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Diagnostic value of thyroglobulin washout in fine-needle aspiration samples for diagnosis and follow-up of differentiated thyroid cancer

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Abstract

Our goal was to assess the effectiveness of fine-needle aspiration thyroglobulin (FNA-Tg) in detecting malignant lymph nodes (LNs) in patients with differentiated thyroid cancer (DTC). We also aimed to determine the factors that affect the accuracy of FNA-Tg. We conducted a retrospective cohort study using the laboratory, ultrasonographic, histopathological, FNA cytology (FNA-C), and FNA-Tg results of 176 DTC patients. We used receiver operating characteristic analysis to identify the cutoff value of FNA-Tg, and binary regression analysis to compare FNA-Tg with other diagnostic parameters. Spearman correlation was utilized to identify factors that influence FNA-Tg. Our study revealed that a cutoff value of 3.14 ng/mL for FNA-Tg had a sensitivity of 91.8% and a specificity of 96.6% in detecting malignant LNs in the entire group. In the subgroup with thyroid tissue, the optimal cutoff value for FNA-Tg was determined to be 15.5 ng/mL. Additionally, FNA-C had a sensitivity of 82.4% and a specificity of 99.4% for the entire group. The combined use of FNA-Tg and FNA-C yielded a sensitivity of 100% and a specificity of 96%, which was found to be more effective than using either test alone. Serum Tg positivity and serum thyroid-stimulating hormone were positively correlated with FNA-Tg levels in detecting malignant LNs. Our study demonstrated that FNA-Tg is a reliable method for detecting LN metastases in DTC patients, with a 3.14 ng/mL cutoff value. However, each center should take into account factors such as serum thyroid-stimulating hormone, serum Tg, and the presence of thyroid tissue when interpreting FNA-Tg results and determining the appropriate cutoff level.

Abbreviations: AUC = area under the ROC curve, DTC = differentiated thyroid cancer, FNA-C = fine-needle aspiration cytology, FNA-Tg = fine-needle aspiration thyroglobulin, LN = lymph node, Tg = thyroglobulin, TSH = thyroid-stimulating hormone, USG = ultrasonography.

Keywords: differentiated thyroid cancer, fine-needle aspiration, thyroglobulin, washout

1. Introduction

Differentiated thyroid cancers (DTCs) are the most frequent malignancies of the thyroid and most cases have long periods of survival.[1,2] Cervical lymph node (LN) metastasis is detected with a rate ranging from 27% to 46% during the diagnosis in DTC patients, and a recurrence rate ranging from 3% to 30% may be seen in the postoperative period.[3,4] Detecting malignant LN metastases in the neck region is an important factor in planning treatment strategies for DTC patients. Until recently, neck ultrasonography (USG) and LN fine-needle aspiration cytology (FNA-C) were accepted as gold standards in detecting LN metastases in DTC patients.[5] While neck USG and FNA-C have acceptable diagnostic powers in detecting recurrences, they may be insufficient in some patients.[6,7] Fine-needle aspiration thyroglobulin (FNA-Tg) washout was first proposed nearly 31 years ago and over the years it has become a widely used reliable method with high sensitivity and specificity for the detection of LN metastases in patients with DTC.[8] However, there is no consensus on the cutoff level indicative of LN metastasis for the FNA-Tg.[9] This study aimed to evaluate the cutoff and diagnostic power of FNA-Tg, as well as the factors that affect it by retrospectively examining real-life data from our center.

2. Materials and methods

2.1. Patient selection

The data of DTC patients admitted to Akdeniz University Hospital between 2014 and 2020 who performed the LN FNA-Tg procedure in the preoperative (before thyroidectomy)

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

This study was approved by the Ethics Committee of Akdeniz University with Approval No (KAEK-593).

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or postoperative (after thyroidectomy) period were retrospectively evaluated. Study approval was received from the Akdeniz University Clinical Research Ethics Committee (Decision No: 2020/KAEK-593). We performed FNA-Tg washout to the DTC patients having ultrasonographic suspicious or indeterminate LNs. LNs with microcalcification, partial cystic appearance, increased peripheral vascularization, or thyroid-like echogenicity in USG were considered suspicious LNs. In addition to hilus absence in USG, LNs with 1 of the characteristics of round shape, increased short axis (≥8 mm in level 2 and ≥ 5 mm in level 3–4), and increased central blood buildup were considered as indeterminate LNs.[10] The study population consisted of 2 groups those having LN resection after FNA-Tg washout and those not. The patients who did not have a surgical procedure after the FNA-Tg washout were followed up actively for at least 2 years. We didn't include the patients in the study follow-up for less than 2 years. The patients having malignancies other than DTC were also excluded from the study.

