

# The Role of Intraoperative Thyroglobuline Level of Lymph Node in the Management of Papillary Thyroid Cancer (Determination of a Cutoff Point)

## Abstract

**Background:** Some studies have shown that a preoperative high concentration of thyroglobulin (Tg) in wash out of fine-needle aspiration cytology of cervical lymph nodes mandate therapeutic lymph node dissection. However, there is disagreement about the minimum concentration of Tg which could have diagnostic value. Hence, according to our literature review, this study is the first one which designed to do intraoperatively. Therefore, this study was conducted and aimed to determine the clinical diagnostic value of Tg lymph nodes in the diagnosis of metastatic thyroid cancer. **Methods:** In a cross-sectional study, 65 patients with papillary thyroid carcinoma (PTC) who were thyroidectomy candidates were chosen and during surgery, before the removal of lymph nodes in the neck, fine-needle sampling was performed and the level of Tg in the samples, nature of the sample sent for biopsy and Tg levels in affected and unaffected lymph nodes were determined. **Results:** The mean levels of washout Tg in malignant and nonmalignant lymph nodes were  $622.1 \pm 66.2$  and  $1.38 \pm 0.43$  ng/ml, respectively, and the difference between the two groups was significant ( $P < 0.001$ ). The Tg cut-off point for the detection of lymph node metastases was 0.7 ng/dl, and according to it, Tg washout sensitivity was 93.8%, specificity of 92.4%, false positives 7.76%, false negatives 6.3%, positive predictive value was 92.3%, and negative predictive value was 93.8% and accuracy was 93.1%. **Conclusion:** Based on the results, Tg level of cervical lymph nodes in patients with PTC is a suitable criterion for the diagnosis of lymph node which can be determined through fine-needle biopsy. Therefore, it is suggested that in patients with suspicion of lymph nodes involvement during surgery, fine-needle biopsy and determination of the Tg level performed.

**Keywords:** Fine-needle aspiration, thyroglobulin, thyroid cancer

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## Introduction

Papillary thyroid carcinoma (PTC) accounted for 80% of thyroid cancers with a usually good prognosis (mortality <10%). PTC is metastasized to regional lymph nodes in 30%–80% of patients at the time of diagnosis.<sup>[1]</sup> Thyroglobulin (Tg) is a glycoprotein produced by the follicular cells of the thyroid and is used as a valuable serum marker for detecting recurrent or persistent well-differentiated thyroid cancer of follicular cell origin.<sup>[2]</sup> Tg measurements and neck ultrasonography every 6–12 months and then annually is recommended in case of absence of disease.<sup>[3]</sup> Besides the interference of Tg in the measurement of Tg antibodies (Tg-Ab), anti-Tg measurements at regular intervals in patients who were positive for anti-Tg is valuable as marker in the follow-up clinical value alone.<sup>[4-6]</sup> Continuous or rising Tg-Ab titers in patients is valuable and could

be related to the relapsed or presence of thyroid carcinoma.<sup>[3,5-7]</sup>

For good surgical planning, this is necessary to determine the cervical lymph node metastasis in thyroid cancers. According to the American Thyroid Association guidelines, ultrasound-guided fine-needle aspiration (FNA) is the best method for recognition of lymph node involvement. However, investigation of the retropharyngeal and some mediastinal lymph node involvement is one of the limitations of ultrasound study.<sup>[8]</sup>

Intraoperative Clinical diagnosis of metastatic lymph node seems to not be sensitive and specific.<sup>[9]</sup> Frozen section is accurate in predicting node metastases in clinically node-negative PTC. However, it is necessary to intraoperative resection of the lymph node and it may harmful.<sup>[10]</sup>

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The strong relationship of elevated level of Tg in cervical lymph nodes and the metastatic PTC have been shown in the literature.<sup>[11]</sup>

So far a study of the relationship between intraoperative Tg wash out of suspicious lymph nodes in the neck, and permanent pathology is not performed up to now, considering the importance of early detection of metastatic lymph node in differentiated thyroid cancer who promote lymph node dissection (LND) is suitable. Finding a test that can diagnose the disease as soon as possible, with reasonable cost absolutely is necessary. Therefore, this study was performed and aimed to determine the concentration of Tg (wash out Tg) of the sample taken with an FNA of lymph nodes of lymph nodes affected and unaffected in PTC during operation and comparison with permanent pathology.

## Methods

The study was a cross-sectional study which was conducted from August 2014 to May 2015 in the Al Zahra hospital. The study population included patients with PTC who candidate for thyroidectomy and LND and people with the previous thyroidectomy who was a candidate for LND and was admitted to the hospital. Inclusion criteria consisted of PTC diagnosis by pathologic assessment and Tg washout possibility of reviewing of lymph node samples. Tg washout impossibility of reviewing for various reasons and lack of PTC pathology in the final pathology report and dissatisfaction of patient for any reason and in any stage of the study was considered as exclusion criteria. A sample size using the standard formula for prevalence studies by 95% confidence interval and the presence of Tg washout in lymph node samples which has been estimated equivalent to 2.0 and acceptance of error rate of 1.0 number of 61 patients were estimated. To ensure further 65 patients were studied.

