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ORIGINAL ARTICLE

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Dynamics of serum antithyroglobulin antibodies in patients with differentiated thyroid cancer

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Abstract

Purpose Serum antithyroglobulin antibodies (sTgAb) affect the reliability of Tg measurement in patients with thyroid cancer. We compared the outcome of patients with detectable and undetectable sTgAb, stratified according to the initial risk of recurrence (RR); also the response to treatment in patients with detectable sTgAb treated with total thyroidectomy (TT) with and without radioiodine remnant ablation (RA) and the sTgAb trend in the long-term follow-up according to the initial response.

Methods We included 432 patients submitted to TT, with or without RA; 106 patients had detectable sTgAb levels. Median follow-up was 53 months.

Results There were no statistically significant differences considering presentation between negative or positive sTgAb subjects. The frequency of structural incomplete response (SIR) in low, intermediate, and high RR was similar. Undetectable sTgAb in patients was achieved in a median of 16 months in ablated patients compared with 11 months in those without RA ($p = 0.0232$). Patients without RA had a higher rate of undetectable sTgAb during the first 12 months. A SIR was observed in 3% of patients with declining sTgAb, in 19% of those with stable levels, and in 43% with increasing sTgAb ($p = 0.004$). The status of no evidence of disease was achieved more frequently in patients with initial sTgAb levels < 200 mUI/l, independently of the initial RR.

Conclusions There was no impact of sTgAb on the initial clinical presentation and the response to therapy in low-risk patients treated with or without RA. sTgAb trend is more useful than an absolute value to predict a SIR.

Keywords Thyroid cancer · Antithyroglobulin antibodies · Risk of recurrence · Response to therapy · Ablation

Introduction

Differentiated thyroid carcinoma (DTC) has an excellent prognosis with 10-year survival rates of 85–93% [1]. Total thyroidectomy (TT) followed by radioiodine remnant ablation (RA) is the usual treatment for DTC; nowadays the therapy is selected according to the risk of recurrence (RR) [2–4]. After this initial approach, serum thyroglobulin (Tg) level is an important marker for identifying those cases with persistent or recurrent disease [5–7]. However, the reliability of serum Tg measurement is significantly impaired by coexistent serum antithyroglobulin antibodies (sTgAb) [8–11]. This concept is so well established that the last American Thyroid Association guidelines for the management of DTC include the Tg and TgAb measurement after initial treatment as an essential tool to assess the ongoing risk stratification [5].

Antithyroglobulin antibodies (TgAb) are produced by immune cells, mostly by lymphocytes that react against thyroid auto antigens and progressively infiltrate the thyroid gland [12]. It is also well known that ~30% of DTC patients have serum TgAb which might interfere with Tg measurement [13, 14], mainly causing false negative results when Tg is measured with immunometric assays, and either, false positive or negative results, when it is measured with radioimmunoassay [15, 16]. In these cases, serum Tg loses its value as a tumor marker, but the change in the TgAb levels over time can be used as a *surrogate* marker, since it has been demonstrated that if TgAb levels decline and become undetectable, together with an undetectable Tg level, it will be indicative of the no evidence of disease

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status [17, 18]. On the other hand, the persistence of stable TgAb levels for a long time, more than 3 or 4 years, represents an alert and might indicate the possibility of persistence or recurrence [19, 20]. It has been observed that TgAb levels disappear gradually with an average of 3 years' time after TT and RA, due to the removal of the Tg antigenic stimulus [18, 21, 22]. In contrast, there are few data about the change in TgAb levels over time in DTC patients treated with TT without RA.

Many studies have reported that the association between papillary thyroid cancer and Hashimoto's thyroiditis (HT) might be an indicator of favorable prognosis but it is unclear whether the presence of TgAb per se has a significant impact in outcomes [23–27].

The aims of this study were: (i) to compare the outcome of DTC patients with detectable and undetectable TgAb levels stratified according to the initial RR, (ii) to compare the response to therapy in patients with detectable TgAb treated with TT with and without RA, and (iii) to evaluate the dynamics of the TgAb levels trend in the long-term follow-up according to the initial response to therapy.

Patients and methods

Data source and study population

We retrospectively reviewed our database containing 549 files records of patients with DTC who were followed-up from January 2015 to February 2018 in the Division of Endocrinology, Hospital de Clinicas—University of Buenos Aires. Inclusion criteria were: (i) age older than 18 years, (ii) detectable serum TgAb levels at some point during the follow-up, (iii) adequate clinical and pathological data to allow an accurate determination of the initial RR, (iv) a minimum follow-up of 12 months after initial treatment with, at least two Tg/TgAb assessments, to define the initial response to therapy. Eighty-seven patients were excluded due to lack of enough time of follow-up (less than 12 months) and 30 patients due to insufficient data in the follow-up. One hundred and six (24.5%) patients of the remaining 432 had detectable serum TgAb levels. The initial treatment was TT for all patients, with or without the concomitant administration of radioiodine RA.

Each patient was stratified by using the eighth edition of the American Joint Committee on Cancer/International Union against Cancer (AJCC/UICC) staging system and the RR was assessed by using the modified risk stratification system from the 2009 ATA guidelines proposed by the American Thyroid Association (ATA) (low, intermediate, and high) [5, 28].

Pathologically lymphocytic thyroiditis

Pathologically proven lymphocytic thyroiditis 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.

Ablation protocol

The decision of RA with radioiodine was taken according to the usual behaviors established historically by the ATA guidelines [5, 29]. Two hundred and ninety-six patients received RA: 35 after stimulation with recombinant human thyrotropin (rhTSH) and 261 after thyroid hormone withdrawal for at least 3 weeks. Radioiodine was administered in all cases with TSH levels above 50 mIU/L. Administered radioiodine doses of ^{131}I ranged from 1.11–5.55 GBq (30–150 mCi ^{131}I). One hundred and thirty-six patients did not receive RA after surgery.

