Clinicopathology of Papillary Thyroid Microcarcinomas

Papiller Tiroid Mikrokarsinomlarının Klinikopatolojisi

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ABSTRACT

Objective: The widespread use of ultrasonography is the main reason for the increase in the detection of papillary thyroid microcarcinomas (PTMs). We evaluated the clinicopathological features of cases diagnosed with PTM in our clinic.
Materials and Methods: In this retrospective study, 354 cases were evaluated. Cytological diagnoses were classified using the 2017 Bethesda System. Statistical analyses were made using IBM SPSS Statistics v. 22. Comparisons between the groups were analyzed with the chi-Square test, Fisher exact chi-square test, Student's t-test, and Mann-Whitney U test.
Results: Forty-eight percent of the cases were diagnosed with PTM and 47.1% with incidental papillary thyroid microcarcinoma (IPTM). The rate of female patients was higher in the IPTM group than in the papillary thyroid carcinoma (PTC) group, and the difference was statistically significant (p<0.001). The co-occurrence of chronic lymphocytic thyroiditis (CLT) was higher in the PTM cases than in the PTC group (41.2% and 36.9%, respectively). The mean TSH value was higher in the PTM group than in the PTC group. Capsular invasion was seen at a higher rate in the PTC group than in the PTM group (p<0.001).
Conclusion: In our study, we observed lower TSH values in cases with IPTM compared to those with PTC at a younger age and in the female gender. We consider that due to the small tumor diameter of IPTMs, their metastasis ability is lower, and therefore they have a good prognosis.

Keywords: Cancer of Thyroid, Thyroiditis, Papillary Thyroid Carcinoma, TSH (Thyroid Stimulating Hormone), Thyroid Nodule, Thyroid Neoplasms

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ÖZET

Amaç: Ultrasonografinin kullanımının yaygınlaşması Papiller tiroid mikrokarsinom (PTM) artışının esas nedenidir. Kliniğimizde PTM tanısı almış olguların klinikopatolojik özelliklerini değerlendirdik.
Yöntem: Retrospektif olarak yapılan çalışmada 354 olgu değerlendirilmektedir. Sitolojik tanılar 2017 Bethesda Sistemi kullanılarak sınıflandırıldı. Çalışmanın istatistikleri IBM SPSS Statistics 22 kullanılarak yapılmış olup, gruplar arası karşılaştırmalar Ki Kare testi, Fisher kesin Ki Kare testi, Student's t-testi ve Mann-Whitney U testi ile analiz edilmektedir.
Bulgular: Olguların %48'i PTM tanılı olup, bunların %47.1'i insidental papiller tiroid mikrokarsinomu (IPTM) tanılıydı. Kadın cinsiyet IPTM grubunda papiller tiroid karsinomu (PTK) grubuna daha yüksek oranda olup, aradaki fark istatistiksel olarak anlamlıydı (p <0.001). Kronik lenfositik tiroidit (KLT) birlikteliği PTM'li olgularda PTK'lu olgulara göre daha yüksek orandaydı (sırasıyla %41.2, %36.9). Tiroid Uyarıcı Hormon (Thyroid Stimulating Hormone - TSH) ortalama değeri PTM grubunda PTK grubuna göre daha yüksek değerlere sahip olduğu görülmektedir. PTK grubunda PTM'e göre kapsül invazyonu daha yüksek oranda görülmektedir (p<0.001).
Sonuç: Çalışmamızda IPTM'li hastaların PTK olgularına göre daha genç yaşta, kadın cinsiyette, daha düşük TSH değerleri gözlemledik. IPTM'ların tümör çapının küçük olması nedeniyle metastaz yeteneğinin daha düşük, dolayısıyla da iyi prognozlu olduklarını düşünmekteyiz.

Anahtar Sözcükler: Tiroid Kanseri, Tiroidit, Papiller Tiroid Karsinomu, Tiroid Uyarıcı Hormon (Thyroid Stimulating Hormone - TSH), Tiroid Nodülü, Tiroid Tümörleri

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INTRODUCTION

Thyroid cancer (TC) is the most common endocrine malignancy (1), and its incidence has been reported to have increased more than twice since 1995 (2). In the literature, with the widespread use of ultrasonography (USG) in thyroid diseases (3) and higher detection of papillary thyroid microcarcinomas (PTM) (4) are considered to be responsible for this increase. In general, patients with TC have a favorable prognosis (5) since all cases reported in recent years being due to the increase in the rate of cases diagnosed with PTM (6).

