Can Serum Thyroglobulin Levels Help to Identify the Involved Neck Compartment of Differentiated Thyroid Carcinoma?

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ABSTRACT

We aimed to evaluate the predictive ability of serum thyroglobulin (Tg) levels on the localization of the metastatic lymph node compartments in locoregional metastases of papillary thyroid cancer (PTC). This retrospective study included 143 patients who underwent neck dissections for a total of 172 for persistent/recurrent locoregional PTC. They were grouped according to the localization of lymph node metastasis (LNM): Central (C-LNM), Lateral (L-LNM), both central and lateral LNM (C + L LNM). To confirm that the Tg cutoff discriminated LNM localizations, the sample was categorized as suppressed (< 0.1 mU/l) or non-suppressed (> 0.1 mU/l) according to TSH and ROC analysis. Mixed-effects models were used to investigate the effect of LNM localization on Tg levels and to eliminate the confounding effects of TSH, tumor burden (defined as the number and the largest diameter of LNM), and RAI. Mean Tg levels were 1.43 µg/l for C-LNM (n = 47), 3.7 µg/l for L-LNM (n = 99), and 8.60 µg/l for C + L LNM (n = 26). Independent of TSH, tumor burden and RAI, the mean Tg levels of L-LNM and C + L LNM groups were not significantly different, while that of C-LNM was significantly lower than those of L-LNM and C + L LNM. To discriminate C-LNM from L-LNM and C + L LNM in patients with TSH > 0.1 mU/l, the optimal cutoff for Tg was 1.05 µg/l (sensitivity = 74.7 %, specificity = 70.4 %, PPV = 87.7 %). L-LNM increases serum Tg levels more than C-LNM in persistent/recurrent locoregional nodal disease of PTC. Tg above 1.05 µg/l may indicate lateral LNM. Tg may be an important marker for the localization of LNM in the neck.

Introduction

Thyroid carcinoma is the most common malignancy of the endocrine system, accounting for 1 % of all newly diagnosed cancers [1] and 80–90 % of them are papillary thyroid carcinoma (PTC) [2, 3]. The prognosis is favorable when thyroid cancers are treated appropriately. Cervical lymph node metastasis (LNM) has been detected in 27–46 % of patients with newly diagnosed PTCs, and 5–20 % of them have locoregional recurrences after initial surgery, often involving cervical lymph nodes and making them candidates for secondary surgical procedures [4, 5]. The presence of cervical LNM increases the risk of locoregional recurrence. Prophylactic central neck dissection reduces locoregional recurrence but is associated with a higher risk of postoperative complications. Therefore, it is recommended to be preferred by high-volume surgeons in high-risk patients with advanced primary tumors [6]. The structural incomplete response to initial therapy results in persistent locoregional disease, occuring in 2–6 % of ATA low-risk, 19–28 % of intermediate-risk, and 67–75 % of high-risk patients [7, 8]. The revised 2009 ATA Management Guidelines for Patients with Thyroid Nodules and DTC recommend surgical management of locoregional disease in the absence of distant metastases [9].

Thyroglobulin (Tg) is a tumor marker for DTC, if anti-Tg antibodies are negative [10, 11]. But routine preoperative measurement of serum Tg or anti-Tg antibodies is not recommended [12]. Nevertheless, it is a reliable marker in patients treated with total thyroidectomy (TTx) and even more consistent – for those – who had remnant ablation or treated with radioactive iodine (RAI). On routine follow-up measures after surgery with or without RAI, serum Tg measurements and neck ultrasonography are performed [12]. Tg levels increase with increasing TSH serum levels and tumor burden in patient with metastatic disease [13, 14]. To our knowledge, few studies have investigated this relation, probably due to the difficulties in estimating the tumor burden with quantitative analysis [13, 15]. While considerably high Tg levels do suggest distant metastasis. The relationship between localization, tumor burden of the metastases, and serum Tg levels is not clear for the moderately increased levels, which almost always indicates locoregional metastases of different neck compartments. Some studies have investigated the Tg cutoff level for distant organ metastasis [16, 17], but to our knowledge, none assessed the variations in serum Tg levels with regard to the involved cervical lymph node compartment in patients with locoregional metastasis. Thus, we aimed to verify the effectiveness of Tg levels to differentiate the localizations of the metastatic lymph node in the neck independent of tumor burden, RAI treatment, and serum TSH levels in patients with persistent/recurrent locoregional metastases.