After the adoption of proposals and coordination, 65 patients suspected for thyroid carcinoma undergoing thyroidectomy were selected and during surgery, at first, based on clinical diagnosis LNs are divided into two groups (according to darkness, hardness, size >5 mm): (1) involved and (2) noninvolved. Before the removal of lymph nodes in the neck FNA cytology (FNAC) was performed and one or more samples were sent for pathological diagnosis. Mentioned lymph node in a separate jar was sent to the pathology laboratory. At the same time, Tg wash out with 1 ml of normal saline was done and was sent for the measurement of Tg. All the Tg samples immediately centrifuged and if the final pathology was not thyroid cancer they were excluded from the study. Obtained results registered in the special checklist that has been designed for this purpose and then entered into the computer and analyzed using SPSS software. The descriptive analysis was used and the results reported as Mean  $\pm$  SD. Collected data were analyzed using software

SPSS version 20 (SPSS Inc., Chicago, Illinois, USA) and statistical tests of *t*-test Student's (to compare quantitative data between two groups), Chi-square (for nominal data and qualitative comparison between the two groups). Also receiver operating characteristic (ROC), to get the sensitivity, specificity, the percentage of false positive and false-negative predictive value and accuracy was used.

## Ethic

All information kept strictly confidential, and patients could at any stage leave the study without any reason. Furthermore, in this study, we observe all principles contained in the Declaration of Helsinki.

## Results

In this study, 70 noninvolved lymph nodes and 70 involved lymph nodes from 65 patients undergoing thyroidectomy were isolated and studied. The mean age of patients was  $39.7 \pm 12.8$  years, and 6 (9.2%) were male. Thyroid pathological findings in 129 lymph nodes (92.1%) was PTC, in 10 lymph nodes (7.1%) was follicular thyroid cancer and in 1 lymph node (0.7%) was anaplastic thyroid cancer. In Table 1, the distribution of age and sex, location of examined lymph nodes, and thyroid

**Table 1: Distribution of age, sex and lymph node site in the two groups of patients with papillary thyroid carcinoma**

Variables	Lymph node involved		P
	No	Yes	
Mean of age (year)	39.1 $\pm$ 13.9	40.4 $\pm$ 11.8	0.69
Sex, n (%)			
Male	4 (12.5)	2 (6.1)	0.37
Female	28 (87.5)	31 (93.9)	
Lymph node site			
Right, level II	13 (18.6)	12 (17.1)	0.73
Right, level III	7 (10)	8 (11.4)	
Right level IV	8 (11.4)	3 (4.3)	
left, level II	14 (20)	16 (22.9)	
left, level III	8 (11.5)	12 (17.1)	
left level IV	9 (12.9)	7 (10)	
Level VI, VII	11 (15.7)	12 (17.1)	
Thyroid pathology			
PTC	63 (90)	66 (94.3)	0.48
FTC	6 (8.6)	4 (5.7)	
ATC	1 (1.4)	0	

Level II: Upper jugular nodes - between posterior belly of digastric muscles superiorly and hyoid bone inferiorly, Level III: Middle jugular nodes - between the hyoid bone and cricoid cartilage, Level IV: Lower jugular nodes - between the cricoid cartilage and the clavicle, Level VI: Visceral space lymph nodes - midline group of cervical nodes from hyoid to sternal manubrium; includes prelaryngeal; pretracheal; and paratracheal subgroups, Level VII: Superior mediastinal nodes - between carotid arteries from top of manubrium superiorly to innominate vein inferiorly, PTC: Papillary thyroid carcinoma, FTC: Follicular thyroid cancer, ATC: Anaplastic thyroid cancer

pathological findings in two groups of involved and uninvolved lymph nodes are shown. According to the results, significant differences were not observed between the two groups. Average levels of Tg washout in malignant and nonmalignant lymph nodes were  $622.1 \pm 66.2$  and  $1.38 \pm 0.43$  ng/ml and the difference between the two groups was significant ( $P < 0.001$ ). Figure 1 shows the ROC area under the curve for the detection of lymph node involvement in the examined samples. Based on the above analysis, the area under the curve was 0.95, which was statistically significant ( $P < 0.001$ ).

According to ROC analysis, the best cut-off point of Tg for the diagnosis of lymph nodes was 0.7 ng/ml and according to it, Tg washout sensitive was 93.8%, specificity was 92.4%, false positives 7.6%, false negative 6.3%, positive predictive value 92.3%, negative predictive value 93.8%, and the accuracy was 93.1%.

