Predictive Value for Disease Progression of Serum Thyroglobulin Levels Measured in the Postoperative Period and After ^{131}I Ablation Therapy in Patients with Differentiated Thyroid Cancer

Michel Toubeau, MD[1]; Claude Touzery, PhD[1]; Patrick Arveux, MD[2]; Gilles Chaplain, MD[3]; Geneviève Vaillant, MD[4]; Alina Berriolo, MD[1]; Jean-Marc Riedinger, PhD[1]; Christophe Boichot, MD[1]; Alexandre Cochet, MD[1]; and François Brunotte, MD[1]

[1]Department of Nuclear Medicine, Centre Georges François Leclerc, Dijon, France; [2]Department of Medical Statistics, Centre Georges François Leclerc, Dijon, France; [3]Department of Radiotherapy, Centre Georges François Leclerc, Dijon, France; and [4]Department of Endocrinology, University Hospital, Dijon, France

The aim of our study was to evaluate and compare in thyroid cancer patients the predictive value for disease progression of thyroglobulin (Tg) levels measured under thyroid-stimulating hormone (TSH) stimulation, in the postoperative period just before ^{131}I ablative therapy and at the time of control 6–12 mo later. **Methods:** Two-hundred twelve consecutive patients treated for a well-differentiated thyroid carcinoma (184 papillary, 28 follicular) with no initial distant metastases were retrospectively studied. All patients had a total or near-total thyroidectomy followed by ablation with 3.7 GBq ^{131}I. Tg levels were determined just before ablative therapy (Tg1) and 6–12 mo later (Tg2). Thresholds of 30 and 10 ng/mL were used for Tg1 and Tg2, respectively. Univariate and multivariate analyses were performed to assess the predictive value for disease progression of the 2 Tg determinations. **Results:** Thirty patients had a Tg1 level > 30 ng/mL. Six to 12 mo later, 30 patients had a Tg2 level > 10 ng/mL, 19 of whom had initially a Tg1 level > 30 ng/mL. Disease progression was reported in 20 patients (9%). Progression-free survival rates were significantly lower in patients with a low Tg1 or Tg2 level but the difference was more important with Tg2. With univariate analysis, 5 variables were significantly associated with disease progression: Tg2, Tg1, node invasion, extrathyroidal extension, and tumor size. With multivariate analysis, only Tg2 (odds ratio [OR] = 16.4; 95% confidence interval [95% CI] = 5.7–47.4; $P < 0.001$) and node invasion (OR = 2.7; 95% CI = 1.0–7.2; $P = 0.04$) had an independent prognostic value. When only initial parameters were considered, Tg1 and node invasion were the 2 independent prognostic factors. The OR decreased for Tg1 (OR = 10.1; 95% CI = 4.0–25.7; $P < 0.001$) but increased for node invasion (OR = 4.4; 95% CI = 1.7–11.2; $P = 0.002$). **Conclusion:** Among all clinical and tumoral variables, lymph node invasion and serum Tg level are 2 important parameters to define the risk of disease progression. Although Tg2 appears more significant than Tg1, both Tg levels measured under TSH stimulation, in the postoperative period and a few months after ablative therapy, have a predictive value. In clinical practice, patients at risk can be selected as soon as the initial lymph node status and Tg1 level are known.

Key Words: differentiated thyroid carcinoma; thyroglobulin; prognostic factors; disease progression

J Nucl Med 2004; 45:988–994

Surgery followed by ^{131}I ablative therapy (IAT) is the initial treatment most often used in patients with a well-differentiated thyroid cancer. The thyroglobulin (Tg) level obtained 6–12 mo after IAT under thyroid-stimulating hormone (TSH) stimulation is regarded as a very good prognostic indicator (*1–7*) and is of decisive importance for the clinical management of patients with a differentiated thyroid carcinoma. The value of the initial Tg level measured in the postoperative period and before IAT has been considered unclear because thyroid remnants may contribute to the production of Tg. For many investigators, total thyroid ablation seems necessary to consider the serum Tg level as a reliable tumor marker. However, a few studies have reported that high initial values of the postoperative Tg level could be related to initial metastases or further recurrences (*8–12*).

For clinicians, the question is to know whether the prognostic information given by the Tg level under TSH stimulation at 6–12 mo can be obtained earlier, at the time of IAT, with sufficient reliability.

Received Oct. 9, 2003; revision accepted Jan. 13, 2004.

