

# Is Hashimoto's thyroiditis a prognostic factor for thyroid papillary microcarcinoma?

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**Abstract.** – **AIM:** The relationship between papillary thyroid carcinoma (PTC) and accompanying Hashimoto's thyroiditis (HT) has been investigated extensively. However, there is no agreement among the authors. We aimed with this study to investigate this relationship in a limited subtype of PTC called papillary thyroid microcarcinoma (PTMC).

**PATIENTS AND METHODS:** Between January 1999 and December 2012, 1923 thyroids were surgically resected in two referral centers and thoroughly inspected for evidence of PTMC. Of these patients, 172 who were diagnosed with PTMC had demographic and pathological features recorded.

**RESULTS:** Fourteen patients (8.1%) were found to have CLN metastases. Eleven (78.6%) of the patients with CLN metastases had tumors larger than 5 mm, and 3 (21.4%) patients with CLN metastases had small tumors ( $\leq 5$  mm), but there was no statistical significance ( $p > 0.05$ ). Accompanying Hashimoto's thyroiditis (HT) was detected in 67 (39%) patients. The CLN metastasis rate was slightly higher in cases with HT in surrounding thyroid tissue. However, there was no statistical significance; the CLN rate was 6.7% ( $n=7$ ) in patients without thyroiditis and 10.4% ( $n=7$ ) with Hashimoto's thyroiditis. Insufficient FNA results in patients with thyroiditis were associated with HT ( $p < 0.05$ ).

**CONCLUSIONS:** Surgeons and other clinicians who play a role in the treatment of thyroid cancers should be aware that some PTMC cases may show a worse course, as with some PTCs, contrary to expectations.

*Key Words:*

Thyroiditis, Papillary thyroid carcinoma, Sentinel lymph node.

proximately 1% of all cancers. In the US, an estimated 10 000 men and 27 200 women were diagnosed with thyroid cancer in 2009<sup>1</sup>. Papillary and follicular carcinomas are well-differentiated cancers of the thyroid gland and are typically curable malignancies<sup>1</sup>. The ten-year average survival rate for middle-aged adults with thyroid carcinoma ranges from 80-95%<sup>2</sup>.

The worldwide incidence of papillary thyroid carcinoma (PTC) has increased; however, the cause of this increase is not clear. Further studies should clarify whether this increase is absolute or the result of improved diagnostic capabilities<sup>3</sup>. The World Health Organization (WHO) in 1998 defined papillary thyroid microcarcinomas (PTMCs) as papillary thyroid carcinomas that were equal to or smaller than 10 mm<sup>4</sup>. In contrast in 1997, Moose et al<sup>5</sup> defined occult thyroid carcinomas (OTCs) as thyroid carcinomas smaller than 10 mm. Microcarcinomas are occult carcinomas that are small,  $\leq 10$  mm in diameter, papillary in type and exhibit benign behavior. PTMCs rarely metastasize to distant sites and have an excellent prognosis with a reported mortality less than 0.5%<sup>6-9</sup>. However, a small number of PTMCs with aggressive behavior require an aggressive surgical approach in the same manner as some large PTCs that have been reported<sup>10</sup>. Several authors<sup>9,11,13</sup> have reported PTMC cases and series that have metastasized to cervical lymph nodes (CLNs), causing recurrence and death. Hashimoto's thyroiditis (HT) is the most common autoimmune thyroid disease and the most common cause of hypothyroidism. HT was first described in 1912 by Hakaru Hashimoto, a Japanese surgeon and pathologist<sup>14</sup>. The pathology is characterized by diffuse lymphocyte infiltration, fibrosis, and parenchymal atrophy. It

## Introduction

Thyroid cancer is the most common head and neck malignancy in the US and accounts for ap-

is also associated with thyroid dysfunction and occasional development of goiter<sup>15</sup>. The association between HT and PTC was first proposed by Dailey et al in 1955<sup>16</sup>.

In this study, we present a retrospective analysis of PTMCs in order to understand their clinical behavior. We focus on the presence of accompanying Hashimoto's thyroiditis (HT) to compare the CLN metastasis rate and other markers, which indicate the aggressiveness of the tumor.

### Patients and Methods

A total of 1923 patients who were treated for thyroid nodules at Baskent University Istanbul Training Hospital and Bakırkoy Training and Research Hospital from January 1999 to December 2012 were included in the analysis. Well-differentiated thyroid carcinomas that were > 10 mm, thyroid lymphomas, poorly differentiated thyroid carcinomas and medullary thyroid carcinomas were excluded. Of these patients, 172 (8.94%) were pathologically identified as having PTMC. The size of the tumor, histopathologic findings, presence of Hashimoto's thyroiditis (HT), multifocality, bilateral presentation, the presence of fine needle aspiration biopsy (FNAB), FNAB results, vascular and lymphatic invasion, cervical lymph node metastases and the age and gender of the patients were recorded and statistically analyzed. The histological criteria used to make a diagnosis of HT included diffuse lymphoplasmacytic infiltration, germinal centers, and enlarged epithelial cells with large nuclei and eosinophilic cytoplasm (Askanazy or Hurthle cells). Non-specific lymphocytic thyroiditis occurring immediately adjacent to a tumor could not be differentiated from perineoplastic inflammation and was not included in number with HT to avoid over-diagnosis in our study.

