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Time trends of thyroglobulin antibody in ablated papillary thyroid carcinoma patients: Can we predict the rate of negative conversion?

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ABSTRACT

Objectives: Persistence of thyroglobulin antibody (TgAb) in patients with papillary thyroid carcinoma (PTC) years after total thyroidectomy (TT) followed by ablation occurs even without any evidence of structural disease. Few studies have studied the natural course of TgAb positivity and factors that may influence this course. The present study evaluated the time trends of TgAb in ablated PTC patients and aimed to identify the predictive factors for the rate of negative conversion of TgAb.

Materials and methods: Overall, 1279 patients who underwent TT and subsequent ablation for PTC, with available data on thyroid peroxidase Ab (TPOAb) and TgAb prior to surgery (preop-) and ablation (abl-) were enrolled. Patients with initial distant metastasis or recurrence during follow-up were excluded.

Results and conclusion: Preop-TgAb was positive in 24.9% of patients (n = 319), whereas abl-TgAb positivity decreased to 12.8% (n = 164). In 164 patients positive for abl-TgAb, TgAb in patients with higher abl-TgAb levels decreased more gradually than those observed in patients with lower abl-TgAb levels ($p < 0.001$). Furthermore, in patients within the same range of abl-TgAb levels, patients positive for abl-TPOAb had a higher rate of negative conversion of TgAb compared with negative patients for abl-TPOAb (log rank $p < 0.001$). TPOAb significantly increased the rate of negative conversion in multivariate analysis adjusted for abl-TgAb (odds ratio 1.59, 95% confidence interval 1.11–2.28, $p = 0.011$). This study clearly showed that abl-TgAb titers and abl-TPOAb status can predict the rate of negative conversion. These findings can guide the optimal timing for additional examination in patients positive for TgAb during follow-up.

Introduction

Persistence of thyroglobulin antibody (TgAb) during follow-up in patients with differentiated thyroid carcinoma (DTC) after complete removal of the thyroid tissue is a challenge for clinicians since TgAb can interfere with thyroglobulin (Tg) measurement which is the most sensitive marker for remnant thyroid [1,2]. TgAb is present in 17%–25% of patients with DTC [3–5] and is an important factor for assessing the dynamic risk stratification, as proposed by Tuttle et al. [6] and adopted by the guidelines of the American Thyroid Association [7]. According to this classification, patients with DTC who underwent total thyroidectomy (TT) followed by radioiodine (RAI) ablation and are positive for TgAb exhibit prognoses similar to those observed between the "excellent response" and "structural incomplete response" groups. However, long-term data regarding the natural course of TgAb titers in these patients (i.e., the disappearance of TgAb and factors affecting the

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timing of negative conversion) are limited.

Previous studies have reported that a median of 2–3 years is required for negative conversion of TgAb [8,9]. The thyroid gland is the only source of Tg and TgAbs are mostly produced by lymphocytes infiltrating the gland; therefore, complete elimination of the thyroid tissue by TT and subsequent RAI ablation of the remnant thyroid tissue results in a progressive decline in TgAb levels and eventually its disappearance [8,9]. However, certain patients may remain positive for TgAb years after ablation even in the absence of evidence of structural disease (no evidence of structural disease, NESD). There are evidences that increased or stationary TgAb titers may be associated with persistence/recurrence of thyroid cancer [4,10–12]. However, there is no consensus on whether or when to performe extensive and/or frequent imaging investigations to detect evidence for structural disease in patients persistently positive for TgAb during follow-up. To clarify this issue, the present study evaluated the time trends of TgAb in patients with papillary thyroid carcinoma (PTC) and NESD, who previously underwent TT and subsequent RAI ablation and aimed to identify predictive factors for the rate of negative conversion of TgAb.

