Can Iodine-131 Whole-Body Scan Be Replaced by Thyroglobulin Measurement in the Post-Surgical Follow-up of Differentiated Thyroid Carcinoma?

Giuseppe Ronga, Artemisia Fiorentino, Enrico Paserio, Alberto Signore, Valerio Todino, Maria A. Tummarello, Mauro Filesi, and Ivo Baschieri

Clinica Medica II, Service of Nuclear Medicine, University of Rome "La Sapienza," and Department of Nuclear Medicine, University of L'Aquila, Italy

This study compared serum thyroglobulin measurement and whole-body scans in the post-surgical follow-up of patients with differentiated thyroid carcinoma. Thyroglobulin levels were measured in 61 patients receiving L-thyroxine therapy after thyroidectomy, and again after suspension of therapy, before performing a whole-body scan with iodine-131. The sensitivity, specificity, and accuracy of thyroglobulin levels, measured during L-thyroxine therapy, for diagnosis of tumor residue or metastases were then calculated and compared with results obtained by diagnostic whole-body scanning. Our data show that neither thyroglobulin levels nor whole-body scans alone can discriminate between patients with or without metastases. Sensitivity reached 95.7%, specificity 100%, and accuracy 96.7% if results of both procedures were also taken into consideration. We conclude that in the management and follow-up of patients with differentiated thyroid carcinoma both parameters need to be evaluated.

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After thyroidectomy and, in most cases, iodine-131 (^{131}I) ablation of residual thyroid tissue, follow-up of differentiated thyroid carcinoma (DTC) is currently based on periodic whole-body scan (WBS) and serum thyroglobulin (Tg) determination, both performed after an adequate period without replacement therapy (*1–5*).

This protocol presumes that withdrawal of thyroxine therapy will result in an increase of endogenous thyroid stimulating hormone (TSH) and increased functional activity of any residual thyroid tissue (Tg synthesis, ^{131}I uptake), information which is important for treatment. However, withdrawing thyroxine induces hypothyroidism, which may not be well tolerated by the patient, and elevated serum TSH levels may stimulate enlargement of any metastases.

Studies are being conducted in an attempt to reduce the number of ^{131}I scans and consequent hypothyroidism. An alternative approach to WBS is the localization of thyroid tumor tissue by the use of labeled anti-Tg monoclonal antibodies (*6,7*) or cell tropic tracers such as thallium-201 (*8*) together with determination of serum Tg levels during suppressive therapy (*9,10*).

In this study, we have compared the results of ^{131}I WBS with serum Tg levels measured both during replacement therapy and after suspension of therapy in 61 patients who underwent thyroidectomy for DTC.

MATERIALS AND METHODS

Patients

Sixty-one patients with histologically confirmed differentiated carcinoma (38 papillary, 14 follicular, and 9 mixed) were followed in our outpatient clinic. Patients with mixed carcinomas were included with those with papillary carcinomas for clinical and prognostic purposes. Duration of follow-up in these patients varied from a few weeks to 30 yr.

Each patient was under treatment with L-thyroxine (2.5–3.5 μg/kg body weight) according to serum FT3 and FT4 levels. Suppression of TSH levels was confirmed by TRH test.

Patients were divided into three groups based on diagnostic criteria: 1) absence of clinical, hormonal or scintigraphic evidence of thyroid activity; 2) presence of residual thyroid tissue and no metastases; and 3) suspected or confirmed local recurrence of tumor and/or presence of metastases. Patients with circulating anti-thyroglobulin antibodies were excluded from the study.

Thyroglobulin Determination

Serum Tg was determined during replacement therapy and after complete suspension of therapy on the same day of diagnostic WBS, as specified in the next paragraph. A non-competitive immunoradiometric assay (IRMA), (Sorin Biomedica, Saluggia, Italy) was used for serum Tg determination. Levels higher than 1000 ng/ml were in some cases difficult to

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For reprints contact: Dr. G. Ronga, Clinica Medica II, Policlinico Umberto I, 00161 Roma, Italy.

determine precisely and, therefore, are reported as >1000. Serum Tg levels ≤5 ng/ml were considered as normal both during and after suspension of suppressive therapy.

