Serum Thyroglobulin and Iodine-131 Whole-Body Scan in the Diagnosis and Assessment of Treatment for Metastatic Differentiated Thyroid Carcinoma

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Because of the limitations of periodic ^{131}I whole-body scans, including suspension of substitution therapy, questionable sensitivity and low yield in detecting metastases in patients who have undergone thyroidectomy, serum thyroglobulin and ^{131}I whole-body scans were evaluated for sensitivity in detecting local, regional or distant metastases in 261 patients with differentiated thyroid carcinoma after total thyroidectomy and ablation. **Methods:** A noncompetitive immunoradiometric assay was used for serum thyroglobulin determination. An ^{131}I whole-body scan was obtained after replacement therapy had been suspended for 6 wk or when TSH reached levels higher than 50 μU/ml. In patients who underwent radiological procedures with iodinated contrast media, the waiting period before the ^{131}I whole-body scan was no less than 10 wk. **Results:** Of the 58 patients with proven metastases who were followed for 12 yr (mean 7 ± 3.3 yr), 51 (88.4%) had high serum thyroglobulin assays performed while under full replacement therapy and 32 (55%) showed clear ^{131}I whole-body scan localization. There were no instances of positive whole-body scans and negative serum thyroglobulin. **Conclusion:** In patients treated with ^{131}I, serum thyroglobulin assay was an excellent method to assess treatment. Patients with metastatic disease and negative whole-body scans with or without serum thyroglobulin exhibited a trend toward higher mortality. This trend may also indicate that the lack of ^{131}I trapping and low thyroglobulin is a sign of metabolic dedifferentiation of otherwise histologically differentiated thyroid tumors.

Key Words: thyroid carcinoma; iodine-131 whole-body scans; serum thyroglobulin

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From the late 1950s through 1980, periodic ^{131}I whole-body scans were obtained from patients who had undergone a thyroidectomy for differentiated thyroid carcinoma (DTC). This approach has several drawbacks:

1. Suspension of substitution therapy for 6 wk;
2. Questionable sensitivity in diagnosing progressive disease; and
3. Expected yield of metastases in this entire population was low.

We therefore evaluated the efficacy of the use of serum thyroglobulin (TG) (*1–6*) as a marker for thyroid tissue growth in a consecutive series of patients who had undergone near-total thyroidectomy and ^{131}I ablation.

MATERIALS AND METHODS

For 12 yr since 1981, 261 patients were followed by periodic determination of thyroglobulin under replacement therapy. The population studied (Table 1) included 178 females and 83 males aged 6 to 84 yr (mean age, 44.5 ± 17.4 yr) who had histologically confirmed DTC. There were 166 cases of papillary and mixed type tumors and 95 follicular type tumors, including four Hurthle cell carcinomas. Mean follow-up was 8 yr (range 0–12 yr; data obtained until December 1992). All patients were treated by near-total thyroidectomy and ablation with 1110–5550 MBq (30–150 mCi) of ^{131}I, according to postoperative evaluation (*7–9*). An ablative dose of 1110–1850 MBq (30–50 mCi) of ^{131}I was given to 68 patients with primary tumors of 1–3 cm in diameter, with no evidence of local, regional or distant spread. A higher ablation dose of 1850–5550 MBq (50–150 mCi) of ^{131}I was given to the rest of our patients, presenting with larger, primary lesions, with capsular or blood vessel invasion and/or evidence of local, regional or distant metastases. This group comprised 193 patients.

From January 1981, all patients were followed at 6-mo intervals during the first 3 yr and yearly thereafter, undergoing a careful clinical examination as well as determination of thyroid-stimulating hormone (TSH) and thyroglobulin. Iodine-131 whole-body scans were obtained in all patients initially following the ablation dose, and repeated 6–36 mo later in the 193 patients who had received the higher ablation dose or whenever there was suspicion of persistent or progressive disease. Other procedures used were ultrasound of the neck when indicated by fine needle aspiration

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TABLE 1
Differentiated Thyroid Carcinoma*

	Patient population				
		Metastases			
	No metastases	TG+ WBS+	TG+ WBS−	TG− WBS−	Total
Patients	203	32	19	7	261
Male	63	12	7	1	83
Female	140	20	12	6	178
Age (mean ± s.d.)	42.1	54.6	54.0	46.4	44.5 ± 17.4
Follow-up (mean ± s.d., yr)	8.3	7.1	7.4	6.0	8.0 ± 3.3
Pathology					
Papillary	134	16	11	5	166
Follicular	69	16	8	2	95

*After thyroidectomy and ablation.
TG = thyroglobulin; WBS = ^{131}I whole-body scan.

and thoracic x-ray. CT of the neck and chest was selectively performed.

