Predicting the Efficacy of First Iodine-131 Treatment in Differentiated Thyroid Carcinoma

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The purpose of this study was to search for predictors of ^{131}I first ablative treatment efficacy in patients with postsurgical remnants after total thyroidectomy for nonmedullary differentiated thyroid carcinoma with no known metastasis. **Methods:** Thirty-seven patients were retrospectively studied. None presented antithyroglobulin antibodies. All patients received 111 MBq of ^{131}I for diagnostic purpose and, 9 days later, 3.7 GBq of ^{131}I for ablative therapy (IAT). To assess the efficacy of treatment, all patients were studied with ^{131}I and with thyroglobulin (Tg) plasma assays 6–15 mo later. Treatment was considered successful if no abnormal uptake was seen on whole-body scan and if the Tg plasma level was lower than 1 ng/ml. **Results:** Ablative treatment was found to be successful in 17 patients [IAT(+)] and unsuccessful in 20 [IAT(−)]. There was no significant difference between the two groups for clinical and histological data, size of thyroid remnants on a 1:1 dot scan and TSH level just before treatment. Although Tg levels were not different in the two groups before scanning dose administration (D0), Tg levels were higher in IAT(−) group 9 days later, just before radioiodine treatment administration (D9) and, in contrast, Tg levels were higher in the IAT(+) group 5 days after treatment administration (D14). Tg percentage change between D9 and D14 was significantly higher in the IAT(+) group and, with an optimal cutoff value of 750%, this parameter would have been able to predict successful treatment in 9 of 10 cases and unsuccessful treatment in 18 of 21 cases. Conversely, Tg percentage change between D0 and D9 was significantly higher in the IAT(−) group and of 11 patients with more than 100% change, 10 belonged to this group. **Conclusion:** The increase in Tg during the first ^{131}I ablative treatment could be a good predictor of treatment efficacy for patients with nonmetastatic differentiated thyroid carcinoma. Conversely, the increase in Tg observed after the administration of the scanning dose of ^{131}I just before ablative therapy is associated with a more frequent incomplete ablation, perhaps reflecting a stunning effect on the thyroid remnants.

Key Words: iodine-131 treatment; thyroid cancer; thyroglobulin

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The presence of remaining tissue after total or near-total thyroidectomy for nonmedullary differentiated thyroid carcinoma (DTC) is very common, as seen on postsurgical ^{131}I whole-body scans. Even if focal accumulation of radioiodine is frequently limited to the thyroid bed and not specific for tumor, surgery is often followed by ^{131}I ablative therapy (IAT) because, despite some controversies, the combination of surgery and ^{131}I treatment seems to be associated with a decreased recurrence rate of DTC and probably improved survival (*1–7*). The assessment of the efficacy of the treatment, which is to know if it will be sufficient to remove all remaining thyroid tissues detected on ^{131}I whole-body scans and to obtain a low level of thyroglobulin (Tg), is impossible at the moment of ablative therapy. It requires further withdrawal of thyroid hormone, several months later, to perform ^{131}I whole-body scan control and Tg measurement, which is more sensitive under TSH stimulation (*8–13*). In this retrospective study, we have reviewed clinical, biological and histological characteristics available at the time of the first radioiodine treatment in patients operated on for DTC to find out if one or more characteristics could be used as good predictors of therapeutic response.

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MATERIALS AND METHODS

Subjects

Fifty-six consecutive patients referred for first radioiodine therapy were reviewed. All patients had undergone a total thyroidectomy for DTC with lymph node dissection. Nineteen patients were not included in this retrospective study: 6 with anti-Tg antibodies because of possible disturbances in Tg measurements, 3 with known distant metastases not sufficiently numerous to constitute a separate group (2 of these also had anti-Tg antibodies) and 10 patients for whom some data were not available. The other 37 patients (34 women and 3 men, ranging in age from 12–77 yr) were included. For each patient, the following data were recorded: age and sex, histological type and size of primary tumor, thyroid capsule involvement and lymph node status. Moreover, associated histological abnormalities were classified as follows: lymphocytic thyroiditis (LT), nodular goiter (NG) or Graves' disease (GD). NG diagnosis was retained only when one or more benign nodules (≥10 mm) had been found on histological examination. At the moment of IAT, TSH level, Tg levels, size of thyroid remnants on a 1:1 dot scan and radioiodine percentage uptake in the neck were also recorded.