Papillary thyroid carcinoma (PTC) represents the majority (~85-90%) of TC cases diagnosed in developed countries (7). According to the World Health Organization, PTM is defined as a tumor with the largest size of ≤10 mm (8), and its incidence is reported to be 1- 36% in autopsies and 24% in surgical materials (9). A significant number of these cases are incidentally detected in the postoperative histopathological examination of the thyroid tissue excised for benign thyroid lesions that were not suspected to be cancerous before surgical treatment (10). Although the prevalence of incidentally diagnosed incidental papillary thyroid microcarcinoma (IPTM) was reported to vary between 7.1 and 16.3% (11), Pagni et al. (12) determined an incidental PTC in 45.2% of patients. Most cases with PTC are clinically silent and have a good prognosis (13), while approximately 10-15% have recurrent or permanent disease, and ~5% of these cases develop distant metastases (7). The recurrence rate in cases diagnosed with IPTM varies between 0 and 5% (14). Studies indicate that IPTMs have a much better prognosis than PTMs, which is related to the multifocal nature of the latter and positive lymph node metastasis (15,16).

Our aim in this study was to retrospectively evaluate patients who underwent surgical treatment for benign or malignant diseases of the thyroid gland and were diagnosed with IPTM and compare the clinicopathological and prognostic parameters between non-incidental PTM and PTC groups.

MATERIALS and METHODS

Our study was carried out after receiving approval from Gülhane Training and Research Hospital Clinical Research Ethics Committee, dated 15.12.2021 and numbered 2021/87. In our study, the data of patients who underwent surgical treatment for thyroid gland neoplasms in our clinic between 2010 and 2020 were retrospectively screened from the patient files and data sets were created. A total of 354 cases whose complete data were accessed were included in the study. Cases with missing data were excluded. The cases were divided into two main groups as PTMs smaller than 1 cm and PTCs larger than 1 cm. The PTM cases were further evaluated in two separate groups as incidental and non-incidental based on clinical and radiological findings. Cytological diagnoses were classified in six categories using the 2017 Bethesda System (17). Bethesda system: 1: non-diagnostic/unsatisfactory, 2: benign, 3: atypia of uncertain significance or follicular lesion of uncertain significance (AUS/FLUS), 4: follicular neoplasm (FN) or suspected FN, 5: suspicion of malignancy; and 6: malignant.

Statistical analysis

The statistical analyses of the study data were performed using IBM SPSS Statistics v. 22. When making comparisons between the groups, the chi-square or Fisher exact chi-square test was used for discrete data, and Student's t-test or the Mann Whitney-U test was used for continuous data. Statistical significance was defined as a p value of less than 0.05.

RESULTS

Of the 354 cases included in the study, 51.98% were diagnosed with PTC and 48.02% with PTM, and 52.94% of PTMs were NIPTM and 47.06% were IPTM. When evaluated in terms of gender, the rate of female patients was 77.97% in the whole PTC group, while it was 82.5% in the IPTM group, indicating a statistically significant difference ($p < 0.001$). It was seen that the female ratio was higher in cases with PTM than in those with PTC (81.18% vs. 75.0%) (Table I).

When the cases were evaluated according to age, while the mean ages of the men and women were similar in all groups except IPTM, the mean age of women in the IPTM group was higher than that of the men (41.57 versus 44.03 years). While there was no patient aged under 20 years in the NIPTM group, only four cases with IPTM (5.0%) were in this age group creating no statistically significant difference (p=0.215). The 41-60 years group represented the age range with the highest number of cases in all diagnostic groups, and there was no proportional difference (44.44-45.65%) between the groups (Table I).

It was determined that chronic lymphocytic thyroiditis (CLT) coexistence was higher in the PTM cases than in the PTC cases (41.2% versus 36.9%). When evaluated in terms of CLT coexistence, although the number of cases in the NIPTM group was proportionally higher (46.7% versus 35.0%) in the IPTM group, the difference was not statistically significant (p=0.220) (Table I).

