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Prognostic value of preoperative anti-thyroglobulin antibody in differentiated thyroid cancer

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Summary

Context: The coexistence of differentiated thyroid cancer (DTC) and thyroid autoimmune disease could represent a better or worse prognosis. This study investigated the prognostic importance of preoperative anti-thyroglobulin antibody (TgAb) in DTC patients.

Design and patients: This retrospective hospital-cohort study enrolled 1171 consecutive DTC patients with preoperative TgAb data, who underwent total thyroidectomy between January 2006 and December 2011. Clinical parameters studied included demographics, primary tumour characteristics, radioiodine therapy, thyroid function tests, preoperative thyroglobulin (Tg) and TgAb levels, and cancer persistence/recurrence.

Results: A total of 254 (21.7%) patients were preoperatively TgAb positive. The percentage positive for thyroid peroxidase (TPO) antibody and lymphocytic thyroiditis was significantly higher in the TgAb-positive group. The TgAb-positive group had a significantly higher rate of lymphatic invasion and lymph node metastasis both overall and in patients without TPOAb and lymphocytic thyroiditis (non-HT group). The mean number of total and central lymph nodes dissected and rate of lateral lymph node dissection were significantly higher in the TgAb-positive group, both overall and in non-HT patients. In regression analysis, preoperative TgAb was an independent risk factor for lateral lymph node metastasis. Over 50.2±14.5 months of follow-up, disease persistence/recurrence was not significantly different between patients with and without TgAb, both overall and in non-HT patients. Preoperative TgAb showed no significant correlation with final disease status.

Conclusion: Positive preoperative serum TgAb is associated with worse primary tumour characteristics but rarely showed poor prognosis, probably due to more aggressive treatment of these subjects.

KEYWORDS

anti-thyroglobulin, Hashimoto's disease, lymph node metastasis, thyroid cancer, thyroidectomy

1 | INTRODUCTION

The incidence of differentiated thyroid cancer (DTC) is about 15.1 cases per 100 000 in 2013 and approximately 1.2 per cent of men and women will be diagnosed with thyroid cancer at some point during their lifetime, based on 2011-2013 data according to SEER Cancer Statistics Review, 1975-2013.[1] Measurement of serum thyroglobulin (Tg), a representative biochemical biomarker of DTC, could be affected

by the presence of the anti-thyroglobulin antibody (TgAb), which falsely lowers or elevates serum Tg levels and reduces the usefulness of serum Tg for the prediction of recurrent disease. The level of TgAb is higher in DTC patients (20%)[2,3] than in the general population (10%), suggesting a potential association between autoimmune thyroid disease and DTC.[4-9] A previous report showed that the frequency of TgAb-positive status is twofold higher in DTC patients than in patients with benign nodules.[10]

It is generally accepted that positive TgAb status occurs in Hashimoto's thyroiditis (HT)[11] and that pathologically proven HT associated with thyroid cancer has a favourable prognosis, compared to thyroid cancer without thyroiditis.[5,8,12] On the other hand, patients with high TgAb levels after total thyroidectomy and/or remnant radioiodine ablation (RRA) for DTC may have a poor prognosis during follow-up,[13,14] suggesting a unique prognostic role for TgAb in DTC patients, different from that observed in HT.

It is unclear whether high TgAb levels in some DTC patients before surgery were derived from pathologically diagnosed thyroiditis associated with DTC or from immunologic responses to thyroglobulin antigens generated by DTC. It was reported that different TgAb epitopes are associated with a less favourable prognosis in DTC patients[15] but there are few studies on the prognosis of patients with high TgAb levels before thyroidectomy.[16] The American Thyroid Association (ATA) guideline revised in 2015 recommends against measurement of TgAb before surgery in DTC patients because of limited data and no available evidence of preoperative TgAb significance.[17] One study based on a nationwide multicenter registry of thyroid cancer showed no significant association with stage of disease, disease-free survival, or overall survival, but provided no detailed clinical information.[16]

Thus, the value of assessment of TgAb at the time of diagnosis as a surrogate prognostic marker requires further clinical study. This study investigated the prognostic significance of TgAb status at the time of DTC diagnosis.