First Iodine-131 Treatment

Patients were referred for IAT 6 weeks to 22 months (median, 3.6 mo) after surgery. On the first day (D0), patients received 111 MBq of ^{131}I. Rectilinear scans of the neck and diagnostic whole-body scans were performed 3 days later (D3). Spot images were obtained for 10 min with a high-energy parallel-hole collimator on a circular analogic or computerized gamma camera. No quantitative dosimetric study was performed, nevertheless, cross-sectional areas corresponding to thyroid remnants on a 1:1 dot scan were measured, and radioiodine cervical uptake on D3 was noted. Radioiodine treatments (3.7 GBq of ^{131}I) were given 6 days later (D9). Post-therapeutic whole-body scans were performed 5 days after treatment administration (D14). Exogenous thyroxine replacement was discontinued 5 wk before diagnostic whole-body scan and was replaced by triiodothyronine for 3 wk. Triiodothyronine was stopped 2 wk before the diagnostic whole-body scan.

TSH and Tg Measurements

Blood samples for serum TSH and Tg assays were drawn on D0 before any radioiodine administration. In 17 of the 37 patients for TSH, and in all patients for Tg, additional samples were obtained on D9 before ^{131}I treatment, and on D14. TSH measurements were performed using a radioimmunoassay on diluted samples (1:10) to take into account high values of TSH (above 50 μUI/ml), except for 13 patients on D0, which were measured without dilution. Tg measurements were performed using a double-antibody radioimmunoassay (ELSA-HTG, Cis Bio International, France), the sensitivity of which is 0.5 ng/ml. This Tg assay measures concentrations up to 500 ng/ml, although with the dilution of the serum

TABLE 1
Patient Data, Histological Characteristics and First Iodine-131 Treatment Results

Patient no.	Sex	Age (yr)	Histological diagnosis	Other histological abnormalities	Size of primary tumor (mm)	Thyroid capsule involvement	Lymph node status	^{131}I treatment result
1	F	34	F	NG	30	No	NA	+
2	F	53	P		6	Yes	Negative	+
3	F	45	P		50	No	Positive	−
4	F	34	P	NG	14	No	Negative	+
5	F	36	P		23	No	Negative	−
6	M	35	F	NG	15	No	NA	+
7	F	24	P	LT	10	No	Negative	−
8	F	33	P	NG	5	Yes	NA	+
9	F	37	P	LT	8	No	NA	−
10	F	59	P	NG	10	No	Negative	−
11	F	40	P		30	Yes	Negative	+
12	F	35	P		15	Yes	Positive	−
13	F	57	P	NG	20	No	Positive	−
14	F	42	P	LT	10	No	Positive	+
15	F	65	F	NG	25	No	Negative	−
16	F	22	P		23	No	Positive	+
17	F	30	P		20	No	Negative	−
18	F	61	P		20	No	Negative	−
19	F	43	P		10	No	Negative	−
20	F	39	P	NG	45	No	Negative	+
21	F	37	P	NG	10	No	Negative	+
22	F	45	P	NG	20	No	Negative	+
23	F	52	P	GD	10	No	Negative	−
24	F	26	P	LT	20	Yes	Positive	−
25	F	71	P		20	Yes	Positive	−
26	F	60	P		9	No	Negative	+
27	F	27	P		30	No	Negative	+
28	F	46	P	LT	13	Yes	Positive	−
29	F	54	P	NG	50	Yes	Negative	+
30	F	36	P	NG	25	No	Negative	−
31	M	12	P		20	Yes	Negative	−
32	F	35	P		30	No	Negative	+
33	M	26	P		20	Yes	Positive	+
34	F	65	P		20	No	Positive	−
35	F	62	P	NG	10	Yes	Positive	+
36	F	58	P	NG	14	Yes	Negative	−
37	F	77	P		13	No	Negative	−

P = papillary carcinoma; F = follicular carcinoma; NG = nodular goiter; LT = lymphocytic thyroiditis; GD = Graves' disease; + = successful treatment; − = unsuccessful treatment; NA = not available.

samples, concentrations of the Tg higher than 500 ng/ml have been measured. Prior screenings of serum for Tg antibody were performed with another radioimmunoassay (ELSA-AB-HTG, Cis Bio International, France).

Tg Variations

Tg variations were expressed as the percentage change in Tg levels between D0 and D9, D0 and D14 and D9 and D14. Taking into account the assay sensitivity of 0.5 ng/ml, percentage changes were calculated only when TgDx and TgDy were ≥0.5 ng/ml. To eliminate artefactual increased counts during the measurement of serum Tg levels on D9 (9 days after scanning dose) or on D14 (5 days after therapeutic dose) due to scattered ^{131}I photons inside ^{125}I photopic, we compared two series of Tg measurements: the first series of results was obtained from 12 samples drawn on D14 and measured some hours later; the second series of results was obtained from the same 12 samples measured 3 months later (that is after ^{131}I decay). The results were not significantly different, with a mean variation of <5%. We concluded that there was no significant influence of ^{131}I serum activity on D14 measurement and consequently on D9 measurement.