Table I. Clinical Presentation of the Patients According to their Histopathological Diagnoses

Histopathological Diagnosis/ Demographic features		PTM			PTC n (%)	TOTAL (PTM + PTC) n (%)
		NIPTM n (%)	IPTM n (%)	Total n (%)		
Gender n (%)	Female	72 (80%)	66 (82.5%)	138 (81.18%)	138 (75.0%)	276 (77,97%)
	Male	18 (20%)	14 (18.25%)	32 (18.82%)	46 (25.0%)	78 (22,03%)
Age	Mean	43.71±12.64	43.6±12.59	43.66±12.54	44.30±14.95	43,99±13,81
	Female	42±11.24	44.03±12.28	42.97±11.71	41.51±13.91	42,24±12,83
	Male	50.56±16.13	41.57±14.84	46.63±15.75	52.70±15.10	50,21±15,46
Age Distribution n (%)	0-20	0	4 (5.0%)	4 (2.35%)	4 (2.17%)	8 (2,26%)
	21-40	40 (44.44%)	30 (37.5%)	70 (41.18%)	68 (36.96%)	138 (38,98%)
	41-60	40 (44.44%)	36 (45.0%)	76 (44.7%)	84 (45.65%)	160 (45,2%)
	≥60	10 (11.1%)	10 (12.5%)	20 (11.76%)	28 (15.22%)	138 (38,98%)
CLT n (%)		42 (46,7%)	28 (35.0%)	70 (41.12%)	68 (36.96%)	68 (36.96%)
Total n (%)		**90 (100%)**	**80 (100%)**	**170 (100%)**	**184 (100%)**	**354 (100%)**

*% ratios are taken along the columns in totals.

PTC: Papillary Thyroid Carcinoma, PTM: Papillary Thyroid Microcarcinoma; NIPTM: Non-incidental Papillary Thyroid Microcarcinoma; IPTM: Incidental Papillary Thyroid Microcarcinoma; CLT: Chronic Lymphocytic Thyroiditis

The mean TSH value of the PTM group was higher than that of the PTC group (4.67 vs. 2.98). The mean TSH value (7.03 versus 2.03) of the NIPTM group was higher compared to the IPTM group. When the TSH values were divided into levels as described, although the PTC and PTM groups had a similar rate of patients with a TSH range of 1.36-1.90, the number of cases in the IPTM group was higher than in the NIPTM group (25.0% vs. 11.1%), but this was not statistically significant (p=0.629). In the NIPTM group, 60% of the cases had a TSH value of >1.35, while TSH > 1.35 was observed in 67.5% of the IPTM group (Table II).

Table II. Evaluation of Histopathological Diagnosis Groups According to the Mean TSH Values and Levels

Histopathological Diagnosis/ TSH		PTM			PTC n(%)
		NIPTM n (%)	IPTM n (%)	Total n (%)	
Mean TSH		7.03±19.73	2.03±2.01	4.67±14.56	2.98±5.76
TSH	≤0.35	16 (17.8%)	28 (16.5%)	54 (15.25%)	26 (14.1%)
Level	0.36-1.35	20 (22.2%)	34 (20.0%)	74 (20.9%)	40 (21.7%)
n (%)	1.36-1.90	10 (11.1%)	30 (17.6%)	62 (17.5%)	32 (17.4%)
	1.91-4.94	32 (35.6%)	60 (35.3%)	130 (36.7%)	70 (38.0%)
(0.35- 4.94) mIU/mL	4.95≤	12 (13.3%)	18 (10.6%)	34 (9.6%)	16 (8.7%)
Total		**90 (100%)**	**80 (100%)**	**170 (100%)**	**184 (100%)**

*Values are given as percentages in all columns. For the total, percentages are given along the lines.
PTC: Papillary Thyroid Carcinoma; PTM: Papillary Thyroid Microcarcinoma; NIPTM: Non-incidental Thyroid Microcarcinoma; IPTM: Incidental Papillary Thyroid Microcarcinoma

In the physical examination of the case groups included in the study, 79.35% of the cases had palpable nodules in the PTC group and 37.5% in the PTC group, indicating a statistically significant difference (p< 0.006). While 46.6% of the cases had palpable nodules in the NIPTM group, the nodules were palpable in 37.5% of the cases in the IPTM group, but this difference did not reach statistical significance (p=0.203) (Table III). Nodule association was seen at a higher rate in cases with NIPTM than in those with IPTM (86.7% versus 80%). There was a higher rate of single nodules in the PTM group compared to the PTC group (29.4% vs. 22.8%), but this difference was not statistically significant (p=0.092) (Table III).