2.2. Data analysis

During this study, we examined various data related to the patients thoroughly, including their demographic information, thyroid and LN operations, postoperative tumor pathology, tumor stage, ultrasonographic characteristics of the sampled LNs, and results of FNA-Tg and FNA-C procedures. FNA-C results were divided into 4 groups: malignant, suspicious for malignancy, benign, and inadequate. We also examined serum thyroid-stimulating hormone (TSH), Tg, and anti-Tg levels during the FNA-Tg procedures. To determine whether LN resection was necessary, we used both FNA-Tg and FNA-C methods together. If the results suggested malignancy, the LN resection was performed. If the results did not suggest malignancy, the patient was actively monitored for at least 2 years. In cases where FNA-C and FNA-Tg results were conflicting, but 1 indicated malignancy, the LN resection was performed. Final LN status was determined in 2 ways: histopathology for patients who underwent LN resection, and clinical, radiological, and cytological findings during the active follow-up period for those who did not. Patients with suspicious USG findings, but benign or acellular FNA-C and nonmalignant FNA-Tg levels, were monitored for at least 2 years for potential malignancy. After intermittent observations (ultrasonographic examinations, repeating FNA-C, and FNA-Tg measurements) during the follow-up period, the final LN status was determined. If there were no findings suggesting malignancy during the follow-up period, the final LN status was considered benign, otherwise, the patient underwent LN resection. After categorizing the final LN status of the patients as benign or malignant, we compared their data and evaluated the diagnostic power of the FNA-Tg method and the factors affecting it.

2.3. Ultrasound-guided FNA-Tg procedure

Ultrasonographic evaluations and aspirations were handled by experienced endocrinologists with a 7–12 MHz focused ultrasonography device (ESAOTE S.P.A, model EA720). Disposable plastic injectors with a 23-gauge needle were used. The aspiration material first sprayed from the needle tip was spread onto the slides, fixed with alcohol, and sent for cytological examination. The aspiration material remaining at the needle tip was washed with 1 mL of saline, and thyroglobulin (Tg) measurement of the resulting sample was performed.[11,12]

2.4. Thyroglobulin assessment

Thyroglobulin levels were measured by a solid-phase enzyme-labeled chemiluminescent immunometric assay method with a Siemens Immulite 2000 device (Siemens Healthcare Diagnostics, Forchheim, Germany). Intra-assay and total coefficients of variations of the thyroglobulin kit were 4.8% (control mean value: 10.0 ng/mL) and 5.6% (control mean value: 10.0 ng/mL), respectively. The analytical sensitivity of thyroglobulin level was 0.2 ng/mL and the detection range was 0.2–300.0 ng/mL.

2.5. Statistical analysis

Statistical analyses were performed with SPSS software 25. χ^2 test, Student *t* test, and Mann–Whitney *U* tests were used for the comparison of the patient's basic data. The Mann–Whitney *U* test was used for the comparison of the FNA-Tg results, serum TSH, and serum Tg values between the 2 groups. Receiver operating characteristic (ROC) curve analysis was used to determine the cutoff level of FNA-Tg, serum Tg, Tg rate, and Tg-difference in the evaluation of malignant LNs. The best cutoff value was determined according to the highest Youden's index. The "Area" (ROC area under the ROC curve [AUC]) value was accepted as the criterion for success, ranging from 0.5 to 1, and values approaching 1 were considered the most successful. Spearman's correlation coefficient was used to evaluate the correlation between FNA-Tg and the other parameters. Binary regression analyses were used for the comparison stage of the FNA-Tg and the other parameters as a diagnostic tool. McNemar's method was used while evaluating the specificity and sensitivity between the 2 diagnostic tests. The Hawass decision protocol was used to determine the superiority between the 2 diagnostic tests. A $P < .05$ was accepted as statistically significant.

3. Results

The data of 262 LNs of 176 patients, 122 (69.3%) women and 54 (30.7%) men, were analyzed in the study. The mean age of the patients was determined to be 48.6 ± 11.9 years for women and 50.9 ± 15.3 years for men. The comparison of the basic data of the patients according to malignant and benign LN involvement is provided in Table 1.

