



Original Research

Clinicopathologic Differences Between Micropapillary and Papillary Thyroid Carcinoma

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Abstract

Objectives: The aim of this study is observing the clinicopathologic features of thyroid papillary microcarcinomas (PTMs) and comparing these features with papillary thyroid carcinoma (PTC).

Methods: A total of 86 surgically treated patients suffering from PTC were evaluated retrospectively. Group 1 (G1) included patients with a tumor <1 cm, while Group 2 (G2) included patients with a tumor >1 cm. The two groups were compared in terms of the preoperative thyroid-stimulating hormone (TSH) level, anti-thyroid peroxidase antibody (anti-TPO) and antithyroglobulin antibody (TgAb) values, multicentricity, the lymphovascular invasion rate, the presence of extrathyroidal extension, and central and/or lateral lymph node metastasis.

Results: There was no statistically significant difference observed between the groups in terms of the preoperative TSH level, anti-TPO, and TgAb values. The rate of multicentricity of the tumor in G2 was 66%, while it was 36% in G1 ($p<0.001$). The lymphovascular invasion rate in G1 was 14.2%, while it was 61% in G2 ($p<0.001$). The extrathyroidal extension rate of the tumor cells in G1 was 21.4%, while it was 63.6% in G2 ($p<0.001$). The central lymph node metastasis rate in G2 was 38.6%, while it was 4.8% in G1 ($p<0.001$). The lateral lymph node metastasis rate in G2 was 20.5%, while it was 0% in G1 ($p<0.001$).

Conclusion: PTMs are generally associated with good prognostic factors with high survival rates. However, the risk factors such as multifocality, extrathyroidal extension, and lymphovascular invasion increasing the recurrence risk are not rare in PTM. Thus, the patients having these histopathological features of the tumor should be followed more carefully.

Keywords: Extrathyroidal extension; lymphovascular invasion; lymph node metastasis; prognosis; thyroid papillary carcinoma; thyroid micropapillary carcinoma.

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The common use of ultrasonography (USG) as a diagnostic tool for thyroid diseases has led to the recognition that there are several untreated individuals with thyroid nodules among normal population. Another aspect of USG application with regard to thyroid nodules is that it allows to evaluate the radiologic features of the nodules and also perform fine-needle biopsies from nodules that have sus-

picious ultrasonographic features, even if those nodules are <1 cm. The US data showed that the thyroid carcinoma incidence has tripled since 1975.^[1] According to the worldwide known endocrine societies, this enormous increase is most likely related to high diagnostic rates of papillary thyroid carcinomas (PTCs), which are 1 cm or less in size and termed papillary thyroid microcarcinomas (PTMs).^[2] Due

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to this developing entity, the clinicopathologic differences between PTCs and PTMs gained more importance while deciding the management of the treatment and follow-up procedures of patients with PTMs.

The prognosis and clinical importance of PTMs are still controversial. While some studies recommend nonoperative treatment due to the high survival rates of the disease, some of the authors take attention to the high incidence rates of local lymph node metastasis and multifocality of the tumor and recommend surgical treatment.^[3-5] In this study, we aimed to observe the clinicopathologic features of the PTMs and also tried to compare these features with PTC.

Methods

After the institutional approval from the Sisli Hamidiye Etfal Training and Research Hospital Ethics Committee, the data of 86 patients who underwent total thyroidectomy, with or without prophylactic or therapeutic central neck dissection (unilateral or bilateral), or therapeutic lateral neck dissection for thyroid carcinoma at the Sisli Hamidiye Etfal Training and Research Hospital between 2011 and 2013 were retrospectively evaluated. Patients who underwent lobectomy with a diagnosis of PTC or PTM after the fine-needle aspiration biopsy and also those diagnosed with PTC or PTM incidentally after lobectomy and not applied completion thyroidectomy were excluded from the study.

Patients were divided into two groups according to the tumor size. Group 1 (G1) consisted of patients with a tumor <1 cm, while Group 2 (G2) consisted of patients with a tumor >1 cm in size. The two groups were compared in terms of the preoperative thyroid-stimulating hormone (TSH) level, anti-thyroid peroxidase antibody (anti-TPO) and antithyroglobulin antibody (TgAb) values, multifocality, lymphovascular invasion, the presence of extrathyroidal extension, and central and/or lateral lymph node metastasis.

Continuous data and categorical data were compared using the Mann-Whitney U test and Fisher's exact test or chi-square test, respectively. All tests were two tailed, and a value of $p < 0.05$ was considered statistically significant.

Results

A total of 86 patients with thyroid carcinoma who underwent thyroidectomy between 2011 and 2013 were included in the study. Twenty-one out of 86 (24.4%) patients were male, while the remaining 65 (75.6%) patients were female. There were 42 patients (31 females, 11 males) in G1 and 44 patients (34 females, 10 males) in G2. The mean ages of the G1 and G2 were 51 and 47 years (range, 20–80) respectively. No statistically significant difference was found between the groups in terms of sex and age.