Iodine-131 and Tg Control

To assess the efficacy of treatment, all patients were studied with ^{131}I 6–15 mo (median, 9 mo) after first IAT. Patients were taken off their thyroid hormone therapy according to the protocol described above. Blood samples for serum TSH and Tg assays were drawn before radioiodine administration for diagnostic whole-body scans. Whole-body scans were performed 3 days after administration of a scanning dose of 111 MBq of ^{131}I and were classified positive if they showed focal abnormal uptake in a pattern of residual or metastatic disease. IAT was considered successful if the ^{131}I whole-body scan was negative and if Tg level was <1 ng/ml. Consequently, patients were classified in two groups according to the result of the first radioiodine treatment: IAT(+) in the case of successful first IAT, IAT(−) in case of positive scan and/or Tg level ≥1 ng/ml.

Statistical Analysis

To determine if there were any significant differences between groups IAT(+) and IAT(−), quantitative data were compared by Student's t-test or by the Mann–Whitney U-test. The chi-square

TABLE 2
Biological Characteristics and First Iodine-131 Treatment Results

Patient no.	TSH (μUI/ml)	Tg (ng/ml)			% change			Tg at control (ng/ml)	^{131}I treatment result
		D0	D9	D14	D0–D9	D0–D14	D9–D14		
1	113	25.5	20.6	626.0	−19	2355	2939	0.8	+
2	103	<0.5	0.7	7.4	—	—	957	<0.5	+
3	>50	10.9	8.9	6.6	−18	−39	−26	0.5	−
4	189	<0.5	1.0	34.1	—	—	3310	<0.5	+
5	108	4.1	56.7	32.5	1283	693	−42	<0.5	−
6	112	13.2	19.0	517.1	44	3817	2622	<0.5	+
7	340	<0.5	0.5	<0.5	—	—	—	<0.5	−
8	>50	0.9	1.3	38.3	44	4156	2846	<0.5	+
9	60	9.3	6.3	163.5	−32	1658	2495	0.6	−
10	139	9.2	11.5	88.0	25	857	665	<0.5	−
11	90	16.0	4.2	515.6	−74	3123	12,176	<0.5	+
12	>50	2.5	3.7	10.0	48	300	170	1.5	−
13	>50	1.2	1.2	5.7	0	375	375	<0.5	−
14	89	2.4	17.1	329.4	613	13,625	1826	<0.5	+
15	62	3.3	7.4	8.1	124	145	9	<0.5	−
16	162	3.5	4.2	9.5	20	171	126	<0.5	+
17	>50	1.6	1.8	5.8	13	263	222	<0.5	−
18	79	3.0	20.6	46.7	587	1457	127	<0.5	−
19	>50	9.4	28.5	27.7	203	195	−3	<0.5	−
20	60	0.8	0.5	48.0	−38	5900	9500	<0.5	+
21	>50	<0.5	<0.5	<0.5	—	—	—	<0.5	+
22	29	<0.5	<0.5	7.1	—	—	—	<0.5	+
23	>50	1.6	16.7	72.8	944	4450	336	<0.5	−
24	>50	<0.5	2.9	2.2	—	—	−24	<0.5	−
25	>50	3.5	14.2	13.6	306	289	−4	1.0	−
26	152	<0.5	<0.5	27.6	—	—	—	<0.5	+
27	111	4.6	5.9	33.8	28	635	473	<0.5	+
28	148	<0.5	0.7	0.8	—	—	14	3.2	−
29	87	<0.5	<0.5	<0.5	—	—	—	<0.5	+
30	93	10.6	29.4	174.0	177	1542	492	<0.5	−
31	184	8.6	21.0	29.7	144	245	41	1.8	−
32	112	3.2	3.7	12.8	16	300	246	<0.5	+
33	>50	3.9	5.2	444.0	33	11,285	8438	<0.5	+
34	127	<0.5	0.5	2.0	—	—	300	<0.5	−
35	137	<0.5	<0.5	39	—	—	—	<0.5	+
36	28	0.7	3.1	3.8	343	443	23	<0.5	−
37	160	9.5	74.4	70.4	683	641	−5	<0.5	−

TSH = thyroid stimulating hormone; Tg = thyroglobulin; + = successful treatment; − = unsuccessful treatment.

test was used for qualitative data. In case of significant differences between the two groups, the sensitivity and specificity of the concerned characteristic in predicting complete efficacy of IAT were calculated and, for quantitative data, the negative predictive value (NPV) and the positive predictive value (PPV) were optimized by searching for the best cutoff value. The Wilcoxon test for paired data was used to compare Tg and TSH levels between D0 and D9, D0 and D14 and D9 and D14 in each group.