Materials and methods

Study design and patients

This single-center, retrospective study included patients with ≥1 cm PTC who underwent TT and subsequent RAI ablation from 2007 to 2012 at the Asan Medical Center, Seoul, Korea. Patients with available data on the levels of preoperative TgAb (preop-TgAb), preoperative TPOAb (preop-TPOAb), TgAb at the time of ablation (abl-TgAb), and TPOAb at the time of ablation (abl-TPOAb) were selected. Those with initial distant metastasis or structural persistent/recurrent disease detected during follow-up (median 5 years) were excluded from the study (Fig. 1). A total of 1279 patients were eligible for analysis. The protocol of this study was approved by the Institutional Review Board of the Asan Medical Center (study number: 2017-0559) and patient consent was waived because of the retrospective design and use of only unidentified clinicopathological information.

Definitions.

Preop-TPOAb and preop-TgAb were defined as TPOAb or TgAb titer checked within 3 months prior to surgery. Abl-TgAb and abl-TPOAb were TgAb and TPOAb titers measured within 5 days prior to RAI ablation. Following surgery, TgAb levels were routinely measured in all patients every 6–12 months. Changes between the preop-TgAb and abl-TgAb levels were classified into two groups: increase or decrease of less than half versus decrease of more than half.

NESD was defined as absence of evidence of disease based on physical examination and imaging studies (e.g., neck ultrasound or computed tomography) at the end of follow-up regardless of the serum Tg levels, as previously reported [13].

Classification of patients

Patients were classified into five groups according to their pattern of change between the preop-TgAb and abl-TgAb levels: group A, remain positive with an increase or decrease of less than half in the TgAb titer; group B, remain positive with a decrease of more than half; group C, negative conversion; group D, positive conversion; and group E, negative at both measurements (Fig. 1).

Patients positive for abl-TgAb (groups A, B, and D) were categorized further according to abl-TgAb levels: group 1, 60 U/mL ≤ abl-TgAb < 100 U/mL; group 2, 100 U/mL ≤ abl-TgAb < 250 U/mL; and group 3, abl-TgAb ≥ 250 U/mL.

Laboratory measurements

The TgAb levels were determined using a radioimmunoassay (BRAHMS anti-Tgn RIA) and a value of ≥60 U/mL was designated as the minimum threshold denoting positivity. The functional sensitivity of this assay (20% interassay variation coefficient) was below 20 U/mL, while the analytical sensitivity from the optimal curve was 5.5 U/mL. The intra-assay and interassay variation coefficients were 2.0% and 3.1%, respectively. In addition, TPOAb levels were measured using a radioimmunoassay (BRAHMS anti-TPOn RIA) and a value of ≥60 U/mL was again considered positive. The functional sensitivity of this assay was below 30 U/mL, and analytical sensitivity was 5.5 U/mL. The