For correspondence or reprints contact: Michel Toubeau, MD, Department of Nuclear Medicine, Centre Georges François Leclerc, 1 rue Professeur Marion, Dijon, France 21000.

E-mail: mtoubeau@dijon.fnclcc.fr

The aim of this study was to evaluate and compare, in patients with no initial distant metastases, the predictive value for disease progression of both Tg levels measured, under TSH stimulation, before and after IAT, taking into account the usual clinical and tumoral factors.

MATERIALS AND METHODS

Patients and Tumor Characteristics

Two-hundred eighty-eight consecutive patients without initial distant metastases, who were treated between January 1990 and December 2000 by a total or near-total thyroidectomy followed by IAT, were studied. In this retrospective study, patients considered with no distant metastases had a normal clinical examination, no foci of uptake outside the thyroid bed on posttherapeutic whole-body scintigraphy (WBS), normal ultrasonography, and a normal chest radiograph. In this series, 42 patients with anti-Tg antibodies and 34 in whom it was not measured were excluded. Two-hundred twelve patients were finally included (59 men, 153 women; age range, 15–79 y; mean age ± SD, 47 ± 15 y). Histologic examination revealed papillary carcinomas in 184 patients and follicular carcinomas in 28 patients (including 7 Hürthle cell carcinomas). Cervical lymph node dissection was not systematically done but was performed in 119 patients (56%) on the basis of lymph node clinical involvement or an abnormal aspect at the time of cervicotomy. According to the pathologic tumor-node-metastasis (pTNM) classification (*13*), lymph node status was pN1 in 56, pN0 in 63, and pNx in 93. Other histopathologic characteristics were also recorded: tumor size, multifocality, bilaterality, extrathyroidal extension, and vascular invasion. Patients and tumor characteristics are presented in Table 1. The median follow-up was 5.1 y (range, 1–12 y).

TABLE 1
Characteristics of Patients

Characteristic	No. of patients	%
Sex		
Male	59	28
Female	153	72
Age (y)		
<45	92	43
≥45	120	57
Histologic subtype		
Papillary	184	87
Follicular	28	13
Tumor size (cm)		
≤4	188	89
>4	24	11
Multifocality		
Absent	123	58
Present	89	42
Bilaterality		
Absent	149	70
Present	63	30
Extrathyroidal extension		
Absent	167	79
Present	45	21
Vascular invasion		
Absent	182	86
Present	30	14
Lymph node invasion		
pNx	93	44
pN0	63	30
pN1	56	26

IAT and Scintigraphic Control

Within a few months after surgery (mean ± SD, 2.7 ± 1.9 mo), patients were given 3.7 GBq ^{131}I after withdrawal of hormone therapy for at least 4 wk. No diagnostic scintigraphy was performed before ^{131}I administration. Posttherapeutic WBS was performed 4 d later, using a single-head γ-camera equipped with a high-energy, parallel-hole collimator (DSX; Sopha Medical Vision). No quantitative measurement of the thyroid uptake was made. To control the IAT efficacy, diagnostic WBS was planned 6–12 mo later (mean ± SD, 7.9 ± 2.7 mo) off hormonal therapy. Images were obtained 2 d after injection of 185 MBq ^{131}I. Afterward, periodic diagnostic WBS associated with Tg determinations off therapy were planned throughout the follow-up period.

Biologic Measurements

Levels of TSH, Tg, and anti-Tg antibodies were measured postoperatively just before IAT and at the time of control. TSH values were measured with a radioimmunoassay (Schering CIS Bio International). Tg levels were determined using an immunoradiometric assay (Sanofi Diagnostic Pasteur), with a low detection limit of 0.7 ng/mL. The range of normal values was 1.5–35 ng/mL. For Tg measurements before IAT (Tg1), a threshold of 30 ng/mL was chosen near the upper limit of the normal range. A threshold of 10 ng/mL was used for Tg measurements 6–12 mo after IAT (Tg2). Anti-Tg antibodies were detected with a radioimmunoassay (Bio-Rad) in all patients. Patients with positive or undetermined values were excluded.

Study Design

Predictive variables of disease progression were studied. Disease progression was defined as the first clinical reappearance of disease, after complete ablation of thyroid remnants. It included all clinical events reported (nodal metastases, local relapses, and distant metastases) and confirmed by imaging modalities or surgery.