2 | SUBJECTS AND METHODS

2.1 | Patients

Subjects met the following inclusion criteria before study enrolment: (i) confirmed primary DTC after thyroidectomy; (ii) measurement of thyroid stimulating hormone (TSH), Tg, and TgAb before total or near-total thyroidectomy; (iii) a follow-up period of more than 3 years for prognostic evaluation, because high TgAb levels tended to decline to a normal range.[7,18] A diagnosis of HT was based on the presence of thyroid peroxidase antibody (TPOAb) or pathologic confirmation of lymphocytic thyroiditis.[19] Non-HT was defined as the absence of TPOAb and lymphocytic thyroiditis. Recent TgAb+ was defined as a positive TgAb at the most recent evaluation. Risk stratification of the DTC patients was performed using the revised ATA guidelines.[17] Low risk was classified as the patient who has no remnant tumour, no local or distant metastasis, no vascular invasion, and no evidence of metastatic foci on the first post-treatment whole body scan (WBS). Intermediate risk was classified as the patient who has microscopic invasion or metastatic foci on the first post-treatment WBS or aggressive histology, or vascular invasion. High risk was classified as the patient who has tumour with gross extrathyroidal extension, incomplete resection, distant metastasis or elevated postoperative serum thyroglobulin. Initially, 1229 consecutive patients with DTC were screened at a tertiary referral hospital between December 2005 and December 2011. Fifty-eight were excluded due to history of other malignancy. A total 1171 were evaluated according to the presence or absence of TgAb. The institutional review board approved the study (KC15RISI0281).

2.2 | Biochemical assays

Tg and TgAb were measured before total thyroidectomy in every patient. After total thyroidectomy and/or RRA, serum Tg and TgAb measurements were also performed in all patients at every visit. Serum TgAb was measured using a competitive radioimmunoassay kit (ZenTech, Angleur, Belgium) with a functional sensitivity of <15 IU/mL. TgAb ≥70 IU/mL was defined as TgAb positive and TgAb <70 IU/mL was defined as TgAb negative.

Serum TPOAb measurement was also performed before surgery. Serum TPOAb was measured via a chemiluminescent immunometric assay using an IMMULITE 2000 analyzer (Siemens Healthcare Diagnostic Products Ltd., Llanberis, Gwynedd, UK) with a functional sensitivity of 28 IU/mL. Serum TPOAb level ≥80 IU/mL was defined as positive, and <80 IU/mL as negative.

2.3 | Treatment and postoperative follow-up

Every patient underwent total or near-total thyroidectomy with or without cervical lymph node (LN) dissection and/or RRA 1-3 months after surgery. After initial follow-up at less than 3 months, an outpatient visit was scheduled every 6 months. Serum Tg and TgAb values were measured on each visit, and neck ultrasound was performed every year. No recurrence on neck ultrasound or no metastatic lesion using other imaging methods (computed tomography, magnetic resonance imaging, diagnostic ^{123}I WBS) was defined as no evidence of disease. Suspicious LNs on radiologic imaging were evaluated using fine needle aspiration cytology (FNAC). Recurrence was confirmed on the basis of FNAC results.

2.4 | Statistical analysis

Continuous variables are reported as a mean±standard deviation or median values and ranges, while categorical variables are reported as absolute numbers and percentages. Intergroup differences were assessed with the independent samples *t*-test (continuous variables) or the chi-squared statistic and Fisher's exact test (categorical variables). The Kaplan-Meier method and log-rank test were used to analyse time-dependent variables. The Cox hazard regression model was used in multivariate analysis. All reported *P* values were

2-sided, and *P*-values <.05 were considered statistically significant. All analyses were performed with SPSS software (Version 22.0, Chicago, IL, USA).