Whole-Body Scan

This was always performed after suspension of therapy. In our protocol, L-thyroxine is suspended 40 days before the WBS and is substituted for the first 22 days with triiodothyronine (80 μg/day). The diagnostic WBS was performed 24 hr after the administration of 74-148 MBq (2-4 mCi) of ^{131}I, using a double-head rectilinear scanner (ITAL-ELETTRONICA). The detection power of our scanner is 0.12 $\mu Ci/cm^2$, as described elsewhere (*11*), with some modifications. In patients with functioning metastases or significant residual thyroid activity, therapeutic doses of ^{131}I, varying from 1480 to 5550 MBq (40-150 mCi) were administered according to the amount and extent of pathologic iodine uptake and the age of the patient. In these cases, a second WBS was performed 48–72 hr after the therapeutic dose of ^{131}I to locate any metastases missed by WBS performed with diagnostic doses of ^{131}I.

Statistics

The Mann Whitney U-test was used to compare Tg levels from the different groups of patients and the Fisher exact probability test was used for calculating the significance of correlation coefficients. Mac-Nemar's test was used to compare the diagnostic value of Tg measurement with diagnostic WBS. Specificity, sensitivity, and accuracy of Tg measurement and WBS were also calculated.

TABLE 2
Clinical and Scintigraphic Data of Patients in Group 2

No.	Pt.	Sex	Histology	Tg1	Tg2	dWBS	^{131}I (mCi)	tWBS
1	GA	F	PAP	5	70	RES	52	RES
2	SS	F	PAP	3.1	89	RES	72	RES
3	VA	F	PAP	1.7	45.2	RES	30.7	RES
4	VA	F	PAP	3	31	RES	54.7	RES
5	CM	F	PAP	14	240	RES	105	RES
6	EI	F	FOLL	16	385	RES	40	RES
7	TA	M	PAP	6.8	32	RES	42.3	RES
8	CO	M	PAP	11	58	RES	104	RES
9	OA	F	MIX	14	40	RES	97	RES
10	ML	F	PAP	6	8.7	RES	75	RES
11	DG	F	PAP	10	28.7	RES	60	RES
12	CG	M	PAP	30	37.6	RES	93	RES
13	SO	F	MIX	24	120	RES	—	—
14	LV	M	PAP	6	40	RES	—	—
15	CM	F	MIX	9	16	RES	—	—
16	SM	F	FOLL	5.8	28	RES	—	—
17	ML	F	PAP	8	25.2	RES	—	—

MIX = mixed carcinoma; PAP = papillary carcinoma; FOLL = follicular carcinoma; Tg1 = serum Tg level during replacement therapy (ng/ml); Tg2 = serum Tg level after suspension of therapy (ng/ml); dWBS = diagnostic whole-body scan; RES = presence of residual thyroid tissue; tWBS = WBS performed after therapeutic dose of ^{131}I.

RESULTS

Clinical and scintigraphic data of the patients are reported in Tables 1, 2, and 3.

After thyroidectomy and, when necessary ^{131}I ablative therapy, 20 patients had either clinically, radiologically, or scintigraphically confirmed metastases. These were observed in the lungs (n = 11), lymph nodes (n = 6), bones (n = 4), or mediastinum (n = 3); four patients had multifocal neoplastic lesions. Six patients had local recurrences and 18 had residual thyroid tissue.