Patients and Methods

Study population and inclusion criteria

This retrospective study included patients who underwent therapeutic neck dissection for persistent/recurrent locoregional LNM in a tertiary care university hospital between January 2006 and August 2020. All data were collected from electronic and manual medical records. University Ethical Committee on human research approved the study (Project Number: İ1–56–21).

Simultaneous serum Tg, TSH and anti-Tg levels before lymph node dissection (LND) were recorded. Results from neck ultrasonography (US), computed tomography (CT) and histopathological exam were analyzed to determine the localization, number and largest diameter of metastatic lymph nodes. The inclusion criteria were as follows: 1) TTx with or without LND for PTC as an initial surgery, 2) persistent/recurrent metastatic cervical lymph node/s found radiologically (US/CT) and proven by Tg washouts and/or FNAC after initial surgery during follow-up period, 3) an appropriate neck dissection for the proven locoregional metastasis and 4) biochemical and structural complete response after neck dissection with or without RAI treatment. Exclusion criteria were as follows: 1) radiologically detectable residual thyroid tissue before neck dissection, 2) anti-Tg antibody positivity, 3) distant metastasis at the time of neck dissection, 4) inoperable cervical LNM, 5) < 1 month time period between thyroidectomy and neck dissection to measure the dip (lowest) Tg level, 6) radiologically detectable (macroscopic) (US/CT) cervical fibro-muscular tissue invasion with LNM, 7) biochemical or structural incomplete response, at the final evaluation performed after neck dissection, and 8) reported residual tissue radiologically before surgery or having had remnant thyroid tissue in histopathological reports.

Thus, in this study we assumed that serum Tg levels in the patients represented tumor burden caused by LNM since the thyroid resection is total, and possible remnant tissue is completely ablated, patients with distant organ metastases are excluded. Tumor burden caused by metastatic lymph nodes were represented with the largest diameter of LNM and number of LNM in histopathology and/or imaging studies. To evaluate the localization of metastatic node/s, preoperative US reports/maps, CT reports, and/or histopathological results after surgery were used.

Localization of LNM and neck dissections were classified and performed respectively, according to the American Head and Neck Society and the American Academy of Otolaryngology classification [18]. Our sample was classified in accordance with the type of dissection central (C) LNM group for central compartment neck dissection, lateral (L) LNM group for lateral compartment neck dissection 3) central + lateral (C + L) LNM group, for those with LNM in both central and lateral neck compartments and both compartments had been dissected in the same session. Lateral compartment dissection was referred right, left or both sides.

Thyroglobulin was measured with immunochemiluminometric DxI 800 assay (Beckman Coulter, USA). The Tg assay used for the analyses has a functional sensitivity of 0.1 mg/l with 95 % confidence.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 and R version 4.1.0. Descriptive statistics were presented as counts and percentages for categorical variables and standard and mean deviations for continuous variables. Normality assumption was tested by Kolmogorov – Smirnov test with Lilliefors Significance Correction. Natural logarithm transformation was applied to the outcome variable to achieve a normal distribution and homogeneous variances. Chi-square test was performed for clustered data and non-parametric analysis of clustered receiver operating characteristics (ROCs), which were performed to account for intracluster correlation among multiple measurements from the same patient. An ROC curve was used to decide the diagnostic value of serum thyroglobulin to distinguish localization of LNM. To increase the specificity and sensitivity of the cutoff Tg level ROC analysis was performed both in the whole sample and in two groups suppressed (< 0.1 mU/l) and non-suppressed (> 0.1 mU/l) according to TSH.

The areas under the curves (AUC) and 95 % confidence intervals for all variables were quantified. Cutoff values were selected using with Youden's index. Measurements were dichotomized according to cutoff values, and specificity, sensitivity and negative and positive predictive values were calculated. To account for the clustered structure of the data, linear mixed-effects models were used to analyze factors that affected serum Tg variation. Serum Tg level was the dependent variable. Simultaneous TSH level, the largest diameter of LNM, the number of LNM, and the condition of receiving RAI after the first surgery independent variables in the model to eliminate their effects on Tg. The Bonferroni correction was applied to control Type I error rate. A p-value of < 0.05 was considered significant.