Thyroglobulin Determination

A noncompetitive immunoradiometric assay (Sorin, Italy) was used for serum thyroglobulin determination. This was performed periodically, without reducing the replacement therapy. Levels higher than 10 ng/ml were considered pathological for this population and an indication of the need to search for thyroid tissue.

Whole-Body Scan

The ^{131}I whole-body scan was performed after replacement therapy had been suspended for 6 wk or when TSH reached levels higher than 50 μU/ml. In patients who underwent radiological procedures with iodinated contrast media, the waiting period before ^{131}I whole-body scan was not less than 10 wk. The urinary iodine should then be lower than 100 μg per gram of creatinine. The scan was done 48–72 hr after a dose of 185 MBq (5 mCi) of ^{131}I. After ablation or ^{131}I treatment the scan was performed 96–120 hr later. Today, the imaging device is a large-field rectangular camera (Elscint, Haifa, Israel).

RESULTS

In 208 of the 261 patients, serum thyroglobulin was consistently lower than 10 ng/ml (Figs. 1, 2); 201 showed no evidence of metastasis and were considered true-negatives. Among the 201 patients considered as true-negatives, 68 had no repeat ^{131}I whole-body scans. This corresponds to the group with the smaller primary lesion who received the lower ablation dose. In every other way, this group was followed as the rest of the patient population and was considered metastasis-free since they showed no sign of persistent disease. The remaining seven of the 208 patients showed metastasis and were thus false-negatives; five had a papillary tumor with involvement of lymph nodes, lung and bone, and two had follicular tumors with lung and bone involvement. In all seven patients, the ^{131}I whole-body scan was also negative (Fig. 2). Disease recurrence in the neck area was detected clinically and by ultrasound, and confirmed by cytological examination. The metastasis of lung and bone was detected mainly by x-ray and CT scan.

Of the 53 patients with thyroglobulin values above 10 and up to 1500 ng/ml, 51 had confirmed metastatic lesions (true-positives). In four cases there was initially a positive thyroglobulin with no evidence of metastasis. Serum antithyroglobulin was negative in these patients (*10*). Iodine-131 whole-body scan was also negative. In one of these four cases, after 2 yr of careful follow-up, metastases in the lymph nodes of the retromanubrial region were diagnosed. In another case, lung metastases were revealed by CT after 3 yr. The other two are under close observation with no

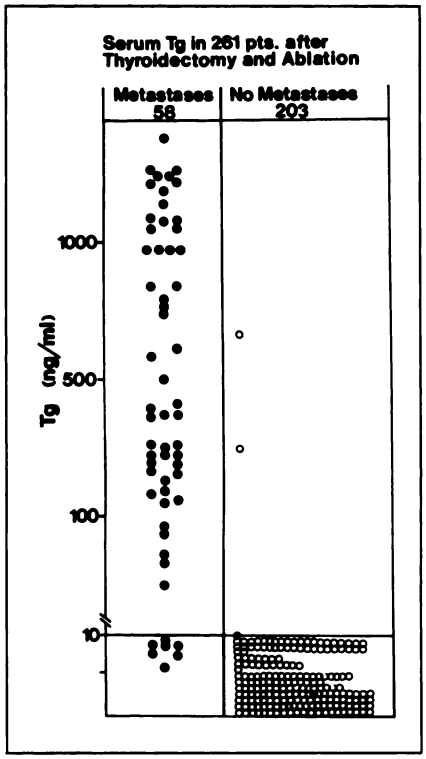

FIGURE 1. Each point in this figure represents the highest value of a series of determinations for each patient. Values higher than 1000 ng/ml thyroglobulin are obtained by appropriate dilution of the sample.

