

Research Article

Predictive Importance of Ultrasonography and Anti-Thyroid Antibodies in the Management of Thyroid Nodules in Indeterminate Cytology

 Sevki Peduk,¹  Suat Benek²

¹Department of Surgical Oncology, Mardin Training and Research Hospital, Mardin, Turkey

²Department of General Surgery, Tekirdag Namik Kemal University, Tekirdağ, Turkey

Abstract

Objectives: The aim of this study is to examine the effects of ultrasonography and serum anti-thyroid antibody (ATAb) levels in predicting malignancy in cases where molecular tests cannot be performed in indeterminate thyroid nodules.

Methods: Ultrasonographic features of the dominant thyroid nodule of a total of 228 patients who were operated for nodular goiter were analyzed and preoperative serum ATAb levels were examined. Especially in Bethesda category 3 nodules correlation of these parameters with malignancy rates and Hashimoto's thyroiditis (HT) was investigated.

Results: Malignancy was detected in 24.5% (12/49) Bethesda Category 3 nodules. Anti-thyroglobulin (Anti-TG) and/or anti-thyroid peroxidase (anti-TPO) positivity in serum 36.5% (72/197) was correlated with histopathologically proven HT ($p=0.001$). Poor prognostic factors were found to be less common in HT-associated papillary thyroid cancer (PTC). Ultrasonographic characteristics such as hypoechogenicity, microcalcification, and border irregularity were significant in predicting malignancy in indeterminate nodules ($p=0.038-0.003-0.004$, respectively). The central vascularization pattern remained in the background compared to other parameters ($p=0.059$). In the presence of ultrasonographic halo, 92.7% (51/55) of the nodules were benign ($p=0.001$).

Conclusion: In the management of thyroid nodules in indeterminate cytology, suspicious ultrasonographic features and Hashimoto's thyroiditis should be encouraging in making the surgical decision.

Keywords: Bethesda system; anti-thyroid antibody; chronic lymphocytic thyroiditis; thyroid cancer.

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Differentiated thyroid cancers progress slowly with long survival. Ito et al. suggested the idea of long-term follow-up instead of surgery especially in papillary microcarcinomas of the thyroid.^[1] Thyroidectomy surgery requires caution in terms of indication and timing because it has serious complications and may require lifelong levothyroxine replacement. For the time being, fine-needle aspiration biopsy (FNAB) is the most important examination in the evaluation of suspected thyroid nodules. FNAB

results have been reported according to the Bethesda system for more than ten years.^[2] With the introduction of the Bethesda system, unnecessary surgeries have decreased, but molecular tests may be required in the management of indeterminate nodules (Bethesda 3). Nodules diagnosed as Bethesda 3 as a result of FNAB have significant malignant potentials. According to the literature data, 16% of nodules that have indeterminate cytology in general population are diagnosed as malignant even after non-invasive fol-

Address for correspondence: Sevki Peduk, MD. Mardin Egitim ve Arastirma Hastanesi Cerrahi Onkoloji Anabilim Dalı, Mardin, Turkey

Phone: +90 555 453 92 85 **E-mail:** hagariii@gmail.com

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licular thyroid neoplasms with papillary-like nuclear characteristics (NIFTPs) are defined and evaluated in the benign category. As in the present study, this rate may be higher in studies in which only operated patient groups are included. Ultrasonography has become the most important examination in the management of these patients especially in secondary healthcare institutions that do not have access to molecular tests. The Thyroid Image Reporting and Data System (TI-RADS), which was developed by American College of Radiology has strengthened the hands of clinicians. This system was based on scoring ultrasonographic features such as border irregularity, hypoechogenicity, microcalcification, longer-than-wide (TTW) shape, increased intra-nodular vascularity, and lobulations in the solid components of cystic nodules. The clinical manifestation that is known as chronic lymphocytic thyroiditis (Hashimoto's thyroiditis) was defined in 1912.^[3] This condition, which is also known as one of the most common causes of hypothyroidism, occurs with thyroid follicular cell damage caused by CD4T lymphocytes.^[4] In Hashimoto's thyroiditis (HT), serum anti-thyroglobulin (anti-TG) and anti-thyroid peroxidase (anti-TPO) elevations are expected in addition to a wide variety of clinical manifestations. There are many articles in the literature elucidating the togetherness of inflammation and cancer.^[5-7] It is already known that HT and papillary thyroid cancer (PTC) exist together, and have better prognostic characteristics.^[8] However, there is no consensus at present on the value of FNAB in predicting malignancy in HT patients.^[9, 10] In the present study, thyroidectomies performed in a 2nd-line hospital were screened retrospectively. Serum anti-thyroid antibody (ATAb) levels and suspicious ultrasonographic features were investigated, and the predictive value of these two parameters was analyzed, especially for Bethesda 3 nodules.

