The Relationship of Clinicopathological Factors of the Tumor with Preoperative TSH Level in Papillary Thyroid Cancers

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ABSTRACT

Objective: Thyroid-stimulating hormone/thyrotropin (TSH) is known to induce malignancies and tissue growth of the thyroid gland. While the relationship of higher levels of TSH with advanced stages of cancer had been published in previous studies, the relationship of the tumor with the clinicopathological factors had not been completely evaluated. The aim of the present study was to evaluate the relationship between highly risky clinicopathological factors with preoperative high levels of TSH.

Materials and Methods: The records of 89 patients (67 females and 22 males) who underwent surgery for differentiated thyroid cancer between 2011 and 2013 were reviewed. The relationship of preoperative TSH between tumor size, multicentricity, lymphovascular invasion, extrathyroidal extension, central neck metastasis, and lateral neck metastasis was evaluated.

Results: The preoperative TSH levels were high in patients with multicentricity (p=0.022), lymphovascular invasion (p=0.018), and central neck metastasis (p=0.002). The prevalence of extrathyroidal extension (p=0.41), lymphovascular invasion (p=0.020), and central metastasis (p=0.009) was significantly high in patients with a TSH level ≥2.5 mIU/L. The preoperative TSH levels were determined as an independent predictive risk factor for central neck metastases (p=0.012) and extrathyroidal extension (p=0.041) in multinomial logistical regression analysis.

Conclusion: The power of radiological imaging for the identification of central neck metastases in preoperative evaluation is limited. The preoperative high level of TSH is an independent predictive factor for central metastases and extrathyroidal extension. It can help to predict tumor staging. Furthermore, related with multicentricity and lymphovascular invasion, it can affect the high risk characteristics of the tumor except the stage. The preoperative TSH level can be considered for the probability of preoperative metastases and can contribute to plan the extent of surgery.

Keywords: Clinicopathological factors, thyroid cancer, thyrotropin/thyroid-stimulating hormone

Introduction

Thyroid cancer is the most frequent endocrine malignancy [1]. The outstanding clinical parameters associated with an increased risk of malignant disease of age (<20 and >70 years), male sex, solitary nodule, nodule size of >4 cm, rapid nodular growth, and radiation exposure history are well known [2].

Thyrotropin (TSH) is a well-accepted thyrocyte growth factor [3]. The relationship of the TSH with differentiated thyroid cancer (DTC) was evaluated several times in previous studies. In previous studies, the increasing risk of thyroid malignancy in thyroid nodules by the higher levels of TSH has been emphasized [4–11]. In recent studies, the relationship between the tumor size and the TSH level is further examined [12–14]. In a recent meta-analysis, a higher serum TSH level involved higher risk of papillary thyroid cancer (PTC) [15]. In a study, TSH receptor expression was found to be an independent factor that affects the prognosis of patients with PTC [16].

Overall, the relationship of clinicopathological factors of the tumor with TSH level and its contribution to preoperative surgical assessment are not fully examined until today. The aim of the present study was to evaluate the relationship between highly risky clinicopathological factors with preoperative high levels of TSH.

Materials and Methods

We examined the records of 89 patients (67 females and 22 males) who underwent surgery for thyroid cancer between 2011 and 2013 retrospectively. The mean age of the patients was 50.7 (20–80) years. In all patients, preoperative ultrasonography (USG), TSH levels, and thyroid function tests were evaluated. Fine needle aspiration biopsy (FNAB) was applied to patients according to the USG findings of the nodules. Patients who were suspected of malignancy in the FNAB results were additionally evaluated with USG for central and lateral neck metastasis. Patients who were suspected clinically or suspected of extrathyroidal extension to the adjacent organ spread were additionally evaluated with magnetic resonance imaging and computed tomography. The FNAB procedure was applied to the lateral neck lymphatic nodes that were suspected of metastasis and confirmed. Preoperative serum TSH values were measured, and the results were recorded in mIU/L. A level of ≥2.5 mIU/L is considered as high. Patients who had antithyroid treatment before surgery were excluded from the study.

All patients underwent surgery conducted by the same endocrine surgeon. In cases with a unifocal intrathyroidal microcarcinoma (<1 cm in diameter) and without cervical lymph node involvement, thyroid lobectomy with isthmusectomy was performed. Total thyroidectomy was primarily performed in other cases. The dissection of the central neck area was performed when there was an enlarged lymph node in preoperative imaging studies or palpated in the central neck region peroperatively. Prophylactic central neck dissection was applied to the cases with a tumor size >4 cm. Neck dissection was performed from levels II to V in case of metastasis to the lateral compartment of the neck in the preoperative evaluation and also in time following thyroid surgery. The dissection descriptions of the central region were performed according to the consensus report of the American Thyroid Association Surgery Working Group [17]. The histopathological parameters of each specimen were evaluated by the same pathologist. All pathological specimens were analyzed for primary tumor size, multifocality/multicentricity, extrathyroidal extension, and cervical (central and lateral) lymph node metastasis (LNM). The specimens were classified according to the tumor, lymph node, and metastasis (TNM) staging system of the 7th edition of the Union for International Cancer Control and the American Joint Committee on Cancer and according to the well-established prognosis classification system of DTC, age, metastasis, extent, and size stage system [18].

