Long-Term Follow-Up of Patients with Papillary and Follicular Thyroid Cancer: A Prospective Study on 715 Patients

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Purpose: This prospective study evaluated the recurrence rate in 715 patients with differentiated thyroid cancer who had no evidence of persistent disease after total thyroidectomy and lymph node dissection in 94% of them followed up by radioiodine ablation (30–100 mCi) and assessed the predictive value of the initial thyroglobulin (Tg) levels for detecting recurrence, both during levothyroxine (LT4) treatment and after TSH stimulation.

Patients and Methods: Patients had Tg determinations performed at 3 months on LT4 treatment (Tg1) and at 9–12 months after stimulation by either thyroid hormone withdrawal or recombinant human TSH (Tg2); the Access kit was used (functional sensitivity of 0.11 ng/ml); they had undetectable anti-Tg antibodies. Patients were followed up annually. Predictive values were calculated by comparing Tg levels (Tg1 and Tg2) and the outcome in terms of recurrence.

Results: During the median follow-up of 6.2 yr, 32 patients had a recurrence. Assuming a cutoff level for Tg1 at 0.27 ng/ml, Tg1 sensitivity and specificity reached 72 and 86%, respectively, whereas predictive positive and negative values were 20 and 99%, respectively. With a cutoff level for Tg2 at 1.4 ng/ml, sensitivity and specificity reached 78 and 90%, respectively, whereas positive and negative predictive values were 26 and 99%, respectively.

Conclusion: This large prospective cohort of patients presented a low rate of recurrence. Initial Tg measurements allow to predict long-term recurrence with an excellent specificity. Stimulated Tg determination presented a slightly higher sensitivity than Tg determination on LT4. TSH stimulation may be avoided when Tg measured 3 months after ablation is less than 0.27 ng/ml during LT4 treatment. **(*J Clin Endocrinol Metab* 96: 1352–1359, 2011)**

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Abbreviations: DTC, Differentiated thyroid cancer; ^{131}I, radioactive iodine; LT4, levothyroxine; p, pathological; RAI, radioiodine ablation; rhTSH, recombinant human TSH; ROC, receiver-operating characteristic; TBS, total body scan; Tg, thyroglobulin; THW, thyroid hormone withdrawal; TNM, tumor node metastasis; US, ultrasonography.

According to the recent American Thyroid Association recommendations (1), radioactive iodine (^{131}I) ablation after total thyroidectomy for differentiated thyroid cancer (DTC) is indicated in patients with moderate to high risk of persistent or recurrent disease, based on age, tumor size, extrathyroidal extension, lymph node status, and histology. ^{131}I ablation allows the eradication of thyroid remnants and improves the diagnostic performances of serum thyroglobulin (Tg) determination (2–6). It also permits the diagnosis and treatment of radioiodine-avid metastasis. When ^{131}I total body scan (^{131}I -TBS) is informative and normal, with low uptake only in small thyroid remnants, low-risk patients will be followed up with serum Tg determination and neck ultrasonography (US), and routine control diagnostic ^{131}I -TBS can be avoided (7–11) when there is no evidence of disease (1). Because the vast majority of low-risk patients will never experience a recurrence (12–17), serum Tg determination should be specific enough to avoid unnecessary investigations or treatments. The availability of sensitive serum Tg assays raised the question of whether and to which extent TSH stimulation improves the diagnostic performances of serum Tg determination over those obtained on levothyroxine (LT4) treatment because basal highly sensitive Tg shows a very good correlation with recombinant human TSH (rhTSH)-stimulated Tg (18).

In this prospective multicentric study, 968 DTC patients who had no focus of uptake after total thyroidectomy detected outside the thyroid bed on the ^{131}I-TBS performed 3–5 d after radioiodine ablation (RAI) were included and had a Tg determination at 3 months on LT4 treatment (Tg1) and at 9–12 months (Tg2) after stimulation obtained by either thyroid hormone withdrawal (THW) or injections of rhTSH. A first report (19) found 30 recurrences after a mean follow-up of 28 months. The comparison of seven Tg assays showed that the two methods with the lowest functional sensitivity at 0.02 and 0.11 ng/ml had the highest sensitivity (81 and 78%, respectively) for the detection of recurrent disease on LT4 but at the expense of a low specificity (42 and 63%, respectively). Using receiver-operating characteristic (ROC) curves for these two methods, a 0.22 and 0.27 ng/ml were considered optimal cutoffs and resulted in a sensitivity of 65% and specificity of 85–87%. It was also found that TSH stimulation slightly improved the diagnostic performances of serum Tg determination.

