Change of Serum Antithyroglobulin Antibody Levels Is Useful for Prediction of Clinical Recurrence in Thyroglobulin-Negative Patients with Differentiated Thyroid Carcinoma

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Objectives: The aim of the study was to evaluate the usefulness of the antithyroglobulin autoantibody (TgAb) value at 6–12 months after remnant ablation in predicting recurrence in differentiated thyroid carcinoma patients who had undetectable thyroglobulin (Tg) values. The change in TgAb concentration measured between the time of remnant ablation (TgAb1) and 6–12 months thereafter (TgAb2) was also evaluated as a possible prognostic indicator.

Patients and Methods: Patients with differentiated thyroid carcinoma who underwent total thyroidectomy followed by ^{131}I remnant ablation between 1995 and 2003 at the Asan Medical Center (Seoul, Korea) were enrolled. Of these, 824 patients with undetectable Tg at 6–12 months after remnant ablation during thyroid hormone withdrawal were the subjects of this study.

Results: TgAb2 was positive in 56 patients. Ten of 56 patients (18%) with positive TgAb2 had recurrence, whereas only 10 of 768 patients (1%) with negative TgAb2 had recurrence during 73.6 months of follow-up ($P < 0.001$). The change between TgAb1 and TgAb2 levels was evaluated in patients with positive TgAb2. TgAb concentration decreased by more than 50% in 21 patients (group 1) and by less than 50% in 16 patients (group 2), and it increased in 19 patients (group 3). The recurrence rates in groups 1, 2, and 3 were 0, 19, and 37%, respectively ($P = 0.016$).

Conclusions: Serum TgAb levels measured at 6–12 months after remnant ablation could predict recurrence in patients with undetectable Tg values. In patients with undetectable Tg and positive TgAb values, a change in TgAb concentration during the early postoperative period may be a prognostic indicator of recurrence. **(*J Clin Endocrinol Metab* 93: 4683–4689, 2008)**

Serum thyroglobulin (Tg) measurement is important for follow-up after thyroid surgery in patients with differentiated thyroid carcinoma (DTC) and for detection of persistent or recurrent thyroid cancer because the only source of Tg is thyroid tissue. However, in the presence of antithyroglobulin autoantibody (TgAb) a "negative Tg" immunometric assay (IMA) result is most likely a false-negative owing to TgAb interference with currently available IMA methodology (1–3). Recent guidelines recommend assessing TgAb quantitatively, with simultaneous measurement of serum Tg, every 6–12 months after surgery (4, 5), and Tg IMA methods should not be used when TgAb is detected (3).

The previously reported prevalence of TgAb in patients with DTC is 10–25%, which was higher than in the general population (6–9). TgAb decreases and eventually disappears in patients who achieve complete remission, although the time lag between the disappearance of antigen and antibody may be up to 3 yr (10).

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Abbreviations: CI, Confidence interval; CT, computed tomography; DxWBS, diagnostic whole-body scan; HR, hazard ratio; IMA, immunometric assay; MIBI, technetium-99m methoxyisobutyl isonitrile; RxWBS, posttreatment whole-body scan; Tg, thyroglobulin; TgAb, antithyroglobulin autoantibody; THW, thyroid hormone withdrawal.

Although persistence or increase in the serum TgAb concentration may be regarded as a marker of persistent disease, there is no general acceptance of the use of TgAb levels in the prediction of prognosis. A few cross-sectional studies and a limited longitudinal series have reported higher frequencies of recurrent or persistent disease associated with persistent TgAb (11–13), but some investigators did not find such correlations (6, 8, 14, 15). Recent longitudinal studies have reported that TgAb levels did not influence disease progression and TgAb decreased continuously after surgery in most patients during 3 yr of follow-up (10, 15). We hypothesized that the changing pattern of TgAb level during early follow-up might differ between patients with recurrent or persistent disease and those who achieve complete remission and remain disease free when serum Tg is undetectable owing to the presence of TgAb.

This study evaluated the clinical significance of TgAb levels measured at the time of the first diagnostic whole-body scan (DxWBS), 6–12 months after remnant ablation, in patients with undetectable Tg values. The changing pattern in TgAb levels between the initial postoperative ^{131}I ablation values and measurements 6–12 months thereafter was also evaluated for possible use as a prognostic indicator of persistent or recurrent disease.