### Statistical Analysis

Descriptive analyses are presented using percentages, means and standard deviations. Tumor size was analyzed as a dichotomous variable (tumor size: ≤ 5 mm; > 5 mm). Similarly, additional histopathological findings were categorized into two groups: with or without thyroiditis. Chi square and Fisher's exact tests were used to analyze categorical data. The association between age and tumor size was tested using a Student's *t*-test. A *p* value of less than 0.05 was considered statistically significant.

### Results

The mean age of patients with PTMC was  $51.06 \pm 13.24$  years (18 to 83) at the time of diagnosis. One hundred forty-three patients were female (83.1%), and 29 were male (16.9%). The female/male ratio was approximately 4.93. One hundred four patients (60.5%) were diagnosed with PTMC based on a FNAB before surgery. In 73 patients (42.4%), the FNAB results were not diagnostic. Other FNAB results (numbers of patients; percentages) were as follows: benign (29; 16.9%), atypical and of undetermined significance (AUS) (1; 0.6%), follicular neoplasm (FN) (13; 7.6%), suspected malignancy (SM) (20; 11.6%), and malignant (36; 20.9%). The performance of preoperative FNAB was not associated with tumor size.

Postoperative pathologic results revealed the following subtypes (numbers of patients; percentages): papillary (108; 62.8%), follicular variant of papillary cancer (54; 31.4%) and follicular (10; 5.8%) from a total of 172 microcarcinomas. The rate of multi-centricity was 26.2% ( $n=45$ ), and the rate of bilateral presentation was 15.1% ( $n=26$ ). The mean tumor diameter was  $5.92 \pm 2.72$  mm, and the smallest tumor diameter was 0.5 mm (Figure 1). There was no significant difference in tumor size between genders ( $p > 0.05$ ).

In 31 (18.02%) cases of PTMC, a CLND (cervical lymph node dissection) was performed. It is unclear from the data whether the CLNDs were performed for treatment or prophylaxis. Fourteen of the patients (8.1%) were found to have CLN metastases. Eleven (78.6%) of the patients with

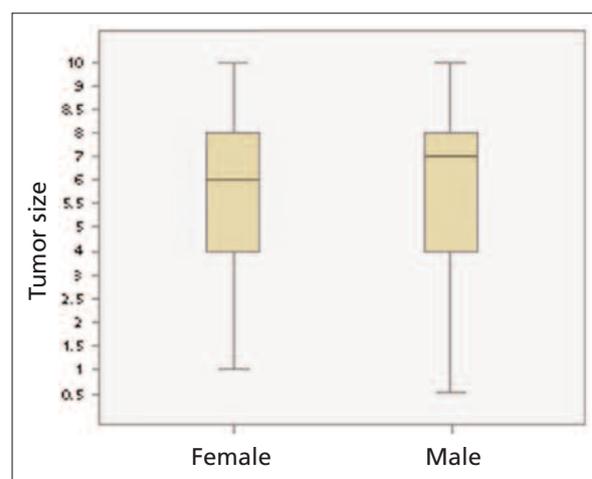


Figure 1. Tumor size between genders.

**Table I.** General characteristics of the patients by tumor size.

	IHT +	HT-
Gender		
Male	5 (7.5%)	81 (77.1%)
Female	62 (92.5%)	24 (22.9%)
FNA		
Sufficient	25 (37.3%)	43 (41%)
Insufficient	42 (62.7%)	62 (59%)
Multicentricity	18 (26.9%)	27 (25.7%)
Bilaterality	12 (17.9%)	14 (13.3%)
Capsular invasion	16 (23.9%)	16 (15.2%)
Vascular invasion	1 (1.5%)	3 (2.9%)
Histopathologic type		
Papillary	38 (40.3%)	70 (66.7%)
FVPC	27 (56.7%)	27 (25.7%)
Follicular	2 (3%)	8 (7.6%)
CLNM	7 (10.4%)	7 (6.4%)
Larger Tumor size (< 5 mm)	35 (52%)	58 (55.2%)

HT+ (Presence of Hashimoto’s thyroiditis) HT- (Presence of Hashimoto’s thyroiditis), FNA (Fine Needle Aspiration), CLNM (Cervical Lymph Node Metastasis).