Methods

The files of a total of 276 patients who underwent thyroid surgery because of nodular goiter in Mardin State Hospital between September 2016 and August 2021 were scanned retrospectively by using the hospital information management system. A total of 228 cases that had data integrity were included in the study and were analyzed in terms of gender and age. Detailed ultrasonography reports were reviewed for the size, echogenicity, contours, and presence of calcification of the dominant nodule. The presence of surrounding regular halo and vascularization patterns were also examined. The aspect ratios of the nodules were not evaluated because these data were not mentioned in most reports. It was observed that the serum ATAb levels were measured in 197 patients in the preoperative period. The values that were below 115 IU/ml for anti-TG and

35 IU/ml for anti-TPO were considered as negative in the measurements that were made with the electrochemiluminescence immunoassay method (Siemens ADVIA Centaur® XPT). The number of bilateral total thyroidectomy, lobectomy, and completion thyroidectomy was 134 (58.8%), 80 (35.1%), and 14 (6.1%), respectively. The preoperative FNAB results were reported by an experienced pathology team according to the Bethesda system. Final pathology reports were classified as malignant and benign. The patients who were diagnosed with PTC were evaluated in terms of tumor sizes, extrathyroidal extensions (ETE), lymphovascular invasion (LVI), capsule invasion, multifocality, and cancer types. The diagnosis of HT was also investigated in non-tumor thyroid tissues, and those who were operated only for diffuse toxic goiter and those who did not undergo preoperative FNAB or whose data could not be accessed were excluded from the study. The statistical calculations were made by using the SPSS v. 22 for Windows. Mann Whitney U test was used for non-parametric data. The correlation between the categorical variables was evaluated with the Pearson's chi-square test, and the predictive values of the multiple variables were calculated with the logistic regression analysis.

Results

A total of 187 (82%) of the 228 patients were female and 41 (18%) were male. The mean age of the patients was found to be 42 (min: 22-max: 78), and the mean diameter of the dominant nodule was 22mm (min: 6-max: 61). It was determined that a second biopsy was not performed in 9 (3.9%) patients whose preoperative FNAB results were reported as unsatisfactory. The number of patients who were reported as Bethesda Category 2-, 3-, 4-, 5-, and 6 were 125 (54.8%), 49 (21.5%), 15 (6.6%), 17 (7.5%), and 13 (5.7%), respectively. These nodules were reported to be malignant in 11.1%, 6.4%, 24.5%, 40%, 70.6%, and 92.3%, respectively. These rates were generally found to be compatible with the literature data. The malignancy rate was found to be 22.3% (51/228) in patients, and 197 patients whose serum ATAb levels were measured, the number of patients considered anti-TG or anti-TPO positive was found to be 72 (36.5%). When the dominant nodules were considered, hypoechogenicity was found in 152 (66.7%) nodules, microcalcification in 30 (13.2%) nodules, and contour irregularity in 42 (18.4%) nodules. The presence of halo and vascularization patterns was not recorded in most reports. The most common benign lesion was adenomatous hyperplasia (143/177) at a rate of 81%, and the most common malignant lesion was PTC (44/51) at a rate of 86% (79.5% classical type) in final pathologies. Other malignant nodules were listed as follicular cancer (6%), medullary

cancer (4%), hurthle cell cancer (2%), poorly differentiated cancer (2%). The proportions of tumor types are summarized in Figure 1. Among the 44 patients who were diagnosed with PTC, 14 (31.8%) were evaluated as papillary microcancers. The number of patients who had chronic lymphocytic thyroiditis in non-tumor thyroid tissues was 85 in the final pathologies, therefore, 37.3% of the 228 patients who were included in the study were diagnosed with HT. A statistically positive correlation was detected between the preoperative serum ATAb elevations and cytopathologically-proven HT ($p < 0.001$). The final pathological characteristics and gender distribution of the HT+ patients were compared with those of the HT- patients. Also, the same parameters were compared in terms of presence of ATAb, and are summarized in Table 1. The PTC rates were higher in HT+ patients, and the ATAb + patients ($p = 0.022 - 0.048$, respectively). It was also observed that other thyroid neoplasms were reported more frequently in both patient groups. Mean-median nodule diameter, mean-median tumor diameter, and multifocality were significantly