TABLE 1
Clinical and Scintigraphic Data of Patients in Group 1

No.	Pt.	Sex	Histology	Tg1	Tg2	dWBS	^{131}I (mCi)	tWBS
1	SM	F	MIX	2	28	NEG	—	—
2	PA	F	PAP	3	2.5	NEG	—	—
3	MD	M	PAP	4.2	5.1	NEG	—	—
4	TA	F	PAP	5	36	NEG	—	—
5	CS	M	PAP	5	47	NEG	—	—
6	DR	F	PAP	3	3	NEG	—	—
7	CP	F	PAP	3	3	NEG	—	—
8	TM	M	FOLL	2.6	8.9	NEG	—	—
9	PA	F	PAP	4.6	17.5	NEG	—	—
10	SE	F	PAP	3	29	NEG	—	—
11	BE	F	PAP	5	39.3	NEG	131	NEG
12	LP	F	PAP	3.4	32	NEG	—	—
13	DL	F	FOLL	2.7	25	NEG	—	—
14	SM	M	PAP	2.9	37.5	NEG	—	—

MIX = mixed carcinoma; PAP = papillary carcinoma; FOLL = follicular carcinoma; Tg1 = serum Tg level during replacement therapy (ng/ml); Tg2 = serum Tg level after suspension of therapy (ng/ml); dWBS = diagnostic whole-body scan; NEG = Negative WBS; tWBS = WBS performed after therapeutic dose of ^{131}I. Patient 11 received 131 mCi of ^{131}I due to suspicion of lymph node metastases.

The means of serum Tg levels during and after suspension of therapy are reported in Figure 1. The trend of mean values is to increase in the three groups both during and after suspension of therapy but no statistically significant difference was observed within and between groups (Mann Whitney U-test). In Group 3, we found a significant correlation ($r = 0.685$, $p < 0.0001$) between levels of Tg during replacement therapy and after suspension of therapy (Fig. 2). This correlation was not observed for Tg levels of patients in Groups 1 and 2.

Tg values of patients from all groups are reported in Figure 3 and show that there are no patients from Group 1 with Tg levels during therapy higher than 5 ng/ml and there are no patients from Group 2 with levels higher than 12 ng/ml. However, out of 23 patients who had normal Tg levels (≤5 ng/ml) during suppressive therapy, 19 (82.6%) reached pathologic levels after suspension of therapy. Of these, four had residual thyroid tissue and five had metastases. Overall, results of WBS after a diagnostic dose of ^{131}I correlated with serum Tg during therapy in only 36 out of 61 cases (59%).

TABLE 3
Clinical and Scintigraphic Data of Patients in Group 3

No.	Pt.	Sex	Histology	Tg1	Tg2	dWBS	^{131}I (mCi)	tWBS
1	BS	M	FOLL	1000	4270	LOC. REC.	98	LOC. REC.
2	TI	F	PAP	954	744	MET. LYM.	120	MET. LYM.
3	CE	F	FOLL	702	1000	MET. Lung	133	MET. Lung
4	RR	F	PAP	85	250	MET. LYM.	107	MET. LYM.
5	SE	F	FOLL	>1000	>1000	LOC. REC. and MET. Lung	143	LOC. REC. and MET. Lung
6	VF	M	PAP	187	990	LOC. REC.	141	LOC. REC.
7	MF	M	PAP	256	1400	LOC. REC.	125	LOC. REC.
8	GA	F	FOLL	69	113	MET. MED.	132	MET. MED.
9	GL	F	PAP	82	150	MET. Bone	100	MET. Bone
10	RF	F	FOLL	214	740	MET. Bone	176	MET. Bone
11	MR	F	FOLL	400	839	MET. Bone	157	MET. Bone
12	VC	F	FOLL	161	490	MET. MED. + MET. Lung	47.3	MET. MED. and MET. Lung
13	CA	F	FOLL	225	521	MET. MED.	128	MET. MED.
14	ZM	F	MIX	42	66	MET. LYM.	101	MET. LYM.
15	MO	F	PAP	45	306	MET. LYM.	140	MET. LYM.
16	CL	M	MIX	24	78	LOC. REC.	124	LOC. REC. and MET. Bone
17	MG	F	PAP	95	721	RES	130	RES and MET. Lung
18	SF	F	FOLL	162	400	NEG	123	MET. Lung
19	AF	M	MIX	8	80	NEG	116	MET. Lung
20	PA	M	PAP	30	160	NEG	160	MET. Lung
21	BI	M	MIX	17	251	NEG	100	MET. Lung
22	CN	F	FOLL	8.8	24.6	NEG	112	MET. Lung
23	BL	F	PAP	4	40	NEG	53	MET. Lung
24	CV	F	PAP	3	72	NEG	175	MET. Lung
25	CC	M	PAP	4.8	473	MET. LYM.	94	MET. LYM.
26	DF	M	PAP	5	41	MET. LYM.	101	MET. LYM.
27	PK	F	PAP	3	80	LOC. REC.	107	LOC. REC.
28	MS	M	PAP	13	1000	NEG	125	NEG
29	SV	M	PAP	240	>1000	NEG	87	NEG
30	GM	F	MIX	293	800	NEG	117	NEG