Serum thyroglobulin and antithyroglobulin antibody (TgAb) measurement

Serum Tg and TgAb were assessed in one of two reference laboratories from Argentina, the same laboratory and assay were used throughout patient's follow-up. Tg assay comprised the Elecsys Tg Electrochemiluminescence Immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). The functional sensitivity was 0.1 ng/ml. TgAb assay comprised the Elecsys Anti-Tg Electrochemiluminescence Immunoassay (RSR Ltd, Pentwyn, Cardiff, UK), values > 20 IU/ml were considered positive, in accord with the manufacturer's recommendations.

Dynamics of change in TgAb levels

In patients who had at least two assessments of Tg and TgAb levels during the first year of follow-up, the trend of TgAb levels over time was calculated according to the following definitions:

- Increase: elevation of TgAb levels more than 50%.
- Stability: fluctuating TgAb levels or either elevation or decrease less than 50%.
- Decrease: decrease of TgAb levels more than 50%.
- Undetectability: at some point during the follow-up.

Response to therapy

The initial response to therapy were assessed based on serum Tg and TgAb measurements, neck ultrasonography (US), diagnostic whole-body scans (dxWBS), and additional morphological/functional images when appropriate. Patients were considered to have an excellent response (ER) to therapy if they had undetectable suppressed Tg values or a stimulated Tg < 1 ng/ml, absence of TgAb, no uptake outside thyroid bed dxWBS (if done), and no suspicious lymph or thyroid bed nodules on neck US. Patients with stimulated serum Tg between 1 and 10 ng/mL or non-stimulated Tg values between 0.2 and 1 ng/mL and no structural evidence of disease or nonspecific findings in the neck US or other cross-sectional images, or with persistent measurable TgAb, were considered as having an indeterminate response (IR). Patients with stimulated serum Tg > 10 ng/mL or nonstimulated Tg levels > 1 ng/mL, or those with increasing TgAb without structural evidence of disease, were classified as having a biochemical incomplete response. Patients with structural incomplete response (SIR) were those showing positive cytology or histology, highly suspicious findings on neck US or findings on dxWBS, and functional or morphological imaging suggesting DTC metastasis.

According to the clinical status at the end of follow-up, patients were classified as having no evidence of disease (NED) if they had undetectable suppressed Tg values or a stimulated Tg < 1 ng/ml, undetectable TgAb, ultrasonographically no suspicious findings, and no evidence of structural disease on any other imaging studies. The remaining group of patients was classified as having an indeterminate, biochemical, or SIR by using the same definitions that were described above. Recurrent disease was defined as having structural or biochemical evidence of disease following a period of NED.

Clinical management during follow-up

Each patient was assessed with Tg and TgAb measurements under hormonal therapy, and neck US every 6 months after initial treatment. Thyroid US was performed using a 13-MHz linear transducer. Central and bilateral neck lymph node compartments and the superior mediastinum were inspected. Suspected lesions were evaluated by US-guided fine needle aspiration cytology (FNAC) and measurement of Tg and TgAb in washing fluid.

In patients with a biochemical incomplete response during the follow-up, morphological or functional imaging was performed. These studies included US, computed tomography (CT), magnetic resonance imaging (MRI), and/or nuclear imaging procedures such as whole-body scans after a diagnostic or therapeutic radioiodine dose or the use of positron emission tomography/CT using fluorine-18 fluorodeoxyglucose (^{18}F-FDG-PET/CT scan). After initial therapy, all patients received hormonal therapy to keep a TSH level according to the RR and response to therapy during the follow-up according to the ATA guidelines.

Statistical analysis

Epidemiological data are presented as the mean ± SEM, with median and range when appropriate. For categorical variables, the number and percent of patients and/or scans within each category was determined. The categorical variables were compared by Pearson Chi-square and the continuous variables by the Mann–Whitney U test. A p value < 0.05 was considered statistically significant. All statistical operations were performed using the Stata 14.1 (Stata Corp, TX, and USA). The Kaplan–Meier method with the log-rank test was used to analyze time to undetectable TgAb. Hazard ratios (HR) and confidence intervals using log-rank analysis were also calculated. Univariate and multivariate cox proportional hazards model were used using time to NED as the outcome variable these results were expressed as the HR with a 95% confidence interval. The initial risk was considered as a covariate.

Results

Patient's characteristics

The demographic and clinical features of the 432 patients included in this study can be observed in Table 1. The majority had the classic variant of papillary thyroid carcinoma (94.2%); they were female (81.7%) and were AJCC stage I (81.3%). According to the ATA RR classification, patients were considered as having low (53.7%), intermediate (26.8%), or high RR (19.4%). The median follow-up in the whole cohort was 53 months (range: 12–354; mean 51 ± 41). There were no statistically significant differences when baseline characteristics were compared in patients with negative and positive TgAb, except for the presence of lymphocytic thyroiditis, as expected (Table 1).

Response to treatment and status at final follow-up in patients with negative and positive antithyroglobulin antibodies according to the initial risk stratification system of the American Thyroid Association

The frequency of SIR after the initial treatment was 6.5% ($n = 15$), 20% ($n = 23$), and 69% ($n = 58$) in low, intermediate, and high RR, respectively. There were no

Table 1 Baseline characteristics of 432 patients with differentiated thyroid cancer included in the study

