

Does Pre-operative TSH Level Affect Pathological Findings in Papillary Thyroid Carcinoma?

Erkan Somuncu, Nezihe Berrin Dodur Önalın

Department of General Surgery, University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Türkiye

ABSTRACT

Objective: Although thyroid-stimulating hormone (TSH) is known to induce thyroid malignancies, the relationship between pre-operative TSH and pathological findings has not been thoroughly evaluated. This study aimed to assess the relationship between pre-operative TSH levels and pathological findings.

Materials and Methods: The records of 156 patients (135 women and 21 men) operated for papillary thyroid cancer (PTC) between January 2017 and June 2020 were retrospectively reviewed and divided according to TSH level 2.5 mIU/L above (50 patients) and below (106 patients). The relationship between pre-operative fine-needle aspiration biopsy (FNAB) result, pathological findings, tumor diameter, multicentricity, lymphovascular invasion, extrathyroidal extension, capsule invasion, and neck (central, lateral) metastasis were compared for pre-operative TSH levels.

Results: There was no significant difference between pre-operative TSH level and lymphovascular invasion, extrathyroidal extension, central and lateral lymph node metastasis, primary tumor size, and multifocality. However, TSH levels were found to be significant above 2.5 mIU/L in patients with capsule invasion positivity ($p=0.007$). TSH levels were significantly lower in our patients with malignant or suspected FNAB ($p=0.015$).

Conclusion: Although pre-operative high TSH levels tend to be more common malignant in the literature, malignancy and suspected FNAB results are obtained in low TSH levels. TSH level should be considered as an independent factor in preoperative diagnosis, and thyroid malignancies should be suspected in cases with a TSH level below 2.5 mIU/L.

Keywords: Differentiated thyroid cancer, papillary thyroid carcinoma, TSH

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INTRODUCTION

Differentiated thyroid cancer (DTC) is the most common malignancy of the endocrine system.^[1] Accurate identification of benign and malignant nodules of the thyroid prevents unnecessary operations. In addition, survival rates of early and middle stage DTC patients may increase significantly with surgical treatment.^[2] Therefore, early diagnosis and timely surgical treatment are particularly important in the treatment and prognosis of patients with PTC. Today, imaging methods, fine-needle aspiration biopsy (FNAB), and molecular tests are used to differentiate benign and malignant thyroid nodules.^[3-5]

However, all these tests cannot always accurately and effectively distinguish between benign and malignant thyroid nodules. Thyroid-stimulating hormone (TSH), a well-known

thyroid growth factor, a large glycoprotein synthesized concerning thyroid hormones, is used in the preoperative assessment as well as in follow-up protocols to monitor post-treatment thyroid cancer recurrence. Many authors have reported that high serum TSH can be used as an essential early warning signal for thyroid cancer screening.^[6-8]

This study aimed to evaluate the relationship between pre-operative TSH levels and pathologic findings in patients operated for papillary thyroid cancer (PTC).

MATERIALS and METHODS

The records of 156 patients (135 women and 21 men) operated for DTC between January 2016 and February 2019 were retrospectively reviewed. Pre-operative ultrasonography (USG), TSH



Address for Correspondence: Erkan Somuncu, Department of General Surgery, University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital, İstanbul, Türkiye
E-mail: dr.somuncu@gmail.com **ORCID ID:** 0000-0002-5622-1983

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levels, and thyroid function tests were noted in all patients. FNAB was performed according to USG findings of nodules.

Patients suspected to have a malignancy in FNAB results were also evaluated for central and lateral neck metastasis with FNAB and USG. Central and lateral neck lymph node dissection were performed in cases with definite or suspected lymph node involvement.

Pre-operative serum TSH levels were measured and the results were recorded in mIU/L. Normal ranges for serum TSH at our institution were 0.5–4.5 mIU/L. The median TSH value was 2.5 mIU/L. Cases above and below this level were divided into two groups and evaluated among clinicopathological factors. The same endocrine surgery team operated all patients. Total thyroidectomy was preferred in most patients, whereas lobectomy with isthmusectomy was preferred in fewer patients with low risk.