MIX = mixed carcinoma; PAP = papillary carcinoma; FOLL = follicular carcinoma; Tg1 = serum Tg level during replacement therapy (ng/ml); Tg2 = serum Tg level after suspension of therapy (ng/ml); dWBS = diagnostic whole-body scan; NEG = negative WBS; LOC. REC. = presence of local recurrence; RES = presence of residual thyroid tissue; MET. LYM. = Regional lymph node metastases; MET. Lung = lung metastases; MET. MED. = mediastinal metastases; MET. Bone = bone metastases; tWBS = WBS performed after therapeutic dose of ^{131}I.

Figure 4 shows the sensitivity, specificity, and accuracy of Tg measurement and diagnostic WBS. Sensitivity of Tg measurement during therapy was 83.3%, whereas sensitivity of diagnostic WBS was only 76.6%. When both Tg levels and diagnostic WBS are considered specificity reaches 100% and sensitivity 95.7%.

Eleven patients (18%) had a negative diagnostic WBS despite the presence of metastases: eight had positive post-therapy WBS, whereas in the other three post-therapy WBS was still negative and the presence of metastases was suspected because of the high Tg levels either during or after suspension of L-thyroxine therapy. Only one of these three patients showed the presence of metastases in the latero-cervical region 5 mo after the last WBS was performed. Five patients with metastases (8.2%) had low levels of Tg during therapy, which increased to above normal after suspension of therapy.

Comparison of cases selected for ^{131}I treatment by the two methods (Tg during therapy and diagnostic WBS) showed a statistically significant difference (MacNemar's test, $p < 0.001$), thus, indicating that the two parameters are not of the same diagnostic value and are not interchangeable (Table 4).

DISCUSSION

This study demonstrates the importance of both Tg determination and WBS in the post-surgical follow-up of differentiated thyroid carcinoma. The aim of our work was to establish if measurement of serum Tg levels alone, during replacement therapy, was adequate in the follow-up of patients with DTC, thus avoiding the need of interrupting therapy to perform a WBS. Results of this study clearly demonstrate that this is not the case and that both parameters must be evaluated (Table 4). Moreover, after suspension of therapy, a second Tg