Patients and Methods

Patients

This study included 1499 consecutive DTC patients who underwent total thyroidectomy followed by immediate ^{131}I remnant ablation between 1995 and 2003, according to the protocol established by the Endocrinology Division of the Asan Medical Center (Seoul, Korea). Patients with anaplastic carcinoma, or with poorly differentiated papillary thyroid carcinoma (such as the insular, tall cell variant) were excluded. Sixty patients with preoperative clinical evidence of extracervical metastasis or with radioiodine uptake outside the thyroid bed on postablation whole-body scans (RxWBSs) were excluded. Patients with no available Tg or TgAb data from the time of ablation and/or 6–12 months thereafter were excluded. Patients who had thyroid bed radioiodine uptake on initial DxWBS were also excluded. Finally, 824 patients with undetectable Tg values 6–12 months after ^{131}I remnant ablation were included in this study. Informed consent for future reviewing of medical records was obtained from all subjects at the time of surgery. The Local Ethics Committee approved the retrospective review protocol.

Initial treatment and follow-up with DxWBS

Five to 6 wk after surgery, during which time thyroid hormone was withheld, ablative doses of ^{131}I (3.7–5.55 GBq, 100–150 mCi) were administered to all patients, and serum Tg and TgAb were measured (these are the Tg1 and TgAb1 values). RxWBSs were obtained 5–7 d after the administration of ^{131}I. No quantitative measurements of thyroid uptake were made. Suppressive treatment with thyroid hormone was initiated just after remnant ablation to decrease serum TSH to subnormal levels without clinical thyrotoxicosis. Thyroid hormone was titrated every 3 months with measurement of serum free T_4 and TSH levels. The DxWBSs with 148 MBq ^{131}I, after thyroid hormone withdrawal (THW), was usually performed 12 months after remnant ablation; serum Tg (Tg2 value) and TgAb (TgAb2 value) levels were obtained at that time. TSH value was greater than 30 mU/liter at DxWBS.

Subsequent follow-up and localization of persistent or recurrent lesion

During follow-up, physical examination was regularly performed on all patients every 3–6 months. DxWBS with 148 MBq ^{131}I and measurement of Tg and TgAb levels during THW were carried out 6–12 months after remnant ablation in every patient, and thereafter every 1 or 2 yr on the basis of clinical suspicion in high-risk patients. When serum Tg during THW was above 2 μg/liter or there was clinical suspicion of recurrence, one or more nonradioiodine imaging methods, such as neck ultrasonography, technetium-99m methoxyisobutyl isonitrile (MIBI) scanning, ^{18}F-deoxyglucose positron emission tomography, or chest computed tomography (CT) were performed to localize normal and/or malignant thyroid tissue.

Definition of recurrence or persistent disease

Recurrence was defined as the reappearance of disease after complete ablation of thyroid remnants in patients with both negative serum Tg and TgAb, which was confirmed by cytological or histopathological information. Persistent disease was defined as the reappearance of disease after complete ablation, which was confirmed by cytological or histopathological information or extracervical ^{131}I uptake on RxWBS after administration of 5.55 GBq ^{131}I to patients with either or both positive Tg and TgAb. Patients who had no evidence of recurrence or persistent disease were defined as disease-free.

Definition of pathologically proven lymphocytic thyroiditis

Pathologically proven lymphocytic thyroiditis in our center was defined as the presence of diffuse lymphocytic and plasma cell infiltrate and oxyphilic cells, and the formation of lymphoid follicles and reactive germinal centers. The infiltration had to occur in a normal region of the thyroid gland, distinct from the site of DTC. A peritumoral inflammatory response was not considered to be pathologically proven thyroiditis.