Patients were then followed up annually according to local procedures, and this report is an update with a longer follow-up of our previous study (19). The objectives of the present study were to estimate in the 715 patients who had both available Tg1 on LT4 therapy and Tg2 after TSH stimulation determinations with a sensitive method and who had no anti-Tg antibodies the predictive values of Tg levels (19) on the long-term risk of recurrence.

TABLE 1. Initial characteristics of the 715 patients

Characteristics	Patients (n = 715)
Women	551 (77%)
Age mean ± SD (range)	47 ± 13 (13–80)
Tumor size (TNM classification)	
T1	176 (24.6%)
T2	403 (56.4%)
T3	52 (7.3%)
T4	84 (11.7%)
Lymph node	
N0	493 (68.9%)
N1	180 (25.2%)
Nx	42 (5.9%)
Classification	
pT1N0/pT1N1/pT1Nx	134/36/6
pT2N0/pT2N1/pT2Nx	290/85/28
pT3N0/pT3N1/pT3Nx	38/10/4
pT4N0/pT4N1/pT4Nx	31/49/4
Stage	
I	399 (55.8%)
II	183 (25.6%)
III	78 (10.9%)
IV	55 (7.7%)
Absence of distant metastasis (M0)	715 (100%)
Histology	
Papillary	618 (86.4%)
Follicular minimally invasive	78 (10.9%)
Follicular widely invasive	19 (2.7%)

Materials and Methods

The multicentric THYRoglobulin for DIAGnosis of recurrent thyroid carcinoma (THYRDIAG) cohort prospectively included patients with differentiated (papillary and follicular) thyroid car-

TABLE 2. Sensitivity, specificity, PPV, and NPV for the diagnosis of long-term recurrence based on Tg1 and Tg2 determinations

Tg	Recurrence	No recurrence
Tg1		
>0.27 ng/ml	23	94
≤0.27 ng/ml	9	589
Tg2		
>1.4 ng/ml	25	70
≤1.4 ng/ml	7	613

Tg	Sensitivity	Specificity	PPV	NPV
Tg1				
Cutoff = 0.27 mg/ml	72%	86%	20%	99%
Tg2				
Cutoff = 1.4 mg/ml	78%	90%	26%	99%

PPV, Positive predictive value; NPV, negative predictive value.

TABLE 3. Characteristics of the patients with recurrence with Tg1 >0.27 ng/ml and Tg2 >1.4 ng/ml (n = 22)

Sex	Age (yr)	History	T TNM	N TNM	Stage	Tg1	Tg2	Stimulation method	Site of recurrence	Time to recurrence (yr)
Female	13	Pap	T4	N1	1	6.1	39	rhTSH	Lung	0.7
Female	50	Pap	T3	N1	3	1	105	rhTSH	LN	3.9
Male	62	Pap	T4	N1	4	3.4	41	rhTSH	Lung	6.0
Female	78	Pap	T4	N0	4	1.3	1.8	rhTSH	Thyr + skin	0.6
Female	50	Pap	T4	N1	4	4.5	51	rhTSH	LN	0.9
Male	62	Pap	T4	N1	4	11.67	20.34	rhTSH	LN	1.8
Male	27	Pap	T4	N1	1	1.7	22	rhTSH	Lung + LN	0.1
Male	36	Pap	T1	N0	1	0.32	1.4	rhTSH	Thyr	0.7
Female	64	Pap	T2	N0	2	9.2	129	rhTSH	Bone	0.4
Male	32	Pap	T1	N1	1	2.9	7.5	rhTSH	LN	2.9
Female	30	Pap	T4	N1	1	1	3.2	rhTSH	LN	4.6
Female	37	Pap	T4	N1	1	0.33	1.9	rhTSH	LN	0.7
Female	50	Pap	T2	N1	3	2	3.2	rhTSH	LN	2.0
Female	55	Pap	T1	N0	1	0.51	7.5	rhTSH	LN	1.5
Female	67	Pap	T1	N0	1	0.77	13	THW	LN	2.5
Female	21	Pap	T4	N0	1	0.56	5.7	THW	LN	5.4
Female	69	Pap	T2	N1	3	1	13	THW	LN	5.9
Female	62	Pap	T2	N0	2	2.01	468	THW	Thyr + lung	2.7
Female	44	Pap	T1	N0	1	0.47	12	THW	LN	1.3
Female	57	Pap	T1	N1	3	0.28	2.2	THW	LN	0.1
Male	65	Foll	T3	N0	3	11	67	THW	Lung	3.4
Male	39	Pap	T4	N1	1	3.8	29	THW	Thyr	1.0