	Antithyroglobulin antibodies			
	Total ($n = 432$)	Negative ($n = 326$)	Positive ($n = 106$)	p
Sex (n, %)				
Female	353 (81.7)	258 (79.1)	92 (86.8)	0.1858[b]
Male	79 (18.3)	68 (20.9)	14 (13.2)	
Age (years)				
Mean (SD)	48 (±15)	49 (±15)	48 (±15)	0.313[a]
Median (range)	50 (18–96)	52 (18–95)	46 (18–85)	
Age at diagnosis of DTC (years)				
Mean (SD)	45 (±16)	42 (±16)	43 (±15)	0.6279[a]
Median (range)	45 (4–90)	45 (5–91)	42 (13–77)	
Histology (n, %)				
Papillary	407 (94.2)	304 (93.3)	103 (97.2)	0.339[b]
Follicular	16 (3.7)	14 (4.3)	2 (1.9)	
Hürthle cell carcinoma	9 (2.1)	8 (2.4)	1 (0.9)	
Stage at diagnosis (8th) (n, %)				
I	351 (81.2)	266 (81.6)	85 (80.2)	0.3128[b]
II	56 (13)	39 (12)	17 (16)	
III	10 (2.3)	9 (2.7)	1 (1)	
IV	15 (3.5)	12 (3.7)	3 (2.8)	
Tumor size (cm)				
Mean (SD)	2.20 (±1.78)	2.23 (±1.84)	2.12 (±1.59)	0.552[a]
Median (range)	1.6 (0.1–13.5)	1.6 (0.2–13.5)	1.55 (0.1–8)	
Lymphocytic thyroiditis (n, %)	126 (29.2)	70 (21.5)	56 (52.8)	0.000[b]
Risk of recurrence (n, %)				
Low	232 (53.7)	179 (54.9)	53 (50)	0.1304[b]
Intermediate	116 (26.9)	80 (24.5)	36 (33.9)	
High	84 (19.4)	67 (20.6)	17 (16.1)	
Radioiodine remnant ablation (RA) (n, %)				
With RA	296 (68.5)	217 (66.6)	79 (74.5)	0.128[b]
Without RA	136 (31.5)	109 (33.4)	27 (25.5)	
Cumulative radioiodine dose (mCi)				
Mean (SD)	268 (±250)	271 (±263)	243 (±231)	0.331[b]
Median (range)	200 (30–1510)	200 (30–1510)	150 (30–1230)	
Time of follow-up (months)				
Median (range)	53 (12–354)	50 (12–354)	59 (12–210)	0.255[a]

SD standard deviation, *DTC* differentiated thyroid cancer, *TgAb* antithyroglobulin antibodies

[a]p values were determined by the Mann–Whitney U test

[b]p values were determined by the χ^2 test

statistically significant differences between patients with positive and negative TgAb (Table 2a–c).

Patients with low, intermediate, and high RR with positive and negative TgAb had similar frequency of SIR at the end of follow-up (Table 2a–c). As expected, patients with detectable TgAb classified as having low and intermediate RR, had less frequency of ER and higher percentages of IR at the initial evaluation and at the end of follow-up (Table 2a, b). The percentage of distant metastases and additional treatments were similar in patients with positive and negative TgAb in all groups of recurrence (Table 2a–c).

Antithyroglobulin antibodies trend and radioiodine RA

Low-risk patients treated with or without RA achieved the same frequencies of SIR or excellent responses both initially and at 36 months of follow-up. As the median follow-

Table 2 Response to treatment and status at final follow-up in patients with negative and positive antithyroglobulin antibodies

(a) Low-risk patients

		Antithyroglobulin antibodies		
	Total ($n = 232$)	Positive ($n = 53$)	Negative ($n = 179$)	p
Initial response to treatment (n, %)				
Excellent response[c]	131 (56.5)	15 (28.3)	116 (64.8)	0.000[b]
Indeterminate response[c]	70 (30.2)	32 (60.4)	38 (21.2)	
Biochemical incomplete	16 (6.8)	5 (9.4)	11 (6.2)	
Structural incomplete	15 (6.5)	1 (1.9)	14 (7.8)	
Structural disease detected during follow-up	7 (3)	3 (5.7)	4 (2.2)	0.200[b]
Structural disease on initial assessment and during follow-up	22 (9.4)	4 (7.5)	18 (10)	0.5316[b]
Clinical status at final follow-up (n, %)				
NED[c]	167 (72)	28 (52.8)	139 (77.7)	0.000[b]
Indeterminate[c]	56 (24.2)	24 (45.3)	32 (17.8)	
Biochemical incomplete	3 (1.3)	1 (1.9)	2 (1.1)	
Structural incomplete	6 (2.5)	0	6 (3.4)	
Time of follow-up (months)				0.4108[a]
Median (range)	47 (12–278)	45 (12–210)	49 (12–278)	

(b) Intermediate risk patients

		Antithyroglobulin antibodies		
	Total ($n = 116$)	Positive ($n = 36$)	Negative ($n = 80$)	p
Initial response to treatment (n, %)				
Excellent response[c]	28 (24)	3 (8.3)	25 (31.3)	0.002[b]
Indeterminate response[c]	39 (33.6)	19 (52.8)	20 (25)	
Biochemical incomplete	26 (22.4)	10 (27.8)	16 (20)	
Structural incomplete	23 (20)	4 (11.1)	19 (23.7)	
Structural disease detected during follow-up (n, %)	19 (16.3)	7 (19.4)	12 (15)	0.464[b]
Structural disease on initial assessment and during follow-up (n, %)	42 (36)	11 (30.6)	31 (38.7)	0.578[b]
Clinical status al final follow-up (n, %)				
NED[c]	47 (40.5)	13 (36.1)	34 (42.5)	0.973[b]
Indeterminate[c]	32 (27.6)	10 (27.8)	22 (27.5)	
Biochemical incomplete	16 (13.8)	6 (16.7)	10 (12.5)	
Structural incomplete	21 (18.1)	7 (19.4)	14 (17.5)	
Time of follow-up (months)				0.2553[a]
Median (range)	58 (12–248)	60 (12–160)	57 (12–248)	

(c) High risk patients

		Antithyroglobulin antibodies		
	Total ($n = 84$)	Positive ($n = 17$)	Negative ($n = 67$)	p
Initial response to treatment (n, %)				
Excellent response	2 (2.4)	0	2 (3)	0.148[b]
Indeterminate response	11 (13.1)	5 (29.4)	6 (9)	
Biochemical incomplete	13 (15.5)	2 (11.8)	11 (16.4)	
Structural incomplete	58 (69)	10 (58.8)	48 (71.6)	
Structural disease detected during follow-up (n, %)	4 (4.8)	1 (5.9)	3 (4.5)	0.808[b]
Structural disease on initial assessment and during follow-up (n, %)	62 (73.8)	11 (64.7)	51 (76.1)	0.316[b]

