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ORIGINAL ARTICLE

The Relationship between Pre-operative Anti-thyroglobulin Antibody Level and Lymph Node Metastasis and Recurrence in Differentiated Thyroid Cancer

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OBJECTIVE

We aimed to investigate the relationship between positivity and level of pre-operative anti-thyroglobulin antibody (TgAb) and stage, recurrence, and metastasis in differentiated thyroid cancer (DTC).

METHODS

Three hundred and thirty-one patients who underwent total thyroidectomy and whose TgAb was measured in the pre-operative and post-operative period were included in the study. The laboratory and clinicopathological data of the patients were recorded from patient files.

RESULTS

Of the 331 patients enrolled, 253 (76.4%) were female and 78 (23.6) were male, and the mean age was 46.7±15.4. The final histopathology results were DTC in 126 (38.1%) patients and benign in 205 (61.9%) patients. TgAb was positive in 26 (20.6%) of 126 patients in the DTC group, while it was positive in 29 (14.1%) of 205 patients in the benign group. In patients with DTC, having lymph node metastasis, recurrence, and receiving radioactive iodine (RAI) ablation were found to be associated with higher pre-operative TgAb levels (p=0.023, p=0.032 and p=0.022, respectively). The TSH level at the time of diagnosis was significantly higher in the DTC group compared to the benign group (p<0.001).

CONCLUSION

In our study, pre-operative TgAb levels were found to be significantly higher in DTC patients with lymph node metastasis or recurrence. We found that pre-operative TgAb level significantly correlated with recurrence and lymph node metastasis.

Keywords: Anti-thyroglobulin antibody; differentiated thyroid cancer; lymph node metastasis; recurrence.

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INTRODUCTION

Thyroid cancer is the most common among endocrine cancers, and its incidence is 3 times higher in women than in men (21 and 7/100,000 population, respectively).[1] Estimated incidence of thyroid cancer by age and sex has increased in both sexes and all ethnicities compared to other malignancies in recent years.[2,3] Differentiated thyroid cancer (DTC) accounts for 80–90% of all thyroid cancer diagnoses. Papillary, follicular, and poorly differentiated types of thyroid cancer are considered as DTC. DTC subtypes are treated similarly despite numerous biological differences.

Serum thyroglobulin (Tg) level is used for recurrent disease follow-up in patients with DTC after initial treatment. However, serum Tg measurements in patients with serum anti-thyroglobulin antibody (TgAb) positive can be misleading. TgAb can be detected in 20% of patients with DTC and in 10% of the general population.[4–6] Following total thyroidectomy and subsequent radioactive iodine (RAI) treatment, serum TgAb levels generally reach undetectable levels within 3–5 years. The decrease in TgAb level has prognostic significance. The decrease in TgAb level above 50% in the first 3 years of the follow-up is associated with the risk of recurrence <3%.[7,8] Stable values at the TgAb level are associated with an approximately 20% risk of recurrence, while increasing values at the TgAb level are associated with an approximately 40% risk of recurrence.

Although there are many studies in the literature investigating the relationship between post-operative TgAb level and DTC stage, metastasis, and recurrence risk, there are limited number of studies investigating the relationship between pre-operative TgAb level and these parameters.

In this study, we aimed to determine the relationship between the positivity and level of pre-operative TgAb and the cancer stage, metastasis status, and recurrence risk in subjects who underwent total thyroidectomy and had TgAb results measured in the pre-operative period.

MATERIALS AND METHODS

The study enrolled 331 patients who underwent total thyroidectomy and those who had TgAb results measured in the pre-operative and post-operative period between January 2012 and May 2019. Ethical committee approval was obtained for the study from the Local Ethics Committee. The study was carried out in accordance with the Principles of Helsinki Declaration. İnformed consent was obtained from all participants. Laboratory and clinicopathological data of the patients such as sex, age at the diagnosis, TgAb positivity and level in the pre-operative period, histopathological subtype of thyroid cancer, lymph node metastasis status, tumor volume, tumor size, TNM stage, risk stratification according to the American thyroid association (ATA), tumor focus number, whether recurrence occurred during follow-up, whether surgical treatment or RAI treatment was performed in those who developed recurrence, TSH levels at the time of diagnosis and TgAb levels in the post-operative period were recorded from the patient files.

