphy; Tg = thyroglobulin levels in patients off suppression therapy.

had elevated thyroglobulin ranging from 12 to more than 600 ng/ml (Fig. 1). In addition, thyroglobulin levels were raised in 13 of 27 (48%) patients with nonfunctional metastases (Table 1). In 7 of 19 patients with nonfunctional neck lymph node metastases or local recurrence, serum thyroglobulin concentrations were elevated (13–300 ng/ml) (Fig. 1). Six of eight patients with nonfunctional distant metastases had elevated thyroglobulin levels, from 47 to more than 600 ng/ml (Fig. 1).

The thyroglobulin levels were undetectable in 15 (27%) patients with metastases after hormone therapy was suspended. Serum thyroglobulin was negative in one patient with a distant metastasis which was detected by ^{131}I whole-body scintigraphy. Thyroglobulin was undetectable in two patients with nonfunctional distant metastases revealed by radiography, CT, and/or bone scintigraphy, and in 12 patients with neck lymph node metastases detected by ultrasonography (Table 1).

Serum thyroglobulin was measured during suppression therapy in 16 patients with metastases. Values were elevated in 12 patients (80%), ranging from 15 to more than 600 ng/ml (Table 2). One patient with multiple functional metastases (No. 6) and another patient with a nonfunctional local lymph node metastasis (No. 16) had undetectable levels (<5 ng/ml), which rose to pathological levels after hormone therapy was suspended. Two patients with nonfunctional, local lymph node metastases (Patients 7 and 12) had undetectable thyroglobulin levels while they were both on and off suppression therapy (Table 2).

The sensitivity, specificity and accuracy of thyroglobulin measurements in the serum of our patients after suspension of suppressive therapy were 73%, 94% and 91%, respectively (Table 3).

Neck Ultrasonography

Neck ultrasonography was used to detect recurrent thyroid carcinoma in 116 patients and was positive in 61 (53%). Fine-needle aspiration biopsy of a mass in the thyroid bed and enlarged lymph nodes, aided by simultaneous sonographic monitoring, was positive for malignancy in 23 patients (Fig. 2). The dimensions of the smallest neck mass found to be malignant on biopsy were 0.9 × 0.7 × 0.6 cm (longitudinal/transverse/anteroposterior). Iodine-131 scintigraphy was negative in all but four patients in whom serum thyroglobulin levels were elevated (Table 4). In seven patients with nonfunctional lymph node metastases, thyroglobulin concentrations ranged between 13 and 300 ng/ml and were undetectable in the remaining 12 (Fig. 1). Fine-needle aspiration biopsy was negative in 20 patients where only benign lymphocytes were found. Diagnoses could not be made for 18 biopsies because there were too few cells. There were no complications associated with biopsy procedures.

One patient with a negative biopsy returned for a follow-up examination 6 mo later, at which time ultrasonography identified possible metastases in an additional lymph node. The biopsy was positive for malignancy, and serum thyroglobulin was elevated (25 ng/ml).

Fifty-five patients with negative sonograms had no other evidence of the recurrence of disease.

TABLE 2
Correlation of Thyroglobulin (Tg) Levels in Patients with Functional and Nonfunctional Metastases on and off Suppression Therapy

Patient no.	Thyroid carcinoma	Metastases	^{131}I Scintigraphy	Tg on suppression therapy ng/ml	Tg off suppression therapy ng/ml
1	Follicular	Lung	Positive	>600	>600
2	Follicular	Lung, bone	Positive	65	150
3	Follicular	Lung, bone, mediastinal nodes	Positive	>600	>600
4	Papillary	Lung, bone, neck and mediastinal nodes	Positive	440	510
5	Papillary	Lung	Positive	56	125
6	Papillary	Lung, bone	Positive	<5	12
7	Follicular	Neck nodes	Negative	<5	<5
8	Follicular	Lung, bone	Positive	140	260
9	Follicular	Lung	Positive	80	240
10	Papillary	Neck nodes	Positive	18	90
11	Follicular	Bone	Positive	580	>600
12	Papillary	Neck nodes	Negative	<5	<5
13	Follicular	Bone	Positive	250	360
14	Papillary	Local recurrence	Positive	55	155
15	Papillary	Neck nodes	Positive	15	400
16	Papillary	Neck nodes	Negative	<5	16