3.1. Diagnostic performance and the optimal cutoff of the FNA-Tg in determining malignant LNs in all patient group

When the cutoff point with the highest Youden's index was taken, the best cutoff value for the FNA-Tg procedure in detecting the malignant LNs was found to be 3.14 ng/mL with a sensitivity of 91.8% and specificity of 96.6% (Table 2). In our study, we determined that the FNA-Tg method had 2.3% false positive and 2.7% false negative rates in detecting malignant LNs.

3.2. Comparison of diagnostic performance of FNA-C, FNA-Tg, and FNA-C + FNA-Tg in determining malignant LNs

Compared to the FNA-C method, the FNA-Tg method was detected to have higher sensitivity and lower specificity in the entire patient group; while it had higher sensitivity and specificity in the subgroup with LN excisions (Table 3). The combined use of the FNA-Tg and FNA-C methods was detected to have higher sensitivity (100%) compared to single uses of these methods. However, it was also determined that this led to a lower specificity compared to using both FNA-Tg and FNA-C methods alone. Basic data is provided in Table 3.

3.3. Diagnostic performances and optimal cutoffs of FNA-Tg, serum Tg level, Tg_rate, and Tg_difference methods in detecting malignant LN

The diagnostic power of these methods was evaluated with ROC analysis and cutoffs were detected with Youden's index in

Table 1

Patient characteristics according to final lymph node status

	Final LN status		
	Malignant	Benign	*P* value
LNs: n (%)	85 (32.4)	177 (67.6)	
Patients			
Gender: male n (%)/female n (%)	28 (32.9)/57 (67.1)	55 (31.1)/122 (68.9)	.761*
Age (years): mean ± SD	47.6 ± 14.3	48.4 ± 13.2	.647†
Primary thyroid tumor			
Size (mm): median (interquartile range)	16 (11)	12 (18)	.010‡
Multiplicity: yes (%)/no (%)/unknown (%)	40/ 55.29/4.70	31.0/67.23/1.77	.106*
Lymphoid invasion: yes (%)/no (%)/unknown (%)	62.35/15.81/4.70	41.8/57.06/1.12	.001*
Vascular invasion: yes (%)/no (%)/unknown (%)	37.64/27.68/4.70	20.33/78.53/1.12	.001*
Extrathyroidal extension: yes (%)/no (%)/unknown (%)	24.70/70.58/4.70	10.73/88.1/1.12	.002*
Stage, n (%)			.009‡
I	58 (68.23)	146 (82.48)	
II	20 (23.52)	24 (13.55)	
III	4 (4.70)	2 (1.12)	
IV	1 (1.17)	2 (1.12)	
Unknown	2(2.35)	3(1.69)	
Diagnostic measurements			
FNA-Tg (ng/mL): median (interquartile range)	2194 (10730)	0.2 (0.0)	<.001‡
Serum Tg (ng/mL): median (interquartile range)	2.0 (33.4)	0.3 (1.4)	<.001‡
(FNA-Tg)-(serum Tg) (ng/mL): median (interquartile range)	1111 (8161)	0.0 (1.4)	<.001‡

Data are expressed as mean ± SD or median (interquartile range).

FNA-Tg = fine-needle aspiration thyroglobulin, LN = lymph node, n = number, SD = standard deviation, Tg = thyroglobulin.

*Derived from a χ^2 test. Data were expressed as n (%) or %.

†Derived from a student *t* test. (mean ± SD).

‡Derived from a Mann–Whitney *U* test (median [interquartile range]) or n (%).

Table 2

Diagnostic performance of the fine-needle aspiration thyroglobulin

	Table counts (n = 262)								
Cutoff value	TN	FN	FP	TP	Sensitivity	Specificity	PPV	NPV	Youden's index
0.25 ng/mL	159	3	18	82	0.965	0.898	0.820	0.982	0.863
0.5 ng/mL	163	5	14	80	0.941	0.921	0.851	0.970	0.862
1 ng/mL	166	7	11	78	0.918	0.938	0.876	0.960	0.856
3.14 ng/mL	171	7	6	78	0.918	0.966	0.929	0.961	0.884
10 ng/mL	175	10	2	75	0.882	0.989	0.974	0.946	0.871
100 ng/mL	175	17	2	68	0.800	0.989	0.971	0.912	0.789

FN = false negative, FP = false positive, NPV = negative predictive value, PPV = positive predictive value, TN = true negative, TP = true positive.