RESULTS

Clinical, histological and biological data of all the subjects are summarized in Tables 1 and 2. All patients presented accumulation of radioiodine in the neck on whole-body scan before treatment as well as 5 days after therapeutic doses with no evidence of cervical lymph node or distant metastasis. First ^{131}I treatment was found to be successful in 17 of 37 patients [IAT(+)]: 15 women and 2 men ranging in age from 22–62 yr. The IAT(−) group consisted of 20 of 37 patients: 19 women and 1 man ranging in age from 12–77 yr. All patients in this group demonstrated focal uptake of radioiodine within the thyroid bed on ^{131}I whole-body scan control 6–15 mo after treatment. In addition, two patients demonstrated focal accumulation of radioiodine in the neck consistent with cervical lymph nodes, which were not confirmed by clinical examination, echography or computed tomography. Scintigraphic abnormalities disappeared in these two patients after a second treatment with 3.7 GBq of ^{131}I. None of the 20 patients IAT(−) had an extracervical ^{131}I uptake consistent with distant metastasis. Despite radioiodine accumulation in the neck on control, Tg was ≥1 ng/ml in only 4 of 20 patients. None of the patients had negative whole-body scan control with Tg ≥ 1 ng/ml.

Comparison between the IAT(+) and the IAT(−) groups showed no significant difference with respect to age, sex, histological type, size of primary tumor and frequency of thyroid capsule involvement. Papillary cancer was much more frequent than the follicular type in the two groups, 15 of 17 patients in the IAT(+) group and 19 of 20 patients in the IAT(−) group. Lymph node sampling, obtained in 33 of 37 patients, was positive in 29% of the patients in the IAT(+) group and in 37% of the patients in the IAT(−) group, showing no significant difference. Many associated histological abnormalities were present, and their frequencies were not quite the same between the two groups: NG were more frequent in the

TABLE 3
Comparison of Thyroglobulin Levels and Percent of Changes between Groups IAT(+) and IAT(−)

	IAT(+)	IAT(−)	p value
Tgl (ng/mliter)			
D0	0.9 (<0.5–25.5)	3.0 (<0.5–10.9)	ns
D9	1.3 (<0.5–20.6)	7.4 (0.5–74.4)†	<0.02
D14	34.1 (0–626)*	10.0 (0.2–174)‡§	ns
Percent change			
D0–D9	20 (−74–613) [10]	144 (−32–1283) [16]	<0.05
D0–D14	3123 (171–13,625) [10]	375 (−39–4450) [16]	<0.02
D9–D14	2622 (126–12,176) [12]	41 (−42–2495) [19]	0.0001

*$p < 0.001$ from TgD0 and TgD9 values of the same group.
†$p < 0.005$ from TgD0 value of the same group.
‡$p < 0.0005$ from TgD0 value of the same group.
§$p < 0.05$ from TgD9 value of the same group.
Results are expressed as median (range). Results are obtained from 17 patients for the IAT(+) group and 20 patients for the IAT(−) group except for percentage change in Tg values for which the numbers in brackets indicate the patient number. All percentage changes reflect an increase between first and second Tg determinations. Tg = thyroglobulin; ns = not significant.

IAT(+) group (9 of 17 patients versus 5 of 20 patients), and LT were more frequent in IAT(−) group (4 of 20 patients versus 1 of 17 patients), but the differences were not significant at a confidence limit of 95%. GD was found in one IAT(−) case (Patient 23).

The measurement of thyroid remnants on 1:1 dot scans showed no significant difference between the two groups [4.35 cm^2 for the IAT(+) group versus 4.06 cm^2 for the IAT(−) group]. Radioiodine uptakes on D3 were nearly the same [3.11% for IAT(+) group versus 3.30% for IAT(−) group]. TSH and Tg values on D0 were not significantly different between the two groups even if median Tg value was higher in the IAT(−) group (see Tables 2 and 3 for Tg values). Additional Tg measurements on D9 and D14 showed significant increase in the IAT(−) group between D0 and D9 and D9 and D14. In the IAT(+) group, Tg was only slightly increased on D9 (the difference was not significant in relation to Tg on D0) but increased dramatically between D9 and D14 (Table 3). Distributions of Tg values on D0, D9 and D14 in each IAT(+) and IAT(−) patient are shown in Figure 1. Tg levels on D9 were significantly higher in the IAT(−) group compared with the IAT(+) group and, in contrast, Tg levels on D14 were higher in the IAT(+) group compared with the IAT(−) group, but here the difference was not significant at a confidence limit of 95% (Table 3). Similarly, percentage change between D0 and D9 (calculated for 26 patients) was significantly higher in the IAT(−) group, percentage changes between D0 and D14 and D9 and D14 (calculated for 26 and 31 patients, respectively) were significantly higher in the IAT(+) group (Table 3). Variations in patients with undetectable Tg on D0, D9 or D14 (percentage change not calculated) are summarized in Table 4. Among seven IAT(+) patients with undetectable Tg on D0, only two showed a slight increase on D9, but five showed a marked increase on D14 (from 7.1–39 ng/ml). Conversely, all IAT(−) patients with undetectable Tg on D0 (four patients) presented a mild increase on D9; three of them also presented an increase on D14 but the Tg levels were much less elevated than in IAT(+) patients (from 0.8–2.2 ng/ml).