For each patient, clinical and histopathologic variables included in the analysis were as follows: age at diagnosis (≥45 y vs. <45 y), sex (male vs. female), histologic subtype (papillary vs. follicular), tumor size (≤4 cm vs. >4 cm), multifocality (present vs. absent), bilaterality (present vs. absent), extrathyroidal extension (present vs. absent), vascular invasion (present vs. absent), and lymph node invasion (present [pN1] vs. absent [pN0 and pNx]).

The biologic variables considered were the TSH and Tg levels measured in the postoperative period just before IAT and 6–12 mo later at the time of control.

Statistical Analysis

Associations between qualitative variables were assessed by the Pearson χ^2 test. For quantitative variables, the means comparison was done with the Student *t* test in the case of a normal distribution or with the Mann–Whitney test otherwise.

Univariate analyses of the prognostic significance of these variables were performed using the Cox model. Multivariate analyses were done to identify prognostic variables of independent statistical significance in predicting disease progression. The Cox proportional hazards model was used with a forward variable selec-

TABLE 2
Evolution of Thyroid Disease After Initial Therapy According to Tg1 and Tg2 Levels (ng/mL)

Evolution	Tg1 ≤ 30		Tg1 > 30	
	Tg2 ≤ 10	Tg2 > 10	Tg2 ≤ 10	Tg2 > 10
Disease progression	4	3	1	12
Isolated elevated Tg	0	6	0	6
Complete remission	163	2	10	1

tion technique. It included all variables that were significant in univariate analysis. Variables were removed from the model if the significance level was >0.20 and retained if the significance level was ≤0.20. Progression-free survival curves were estimated using the actuarial method and compared with the log-rank test. $P < 0.05$ was considered statistically significant.

Tabulation, univariate and multivariate analyses, logistic regression, and progression-free survival curves were performed using Stata Statistical Software (Stata Corp.).

RESULTS

At the time of IAT, thyroid remnants were present on posttherapy scans in all patients except one. The median Tg1 value was 9 ng/mL (range, 0–2,470 ng/mL). In one patient, a very high level of Tg1 (2,470 ng/mL) was observed and controlled, raising the possibility of initial distant metastases. The posttherapeutic WBS showed no foci of uptake outside the thyroid bed but only a large thyroid remnant, confirmed by ultrasonography. No pathologic lymph node was evident. The chest radiograph was also normal. As the Tg level and the scintigraphic image normalized progressively with time, distant metastases were ruled out. In 4 other patients, cervical node metastases were immediately suspected on posttherapeutic scintigraphy, evident on ultrasonography and confirmed a few months later by surgery. These 4 patients, in whom node metastases were associated with high Tg1 values (range, 138–448 ng/mL), were excluded from further analysis.

Among the 208 patients clinically free of disease at the time of IAT, 30 patients had a Tg1 level > 30 ng/mL. At the time of control, 6–12 mo later, 30 patients had an elevated Tg2 level, 19 of whom had initially a Tg1 level > 30 ng/mL. After initial therapy, considering the whole follow-up, 176 patients (85%) were progressively in complete remission, with an undetectable Tg level off therapy. One patient, after complete remission, presented a significant increase of the Tg level off therapy 2 y later, with evidence of bone metastases. Four patients, despite a low and stable Tg level, presented evidence of disease progression (3 local recurrences, 1 lung metastases). In 27 patients, the Tg level never normalized but remained high or increased; 15 of them presented a clinical evolution (12 nodal metastases, 1 local recurrence, 2 distant metastases). In the other 12 patients, despite a persistent elevated Tg level, a complete work-up showed no clinical evidence of disease. Evolution of thyroid disease according to Tg1 and Tg2 levels is presented in Table 2.

Finally, only 20 patients (9%) presented a disease progression. The median time to diagnosis was 2.4 y (range, 0.7–7.2 y). Eighty percent of the clinical events occurred before 5 y. Ultrasonography was contributory in 12, CT in 5, and WBS in only 3 patients. The initial lymph node status in these patients (pN0 = 5%, pNx = 30%, pN1 = 65%) was significantly different ($P < 0.0001$) compared with that of disease-free patients (pN0 = 32%, pNx = 47%, pN1 = 21%). The median Tg1 level also differed significantly compared with that of patients clinically free of disease (41.5 and 6.7 ng/mL, respectively; $P < 0.002$).