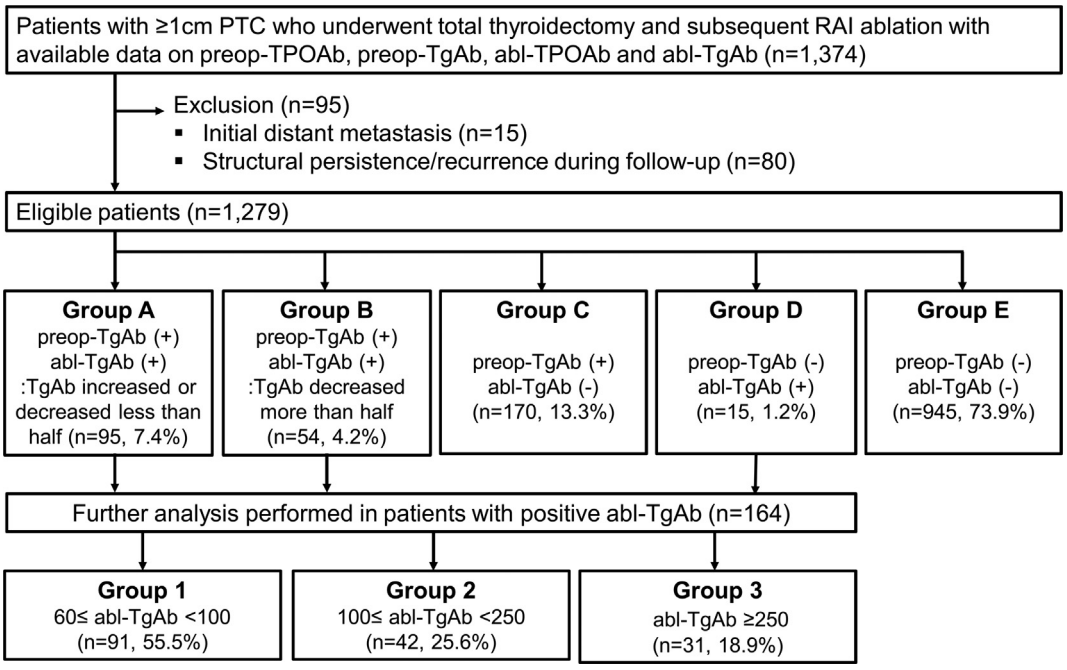

Fig. 1. Distribution of patients included in this study.

intra-assay and interassay variation coefficients were 2.9% and 3.9%, respectively.

Statistical analysis

R version 3.5.0 and the R libraries survival, survminer, car, Cairo, and dplyr were used for data analysis (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org). Continuous variables are presented as medians with interquartile ranges or mean with standard deviation, analyzed using the Mann–Whitney *U* test or *t*-test, respectively. Categorical variables are presented as numbers with percentages and were compared using Pearson's χ^2 test. TgAb positivity curves were constructed using the Kaplan–Meier method and variables associated with the negative conversion of TgAb were evaluated using the Cox proportional hazard models. A p-value < 0.05 denoted statistical significance.

Results

Patterns of change in TgAb levels prior to and after surgery

Approximately 24.9% of the overall patient population were positive for preop-TgAb (319/1279 patients in groups A, B, and C). During ablation, positivity for preop-TgAb rapidly decreased to 12.8% (164/1279 patients in groups A, B, and D). Fig. 2 illustrates the pattern of change between preop-TgAb and abl-TgAb levels in patients belonging to groups A to D. Approximately half of the patients positive for preop-TgAb showed negative conversion of TgAb at the time of ablation, whereas a very small portion of patients (1.2%) showed positive conversion. Further analyses were performed in 164 patients belonging to groups A, B, and D, aiming to evaluate the time trends of TgAb in patients positive for TgAb following thyroidectomy.

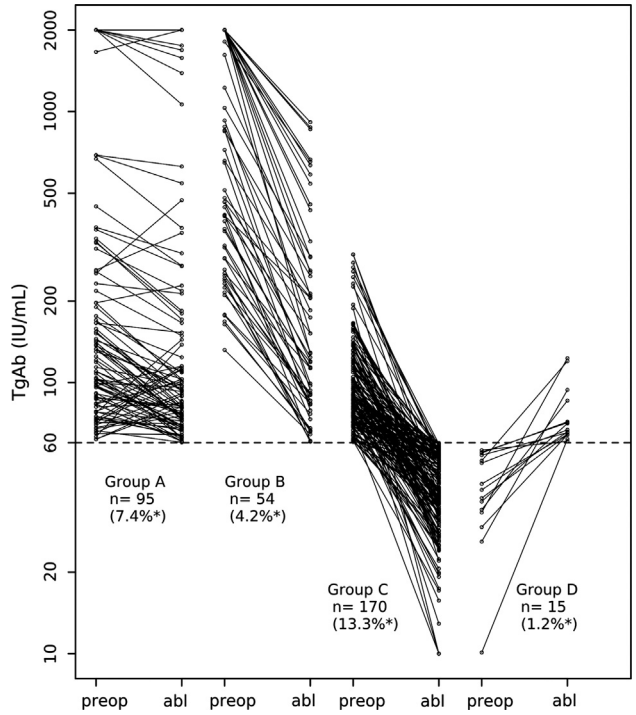

Fig. 2. Patterns of change between the preop-TgAb titer and levels of abl-TgAb: group A, remain positive with an increase or decrease of less than half; group B, remain positive with a decrease of more than half; group C, negative conversion; and group D, positive conversion. The proportion of patients positive for preop-TgAb was 23.6% (group A + group B + group C), and that of patients positive for abl-TgAb was 11.9% (group A + group B + group D). *Calculated from the total number of patients (n = 1297) Abbreviations: preop, preoperative; abl, ablation.