Measurement of Tg, TgAb, and TSH

Serum Tg, TgAb, and TSH measurements were performed at the time of DxWBS or when therapeutic doses of ^{131}I were administered during THW, as previously reported (16). Serum Tg levels were measured by immunoradiometric assay (ELSA-hTG kit; Schering-CIS Bio-International; Gif-sur-Yvette, France) with a functional sensitivity of 1 μg/liter. We were unable to standardize serum Tg against the CRM-457 protocol but instead developed our own Tg-reference interval according to the laboratory medicine practice guidelines suggested by the National Academy of Clinical Biochemistry (available at http://www.nacb.org/Impg/main.stm). Our generated Tg-reference interval was approximately 1.0–27.4 μg/liter (mean, 5.2 μg/liter). Serum TgAb levels were determined by radioligand assay (HENNING test anti-Tg; BRAHMS Diagnostica, Berlin, Germany), and TgAb values greater than 100U/ml were considered positive. The functional sensitivity (20% interassay variation coefficient) was approximately 31 U/ml, whereas the analytical sensitivity from the optimal curve was 20 U/ml. The assay had a measuring maximum of 10,000 U/ml. Intraassay and interassay coefficients of variation were 3.1 and 4.5%, respectively. Serum TSH was measured by radioimmunometric assay (SPAC-S TSH kit; Daiichi, Tokyo, Japan), with a normal range of 0.5–5.0 mU/liter, an intraassay coefficient of variation of 2.1%, and an interassay coefficient of variation of 2.5%.

^{131}I whole-body scanning and other imaging studies

DxWBS was routinely scheduled 6–12 months after remnant ablation and every 1–2 yr thereafter. In practice, most DxWBS protocols were performed 12 months after remnant ablation. After 4 wk of THW, 148 MBq ^{131}I was administered, and DxWBS was conducted as previously reported (16). Afterward, periodic DxWBS with Tg measurement after THW was planned throughout the follow-up period in high-risk patients. RxWBS, after therapeutic doses of 5.55 GBq ^{131}I, was performed 2 and 7 d after dosing. All patients were advised to restrict dietary iodine

intake for at least 15 d before administration of radioiodine. In low-risk patients, annual neck ultrasonography analysis was performed.

Statistics

Associations between variables were analyzed using contingency tables and Fisher's exact test, as appropriate. Student's *t* test was used to compare continuous variables such as age and tumor size. The Kaplan-Meier method with the log-rank test was used to compare recurrence between groups. Cox proportional hazard model and the forward stepwise method were used to analyze various prognostic factors for disease-free survival and recurrence. The relative importance of prognostic factors is presented as a hazard ratio (HR) with a 95% confidence interval (CI) calculated using binomial distribution. *P* values are two-sided throughout; $P < 0.05$ was considered statistically significant. R version 2.6.1, and the R libraries survival, car and Cairo was used to analyze data and to draw survival curves (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org) (17).

Results

Patient characteristics

A total of 824 patients (77 men and 747 women) with undetectable serum-stimulated Tg and no visible remnant uptake on the first DxWBS were included in this study. Their mean age was 46.0 ± 11.6 yr (range, 13.0–76.4 yr). Histopathological types were distributed as follows: 728 conventional papillary carcinoma, 51 follicular variant papillary carcinoma, and 55 follicular carcinoma (including 11 Hürthle cell carcinoma). The frequencies of tumor size above 4 cm, multifocality, extrathyroidal invasion, and lymph node metastases were 7, 35, 53, and 50%, respectively. No patient showed distant metastases at the time of remnant ablation; this was an exclusion criterion. The stagings by TNM (Tumor, lymph Node, Metastasis—a classification system of the International Union Against Cancer and the American Joint Committee on Cancer, revised in 2002) were as follows: stage I in 374 patients, stage II in 33, stage III in 386, and stage IV-A in 31. TgAb1 was positive in 12.4% of patients at the time of initial remnant ablation just after surgery.

Diagnosis of recurrence or persistent disease

Twenty patients (1 man and 19 women) showed recurrence or persistent disease as shown in Table 1. Their mean age was 51.5 ± 12.8 yr (range, 33.1–73.8 yr). Nineteen patients had recurrent or persistent disease in the cervical lymph nodes and two in the lung. The mean interval between the time of Tg2 measurement and confirmation of recurrence or persistent disease was 50.4 ± 21.7 months (range, 16.2–118.5 months). Ultrasonographically guided fine needle aspiration detected recurrent or persistent disease in 18 patients and ^{18}F-deoxyglucose positron emission tomography scans localized disease in 10 of these patients (so both tests were positive in these 10 cases). One of the following imaging techniques identified recurrence or persistent disease in the remaining two patients: chest CT with ^{131}I-RxWBS, or chest CT with CT-guided percutaneous needle aspiration. All patients with recurrence or persistent disease had papillary carcinoma. Patients with recurrent/persistent disease

TABLE 1. Patients with recurrent or persistent disease confirmed by cytological or histopathological data or extracervical ^{131}I uptake on RxWBS