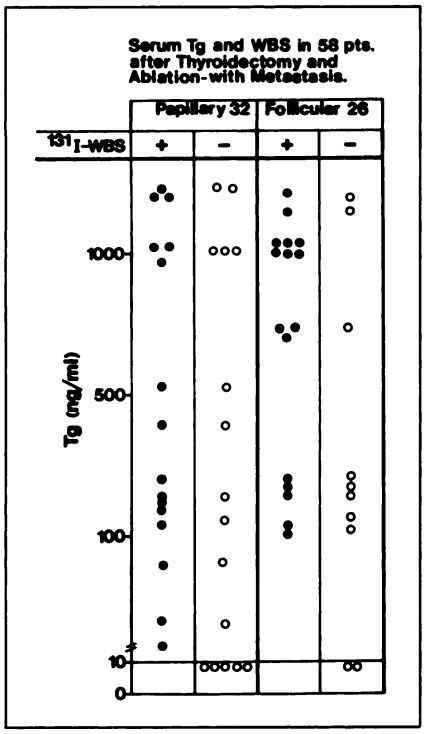

FIGURE 2. Distribution of positive and negative ^{131}I whole-body scan and thyroglobulin according to pathology. All positive ^{131}I whole-body scans had corresponding high thyroglobulin values.

evidence of metastasis, as yet. No information of value was provided by ^{201}Tl scanning in these patients.

Of the total 58 patients with proven metastases, the ^{131}I whole-body scan clearly demonstrated the presence, size and location of extrathyroidal iodophilic tissue in 32. It should be noted that in some cases imaging after the treatment dose allowed us to detect more lesions than those visualized in the pretreatment diagnostic ^{131}I whole-body scan. Of the 26 patients with nonpositive ^{131}I whole-body scan, two with a very high thyroglobulin level and evidence of lung and bone metastases were nevertheless treated with ^{131}I at a dose of 3700 MBq (100 mCi) but showed no specific concentration of ^{131}I or reduction in thyroglobulin levels following treatment.

In this patient population, the overall mortality was 11.5% (30/261). Among patients with metastases, the mortality was 52% (30/58). A trend of increasing mortality was seen when in the presence of metastases ^{131}I whole-body scan and/or thyroglobulin were negative (Table 2).

TABLE 2
Mortality in 58 Metastatic Patients

Total Thyroidectomy and Ablation			
TG	WBS	Number of patients	Percent
Positive	Positive	14/32	44
Positive	Negative	11/19	58
Negative	Negative	5/7	71
Total		30/58	52

TG = thyroglobulin; WBS = ^{131}I whole-body scan.

TABLE 3
Serum Thyroglobulin (TG)

261 Ablated patients		
TG (ng/ml)	Metastasis Present	Absent
>10	51	2
<10	7	201
Sensitivity	88%	
Specificity	99%	
Accuracy	96.5%	

DISCUSSION

In this population of 261 DTC-ablated patients, serum thyroglobulin showed a sensitivity of 88%, a specificity of 99% and an accuracy of 96.5% in the recognition of the 58 patients with confirmed metastases (Table 3). Among this population with metastatic disease, 22 were diagnosed while on follow-up protocol; metastatic spread was present at the time of diagnosis and persisted after initial surgery in 36 patients. Similar levels of sensitivity have been reported previously when studies were performed under the same conditions of continuing replacement treatment with low TSH values (*3–11*). In contrast, the whole-body scan had a sensitivity of only 55% (Table 4), a finding similar to that reported by Tubiana (*12*) and Simpson et al. (*13*). Tubiana found clear concentration in 57% of papillary tumors and 60% of follicular tumors; Simpson and associates reported 45% in papillary and 60% in follicular tumors. In our population, the sensitivity of ^{131}I whole-body scans for metastatic detection was 50% in patients with papillary carcinoma and 61.6% in patients with follicular carcinoma. All patients with a positive ^{131}I whole-body scan also had positive thyroglobulin findings (Fig. 2) (Table 5). The periodic performance of ^{131}I whole-body scans in addition to thyroglobulin determination does not improve sensitivity in recognizing the spread of disease. Comparing both tests has been the subject of previous publications (*2,4,14*) and of an editorial by Blahd (*15*).