Influence of TSH Variation

We searched for a possible correlation between TSH and Tg variations between D0 and D9 to D14. TSH was measured on D0, D9 and D14 in 17 patients. TSH levels increased significantly between D0 and D9, D0 and D14 and D9 and D14 (Table 5), but no correlation was found between TSH and Tg variations (D0–D9: $r = 0.12$, $p = 0.64$; D0–D14: $r = 0.22$, $p = 0.39$; D9–D14: $r = 0.29$, $p = 0.27$).

Searching for the Best Predictive Parameter(s)

Parameters that showed significant differences between the two groups (TgD9, percentage change between D0 and D9, between D0 and D14 and between D9 and D14) were investigated to determine the best cutoff value for an accurate classification of patients according to first IAT efficacy. The distributions of the percent of changes between D0 and D9, D0 and D14 and D9 and D14 in each group are shown in Figures 2, 3 and 4. The best cutoff values for each parameter are listed in Table 6 with corresponding PPV and NPV. According to this method, the best predictor was the percentage change between D9 and D14 calculated in 31 of 37 patients, with a cutoff value of 750%, which permitted a good classification of 27 of 31 patients. From 10 patients with a percentage change between D9 and D14 ≥ 750%, the first IAT proved successful in 9; conversely, from 21 patients with a percentage change between D9 and D14 < 750%, 18 showed positive whole-body scan on control. With this cutoff value, the sensitivity of the percentage change between D9 and D14 to predict successful treatment was 75%, the specificity was 95%, the PPV was 90% and the NPV was 86%. Four patients were incorrectly classified: one of the IAT(−) group (Patient 9: whole-body scan positive and Tg on control at 0.6 ng/ml) with percentage change between D9 and D14 at 2495% and three of the IAT(+) group (Patients 16, 27 and 32) with percentage changes between D9 and D14 at

TABLE 4
Changes in Thyroglobulin Levels for Patients with Thyroglobulin below Detection Limit on D0

	IAT(+) (n = 7)	IAT(−) (n = 4)
TgD9 ≥ 0.5 ng/ml	2	4
(Tg levels in ng/ml)	(0.7 and 1.0)	(0.5, 0.5, 0.7 and 2.9)
TgD14 ≥ 0.5 ng/ml	5*	3†
(Tg levels in ng/ml)	(7.1, 7.4, 27.6, 34.1, 39)	(0.8, 2 and 2.2)

*The two IAT(+) patients with Tg ≥ 0.5 ng/ml on D9 have also Tg ≥ 0.5 ng/ml on D14.
†One IAT(−) patient with Tg = 0.5 ng/ml on D9 has Tg < 0.5 ng/ml on D14.
Tg = thyroglobulin.

TABLE 5
TSH Variations

TSH (μUI/ml) (n = 17)		
D0	D9	D14
105.06 ± 41.3 (28–184)	153.41 ± 41* ± 63.42 (46–319)	176.29†‡ ± 73.99 (73–322)

Results are expressed as mean ± s.d.
*$p < 0.0005$ from TSH D0 value.
†$p < 0.0005$ from TSH D0 value.
‡$p < 0.01$ from TSH D9 value.

126%, 473% and 246%. The IAT(−) patient with percentage change between D9 and D14 at 2495% (Patient 9) was one of the four with LT in this group.

Percentage change between D0 and D9 was not the best predictive parameter according to our method; nevertheless, it had a good NPV (91%). Among 11 patients with percentage change between D0 and D9 ≥ 100%, 10 patients belonged to the IAT(−) group; conversely, among 15 patients with percentage change between D0 and D9 < 100%, only 6 belonged to the IAT(−) group.

DISCUSSION

The analysis of characteristics available in 37 patients referred for first IAT after total thyroidectomy for nonmetastatic DTC has permitted us to highlight a frequent increase in the Tg level 5 days after administration of radioiodine treatment. Tg increase was more frequent and often higher in the case of successful ablation as demonstrated through whole-body scan control and Tg determination 6–15 mo later. A strong correlation was observed between ablative treatment efficacy and the percentage change in Tg level calculated between the value obtained just before administration of radioiodine treatment and the value obtained 5 days later. An optimal cutoff value of 750% has been determined, and successful ablation was observed for 90% of the patients above this cutoff value and, in contrast, for only 14% of patients below it.