Patient no.	Age (yr) /sex	Tg1 (μg /liter)	TgAb1 (U/ml)	Tg2 (μg /liter)	TgAb2 (U/ml)	Duration before localization (months)	Additional diagnostic maneuver[a]	Site of recurrence or persistent disease	Treatment modalities in addition to T_4 therapy
1	54/F	1.2	<20	<1	<20	118	PET(+), USFNA(+)	Cervical LN	Surgery
2	56/F	1.6	37	<1	<20	45	PET(+), USFNA(+)	Cervical LN	Surgery
3	57/M	1.6	<20	<1	<20	60	PET(+), USFNA(+)	Cervical LN	Supportive care
4	73/F	3.2	<20	<1	<20	48	CT(+), PCNA(+)	Lung	Supportive care
5	36/F	5.3	<20	<1	<20	35	PET(+), USFNA(+)	Cervical LN	Surgery
6	33/F	<1	69.3	<1	20.9	32	PET(+), USFNA(+)	Cervical LN, mediastinum	Surgery, ^{131}I
7	45/F	<1	<20	<1	33.4	32	USFNA(+), CT(+)	Cervical LN	Surgery
8	40/F	1.2	141	<1	60	74	PET(−), USFNA(+)	Cervical LN	Surgery
9	72/F	7.9	58	<1	86.2	16	MIBI(+), USFNA(+)	Cervical LN	Surgery
10	43/F	<1	<20	<1	99.7	55	USFNA(+)	Cervical LN	Surgery
11	73/F	4.7	<20	<1	103	43	CT(+), RxWBS(+)	Cervical LN, lung	^{131}I
12	48/F	<1	158	<1	133	63	USFNA(+), MIBI(−)	Cervical LN	Surgery
13	59/F	<1	132	<1	191	57	PET(−), USFNA(+)	Cervical LN	Surgery, ^{131}I
14	47/F	<1	246	<1	299	58	USFNA(+)	Cervical LN	Surgery, ^{131}I
15	44/F	<1	332	<1	413	40	PET(+), USFNA(+)	Cervical LN	Surgery
16	53/F	<1	599	<1	486	39	PET(+), USFNA(+)	Cervical LN	Surgery
17	34/F	1.6	299	<1	646	72	USFNA(+)	Cervical LN	Surgery
18	35/F	<1	2156	<1	2414	46	PET(+), USFNA(+)	Cervical LN	Surgery
19	63/F	<1	1915	<1	2884	33	PET(+), USFNA(+)	Cervical LN	Ethanol injection
20	56/F	<1	6075	<1	3762	40	PET(+), USFNA(+)	Cervical LN	Surgery

Tg1 and TgAb1, serum Tg and TgAb measured at the time of ^{131}I remnant ablation; Tg2 and TgAb2, serum Tg and TgAb measured 6–12 months after remnant ablation during thyroid hormone withdrawal; PET, Positron emission tomography; USFNA, ultrasonography-guided fine needle aspiration; F, female; M, male; LN, lymph node; PCNA, percutaneous needle aspiration.

[a] Interval between the time of the first diagnostic scan and the time of clinical recurrence as determined by an additional diagnostic test, as listed in the table.

TABLE 2. Clinicopathological factors correlated with TgAb levels measured 6–12 months after remnant ablation

	Total	TgAb2-positive	TgAb2-negative	*P* value
n	824	56	768	
Age (yr)	46 ± 12	44 ± 13	46 ± 12	0.28
Gender (male/female)	77/747	3/53	74/694	0.47
Size (cm)	2.0 ± 1.3	2.1 ± 1.0	2.0 ± 1.3	0.52
Multifocality	287 (35)	27 (48)	260 (34)	0.04
Lymph node metastasis				
None	409 (50)	11 (20)	398 (52)	<0.001
N1a	341 (41)	32 (57)	309 (40)	
N1b	74 (9)	13 (23)	61 (8)	
Extrathyroid extension	435 (53)	39 (69)	396 (52)	0.01
Pathologically proven thyroiditis	172 (21)	22 (39)	150 (20)	0.001

Data represent mean ± SD or number (percent). Tg2 and TgAb2, Serum Tg and TgAb measured 6–12 months after remnant ablation during THW; TgAb2 positive, TgAb values greater than 100 U/ml were considered positive.

according to the TNM stages were as follows: 7 (2%) in stage I; 11 (3%) in stage III; and 4 (13%) in stage IV-A.