Based on these findings, patients with differentiated thy-

TABLE 4
Iodine-131 Whole-Body Scan (WBS)

261 Ablated Patients		
WBS	Metastasis Present	Absent
Positive	32	0
Negative	26	203
Sensitivity	55%	
Specificity	100%	
Accuracy	90%	

TABLE 5
Total Thyroidectomy and Ablation

261 Patients					
		Metastasis			
		Present		Absent	
TG	WBS	No.	%	No.	%
Positive	Positive	32	55	—	—
Positive	Negative	19	33	2	1
Negative	Negative	7	12	201	99
Total		58	100	203	100

Tg = thyroglobulin; WBS = ^{131}I whole-body scan.

roid carcinoma following surgery and ablation undergo the following:

1. Clinical examination every 6 mo for the first 3 yr and yearly thereafter;
2. Serum thyroid stimulating hormone and thyroglobulin determinations at each clinical visit;
3. Ultrasound of neck yearly for the first 3 yr and thereafter once every 2 yr;
4. Thoracic x-ray every 2 yr.

When the clinical examination or any of these procedures raise suspicion of active disease, ^{131}I whole-body scan is performed.

A positive ^{131}I whole-body scan justifies the therapeutic use of ^{131}I. In patients treated with ^{131}I, thyroglobulin proved very useful in the assessment of treatment results and in the indication and timing of further treatment. We observed a good correlation between the clinical and radiological response to treatment and the changing values of serum thyroglobulin, as seen in Figures 3, 4, and 5. Higher thyroglobulin values and their trend over time are a major factor in our decision for retreatment, while a continuously low thyroglobulin value obtained after ^{131}I treatment is taken as an indication to temporarily withhold ^{131}I diagnostic or therapeutic action. This positively matched metastatic group (thyroglobulin+ and ^{131}I whole-body scan+) with 16 papillary and 16 follicular tumors had a mortality of 44% (Table 2) at a mean follow-up of 7.1 yr. In 19 patients with proven metastasis (11 papillary and 8 follicular tumors), there was a mismatch, i.e., a high thyroglobulin but a negative ^{131}I whole-body scan. In these patients, when ^{131}I was of no therapeutic use, surgery, radiotherapy and chemotherapy were selectively employed. At a mean follow-up of 7.4 yr, their mortality was 58%.

Among the population with metastatic disease, seven patients showed negative matching, with thyroglobulin lower than 10 ng/ml and a negative ^{131}I whole-body scan (Table 5). These cases were diagnosed by their metastatic manifestations and local invasion. Five patients had papillary carcinoma and two had follicular carcinoma. The average age of this group was 46.4 yr and the mean follow-up was 6.0 yr. Mortality was 71% (Table 2).

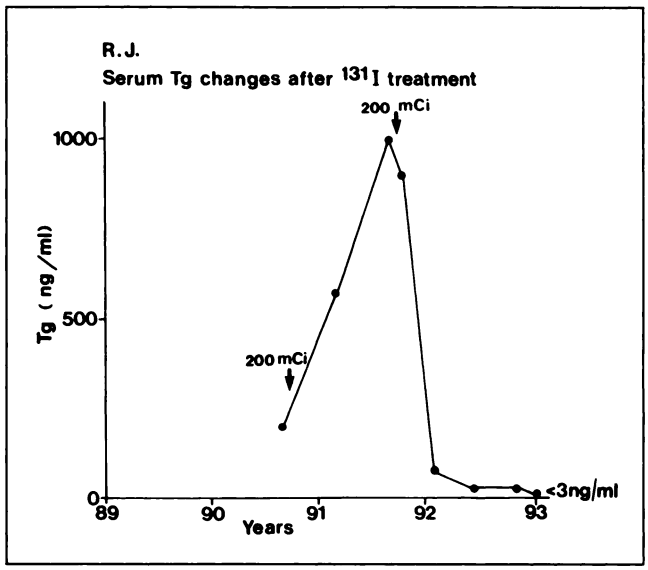

FIGURE 3. A 60-yr-old female presented with a large, painful osteolytic lesion of the head of the right humerus which proved to be follicular carcinoma of the thyroid. After total thyroidectomy, the lesion had high ^{131}I uptake. After the second ^{131}I treatment, there was a marked lessening of pain, and the thyroglobulin levels showed a downward trend. Two years later, the lesion is sclerosing and the right shoulder is perfectly functional.