## Discussion

The high levels of Tg are accepted as a trusted marker in patients with differentiated thyroid cancer or as the continued presence of the disease in people. In many cases, continue presence of the disease in patients has been seen with lymph node involvement that these lymph nodes may be have been left in place at the time of surgery or recurred.<sup>[2,3]</sup> Therefore, this study performed and aimed to determine Tg levels in cervical lymph nodes both affected and unaffected in patients with thyroid carcinoma and to determine the diagnostic value of Tg in determining lymph node involvement in these patients.

Based on the results of our study, Tg level in the lymph nodes in the pathologic assessment which was cancerous was considerably and significantly higher than lymph nodes that were unaffected. This marker of lymph node has a high diagnostic value in determining cancer of cervical lymph nodes and therefore is used in patients with differentiated thyroid cancer.

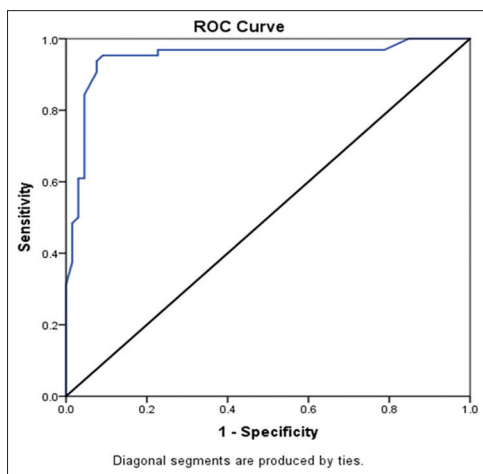


Figure 1: Area under the receiver operating characteristic

Possibly by measurement of Tg level in the lymph nodes in the neck can largely understood the involvement of the glands. Based on the results of Tang *et al.* in 2016, Tg level of cervical lymph nodes in patients with PTC along with FNAC increase accuracy of the assessment of metastatic disease. This test with cut-off 1.0 ng/ml can detect metastatic lymph nodes even in the presence of incompetence cytology and have sensitivity and specificity about %95.<sup>[12]</sup> They concluded that Tg washout level is suitable for the diagnosis of lymph node which can be determined through fine needle biopsy. Therefore, it is suggested that in patients with suspicion of lymph nodes involvement before surgery, fine-needle biopsy and determination of the Tg level performed. Some studies represent that the test may have been altered in some patients by the presence of high level of Tg-Ab. Therefore, this test should interpreted with caution. In this regard, a study was conducted in 2015 by Jo *et al.*, 370 suspicious lymph nodes from 273 patients with thyroid carcinoma were evaluated for Tg level and Tg-Ab. Fifty-five LNs (14.9%) were from positive serum Tg-Ab (Tg-Ab+) patients. Serum Tg and FNA-Tg levels were significantly lower in patients with Tg-Ab+ than in those with Tg-Ab-negative.<sup>[13]</sup> In a study by the Moon *et al.* in 2013, in 419 patients with PTC, FNA-Tg gage were evaluated to assess the cut-off value in diagnosing malignant LNs. In this study 190 lymph nodes were malignant, and 338 were benign. Mean level of FNA-Tg in malignant were 521.2 (3676.8) ng/ml. According to the results, a cut-off 1.0 ng/ml of FNA-Tg is the best cut-off point to determine the nature of lymph nodes in patients with differentiated thyroid cancer with sensitivity, 93.2%; specificity, 95.9%. Although FNA-Tg together with FNAC showed superior diagnostic value (sensitivity, 98.4%; specificity, 94.4%) in comparison with either FNAC or FNA-Tg alone.<sup>[14]</sup> In another study Jeon *et al.* in 2015 cut-off point of 1.0. In a patient with the low serum Tg, the sensitivity and specificity of the FNA-Tg cut-off value of 1.0  $\mu\text{g/L}$  were 93% and 100%, respectively.<sup>[15]</sup> and in a study of Holmes *et al.* in 2014 cut-off point of 0.2 ng/ml was the best.<sup>[16]</sup> In our study, the best cut-off point of Tg for the diagnosis of lymph nodes was 0.7, and according to it, Tg washout sensitive was 93.8%, specificity was 92.4%, false positives 7.6%, false negative 6.3%, positive predictive value 92.3%, negative predictive value 93.8% and the accuracy level was 93.931% that is comparable with the other studies.

Our study limitation was the time of expectancy to prepare Tg washout result that it can resolved by sending the Tg washout samples at first and during thyroidectomy the result will be ready in about 20–30 min. The most advantage of our study is that up to now there is no study to determine the Tg washout of metastatic LN “intraoperatively,” and unlike the other study such as frozen section, it does not need the specialist to the measurement of Tg.

## Conclusion

Based on the obtained results, the level of Tg of cervical lymph node metastasis in PTC patients is suitable criteria for the diagnosis of lymph node involvement. Therefore, based on our study, this test can be used intraoperative in replace of sentinel lymph node biopsy and frozen section for decision making of LND in any cervical compartment. In this way, may be obviate unnecessary LND and their complications.

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## Conflicts of interest

There are no conflicts of interest.

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