TABLE 3
Comparison of Diagnostic Reliability of Tg and WBS for Detecting Metastases or Recurrences

	Thyroglobulin*				Whole-body scintigraphy		
	M+†	M−	Total		M+	M−	Total
Tg >5 mg	40	18	58	WBS+	28	0	28
Tg <5 mg	15	286	301	WBS−	27	304	331
Total	55	304	359	Total	55	304	359
	Sensitivity 73%				Sensitivity 51%		
	Specificity 94%				Specificity 100%		
	Accuracy 91%				Accuracy 92%		

*Tg = thyroglobulin levels in patients off suppression therapy; †M = metastases.

Iodine-131 Whole-Body Scintigraphy

Diagnostic ^{131}I whole-body scintigraphy was negative in 304 patients without evidence of neoplastic tissue and positive in 28 of 55 patients (51%) with metastases or recurrences (Table 3). After a therapeutic dose of ^{131}I, whole-body scintigraphy revealed new localizations of metastases in 4 of 28 patients with functional metastases. In two patients with known functional lung metastases, additional bone metastases were detected; and in two patients with bone metastases, previously occult lung metastases were revealed. Twenty-seven patients had negative radioiodine scintigraphy despite the presence of metastases. Eight of them had positive distant metastases detected by conventional radiography, computed tomography and/or bone scintigraphy; 19 had neck lymph node metastases detected by ultrasonography (Table 1). Serum thyroglobulin levels were elevated in 13 of 27 patients with negative radioiodine scintigraphy. The sensitivity of ^{131}I whole-body scintigraphy was 51%, its specificity 100% and accuracy 92% (Table 3).

DISCUSSION

Whole-body scintigraphy with ^{131}I has been used as a major method to detect metastatic or recurrent disease in patients with differentiated thyroid carcinoma. It is a highly specific procedure, with recently reported sensitivities of 80% (*18*), 76.6% (*19*) and 68.2% (*20*). The sensitivity of radioiodine scintigraphy was 51% in our patients after surgical thyroidectomy and radioiodine ablation of the thyroid remnant (Table 3). The reason for this discrepancy is that our follow-up was based mainly on the combined use of three diagnostic modalities: ^{131}I

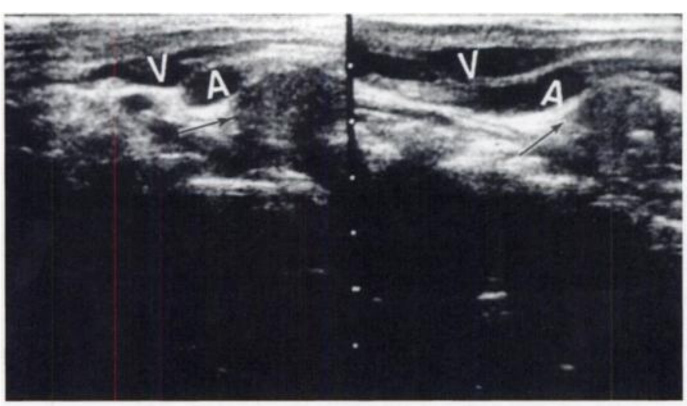

FIGURE 2. Sonograms show postoperative recurrence of thyroid carcinoma. (Left) Transverse section on left side. Just medial to the common carotid artery (A) and internal jugular vein (V) is hypoechoic mass (arrow) due to recurrent carcinoma. (Right) Longitudinal section on right side. The mass (arrow) is easily seen.