Table 3

Diagnostic performances of fine-needle aspiration thyroglobulin and fine-needle aspiration cytology in differentiated thyroid cancer

Include LNs	Diagnosis modality	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Surgically resected LNs only (n = 104)	FNA-C	82.4*	94.7*	98.6	54.5
	FNA-Tg (cutoff value, 3.14 ng/mL)	91.8*	100.0*	100.0	73.1
	FNA-Tg (3.14 ng/mL) + FNA-C	100.0	94.7	98.8	100.0
Surgically resected LNs and LNs followed up for 24 months or more (n:262, entire patient group)	FNA-C	82.4*	99.4*	98.6	92.1
	FNA-Tg (cutoff value, 3.14 ng/mL)	91.8*	96.6*	92.9	96.1
	FNA-Tg (3.14 ng/mL) + FNA-C	100.0	96.0	92.4	100.0

FNA-C = fine-needle aspiration cytology, FNA-Tg + FNA-C = combination of FNA-Tg and FNA-C, FNA-Tg = fine-needle aspiration thyroglobulin, LN = lymph node, NPV = negative predictive value, PPV = positive predictive value.

*$P < .05$ vs FNA-Tg + FNA-C, derived from a McNemar test.

all patient groups (Table 4). The FNA-Tg method was found to be the best in detecting malign LNs. It was determined that the Tg rate and the Tg_difference had similar powers in detecting the malignant LNs, while serum Tg had the lowest performance. It was seen that as Tg rate, Tg_difference, and serum Tg values increased, specificity increased, however sensitivity relatively decreased (Fig. 1 and Table 4).

3.4. Parameters affecting the FNA-Tg cutoff

3.4.1. The presence of thyroid gland. Figure 2 illustrates the ROC curves of the FNA-Tg by the presence of the thyroid gland. Group A represents the whole population (with and without a thyroid gland), and the cutoff level of FNA-Tg was found 3.14 ng/mL in this group (sensitivity, 91.8%; specificity, 96.6% AUC, 0.967 (95% confidence interval [CI], 0.939–0.994)).

Table 4

Cutoffs and performances of different diagnostic methods in differentiated thyroid cancer

	Cutoff value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden's index	AUC
Serum Tg (ng/mL)	1.07	68.92	63.95	45.13	82.71	0.329	0.698
Tg_rate (FNA-Tg/serum Tg)	6.3	79.73	94.77	86.76	91.57	0.74497	0.898
Tg_difference (ng/mL) (FNA-Tg - serum Tg)	2.84	87.84	97.67	94.2	94.92	0.855	0.905
FNA-Tg (ng/mL)	3.14	0.918	0.966	0.929	0.961	0.884	0.967

AUC = area under the ROC curve, FNA-Tg = fine-needle aspiration thyroglobulin, NPV = negative predictive value, PPV = positive predictive value, Tg = thyroglobulin.

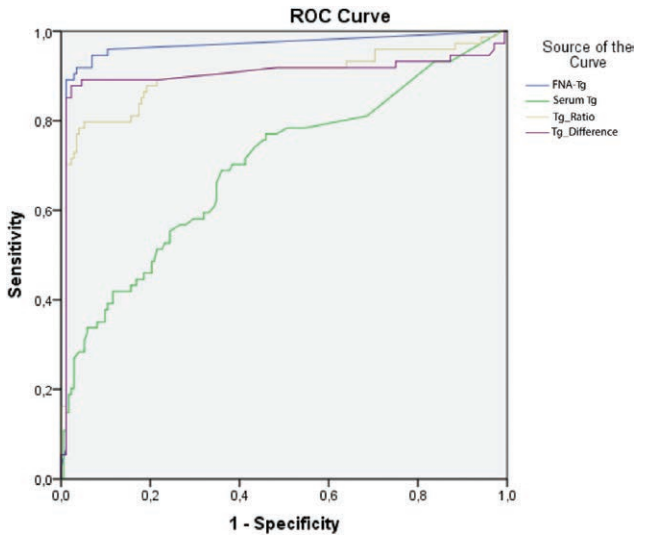

Figure 1. ROC curves for FNA-Tg, serum Tg, Tg_rate, and Tg_difference methods. FNA-Tg = fine-needle aspiration thyroglobulin, ROC = receiver operating characteristic, Tg = thyroglobulin.