By analyzing the specimen reports, the relationship of preoperative TSH between tumor size, multicentricity, lymphovascular invasion, extrathyroidal extension, central neck metastasis, and lateral neck metastasis was evaluated. The approval of the ethical committee of İstanbul Health Sciences University Şişli Hamidiye Etfal Training and Research Hospital was obtained to conduct the study. Informed consent was obtained from the patients prior to the study.

Statistical Analysis

Data were analyzed using the SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Mann–Whitney U test and ANOVA were used to compare binary data. Multinomial logistical regression analysis was used to analyze the predictive value of TSH (<2.5 vs >2.5 mIU/L). P values were two-sided all throughout. A $p<0.05$ was considered as statistically significant.

Results

Tables 1 and 2 show the relationship of clinicopathological factors with preoperative TSH level. The preoperative TSH levels were high in patients with multicentricity (p=0.022), lymphovascular invasion (p=0.018), and central neck metastasis (p=0.002). The prevalence of extrathyroidal extension (p=0.41), lymphovascular invasion (p=0.020), and central metastasis (p=0.009) was significantly high in patients with a TSH level ≥2.5 mIU/L.

The preoperative TSH levels were determined as an independent predictive risk factor for central neck metastasis (p=0.012), lymphovascular invasion (p=0.021), and extrathyroidal extension (p=0.041) in multinomial logistical regression analysis.

Discussion

The idea of "higher levels of TSH is related with more aggressive DTC" is widely accepted in the literature [4–16]. Tumor aggressivity is thought to be related with the potential of metastasis to the lymph nodes primarily to the central neck area. However, the power of radiological imaging for the identification of central neck metastases in preoperative evaluation is limited [19].

To manage DTC and to propose the prognosis of the patients following treatment, clinicians

Table 1. The clinicopathological factors and preoperative TSH level.

Clinical and pathological properties	Preoperative TSH (mIU/L)		p
Tumor size (cm)	2.06±2.82 (min: 0.005, max: 23.73)		0.546
Multicentricity (+/−)	2.78±0.94	1.46±1.10	0.022
Lymphovascular invasion (+/−)	2.79±4.08	1.56±1.29	0.018
Extrathyroidal extension (+/−)	2.14±2.02	2.00±3.32	0.147
Central metastasis (+/−)	3.66±5.12	1.56±1.26	0.002
Lateral metastasis (+/−)	3.81±6.65	1.81±1.69	0.236

Table 2. The relationship of the clinicopathological factors with a TSH level of 2.5 (mIU/L).

	TSH <2.5 (mIU/L)	TSH >2.5 (mIU/L)	p	Odds ratio	95% confidence interval
Extrathyroidal extension	24/66 (36.4%)	14/23 (60.9%)	0.410	2.722	2.722–7.225
Lateral metastasis	8/66 (12.1%)	3/23 (13.0%)	1.000		
Tumor size (cm)					
0–2	52/66 (78.8%)	17/23 (73.9%)	0.528		
2–4	12/66 (18.2%)	4/23 (17.4%)			
>4	2/66 (3.0%)	2/23 (18.0%)			
Multicentricity	26/66 (39.4%)	14/23 (60.9%)	0.075	2.393	0.905–6.326
Lymphovascular invasion	22/66 (33.3%)	14/23 (60.9%)	0.020	3.111	1.166–8.301
Central metastasis	11/66 (16.7%)	10/23 (43.5%)	0.009	3.846	1.348–10.971

have been working to find more factors and markers. In addition, the relationship of TSH with DTC has always been a challenging subject in the development, progress, and treatment of this disease [4–14]. In our study, TSH levels were found to be significant in the presence of multicentricity and lymphovascular invasion with the histopathological aggressivity properties of tumor. Furthermore, in case of central metastasis, TSH levels were significantly high. For the evaluation of the TSH with a baseline level of 2.5 mIU/L, the prevalence of extrathyroidal spread (p=0.41), lymphovascular invasion (p=0.020), and central neck metastasis (p=0.009) was significantly higher in cases with >2.5 mIU/L. Similar to the current literature, our study demonstrated that preoperative higher serum TSH concentrations are associated with higher thyroid cancer stage [7–9, 18, 20, 21] versus a minority of studies [22–28] that showed no relationship. A good overall response to this contradiction could be the up-to-date meta-analysis by Zheng et al. [26], including 56 studies with 20,227 cases of thyroid cancer of which they concluded that the risk of PTC is associated with a significant increase in serum TSH level.