3 | RESULTS

3.1 | Clinical characteristics of DTC subjects according to TgAb

A total of 1171 patients were included in this study. The mean age at diagnosis was 47.1±12.0 years (range 11-80), and 948 (81.0%) were female. The mean tumour size was 1.2±0.9 cm. There were 917 patients (78.3%) in the TgAb-negative group and 254 (21.7%) in the TgAb-positive group (Table 1). The percentages positive for TPOAb (42.6% vs 8.6%) and lymphocytic thyroiditis on pathology (68.5% vs 14.3%) were significantly higher in the TgAb-positive group (*P*=.000). The TgAb-positive group had a significantly higher rate of lymphatic invasion (31.9% vs 24.3%, *P*=.014) and LN metastasis (56.3% vs 44.9%, *P*=.007). The tumour encapsulation rate was lower in the TgAb-positive group (14.6% vs 24.9%, *P*=.001). There were no statistical differences in terms of extrathyroid extension, ATA risk classification and the proportion receiving RRA between the two groups. TgAb-positive patients showed higher LN metastasis rate than those without TgAb on the ATA low, intermediate and high risk groups, respectively (TgAb−: 23.8%, 50.9%, 69.8% vs TgAb+: 38.5%, 61.9%, 75.9%).

3.2 | Clinical characteristics of non-HT DTC subjects according to TgAb

As lymphocytic thyroiditis on postoperative pathology also reflected thyroiditis as well as positive serum TPOAb, we performed another analysis after excluding patients (n=365) with either serum TPOAb or lymphocytic thyroiditis on pathology to refine the role of TgAb as a prognostic factor (non-HT group). Among these 806 non-HT patients, 55 (6.8%) were TgAb positive (Table 2). Proportion of recent TgAb+ was significantly different between non-HT and HT patients (4/806 (0.5%) vs 20/365 (5.5%), *P*=.000). Among all patients, the results were almost the same (Table 1) for non-HT subjects, with an increased lymphatic invasion rate in the TgAb-positive group (41.8% vs 25.5%,

TABLE 1 Baseline clinical characteristics and risk stratification of 1171 DTC patients according to TgAb

	TgAb (−)	TgAb (+)	*P* values
N (%)	917 (78.3)	254 (21.7)	
Female (%)	716 (78.1)	232 (91.3)	.000
Age at diagnosis, mean±SD (min-max)	47.3±12.1 (11-80)	46.3±11.6 (16-74)	.210
TSH, mean±SD	2.26±2.16	2.65±2.47	.025
TPO Ab+, n (%)	78/904 (8.6)	107/251 (42.6)	.000
Histology type (%)			.632
Papillary	901 (98.3)	251 (98.8)	
Follicular	13 (1.4)	3 (1.2)	
Papillary+Follicular	3 (0.3)	0 (0.0)	
Tumour size	1.2±1.0 (0.1-10.0)	1.2±0.7 (0.3-5.0)	.720
Extrathyroidal extension (%)	494 (53.9)	122 (48.0)	.099
No	423 (46.1)	132 (52)	
Microscopic	440 (48.0)	108 (42.5)	
Macroscopic	54 (5.9)	14 (5.5)	
Tumour encapsulation (%)	225/903 (24.9)	36/247 (14.6)	.001
Multiplicity (%)	308/914 (33.7)	98/254 (38.6)	.148
Vascular invasion (%)	30/916 (3.3)	6/254 (2.4)	.456
Lymphatic invasion (%)	222/915 (24.3)	81/254 (31.9)	.014
LN metastasis (%)	411 (44.8)	143 (56.3)	.007
Thyroiditis on pathology[a] (%)	131 (14.3)	174 (68.5)	.000
BRAF mutation (%)	425/523 (81.3)	123/164 (75.0)	.082
ATA risk (%)			.790
Low	282 (30.8)	78 (30.7)	
Intermediate	519 (56.6)	147 (57.9)	
High	116 (12.6)	29 (11.4)	
Radioiodine ablation (%)	731 (79.7)	215 (84.6)	.078

[a]Lymphocytic thyroiditis on postoperative pathology.