Baseline sample characteristics

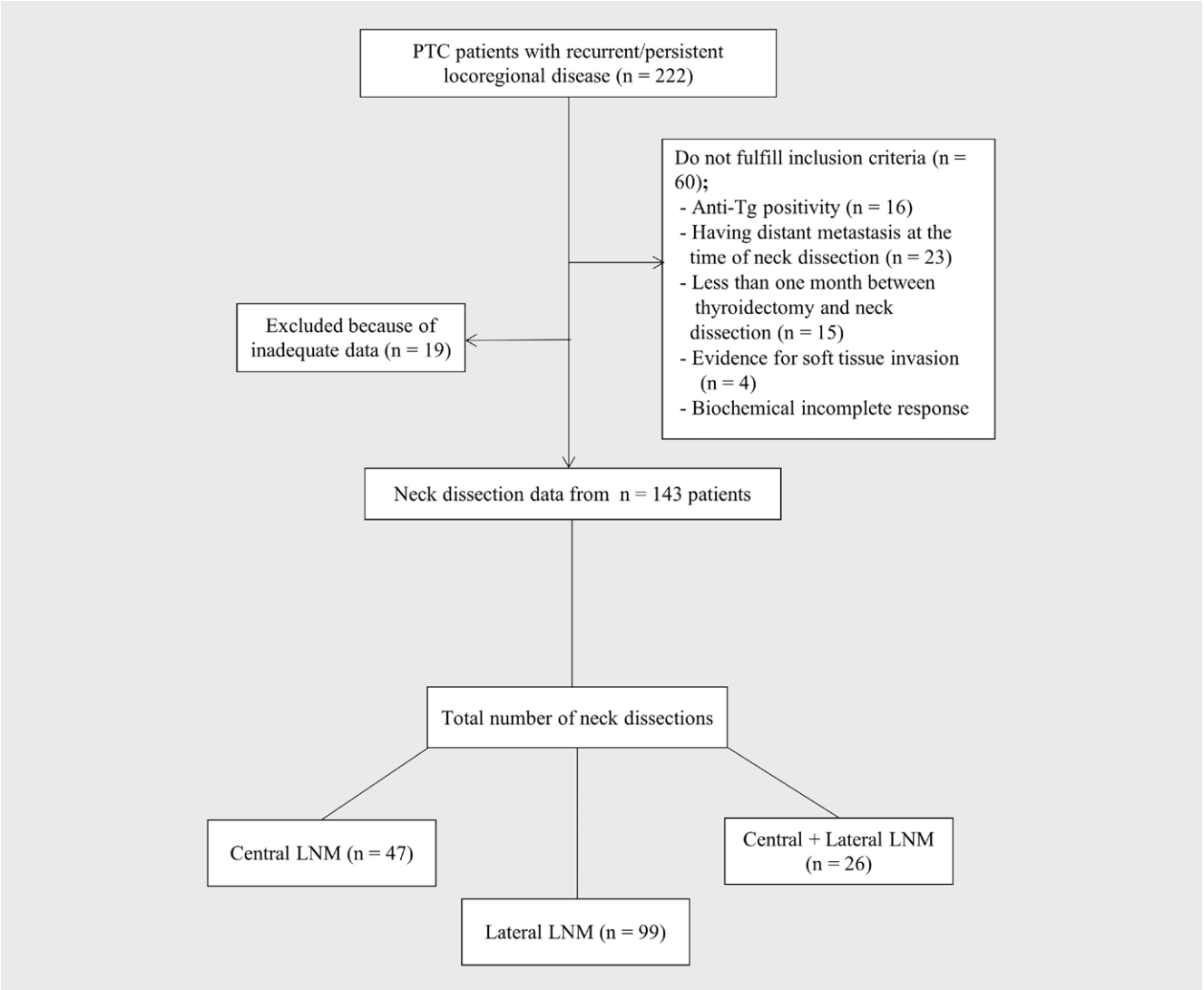
We enrolled 222 patients diagnosed with PTC who underwent neck dissection for persistent/recurrent locoregional LNM, between January 2006 and August 2020 at University Hospitals. After assessing the eligibility criteria and data, 143 patients underwent neck dissections for a total of 172 for persistent/recurrent locoregional PTC. Of them, 19 underwent neck dissection twice, and 5 for three times due to recurrence. Flow diagram of the sampling is shown in ▶ **Fig. 1**.