Beyond the sufficiently evaluated relationship of preoperative TSH level with the tumor size depending on the growth factor of the hormone on the thyroid tissue, other characteristics of the disease with the hormone should be questioned. Haymart et al. [7] first reported that a higher TSH is associated with not only incidence of DTC but also advanced stage of DTC. Kim et al. [20] concluded that advanced TNM stage, lateral LNM, and extrathyroidal extension are significantly correlated with preoperative high TSH levels. Their study also reported that a high TSH level is a predictive factor for extrathyroidal extension and lateral lymph node involvement in DTC. We did not determine a significant difference about the relationship of the tumor with TSH levels. This could be due to a smaller sample size and the majority of the cases were in the T1 group. McLeod et al. [22, 23] emphasized the relationship of prognostic markers (neck nodal metastasis, tumor size, distant metastasis, and extrathyroidal extension) of DTC to serum TSH concentration and reported that the preoperative serum TSH level is related with gross extrathyroidal extension, higher DTC stage, and neck node metastasis. In a cross-sectional cohort study, it was concluded that high TSH levels increased the risk of malignancy and the rate of LNM.

Lymphatic metastases of PTC primarily and frequently occur in the central neck area [28, 29]. In PTC management, the challenges of the central neck region radiological imaging, metastases to this area, and arguments of performing the paratracheal lymph node dissection with total thyroidectomy for PTC are still ongoing issues [19, 30]. The difficulty of radiological imaging of the central neck area preoperatively hampers the surgeon to fully manage the disease preoperatively. Recent studies did not mention this topic as much as compare the relationship of TSH level with the diagnosis of PTC. However, preoperative full evaluation of the disease would enable the surgeon to make a correct decision about the extent of surgery. The central neck dissection method (prophylactically routinely, prophylactically for isolated metastatic disease in the lateral compartment, and performed selectively following the intraoperative evaluation of the lymph nodes in the central compartment) is still controversial due to this reason [31]. In addition to radiological instruments and clinical examination, laboratory findings can also aid to plan the surgery.

In our study, the central metastasis risk of cases with a TSH level >2.5 mIU/L was four times higher than those with a TSH level <2.5 mIU/L. Moreover, a TSH level >2.5 mIU/L was an independent risk factor for extrathyroidal extension and central neck metastasis. Both of these properties of the tumor increase the TNM stage especially in patients over 45 years [18]. Patients with a TSH level >2.5 mIU/L could be evaluated for central neck metastases both preoperatively and peroperatively. The preoperative TSH levels could be in the criteria of planning the prophylactic central neck dissection. Gao et al. [32] studied the relationship of TSH levels with USG findings in borderline papillary thyroid microcarcinoma (PTMC). In their study, it was concluded that positive FNAB findings, suspicious imaging, a >7 mm diameter of tumor, and serum TSH levels of ≥2.5 mIU/L are independent predictors for central LNM in PTMC. In these cases of PTMC, prophylactic central lymph node dissection could be planned. In addition, the present study supports our results of "higher TSH levels brings the aggressiveness of tumor with it". Kim et al. [20] examined the relationship of lateral LNM and extrathyroidal extension of DTC with TSH. They concluded that preoperative high TSH levels may offer high-risk features with extrathyroidal extension and lateral LNM. They also argued that TSH levels may be used as a preoperative determiner for the extension of DTC surgery.

Consistent with our analysis, other studies reported that extrathyroidal extension [22, 31] and LNM [16, 33] are associated with serum TSH concentration. By reviewing all of these studies, we also found that preoperative TSH levels are an independent predictive risk factor for these two clinicopathological factors.

A previous study by Li et al. [34] reported that especially with a TSH level ≥2.5 mIU/L (p=0.003 and p=0.03), the high TSH levels of the patients are found in central LNM (p=0.001) and lateral LNM (p=0.002). Compared with our results of central (p=0.002) and lateral (p=0.236) metastases, central metastases were significant and correlated with their study. We believe that the difference of lateral metastasis could be due to a smaller sample size (n=420 vs n=89).

Similar to Kim et al. [20], Li et al. [34] also concluded that TSH level can be used to decide to perform central neck dissection and to determine the extent of surgery.

The main limitations of our study were small sample size and retrospective characteristics. Further studies may help focus on long-term follow-up outcomes.

The preoperative high level of TSH is an independent predictive factor for central metastases and extrathyroidal extension. It might help to predict the tumor staging. Furthermore, related with multicentricity and lymphovascular invasion, it can affect the high risk characteristics of the tumor except the stage. We conclude that the preoperative TSH level might be considered for the probability of preoperative metastases and might contribute to plan the extent of surgery especially for therapeutic or prophylactic central neck dissection.

Ethics Committee Approval: Ethics Committee approval was received for this study from the ethics committee of İstanbul Health Sciences University Şişli Hamidiye Etfal Training and Research Hospital.

Informed Consent: Informed consent was obtained from the patients who participated in this study.

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