Predictive variables for disease progression were studied. The lymph node status was among the studied variables. As illustrated in Figure 1, progression-free survival curves were not significantly different between pNx and pN0 patients ($P = 0.18$), and the 2 groups of patients were combined together, versus the pN1 patients. With univariate analysis, 5 variables were significantly associated with disease progression (Table 3). Ranking in decreasing order of odds ratio (OR) values were Tg2 level > 10 ng/mL, Tg1 level > 30 ng/mL, lymph node invasion, extrathyroidal extension, and tumor size > 4 cm. The most important were Tg2 and Tg1 with very high ORs. When we reexamined our data by multivariate analysis (Table 4), only Tg2 (OR = 16.4, 95% confidence interval [95% CI] = 5.7–47.4; $P < 0.001$) and node invasion (OR = 2.7; 95% CI = 1.0–7.2; $P = 0.048$) remained as independent prognostic factors. When only parameters known just before IAT were considered, Tg1 and node invasion were the only 2 independent predictive factors (Table 5). Despite the presence of thyroid remnants, the Tg1 OR was significant (OR = 10.1; 95% CI = 4.0–25.7; $P < 0.001$) but was lower than the Tg2 OR in the previous analysis. In contrast, the OR increased for the lymph node invasion (OR = 4.4; 95% CI = 1.7–11.2; $P = 0.002$).

As Tg1 threshold was arbitrarily chosen at 30 ng/mL, this cutoff value was checked later on with a receiver-operating-

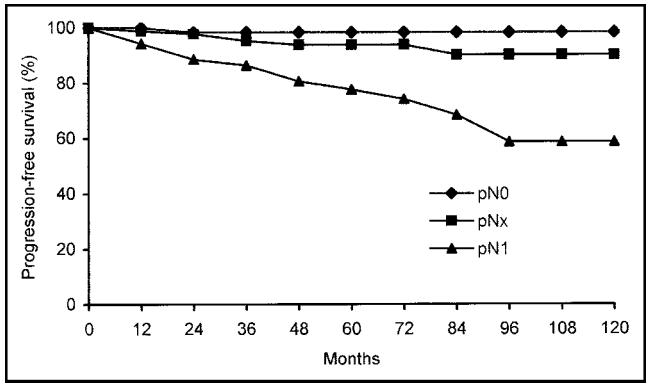

FIGURE 1. Progression-free survival curves according to initial lymph node status. There was no significant difference ($P = 0.18$) between pN0 and pNx patients. A significant difference was found between pN0 and pN1 ($P = 0.0001$) and between pNx and pN1 ($P < 0.0001$).

TABLE 3
Univariate Analysis of Predictive Factors for Disease Progression 6–12 Months After IAT

Predictive factor	OR	95% CI	*P* value
Tg2 > 10 ng/mL	22.6	8.2–62.5	<0.001
Tg1 > 30 ng/mL	12.5	5.0–31.5	<0.001
Node invasion	6.0	2.4–15.0	<0.001
Extrathyroidal extension	3.2	1.3–7.9	0.009
Tumor size > 4 cm	3.1	1.1–8.5	0.03

OR = odds ratio; 95% CI = 95% confidence interval.

characteristic analysis. Taking into account the clinical events that occurred during the follow-up, the accuracy was calculated from 5 to 100 ng/mL, in steps of 5 ng/mL, and ranged from 48% to 90%. The best accuracy was obtained for Tg1 values between 30 and 100 ng/mL.

The prognostic role of Tg1 and Tg2 levels was also illustrated with the progression-free survival curves (Figs. 2 and 3). Disease progression was more frequent among patients with Tg1 levels > 30 ng/mL compared with that among patients with Tg1 levels ≤ 30 ng/mL. At 5 y, progression-free rates were 66% and 96%, respectively ($P < 0.0001$). The difference was more important with Tg2. Progression-free rates were 55% and 97% ($P < 0.0001$).

Possible factors to explain the importance of high Tg1 levels were analyzed. No correlation was found with the TSH level or the time interval from surgery. In the group with Tg1 levels > 30 ng/mL and in the group with Tg1 levels ≤ 30 ng/mL, the medians of TSH values did not differ significantly. They were 64.9 and 74.8 mIU/mL, respectively (not significant). The time interval between surgery and Tg1 measurement was also similar in the 2 groups, 2.4 ± 1.5 mo (mean ± SD) versus 2.6 ± 2.0 mo (not significant). Statistical associations were sought between high Tg1 levels and other histopathologic features. With a logistic regression model, extrathyroidal extension was found as the only independent predictive factor of high Tg1 values (OR = 2.7; 95% CI = 1.2–6.3; $P = 0.02$).