Clinicopathological factors according to TgAb2

Among the 824 patients, 56 (6.8%) had TgAb values greater than 100 U/ml at the first DxWBS (so were TgAb2-positive), as shown in Table 2. There were no differences in age, gender, or tumor size between the TgAb2-positive and TgAb2-negative groups ($P = 0.28$, $P = 0.47$, and $P = 0.52$, respectively). Multifocal DTC was slightly more common in the TgAb2-positive group (48 *vs.* 34%; $P = 0.04$). Central and lateral cervical lymph node metastasis was seen in 32 (57%) and 13 (23%) of TgAb2-positive patients ($P < 0.001$), respectively, and was more common than in TgAb2-negative patients. Extrathyroidal extensions were noted in 39 (69%) and 396 (52%) patients of the TgAb2-positive and TgAb2-negative groups, respectively ($P = 0.01$). Twenty-two patients (39%) in the TgAb2-positive group and 150 (20%) in the TgAb2-negative group had pathologically proven lymphocytic thyroiditis ($P = 0.001$). Diffuse hyperplasia, consistent with Graves' disease, was found in 23 (3%) patients and was not associated with the presence of TgAb1 or TgAb2. Histopathological evidence of Hashimoto's thyroiditis or Graves' disease was not associated with clinical recurrence in this group of patients. TgAb2-positive patients according to the TNM stages were as follows: 27 (7%) in stage I; 1 (3%) in stage II; 21 (5%) in stage III; and 7 (23%) in stage IV-A.

Association of recurrent/persistent disease with TgAb2 values

Among the 56 patients with positive TgAb2, 10 patients (18%) were confirmed to have recurrent/persistent disease during the median 73.6 months of follow-up, whereas only 10 of 741 patients (1%) in the TgAb2-negative group had recurrent/persistent disease (log-rank statistics = 58.6, $P < 0.001$; Fig. 1A). The clinicopathological factors associated with recurrent/persistent disease were tumor size and extrathyroidal extension in univariate analysis ($P = 0.02$ and $P < 0.001$, respectively; Table 3). In multivariate analysis, positive TgAb2 was independently as-