Even though the p value (log rank test) for the three survival curves was 0.23, there was a clear trend in median survival time: 11 yr for the positive matched patients; 8 yr for the mismatched; and 7 yr for the negative matched. The same trend was found when we analyzed thyroglobulin-positive and thyroglobulin-negative patients (median survival, 11 and 7 yr, respectively, p = 0.10) and ^{131}I whole-body scan-positive and ^{131}I whole-body scan-negative patients (median survival, 11 and 8 yr, respectively, p = 0.31). Life tables and survival curves were calculated by the product limit-estimate method (Kaplan Meir). Percentage mortality (Fig. 5) shows the same trend.

The absence of iodine trapping and its direct consequence, the impossibility of benefiting from ^{131}I therapy, could be the main cause of increased risk of mortality. Tubiana (*12*) also showed increased mortality in patients with no ^{131}I tumor concentration. In 295 patients with active disease, he reported a 5-yr survival rate of 20% for those with non-^{131}I-trapping metastases versus 68% for those with ^{131}I-concentrating metastases.

Thomas-Morvan et al. (*16*) demonstrated a dependency between iodine incorporation into thyroid tumor cells and the adenylate cyclase (AC) response to TSH stimulation at the cell membrane level in vitro. That is, reduced AC responsiveness, a form of dedifferentiation, correlated better with diminished iodine concentration than with cell morphology or tissue architecture.

The absence of serum thyroglobulin in the developing metastatic DTC could be another manifestation of dedifferentiation. Again, there is a degree of TSH-thyroglobulin dependency (*16,17*). In our patient population, thyroglob-

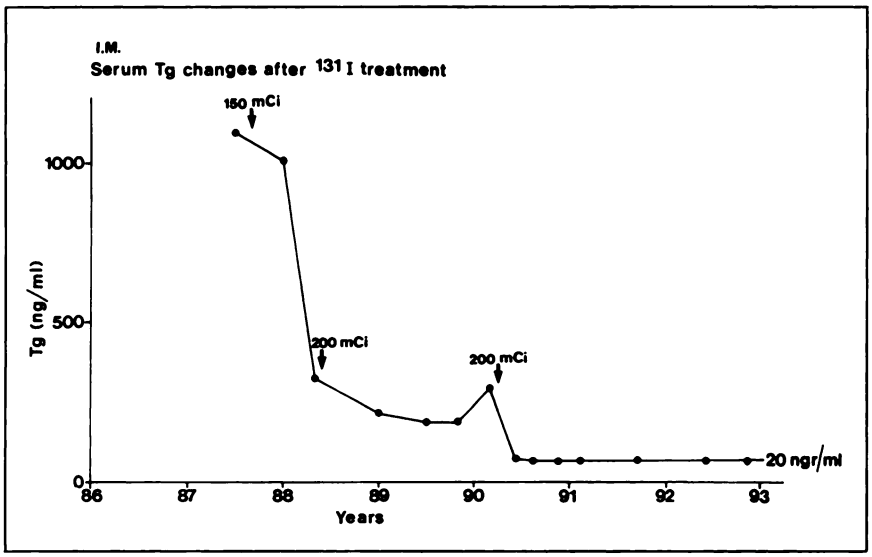

FIGURE 4. A 70-yr-old male with lung and bone metastases originating in follicular thyroid carcinoma. There was an initially high thyroglobulin value and high concentration of ^{131}I in the lesion. Good clinical and radiological response with a corresponding reduction in thyroglobulin levels has been observed.

ulin increased when substitute therapy was stopped, but the increase was not significant in the group with thyroglobulin values of less than 10 ng/ml and TSH stimulation did not modify the sensitivity of the marker. Ruiz-Garcia and colleagues (*18*) found that high values of thyroglobulin 1 mo after surgery had poor prognostic significance because they represented the great majority of patients with metastases. Nevertheless, with regard to metastatic patients only, a thyroglobulin level lower than 10 ng/ml in the presence of untreated metastasis could be considered of poor prognostic value, as seen in our negative matched group.