Table 2 (continued)

(c) High risk patients

		Antithyroglobulin antibodies		
	Total ($n = 84$)	Positive ($n = 17$)	Negative ($n = 67$)	p
Clinical status at final follow-up (n, %)				
NED	10 (11.9)	2 (11.8)	8 (12)	0.948[b]
Indeterminate	12 (14.2)	3 (17.6)	9 (13.4)	
Biochemical incomplete	13 (15.5)	2 (11.8)	11 (16.4)	
Structural incomplete	49 (58.4)	10 (58.8)	39 (58.2)	
Time of follow-up (months)				0.6926[a]
Median (range)	57 (12–354)	71 (12–166)	43 (11–354)	

NED no evidence of disease

[a]p values were determined by the Mann–Whitney U test

[b]p values were determined by the χ^2 test

[c]Groups with statistically different outcomes

up of patients treated without RA was 27 months (range 16–42), it was not possible to compare the responses between these groups beyond 36 months of follow-up (Table 3).

Undetectable TgAb levels in patients treated with RA were achieved in a median of 16 months (range 11–62) *vs.* 11 months (range 6–21) in patients treated without RA ($p = 0.0232$). The trend of TgAb levels in the first 12 months was clearly different: non-ablated patients had a higher rate of undetectable levels while patients who received RA showed a more stable TgAb concentration during follow-up (Fig. 1).

Antithyroglobulin antibodies levels at first postoperative evaluation

The median initial TgAb levels were 127 IU/ml (range: 0–3320). According to the RR, the values were: 116 IU/ml (range: 0–2000) in low RR patients, 182 IU/ml (range: 25–3320) in intermediate RR patients, and 96 IU/ml (range: 0–640) in high RR patients ($p = 0.617$). The initial mean levels in patients with SIR were 480 IU/ml (±420 IU/ml) and in patients without SIR 280 IU/mL (±36 IU/ml) ($p = 0.098$). The initial TgAb levels did not correlate with the presence of SIR at the initial assessment. In the ROC curve we observed that there was not a specific TgAb level which might predict the presence of SIR to treatment (Fig. 2).

Antithyroglobulin antibodies trend during the first year of follow-up in patients without apparent clinical disease ($n = 70$)

Patients with an initial structural incomplete disease were excluded for this analysis. A SIR at the end of follow-up was observed in the 3% of patients with decreasing TgAb levels, in the 19% with stable levels, and in the 43% of patients with increasing levels. Therefore, the status of no evidence of disease was achieved in 51.5% of patients with decreasing TgAb levels, in 31% of those with stable values while in none with increasing levels. The optimal cutoff value of the TgAb at 12 months of follow-up to predict a SIR as final status was established at 160 IU/ml, with a sensitivity (S) of 75% and a specificity (E) of 71.9%. A TgAb level lower than 38 IU/ml predicted an undetectable outcome at some point of the follow-up with an S of 90% and an E of 74%. Consequently, the TgAb trend was more useful than an absolute value of TgAb at the initial assessment or at the first year of follow-up to predict the final outcome.

Discussion

The incidence of TgAb is approximately twofold higher in DTC patients, especially in papillary thyroid carcinoma [30, 31], compared with the general population (20% *vs.* 10%, respectively), suggesting an association between autoimmune thyroid disease and DTC [8, 13, 21, 32–34]. Indeed, many studies reported an association between HT and DTC [14, 31, 35–37].

There were controversial reports about the relationship between lymphocytic thyroiditis and anti-TgAb with the outcome in DTC patients [23–27]. In general, lymphocytic thyroiditis is considered a favorable prognostic factor for papillary thyroid cancer (longer disease-free survival and decreased mortality), although this has not always achieved statistical significance using multivariate analysis [23–26, 31, 38, 39]. Lymphocytic thyroiditis is highly correlated

Table 3 Baseline characteristics and comparison of the responses to therapy in patients with detectable TgAb with and without radioiodine remnant ablation

	Radioiodine remnant ablation (RA)		
	Without RA ($n = 23$)	With RA ($n = 30$)	p
Sex (n, %)			
Female	18 (78.3)	27 (90)	0.237[b]
Male			
Age (years)			
Median (range)	42 (27–69)	44 (29–76)	0.2697[a]
Histology (n, %)			
Papillary	22 (95.7)	30 (100)	0.249[b]
Follicular	1 (4.3)	0	
Lymphocytic thyroiditis (n, %)	17 (56.7)	14 (60.9)	0.741[b]
Initial TgAb median (range)	9.7 (0–100)	4.9 (0–59)	0.1435[a]
TgAb trend at 12 months (n, %)			
Undetectable	5 (21.7)	1 (3.3)	0.006[b]
Decreased	14 (60.9)	15 (50)	
Stable	1 (4.3)	6 (20)	
Increased	3 (20.1)	2 (6.7)	
Unknown	0	6 (20)	
Initial response to treatment *(n, %)*			
Excellent response	8 (34.8)	7 (23.4)	0.610[b]
Indeterminate response	15 (65.2)	21 (70)	
Biochemical incomplete	0	1 (3.3)	
Structural incomplete	0	1 (3.3)	
Clinical status at 36 months of follow-up (n, %)			
NED	8 (34.8)	9 (30)	0.442[b]
Indeterminate	15 (65.2)	19 (63.3)	
Biochemical incomplete	0	0	
Structural incomplete	0	2 (6.7)	
Time to undetectable TgAb (at 36 months)			
Median (range)	11.25 (6–21)	16 (11–36)	0.0232[a]
Time of follow-up (months)			
Median (range)	27 (16–42)	82 (27–210)	