TABLE 4
Multivariate Analysis of Predictive Factors for Disease Progression 6–12 Months After IAT

Predictive factor	OR	95% CI	*P* value
Tg2 (ng/mL)			
≤10*	1		
>10	16.4	5.7–47.4	<0.001
Node invasion			
Absent*	1		
Present	2.7	1.0–7.2	0.048

*Reference category.
OR = odds ratio; 95% CI = 95% confidence interval.

TABLE 5
Multivariate Analysis of Predictive Factors for Disease Progression Before IAT

Predictive factor	OR	95% CI	*P* value
Tg1 (ng/mL)			
≤30*	1		
>30	10.1	4.0–25.7	<0.001
Node invasion			
Absent*	1		
Present	4.4	1.7–11.2	0.002

*Reference category.
OR = odds ratio; 95% CI = 95% confidence interval.

Finally, at the time of IAT and at the time of control, node invasion and high Tg levels under TSH stimulation were the 2 prognostic variables outlined by multivariate analysis. Patients at risk of disease progression were patients with an elevated Tg1 or Tg2 level or a nodal invasion. Taking into account the 2 prognostic variables combined together, the 5-y progression rate was estimated in a subgroup of 109 patients followed-up during 5 y or more. Fourteen of 16 clinical evolutions (87.5%) were reported in the patients with a node invasion or an elevated Tg1 or Tg2 level (Tables 6 and 7). The positive predictive value (PPV) and the negative predictive value (NPV) of the 2 prognostic variables were calculated. Considering the node invasion combined with Tg1, these values were 37% and 97%, respectively. Using Tg2, similar values were obtained, 40% and 97%, respectively.

DISCUSSION

In this study of 212 patients with differentiated thyroid carcinoma, all patients had a total or near-total thyroidectomy followed by IAT. The follow-up schedule was the same in all cases, providing a homogeneous clinical management of the studied population. Only 9% of the patients presented clinical recurrences with a median follow-up of 5 y. This small number is similar to that of other reports

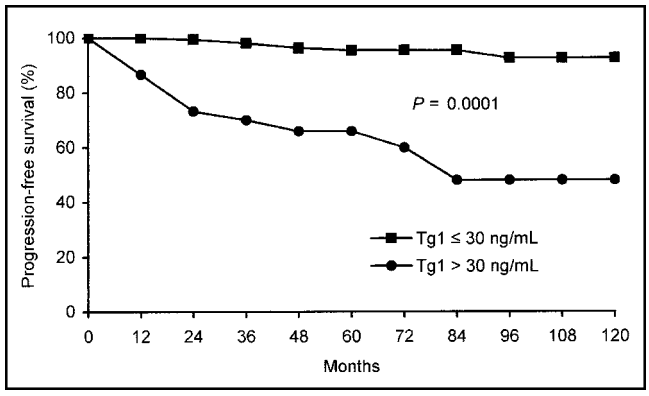

FIGURE 2. Progression-free survival curves according to Tg1 level measured in postoperative period just before IAT.

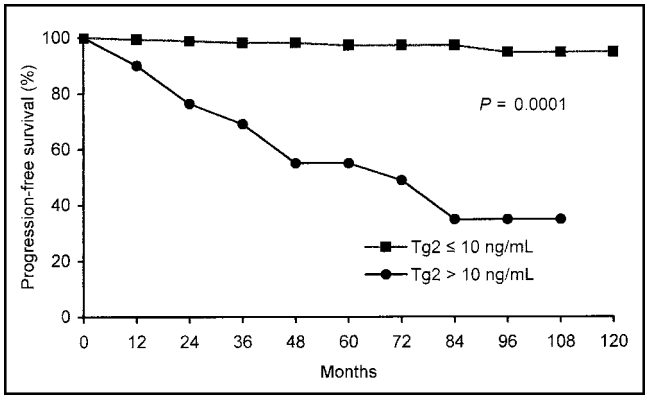

FIGURE 3. Progression-free survival curves according to Tg2 level measured 6–12 mo after IAT.

(*14–17*). With the help of ultrasonography, lymph node metastases were often found, even in two thirds of the patients who had a cervical node dissection. Diagnostic WBS was of little help; many recent studies have shown its poor usefulness, in contrast to ultrasonography (*18–22*).