TABLE 2 Patient characteristics and risk stratification in 806 patients without thyroid peroxidase antibody and lymphocytic thyroiditis on pathology

	TgAb (−)	TgAb (+)	*P* values
N (%)	751 (93.2)	55 (6.8)	
Female (%)	565 (75.2)	49 (89.1)	.020
Age at diagnosis, mean±SD	47.3±12.1	46.3±11.6	.210
TSH, mean±SD	2.16±1.89	2.16±1.42	.994
Tumour size	1.2±1.0	1.2±0.7	.720
Extrathyroidal extension (%)			.684
No	338 (45.0)	24 (43.6)	
Microscopic	367 (48.9)	26 (47.3)	
Macroscopic	46 (6.1)	5 (9.1)	
Tumour encapsulation (%)	195/742 (26.3)	9/54 (16.7)	.118
Multiplicity (%)	244/748 (32.6)	23/55 (41.8)	.162
Vascular invasion (%)	27/750 (3.6)	4/55 (7.3)	.172
Lymphatic invasion (%)	191/749 (25.5)	23/55 (41.8)	.008
LN metastasis (%)	350 (46.6)	36 (65.5)	.007
BRAF mutation (%)	347/419 (82.8)	24/33 (72.7)	.146
ATA risk (%)			.371
Low	225 (30.0)	16 (29.1)	
Intermediate	426 (56.7)	28 (50.9)	
High	100 (13.3)	11 (20.0)	
Radioiodine ablation (%)	608 (81.0)	51 (92.7)	.029

P=.008). However, the RRA treatment rate was higher in the TgAb-positive group (92.7% vs 81.0%, *P*=.029).

3.3 | Tumour characteristics of TgAb-positive subjects according to HT

To explore prognostic significance of HT, we divided all patients with TgAb into two groups: HT versus non-HT. Patients with TgAb and non-HT were older, had lower TSH levels and higher ATA risk, and showed more frequently vascular invasion, extrathyroidal extension, LN metastasis, and lymphatic invasion than those with TgAb and HT, even though several parameters were not statistically significant (Table S1). However, the recurrence rate was not different between both groups (3 [5.5%] vs 11 [5.5%], *P*=.983).

3.4 | Lymph node metastasis and TgAb

As prior analysis showed a consistent association between TgAb-positive status and lymphatic invasion with LN metastasis, we closely examined the relationship between TgAb levels and LN metastasis/dissection status after total thyroidectomy. There were significant differences in the mean numbers of total (11.2±15.9 vs 18.4±19.2, *P*=.000) and central LNs dissected (7.1±6.2 vs 12.0±8.4, *P*=.000) between TgAb-negative and TgAb-positive groups (Table 3). Similarly,

TABLE 3 Lymph node dissection status and lymph node metastasis in patients according to TgAb

Whole patients	TgAb (−)	TgAb (+)	*P* values
N (%)	917 (78.3)	254 (21.7)	
Number of LND	11.2±15.9	18.4±19.2	.000
Number of central LND	7.1±6.2	12.0±8.4	.000
Number of lateral LND	4.0±13.2	6.4±15.9	.029
Site of LN dissection (%)	798 (87.0)	235 (92.5)	.008
Central only	684 (74.6)	184 (72.4)	
Central+Lateral	109 (11.9)	49 (19.3)	
Lateral only	5 (0.5)	2 (0.8)	
Number of metastatic LN	2.1±4.2	3.3±6.0	.003
Number of metastatic central LN	1.5±2.7	2.1±3.3	.005
Number of metastatic lateral LN	0.6±2.5	1.2±3.6	.017
LN metastasis (%)	411 (44.8)	143 (56.3)	.007
Central	394 (43.0)	139 (54.7)	.001
Lateral	99 (10.8)	42 (16.5)	.013

LND, lymph node dissection; TgAb, thyroglobulin antibody.

the mean numbers of metastatic LNs were significantly higher in the TgAb-positive group (3.3±6.0 vs 2.1±4.2, *P*=.003). The location of LN dissection was different between the groups, and the lateral LN dissection rate was higher in the TgAb-positive group (*P*=.008). The same analysis was performed in non-HT patients (Table S2). The numbers of LNs dissected and metastatic LNs (especially lateral LNs) were also higher in the TgAb-positive group.

As there is a relationship between TgAb positivity and lateral LN metastasis, we performed univariate and multivariate analyses of risk factors for lateral LN metastasis in non-HT patients. Positive preoperative TgAb, along with female sex, extrathyroidal extension and central LN metastasis were independent clinical variables predictive of lateral LN metastasis (Table 4).