Group B represents the patients with the thyroid gland and the FNA-Tg cutoff was found to be 15.5 ng/mL in this group (sensitivity, 100.0%; specificity, 94.3%; AUC, 0.952; 95% CI, 0.887–1.000). Group C represents the patients without the thyroid gland and the FNA-Tg cutoff was detected as 3.14 ng/mL in this group (sensitivity, 88.5%; specificity, 97.9%, AUC, 0.968; 95% CI, 0.935–1.000).

3.4.2. Serum TSH and thyroglobulin. The potential effect of serum TSH and serum Tg levels on FNA-Tg was evaluated with the regression analysis in all groups. FNA-Tg level of 3.14 ng/mL, which was the diagnostic tool for the entire study group, was used as the dependent variable, and nonsuppressed serum TSH (serum TSH level > 0.55 mIU/L), and serum Tg positivity (serum Tg level > 0.2 ng/mL) were used as the independent variables.

3.4.3. Serum thyroglobulin. We determined that the patients with serum Tg positivity had higher odds of the detection of malignant LNs with FNA-Tg (odds ratio [OR], 2.048; 95% CI, 1.010–4.153; $P = .047$) (Table 5).

3.4.4. Serum TSH. While no significant relationship was detected between the nonsuppressed serum TSH and FNA-Tg in the regression analyses (OR, 1.612; 95% CI, 0.909–2.857; $P = .102$) (Table 5), a positive correlation was detected in all groups between the serum TSH and the FNA-Tg in the correlation analysis ($R = 0.152$; $P = .017$).

3.4.5. Serum anti-Tg level. There was no statistically significant difference between FNA-Tg levels of the patients with negative and positive serum anti-Tg levels (0.3 [24.3] ng/mL and 0.2 [113.1] ng/mL, respectively, $P = .439$).

3.4.6. Association between serum thyroglobulin and thyroid gland in detecting malign LNs. Serum Tg level was higher in patients with thyroid gland in all patient groups; ($P < .001$) but there was no statistical difference in serum Tg level according to thyroid gland status in the subgroup of surgically resected LNs ($P = .066$) (Table 6).

4. Discussion

Different studies have reported quite different cutoff levels with different sensitivity and specificity rates for FNA-Tg in determining LN metastasis of DTC.[9] While the latest guidelines suggest using FNA-Tg levels less than 1 ng/mL to indicate benign results, they also recommend additional examinations to deal with confounding factors. There is currently no standardized cutoff level.[10,13] So, in our study, we documented the unique FNA-Tg cutoff of our medical center with real-life data and exhibited the factors affecting it. We also reported how to interpret the FNA-Tg results in the presence of confounding factors.

We found FNA-Tg to be more specific and sensitive than FNA-C in patients with malign LN histopathology. It is valuable when the FNA-C results are inadequate or acellular in clinical practice. The combined use of the FNA-Tg and FNA-C methods increased the sensitivity but decreased the specificity. In the previous studies, the combined use had a sensitivity ranging from 97% to 100% and a specificity ranging from 94% to 100% in detecting malignant LNs.[14,15] We strongly recommend the combination of these methods when evaluating the LNs of DTC patients.

We found the FNA-Tg had the best diagnostic performance compared to other laboratory methods such as Tg_rate, Tg_difference, and serum Tg. Our study showed the Tg rate cutoff was higher, resulting in lower sensitivity and specificity than in previous studies.[16,17] Also, in our study, the optimal cutoff level, sensitivity, and specificity for Tg_difference were higher than in previous studies.[14] These could be due to the differences in the patient population and laboratory kits used. We found the serum thyroglobulin had the lowest diagnostic performance (AUC, 0.698) compared to all laboratory methods. We believe these methods should be used as complementary tools to interpret blood contaminations or confirm gray zone results of FNA-Tg instead of being used alone.