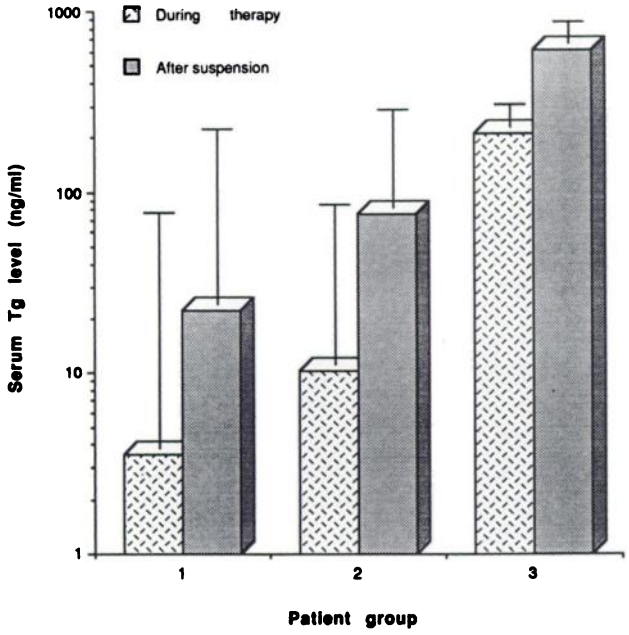

FIGURE 1
Serum thyroglobulin levels during replacement therapy and after suspension of therapy in the three groups of patients. Differences between the groups are not statistically significant. Data are mean ± s.e.m.

determination should be performed which may be of additional importance for a therapeutic decision.

The sensitivity of Tg determination during replacement therapy is higher than the sensitivity of a diagnostic WBS (83% and 76.6%, respectively) but by combining the two parameters the sensitivity reaches 95.7%. The sensitivity of Tg determination after suspension of therapy (data not shown) is 100%, but the specificity is as low as 12.9% and, therefore, this measurement must be considered only together with the other two parameters.

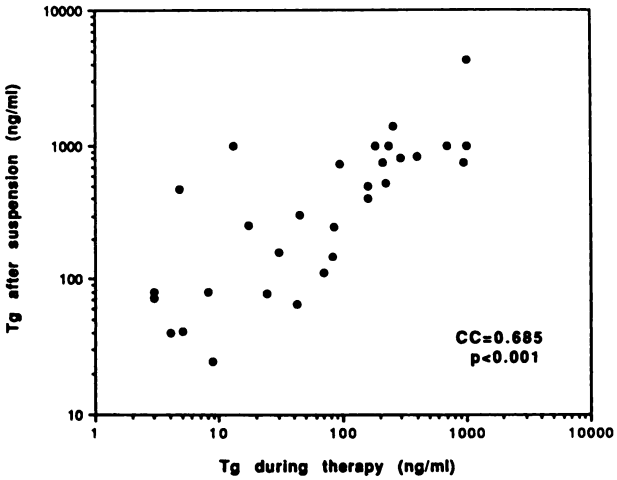

FIGURE 2
Correlation between Tg levels during replacement therapy and after suspension of therapy in patients of Group 3.

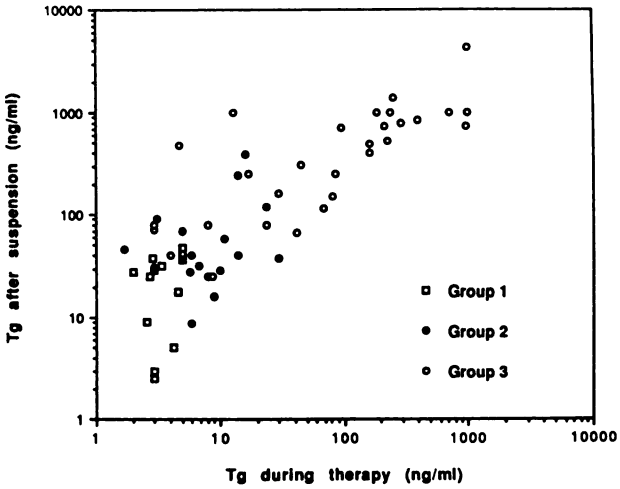

FIGURE 3
Distribution of Tg levels (during and after suspension of therapy) in all groups of patients. It can be seen that it is not possible to clearly separate patients belonging to the three groups on the basis of Tg levels.

In patients with residual thyroid tissue (shown in Table 2), the specificity of Tg determination is, of course, very low (23.5%) and affects the calculation of specificity when all patients are considered. Therefore, it is also important to perform a diagnostic WBS soon after surgery to determine the presence of residual thyroid tissue.