3.5 | Final outcome and TgAb

During a mean follow-up of 50.2 months (36-112 months), 45 patients (3.8%) had LN recurrence: 31 (3.4%) were TgAb negative and 14 (5.5%) were TgAb positive (*P*=.118; Table 5). Among the 45 patients with recurrent disease, 34 underwent surgery including neck lymph node dissection and 11 received radiofrequency ablation therapy. Three patients had distant metastases: 1 (0.1%) was TgAb negative and 2 (0.8%) were TgAb positive. While 9.1% (N=23) of patients with preoperative TgAb showed TgAb positivity at the last follow-up, only 0.1% (N=1) of patients without preoperative TgAb showed TgAb positivity (*P*=.000). The recurrence rate showed no significant difference between patients with and without preoperative TgAb, both overall and in non-HT patients. Three (0.4%) patients had distant metastasis in the follow-up period, and a few more had distant metastasis in the TgAb-positive group (3.6% vs 0.1%, *P*=.000).

TABLE 4 Univariate and multivariate analyses of risk factors for lateral LN metastasis in patients without HT[a]

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* values	HR (95% CI)	*P* values
Female	*0.56 (0.36-0.88)*	.012	*0.47 (0.28-0.78)*	.003
Age≥50	*0.58 (0.37-0.89)*	.013	*0.71 (0.44-1.15)*	.168
Extrathyroidal extension	*3.75 (2.25-6.25)*	.000	*2.83 (1.63-4.92)*	.000
Tumour encapsulation	*1.07 (0.66-1.75)*	.777	*1.32 (0.76-2.27)*	.321
Preoperative TSH≥4.05	*1.71 (0.88-3.33)*	.113	*1.82 (0.87-3.81)*	.113
Preoperative TgAb+	*2.64 (1.38-5.04)*	.003	*2.63 (1.26-5.48)*	.010
Central LN metastasis	*7.74 (4.44-13.48)*	.000	*5.88 (3.30-10.49)*	.000

[a]HT: TPOAb (+) or presence of lymphocytic thyroiditis on pathology.

TABLE 5 Final disease status according to TgAb status in whole patients and patients without HT[a]

	Whole patients				Patients without HT[a]			
		TgAb (−)	TgAb (+)	*P* values		TgAb (−)	TgAb (+)	*P* values
N (%)	1171	917 (78.3)	254 (21.7)		806	751 (93.2)	55 (6.8)	
Recent TgAb+ (%)[b]	24 (2.0)	1 (0.1)	23 (9.1)	.000	4 (0.5)	1 (0.1)	3 (5.5)	.000
Recurrence, n (%)	45 (3.8)	31 (3.4)	14 (5.5)	.118	33 (4.1)	30 (4.0)	3 (5.5)	.598
Recurrence-free period (month)	50.2±14.5	49.9±14.6	51.1±14.4	.582	49.0±16.6	48.8±16.3	52.8±19.6	.083
Distant metastases (%)	3 (0.3)	1 (0.1)	2 (0.8)	.120	3 (0.4)	1 (0.1)	2 (3.6)	.000

[a]HT: TPOAb (+) or presence of lymphocytic thyroiditis on pathology.
[b]Recent TgAb+: a positive TgAb at the most recent evaluation.

TABLE 6 Univariate and multivariate analyses of prognostic factors for recurrence disease in whole patients

	Univariate analysis		Multivariate analysis	
	Log-rank statics	*P* values	HR (95% CI)	*P* values
Female	*0.36*	.550	*0.86 (0.42-1.77)*	.685
Age≥50	*7.60*	.006	*0.52 (0.26-1.03)*	.062
LN metastasis	*24.25*	.000	*3.84 (1.70-8.70)*	.001
Extrathyroidal extension	*8.47*	.004	*2.12 (1.04-4.33)*	.039
Tumour encapsulation	*0.10*	.747	*1.20 (0.56-2.54)*	.652
Preoperative TSH≥4.05	*0.00*	.995	*0.75 (0.27-2.12)*	.591
Preoperative TgAb+	*2.39*	.122	*1.44 (0.71-2.94)*	.310
Recent TgAb+[a]	*1.76*	.184	*1.30 (0.29-5.91)*	.732

[a]Recent TgAb+: a positive TgAb at the most recent evaluation.