RA radioiodine remnant ablation, *TgAb* antithyroglobulin antibodies, *NED* no evidence of disease

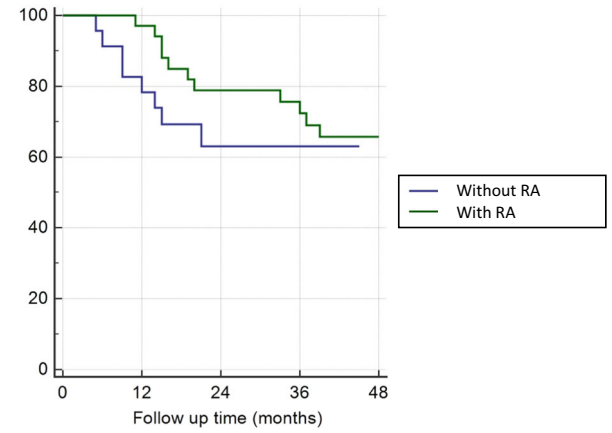
[a]p values were determined by the Mann–Whitney U test

[b]p values were determined by the χ^2 test

with the serological presence of thyroid antibodies; however, whether the presence of TgAb per se has prognostic significance remains controversial [14, 21, 36, 40, 41]. Our study compared the outcome of DTC patients with detectable and undetectable TgAb levels, taking into account not only the initial RR, but also the response to therapy. The frequency of SIR in patients with detectable and undetectable TgAb levels of low, intermediate, and high RR was similar, not reaching statistical significant differences.

In the last years, the use of radioiodine RA has been reconsidered, and currently, a rather large number of DTC patients are not treated with radioiodine [5]. In these cases, the change of the serum Tg levels over the time, more than its absolute value (undetectable or detectable), still represents a strong tumor marker [6, 7]. At the same time, the persistence of stable levels of TgAb for a long period or the increase of TgAb levels after TT and RA represent an alert indicating the possibility of persistence or recurrence of the disease [19, 20].

While the use of TgAb trend as a *surrogate* marker has been recognized as a valuable tool in patients treated with TT and RA [19], few data has been reported about the changes of TgAb levels in patients treated with TT without RA [42, 43]. The disappearance of the antigenic stimulus (i.e., the absence of any thyroid tissue) induces a progressive reduction and ultimately a disappearance of thyroid antibody production, although the survival of a substantial fraction of plasma cells can be responsible of a temporary



RA: radioiodine remnant ablation; NED: no evidence of disease

Fig. 1 Kaplan–Meier curve: time to undetectable antithyroglobulin antibodies in low-risk patients with and without radioiodine remnant ablation

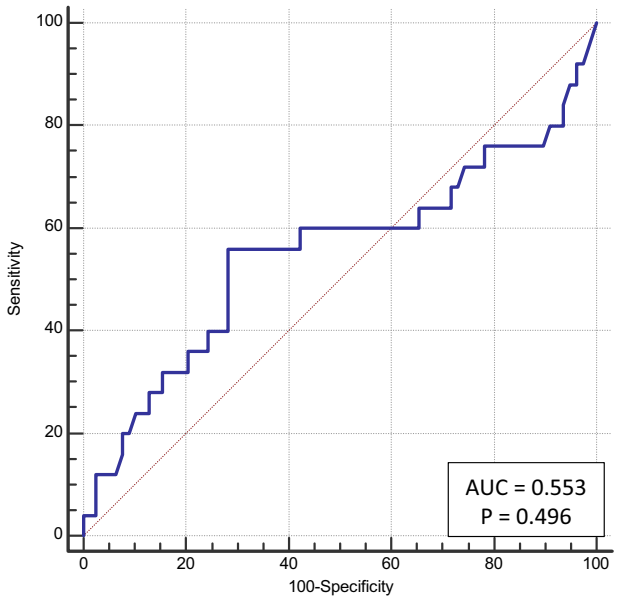


Fig. 2 Correlation of antithyroglobulin antibodies levels at first post-operative evaluation in patients with structural incomplete response during follow-up

persistence of humoral immunity [44]. The question of whether the presence of a normal postoperative thyroid remnant could maintain the stimulus for the antibody production, thus affecting the disappearance of the serum TgAb, has not been clarified yet. As a consequence, the positivity of TgAb levels in the follow-up of patients with DTC and positive TgAb treated with TT but without RA represents a matter of concern. We compared the response to therapy in low-risk patients with detectable TgAb levels treated with TT with and without RA; both groups achieved the same initial and final response to treatment. However, TgAb became negative in a longer period in patients treated with RA and the trend of TgAb levels in the first 12 months was significantly different: more patients treated without RA had undetectable TgAb levels while those ablated patients had a higher proportion of stable TgAb levels during this period. This situation was also reported in a previous study [20]. Transient increases or stable levels in TgAb concentration can occur after ^{131}I therapy and a prolonged period may be necessary for their return to baseline concentrations [18, 19]. It is now clear that removing the Tg antigenic stimulus by TT and RA results in the eventual disappearance of TgAb over a median time of 3 years [18, 21, 22]. Conversely, TgAb concentrations may rise, or become detectable *de novo*, in response to an acute increase in Tg antigen after either the initial or secondary thyroid surgeries [45], FNA biopsy [46, 47], or radioiodine therapy [30, 48, 49]. More importantly, a high number of studies have reported that the de novo appearance, persistence, or a rising trend in TgAb concentrations in the postoperative period is a significant risk factor for persistent/recurrent disease [8, 19, 21, 32, 50, 51].

Accordingly, we found that the initial TgAb levels did not correlate with the presence of SIR and TgAb trend is more useful than the absolute value of TgAb at the initial assessment or at the year of the follow-up.

One of the strengths of our study was the evaluation of the dynamics of TgAb in patients treated without RA compared with those who had received it, and we observed that TgAb became undetectable earlier in the first group of patients. However, there are several limitations in our study, such as its retrospective design, the low number of patients in each of the individual groups when they were divided by the presence of TgAb and RR, in addition to the short follow-up of the cohort.