Furthermore, we observed an inconstant Tg increase between the value obtained just before scanning dose administration and the value obtained 9 days later, just before ablative dose administration. An important result of our study is that a significant relationship was demonstrated to exist between this increase and the likelihood of unsuccessful ablation: the abla-

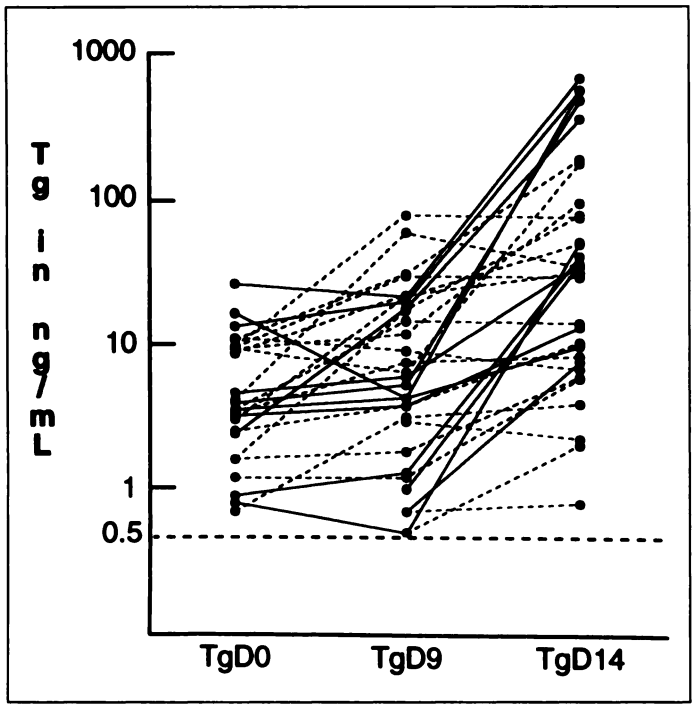

FIGURE 1. Tg variations between D0, D9 and D14 in IAT(−) (dashed lines) and IAT(+) (solid lines) patients. Eleven patients with Tg < 0.5 ng/ml on D0 and/or D9 are not represented between D0 and D9. Six patients with Tg < 0.5 ng/ml on D9 and/or D14 are not represented between D9 and D14.

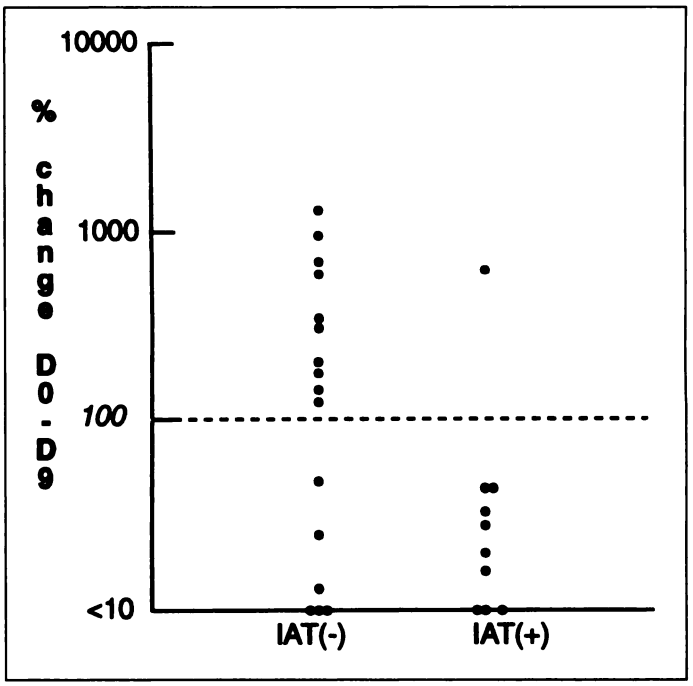

FIGURE 2. Percentage change in Tg in IAT(−) and IAT(+) patients between D0 and D9. Eleven patients with Tg < 0.5 ng/ml on D0 and/or D9 are not represented. Dashed line denotes the best cutoff value (100%, see text for definition).

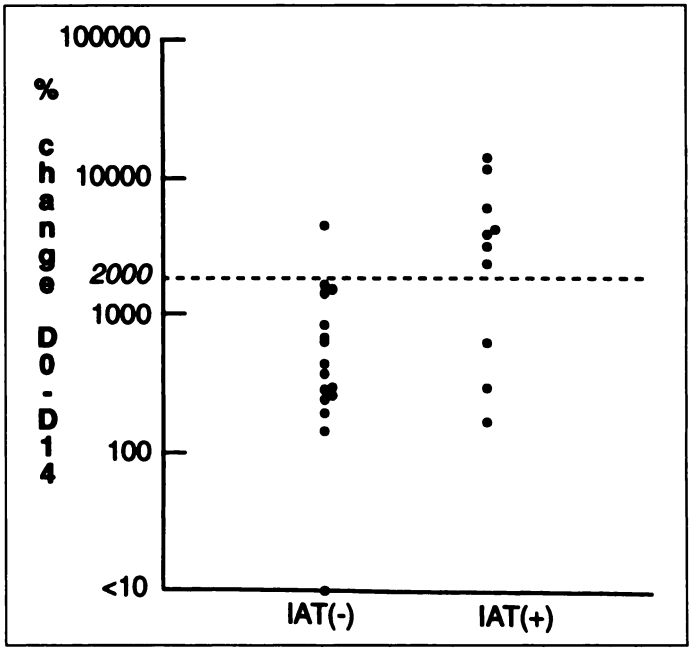

FIGURE 3. Percentage change in Tg in IAT(−) and IAT(+) patients between D0 and D14. Eleven patients with Tg < 0.5 ng/ml on D0 and/or D14 are not represented. Dashed line denotes the best cutoff value (2000%, see text for definition).