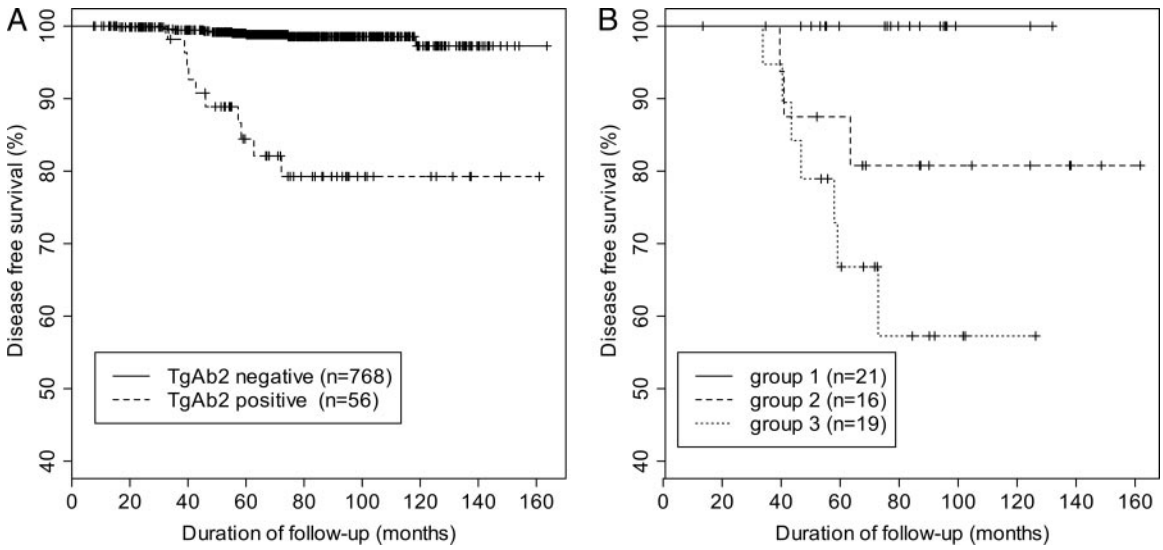

FIG. 1. A, Clinical outcome according to serum TgAb level 6–12 months after high dose ^{131}I remnant ablation during THW in patients with undetectable Tg. B, Disease-free survival according to changes in TgAb between the time of remnant ablation and 6–12 months thereafter in patients who had undetectable Tg with positive TgAb values. TgAb2, Serum TgAb measured 6–12 months after remnant ablation during THW; TgAb1, TgAb at the time of remnant ablation; TgAb2-positive, TgAb2 values greater than 100 U/ml were considered to be positive; group 1, patients whose TgAb2 concentration was less than half the TgAb1 level; group 2, patients whose TgAb2 concentration was less than that of TgAb1 but more than half of that of TgAb1; group 3, patients with higher TgAb2 than TgAb1 concentrations.

TABLE 3. Association of recurrent or persistent disease with variable clinicopathological factors in study subjects (n = 824)

	Univariate analysis			Multivariate analysis		
	Log-rank statistics	df	*P* value	HR	95% CI	*P* value
Age ≥45 (yr)	1.10	1	0.29			0.38
Gender (male)	0.41	1	0.52			0.82
Size ≥4 cm	5.75	1	0.02	3.73	1.24–11.23	0.02
Multifocality	0.26	1	0.61			0.37
Lymph node metastasis	4.51	2	0.11			
N1a						0.90
N1b						0.70
Extrathyroid extension	11.40	1	0.001	6.05	1.38–26.53	0.02
Pathologically proven thyroiditis	1.02	1	0.31			
Positive TgAb2	58.61	1	<0.001	10.59	4.36–25.71	<0.001

Positive TgAb2, serum TgAb more than 100 U/ml, measured 6–12 months after remnant ablation during THW. df, Degree of freedom.

sociated with shorter disease-free survival time (HR = 10.6; 95% CI, 4.4–25.7; $P < 0.001$). Extrathyroidal extension (HR = 6.05; 95% CI, 1.4–26.5; $P = 0.02$) and larger tumor size (HR = 3.73; 95% CI, 1.2–11.2; $P = 0.02$) showed independent association with recurrent/persistent disease (Table 3, *right*).

Correlation of recurrent/persistent disease with change in TgAb levels between the time of remnant ablation and 6–12 months thereafter

The changes in TgAb values between the time of remnant ablation and 6–12 months thereafter were evaluated. Fifty-six patients with positive TgAb2 were divided into three groups according to changes in TgAb concentration between TgAb1 and TgAb2, as shown in Table 4. TgAb concentration decreased more than 50% in 21 patients (group 1) and decreased less than 50% in 16 patients (group 2). The TgAb concentration increased over the 6–12 months period in 19 patients (group 3). There were no significant differences in TgAb2 level, age, gender, tumor size, multifocality, cervical lymph node metastasis, or extrathyroidal extension between these three groups. None of 21 patients, 3 of 16 patients (19%), and 7 of 19 patients (37%) had recurrent/persistent disease in group 1, group 2, and group 3, respectively (log-rank statistics = 8.3; $P = 0.016$; Fig. 1B).

Discussion

We studied the clinical outcomes of 824 patients with undetectable Tg2 values who were treated with total thyroidectomy followed by ^{131}I remnant ablation. The presence of TgAb could predict persistent disease or early recurrence, whereas absence of TgAb in patients with undetectable Tg levels might predict long-term remission. We showed that the change in TgAb level from the time of remnant ablation to 6–12 months thereafter, might be a good prognostic indicator in patients who had undetectable Tg with positive TgAb values.

The main focus of this study was to determine whether the changing pattern of TgAb levels could be used as a prognostic indicator early after surgery. Complete elimination of follicular cells by total thyroidectomy followed by remnant ablation should lead to cessation of antigenic stimuli and consequently a progressive decline in TgAb concentration, eventually resulting in complete TgAb disappearance. Thus, persistence of TgAb for a long period of time after initial treatment or increasing TgAb concentration indicates persistence of Tg-producing tissues, which reflects persistent or recurrent DTC because all normal follicular cells have already been destroyed. Chiovato *et al.* (10) showed that TgAb disappeared after ablation of thyroid tissue

TABLE 4. Association of recurrent or persistent disease with changes in TgAb level between the time of remnant ablation and 6–12 months thereafter in patients with positive TgAb2