whole-body scintigraphy, serum thyroglobulin measurement and neck ultrasonography. In patients with negative radioiodine scintigraphy and elevated thyroglobulin levels, a more thorough search was made using conventional radiography, CT and/or bone scintigraphy. These additional modalities enabled us to detect distant, nonfunctional metastases in six patients. Furthermore, unknown lesions in the neck were revealed when ultrasonography and ultrasound-guided biopsy were used. Iodine-131 scintigraphy was negative in 19 of 27 patients with tumor tissue confined to the neck region (Fig. 1). These findings agree with the results of others who also used neck ultrasonography in managing patients with thyroid carcinoma (*12,14*). Lubin et al. found that ^{131}I whole-body scintigraphy had a sensitivity of 55% (*12*), while Müller-Gärtner and Schneider reported that iodine scintigraphy was positive in 63% of patients with metastases from papillary carcinoma and in 50% of patients with follicular carcinoma (*14*). Some authors have reported that measurements of serum thyroglobulin can be a more sensitive indicator of recurrent disease than radioiodine scintigraphy (*5,6,11,12,14,17,19*). Indeed, elevated thyroglobulin levels were measured in 40 (73%) of our patients with distant metastases, neck lymph nodes or local recurrence after suspension of suppression therapy, and ^{131}I scintigraphy was positive in 28 (51%) patients (Table 3). Thirteen of 27 patients with nonfunctional metastases and all but one patient with functional metastases had increased thyroglobulin levels.

It was suggested that the likelihood of detecting metastases or recurrences increases when higher doses of ^{131}I are given to patients with elevated thyroglobulin levels and negative diagnostic ^{131}I scintigraphy (*9,15,20–25*). Thus, this higher sensitivity was demonstrated after therapeutic doses (3.7–5.55 GBq, 100–150 mCi) of ^{131}I, with detection rates as high as 84% (*15*). The therapeutic effect of this approach is controversial and remains to be validated.

The use of therapeutic doses of ^{131}I to detect metastases or the recurrence of thyroid carcinoma leads to unnecessary treatment of patients without functional metastases (*12,21*). This rationale was substantiated by Edmonds and Kermode (*26*) who found that the ability of tumor cells to secrete thyroglobulin does not necessarily imply that they can concentrate radioiodine, and that the relationship between these two cellular functions varies from tumor to tumor.

Serum thyroglobulin levels were undetectable in 27% of our patients with metastases. One patient with distant functional metastases, two with distant nonfunctional ones, and 12 patients with nonfunctional neck lymph-node metastases or local recurrence had thyroglobulin values below 5 ng/ml (Table 1). These findings indicate that the sensitivity of thyroglobulin measurements has limitations, especially in the neck region. Several explanations are possible for the false-negative thyroglobulin results including the small size of the neoplastic tissue with a reduction of synthesis or release of normal thyroglobulin, synthesis of abnormal thyroglobulin or the lack of ability to produce thyroglobulin at all.

On the other hand, the presence of neoplastic tissue was suspected in 18 patients with persistently elevated thyroglobulin levels and no other signs of disease. These patients were included in the protocol with more frequent, thorough follow-ups.

Serum thyroglobulin results were negative in our patients without evidence of carcinoma while they were on suppression therapy. Only 2 of 16 patients with metastases (Patients 6 and 16) had normal thyroglobulin concentrations on suppression therapy, but elevated levels after therapy was suspended. These were by far the lowest values in the nonsuppressed results (Table 2). Many authors reported a higher sensitivity of

TABLE 4
Iodine-131 Whole-Body Scintigraphy and Thyroglobulin Levels in Patients with Positive Neck Ultrasonography

	WBS-positive		WBS-negative		
	Papillary	Follicular	Papillary	Follicular	Total
Tg >5 ng/ml*	3	1	7	0	11
Tg <5 ng/ml	0	0	10	2	12
Total	4		19		23