Table 1
Baseline characteristics of patients positive for ablation-TgAb.

	abl-TgAb			*p*-value
	Group 1 < 100 U/mL (n = 91)	Group 2 100–250 U/mL (n = 42)	Group 3 ≥250 U/mL (n = 31)	
Age (years)	47.1 ± 13.2	45.3 ± 11.0	45.7 ± 11.6	0.479
Sex (female)	81 (89.0%)	36 (85.7%)	29 (93.5%)	0.571
Primary tumor size (cm)	1.5 (1.2–2.0)	1.5 (1.2–1.8)	1.5 (1.4–2.0)	0.754
Interval between TT and ablation (months)	2.7 (1.6–3.8)	2.0 (1.5–3.7)	2.6 (1.8–3.5)	0.444
Tg at ablation (ng/mL)				0.134
< 1.0	77 (84.6%)	40 (95.2%)	29 (93.5%)	
1.0–1.9	8 (8.8%)	0 (0%)	0 (0%)	
2.0–10.0	6 (6.6%)	2 (4.8%)	2 (6.5%)	
CLT	67 (73.6%)	27 (64.3%)	23 (74.2%)	0.502
T stage				0.791
T1	79 (76.0%)	48 (82.8%)	22 (73.3%)	
T2	22 (21.2%)	8 (13.8%)	7 (23.3%)	
T3	3 (2.9%)	2. (3.4%)	1 (3.3%)	
N stage				0.131
N0	24 (26.4%)	15 (35.7%)	9 (29.0%)	
N1a	48 (52.7%)	20 (47.6%)	10 (32.3%)	
N1b	19 (20.9%)	7 (16.7%)	12 (38.7%)	
RAI dose (mCi)				0.556
30	19 (20.9%)	11 (26.2%)	5 (16.1%)	
80	30 (33.0%)	11 (26.2%)	7 (22.6%)	
150	42 (46.2%)	20 (47.6%)	19 (61.3%)	

Abbreviations: CLT, chronic lymphocytic thyroiditis; TT, total thyroidectomy; Tg, thyroglobulin; RAI, radioactive iodine; mCi, millicurie.
T and N stages were determined according to the Eighth Edition of the staging system established by the American Joint Committee on Cancer Tumor, Nodes, and Metastasis (AJCC TNM).

Baseline clinicopathological characteristics in patients positive for abl-TgAb

Table 1 summarizes the baseline clinicopathological characteristics of 164 patients positive for abl-TgAb according to abl-TgAb levels defined earlier in this article. Most of the patients were females with a median primary tumor size of 1.5 cm. The interval between TT and RAI ablation ranged 2.0–2.7 months and was not different between the groups (p = 0.444). Most patients had Tg level below 1.0 ng/mL at the time of ablation. The proportions of concurrent chronic lymphocytic thyroiditis (CLT), T stage, N stage, and dosage of RAI ablation did not differ among the three groups.

Serial changes in TgAb levels according to abl-TgAb

Fig. 3A shows the time trends of TgAb from the date of ablation observed in 164 patients. Although all patients had NESD and the majority showed negative conversion of TgAb during the follow-up, patients positive for TgAb several years after treatment were also reported. Fig. 3B offers a more detailed analysis of the rate of negative conversion using Kaplan–Meier curves according to three ranges of ablation-TgAb titers in groups 1–3. Significant difference was observed between the groups in the rate of negative conversion with patients in group 1 having highest rate and patients in group 3 the lowest (log rank $p < 0.001$).