	TgAb2-positive group (n = 56)			
	Group 1	Group 2	Group 3	*P* value
n	21	16	19	
Median TgAb2 (U/ml)	204 (102–802)	481 (102–3762)	272 (103–2884)	0.59
Age (yr)	43 ± 12	42 ± 13	48 ± 14	0.24
Gender (male/female)	1/20	1/15	1/18	0.99
Size (cm)	1.8 ± 1.0	2.2 ± 0.7	2.3 ± 1.3	0.13
Multifocality	9 (43)	9 (56)	12 (47)	0.75
Lymph node metastasis				
None	3 (14)	4 (25)	4 (21)	0.19
N1a	16 (76)	8 (50)	8 (42)	
N1b	2 (10)	4 (25)	7 (37)	
Extrathyroid extension	12 (57)	12 (75)	15 (79)	0.31
Pathologically proven thyroiditis	9 (43)	6 (38)	7 (37)	0.94

TgAb2 data represent median (range) and other data represent mean ± SD or number (%). TgAb2, Serum TgAb measured 6–12 months after remnant ablation during THW; TgAb1, TgAb at the time of remnant ablation; group 1, patients whose TgAb2 concentration was less than half that of TgAb1; group 2, patients whose TgAb2 concentration was less than that of TgAb1 but more than half of that of TgAb1; group 3, patients who had greater TgAb2 than TgAb1 concentrations.

and the median disappearance was 3 yr. In this work, 25% of subjects had persistent or metastatic disease, and the changing patterns of their TgAb levels differed from those of patients without thyroid tissue. The percentage of patients with positive TgAb was higher in those in whom remnant thyroid tissue persisted than in those without such tissue and markedly decreased within 2 yr, especially in patients without remnant thyroid tissue. Gorges *et al.* (15) recently reported that the percentage of TgAb-positive patients decreased from 28% to less than 10% within 3 yr of surgery, and the median serum half-life of TgAb in treated DTC cases was 10 wk. Therefore, we assumed that if the source of Tg were completely removed, the TgAb concentration would decreased rapidly, even within 6–12 months, and we could use this TgAb change as a prognostic indicator.

Previous studies on the clinical significance of TgAb in DTC are open to dispute. A few studies have used less sensitive hemagglutination inhibition methods (6, 18) and did not use the same TgAb assay for the entire study period (7, 12). Recent guidelines have recommended that serum Tg should ideally be measured in the same laboratory using the same assay method and TgAb should be quantitatively assessed with every measurement of serum Tg (4). Most studies have reported that TgAb level did not show any association with poor prognosis after surgery. These authors measured TgAb at the time just after surgery or ablation and did not exclude patients with metastatic disease (6, 8, 10, 15). Even in the absence of remnant thyroid tissue, conversion to TgAb-negative status may require time. Continuous antigenic stimulation from a known metastatic focus might confuse the analysis of changes in TgAb levels. The present study included patients with negative Tg, assessed 6–12 months after remnant ablation, to permit the natural decline in TgAb levels and to apply TgAb levels as prognostic factors in patients with no theoretically possible Tg source. We also excluded patients with metastatic disease and those with positive Tg to focus on the prognostic value of TgAb in patients with negative Tg.

The prevalence of positive TgAb in patients with DTC was reported to be higher than in the general population. The high prevalence of autoantibody is probably because a higher percentage of patients with DTC are female (9, 19, 20). The timing of TgAb measurement may have an effect on the prevalence of positive TgAb values in patients after total thyroidectomy followed by remnant ablation. Previous studies have reported that TgAb continuously decreased in most patients after surgery, and about half became TgAb-negative after 1–1.5 yr of follow-up (15). In the present study, 6.8% of the 824 patients were positive for TgAb at the time of the first diagnostic scan. The rate of TgAb positivity may have been underestimated because we included patients with undetectable Tg values at the time of initial scan. The overall prevalence of positive TgAb at the time of remnant ablation was 12.4%; this is in agreement with the previous data yielding values of 10–25%.