Among the 5 predictive factors for disease progression found by univariate analysis, size > 4 cm, extrathyroidal extension, and lymph node invasion are well-known prognostic factors (*15-17,23–25*). With multivariate analysis, lymph node invasion was the only morphologic predictive factor. In this series, pN0 patients were pooled with pNx patients in whom node dissection was not performed because of a normal aspect at the time of cervicotomy. It was previously determined that recurrence-free survival curves did not differ significantly between these 2 groups.

In this study, age did not appear as a predictive variable of recurrence. This was unexpected as age is an important prognostic factor in thyroid cancer patients (*14–15,23–25*). This is probably related to the small number of recurrences reported and also to the high incidence of nodal recurrences observed in this series in younger patients. Seven of 12 nodal recurrences were found in patients <45 y old, whereas all local and distant recurrences were observed in patients >45 y old.

Above all, the 2 major factors to predict the clinical evolution were the biologic factors, the Tg1 and Tg2 levels measured before and after IAT. In univariate analysis, the Tg2 level measured 6–12 mo after therapy was the most important predictive factor among all parameters. When Tg1 and Tg2 were entered into a multivariate model, only Tg2 emerged as a stronger predictive factor, in association with the lymph node invasion. The Tg level measured several months after IAT is a well-known marker of the disease course. Undetectable levels under TSH stimulation are good indicators of the disease-free status, whereas elevated levels correlate with persistent disease (*6,19*). For Tg2, a threshold of 10 ng/mL was used in the analysis. A Tg2 level above 10 ng/mL is considered pathologic by many investigators because such levels are highly predictive of recurrences (*4,7,26*). This has been determined even when WBS performed at the same time is negative (*2,3,6*). As observed recently by Mazzaferri et al., this cutoff, albeit arbitrary, is often used for empiric ^{131}I therapy (*27*).

The prognostic value of the initial Tg level measured in the postoperative period just before IAT is often debated because of the presence of thyroid remnants that contribute to the Tg synthesis. In our series, although functional thyroid remnants were observed in all patients except one on the posttherapeutic WBS, Tg1 levels above 30 ng/mL were significantly associated with disease progression. Tg1 had a reliable prognostic value but was less significant than Tg2. Until now, only a few reports have demonstrated the prognostic value of the Tg1 level. Some have shown that the Tg1 measurement could be an early indication of the existence of a metastatic disease (*7–9,11*), but most metastases were initial metastases discovered on posttherapeutic WBS. The purpose of this study was to analyze the possible role of Tg1 on the course of the disease, in patients clinically free of disease after the initial therapy. This is why 4 patients with very high Tg1 levels, in whom initial node metastases were discovered at the time of IAT, were excluded from the analysis. Others have pointed out that patients with high Tg1 levels were at increased risk of recurrence (*10,12*). But no hypothesis was suggested to explain the high Tg1 levels in patients in whom recurrence developed. In our study, factors as the TSH stimulation level and the time interval between surgery and Tg1 measurement were eliminated. By logistic regression analysis, Tg1 levels above 30 ng/mL were demonstrated to be significantly associated with the extrathyroidal extension, suggesting a basis for the pejorative evolution of these patients. Interestingly, in the study of Hall et al., the median Tg1 level was particularly high in

TABLE 6
Distribution of Clinical Events After 5-Year Follow-Up According to Tg1 Level and Lymph Node Status

Tg1 level and lymph node status	No events	Events
N− and Tg1 ≤ 30 ng/mL	69	2
N+ or Tg1 > 30 ng/mL	24	14

N− = node invasion absent; N+ = node invasion present.

TABLE 7
Distribution of Clinical Events After 5-Year Follow-Up According to Tg2 Level and Lymph Node Status

Tg2 level and lymph node status	No events	Events
N− and Tg2 ≤ 10 ng/mL	72	2
N+ or Tg2 > 10 ng/mL	21	14

N− = node invasion absent; N+ = node invasion present.

stage III patients presenting an extrathyroidal extension (*10*). In all of these reports, no comparison was done with Tg2. In our study, we evaluated and compared the prognostic value of the 2 Tg determinations in the same patients. Despite a lower OR, Tg1 had a significant prognostic value at the time of initial therapy.