Pap, Papillary; Foll, follicular; LN, lymph node; Thyr, thyroid bed; T, tumor; N, nodes.

cinoma in 27 centers between June 2000 and October 2003. Patients were enrolled in the study if they: 1) underwent a total thyroidectomy that was completed by central neck dissection in 94% of cases, resulting in apparent complete resection of neoplastic foci; 2) had ^{131}I (30–50 mCi in 35 cases and 100 mCi in 680 cases) postoperatively; and 3) had no focus of uptake detected outside the thyroid bed on the total body scan (TBS) performed 3–5 d after ^{131}I therapy. All patients were then treated with LT4. After obtaining their written informed consent, patients were enrolled in the study.

A serum Tg determination (Tg1) was obtained on LT4 therapy at 3–4 months after RAI. Nine to 12 months after RAI, follow-up control consisted in a ^{131}I -TBS 2 d after the administration of 4–5 mCi ^{131}I and in a second Tg (Tg2) determination. This follow-up control was performed after TSH stimulation, obtained after either THW for 3–5 wk or rhTSH injections (0.9 mg im for 2 consecutive days). At the time of the protocol initiation, neck US was not a routine procedure in many centers; however, it was routinely performed during the subsequent follow-up. Then follow-up assessments were planned on a yearly basis and consisted in a clinical examination with serum Tg determination on LT4 treatment and neck US at various frequencies. According to local practice, a control diagnostic ^{131}I-TBS and serum Tg determination after TSH stimulation was routinely performed in only a minority of patients. Outcome was recorded annually and patients were classified as without or with evidence of disease. Neck recurrence was confirmed by a fine-needle biopsy or surgical biopsy, and ^{131}I uptake or typical imaging features on ^{131}I-TBS confirmed distant metastases. Each recurrence site was prospectively recorded. In the case of an elevated Tg level during follow-up, the decision to perform some additional imaging testings was taken by a local oncology center in accordance with the available guidelines (20, 21). The protocol was approved by the Bicêtre Ethics Committee, Kremlin Bicêtre, France, and by the institution review board of each participating center.

Among the 27 participating oncology centers, 11 included 15 patients or less, nine included 16–50 patients, and seven centers included 51–112 patients. Data collected for each patient included demographic characteristics (age, gender), date and extent of surgery, histological type of the primary thyroid tumor, pathological (p) lymph node metastasis classification, date of ^{131}I ablation and postablation results, dates and results of Tg1 and Tg2 samplings, method of TSH stimulation used for Tg2, and serum TSH levels corresponding to Tg1 and Tg2. Date and location of recurrence were collected.

Tg measurements were obtained with the Tg Access kit (Beckman-Coulter, Fullerton, CA), with a functional sensitivity of 0.11 ng/ml. Presence of Tg-antibody was considered if Tg-antibody determination was greater than 5 ng/ml, and these patients with anti-Tg antibodies were followed up but were excluded from the analysis for the predictive values of Tg determination. The results of serum Tg determinations were reported blindly from the clinical status of the patients.

TABLE 4. Characteristics of the patient with recurrence with Tg1 >0.27 ng/ml and Tg2 ≤1.4 ng/ml (n = 1)

Sex	Age (yr)	History	T TNM	N TNM	Stage	Tg1	Tg2	Stimulation method	Site of recurrence	Time to recurrence (yr)
Male	53	Pap	T2	N1	3	0.33	0.25	rhTSH	LN	1.3

Pap, Papillary; LN, lymph node.