CLN metastases had tumors larger than 5 mm in diameter, and 3 (21.4%) patients with CLN metastases had small tumors ( $\leq 5$  mm), but there was no statistical significance ( $p > 0.05$ ). General characteristics of the patients by tumor size are shown in Table I.

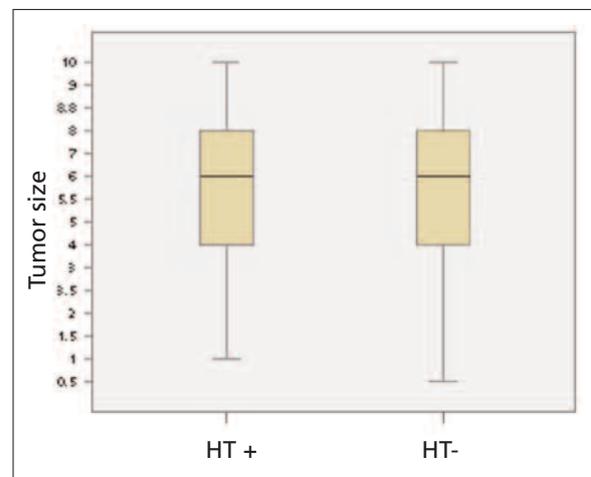
Accompanying Hashimoto’s thyroiditis (HT) was detected in 67 (39%) patients (Figure 2). The HT diagnosis was based on pathologic specimens. The CLN metastasis rate was slightly higher in cases with the presence of thyroiditis in the surrounding thyroid tissue. However, there was no statistical significance; the rate of CLN involvement was 6.7% (n=7) in patients without thyroiditis and 10.4% (n=7) in patients with Hashimoto’s thyroiditis. Bilateral presentation, multifocality, capsular invasion, vascular invasion, and tumor size were not associated with HT. Insufficient FNA results for patients with thyroiditis were associated with HT ( $p < 0.05$ ). General characteristics of the patients with HT are shown in Table II.

Postoperative pathologic results revealed capsular invasion in 32 patients (18.6%) and vascular invasion in 4 patients (2.3%). All PTMCs with vascular invasion were greater than 5 mm, but there was no statistically significant difference based on tumor size ( $p > 0.05$ ). Also, the CLN metastasis rate was not associated with capsular or vascular invasion. The number of PTMCs larger than 5 mm with thyroid capsular invasion was 25 (78.1%), and 7 (21.9%) PTMC tu-

mors were small ( $\leq 5$  mm); this result demonstrated a statistical significance between tumor size and capsular invasion ( $p < 0.05$ ).

### Discussion

PTMC is a variant of PTC measuring  $\leq 10$  mm in diameter<sup>13</sup>. Although an indolent course for PTMCs has been reported in the literature<sup>17,18</sup>, in some publications, PTMCs have been shown to behave more aggressively and may manifest with CLN metastases<sup>17</sup>. In our study, we found a CLN metastasis rate of 8.1%. Many papers in the lit-



**Figure 2.** Tumor size between HT.

**Table II.** General characteristics of the patients with HT.

	Tumor size (0-5 mm)	Tumor size (6-10 mm)
Gender		
Male	9 (11.4%)	73 (78.5%)
Female	70 (88.6%)	20 (21.5%)
FNA		
Sufficient	42 (53.2%)	62 (66.7%)
Insufficient	37 (46.8%)	31 (33.3%)
Multicentricity	17 (21.5%)	28 (30.1%)
Bilaterality	8 (10.1%)	18 (19.4%)
Capsular invasion	7 (8.9%)	25 (26.9%)
Vascular invasion	0 (0%)	4 (4.3%)
Histopathologic type		
Papillary	46 (39.2%)	62 (66.7%)
FVPC	31 (58.2%)	23 (24.7%)
Follicular	2 (2.5%)	8 (8.6%)
CLNM	3 (3.8%)	11 (11.8%)
HT+	32 (40.5%)	35 (37.6%)

HT+ (Presence of Hashimoto's thyroiditis), FNA (Fine Needle Aspiration), CLNM (Cervical Lymph Node Metastasis).

erature have reported higher CLN metastases rates, but in these cited studies, a routine central neck dissection was performed to either detect subclinical CLN metastases or for prophylaxis<sup>19-22</sup>. Due to the small tumor size and low likelihood of capsular invasion, the indication for radioactive iodine (RAI) is almost always the presence of CLN metastasis, and additional RAI treatment may be given without a CLND.