The median time for negative conversion of TgAb in 50% of patients in groups 1, 2, and 3 was 0.6, 0.8, and 3.3 years, respectively (Table 2). Accordingly, the median time for negative conversion of TgAb in 90% of patients was 2.1, 3.7, and 5.5 years, respectively. Patients in groups 1 and 2 had a higher rate of negative conversion (odds ratio [OR] 3.57,

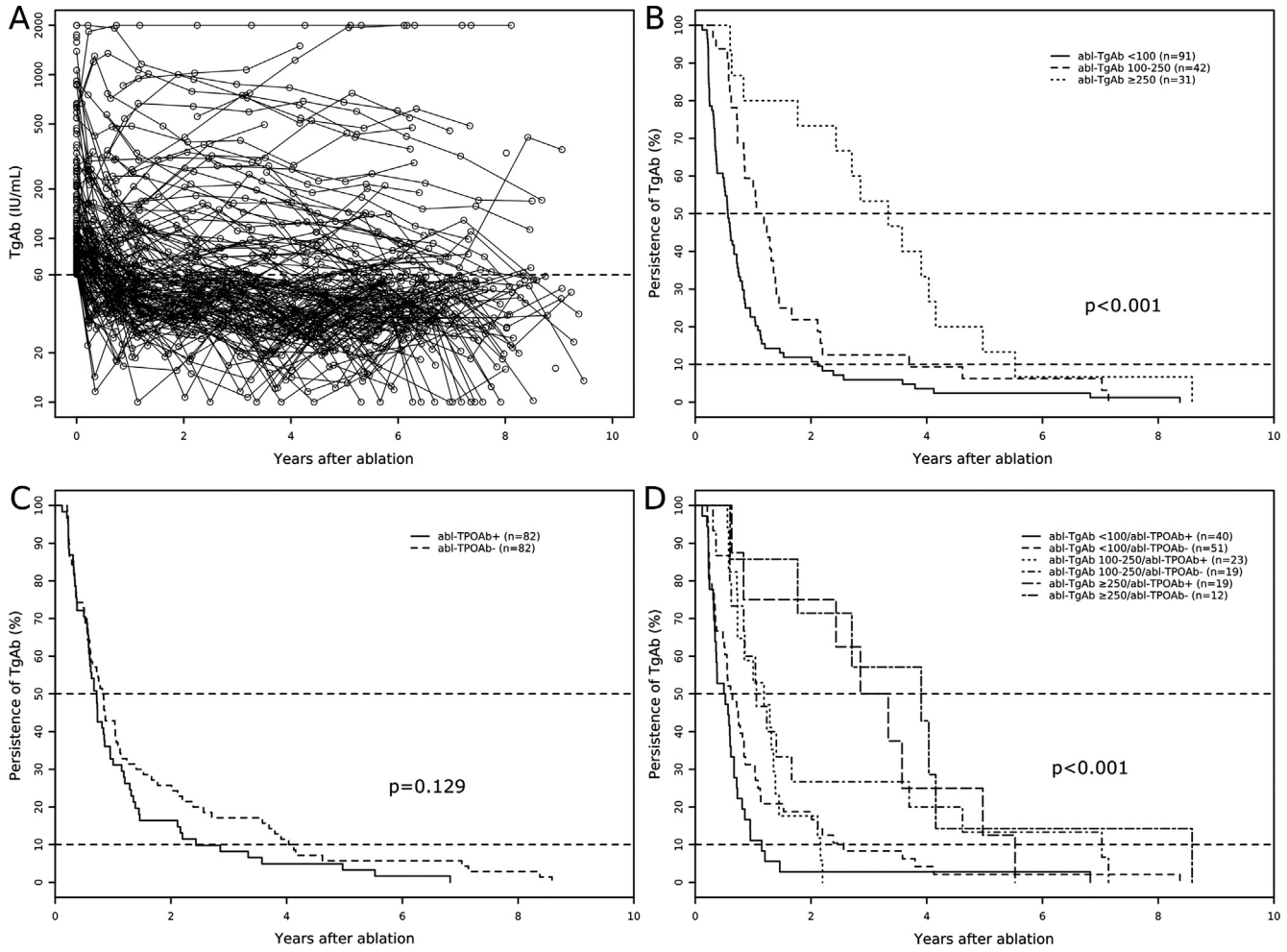

Fig. 3. (a) Time trends of the TgAb titer during the follow-up. Kaplan–Meier curves for the rate of negative conversion of TgAb according to (b) abl-TgAb, (c) abl-TPOAb, and (d) both abl-TgAb and abl-TPOAb levels.