The previously reported prevalence of lymphocytic thyroiditis in DTC patients was also significantly higher than in the general population, ranging from 11–38% (21–23). Histopathological evidence of lymphocytic thyroiditis was confirmed in 21% of our study population. This was not associated with recurrent/persistent disease. About 47% of patients with positive TgAb values at the time of remnant ablation were shown to have lymphocytic thyroiditis at pathological examination, and this suggested that TgAb expression may be associated with autoimmune thyroiditis. Elevated TgAb concentrations associated with autoimmune thyroiditis may decrease continuously and disappear after thyroidectomy and remnant ablation. Therefore, sustained positive TgAb levels or increasing TgAb concentrations could be evidence of persistent malignant thyroid tissue and may be a prognostic indicator of poor outcome.

In the present study, 1.2% of patients with undetectable serum Tg and negative TgAb values experienced recurrence. Previous studies exploring the prognostic value of serum Tg levels at the time of the initial diagnostic scan also showed 0.9–1.6% recurrence rates in patients with undetectable Tg values and negative TgAb (24–26). Therefore, the false-negative frequency of serum Tg values in this study is similar to previous data. These false-negative results may indicate that TgAb levels below the cutoff value may interfere with the Tg assay. A change in tumor properties including histological dedifferentiation may result in false-negative results. Most recurrence in the present study was limited to the cervical area. However, patient 4 showed lung metastasis without elevated Tg and TgAb level after remnant ablation. She was diagnosed with metastasis of papillary thyroid carcinoma during work-up of an incidentally discovered small lung nodule found during admission for community-acquired pneumonia. This clinical situation is certainly unusual.

The prognostic value of TgAb is time-dependent. Previous reports showed that positive TgAb levels became converted to negative in most patients after 2–3 yr of follow up (10, 15). The number of patients with positive TgAb level might further decrease with time, and the recurrence-predictive value of TgAb could thus increase. However, the use of the TgAb value as a prognostic indicator would be more important within the first year after remnant ablation than after 3 yr. In this study, the positive recurrence-predictive value of TgAb2 was 17.9%, whereas that of TgAb1 was only 7.8%. Although the criteria for TgAb change were arbitrarily determined (such as a decrease of less than 50%, or increase from ablation to a time 6–12 months later), the positive predictive value of TgAb change was 28.6%. No clinicopathological factor other than a change in TgAb concentration was associated with recurrence or persistent disease in patients with undetectable Tg2 and positive TgAb2. All patients who showed rapid decreases (to less than 50% of initial levels) in concentrations of TgAb were disease-free. Most patients in the TgAb2-positive group with persistent disease were found to have increased TgAb concentrations. Therefore, we propose that measurement of the changing pattern of TgAb expression in the early postoperative period could be an important follow-up strategy for TgAb-positive patients provided the same TgAb assay method is used throughout the study. Recent guidelines state that Tg IMA methodology cannot be used when TgAb is present (3). In this situation, serial TgAb monitoring could be the primary surrogate tumor-marker test.

There were some limitations to this study. First, we did not check whether TgAb values less than 100U/ml could affect serum Tg measurements. We used only one TgAb assay method during the entire study period. We did not apply other manufacturers'

methods. Second, we did not distinguish cases where TgAb2 levels were obtained at 6 months from those where TgAb2 was measured at 12 months. If the TgAb level is declining, this change between initial measurement and TgAb2 may be greater if the measurement is performed 12 months after remnant ablation rather than 6 months thereafter. The period between ablation and the first DxWBS in this study varied from 6–12 months, although most of measurements were performed at 12 months. Therefore, we could not analyze any differences between data obtained 6 months or 12 months after remnant ablation. Third, we did not measure prethyroidectomy TgAb in all patients. The prethyroidectomy TgAb level would have been a more reliable control value than TgAb concentration at the time of remnant ablation because the TgAb concentration is likely to be unstable at the time of ^{131}I treatment, owing to opposing influences of decreased thyroid mass and acutely increased Tg during surgery. In this context, further work comparing prethyroidectomy TgAb levels and TgAb values in the early postoperative period is warranted. However, this is the first study on the prognostic value of the changing pattern of TgAb levels that used the same TgAb assay method throughout.

In conclusion, serum TgAb levels measured at 6–12 months after high dose ^{131}I remnant ablation during THW may be useful to predict recurrent or persistent disease in patients with undetectable Tg values. In DTC patients with undetectable Tg but positive TgAb levels, the change in TgAb concentrations measured between the time of remnant ablation and 6–12 months thereafter may be a novel prognostic indicator useful in the early postoperative period.

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