Cox regression analysis identified metastatic LN at diagnosis (odds ratio [OR] 3.842, *P*=.001) and extrathyroidal extension (OR 2.119, *P*=.039) but not preoperative and recent TgAb+ as essential predictive factors for recurrent disease (Table 6). When the same analysis was performed in non-HT patients, the presence of preoperative TgAb showed no significant predictive value for recurrent disease (Table S3). However, recent TgAb status was an independent predictor of recurrence in patients without HT (OR 10.4, *P*=.041).

4 | DISCUSSION

We evaluated 1171 DTC patients with data for preoperative TgAb levels and showed that positive preoperative TgAb might be associated with unfavourable characteristics of the primary tumour, including lymphatic invasion, LN metastasis, and increased rate of lateral LN metastasis. However, the actual disease recurrence rate during follow-up was not associated with TgAb.

It is known that the prevalence of HT is higher in patients with DTC. The serologic presence of TPOAb or TgAb is highly correlated with lymphocytic thyroiditis. While TPOAb is believed to fix complement and can be used to diagnose HT and hypothyroidism more accurately than TgAb, TgAb may be more tumour specific than TPOAb.[20] In particular, high TgAb levels can weakly predict thyroid carcinoma in patients with thyroid nodules, in contrast with TPOAb.[10]

We assume that the nature of TgAb in DTC might be different from that in autoimmune thyroid disease. This could be explained by several immunodominant regions recognized by human TgAb in thyroglobulin. Fiore et al.[21] suggested two different autoimmune mechanisms: one in autoimmune thyroiditis and the other in DTC due to different epitope patterns of TgAb. Increasing postoperative TgAb in some patients could be additional evidence for diverse autoimmune mechanisms.

As TgAb status can change with time and TgAb can interfere with Tg measurement, serum Tg and TgAb should be measured simultaneously in patients with DTC.[22] TgAb generally declines to less than 10% by 3 years after surgery.[7] The prognostic significance of TgAb remains controversial.[7,10,23,24] One study reported that patients with postoperative TgAb are more likely to have persistent disease than those without TgAb.[14] A rising trend in TgAb levels after thyroidectomy could reflect recurrence in patients without HT.[25] Several prior studies were conducted in preoperative settings[14,16,26] but the small number and varied clinical settings of patients prevented any strong conclusion. As solid data are still lacking about the relationship between preoperative TgAb and cancer prognosis, including recurrent or persistent disease, preoperative serum TgAb measurement is not recommended in the current guidelines.[17]

As serum TgAb level is familiar to physicians who treat DTC patients, TgAb measurement for use as a prognostic biomarker before total thyroidectomy would be useful for therapeutic decision-making regarding the extent of surgery or RRA dose. Although many clinical studies composed of total thyroidectomy patients evaluated the prognostic value of postoperative TgAb, there are no reliable studies on preoperative TgAb as a predictive marker for prognosis of DTC in a single hospital setting with a large number of study subjects.

In our initial evaluation of all study subjects including PTC with HT, positive preoperative TgAb was associated with a high rate of lateral and overall LN metastasis. This result is similar to that of a study of HT and DTC.[27] The authors found that patients with HT and PTC had more LN dissection, more LN metastasis, and more multifocal lesions than non-HT PTC patients. However, that study only considered TPOAb, not TgAb, as a serologic marker for HT. One case report showed that the appearance of TgAb may indicate the presence of metastatic LNs, but only in a limited number of subjects.[28] These findings differed from those of a recent study by Zhu et al.,[29] which conducted a retrospective survey of 763 patients to examine the risk factors for central and lateral neck LN metastases in PTC associated with HT. A total of 277 (36.3%) patients with PTC and HT had a lower central LN metastasis rate than those with PTC and non-HT, indicating a protective effect. The difference between this study and ours was the definition of Hashimoto's thyroiditis: they included only patients with pathologically proven Hashimoto's thyroiditis and excluded TPOAb-positive only patients.