95% confidence interval [CI] 2.00–6.39, p < 0.001 for group 1; OR 1.92, 95% CI 1.02–3.64, p = 0.004 for group 2) than those in group 3 (Fig. 4).

Impact of abl-TPOAb levels on the rate of negative conversion of TgAb

Changes in TgAb levels were evaluated according to the abl-TPOAb status. The median time for negative conversion of TgAb in patients with positive and negative abl-TPOAb status was 0.7 and 0.8 years for 50% of patients and 2.4 and 4.1 years for 90% of patients, respectively. As shown in Fig. 3C, according to the abl-TPOAb status, the rate of negative conversion did not show any difference between the two groups (OR 1.31, 95% CI 0.92–1.87, p = 0.129).

However, the results were different when the statuses of abl-TgAb

Table 2
Impact of abl-TgAb and abl-TPOAb on the rate of negative conversion of TgAb.

	N	N of NC	Median years for NC in 50% patients	Median years for NC in 90% patients	Odds ratio for negative conversion (95% CI)	*p*-value
abl-TgAb						
abl-TgAb < 100 U/mL	91	84 (92.3%)	0.6	2.1	3.57 (2.00–6.39)	< 0.001
abl-TgAb 100–250 U/mL	42	32 (76.2%)	0.8	3.7	1.92 (1.02–3.64)	0.044
abl-TgAb ≥ 250 U/mL	31	15 (48.4%)	3.3	5.5	1.0 (Ref)	–
abl-TPOAb						
Negative	82	61 (74.4%)	0.7	2.4	1.0 (Ref)	–
Positive	82	70 (85.4%)	0.8	4.1	1.31 (0.92–1.87)	0.129
abl-TgAb/abl-TPOAb						
abl-TgAb < 100/abl-TPOAb+	40	36 (90.0%)	0.5	1.1	6.10 (2.51–14.83)	< 0.001
abl-TgAb < 100/abl-TPOAb-	51	48 (94.1%)	0.6	2.6	3.69 (1.56–8.72)	0.003
abl-TgAb 100–250/abl-TPOAb+	23	17 (73.9%)	1.2	2.2	2.97 (1.14–7.71)	0.025
abl-TgAb 100–250/abl-TPOAb-	19	15 (78.9%)	1.1	7.0	1.93 (0.74–5.01)	0.175
abl-TgAb ≥ 250/abl-TPOAb+	19	8 (42/1%)	2.8	5.5	1.41 (0.49–4.11)	0.522
abl-TgAb ≥ 250/abl-TPOAb-	12	7 (58.3%)	3.9	8.6	1.0 (Ref)	–

Abbreviations: NC, negative conversion; CI, confidence interval.

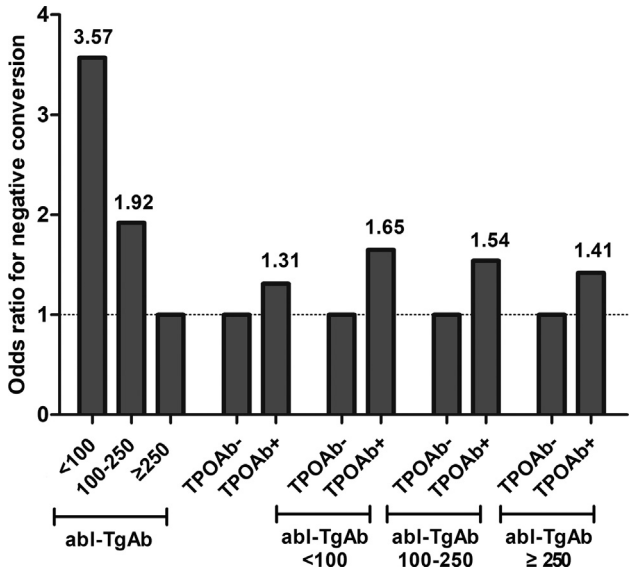

Fig. 4. Odds ratio for negative conversion of TgAb.