Dissection of the central neck area was performed in preoperative imaging studies with enlarged lymph nodes or when palpated in the central neck region during surgery. Lateral neck dissection was performed for suspicious lymph nodes detected by the US or for metastatic lymph nodes confirmed by FNAB. Primary tumor size, multifocality, extrathyroidal extension, capsule invasion, surgical margin, and cervical (central and lateral) lymph node metastasis (LNM) were not-

ed for all cases. The relationship between pre-operative TSH and age, pre-operative needle biopsy diagnosis, tumor size, multifocality, lymphovascular invasion, extrathyroidal extension, capsule invasion, central neck metastasis, and lateral neck metastasis was evaluated. Informed consent was obtained from the patients before starting the study.

Statistical Analysis

Data were analyzed using the Statistical Packages for the Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA). Mann-Whitney U test or T-test were used to compare binary data. $P < 0.05$ was considered as statistically significant.

RESULTS

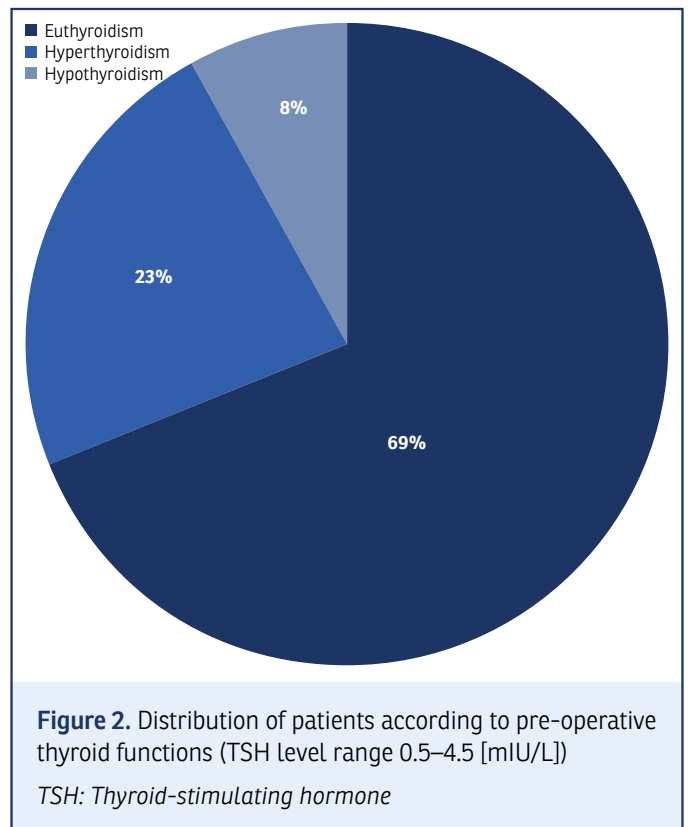
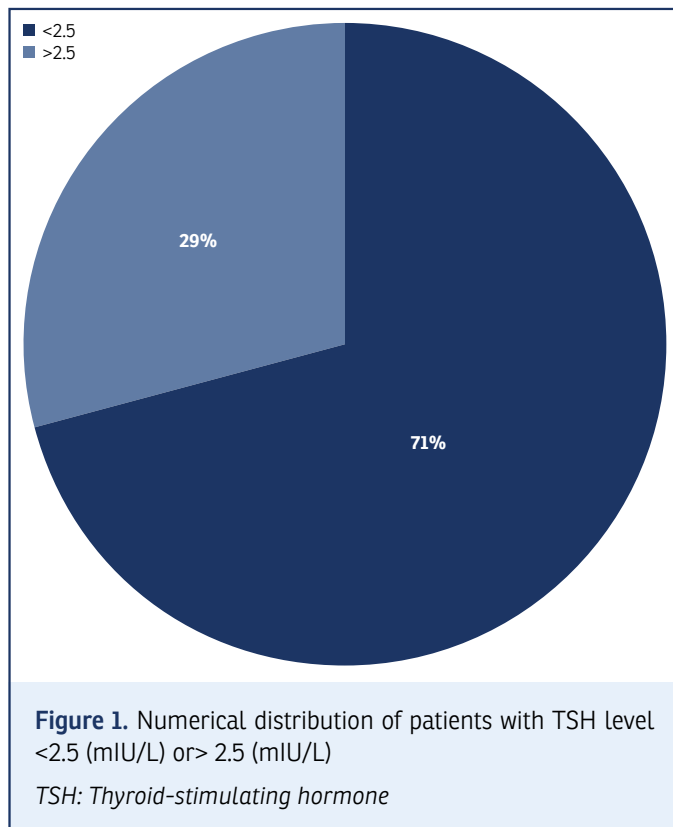
Table 1 shows the characteristics of PTC and relationship between clinicopathological factors and preoperative TSH levels. The mean age of the patients was 44.79 ± 12.96 . The age range of patients was between 18 and 75 years old. The diameter of the detected nodules was ranging from 0.1 cm to 4.5 cm (mean: 1.53 ± 1.27 cm).