Statistical analysis

Descriptive quantitative data were expressed in mean and SD and qualitative data were expressed in percentage. The median follow-up was estimated by the inversed Kaplan-Meier method. Patients without recurrence were censored at the date of their last follow-up. Recurrence rate was estimated by the Kaplan-Meier method and given with Rothman 95% confidence interval. Diagnostic accuracy values were estimated by comparing the results of the Tg determination (Tg1 or Tg2) with the status of patients, expressed in terms of recurrence/absence of recurrence. All recurrences identified either on the control ^{131}I-TBS performed 9–12 months after ablation or during the subsequent follow-up were considered. Serum Tg levels were classified as positive or negative using a cutoff level that corresponded to the Tg level maximizing the sum of sensitivity plus specificity, which was deduced from the ROC curve.

Data were analyzed using SAS system statistical software version 9.1 (SAS Institute, Cary, NC).

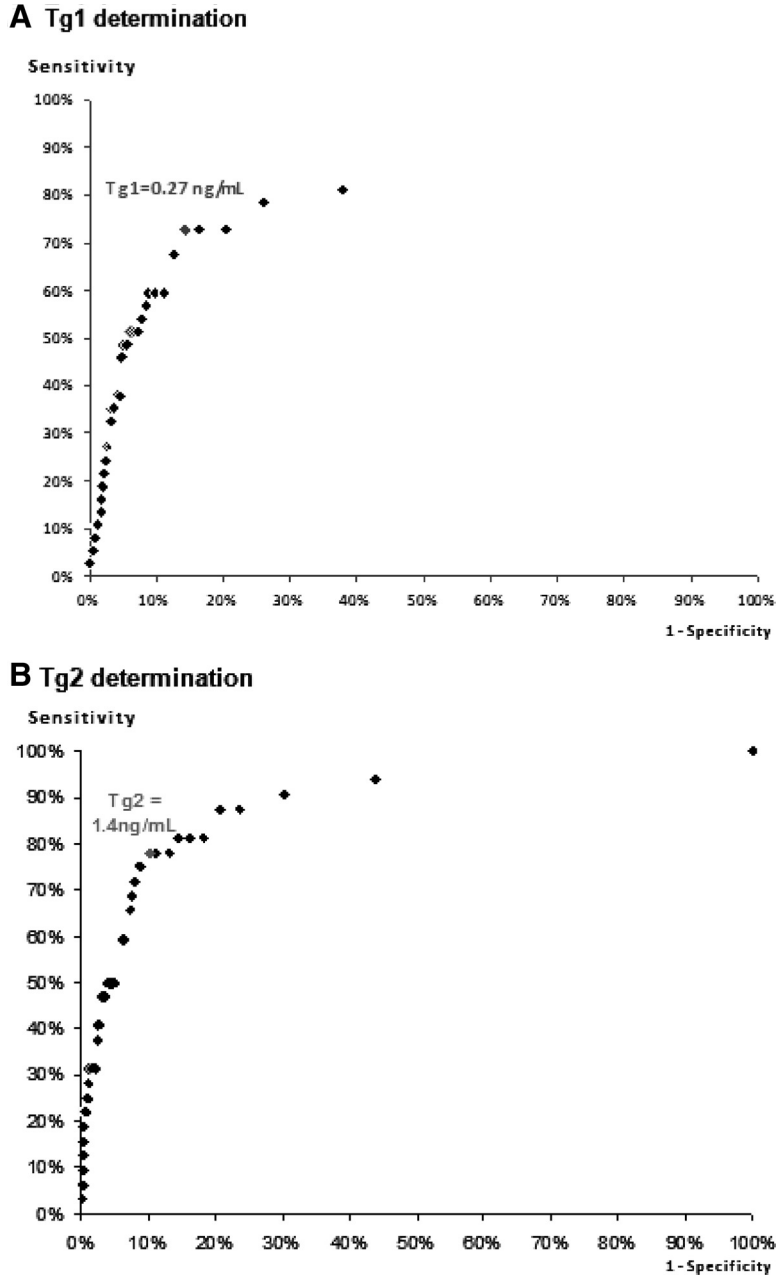

FIG. 1. ROC curves for Tg1 determination and for Tg2 determination, A, Tg1 determination. B, Tg2 determination.