In summary, our study shows that the prognosis of DTC in patients with detectable and undetectable TgAb is similar, even after considering the initial RR. RA influences the trend of TgAb during the first year of follow-up, but not the response to therapy at the end of follow-up when the RR is considered. Our study confirms previous data regarding the usefulness of the TgAb trend, which can be surely used as a surrogate marker, and that it is more useful than an absolute TgAb value to predict a structural incomplete response to therapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Institutional Review Board.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. S.A. Hundahl, I.D. Fleming, A.M. Fremgen, H.R. Menck, A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the US, 1985–1995. Cancer **83**, 2638–2648 (1998)
2. R.M. Tuttle, H. Tala, J. Shah, R. Leboeuf, R. Ghossein, M. Gonen, M. Brokhin, G. Omry, J.A. Fagin, A. Shaha, Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid **20**, 1341–1349 (2010)
3. M.G. Castagna, F. Maino, C. Cipri, V. Belardini, A. Theodoropoulou, G. Cevenini, F. Pacini, Delayed risk stratification, to include the response to initial treatment (surgery and radioiodine ablation), has better outcome predictivity in differentiated thyroid cancer patients. Eur. J. Endocrinol. **165**, 441–446 (2011)
4. F. Pitoia, F. Jerkovich, C. Urciuoli, A. Schmidt, E. Abelleira, F. Bueno, G. Cross, R.M. Tuttle, Implementing the modified 2009 American Thyroid Association risk stratification system in thyroid cancer patients with low and intermediate risk of recurrence. Thyroid **25**, 1235–1242 (2015)
5. B.R. Haugen, E.K. Alexander, K.C. Bible, G. Doherty, S.J. Mandel, Y.E. Nikiforov, F. Pacini, G.W. Randolph, A.M. Sawka, M. Schlumberger, K.G. Schuff, S.I. Sherman, J.A. Sosa, D.L. Steward, R.M. Tuttle, L. Wartofsky, American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid **26**, 1–133 (2015)
6. C. Durante, T. Montesano, M. Attard, M. Torlontano, F. Monzani, G. Costante, D. Meringolo, M. Ferdeghini, S. Tumino, L. Lamartina, A. Paciaroni, M. Massa, L. Giacomelli, G. Ronga, S. Filetti, Long-term surveillance of papillary thyroid cancer patients who do not undergo postoperative radioiodine remnant ablation: is there a role for serum thyroglobulin measurement? J. Clin. Endocrinol. Metab. **97**, 2748–2753 (2012)
7. L. Kashat, S. Orlov, D. Orlov, J. Assi, F. Salari, P.G: Walfish, Serial post-surgical stimulated and unstimulated highly sensitive thyroglobulin measurements in low and intermediate-risk papillary thyroid carcinoma patients not receiving radioactive iodine. Endocrine **54**, 460–466 (2016)
8. J.K. Chung, Y.J. Park, T.Y. Kim, Y. So, S.K. Kim, D.J. Park, D.S. Lee, M.C. Lee, B.Y. Cho, Clinical significance of elevated level of serum antithyroglobulin antibody in patients with differentiated thyroid cancer after thyroid ablation. Clin. Endocrinol. **57**, 215–221 (2002)
9. S. Mariotti, G. Barbesino, P. Caturegli, M. Marino, L. Manetti, F. Pacini, R. Centoni, A. Pinchera, Assay of thyroglobulin in serum with thyroglobulin autoantibodies: an unobtainable goal? J. Clin. Endocrinol. Metab. **80**, 468–472 (1995)
10. C.A. Spencer, L.M. Bergoglio, M. Kazarosyan, S. Fatemi, J.S. LoPresti, Clinical impact of thyroglobulin (Tg) and Tg autoantibody method differences on the management of patients with differentiated thyroid carcinomas. J. Clin. Endocrinol. Metab. **90**, 5566–5575 (2005)
11. C. Spencer, I. Petrovic, S. Fatemi, Current thyroglobulin autoantibody (TgAb) assays often fail to detect interfering TgAb that can result in the reporting of falsely low/undetectable serum Tg IMA values for patients with differentiated thyroid cancer. J. Clin. Endocrinol. Metab. **96**, 1283–1291 (2011)