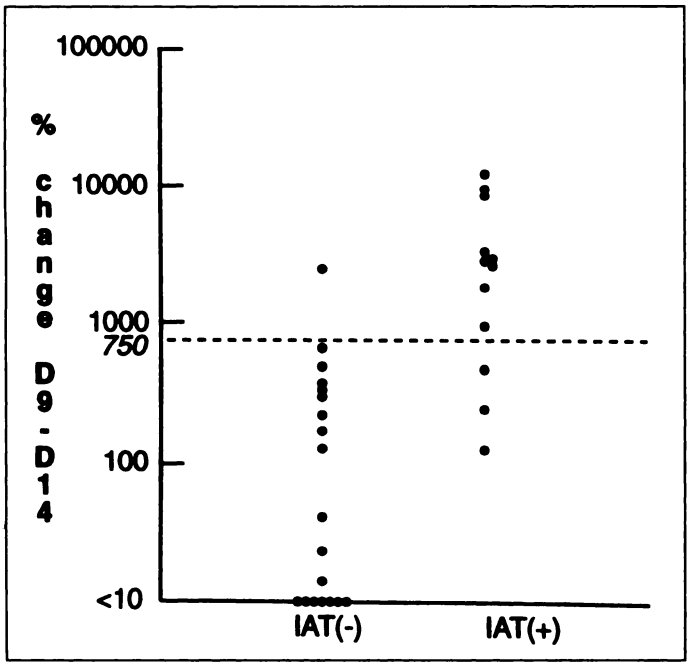

FIGURE 4. Percentage change in Tg in IAT(−) and IAT(+) patients between D9 and D14. Six patients with Tg < 0.5 ng/ml on D9 and/or D14 are not represented. Dashed line denotes the best cutoff value (750%, see text for definition).

tive treatment was found to be successful in only 1 of 11 patients with percentage change between D0 and D9 ≥ 100%.

Even if ^{131}I ablative therapy is controversial, many authors suggest that this treatment be performed after thyroid surgery for nonmedullary DTC to ablate residual thyroid tissue even if the uptake of ^{131}I is limited to the thyroid bed (*1–7*). In our study, all the patients have preliminarily undergone a total thyroidectomy. This kind of surgery is recommended for eradicating multicentric disease and creating a suitable environment for ^{131}I ablative therapy, aiding in avoiding complications and enhancing treatment efficacy (*14–19*).

In our study, age, sex, histological type of primary tumor, serum TSH levels and serum Tg levels on D0 did not correlate with the outcome of ^{131}I treatment. This is in agreement with other published reports (*19–21*). It has been reported previously that the success of the ablative treatment was related to the mass of the remnant tissues (*16,21–23*). In a recent study, complete ablation was obtained in 87.5% of the patients when the mass of the remnant tissue was less than 5 g and in 52.2% of the patients when it was more than 5 g. This discrepancy seems to be essentially due to a difference in initial absorbed dose (*21*). On the other hand, in our study, the response to the treatment seems to be independent of the size of the remnant tissue estimated by planimetry of residual thyroid areas. This might be due to the fact that most of the remnants in our population are relatively small, probably less than 5 g, as suggested by the average uptake of ^{131}I at 72 hr (3.2%), which is compared with the average uptake of about 20% obtained in the above study for the population with more than 5 g of remnant tissue.

To the best of our knowledge, variations of Tg levels after radioiodine scanning or ablative dose administration have never been correlated with the outcome of ^{131}I ablative treatment. Our study indicates that these variations are independent of the TSH variations and are not related to the presence of scattered ^{131}I photons inside photopic ^{125}I during the Tg measurements. We have not been able to correlate the Tg variations with dosimetric data after radioiodine scanning or ablative dose administration because this was not a prospective study. Quantitative dosimetric measurements are not routinely performed in our department, especially due to the low reliability of the results when remnants are small and when special or dedicated facilities are not available (*24,25*). However, the hypothesis can be made that the increase in plasma Tg level after ^{131}I administration is related to the uptake of radioiodine in residual thyroid tissue and is explained by radiation-induced cellular effects such as cytolysis and membrane damage, as previously described with external radiotherapy (*26,27*). Our results indicate that this phenomenon is present after ablative dose administration as well as after scanning dose administration, although it is less frequent and of lesser importance in this case. Previous studies have shown that the outcome of ^{131}I treatment is related to the radiation dose to the thyroid remnants. It has been reported that successful ablation was obtained in about 75% of patients when a cumulative absorbed dose of at least 300–400 Gy was delivered (*25,28,29*). A more recent study (*21*) has indicated that the initial absorbed dose is perhaps more important than the cumulated absorbed dose, particularly for remnants having a mass of more than 5 g. This report indicates that a good response is observed when the initial dose rate is above 3 Gy/hr irrespective of the cumulative absorbed dose rate. We can assume that the Tg increase is dependent of the cumulative absorbed dose, or even of the initial dose rate, delivered to the residual thyroid tissue. We believe that this is the reason why