Results

Among the 968 patients included in the THYRDIAG study, the 715 who had both Tg1 on LT4 therapy and Tg2 under TSH stimulation determinations and had no anti-Tg antibodies were updated for the present analysis. The clinical characteristics of the 715 patients (551 females, 164 males, mean age 47 yr, range 13–80 yr) are reported in Table 1. Thyroid cancer was papillary in 618 cases (86%), follicular minimally invasive in 78 (11%), and follicular widely invasive in 19 (3%) cases. Initial treatment consisted in total thyroidectomy in all cases, with lymph node dissection performed in 673 patients (94%). Tumor stages, classified according to the 2002 p tumor node metastasis (TNM) scoring system (22), are shown in Table 1. Lymph node metastases were present in 180 cases (25%; pN1) and absent in 493 cases (69%; pN0) and unknown in 42 cases (6%; pNx). Median follow-up was 6.2 yr (range 9 months to 9.6 yr) on April 1, 2010, the cutoff date of the analysis, with follow-up longer than 1 yr in 635 patients.

Recurrences

Thirty-two recurrences were identified either at the 9-month ^{131}I-TBS control (n = 10) or during the subsequent follow-up (n = 22), with 26 recurrences found during the first 5 yr of follow-up. The recurrence rate reached 4.2% at 5 yr [$IC_{95\%}$ = (2.9–6.1)]. Among the 715 patients, none of the 35 patients who had been treated with ^{131}I activity less than 100 mCi had a recurrence. All the 32 patients who presented recurrences had been treated with 100 mCi ^{131}I. These recurrences occurred in the thyroid bed in four cases (13%); neck lymph nodes in 17 cases (53%); lungs in four cases (13%); both the thyroid bed and lungs in one case (3%); neck lymph nodes and lungs in one case (3%); the thyroid bed, neck lymph nodes, and lungs in 2 cases (6%); bones in one case (3%); in lymph nodes, lungs, and bones in one case (3%); and thyroid bed and skin in one case (3%). Among the 32 recurrences, 17 (53%) occurred within the first 2 yr, and five

TABLE 5. Number of recurrences according to the Tg1 and Tg2 levels

	Tg2 ≤1.4 ng/ml	Tg2 >1.4 ng/ml
Tg1 ≤0.27 ng/ml (n = 598)	Six recurrences among 572 patients (1.0%)	Three recurrences among 26 patients (11.5%)
Tg1 >0.27 ng/ml (n = 117)	One recurrence among 48 patients (2.1%)	22 recurrences among 69 patients (31.9%)

(29%) were distant metastasis. In the 15 patients with a recurrence diagnosed after 2 yr (47%), six (40%) occurred at distant sites.

Thirty-one recurrences occurred in the 618 patients with papillary cancers (5%) and one in the 19 patients with follicular widely invasive cancer (5%). Seven recurrences occurred in the 424 pT1-T2, N0 patients (1.7%), nine in the 121 pT1-T2, N1 patients (7.4%), five in the 69 pT3-T4, N0 patients (7.2%), and 11 in the 59 pT3-T4, N1 patients (18.6%). There was no recurrence among tumors classified Nx.

Serum Tg determinations

The data from the 715 patients were analyzed for the estimation of the predictive values, among whom 32 patients had a recurrence. The ROC curve showed that a cutoff at 0.27 ng/ml for Tg1 maximized sensitivity (72%) and specificity (86%) (Table 2). Using this cutoff, 117 patients (16%) had positive Tg1 level among whom 23 had a recurrence (Tables 3 and 4), leading to a positive predictive value of 20%; among the other 598 patients (84%) who had a negative Tg1 level, 589 patients did not experience any recurrence, leading to a negative predictive value at 99% (see Table 2).

There were, respectively, 395 and 320 patients stimulated by rhTSH and THW at Tg2 determination. The proportion of recurrence was similar among the two groups. The ROC curve showed that a cutoff at 1.4 ng/ml for Tg2 maximized sensitivity at 78% and specificity at 90% (Fig. 1B and Table 2). Using this cutoff, among the 95 patients with positive Tg2 determination, 25 patients had a recurrence (Tables 4–6), leading to a positive predictive value at 26%. Among the 620 patients whose Tg2 determination was negative, 613 did not experience any recurrence, leading to a negative predictive value at 99% (Table 5). The cutoff values of 0.27 and 1.4 ng/ml determined using ROC curves for Tg1 and Tg2, respectively, discriminated well between patients who experienced a recurrence and those who remained free of disease (Fig. 2).