12. F. Latrofa, D. Ricci, L. Montanelli, R. Rocchi, P. Piaggi, E. Sisti, L. Grasso, F. Basolo, C. Ugolini, A. Pinchera, P. Vitti, Lymphocytic thyroiditis on histology correlates with serum thyroglobulin autoantibodies in patients with papillary thyroid carcinoma: impact on detection of serum thyroglobulin. J. Clin. Endocrinol. Metab. **97**, 2380–2387 (2012)
13. F. Pacini, S. Mariotti, N. Formica, R. Elisei, S. Anelli, E. Capotorti, A. Pinchera, Thyroid autoantibodies in thyroid cancer: incidence and relationship with tumour outcome. Acta Endocrinol. **119**, 373–380 (1988)
14. E. Fiore, T. Rago, F. Latrofa, M.A. Provenzale, P. Piaggi, A. Delitala, M. Scutari, F. Basolo, G. Di Coscio, L. Grasso, A. Pinchera, P. Vitti, Hashimoto's thyroiditis is associated with papillary thyroid carcinoma: role of TSH and of treatment with L-thyroxine. Endocr. Relat. Cancer **18**, 429–437 (2011)
15. F. Latrofa, D. Ricci, E. Sisti, P. Piaggi, C. Nencetti, M. Marino, P. Vitti, Significance of low levels of thyroglobulin autoantibodies associated with undetectable thyroglobulin after thyroidectomy for differentiated thyroid carcinoma. Thyroid **26**, 798–806 (2016)
16. C. Spencer, I. Petrovic, S. Fatemi, J. LoPresti, Serum thyroglobulin (Tg) monitoring of patients with differentiated thyroid cancer using sensitive (second-generation) immunometric assays can be disrupted by false-negative and false-positive serum thyroglobulin autoantibody misclassifications. J. Clin. Endocrinol. Metab. **99**, 4589–4599 (2014)
17. F.A. Verburg, M. Luster, C. Cupini, L. Chiovato, L. Duntas, R. Elisei, U. Feldt-Rasmussen, H. Rimmele, E. Seregni, J.W. Smit, C. Theimer, L. Giovanella, Implications of thyroglobulin antibody positivity in patients with differentiated thyroid cancer: a clinical position statement. Thyroid **23**, 1211–1225 (2013)
18. L. Chiovato, F. Latrofa, L.E. Braverman, F. Pacini, M. Capezzone, L. Masserini, L. Grasso, A. Pinchera, Disappearance of humoral thyroid autoimmunity after complete removal of thyroid antigens. Ann. Intern. Med. **139**, 346–351 (2003)
19. W.G. Kim, J.H. Yoon, W.B. Kim, T.Y. Kim, E.Y. Kim, J.M. Kim, J.S. Ryu, G. Gong, S.J. Hong, Y.K. Shong, Change of serum antithyroglobulin antibody levels is useful for prediction of clinical recurrence in thyroglobulin-negative patients with differentiated thyroid carcinoma. J. Clin. Endocrinol. Metab. **93**, 4683–4689 (2008)
20. Y. Tsushima, A. Miyauchi, Y. Ito, T. Kudo, H. Masuoka, T. Yabuta, M. Fukushima, M. Kihara, T. Higashiyama, Y. Takamura, K. Kobayashi, A. Miya, T. Kikumori, T. Imai, T. Kiuchi, Prognostic significance of changes in serum thyroglobulin antibody levels of pre- and post-total thyroidectomy in thyroglobulin antibody-positive papillary thyroid carcinoma patients. Endocr. J. **60**, 871–876 (2013)
21. R. Gorges, M. Maniecki, W. Jentzen, S.N. Sheu, K. Mann, A. Bockisch, O.E. Janssen, Development and clinical impact of thyroglobulin antibodies in patients with differentiated thyroid carcinoma during the first 3 years after thyroidectomy. Eur. J. Endocrinol. **153**, 49–55 (2005)
22. D. Thomas, V. Liakos, E. Vassiliou, F. Hatzimarkou, A. Tsatsoulis, P. Kaldrimides, Possible reasons for different pattern disappearance of thyroglobulin and thyroid peroxidase autoantibodies in patients with differentiated thyroid carcinoma following total thyroidectomy and iodine-131 ablation. J. Endocrinol. Investig. **30**, 173–180 (2007)
23. K.C. Loh, F.S. Greenspan, F. Dong, T.R. Miller, P.P. Yeo, Influence of lymphocytic thyroiditis on the prognostic outcome of patients with papillary thyroid carcinoma. J. Clin. Endocrinol. Metab. **84**, 458–463 (1999)
24. B. Singh, A.R. Shaha, H. Trivedi, J.F. Carew, A. Poluri, J.P. Shah, Coexistent Hashimoto's thyroiditis with papillary thyroid carcinoma: impact on presentation, management, and outcome. Surgery **126**, 1070–1076 (1999)