The pre-operative TSH level was below 2.5 mIU/L in 91 women and 15 men. Of the patients with TSH levels above 2.5 mIU/L preoperatively, 44 were female, and six were male, as shown in Figure 1. All patients were divided into three groups according to their pre-operative thyroid functions. As shown

Table 1. The relationship of the clinicopathological factors with a TSH level in PTC patients

	TSH <2.5 (mIU/L)		TSH >2.5 (mIU/L)		p
	n	%	n	%	
Male sex	15/106	14	6/50	12.1	0.785
Extrathyroidal extension	10/106	9.4	9/50	18.1	0.232
Tumor size (cm)					
0–1	50/106	47.1	13/50	26	0.148
1–4	52/106	49	35/50	70	
>4	5/106	4.7	2/50	4	
Multifocality	39/106	36.7	20/50	40	0.786
Lymphovascular invasion	17/106	16	12/50	24.2	0.282
Central metastasis	6/106	5.6	6/50	12	0.248
Capsul invasion	18/106	16.9	19/50	38	0.007
Pre-operative FNAB					
Benign	38/106	35.8	5/50	10	0.015
Suspicious	13/106	12.2	12/50	24	
Malign	55/106	51.8	33/50	66	
Lateral metastasis	5/106	4.7	3/50	6	0.696

TSH: Thyroid-stimulating hormone; PTC: Papillary thyroid cancer; FNAB: Fine-needle aspiration biopsy



in Figure 2, the number of patients with hyperthyroidism is higher than the hypothyroid group.

In these patients with PTC, TSH levels were predominantly below 2.5 mIU/L regardless of the preoperative FNAB result. There was no significant difference between patients with suspected or malignant FNAB results. However, TSH levels were below 2.5 mIU/L in 38 of the patients with preoperatively benign FNAB, and five of them were above 2.5 mIU/L ($p=0.015$).

TSH levels were found to be significant above 2.5 mIU/L in patients with capsule invasion positivity ($p=0.007$). There was no significant difference between other clinicopathological factors and preoperative TSH levels.

DISCUSSION

The majority of thyroid cancers are PTC. PTC often originates from thyroid follicular epithelial cells with slow progression. Still, some histological subtypes are prone to extrathyroid invasion, vascular invasion, and distant metastasis, with a high recurrence rate and relatively poor prognosis.^[7,8]

The idea that a high level of TSH is associated with more aggressive DTC, especially in patients with hypothyroidism, is widely accepted in the literature. Clinicians are trying to find more effective factors and markers to diagnose PTC

and prevent unnecessary surgical interventions and to predict the prognosis of patients after treatment. The relationship between TSH level and DTC has always been a problematic issue in the development, progression, and treatment of this disease.^[9-14]

The potential of being aggressive in the tumor cell is thought to be due to metastasis to lymph nodes, especially metastasis to the central neck region. Although USG, computerized tomography, or magnetic resonance imaging is used for pre-operative diagnosis, evaluation of lymph nodes, and identification of metastases, the power of radiological imaging is sometimes insufficient.^[15]

In the statements in the treatment guidelines for thyroid cancer, the decreasing TSH hormone mentions that thyroid nodules have functions and that functional nodules are less likely to be malicious. Although many researchers have said, but not yet fully elucidated, numerous animal experiments and clinical observation results with elevated serum TSH levels may be an estimator of DTC.^[6-15] Nevertheless, malignancy should not be neglected even in cases of hyperthyroidism with decreased serum TSH levels.^[16,17]

This study showed that serum TSH level is an independent risk factor for PTC. Decreasing serum TSH levels were sig-

nificantly higher in the majority of cases. Unlike other studies or guidelines, there is evidence that serum TSH concentration may provide proof that it is an independent factor in pathological outcomes.

Cervical LNM is a risk factor for increasing the recurrence rate and decreasing the survival rate in PTC patients, especially those over 45 years of age. Cervical LNM may not always be detected by preoperative imaging or intraoperative examination. Sometimes, it can be diagnosed after prophylactic central lymph node dissection. Therefore, cervical LNM changes the stage and postoperative management of PTC.^[18–21] The results of the study did not find a significant relationship between serum TSH level and central and lateral LNM in PTC.