FNA-Tg is a valuable diagnostic method for detecting LN metastasis, but the clinician should be careful with the factors affecting accuracy. A study showed that the thyroid gland's presence was ineffective in the accuracy of the FNA-Tg cutoff.[18] But in another study, Lee et al[17] reported that the diagnostic performance of FNA-Tg was affected by the presence of thyroid tissue and documented different cutoffs in patients with and without thyroid tissues. Moon et al[14] revealed the thyroid gland as a factor affecting the FNA-Tg cutoff. We determined the FNA-Tg cutoff as 15.5 ng/mL in patients with thyroid gland with a sensitivity of 100% and a specificity of 94.3%, but in patients without thyroid gland, the FNA-Tg cutoff was found as 3.14 ng/mL with a sensitivity of 88.5% and a specificity of 97.9%. Our results indicate, as in the previous studies, that the presence of thyroid tissue affects sensitivity, specificity, and the

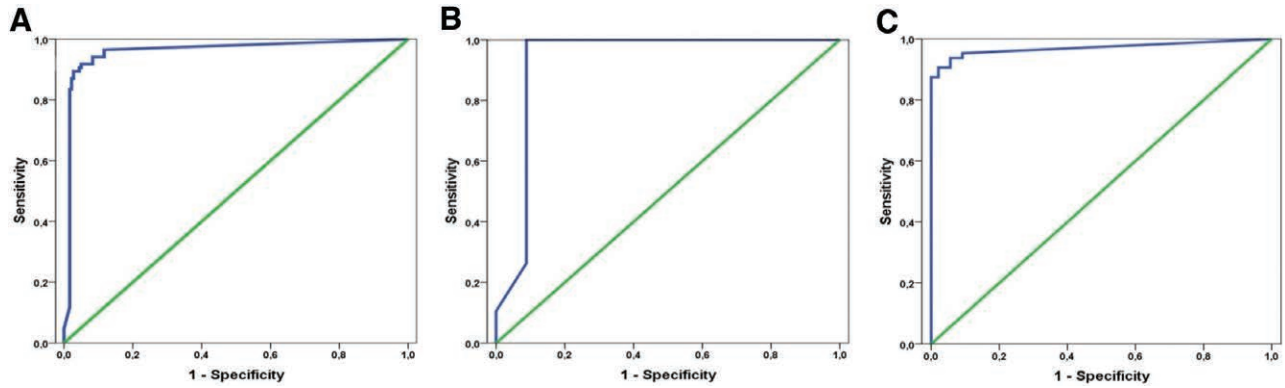

Figure 2. ROC curves for the FNA-Tg in accordance with the presence of thyroid gland. (A) All patients. (B) Patients with thyroid gland. (C) Patients without thyroid gland. FNA-Tg = fine-needle aspiration thyroglobulin, ROC = receiver operating characteristic.

Table 5

Logistic regression analysis of serum TSH and thyroglobulin with the diagnosis using fine-needle aspiration cutoff value 3.14 ng/mL

		95% Confidence interval for odds ratios		
	Odds ratio	Lower limit	Upper limit	*P* value
Nonsuppressed Serum TSH	1.612	0.909	2.857	.102
Serum thyroglobulin positivity	2.048	1.010	4.153	.047

TSH = thyroid-stimulating hormone.

cutoff value of the FNA-Tg. The sensitivity is higher in patients with thyroid tissues, and specificity is higher in patients without thyroid tissues. Mainly, the thyroid gland seems to make its effect via serum thyroglobulin production, and as serum Tg differs due to the thyroidectomy status, the FNA-Tg cutoff is affected.

In our study, we detected a positive correlation between the serum Tg positivity (Tg >0.2 ng/mL) and FNA-Tg. Moon, et al[14] reported a positive correlation between the serum thyroglobulin and the FNA-Tg for both benign and malignant LNs in their study. Jeon et al[16] evaluated 160 LNs and reported that high sensitivity and specificity could only be reached with different FNA-Tg cutoffs for the groups with serum Tg positivity (>1.0 μg/L) and negativity (≤1.0 μg/L). Serum Tg may cause false positive FNA-Tg results via blood contamination in benign LNs and also may be a confounding factor for the true malignant LNs producing relatively low amounts of Tg in the gray zone. To confirm the malignancy of the LN, a cytological examination and a higher FNA-Tg level than serum Tg may be helpful. All these make it reasonable to use different FNA-Tg cutoffs according to thyroid presence and serum Tg positivity.