A particular comment must be made concerning five patients (Patients 19, 22, 23, 24, and 28 of Table 3) in which we found a negative diagnostic WBS and Tg levels within the normal or borderline (≤13 ng/ml) range. On the basis of Tg levels and diagnostic WBS, these patients would have been considered free of any local recurrence or metastases but Tg levels after suspension of therapy were high in all cases and led us to administer a therapeutic dose of ^{131}I to elicit possible metastases. Four out of these five had metastases. The explanation may be that partial loss of iodine uptake capacity by metastatic cells means that visualization is only possible with high doses of ^{131}I.

TABLE 4
Identification of Patients to Be Treated with ^{131}I Based on the Tg Value During Hormone Therapy and/or on the Diagnostic WBS

	Tg ≤ 5	Tg > 5	Total
dWBS NEG	3	16	19
dWBS RES/POS	20	22	42
Total	23	38	61

Tg = serum Tg level during replacement therapy (ng/ml); dWBS = diagnostic whole-body scan; NEG = negative WBS; RES = presence of residual thyroid tissue; POS = positive WBS for presence of metastases. Mac Nemar's test $p < 0.001$.

	Tg1			dWBS			Tg1+dWBS		
	M+	M-	Tot	M+	M-	Tot	M+	M-	Tot
Tg>5	25	13	38	T+ 36	0	36	T+ 45	0	45
Tg≤5	5	18	23	T- 11	14	25	T- 2	14	16
Tot	30	31	61	Tot 47	14	61	Tot 47	14	61

	Tg1	dWBS	Tg1+dWBS
Sensitivity:	83.3	76.6	95.7
Specificity:	58.1	100	100
Accuracy:	70.5	82.0	96.7

FIGURE 4
The calculation of sensitivity, specificity and accuracy of diagnosis of metastases on the basis of Tg levels during replacement therapy (Tg1), on the basis of the diagnostic whole-body scan (dWBS), or taking both parameters into consideration (Tg1+dWBS). When only Tg determination was considered, M+ indicates patients with metastases. When WBS was considered, M+ indicates patients with metastases or residual thyroid tissue. T+M+ indicates the number of true-positives in which the WBS correctly identified either metastases or residual thyroid tissue. Tot=total of cases in rows and columns.

Three patients (28, 29, and 30 of Table 3) had persistently negative diagnostic WBS despite a marked increase in Tg levels after suspension of therapy. In these cases, a therapeutic WBS should be performed to detect metastases. These patients were over 45 yr old with papillary (n = 2) or mixed (n = 1) carcinoma; all received at least two therapeutic doses of ^{131}I within a few months. The probable reasons for the discrepancy between the WBS and Tg levels were the decreased iodine uptake activity of papillary carcinoma and the reduced TSH secretion in older subjects (*12*). If metastases should appear, these patients would be treated, in all probability, with conventional chemotherapy and/or surgery. Therefore, these patients were closely followed and, to date, only one has shown clinical and radiologic signs of metastatic recurrence in the laterocervical region and has been referred to surgery.

A certain degree of functional autonomy of neoplastic tissue was observed in several patients (Table 3). Tg levels were high both during and after suspension of therapy, with little variation between the two measurements.