Capsule invasion may also be considered as an extrathyroidal extension. In the pathology reports in our hospital, capsule invasion was defined as no extrathyroidal invasion of the tumor. This factor was correlated with increased serum TSH levels ($p=0.007$). When FNAB results and serum TSH levels were evaluated, we found a significant malignancy in patients with low TSH levels but had benign preoperative results ($p=0.015$). As for the suspected or malignant results, the TSH level was increased, as mentioned in the literature. Serum TSH level has an absolute clinical value in the identification of benign thyroid nodules and DTC.^[22,23]

As mentioned in the literature, increased TSH levels guide regular follow-up in nodular thyroid disease. TSH level is an essential factor in determining the condition. Although it is closely related to the increased serum TSH level in the literature, there is a risk of malignancy at the decreasing serum TSH level and should not be ignored. The preoperative TSH level is an independent predictor for clinicopathological factors.

High false negative rates of FNABs have been reported at various rates in the literature. Depending on the tumor size, type and whether it is solid or cystic, this rate rises up to 30%. In addition, factors such as the experience of the cytopathologist and the optimum conditions for biopsy sampling also affect the calculation of this ratio.^[24,25] Similarly, we think that the rate of false negative FNAB in our study is due to the inexperience of our cytopathologist and technical inadequacy in preparing the sample. This issue is one of the limitations of our study. Other limitations of our study were that it was evaluated retrospectively and the number of cases was limited. Therefore, the sample selection may be somewhat biased. Therefore, whether TSH levels can be used as a predictor for PTC screening should still be confirmed by prospective large-scale studies.

CONCLUSION

Increased serum TSH levels are closely related to the formation and development of DTC. It may be a critical biochemical marker for predicting the clinicopathological risks of PTC in nodular thyroid disease.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital Ethics Committee (No: 2020.06.35, Date: 18/06/2020).

Informed Consent: Written informed consent was obtained from all patients.

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REFERENCES

- Schmidbauer B, Menhart K, Hellwig D, Grosse J. Differentiated thyroid cancer-treatment: state of the art. *Int J Mol Sci* 2017;18:1292. [\[CrossRef\]](#)
- Sahli ZT, Umbricht CB, Schneider EB, Zeiger MA. Thyroid nodule diagnostic markers in the face of the new NIFTP category: time for a reset? *Thyroid* 2017;27:1393–9. [\[CrossRef\]](#)
- Bae JM, Hahn SY, Shin JH, Ko EY. Inter-exam agreement and diagnostic performance of the Korean thyroid imaging reporting and data system for thyroid nodule assessment: real-time versus static ultrasonography. *Eur J Radiol* 2018;98:14–9. [\[CrossRef\]](#)
- Tugendsam C, Petz V, Buchinger W, Schmoll-Hauer B, Schenk IP, Rudolph K, et al. Ultrasound criteria for risk stratification of thyroid nodules in the previously iodine deficient area of Austria - a single centre, retrospective analysis. *Thyroid Res* 2018;11:3. [\[CrossRef\]](#)
- Mendes GF, Garcia MR, Falsarella PM, Rahal A, Cavalcante Junior FA, Nery DR, et al. Fine needle aspiration biopsy of thyroid nodule smaller than 1.0 cm: accuracy of TIRADS classification system in more than 1000 nodules. *Br J Radiol* 2018;91:20170642. [\[CrossRef\]](#)
- Liu TR, Su X, Qiu WS, Chen WC, Men QQ, Zou L, et al. Thyroid-stimulating hormone receptor affects metastasis and prognosis in papillary thyroid carcinoma. *Eur Rev Med Pharmacol Sci* 2016;20:3582–91.
- Lin Y, Li T, Liang J, Li X, Qiu L, Wang S, et al. Predictive value of preablation stimulated thyroglobulin and thyroglobulin/thyroid-stimulating hormone ratio in differentiated thyroid cancer. *Clin Nucl Med* 2011;36:1102–5. [\[CrossRef\]](#)
- Freudenthal B, Williams GR. Thyroid stimulating hormone suppression in the long-term follow-up of differentiated thyroid cancer. *Clin Oncol (R Coll Radiol)* 2017;29:325–8. [\[CrossRef\]](#)