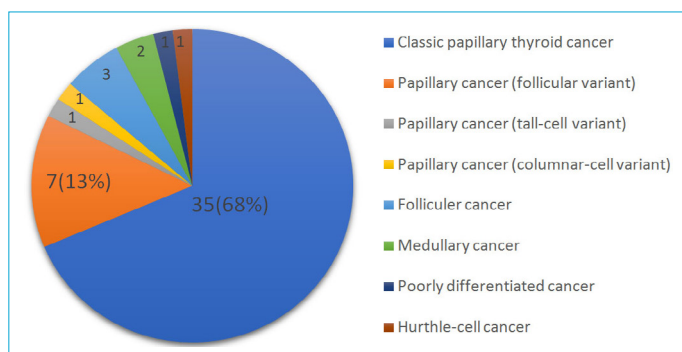


Figure 1. Distribution of cancer types.

lower in PTC in ATAb + patients. Poor prognostic factors such as mean-median nodule diameter, mean-median tumor diameter, and extrathyroidal spread were lower in the HT+ patients with PTC, and the rate of occult cancer was statistically higher. Also, although not at a statistically significant level, the rates of metastatic lymph nodes were higher in PTC in HT- patients (21% / 16%).

Border irregularity of the nodule is the most important independent variable in predicting PTC in the logistic regression analysis performed by considering ultrasonographic features and laboratory examinations ($p = 0.001$). When only Bethesda 3 nodules were considered, ATAb positivity was found to be a stronger predictor ($p = 0.005$) (Table 2). The relationship between malignancy and ultrasonographic features is summarized in Table 3. In the presence of ultrasonographic halo around the nodule, 92.7% (51/55) of the nodules were found to be benign ($p = 0.001$). This rate was 78.6% in the presence of HT. Considering the 197 patients whose ATAb levels were measured, nodules with halo 87.5% were benign, while it was 82.4% in only ATAb+ patients. When the nodules with Bethesda 3 diagnosis were considered, no malignancies were detected in any of the 12 nodules with halo presence. While the incidence of malignancy was 36% in nodules with a central vascularization pattern ($p = 0.083$) those with no vascularization data, no visible vascularization, and peripheral-type vascularization were found to be malignant at a rate of 28.1%, 20%, and 16.7%, respectively. The malignancy rate was found to be 42.9% in the presence of central vascularization only in nodules diagnosed with Bethesda 3 ($p = 0.059$).

Table 1. Comparison of gender and pathological parameters in terms of ATAb positivity and presence of HT.

Variables	ATAb+(n=72)	ATAb-(n=125)	p	HT+(n=85)	HT-(n=143)	p
Gender						
F	63 (37.7%)	104 (62.3%)	0.41	78 (41.7%)	109 (58.3%)	0.003
M	9 (30%)	21 (70%)		7 (17.1%)	34 (82.9%)	
Nodule diameter* (median mm)	19	21	0.040	17	22	0.006
Total malignancy rates	22 (30.6%)	29 (23.2%)	0.094	25 (29.4%)	26 (18.2%)	0.049
Total PTC rates	20 (27.8%)	24 (19.2%)	0.048	23 (27.1%)	21 (14.6%)	0.022
Malignancy rates in indeterminate nodules	7 (43.8%)	5 (15.2%)	0.029	8 (53.3%)	4 (11.8%)	0.002
PTC rates in indeterminate nodules	7 (43.8%)	3 (9.1%)	0.005	7 (46.7%)	3 (8.8%)	0.002
Occult cancer rates	7 (31.8%)	7 (24.1%)	0.20	10 (40%)	4 (15.4%)	0.049
Tumor diameter* (median mm)	16	24	0.043	14	23.5	0.006
Extrathyroidal extension rates	4 (18.1%)	12 (41.3%)	0.089	3 (12%)	13 (50%)	0.048
Multifocality rates	2 (9.1%)	9 (31%)	0.037	3 (12%)	8 (30.7%)	0.200
Lymphovascular invasion rates	3 (13.6%)	10 (34.4%)	0.088	5 (20%)	8 (30.7%)	0.500
Positive surgical margin rates	2 (9.1%)	3 (10.3%)	0.76	2 (8%)	3 (11.5%)	0.810

Chi-squared, *Mann-Whitney; HT: Hashimoto's thyroiditis; ATAb: Anti-thyroid antibody; PTC: Papillary thyroid cancer.

Table 2. Predictive values of the independent variables (for PTC).

Variables	p (Bethesda 3)	p (Total)
Hypoechoogenicity	0.136 (OR=1.13)	0.059 (OR=1.69)
Microcalcification	0.085 (OR=0.82)	0.025 (OR=1.11)
Border irregularity	0.019 (OR=1.04)	0.001 (OR=3.18)
Central vascularization pattern	0.093 (OR=1.35)	0.199 (OR=1.41)
ATAb positivity	0.005 (OR=1.14)	0.048 (OR=2.11)

Logistic regression analysis (CI= 95%); PTC: Papillary thyroid cancer.