For the determination of Tg1 threshold, to our knowledge, no reference exists in the literature about the normal distribution of postoperative Tg values in thyroidectomized patients. Very few investigations have studied the prognostic value of Tg1. Thresholds used vary from 10 to 69.7 ng/mL. In the series of Oyen et al., a cutoff value of 10 ng/mL was chosen before ablation because no initial metastases were found below this value (*7*). However, this cutoff was too low to discriminate between patients with thyroid remnants and those with initial distant metastases who represented only 16% of the patients. Ruiz-Garcia et al. used a cutoff of 23 ng/mL, chosen at the upper limit of the normal range in his laboratory (*12*). Hall et al., after examining several different values, selected a threshold of 20 ng/mL as the optimum cutoff point because the hazard of recurrences was greatest at this level (*10*). Ronga et al. performed a receiver-operating-characteristic curve analysis and showed that a threshold of 69.7 ng/mL gave the best PPV for the presence of metastases (*9*). This higher value of cutoff was related to the population of patients studied. Ronga et al. included many patients with initial distant metastases. In the absence of available references, the choice of a threshold was necessarily somewhat arbitrary. Any value chosen between 30 and 100 ng/mL would not have changed the accuracy. This could explain the various values used by other authors. The 30 ng/mL value was in the lower range of the best accurate values and yielded the best sensitivity.

Finally, considering all results of multivariate analyses, patients at risk of disease progression were patients with a high Tg1 or Tg2 level under TSH stimulation or a node invasion. The PPV of these 2 variables combined together was low. Baudin et al. reported recently a low PPV of the Tg level measured during the first year of follow-up (*28*). This was related to the low recurrence rate in his series and to a progressive decrease of Tg levels in a significant percentage of patients. A low progression rate was also observed in our series. Furthermore, only clinical events proven by imaging modalities or surgery were considered. Twelve patients with a high Tg2 level maintained a Tg level above 10 ng/mL during the whole follow-up without evidence of disease.

Conversely, it was worth noting the high NPV of a low Tg level associated with the absence of node invasion. This concerned two thirds of our patients for whom the likelihood of complete remission was very high. Interestingly, these PPVs and NPVs were the same, using either Tg1 or Tg2. These results reinforce the idea that the Tg1 threshold of 30 ng/mL, arbitrarily chosen at the upper limit of the normal range, was relevant.

CONCLUSION

Although Tg2 appears more significant than Tg1, both Tg levels, measured under TSH stimulation in the postoperative period and after ablative therapy, have a predictive value for disease progression. Taking into account the lymph node status, patients at risk are the same before and after IAT. In clinical practice, they can be selected as soon as Tg1 is known. In patients with a low Tg1 level and no node invasion, who represent the majority of our population, the risk of a clinical evolution is very low. In these patients, the need for periodic scintigraphic controls and Tg determinations under TSH stimulation seems questionable and clinical management should be as minimal as possible. Conversely, patients with a node invasion or a high Tg1 level should benefit from a more intensive follow-up.