and abl-TPOAb were considered together to determine the rate of negative conversion. Fig. 3D shows the Kaplan–Meier curve for TgAb positivity in the following six groups: (a) abl-TgAb < 100 U/mL and positive for abl-TPOAb (abl-TPOAb+), (b) abl-TgAb < 100 U/mL and negative for abl-TPOAb (abl-TPOAb-), c) abl-TgAb 100–250 U/mL and abl-TPOAb+, (d) abl-TgAb 100–250 U/mL and abl-TPOAb-, (e) abl-TgAb ≥ 250 U/mL and abl-TPOAb+, and (f) abl-TgAb ≥ 250 U/mL and abl-TPOAb-. As shown in Fig. 3D and Table 2, the median time for negative conversion in 50% of patients within the same range of abl-TgAb levels were similar according to the abl-TPOAb status. However, the rate differed gradually over time and the median time for negative conversion in 90% of patients within the same range of abl-TgAb levels showed a significant difference between patients positive for abl-TPOAb and those negative for abl-TPOAb. Positive patients for abl-TPOAb had a higher rate of negative conversion of TgAb compared with negative patients as shown in Fig. 4. Differences in the rate of negative conversion were statistically significant among the six groups (log rank $p < 0.001$). Multivariate analysis, adjusted for abl-TgAb, indicated an independent role of abl-TPOAb in the rate of negative conversion of TgAb (OR 1.59, 95% CI 1.11–2.28, $p = 0.011$).

Discussion

This retrospective study of patients with PTC, treated with TT and subsequent RAI ablation and having NESD, examined the time trends of TgAb after surgery and revealed differences in the time required for negative conversion, initially based on abl-TgAb levels. Although the time for negative conversion of TgAb in 90% of patients positive for abl-TgAb with levels < 100 U/mL was 2.1 years, a median of 5.5 years was required in patients with abl-TgAb levels ≥ 300 U/mL. In other words, 10% of patients with abl-TgAb levels ≥300 U/mL may be positive for TgAb up to 5.5 years after ablation even in the absence of structural disease. This finding indicated that a certain length of time is required for the disappearance of TgAb, especially when the initial levels are high and that watchful waiting prior to performing extensive imaging studies can be a reasonable option for them. However, most patients with positive but low abl-TgAb levels are converted to negative TgAb status in approximately 2 years. Therefore, attention should be paid to TgAb levels persisting several years after treatment in these patients. An important basic premise for this conclusion is that TgAb trends were monitored using the same method since TgAb assays display substantial inter-method variability and sensitivity limits also vary widely [14].

Although the status of TPOAb (the most sensitive marker for the detection of CLT) [15] was not associated with the rate of negative conversion, it significantly lowered the TgAb positivity when considered together with abl-TgAb. The differences in the median time required for negative conversion in 90% of patients within the same range of abl-TgAb levels but with different abl-TPOAb status were considerable (8.6 years for patients with abl-TgAb levels ≥250 U/mL and abl-TPOAb- status versus 5.5 years for patients with abl-TgAb levels ≥250 U/mL and abl-TPOAb + status). As much as 7.5 years of difference in median time required for negative conversion in 90% of patients between those with abl-TgAb < 100/abl-TPOAb + and abl-TgAb ≥ 250/abl-TPOAb- were noted even in the absence of evidence for any structural diseases. Taken together, by measuring the TgAb titers and identifying the status of TPOAb at the time of ablation, the clinicians can estimate the time required for negative conversion of TgAb and thus decide when to perform extensive imaging work-up in patients with persistently positive TgAb.

To the best of our knowledge, this is the first study indicating TPOAb as a predictive factor for the rate of negative conversion. Although still elusive, the rapid negative conversion observed in patients positive for TPOAb may be related to the different qualitative properties in thyroid autoantibodies, as proposed by Lazarus et al. [16]. They reported that TgAb showed different patterns in epitope reactivity (restricted and unrestricted) among patients with DTC. Patients with the restricted pattern had significantly higher rates of persistent/recurrent disease compared with those with the unrestricted pattern. These results indicate that TgAb epitope restriction may be a prognostic factor. The investigators stated that epitope-restricted TgAbs may target more aggressive Tg molecules with thyroid growth-promoting properties. In contrast, unrestricted TgAbs may represent a physiological response to the release of Tg after surgery or ablation of the thyroid tissue, exerting a beneficial effect through binding and clearing excess Tg from the immune system. This interpretation may be adopted for the results of the present study, as we hypothesize that TgAb in patients positive for TPOAb may have an unrestricted epitope pattern, with levels decreasing more rapidly after complete removal of the thyroid tissue. Further studies are warranted to assess this hypothesis.