Baseline characteristics of the whole sample are shown in ▶ **Table 1**. Mean age was 47.0 ± 13.1 years, and 73.3 % (n = 126) were females. The mean age of diagnosis was 38.3 ± 12.5 years, and disease duration at the time of neck dissection was 3.7 ± 4.0 years. 90.1 % (n = 155) of the sample had stage I PTC, and the rest (9.9 %, n = 17) had stage II PTC. Age, sex, age at diagnosis, disease duration at the time of neck dissection, largest diameter of primary tumor and TSH levels were not significantly different between the LNM groups (▶ **Table 1**).

The number of metastatic nodes was higher in the C + L LNM group than those of the other groups ($p < 0.001$). While that of C LNM and L LNM groups did not differ from each other ($p = 1.000$) (▶ **Table 1**). C + L LNM group had similar, mean largest diameter of metastatic nodes with C LNM and L LNM groups, whereas L LNM group had higher mean largest diameter than C LNM group ($p = 0.043$) (▶ **Table 1**).

The mean pre-neck dissection Tg levels were 1.43 ± 2.59 µg/l for C LNM, 3.7 ± 5.78 µg/l for L LNM, and 8.60 ± 15.94 µg/l for C + L LNM groups. While the difference between Tg levels of L LNM and C + L LNM groups was not significant ($p = 0.183$), C LNM group exhibited significantly lower mean Tg level than those of other groups (L LNM $p = 0.006$ and C + L LNM $p < 0.001$) (▶ **Table 1**).

RAI was administered to approximately 80 % (n = 137) of the patients after initial surgery and 66 % (n = 113) after neck dissection for persistent/recurrent locoregional disease.



▶ **Fig. 1** Flow diagram of the sampling recurrent/persistent PTC patients (n = 222).; PTC: Papillary Thyroid Carcinoma, Tg: Thyroglobulin, LNM: Lymph Node Metastasis.

▶ **Table 1** Descriptive and clinical characteristics of the study samples (n = 172).

	C LNM n = 47	L LNM n = 99	C + L LNM n = 26	p
Female	32 (68.1 %)	74 (74.7 %)	20 (76.9 %)	0.658
Stage*, n (%)				0.834
I	43 (91.5 %)	88 (88.9 %)	24 (92.3 %)	
II	4 (8.5 %)	11 (11.1 %)	2 (7.7 %)	
Age, mean ± SD	48.0 ± 11.3	47.9 ± 13.2	42.4 ± 14.5	0.247
Age at diagnosis, mean ± SD	39.4 ± 11.3	38.5 ± 12.6	34.2 ± 14.1	0.989
Disease duration**, mean ± SD	3.91 ± 3.45	3.87 ± 4.32	2.91 ± 3.89	0.582
Diameter of primary tumor (mm), mean ± SD	16.88 ± 12.03	17.14 ± 10.45	20.76 ± 11.88	0.311
Number of LNM, mean ± SD	2.81 ± 2.68	3.34 ± 3.61	6.00 ± 3.45[a]	**< 0.001**
The largest diameter of LNM (mm), mean ± SD	11.07 ± 5.79	13.94 ± 6.38[b]	13.51 ± 7.21	**0.046**
Tg, µg/l, mean ± SD	1.43 ± 2.59[c]	3.70 ± 5.78	8.60 ± 15.94	**< 0.001**
TSH (mU/l), mean ± SD	1.53 ± 2.91	2.30 ± 8.06	0.74 ± 1.23	0.201

LNM: Lymph Node Metastasis; C: Central; L: Lateral; C + L: Central + Lateral; Tg: Thyrogloblin.; [a]Different from C and L (p < 0.001).; [b]Different from C (p = 0.043).; [c]Different from L and C + L (natural logarithm was applied, p = 0.006 and p < 0.001, respectively).; *There were no patients with stage III or IV thyroid cancer.; **Years, at the time of neck dissection.