Among the 117 patients with a Tg1 greater than 0.27 ng/ml (Table 4), TSH-stimulated Tg2 determination was greater than 1.4 ng/ml in 69 patients, among whom 22 patients had a recurrence (32%), whereas Tg2 was 1.4 ng/ml or less in 48 patients, among whom only one (2%) had a recurrence (Table 5).

Among the 598 patients with Tg1 less than 0.27 ng/ml, only 26 patients had a Tg2 greater than 1.4 ng/ml, among whom three experienced a recurrence. Two of these recurrences occurred in lymph nodes between 1 and 2 yr after RAI therapy, whereas one patient recurred in the thyroid bed, lymph nodes, and lungs 6 yr after RAI.

Among the 572 patients with both Tg1 less than 0.27 ng/ml and Tg2 less than 1.4 ng/ml, 6 experienced a recurrence (Table 7). Three of these patients had an isolated neck recurrence, with undetectable Tg levels on LT4 at the time of recurrence. Recurrent disease was found on the control ^{131}I TBS in one patient (confirmed by neck US) at 0.8 yr and on ultrasound at 0.8 yr and 4.8 yr in the other two. The other three patients developed distant metastases, and Tg levels were detectable on LT4 in two of them at the time of recurrence (1.7 ng/ml in the patient who recurred at 6.3 yr and 1.8 ng/ml in the patient who recurred at 6.2 yr) but remained undetectable both on LT4 and after TSH stimulation in the remaining patient who developed at 1.8 yr a cranial bone metastasis, discovered on a diagnostic ^{131}I-TBS performed for local tumefaction and pain and confirmed on a magnetic resonance imaging.

Among the 32 patients who experienced a recurrence, there was no relationship between the Tg1 or Tg2 levels and the time to recurrence. Median Tg1 and Tg2 levels (0.5 and 3.4 ng/ml, respectively) in patients with isolated neck recurrence were lower than the median levels in patients with recurrence at distant sites (1.7 and 22 ng/ml, respectively).

Among the nine patients who experienced a recurrence and had Tg1 less than 0.27 ng/ml, four had stage 1 cancer (T1N0 in one, T2N1 in three patients), three had stage 3

TABLE 6. Characteristics of patients with recurrence with Tg1 ≤0.27 ng/ml and Tg2 >1.4 ng/ml (n = 3)

Sex	Age (yr)	History	T TNM	N TNM	Stage	Tg1	Tg2	Stimulation method	Site of recurrence	Time to recurrence (yr)
Male	55	Pap	T4	N1	4	0.27	2.4	rhTSH	Thyr + LN + Lung	6.3
Female	31	Pap	T2	N1	1	0.13	3.4	THW	LN	2.1
Female	39	Pap	T2	N1	1	0.1	2.4	THW	LN	1.5

Pap, Papillary; Thyr, thyroid bed; LN, lymph node.

TABLE 7. Characteristics of patients with recurrence with Tg1 ≤0.27 ng/ml and Tg2 ≤1.4 ng/ml (n = 6)

Sex	Age (yr)	History	T TNM	N TNM	Stage	Tg1	Tg2	Stimulation method	Site of recurrence	Time to recurrence (yr)
Male	79	Pap	T4	N0	4	0.1	0.12	rhTSH	LN + Lung + Bone	1.8
Male	55	Pap	T3	N0	3	0.16	0.3	rhTSH	Lung	6.3
Female	49	Pap	T2	N1	3	0.1	0.64	rhTSH	Thyr + LN + Lung	6.2
Male	35	Pap	T2	N1	1	0.17	0.55	rhTSH	LN	0.8
Female	77	Pap	T3	N1	3	0.1	0.99	THW	Thyr	4.8
Female	54	Pap	T1	N0	1	0.1	0.15	THW	Thyr	0.2

Pap, Papillary; LN, lymph node; Thyr, thyroid bed.

cancer (T2N1, T3N0, and T3N1), and two had stage 4 cancer (T4N0 and T4N1).