TgAb positivity status: Those with a TgAb level above the reference value were considered positive and those within the reference value range were considered negative (TGAb normal range: 0–115 U/mL). Tumor volume was calculated by the formula [width (mm)×length (mm) × thickness (mm)] ×Π/6. The largest tumor size was recorded in those given two diameters of the tumor. Those whose tumor diameter could not be calculated were recorded as separate groups. TNM stage: Tumors were stratified according to 8th AJCC TNM classification system. ATA risk stratification: Patients were classified according to the ATA risk stratification (low, moderate, and high risk). Tumor focus number: Single-focus tumors are grouped as single-focus, and those with more than one focus are grouped as multifocal tumors. Post-operative TgAb level: TgAb values in the 2nd year after thyroidectomy, and the last TgAb values if there was no value in the 2nd year were recorded.

Statistical Analysis

Statistical analysis was carried out by the Statistical Package for the Social Sciences 22.0 program. According to the distrubition characteristics of varieables, continuous varieables were given as mean±standard deviation or median (min-max). To compare the differences of independent groups, Independent samples t-test, Mann-Whitney U-test, and Chi-square test were used. Pearson and Spearman test were used for correlation analysis. P<0.05 value was considered statistically significant.

RESULTS

Of the 331 patients enrolled in the study, 253 (76.4%) were female and 78 (23.6) were male, and the age at diagnosis was 46.7±15.4. The age was 44.9 in the DTC group and 48.0 in the benign group. Ninety-seven of 126 patients in the DTC group and 154 of 205 patients

Table 1 Demographic, pathological, and laboratory features of patients who underwent thyroidectomy

Variables	All patients (n=331)	n	%
Age at diagnosis (years)		46.7	
	Differentiated thyroid cancer group (n=126)	45	
	Benign group (n=205)	47.9	
Gender			
	Male	78	23.6
	Female	253	76.4
Histopathological result (n=331)			
	Benign	205	61.9
	Differentiated thyroid cancer	126	38.1
Differentiated thyroid cancer subtype (n=126)			
	Papillary microcarcinoma	49	38.9
	Papillary thyroid cancer	72	57.1
	Follicular thyroid cancer	4	3.2
	Poorly differentiated thyroid cancer	1	0.8
TNM stage (n=126)			
	I	115	91.3
	II	7	5.6
	III	3	2.4
	IVb	1	0.8
ATA risk stratification (n=126)			
	Low	32	25.4
	Intermediate	88	69.8
	High	6	4.8
RAI treatment status (n=126)			
	No	35	27.8
	Yes	91	72.2
Recurrence (n=126)			
	No	112	88.9
	Yes	14	11.1
Surgical treatment after recurrence (n=14)			
	No	3	21.4
	Yes	11	78.6
RAI treatment after recurrence (n=14)			
	No	8	57.1
	Yes	6	42.9
Tumor focus number (n=126)			
	Multiple	48	38.1
	Single	78	61.9
Lymph node metastasis status (n=126)			
	No	91	72.2
	Yes	35	27.8

TNM: The tumor, node, metastasis; ATA: American thyroid association; RAI: Receiving radioactive iodine

in the benign group were women. We found no difference between the DTC group and the benign group in terms of gender and age (p=0.473 and p=0.076, respectively). The final histopathology results of patients who underwent total thyroidectomy were DTC in 126 (38.1%) patients and benign in 205 (61.9%) patients. In DTC group, papillary thyroid cancer was found in 72 (57.1%) patients, thyroid papillary microcarcinoma in 49 (38.9%) patients, follicular type thyroid cancer in 4 (3.2%) patients, and poorly DTC in one patient (0.8%). When the tumor stages of DTC patients were examined, it was detected as Stage I in 115 patients (91.3%), Stage II in seven patients (5.6%), Stage III in three patients (2.4%), and Stage IVb in one

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patient (0.8%). According to the current ATA stratification system, in the DTC group, 32 patients (25.4%) were in low risk, 88 patients (69.8%) were in moderate risk, and six patients (4.8%) were in high-risk group. In the DTC group, 91 (72.2) patients received RAI treatment, and 35 patients (27.8%) did not receive RAI treatment. During follow-up, recurrence occurred in 14 (11.1%) of 126 patients in the DTC group. It was determined that 11 (78.6%) of the patients with recurrence were re-operated and 6 (42.9%) patients received RAI treatment again due to recurrence. Multifocal tumor foci were detected in 48 patients (38.1%) and single tumor focus in 78 patients (61.9%) in the DTC group. Lymph node metastasis was detected in 35 patients (27.8%) in the DTC group (Table 1).