Positivity for preoperative TgAb in the present study was observed in 23.6% of patients (279/1607), which is consistent with previously reported rates (17%–25%) [3–5]. However, this prevalence decreased to 11.9% shortly after surgery, which is similar to the prevalence reported in the general population (approximately 10%) [17]. This two-fold increase in the prevalence of TgAb in patients with DTC may be attributed to several factors including female predominance [5,10,18], enhanced presentation of thyroid antigens to the immune system [3], and a higher incidence of concurrent CLT [19,20]. A small portion of patients (1.2%) experienced positive conversion of TgAb during the post-surgical period; this may be a transient rise as an apparent immune reaction to surgery [9]. Recent studies have established that changes in TgAb levels correlate with the course of DTC. Increased or stationary TgAb levels indicate possible structural persistent/recurrent disease [4,10–12] whereas, decreased levels may indicate successful treatment [21]. Although attention should be paid in patients with increased titers of TgAb for disease recurrence, consideration of the abl-TgAb levels may be helpful in avoiding unnecessary extensive imaging examination in this setting.

Matrone et al. recently reported changing trends of TgAb in patients with DTC without RAI ablation [22]. The results of that study revealed that TgAb levels decreased progressively in these patients and that the initial postoperative TgAb levels influenced the time required for negative conversion of TgAb. These findings are in agreement with those of the present study. In addition, the extent of lymphocytic infiltration–not investigated in the current study other than the fact of coexistence–had a significant impact on the time required for TgAb disappearance in the cited study. However, the results of this study did not identify the predictive role of TPOAb on the rate of negative conversion of TgAb.

In this study, serial changes in TgAb levels were evaluated over a relatively long period by using the same TgAb assay in a homogeneous cohort of patients with complete removal of the thyroid tissue. We excluded all patients with initial distant metastasis and recurrence during follow-up to focus on the TgAb trends in patients with NSED. There are many previous studies reporting about the association between the TgAb status and the prognosis in patients with differentiated thyroid carcinoma [4,10–12]. However, by focusing on patients with NSED, our study was able to provide detailed data on how much time is required for the negative conversion of TgAb even in the absence of structural disease. Nevertheless, we cannot eliminate the false-negative cases (no evidence of recurrence found, although structural disease exits) which need further follow-up. Another strength for this study is that, for the first time, we determined the median time required for negative conversion of TgAb in 50% and 90% of patients separately, and according to different TgAb and TPOAb levels during ablation, revealing a predictive significance. A limitation of the present study is the lack of data on the serial postoperative TPOAb levels during the entire duration of the follow-up as routine measurement of postoperative TPOAb is not recommended by current standards. Also, although high and similar prevalence of CLT was found in patients of group 1 to 3, the evaluation of the degree of lymphocytic infiltration at histology was not available in this study which TPOAb is correlated with, and could give more information about the relationship with prognosis. Other potential limitation is that since we applied the cut-off value of 60 U/mL to define TgAb positivity as addressed by our assay and as previous studies applied [10,23], we could not eliminate the possible interference with Tg measurement at TgAb levels between 20 U/mL (functional sensitivity) and 60 U/mL [24].

In conclusion, this study, focusing on the patients with complete removal of the thyroid tissue and NESD, examined the patterns of serial change in the levels of TgAb and revealed that higher abl-TgAb levels required a longer period for negative conversion. Furthermore, the status of abl-TPOAb was shown to influence the rate of negative conversion by 3–5 years. The variation in time until the disappearance of TgAb according to TgAb and TPOAb levels at the time of ablation should be taken into consideration during follow-up to determine the optimal timing for additional examination in patients persistently positive for TgAb.

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Declaration of interest

The authors declare no potential conflict of interest.

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