*Thyroglobulin levels in patients off suppression therapy.

thyroglobulin measurements in patients who were off thyroid hormone therapy, and this is generally considered as a more reliable approach (*9,13–15,17,19*). Others, however, suggested that determining thyroglobulin levels in patients on thyroid hormone therapy might be reliable enough and could even replace ^{131}I whole-body scanning in the follow-up of patients with differentiated carcinoma (*7,10,11*). The approach of using thyroglobulin assays in patients on suppressive therapy would be desirable because it would avoid the hypothyroid morbidity associated with suspending hormone therapy.

Thyroglobulin measurements enabled us to detect metastases or the recurrence of disease in some patients before they were revealed by other diagnostic modalities. In three of our patients, elevated thyroglobulin levels preceded the detection of metastases by other methods. In two patients, cervical lymph node metastases were detected by ultrasonography and ultrasound-guided biopsy and in one patient, lung metastases were determined by ^{131}I scintigraphy and radiography a few months to 2 yr after measuring the first increase in thyroglobulin levels. These findings could be explained by the presence of occult tumor foci capable of producing thyroglobulin, but not detectable by clinical, radiological, ultrasonography with ultrasound-guided biopsy or scintigraphic methods.

There are controversial reports about the effectiveness of methods for detecting residual and/or recurrent disease in the thyroid bed and local neck structure. According to Aiello et al. (*16*), ^{131}I whole-body scintigraphy was superior to measuring serum thyroglobulin, but false-negative whole-body scintigraphy results in patients with local metastases also were demonstrated in their study and by others. In addition, it is important to emphasize that evidence of ^{131}I localization in the thyroid bed is not specific for tumor. For most patients, the literature refers to activity confined to the thyroid bed on whole-body scintigraphy with uncertainty as to whether it reflects residual normal or malignant tissue (*15,16,25*). Besides, many cervical metastases are not clinically palpable; the reported ability to detect metastatic lymph nodes by palpation is about 30% (*27*).

Ultrasonography provides a tool to reveal occult neck masses by other methods and further evaluate them by ultrasound-guided biopsy. Also, ultrasonography with ultrasound-guided biopsy can determine whether the activity shown on whole-body scintigraphy in the neck region, and especially that limited to the thyroid bed, reflects residual normal or malignant tissue. Adding this method to our follow-up protocol enabled us to establish the diagnosis of lymph node metastases or local recurrence in 19 patients with negative ^{131}I whole-body scintigraphy; 12 of these patients also had negative thyroglobulin measurements (Table 4). Favorable results with ultrasonography were obtained despite several aspiration biopsies that could not be diagnosed because they were hypocellular and lacked a tissue core specimen for histological analysis. Ultrasonography and ultrasound-guided biopsy have been shown to be accurate, safe techniques for detecting neck lymph node metastases and local recurrences (*28*). It is still controversial as to whether the patients will benefit from treating lymph node metastases. Although some authors found that nodal involvement was a significant factor in the decreased 10-yr survival of patients, when compared with similar people who had no such lymph node metastases (*29*), others reported that the extent of nodal involvement did not appear to influence their survival; therefore, detection might not be important (*30*). The possibility of detecting local, non-nodal recurrence in patients with invasive disease was of great importance.