TABLE 6
Quality of Prediction of Successful First IAT with Best Cutoff Value for TgD9, Percent Change between D0 and D9, D0 and D14 and D9 and D14

Parameter	Best cutoff value	PPV	NPV	No. of patients well classified	No. of patients badly classified
TgD9* (n = 37)	0.5 ng/ml	1	0.63	25	12
Percent change between D0 and D9* (n = 26)	100%	0.60	0.91	19	7
Percent change between D0 and D14† (n = 26)	2000%	0.88	0.83	22	4
Percent change between D9 and D14† (n = 31)	750%	0.90	0.86	27	4

*Patients are classified in a successful IAT group if TgD9 or percent change between D0 and D9 are lower than cutoff value (0.5 ng/ml and 100%, respectively).

†Patients are classified in successful IAT group if percent changes between D0 and D14 or D9 and D14 are superior or equal to cutoff values (2000% and 750%, respectively).

See text for definition of best cutoff values and percent changes.

percentage change after ablative dose administration is a good predictor of treatment efficacy. The only patient with an elevated percentage change after ^{131}I ablative dose administration and unsuccessful treatment (Patient 9) presented an LT; the lower efficacy of treatment in this case could be due to a less homogeneous uptake and to a shorter biologic half-life of ^{131}I as previously described (*30*).

An important finding of our study is that, after a scanning dose of ^{131}I, a percentage change in Tg level ≥100% is associated with a poor therapeutic response. Moreover, we observed that the Tg increase 9 days after a scanning dose is significant only in the IAT(−) group, whereas the Tg values are nearly the same before and after scanning dose administration in the IAT(+) group. These findings suggest that radiation-induced disturbances could be present even with low doses of ^{131}I and could have an opposite effect on subsequent uptake of radioiodine for ablative therapy. This is in accordance with previous reports that described a "stunning" effect of ^{131}I scanning doses on remnant tissues (*31,32*). In a recent study (*32*), the uptake of thyroablative doses by postoperative remnants was visually compared after a diagnostic whole-body scan with ^{131}I (111–370 MBq) and ^{123}I (11 MBq), a pure gamma emitter that delivers a significantly lower absorbed dose than ^{131}I, a β emitter. The uptake was impaired in 20 of 26 patients in the ^{131}I group and in none of 14 patients in the ^{123}I group. In another recent report (*33*), an opposite effect after 370 MBq of ^{131}I has been described compared with doses of 185 and 37 MBq. Our findings suggest that the rise in Tg level after ^{131}I scanning dose administration increases the likelihood of a stunning effect during subsequent ^{131}I treatment. We are not aware of the length of this effect, but our results suggest that it still could be present 9 days after diagnostic ^{131}I administration.

CONCLUSION

We must stress the fact that the use of our results in another laboratory, and especially of the cutoff values of 100% and 750% for percentage changes between D0 and D9 and D9 and D14, would require some precautions because our findings probably depend on the scanning dose (111 MBq of ^{131}I) and on the method used for measuring Tg. Indeed, it is well known that there are many differences between Tg assays in terms of calibration and sensitivity (*34–37*). Another limitation is that predicting efficacy of the ablative treatment on thyroid remnants that are mainly constituted of normal thyroid tissue probably does not eliminate the necessity for performing whole-body scan control and Tg measurement some months later to search for recurrent or metastatic disease.

Tg variation seems to be a good indicator of radiation-induced disturbances in thyroid tissue after scanning or therapeutic dose of ^{131}I. The increase in Tg after ^{131}I therapeutic dose during first ^{131}I ablative therapy for nonmedullary DTC appears to be a reliable predictor of ablative treatment efficacy in patients with no distant metastasis, whereas the increase in Tg after ^{131}I scanning dose seems to be associated with the previously described stunning effect.

Further studies are required to confirm these results and to indicate if Tg variations (a) can predict not only the disappearance of thyroid remnants but also the absence of recurrent disease, (b) can predict the efficacy of ^{131}I treatment in recurrent or metastatic disease and (c) can help us to adapt ^{131}I scan and therapy to avoid the stunning effect.

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