9. Haymart MR, Repplinger DJ, Levenson GE, Elson DF, Sippel RS, Jaume JC, et al. Higher serum thyroid stimulating hormone level in thyroid nodule patients is associated with greater risks of differentiated thyroid cancer and advanced tumor stage. *J Clin Endocrinol Metab* 2008;93:809–14.
10. Haymart MR, Glinberg SL, Liu J, Sippel RS, Jaume JC, Chen H. Higher serum TSH in thyroid cancer patients occurs independent of age and correlates with extrathyroidal extension. *Clin Endocrinol (Oxf)* 2009;71:434–9.
11. Fiore E, Rago T, Provenzale MA, Scutari M, Ugolini C, Basolo F, et al. Lower levels of TSH are associated with a lower risk of papillary thyroid cancer in patients with thyroid nodular disease: thyroid autonomy may play a protective role. *Endocr Relat Cancer* 2009;16:1251–60. [\[CrossRef\]](#)
12. Jin J, Machekano R, McHenry CR. The utility of preoperative serum thyroid-stimulating hormone level for predicting malignant nodular thyroid disease. *Am J Surg* 2010;199:294–7. [\[CrossRef\]](#)
13. Zeng Q, Liu J, Zhu J, Hu G. Association between preoperative serum thyroid-stimulating hormone level and nonfunctioning malignant nodule thyroid disease. *Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi [Article in Chinese]* 2014;28:1931–3.
14. Al-Bader A, Zawawi F, Singer Z, Mlynarek A, Hier M, Tamilia M, et al. Preoperative TSH and thyroglobulin levels: would it predict thyroid cancer? *Otolaryngol Pol* 2015;69:21–5. [\[CrossRef\]](#)
15. Bestler E, Aygun N, Yılmaz Özgüven MB, Yetkin SG, Mihmanli M, Isgor A, et al. The evaluation of the localization and the extent of lymphatic dissection in central neck dissection. *Med Bull Sisli Etfal Hosp [Article in Turkish]* 2016;50:228–33. [\[CrossRef\]](#)
16. Aksoy SÖ, Sevinç Aİ, Durak MG. Hyperthyroidism with thyroid cancer: more common than expected? *Ann Ital Chir* 2020;91:16–22.
17. Tam AA, Ozdemir D, Alkan A, Yazicioglu O, Yildirim N, Kilicyazgan A, et al. Toxic nodular goiter and thyroid cancer: Is hyperthyroidism protective against thyroid cancer? *Surgery* 2019;166:356–61. [\[CrossRef\]](#)
18. Kim SS, Lee BJ, Lee JC, Song SH, Kim BH, Son SM, et al. Preoperative serum thyroid stimulating hormone levels in well-differentiated thyroid carcinoma is a predictive factor for lateral lymph node metastasis as well as extrathyroidal extension in Korean patients: a single-center experience. *Endocrine* 2011;39:259–65. [\[CrossRef\]](#)
19. Suh CH, Baek JH, Choi YJ, Lee JH. Performance of CT in the preoperative diagnosis of cervical lymph node metastasis in patients with papillary thyroid cancer: a systematic review and meta-analysis. *AJNR Am J Neuroradiol* 2017;38:154–61. [\[CrossRef\]](#)
20. Sitges-Serra A, Lorente L, Mateu G, Sancho JJ. Therapy of Endocrine Disease: Central neck dissection: a step forward in the treatment of papillary thyroid cancer. *Eur J Endocrinol* 2015;173:R199–206. [\[CrossRef\]](#)
21. Gao Y, Qu N, Zhang L, Chen JY, Ji QH. Preoperative ultrasonography and serum thyroid-stimulating hormone on predicting central lymph node metastasis in thyroid nodules as or suspicious for papillary thyroid microcarcinoma. *Tumour Biol* 2016;37:7453–9. [\[CrossRef\]](#)
22. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al; American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid* 2009;19:1167–214. Erratum in: *Thyroid* 2010;20:942. [\[CrossRef\]](#)
23. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* 2016;26:1–133. [\[CrossRef\]](#)
24. Pinchot SN, Al-Wagih H, Schaefer S, Sippel R, Chen H. Accuracy of fine-needle aspiration biopsy for predicting neoplasm or carcinoma in thyroid nodules 4 cm or larger. *Arch Surg* 2009;144:649–55. [\[CrossRef\]](#)
25. Agcaoglu O, Aksakal N, Ozcinar B, Sarici IS, Ercan G, Kucukyilmaz M, et al. Factors that affect the false-negative outcomes of fine-needle aspiration biopsy in thyroid nodules. *Int J Endocrinol* 2013;2013:126084.