CONCLUSION

Our present and previous data (*31,32*) indicate that neither ^{131}I whole-body scintigraphy nor the determination of thyroglobulin levels by themselves are adequate to detect recurrent or metastatic disease in patients with differentiated thyroid carcinoma after total thyroidectomy and radioiodine ablation of the remnant. Our experience suggests that the combined use of three diagnostic modalities, measurements of serum thyroglobulin, neck ultrasonography with biopsy to detect tumor tissue in the neck region and ^{131}I whole-body scintigraphy, gives the best results in the follow-up of these patients. In considering the cost-effectiveness of long-term management, we also propose an approach of taking into account the patient's individual risk for recurrent or metastatic disease (*33–35*). In all patients with differentiated thyroid carcinoma, we make an initial assessment using these three methods approximately 3–6 mo after radioiodine ablation of the thyroid remnant. Subsequent follow-up using thyroglobulin measurements on suppression therapy and neck ultrasonography is done yearly for low-risk patients, with the addition of ^{131}I whole-body scintigraphy and thyroglobulin measurements during suspension of suppression therapy every 3–5 yr. In high-risk patients, a more aggressive approach is justified using the thyroglobulin determination, neck ultrasonography and ^{131}I whole-body scintigraphy at least once a year.

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Antibody Responses to Macrocycles in Lymphoma

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Metallic radioimmunoconjugates have promise for radioimmunoimaging and therapy. Macrocyclic chelating agents allow formation of stable metallic radioimmunoconjugates but have been reported to be immunogenic. This study assesses human antibody responses in patients that were imaged or treated with radiolabeled Lym-1 containing the macrocyclic chelators 1,4,8,11-tetraazacyclotetradecane-N,N′,N″,N‴-tetraacetic acid (TETA) or 1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid (DOTA). **Methods:** One to six doses (median 1) and 6 to 285 mg (median 33) ^{67}Cu-2IT-BAT (2-iminothiolane bromoacetamidobenzyl TETA)- or ^{111}In-2IT-BAD (2-iminothiolane bromoacetamidobenzyl DOTA)-Lym-1 were administered to each of 18 patients with lymphocytic malignancies. Solid-phase ELISA, utilizing unchelated Lym-1 or human serum albumin conjugated to DOTA, TETA or 2IT-bromoacetamidobenzyl-ethylenediaminetetraacetic acid (BABE) as coating antigens, was used to characterize antibody responses against ^{67}Cu-2IT-BAT-Lym-1 and ^{111}In-2IT-BAD-Lym-1 by quantitating antibodies against the Lym-1, DOTA, TETA or 2IT moieties, respectively. **Results:** None of the patients had evidence for serum sickness. No patient that received ^{111}In-2IT-BAD-Lym-1 developed antibodies to Lym-1 or DOTA. Two (15%) of the 13 patients that received ^{67}Cu-2IT-BAT-Lym-1 developed antibodies against both TETA and Lym-1, and an additional patient developed antibodies against Lym-1 only. No patient developed an antibody response solely against the macrocycle, nor did any of the patients generate antibodies against the 2IT molecule. HAMA levels were many times greater in amount than HATA levels even when their relative molecular masses were considered. **Conclusion:** Although macrocycles such as DOTA and TETA, and other chelates, can be haptens and thus potentially immunogenic, our findings do not support the view that macrocycles are more immunogenic than other radiometal chelating agents.

Key Words: lymphoma; radioimmunotherapy; HAMA; anti-macrocycle antibodies

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Metallic radionuclides, such as ^{111}In, ^{90}Y and ^{67}Cu, have great promise for radioimmunoimaging or therapy when chelated in a stable manner. Since Moi et al. (*1*) described the synthesis of macrocyclic bifunctional chelating agents, macrocycles have been shown to provide stable radioimmunoconjugates for several radionuclides (*2–7*). Stable macrocyclic radioimmunoconjugates prevent escape of the radiometal, thereby avoiding subsequent radiometal uptake by the normal tissues that can lead to toxicity (*8,9*). Therefore macrocyclic chelators have potential clinical applicability (*10–14*).

Kosmas et al. (*15,16*) reported humoral immune responses against the macrocyclic chelating agent benzyl-DOTA in patients receiving ^{111}In- and ^{90}Y-labeled monoclonal antibodies. All six patients that received intraperitoneal therapy with ^{90}Y-DOTA-HMFG1 developed antibodies specific for DOTA, and three patients had clinical evidence for serum sickness.

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