Finally, the serum TSH at Tg1 was less than 0.1 mU/liter in 264 patients, and 81% of them had a serum Tg1 less than 0.27 ng/ml; this percentage was similar in patients with detectable serum TSH levels. Furthermore, Tg2 became detectable in 4.2% of these patients with Tg1 less than 0.27 ng/ml, and again this percentage was similar in patients with detectable serum TSH level.

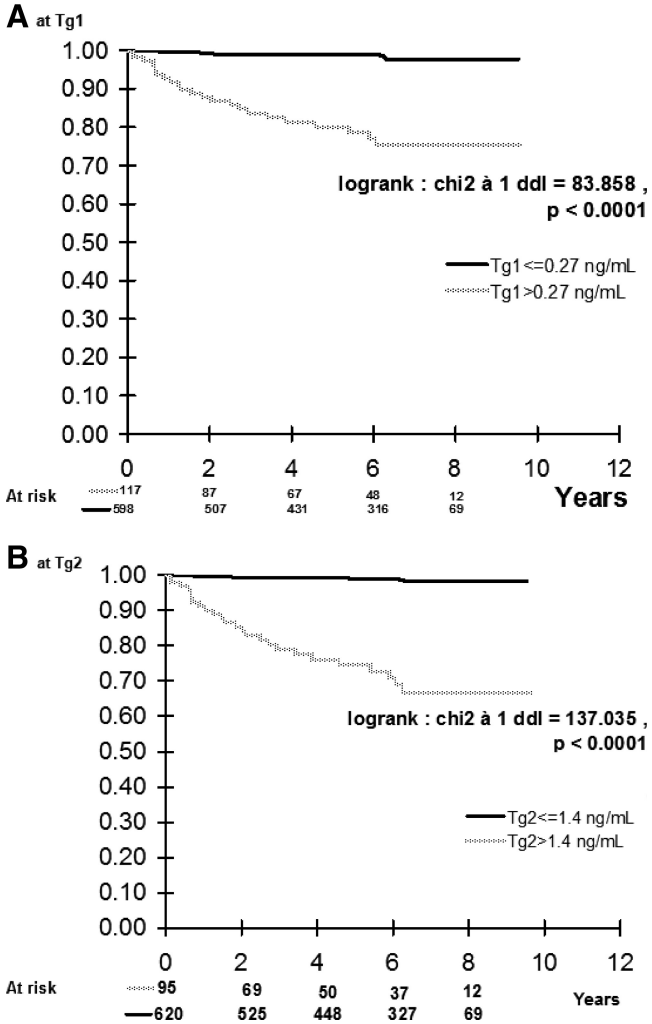

FIG. 2. Time without recurrence according to the Tg level determination. A, At Tg1. B, At Tg2.

Discussion

To our knowledge, this is the first prospective study using a sensitive Tg method that includes only patients who had no focus of uptake detected outside the thyroid bed on the ^{131}I-TBS. These patients represent the great majority of cases in clinical practice. The goal of this extended follow-up study was to define the predictive values of Tg determination both on LT4 (Tg1) and TSH stimulated (Tg2) on the risk of recurrence of thyroid cancer.

The present study was performed on 715 patients from the 968 patients of the original series and 32 recurrences found after a median follow-up of 6.2 yr. The recurrence rate among the 253 excluded patients (122 patients who either had not both Tg1 and Tg2 performed and 142 patients with positive anti-Tg antibodies or both) was 2.2% at 2 yr and 6.2% at 5 yr. This recurrence rate is similar to that observed in the 715 patients included in the study, and excluding these patients probably did not introduce any bias.

Of the 32 recurrences, 17 occurred within the first 2 yr and 29 during the first 5 yr. Both median Tg1 and Tg2 were lower in patients with neck recurrences than in those with recurrence at distant sites, and this is probably related to the smaller burden of disease in patients with neck recurrence. This indicates that even low serum Tg levels should be taken into consideration and that neck US should be performed in all patients, in accordance with guidelines (1). This is further emphasized by the discovery of a neck recurrence in three patients whose serum Tg1 and Tg2 at baseline were undetectable and in whom serum Tg on LT4 was still undetectable at the time of recurrence. It is, however, questionable whether their survival rate would have been different with a delayed diagnosis and with a detectable serum Tg, as these neck recurrences consisted of small foci of disease. In two of the three patients with distant metastasis and negative Tg1 or Tg2, there was a progressive increase of serum Tg during follow-up, but in the remaining patient (who was T4N0), serum Tg remained undetectable despite cranial bone metastasis discovered on a follow-up ^{131}I-TBS and confirmed on radiological imaging.