At the diagnosis of DTC, the mean TSH level of all patients was 1.41±1.54, the mean values of TSH in the DTC group was 1.76±1.45, the mean values of TSH in the benign group were 1.19±1.58, and TSH value at the diagnosis was found to be higher in DTC group (p<0.001). In the pre-operative period, TgAb values were negative in 276 patients (83.4%) and positive in 55 patients (16.6%). While TgAb was positive in 26 (20.6%) of 126 patients in the DTC group, TgAb was positive in 29 (14.1%) of 205 patients in the benign group (p=0.117). In the TgAb positive group, pre-operative mean TgAb level was 743.88±978.11 IU/ml in the DTC group, 880.63±1053.30 IU/ml in the benign group, and we did not find any difference between the groups (p=0.577) (Table 2).

We did not find any relationship between pre-operative TgAb positivity and parameters such as TNM stage (p=0.119), lymph node metastasis (p=0.416), receiving RAI treatment (p=0.868), recurrence (p=0.732), surgical treatment due to recurrence (p=0.396), RAI treatment due to recurrence (p=0.165), and tumor focus number (p=0.947) (Table 3).

In the TgAb positive group, there were no lymph node metastases in 17 of 26 patients with DTC, and nine of 26 patients with DTC have had lymph node metastases. In the group with lymph node metastasis, we found that the mean value of TgAb was higher than the group without lymph node metastasis (1356.20±1163.77 IU/ml, 419.71±703.64 IU/ml, respectively, p=0.043). No recurrence was observed in 24 of 26 patients with DTC, and two of them had recurrence. Mean TgAb level was higher in patients with recurrent disease than those without recurrence (2492.00±718.42 IU/ml, 598.20±854.15 IU/ml, respectively, p=0.043). According to the current ATA stratification system of 26 patients with DTC, nine were in the low-risk group and 17 were in the moderate risk group. We did not find any difference between the intermediate risk group and the low-risk group in terms of TgAb level (847.97±1007.37 IU/ml, 547.26±945.27 IU/ml, respectively, p=0.374). Of the 26 patients with DTC, 19 received RAI treatment, seven did not receive RAI treatment. In patients who received RAI treatment, mean TgAb level was found to be significantly higher than those who did not receive RAI treatment (959.35±1068.51 IU/ml, 159.02±122.37 IU/ml, respectively, p=0.022). Of the 26 patients with DTC, ten had multifocal tumors and 16 had single focus tumors. We found no difference between the groups in terms of mean TgAb level (463.66±530.41 IU/ml, 919.02±1157.85 IU/ml, respectively, p=0.562) (Table 4).

In the correlation analysis, we found significant correlations between pre-operative TgAb level and recurrence (p=0.032) and lymph node metastasis (p=0.023).

Table 2 Comparison of demographic and laboratory parameters of DTC group and benign group

Variables	DTC (n=126)		Benign (n=205)		p
	n	%	n	%	
Age (years)	44.96±14.4		48.04±15.8		0.076
Gender					0.473
Female	97		154		
Male	29		51		
TSH (µU/mL)	1.76±1.45		1.19±1.58		<0.001
Pre-operative TgAb positive	26	20.6	29	14.1	0.117
Pre-operative TgAb levels	743.88±978.11		880.63±1053.30		0.577

DTC: Differentiated thyroid cancer; TSH: Thyroid-stimulating hormone; TgAb: Thyroglobulin antibody

DISCUSSION

In our study, pre-operative TgAb levels were found to be significantly higher in DTC patients with lymph node metastasis or recurrence. We found that pre-operative TgAb level significantly correlated with recurrence and lymph node metastasis. In addition, TSH value at the diagnosis was found to be higher in the DTC group than in the benign group. No significant relationship was found between the positivity or level of pre-operative TgAb and parameters such as tumor focus number, stage, ATA risk classification, and RAI treatment.