The preoperative TSH, TgAb, and anti-TPO values were

compared, and no statistically significant difference was observed between the groups (Table 1).

The multifocality rate of the tumor in G2 was 66% (29 of 44 patients), while it was 36% (15 of the 42 patients) in G1. The difference between the groups was statistically significant ($p < 0.001$). The lymphovascular invasion rate in G1 was 14.2% (6 of 42 patients), while it was 61% (27 of 44 patients) in G2, and there was a significant difference between the groups ($p < 0.001$). Extrathyroidal extension rate of the tumor cells in G1 was 21.4%, while it was 63.6% in G2. The difference between the groups was also statistically significant ($p < 0.001$) (Table 2).

The central lymph node metastasis rate in G2 was 38.6%, while it was 4.8% in G1. The difference between the groups was statistically significant ($p < 0.001$). The lateral lymph node metastasis rate in G2 was 20.5%, while it was 0% in G1. The difference between the groups was statistically significant ($p < 0.001$) (Table 3).

Table 1. Preoperative Values of TSH, Anti- Tg, and Anti- TPO

	Group 1 (n=42)	Group 2 (n=44)	p
Age (mean±SD) (min-max)	51.2±10 (31-67)	47.9±15.7 (20-80)	0.32
Gender female/male (n)	31/11	10/34	0.709
TSH (mIU/L) (mean±SD) (min-max)	1.77±1.44 (0.01-5.69)	2.44±3.98	0.721
Anti-TPO	5/20	9/18	0.355
Anti-Tg	5/25	7/24	0.749
Surgical procedure (n)			
TT	37	18	
TT+UCND	3	9	
TT+BCND	1	6	
TT+UCND+LND	-	1	
TT+BCND+LND	1	10	

TSH: thyroid- stimulating hormone; anti- Tg: anti thyroglobulin antibody; anti- TPO: antithyroid peroxidase; n: number; TT: Total thyroidectomy; UCND: Unilateral central neck dissection; BCND: Bilateral central neck dissection; LND: Lateral neck dissection.

Table 2. The Multicentricity, Lymphovascular Invasion, and Extrathyroidal Extension Rates of the Groups According to the Pathologic Evaluation of the Thyroidectomy Specimens

Pathological evaluation	Group	Present (%)	Not-Present (%)	p
Multifocality	G1	15 (36)	27 (64)	<0.001
	G2	29 (66)	15 (34)	
Lymphovascular invasion	G1	6 (14.2)	36 (85.8)	<0.001
	G2	27 (61)	17 (39)	
Extrathyroidal extension	G1	9 (21.4)	33 (78.6)	<0.001
	G2	28 (63.6)	16 (36.4)	

Table 3. The Central and Lateral Lymph Node Metastases Rates

Pathological evaluation	Group	Present (%)	Not-Present (%)	p
Central lymph node metastasis	G1	2 (4.8)	40 (95.2)	<0.001
	G2	17 (38.6)	27 (61.4)	
Lateral lymph node metastasis	G1	0 (0)	42 (100)	<0.001
	G2	9 (20.5)	35 (79.5)	

Discussion

The USG-guided fine-needle aspiration biopsy has been the milestone for the increasing incidence of PTMs. Another reason for the increasing incidence of PTMs is a more accurate evaluation of the pathologic specimen of thyroidectomies.^[6, 7] PTMs are generally classified as well-prognosed tumors. Despite this good prognosis, the management of these tumors is still controversial. In the current study, we reported the data of 86 patients with PTMs and tried to figure out if there was a correlation between these surgically treated patients and poor prognostic PTC factors.

The PTM prognosis is almost excellent. A total of 18.445 patients with PTMs who underwent surgery from the American SEER database were evaluated. The 10-year and 15-year overall survivals were found as 94.6% and 90.7%, respectively. In addition, disease-specific survivals were reported at 99.5% and 99.3%, respectively. The age >45, male gender, lymph node metastases, extrathyroidal extension, and distant metastases were demonstrated as independent risk factors for overall survival. The presence of two or more of these risk factors were also strongly associated with the carcinoma-related mortality.^[8, 9] Hay et al.^[10] studied 900 patients with PTM in a 60 years period with a mean follow up of 17.2 years and found the 20 year and 40 year recurrence rates as 6% and 8%, respectively. Multifocality, lymph node metastasis and a tumor size >5mm were reported to be the risk factors in a large series of patients.^[10, 11]

Recently, in a study of 8.676 patients with PTM; when the patients with contralateral lobe recurrence were removed throughout the lobectomy patients, it was detected that the recurrence was mostly seen in the regional lymph nodes. An increased tumor diameter, multifocality, microscopic extrathyroidal extension, and central lymph node metastasis were determined as risk factors in both all the recurrences and the contralateral lobe recurrences in lobectomy patients.^[12]