REFERENCES

1. Duren M, Siperstein AE, Shen W, Duh QY, Morita E, Clark OH. Value of stimulated serum thyroglobulin levels for detecting persistent or recurrent differentiated thyroid cancer in high- and low-risk patients. *Surgery.* 1999;126:13–19.
2. Pacini F, Lippi F, Formica N, et al. Therapeutic doses of iodine-131 reveal undiagnosed metastases in thyroid cancer patients with detectable serum thyroglobulin levels. *J Nucl Med.* 1987;28:1888–1891.
3. Pineda JD, Lee T, Ain K, Reynolds JC, Robbins J. Iodine-131 therapy for thyroid cancer patients with elevated thyroglobulin and negative diagnostic scan. *J Clin Endocrinol Metab.* 1995;80:1488–1492.
4. Roelants V, Nayer PD, Bouckaert A, Beckers C. The predictive value of serum thyroglobulin in the follow-up of differentiated thyroid cancer. *Eur J Nucl Med.* 1997;24:722–727.
5. Schlumberger M, Mancusi F, Baudin E, Pacini F. ^{131}I therapy for elevated thyroglobulin levels. *Thyroid.* 1997;7:273–276.
6. Schlumberger M, Baudin E. Serum thyroglobulin determination in the follow-up of patients with differentiated thyroid carcinoma. *Eur J Endocrinol.* 1998;138: 249–252.
7. Oyen WJ, Verhagen C, Saris E, van den Broek WJ, Pieters GF, Corsten FH. Follow-up regimen of differentiated thyroid carcinoma in thyroidectomized patients after thyroid hormone withdrawal. *J Nucl Med.* 2000;41:643–646.
8. Grunwald F, Menzel C, Fimmers R, Zamora PO, Biersack HJ. Prognostic value of thyroglobulin after thyroidectomy before ablative radioiodine therapy in thyroid cancer. *J Nucl Med.* 1996;37:1962–1964.
9. Ronga G, Filesi M, Ventroni G, Vestri AR, Signore A. Value of the first serum thyroglobulin level after total thyroidectomy for the diagnosis of metastases from differentiated thyroid carcinoma. *Eur J Nucl Med.* 1999;26:1448–1452.
10. Hall FT, Beasley NJ, Eski SJ, Witterick IJ, Walfish PG, Freeman JL. Predictive value of serum thyroglobulin after surgery for thyroid carcinoma. *Laryngoscope.* 2003;113:77–81.
11. Tenenbaum F, Corone C, Schlumberger M, Parmentier C. Thyroglobulin measurement and postablative iodine-131 total body scan after total thyroidectomy for differentiated thyroid carcinoma in patients with no evidence of disease [letter]. *Eur J Cancer.* 1996;32A:1162.
12. Ruiz-Garcia J, Ruiz de Almodovar JM, Olea N, Pedraza V. Thyroglobulin level as a predictive factor of tumoral recurrence in differentiated thyroid cancer. *J Nucl Med.* 1991;32:395–398.
13. Thyroid gland. In: Sobin LH, Wittekind C, eds. *TNM Classification of Malignant Tumors*. New York, NY: Wiley-Liss Publishers; 2002:52–56.
14. Schlumberger MJ. Papillary and follicular thyroid carcinoma. *N Engl J Med.* 1998;338:297–306.
15. Tubiana M, Schlumberger M, Rougier P, et al. Long-term results and prognostic factors in patients with differentiated thyroid carcinoma. *Cancer.* 1985;55:794–804.
16. DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. *J Clin Endocrinol Metab.* 1990;71: 414–424.

17. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med.* 1994;97:418–428.
18. Cailleux AF, Baudin E, Travagli JP, Ricard M, Schlumberger M. Is diagnostic iodine-131 scanning useful after total thyroid ablation for differentiated thyroid cancer? *J Clin Endocrinol Metab.* 2000;85:175–178.
19. Pacini F. Follow-up of differentiated thyroid cancer. *Eur J Nucl Med Mol Imaging.* 2002;29(suppl 2):S492–S496.
20. Pacini F, Molinaro E, Castagna MG, et al. Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. *J Clin Endocrinol Metab.* 2003;88:3668–3673.
21. Wartofsky L. Using baseline and recombinant human TSH-stimulated Tg measurements to manage thyroid cancer without diagnostic ^{131}I scanning. *J Clin Endocrinol Metab.* 2002;87:1486–1489.
22. Mazzaferri EL, Kloos RT. Is diagnostic iodine-131 scanning with recombinant human TSH useful in the follow-up of differentiated thyroid cancer after thyroid ablation? *J Clin Endocrinol Metab.* 2002;87:1490–1498.
23. Simpson WJ, McKinney SE, Carruthers JS, Gospodarowicz MK, Sutcliffe SB, Panzarella T. Papillary and follicular thyroid cancer: prognostic factors in 1,578 patients. *Am J Med.* 1987;83:479–488.
24. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. *Surgery.* 1993;114:1050–1057.
25. Tennvall J, Biorklund A, Moller T, Ranstam J, Akerman M. Is the EORTC prognostic index of thyroid cancer valid in differentiated thyroid carcinoma? Retrospective multivariate analysis of differentiated thyroid carcinoma with long follow-up. *Cancer.* 1986;57:1405–1414.
26. Schlumberger M, Travagli JP, Fragu P, Gardet P, Lumbroso J, Parmentier C. Follow-up of patients with differentiated thyroid carcinoma: experience at Institut Gustave-Roussy, Villejuif. *Eur J Cancer Clin Oncol.* 1988;24:345–350.
27. Mazzaferri EL, Robbins RJ, Spencer CA, et al. A consensus report of the role of serum thyroglobulin as a monitoring method for low-risk patients with papillary thyroid carcinoma. *J Clin Endocrinol Metab.* 2003;88:1433–1441.
28. Baudin E, Do CC, Cailleux AF, Leboulleux S, Travagli JP, Schlumberger M. Positive predictive value of serum thyroglobulin levels, measured during the first year of follow-up after thyroid hormone withdrawal, in thyroid cancer patients. *J Clin Endocrinol Metab.* 2003;88:1107–1111.