As HT per se might indicate the occurrence of PTC and subsequent prognostic effects including LN metastasis,[30] we wanted to identify the isolated effect of TgAb on LN metastasis without HT or TPOAb effects. We analysed LN metastasis in the same study population, after excluding HT patients. Essentially, the same result was obtained, showing that a high rate of lateral and overall LN metastasis was observed in TgAb-positive patients, which was an important finding in this study. We also found that TgAb was an independent risk factor for lateral LN metastasis (Table 4). The reason why TgAb indicates a high frequency of LN metastasis, especially lateral LN metastasis, could be explained as a cancer-specific immune reaction. If LN metastasis develops from the primary tumour, cancer cells are confined within the LNs, which induce a cancer-specific immune response, and TgAb levels might rise as a result.[31,32] We can speculate that progression of DTC to LN metastasis induces antigenicity and might induce higher TgAb as a result of a localized immune response, in which tumour cells display HLA-restricted antigens that can be selectively or specifically recognized by T cells followed by B-cell recruitment.[33] And in our study, proportion of recent TgAb+ is significantly different between non-HT and HT. It means that most of the TgAb is due to the autoimmune process, and the TgAb due to the actual cancer-specific response may be considered to be present only in some cases.

It is known that if LN metastasis is present at diagnosis in DTC patients, there is a high probability of recurrent or persistent disease.[34] However, in our study, there was no significant difference in the recurrence rate between TgAb-negative and TgAb-positive groups, even though TgAb-positive patients showed more frequent LN metastasis, especially lateral LN, at diagnosis than did TgAb-negative patients. The same results were observed in non-HT patients.

The finding of no difference in recurrence rate in the present study was similar to that of a multicenter cancer registry study by McLeod et al.,[16] which reported that TgAb status was not associated with disease-free survival or overall survival. However, that study was composed of patients with perioperative TgAb (preoperatively or within 3 months of surgery), not solely among those with preoperative TgAb. These findings are in disagreement with the results of a recent multicenter study by Durante et al.,[14] which evaluated 1240 patients from 10 hospitals and reported that there were twice as many high-risk patients who were TgAb-positive. Persistent/recurrent disease was also significantly more common among TgAb positive patients. However, their study was composed of data from postoperative patients (one to twelve months after primary treatment).

Discordance between more lateral LN metastasis associated with TgAb positivity and the subsequent absence of an increased recurrence rate might be due to more aggressive prophylactic or therapeutic dissection of additional metastatic LNs in TgAb-positive patients. Jones et al.[30] found that HT seems to be associated with a sonographic pattern of an increased number of enlarged cervical LNs. Although the presence of TgAb indicates initial tumour aggressiveness in DTC, more active treatment, such as increased LN dissection, might have favourable effect on disease recurrence in the final outcome.[35-37]

Another reason may be due to the low recurrence rate relative to the number of study subjects, that is, less than 10%. Third, as initial surgery including more extensive LN dissections in patients with TgAb lead to more LN metastasis, these patients had by ten per cent more RRA treatments than patients without TgAb in this study, and the recurrence rate of each group seemed to be affected by the RRA treatment rate. Thus, a stable final outcome in TgAb-positive DTC patients may be the result of initial aggressive LN dissection and larger doses of RRA.

Although in this study we focused on TgAb, additional analysis was performed to examine the influence of coexistent HT on outcomes. Patients with TgAb and non-HT showed more aggressive tumour behaviours, like more frequent vascular invasion, than those with TgAb and HT, indicating protective effects of HT on patients with TgAb.

The strengths of this study are as follows: (i) a large number of patients were included. (ii) Every patient had a complete data set for preoperative TgAb, and almost all patients had TPOAb data. (iii) With routine LN dissection, staging and LN metastasis status could clearly be determined in most patients. However, as this is a retrospective study through clinical data review, we cannot ignore a possibility of selection bias.

In conclusion, positive preoperative serum TgAb level was associated with worse primary tumour characteristics, but rarely showed a poor prognosis, probably due to more aggressive treatment in these subjects. However, the basic immune mechanism of TgAb induction in LN metastasis among DTC patients should be clarified in a future study.

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CONFLICT OF INTEREST

The authors have nothing to disclose.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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