Table 3 Relationship between pre-operative TgAb positivity and clinicopathological parameters

Variables	TgAb positive DTC (n=26)		TgAb negative DTC (n=100)		p
	n	%	n	%	
Lymph node metastasis					
Yes	9	34.6	26	26.5	0.416
No	17	65.4	72	73.5	
TNM stage					
Stage I	26	100	88	89.8	0.119
Advanced stages	0	0.0	10	10.2	
RAI treatment					
Yes	19	73.1	70	71.4	0.868
No	7	26.9	28	28.6	
Recurrence					
Yes	2	7.7	12	12.2	0.732
No	24	92.3	86	87.8	
Recurrent DTC					
Re-operated	1	50.0	10	83.3	0.396
Had not re-operate	1	50.0	2	16.7	
Recurrent DTC					
Received again RAI	2	100.0	4	33.3	0.165
Did not receive again RAI	0	0.0	8	66.7	
Tumor Focus number					
Mulifocal	61	62.2	37	37.8	0.947
Single	16	61.5	61	62.2	

TgAb: Thyroglobulin antibody; DTC: Differentiated thyroid cancer; TNM: The tumor, node, metastasis; RAI: Receiving radioactive iodine

Table 4 The association between the level of TgAb and clinicopathological parameters in patients with positive pre-operative TgAb

Variables	Mean±SD	P
Lymph node metastasis (n=17)		
No (n=17)	419.71±703.64	**0.043**
Yes (n=9)	1356.20±1163.77	
Recurrence		
No (n=24)	598.20±854.15	**0.043**
Yes (n=2)	2492.00±718.42	
ATA risk		
Low risk (n=9)	547.26±945.27	0.374
Intermediate risk (n=17)	847.97±1007.37	
RAI treatment		
Received RAI (n=19)	959.35±1068.51	**0.022**
Didn't receive RAI (n=7)	159.02±122.37	
Tumor focus number		
Multifocal (n=10)	463.66±530.41	0.562
Single (n=16)	919.02±1157.85	

TgAb: Thyroglobulin antibody; ATA: American thyroid association; RAI: Receiving radioactive iodine

In the present study, the number of male patients was less than the number of female patients in both the DTC group and among all patients who underwent thyroidectomy. In studies with patients who underwent thyroidectomy, it was determined that the majority of patients were women.[9,10] In some studies, the age of the patients was lower in the malignant group,[9] while in some studies, there was no difference in age in the malignant and benign groups.[10]

In our study, the mean TSH value at the diagnosis was higher in the DTC patients than in the benign group. In the previous studies with patients who underwent total thyroidectomy, TSH values were found to be higher in patients whose histopathology results were malignant compared to those whose histopathology results were benign.[9,11–14] It is thought that one of the reasons for this high TSH level in those with malignant histopathology results is that TSH itself has a trophic effect on the growth of thyroid cancer and this condition is mediated by the TSH receptors on thyeroid cancer cells. As another reason, it is thought that patients who have low concentrations of TSH may be developing autonomic function associated with lower malignancy rates.

In our study, although positivity of TgAb was more frequent and the mean TgAb level was higher in the malignant group, these findings were not statistically significant. We think that this may be due to the relatively small sample size of our study population. In several studies, it has been shown that positivity of pre-operative TgAb is more frequent in patients who have malignancy than those with benign histopathology.[9,10] Liu et al.[9] found that TgAb positivity is an independent predictor for malignancy. Hosseini et al.[10] showed that patients with a pre-operative TgAb level ≥30 IU/ml had higher malignancy rate compared to patients with a pre-operative TgAb level <30 IU/ml.

In some studies, it has been demonstrated that the risk of recurrent or persistent disease is not associated with pre-operative TgAb positivity,[15] but rather with the change in post-operative TgAb levels.[16] Qin et al.[12] did not find any significant difference between TgAb positive DTC patients and TgAb negative DTC patients in terms of lymph node metastasis and stage. In our study, similar results were found in terms of the pre-operative TgAb positivity.

In our study, it was found that there was a relationship between pre-operative TgAb level and both lymph node metastasis and recurrence. Li et al.[17]

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showed that pre-operative TgAb positivity was associated with the primary tumor diameter greater than 1 cm, and TgAb level and TSH level were associated with central lymph node metastasis. Seo et al.[18] reported that tumor recurrence frequency was higher in patients with TgAb >140 U/mL than in DTC patients with TgAb <140 U/mL.

Our study has some limitations. One of them is that the study population is small, and another is that the presence of autoimmune thyroid disease before thyroidectomy was not taken into consideration.

CONCLUSION

In conclusion, measuring the pre-operative TgAb of patients with clinical and ultrasonographic suspicious findings in terms of malignancy may provide information about which patients have a high risk of recurrence and lymph node metastasis. In this context, more comprehensive studies are needed.

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Conflict of Interest: All authors declared no conflict of interest.

Ethics Committee Approval: The study was approved by the Necmettin Erbakan University Faculty of Medicine Ethics Committee (no: 2019/1998, date: 12/07/2019).

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