Table 3. Malignancy rates of ultrasonographic features

Ultrasonographic features	Bethesda Category 3 (n=49)	p	Total (n=228)	p
Hypoechoogenicity	9 (37.5%)	0.038	40 (26.3%)	0.043
Microcalcification	6 (60%)	0.003	11 (36.7%)	0.044
Border irregularity	10 (43.5%)	0.004	16 (38.1%)	0.007
Central vascularization Pattern	6 (42.9%)	0.059	9 (36%)	0.083
Presence of halo (n=55)	0		4 (7.3%)	

Chi-squared.

Discussion

Elevated serum ATAb levels may not be sufficient alone for the diagnosis of chronic lymphocytic thyroiditis; however, HT can be proven histopathologically in more than half of such patients. It has been reported that this rate exceeds 75% in patients whose serum anti-TG and anti-TPO levels increase together.^[11] The positive correlation was shown in the present study between the positivity of anti-TG or anti-TPO and the diagnosis of HT in the final pathology. Antibody measurements do not have satisfactory specificity in the diagnosis of HT because elevated serum ATAb levels can be detected in subacute thyroiditis and even in healthy population. Also, 10% of HT+ patients have negative ATAb levels.^[12] The relations between HT and PTC were reported at different rates in many studies.^[13-15] Although Paulson et al. reported 43.8% regarding the association between HT and PTC,^[16] this can be considered as an average of 23% according to the literature data.^[17] Those who associate these relations with chronic inflammation leading to neoplasia are in the majority. It is also considered that elevated thyrotropin (TSH) levels in mid-to-advanced stages of HT induce the development of well-differentiated thyroid cancers.^[18] The fact that HT is the most common cause of hypothyroidism especially in western societies may make this more meaningful. There are articles in the literature reporting that PTC progresses with less recurrence and longer survival in the presence

of HT and ATAb in serum.^[19-21] Small tumor diameter, less ETE, and fewer metastatic lymph nodes were proven in many studies in PTC cases associated with HT, as was the case in the present study.^[22] As summarized in Table 1, it was found that nearly all of the good prognostic factors were higher in both the ATAb + Group and the HT+ Group, especially the smaller tumor diameter and less multifocality in the ATAb + Group was found to be meaningful. The TI-RADS Classification, which is used by considering the borders, echogenicity, calcification patterns, and aspect ratios of nodules in ultrasonographic evaluation, has a high sensitivity in predicting malignancy.^[23] The relation with high malignancy rates was demonstrated especially in nodules diagnosed with intermediate cytology even when hypoechoogenicity, presence of microcalcification, and border irregularity were considered separately. For this reason, surgery should almost always be considered in the first line in TI-RADS 4B and 5 nodules whose malignancy rates vary between 65-95% according to the literature data.^[24] There are articles supporting that increased central vascularization in doppler ultrasonography is not a reliable predictor. In our study, it can be mentioned that the central vascularity seen in the nodules diagnosed with Bethesda 3 increases the risk of malignancy, but it was not possible to prove this statistically.^[25] It is mentioned in the literature that the presence of regular surrounding halo in benign nodules in ultrasonographic examination is higher than in malignant nodules, as was the case in our study.^[26] However, it is already known that nodules that have regular and circumferential halo can sometimes be diagnosed as malignant, and therefore, it is understood that although malignancy is avoided in the presence of halo, it cannot be excluded.

Limitations

It was not possible to perform statistical analyses by evaluating both antibody levels separately because serum anti-TG and anti-TPO measurements were not homogeneously distributed in the present study. The aspect rate of the nodules was not specified in the report in most of the cases included in the present study, and therefore, other parameters included in the TI-RADS were included, and vascular pattern and scintigraphic characteristics could not be included in the analyses at desired rates because the numbers of scintigraphy and doppler examinations were limited.

Conclusion

Good prognostic factors such as small tumor diameter, fewer ETE, and fewer metastatic lymph nodes in HT-associated PTC, may be associated with frequent and short-term follow-up or with the anti-tumoral effects of autoimmunity.

Due to ATAb positivity and ultrasonographic features, patients with suspected HT can be decided to have surgery earlier, especially for Bethesda 3 nodules, without the need for additional tests. We believe that suspicious ultrasonographic characteristics must be the main determinant for operating on the nodules with this diagnosis. Surgery options must be kept in the background for nodules with low risk in the presence of a smooth halo in ultrasonographic examination.

Disclosures

Ethics Committee Approval: Turkish Republic Mardin Governorship Provincial Directorate of Health Number: E-37201737-949 Date: 15.11.2021.

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