It is known that synthesis and secretion of Tg by tumor cells is a process independent of the iodine uptake capacity of these cells (*13*). In our study, we found patients in whom Tg production was abolished but ^{131}I uptake was not. On the other hand, we found eight patients in whom Tg secretion by tumor cells was still present but ^{131}I uptake was abolished after suspension of replacement therapy. This may also be explained as functional autonomy of neoplastic tissue and, in some cases, as lack of TSH dependency. TSH levels attained during suspension of hormone therapy are important from both the diagnostic and therapeutic points of view. Edmonds et al. (*14*) have demonstrated that serum TSH levels >30 μU/ml are needed to induce uptake activity of differentiated tumor cells. A small percentage of patients, particularly those followed for a long period of time for DTC, do not show elevated TSH levels after withdrawal of therapy in spite of apparently total thyroid ablation. This could be due either to self-administration of thyroxine or to a true lack of response of the hypothalamic-pituitary axis (*15,16*). These patients do not benefit from a prolonged period of withdrawal of L-thyroxine therapy. As previously reported by us and other authors, 18 days of complete hormone withdrawal is sufficient to obtain a good TSH response in patients with normal hypothalamic-pituitary function (*17,18*). The increase in TSH is usually greater in patients under 45 yr of age, but even in older patients TSH levels rise above 30 μU/ml after an adequate period of suspension of therapy (*17*). We have also observed that patients with low TSH levels and negative WBS do not benefit from exogenous TSH administration before performing a new WBS (unpublished observation). Thus, we do not routinely measure TSH levels before performing a diagnostic WBS.

CONCLUSIONS

In the follow-up of DTC, thyroglobulin determination has good sensitivity but low specificity and therefore cannot replace the WBS. The two methods identify different cases to be treated with ^{131}I.

In light of these results, it appears that optimal follow-up for these patients should be based on a combination of the two methods since neither alone is sufficiently sensitive or specific.

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Editorial
Serum Thyroglobulin in the Management of Thyroid Cancer

Although the majority of thyroid adenocarcinomas can be removed surgically, there is often uncertainty as to the completeness of the resection and the presence of local or distant histologic metastases despite the absence of clinically detectable abnormalities. Radioiodine ^{131}I has been used as adjunctive therapy in the management of thyroid adenocarcinoma for more than 40 yr. There is mounting evidence indicating an increased rate of survival and a decreased tumor recurrence rate in patients who have received radioiodine therapy. Ablation with radioiodine of any residual thyroid tissue that has not been removed surgically appears to be well accepted management since complete ablation of normal thyroid tissue usually assures radioiodine uptake in remaining tumor deposits and tumor metastases (*1*).

The efficacy of radioiodine therapy with rare exception is related directly to tumor uptake and retention. Efficient uptake and response to therapy is observed in tumors that are of differentiated cell types such as papillary or follicular, whereas undifferentiated tumors and Hürthle cell and medullary carcinomas rarely concentrate radioactive iodine. Effective tumor uptake is ~0.5% of the dose per gram with a biologic half-life of ~4 days (*2*). From the administration of 5.55 GBq ^{131}I, a tumor will receive ~25,000 cGy or five times the absorbed dose that can be delivered by a course of external radiation therapy. Ablation of small thyroid remnants after near total thyroidectomy may be accomplished with the administration of 2.78 to 3.70 GBq ^{131}I. Repeat doses are given at intervals of 4–6 mo until no imaging evidence of residual thyroid or functioning tumor tissue is demonstrable.

The recurrence of tumor following radioiodine ablation of all functioning tumor tissue has been found in more than 50% of patients who had tumor metastases at the time of therapy and in 25% of patients who did not have metastases (*3*). Recurrences have been observed after 5 to 10 yr of negative diagnostic studies (*3,4*). In view of the possibility of late recurrence, all patients in whom total radioiodine ablation has been obtained should be followed for at least 10 yr to assure that they remain free of recurrent functioning tumor.

Although whole-body imaging with radioiodine is considered to be the most sensitive means of detecting recurrent disease, it is a formidable procedure requiring withdrawal of thyroid hormone and periods of symptomatic hypothyroidism. In recent years there have been numerous reports suggesting that the determination of serum thyroglobulin (Tg) may be as

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For reprints contact: William H. Blahd, MD, Wadsworth Div. (691-W115), VA Medical Ctr., Wilshire & Sawtelle Blvds., Los Angeles, CA 90073.