Cutoff levels determined by ROC curves were 0.27 ng/ml for Tg1 and 1.4 ng/ml for Tg2. The higher cutoff level for Tg2 is probably related to the persistence of small amount of normal tissue that has been irradiated but is still present at 9–12 months and that will disappear during the subsequent follow-up, rather than to neoplastic foci (23).

The large majority (84%) of patients had a Tg1 0.27 ng/ml or less, and TSH stimulation did not increase the negative predictive value of Tg determination on the risk of recurrence, which was 99% in both conditions. Therefore, TSH-stimulated Tg determination may be avoided in patients with Tg1 less than 0.27 ng/ml, and this would result in a lower cost of follow-up. In France, if we consider that 80% of the 4000 patients with clinical thyroid cancer diagnosed annually have no evidence of disease after the initial treatment and that rhTSH is used as a stimulation method in 50% of them, this would decrease the annual cost of follow-up by 1,200,000€, representing 450€ per patient and 44% of the annual cost of management of DTC patients with no evidence of disease. Considering that Tg after TSH stimulation allowed the discovery of 0.5% (three of 598) recurrences that were not detected by Tg determination on LT4 therapy, the cost to detect one recurrence is 89,700€, which is not considered as cost effective by health economists (24). Moreover, avoidance of TSH stimulation would permit to maintain the quality of life in the remaining 50% of patients who would then not undergo a prolonged THW.

However, in the other 16% patients who had Tg1 greater than 0.27 ng/ml, Tg2 discriminated better between patients who will experience a recurrence because 32% of these patients with Tg2 1.4 ng/ml or greater (22 of 69) had recurrence, and only 2% (one of 48) of those with a Tg2 less than 1.4 ng/ml. Determining a cutoff value for each method of TSH stimulation method, withdrawal, or rhTSH used for Tg2 determination seems to be particularly relevant, but the limited number of events (32 recurrences) prohibited such determination. Diagnostic performances on Tg2 determination are thus given globally, whatever the method of TSH stimulation used.

This study also demonstrates that the serum TSH level, even when it is undetectable at the time of the Tg1 determination, does not have an impact on the diagnostic performances of Tg1. The conclusions of this study can be applied to all the patients, whatever the serum TSH level may be.

This study has some limitations. First, the median follow-up among the 715 patients in the study is only 6.2 yr, but the large majority of recurrences occur during the 5 first years after initial treatment (1, 13, 14). Second, all of the patients were prospectively followed up in 27 different referral centers, with differences in local procedures for long-term follow-up. All patients had a serum Tg determination on LT4 treatment and a clinical examination on a yearly basis, which were therefore performed several times during the study. Neck US was not performed in all patients each year but was performed one or several times during follow-up in all patients. Therefore, considering a median follow-up of 6.2 yr, the probability that a recurrence was not discovered during 2 consecutive years is probably low. Furthermore, patients were followed up in accordance to available guidelines (20, 21) by local practitioners, and difficult cases were discussed with colleagues. To reflect real-life practice, no precise walkthroughs were provided to clinicians implicated in this study, and this may as well have delayed the diagnosis of morphological recurrence in some cases. On the other hand, clinicians may perform more compulsive follow-up in patients with a detectable serum Tg, and this may decrease the rate of false-negative determinations; however, most patients were followed up on several occasions and the percentage of patients lost to follow-up after the 9- to 12-month control (11%) was similar among patients with a Tg1 below or above 0.27 ng/ml.

In conclusion, negative predictive value for recurrence of sensitive Tg determination on LT4 at 3–4 months after RAI is 99% and is indeed similar for TSH-stimulated Tg levels at 9–12 months. TSH stimulation improves the positive predictive value of serum Tg determination only in patients with a Tg level on LT4 greater than 0.27 ng/ml, and its use may be restricted to these patients.

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