The effect of lymph node metastases localization on Tg level

We analyzed the effect of LNM localization on Tg level using mixed-effects model. The number of metastatic nodes, the largest diameter of the metastatic nodes and serum TSH levels were significantly associated with higher Tg levels (p = 0.028, p = 0.015, p < 0.001, respectively), whereas receiving RAI after initial surgery is associated with lower Tg levels (p = 0.033).

After adjusting for the possible confounding factors, such as number of metastatic nodes, the largest diameter of metastatic nodes, serum TSH levels and RAI treatment, the mixed-effects model revealed that mean pre-neck dissection Tg levels of patients with L LNM was significantly higher than those with C LNM (with a mean difference 1.76 ± 1.26 µg/l 95 % CI 1.12–2.76) (p = 0.014). In addition, metastases on central + lateral compartment rather than central compartment increased Tg level to a mean ± SD 2.53 ± 1.38 µg/l (95 % CI 1.33–4.79) (p = 0.002). However, Tg levels was not significantly associated on lateral compartment metastasis and central + lateral compartment metastasis (p = 0.13).

Biochemical response after additional therapy for persistent/recurrent locoregional disease was not associated with RAI treatment after neck dissection (for whole sample p = 0.853, C LNM group p = 0.119, L LNM group p = 0.117, C + L LNM group p = 0.255).

Diagnostic ability of thyroglobulin level to predict localization of lymph node metastases

ROC curve were used to determine the cutoff Tg level that could discriminate metastatic compartments (▶ **Tables 2** and **3**). To discriminate C LNM from L LNM, the optimal cutoff was 1.05 µg/l with the AUC of 0.651 ± 0.049 (p = 0.003, 95 % CI = 0.555–0.747). To discriminate C LNM from L LNM and C + L LNM, the optimal cutoff was 1.05 µg/l with an AUC of 0.672 ± 0.045 (p < 0.001, 95 % CI = 0.584–0.760) (▶ **Table 2**). The sample was divided into two groups according to the TSH value as < 0.1 mU/l (suppressed, n = 79) and > 0.1 mU/l (non-suppressed, n = 94). Tg levels were not significantly different between C LNM and other groups with suppressed TSH. To discriminate C LNM from L LNM in the group with non-suppressed TSH, the optimal cutoff was 1.06 µg/l with the AUC of 0.703 ± 0.060 (p < 0.001, 95 % CI = 0.586–0.819). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 70.7 %, 70.4 %, 83.7 % and 52.8 % for this cutoff, respectively. To dis-

▶ **Table 2** The results of ROC curve analysis in the whole group (n = 172).

	C LNM vs. L LNM (95 % CI)	C LNM vs. L and C + L LNM (95 % CI)
Cutoff (µg/l)	1.05	1.05
AUC	0.651 ± 0.049 (0.555–0.747)	0.672 ± 0.045 (0.584–0.760)
Sensitivity	56.6 % (46.8–65.9 %)	61.9 % (53.2–69.9 %)
Specificity	72.3 % (58.2–83.0 %)	72.3 % (58.2–83.0 %)
Positive predictive value (PPV)	81.1 % (70.4–88.6 %)	85.7 % (77.1–91.4 %)
Negative predictive value (NPV)	44.2 % (33.6–55.3 %)	41.4 % (31.4–52.3 %)

LNM: Lymph Node Metastasis; C: Central; L: Lateral; CL: Central + Lateral; CI: Confidence interval; AUC: Area under the ROC curve.

▶ **Table 3** The results of ROC curve analysis in the group with non-suppressed TSH (n = 94).

	C LNM vs. L LNM (95 % CI)	C LNM vs. L and C + L LNM (95 % CI)
Cutoff (µg/l)	1.06	1.05
AUC	0.703 ± 0.060 (0.586–0.819)	0.714 ± 0.058 (0.603–0.824)
Sensitivity	70.7 % (58–80.8 %)	74.7 % (63.8–83.2 %)
Specificity	70.4 % (51.5–84.2 %)	70.4 % (51.5–84.2 %)
Positive predictive value (PPV)	83.7 % (71–91.5 %)	87.7 % (77.2–93.5 %)
Negative predictive value (NPV)	52.8 % (37–68 %)	50 % (34.9–65.2 %)

LNM: Lymph Node Metastasis; C: Central; L: Lateral; CL: Central + Lateral; CI: Confidence interval; AUC: Area under the ROC curve.

criminate C LNM from L LNM and C + L LNM, the optimal cutoff was 1.05 µg/l with an AUC of 0.714 ± 0.058 ($p < 0.001$, 95 % CI = 0.603–0.824) Sensitivity, specificity, PPV and NPV were 74.7 %, 70.4 %, 87.7 %, and 50 % for this cutoff, respectively (▶ **Table 3**).