25. E. Kebebew, P.A. Treseler, P.H. Ituarte, O.H. Clark, Coexisting chronic lymphocytic thyroiditis and papillary thyroid cancer revisited. World J. Surg. **25**, 632–637 (2001)
26. K. Kashima, S. Yokoyama, S. Noguchi, N. Murakami, H. Yamashita, S. Watanabe, S. Uchino, M. Toda, A. Sasaki, T. Daa, I. Nakayama, Chronic thyroiditis as a favorable prognostic factor in papillary thyroid carcinoma. Thyroid **8**, 197–202 (1998)
27. C. Ugolini, F. Basolo, A. Proietti, P. Vitti, R. Elisei, P. Miccoli, A. Toniolo, Lymphocyte and immature dendritic cell infiltrates in differentiated, poorly differentiated, and undifferentiated thyroid carcinoma. Thyroid **17**, 389–393 (2007)
28. M.B. Amin, S. Edge, F. Greene, D.R. Byrd, R.K. Brookland, M. K. Washington, J.E. Gershenwald, C.C. Compton, K.R. Hess, D. C. Sullivan, J.M. Jessup,J.D. Brierley, L.E. Gaspar, R.L. Schilsky, C.M. Balch, D.P. Winchester, E.A. Asare, M. Madera, D.M. Gress, L.R. Meyer (Eds), *AJCC Cancer Staging Manual*, 8th edn. (Springer, New York, 2017)
29. D.S. Cooper, G.M. Doherty, B.R. Haugen, R.T. Kloos, S.L. Lee, S.J. Mandel, E.L. Mazzaferri, B. McIver, F. Pacini, M. Schlumberger, S.I. Sherman, D.L. Steward, R.M. Tuttle, Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid **19**, 1167–1214 (2009)
30. A. Kumar, D.H. Shah, U. Shrihari, S.R. Dandekar, U. Vijayan, S. M. Sharma, Significance of antithyroglobulin autoantibodies in differentiated thyroid carcinoma. Thyroid **4**, 199–202 (1994)
31. S.L. Souza, L.V. Montalli Da Assumpção, L.S. Ward, Impact of previous thyroid autoimmune diseases on prognosis of patients with well-differentiated thyroid cancer. Thyroid **13**, 491–495 (2003)
32. C.A. Spencer, M. Takeuchi, M. Kazarosyan, C.C. Wang, R.B. Guttler, P.A. Singer, S. Fatemi, J.S. LoPresti, J.T. Nicoloff, Serum thyroglobulin autoantibodies: prevalence, influence on serum thyroglobulin measurement and prognostic significance in patients with differentiated thyroid carcinoma. J. Clin. Endocrinol. Metab. **83**, 1121–1127 (1998)
33. J.G. Hollowell, N.W. Staehling, W.D. Flanders, W.H. Hannon, E. W. Gunter, C.A. Spencer, L.E. Braverman, Serum thyrotropin, thyroxine, and thyroid antibodies in the United States population (1988 to 1994): NHANES III. J. Clin. Endocrinol. Metab. **87**, 489–499 (2002)
34. U. Feldt-Rasmussen, A.K. Rasmussen, Autoimmunity in differentiated thyroid cancer: significance and related clinical problems. Hormones **9**, 109–117 (2010)
35. S.D. Larson, L.N. Jackson, T.S. Riall, T. Uchida, R.P. Thomas, S. Qiu, B.M. Evers, Increased incidence of well-differentiated thyroid cancer associated with Hashimoto thyroiditis and the role of the PI3k/Akt pathway. J. Am. Coll. Surg. **204**, 764–775 (2007)
36. H.S. Kim, Y.J. Choi, J.S. Yun, Features of papillary thyroid microcarcinoma in the presence and absence of lymphocytic thyroiditis. Endocr. Pathol. **21**, 149–153 (2010)
37. K.W. Kim, Y.J. Park, E.H. Kim, S.Y. Park, J. Park do, S.H. Ahn, J. Park do, H.C. Jang, B.Y. Cho, Elevated risk of papillary thyroid cancer in Korean patients with Hashimoto's thyroiditis. Head. Neck. **33**, 691–695 (2011)
38. S. Gupta, A. Patel, A. Folstad, C. Fenton, C.A. Dinauer, R.M. Tuttle, R. Conran, G.L. Francis, Infiltration of differentiated thyroid carcinoma by proliferating lymphocytes is associated with improved disease-free survival for children and young adults. J. Clin. Endocrinol. Metab. **86**, 1346–1354 (2001)
39. E.Y. Kim, W.G. Kim, W.B. Kim, T.Y. Kim, J.M. Kim, J.S. Ryu, S.J. Hong, G. Gong, Y.K. Shong, Coexistence of chronic lymphocytic thyroiditis is associated with lower recurrence rates in patients with papillary thyroid carcinoma. Clin. Endocrinol. **71**, 581–586 (2009)
40. F. Consorti, M. Loponte, F. Milazzo, L. Potasso, A. Antonaci, Risk of malignancy from thyroid nodular disease as an element of clinical management of patients with Hashimoto's thyroiditis. Eur. Surg. Res. **45**, 333–337 (2010)
41. E.S. Kim, D.J. Lim, K.H. Baek, J.M. Lee, M.K. Kim, H.S. Kwon, K.H. Song, M.I. Kang, B.Y. Cha, K.W. Lee, H.Y. Son, Thyroglobulin antibody is associated with increased cancer risk in thyroid nodules. Thyroid **20**, 885–891 (2010)
42. O. Yamada, A. Miyauchi, Y. Ito, A. Nakayama, T. Yabuta, H. Masuoka, M. Fukushima, T. Higashiyama, M. Kihara, K. Kobayashi, A. Miya, Changes in serum thyroglobulin antibody levels as a dynamic prognostic factor for early-phase recurrence of thyroglobulin antibody-positive papillary thyroid carcinoma after total thyroidectomy. Endocr. J. **61**, 961–965 (2014)
43. A. Ernaga-Lorea, M.C. Hernandez-Morhain, E. Anda-Apinaniz, J. J. Pineda-Arribas, I. Migueliz-Bermejo, N. Eguilaz-Esparza, A. Irigaray-Echarri, Prognostic value of change in anti-thyroglobulin antibodies after thyroidectomy in patients with papillary thyroid carcinoma. Clin. Transl. Oncol. **20**, 740–744 (2017)
44. M.K. Slifka, R. Antia, J.K. Whitmire, R. Ahmed, Humoral immunity due to long-lived plasma cells. Immunity **8**, 363–372 (1998)
45. U. Feldt-Rasmussen, M. Blichert-Toft, C. Christiansen, J. Date, Serum thyroglobulin and its autoantibody following subtotal thyroid resection of Graves' disease. Eur. J. Clin. Investig. **12**, 203–208 (1982)
46. S.A. Polyzos, A.D. Anastasilakis, Alterations in serum thyroid related constituents after thyroid fine-needle biopsy: a systematic review. Thyroid **20**, 265–271 (2010)
47. S. Benvenga, L. Bartolone, S. Squadrito, F. Trimarchi, Thyroid hormone autoantibodies elicited by diagnostic fine needle biopsy. J. Clin. Endocrinol. Metab. **82**, 4217–4223 (1997)
48. U. Feldt-Rasmussen, K. Bech, J. Date, P.H. Petersen, K. Johansen, A prospective study of the differential changes in serum thyroglobulin and its autoantibodies during propylthiouracil or radioiodine therapy of patients with Graves' disease. Acta Endocrinol. **99**, 379–385 (1982)
49. I.G. Rubio, M.N. Silva, M. Knobel, R. Romão, R. Possato, E.M. Gebrin, C. Buchpiguel, G. Medeiros-Neto, Peripheral blood levels of thyroglobulin mRNA and serum thyroglobulin concentrations after radioiodine ablation of multinodular goiter with or without pre-treatment with recombinant human thyrotropin. J. Endocrinol. Investig. **30**, 535–540 (2007)
50. J.H. Seo, S.W. Lee, B.C. Ahn, J. Lee, Recurrence detection in differentiated thyroid cancer patients with elevated serum level of antithyroglobulin antibody: special emphasis on using (18) F-FDG PET/CT. Clin. Endocrinol. **72**, 558–563 (2010)
51. A. Adil, R.A. Jafri, A. Waqar, S.A. Abbasi, A.H. Matiul-Haq Asghar, A. Jilani, I. Naz, Frequency and clinical importance of anti-Tg auto-antibodies (ATG). J. Coll. Physicians Surg. Pak. **13**, 504–506 (2003)