We evaluated the association between serum Tg and thyroid gland and found no statistical difference in serum Tg level according to thyroid gland status in malign LNs. However, in another study, serum Tg levels were statistically higher in malign LNs when there is a thyroid gland.[14] The difference may result from the patient populations. We hypothesize that metastatic LNs producing high amounts of Tg may have caused markedly elevation of serum Tg regardless of thyroid status in our study.

A positive correlation between serum TSH and FNA-Tg was also detected in our study. However, after conducting regression analysis, we didn't find any significant difference between nonsuppressed TSH (TSH >0.55) and FNA-Tg. This could be attributed to the limited number of patients with high TSH levels. Moon et al[16] have reported that TSH increase has no effect on FNA-Tg measurements in benign LNs, but there is a clear correlation between TSH increase and FNA-Tg in malignant LNs. They have recommended using different FNA-Tg cutoff values based on serum TSH levels. We suggest considering the interaction between serum TSH and FNA-Tg when evaluating the malignancy of LN.

Our study found that anti-Tg positivity did not affect the FNA-Tg levels in malignant LNs. However, previous studies have reported different results. For instance, Jeon et al[19] reported that anti-Tg antibodies led to lower FNA-Tg levels and sensitivity. In contrast, Boi et al[20] found that the FNA-Tg values were unaffected in patients with or without anti-Tg antibodies in malign LNs. They suggested that high Tg concentration in metastatic LNs saturates the antibody binding sites in LNs, causing FNA-Tg levels to remain significantly high for malignancy. Our study supports this hypothesis.

The FNA-Tg results can also be affected by the technical proficiency of the operator. Blood contamination may occur, especially in LNs near blood vessels and the thyroid gland.

Our research found that 5 patients had FNA-Tg results above 3.14 ng/mL but lower than their serum Tg levels. These patients had malignant pathological results. We hypothesize that the lower FNA-Tg levels in the malignant LNs may be due to either the tumor's dedifferentiation in the metastatic malignant LNs or the aspirated area not coinciding with the metastasis area due to focal metastasis in the LNs.[21,22] In another 5 patients, FNA-Tg values were below 3.14 ng/mL, but the FNA-C and pathology results were malignant, and all were negative for anti-Tg antibodies. We believe this situation may be related to the potential "hook" effect in Tg measurement. Therefore, if FNA-Tg levels do not align with clinical and USG findings, the sample should be diluted and restudied. Additionally, it should be noted that differentiated thyroid carcinoma can secrete different Tg isoforms, and FNA-Tg measurements may be affected by the antibodies used in the kits.[23,24]

Our study is retrospective and conducted at a single center. When determining the final status of the LNs, we relied on follow-up period findings in cases where there was no histopathology available. This means that there is a small chance of misdiagnosis for some LNs. However, we took steps to minimize this risk by closely monitoring patients for potential malignancies for at least 2 years. We used repeated USG observations, FNA-C, and FNA-Tg procedures as needed. Also, it is worth noting that the sensitivity of Tg measurement kits can vary from center to center, making it difficult to detect the same cutoff in all centers.[25]

In conclusion, we determined an FNA-Tg cutoff value of 3.14 ng/mL of our center with high sensitivity and specificity in detecting the LN metastases. Our study revealed that the FNA-Tg had a higher diagnostic sensitivity than the FNA-C

Table 6

Serum thyroglobulin level according to thyroidectomy status

	Included LNs					
	a) All cases			b) Surgically resected LNs		
	No thyroidectomy (n = 59)	Thyroidectomy (n = 203)	*P*	No thyroidectomy (n = 31)	Thyroidectomy (n = 73)	*P*
Serum Tg	2.4 (21.3)*	0.4 (1.7)	<.001	5.0 (65.9)*	1.5 (21.8)	.066

Data are expressed as median (interquartile range).

LN = lymph node, Tg = thyroglobulin.

*$P < .001$ (derived from a Mann–Whitney *U* test) compared with thyroidectomy cases.

and that joint use of the FNA-Tg and FNA-C methods had a higher diagnostic power than using these tests separately. Serum TSH, serum Tg, and the presence of thyroid tissue were found as the affecting factors of FNA-Tg level, so it is important to take into account them when interpreting the FNA-Tg results.

Author contributions

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Investigation: Sinem Kargun, Mustafa Aydemir, Nusret Yilmaz, Ramazan Sari.
Writing – original draft: Sinem Kargun.
Writing – review & editing: Sinem Kargun.
Validation: Sebahat Ozdem.

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