Discussion

To the best of our knowledge, this is the first study that examined the relationship between serum Tg levels and the location of metastatic neck lymph nodes in PTC patients. We found that the increase in TSH and the tumor burden (defined as the largest diameter and number of metastatic nodes) resulted in higher serum Tg levels which was consistent with the literature [13–15]. The patients who had recurrences in the lateral compartment had significantly higher Tg levels, when compared to those with the central lymph node metastasis.

Rosenbaum-Krumme et al. showed a positive correlation of serum Tg and tumor mass in their study which quantitatively examined the relationship between tumor burden and Tg via a mathematical formulation mainly by using serum Tg level [15]. Authors of a French study showed the significant relationship between Tg and tumor burden, in a group of 75 PTC patients who had undergone thyroidectomy and completely ablated thyroid residue. 'Tg/TSH' was used to eliminate the effect of TSH and tumor burden defined as number of metastatic lymph nodes and their total surface area/volume [13]. However, they assumed that the effect of TSH on Tg is linear. Although both parameters are positively correlated, it is unclear if it was linear. Consistent with the literature we found that TSH level is positively correlated with Tg level before neck dissection. We believe the mixed-effects regression model provides a sensitive adjustment for the possible confounders. Our results showed a correlation between involved compartment and serum Tg levels prior to LND in persistent/recurrent locoregional PTC cases. C LNM resulted in significantly lower serum Tg levels than lateral or both central and lateral LNM in spite of the possible confounding effects of serum TSH levels, tumor burden and RAI treatment.

The limitations of our study were its retrospective design, lack of volumetric measurements for metastatic lymph nodes, and the relatively small sample size of the C + L LNM group compared to the other groups. The mean Tg level of C + L LNM was twofold higher than that of L LNM; but, the difference was not significant between the groups which may be due to the small sample size of C + L LNM group. In addition, it was not possible to detect a cutoff Tg level in the suppressed group in ROC analyzes because there were many overlapping thyroglobulin values.

Neck US for all compartments in experienced hands and Tg wash outs are the gold standards for preoperative diagnosis of recurrent disease [19–21]. Preoperative metastatic lymph node mapping by an experienced sonographer, becomes even more important since the risk of complications is higher in repeated neck dissections. The serum Tg levels may be used to help the sonographers for the localization of LNM. The cutoff values for whole sample we found are not high diagnostic accuracy due to significant overlap in the TSH suppressed group and a high variance in Tg values. The Tg values for TSH suppressed group were not significantly different between C-LNM and other groups. In contrast, in the non-suppressed group, the cutoff to discriminate C LNM from L LNM and C + L LNM has a higher diagnostic accuracy.

Our findings suggest that non-suppressed Tg level above 1.05 µg/l indicates lateral or central + lateral LNM, while levels below 1.05 µg/l indicates central LNM. Discordance between LNM localization and Tg level may lead the sonographer and/or clinician for further investigation of the lateral compartment. If non-suppressed Tg level is above 1.05 µg/l and lateral LNM was not detected on neck sonography, a second look ultrasonography may be useful. The pathophysiological mechanism under this significant difference is is difficult to elucidate, but it may be related to complex lymphatic drainage of different neck compartments.

Conclusion

In patients followed up after initial therapy for PTC, persistent/recurrent lateral nodal disease increases serum Tg more than the central one. In the presence of moderately elevated serum Tg level, Tg values above 1.05 µg/l may indicate a nodal disease in the lateral compartment. Serum thyroglobulin levels may be an important determinant for the localization of metastatic lymph nodes in the neck and, may help to optimize preoperative US and surgical approach for persistent/recurrent locoregional disease.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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