However, CLN dissection is associated with surgical risks, such as hypocalcemia and recurrent laryngeal nerve palsy. The cost-effectiveness of the procedure is debatable as well because of the low rate of recurrence<sup>23-25</sup>. The 2009 guidelines from the American Thyroid Association (ATA) suggested that near-total or total thyroidectomy without prophylactic central neck dissection may be appropriate for small (T1 or T2), noninvasive, clinically node-negative PTCs and most follicular cancers. The recommendation rating was 'C', which indicates a recommendation based on expert opinion<sup>26</sup>. If central LN dissections are performed by skilled surgeons, the likelihood of permanent hypoparathyroidism may decrease. Therefore, prophylactic central LN dissection can be recommended for PTMC patients. Otherwise, intraoperative examination of ipsilateral central LN metastasis may be useful for developing a prognosis for patients with PTMC and tailoring postoperative management<sup>27</sup>.

There has long been a controversy in the literature about a possible link between HT and PTC. Conflicting reports continue to emerge; some suggest a positive correlation between the two, and

even a cause-and-effect relationship where the activated inflammatory response present in HT creates a favorable setting for malignant transformation. The inflammatory response may cause DNA damage through formation of reactive oxygen species (ROS), resulting in mutations that eventually lead to the development of PTC<sup>30</sup>. Hashimoto's thyroiditis (HT) is associated with an increased risk of developing PTC. The relationship between thyroid autoimmunity and cancer remains controversial. In a retrospective non-randomized study<sup>31</sup>, it was shown that the presence of thyroglobulin antibody is an independent factor in the development of PTC. Numerous data from the literature on the subject and multi-center meta-analyses demonstrate that PTC coexists almost three times more often with Hashimoto's thyroiditis, and its concomitant occurrence reported in various publications ranges from 0.5 to 58%. In a systematic literature review, Jankovic et al<sup>28</sup> reported that population-based FNA studies did not find a statistically significant correlation between HT and PTC, but thyroidectomy studies<sup>29</sup>, which reported a statistically significant positive correlation, are subject to selection bias. We agree in our study with Jankovic et al<sup>28</sup> on the cause of the high occurrence of HT. The HT rate in our study was 39%, which is similar to the rate found in the literature.

It is questionable whether or not underlying HT is a worse prognostic factor for PTMC. Some of the data presented in the literature<sup>26-29</sup> suggest a positive correlation between positive thyroglobulin antibody results or the presence of underlying HT and CLN metastases in patients with PTC

and PTMC. We found a higher appearance of CLN metastases in patients with HT, but it was not statistically significant. Ahn et al<sup>30</sup> reported that patients with PTC were four times more likely to have a coexisting HT compared to patients with other thyroid diseases, suggesting a link between chronic inflammation and cancer development in the thyroid gland. There was also a trend in patients with PTC and HT for a better prognosis, including smaller tumor sizes, a lower frequency of LN metastasis, lower MACIS scores, and higher disease-free and overall survival rates, than in patients with PTC alone, although these findings were not statistically significant. In a large retrospective study<sup>31</sup>, 0.7% cancer-specific mortality and a 95% relapse-free 10-year survival rate were reported in patients with chronic thyroiditis compared to 5% mortality and an 85% relapse-free 10-year survival rate without chronic thyroiditis. In our study, bilaterality, capsular invasion, vascular invasion and tumor size were not associated with the presence of HT ( $p > 0.05$ ). Based our results, the presence of HT is not a worse prognostic factor. However, data in the medical literature on the relationship between PTC and HT were not primarily focused on tumor size or incidentalomas.

Some authors<sup>32-35</sup> have reported that there is no relationship between the BRAF (V600E) gene mutation, which is a marker of aggressiveness in PTMCs, and the presence of HT. However, other poor prognostic factors do not seem to be associated with HT. Due to the high probability of CLN metastases, a prophylactic CLND may be considered for patients with HT, especially for patients with tumors larger than 5 mm. Insufficient FNA results in patients with thyroiditis were associated with HT ( $p < 0.05$ ). This may be associated with pseudonodules in HT, which can be confused with real nodules. Yildirim et al<sup>36</sup> reported that sonoelastography was found to have increased sensitivity for true nodule diagnosis compared with conventional grey scale ultrasonography and may eliminate performance of unnecessary FNABs. We recommend that clinicians repeat FNABs or if possible confirm negative and insufficient FNABs with elastography for patients with HT.

## Conclusions

Despite their indolent nature, PTCs can behave aggressively in some cases. PTMCs tend to act

like PTCs. Surgeons and other clinicians who play a role in the treatment of thyroid cancers should be aware that some PTMC cases may show a worse course, as with some PTCs, contrary to expectations. We recommend treatment of PTMCs with a method similar to PTC treatment. However, underlying HT may be considered a risk factor for CLN metastasis. If an accompanying HT has been detected, an ipsilateral prophylactic central neck dissection may be in order. In our study, we investigated only those pathologic features that may indicate a worse prognosis.

## Conflict of Interest

The Authors declare that there are no conflicts of interest.

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