Van Herle et al. (*19*) demonstrated that the presence of the differentiating agent 13-cis-retinoic acid in thyroid follicular tumor cells in vitro substantially improves radioiodine trapping and TSH binding by these cells. Although in vitro findings cannot be extrapolated to the in vivo situation, the possibility apparently exists. If so, this could change therapeutic attitudes and probably the prognosis of mismatched and negatively matched thyroglobulin-^{131}I whole-body scan patients.

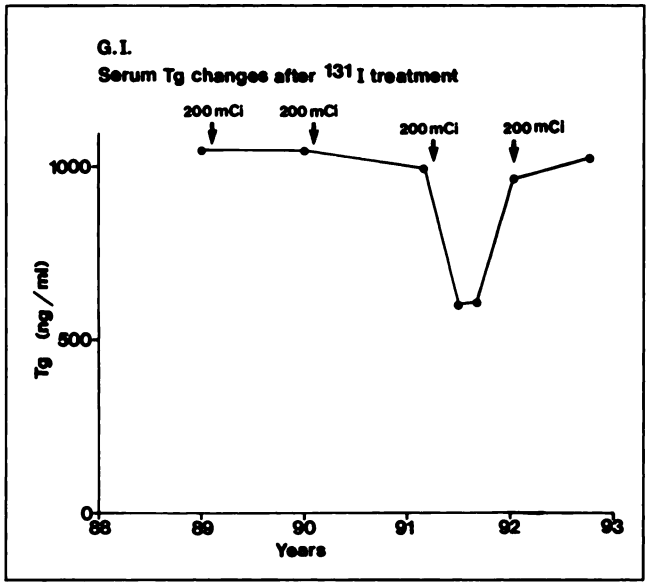

FIGURE 5. A 40-yr-old male with massive lymph node, lung and bone metastases of a papillary carcinoma of the thyroid. Although there was ^{131}I uptake, the clinical and radiological response has been poor and there has been no decrease in thyroglobulin.

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FIRST IMPRESSIONS

A pinhole pertechnetate thyroid scan of a male with suspected Grave's disease.

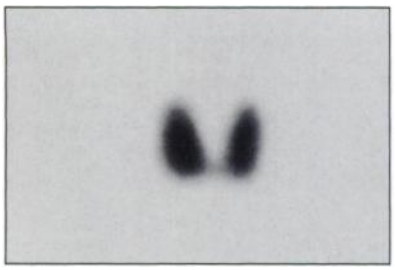

FIGURE 1.

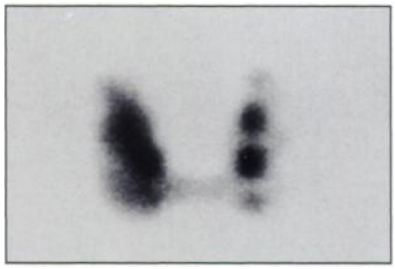

FIGURE 2.

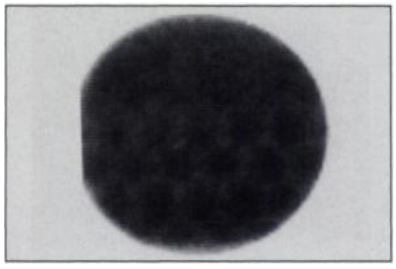

FIGURE 3.

PURPOSE

This 69-yr-old man was referred for evaluation of hyperthyroidism. The multinodular appearance on the initial study (Fig. 1) did not correlate with the smooth gland on palpation. A parallel-hole view on another camera demonstrated a gland consistent with Grave's disease (Fig. 2). A repeat "flood" revealed the reason for the discrepancy (Fig. 3).

TRACER

Technetium-99m-pertechnetate

ROUTE OF ADMINISTRATION

Intravenously

TIME AFTER INJECTION

20 minutes

INSTRUMENTATION

General Electric gamma camera; Siemens gamma camera

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INSTITUTION

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