The serum level of TSH, a pituitary hormone that regulates the thyroid hormone metabolism, has been previously shown as a prognostic factor for the PTC.^[13–15] TPO-Ab and Tg-Ab are the other important clinical tests that are also known as potential prognostic PTC factors.^[16–18]

Wu et al.^[18] studied 2.132 patients who underwent thyroidectomy due to nonautoimmune thyroid diseases and observed that patients with PTC showed a higher rate of TgAb positivity and a higher TSH level than patients with multinodular goiter. Kim et al.^[16] collected the data of 323 patients with PTM and found that TgAb had a higher prevalence in patients with PTM and lymphocytic thyroiditis (LT). In our study, there was no statistically significant difference between the groups in terms of TSH levels and the TgAb, and anti-TPO positivity. The difference between our study and Kim's study may be that LT was not taken into consideration and the limited number of patients in our study.

Although multifocality is associated with an increased risk of recurrence, distant metastasis and mortality in PTC patients, it is related with the local recurrence in patients with PTM.^[12]

The frequency of multifocality in PTMs is reported to be 15%–32%. In our study, this rate was found to be 36% in PTM, which is compatible with the existing literature.^[10, 12, 18–20] In the current study, there was a statistically significant difference in terms of multifocality between patients with PTC and those with PTMs (66% vs. 36%; $p<0.001$). The significantly lower multifocality rate of PTM compared to that of PTC can mean that PTM has a lower risk of recurrence. The multifocality feature has to be taken into consideration because of its presence in one-third of patients with PTM considering it is also a risk factor for recurrence in PTM.

Lymphovascular invasion (LVI) is an important and independent risk factor for the local and distant recurrence, disease-free and overall survival rates, and prognosis of the patients with PTC.^[21] LVI is a risk factor for central and lateral lymph node metastases.^[22, 23]

Kim et al.^[24] studied 662 patients with PTC in a single institution and found that 33% of them had LVI. In this study, the authors observed a significant relation between LVI and lateral and central cervical lymph node metastases. The incidence of pathological central lymph node metastases in patients with N0 PTM was 33%, and they reported that LVI was one of the risk factors for clinical microscopic central metastasis. In our study, 14% of the patients with PTM had LVI invasion, while 61% of the patients with PTC had LVI ($p<0.001$). The difference between the groups was statistically significant. This finding is in compliance with our study demonstrating the lower rates of central and lateral metastases in PTM compared to PTC.

There were statistically significant differences between the groups in terms of central and lateral lymph node metastases. A total of 4.8% of patients with PTM had metastasis in central lymph nodes, while 38.6% of the patients with PTC had metastasis in central lymph nodes ($p<0.001$). There

were no patients in the PTM group with lateral lymph node metastasis, while 9 patients (20.5%) with PTC had metastasis in lateral lymph nodes ($p < 0.001$). In some of the studies, patients with PTM have been reported to have cervical lymph node metastasis with a rate of 3% up to 17% after the evaluation of the pathology specimen.^[25, 26] In the current study, the low rate of lymph node metastasis in patients with PTM may be related to the low rate of clinical lymph node metastasis and rarely performed prophylactic central neck dissection. The central lymph node metastasis is a risk factor for local recurrence.

The American Thyroid Association (ATA) guideline classifies PTC with minimal extrathyroidal extension (mETE) at intermediate risk of persistent/recurrent disease and recommends thyroidectomy and radioactive iodine ablation for the patients with PTC with ETE.^[27] But the treatment options for the patients with PTMs with ETE are not clear. Extrathyroidal extension is a negative factor upon survival both for PTC^[28, 29] and PTM.^[8, 12]

In our study, 21.4% of the patients in the PTM group had ETE, while 63.6% of the patients in the PTC group had ETE. The difference was statistically significant ($p < 0.001$). Despite the higher recurrence risk in PTC regarding ETE, this feature is also not rare in PTM. The American Joint Committee on Cancer (AJCC) has published the 8th edition of the TNM carcinoma staging manual that is used for predicting the disease-specific survival, which is different from the ATA guidelines.^[30] One of the major changes in the recent manual was the removal of the minimal extrathyroidal extension definition, which is detected only on histologic examination, from the explanation of T3 disease. Due to this change, the minimal extrathyroidal extension will no longer have an impact on either T category or overall disease stage.^[31] The debate on this subject seems to continue in the future.

The main limitations of our study are its being retrospective and having a limited number of patients.

Conclusion

TPMs are generally associated with good prognostic factors and high survival rates. The properties associated with tumor aggressiveness of PTM are lower than in other papillary carcinomas. In addition, the risk factors such as multifocality, ETE, and LVI increasing the recurrence risk are not rare in PTM. Thus, the patients having these histopathological tumor features should be followed more carefully.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of Health Sciences University, Sisli Hamidiye Etfal Training and Research Hospital.

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Conflict of Interest: The authors declare that there are no any conflicts of interests with any company or organization.

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