When the diagnostic groups were evaluated according to the nodular echogenicity characteristics on USG, although there was a higher rate of hypoechoic nodules (48.9% versus 65%) in the IPTM group than in the NIPTM group, the difference was not statistically significant (p=0.077). Solid appearance was present at a higher rate in the IPTM diagnosis group than in the NIPTM diagnosis group (51.1% versus 60%) (Table III).

Table III. Radiological Features

Histopathological Diagnosis/ Nodule		PTM			PTC N (%)
		NIPTM n (%)	IPTM n (%)	Total n (%)	
Palpable Nodule		42 (46.6%)	30 (37.5%)	72 (42.4%)	146 (79.35%)
Nodule	Present	12 (13.3%)	16 (20%)	28 (16.5%)	28 (15.2%)
	Not present	78 (86.7%)	64 (80%)	142 (83.5%)	156 (84.8%)
Multiple nodules		44 (48.9%)	38 (47.5%)	82 (48.2%)	96 (52.2%)
Single nodule		26 (28.9%)	24 (30%)	50 (29.4%)	42 (22.8%)
USG	Hypoechoic	44 (48.9%)	52 (65%)	96 (56.5%)	98 (53.3%)
	Solid	46 (51.1%)	48 (60%)	94 (55.3%)	96 (52.2%)
Total		**90 (100%)**	**80 (100%)**	**170 (100%)**	**184 (100%)**

*Values are given as percentages in all columns
PTC: Papillary Thyroid Carcinoma; PTM: Papillary Thyroid Microcarcinoma; NIPTM: Non-incidental Papillary Thyroid Microcarcinoma; IPTM: Incidental Papillary Thyroid Microcarcinoma; USG: Ultrasonography

A total 336 fine-needle aspiration biopsies (FNABs) were performed among the 354 cases. When we compared the PTC group with the PTM group, the rate of DC-1 cytological diagnoses was statistically significantly higher in the PTM group (49.4% vs. 60.2%; p<0.001). Although DC-1 cytological diagnoses were made at a higher rate in the IPTM group compared to the NIPTM group (42.5% vs. 46.7%), the difference was not statistically significant (p=0.067). For NH, a DC-2 cytological diagnosis, the greatest difference was seen between the PTC and IPTM groups (2.4% vs. 5.4%), but this was not statistically significant (p=0.894). DC-3 cytological diagnoses were made at a higher rate in the IPTM group than in the NIPTM group (8.11% vs. 2.17%). DC-4 cytological diagnoses were observed only in the NIPTM group. DC-5 cytological diagnoses were seen at a higher rate in the PTC group (11.76%) compared to the PTM group (7.2%). There was no DC-6 cytological diagnosis in the IPTM group, while the NIPTM group had a higher rate of these diagnoses compared to the PTC group (41.3% vs. 29.3%) (Table IV).

Table IV. Comparison of Histopathological Diagnosis and FNAB Diagnoses: Bethesda System

Histopathological/ Cytological Diagnosis		PTM			PTC n (%)
		NIPTM n (%)	IPTM n(%)	Total n(%)	
DC-1	Non-diagnostic	42 (46.7%)	58 (72.5%)	100 (60.2%)	84 (49.4%)
DC-2	Benign	2 (3.2%)	4 (5.4%)	6 (3.6%)	10 (5.9%)
DC-3	AUS/FLUS	2 (2.17%)	6 (8.11%)	8 (4.82%)	6 (3.53%)
DC-4	FN/HCN	2 (2.17%)	0	2 (1.2%)	0
DC-5	Suspicious	6 (6.5%)	6 (8.1%)	12 (7.2%)	20 (11.76%)
DC6	Malign	38 (41.3%)	0	38 (22.89%)	50 (29.4%)
Total	**FNAB**	**92 (100%)**	**74 (100%)**	**166 (100%)**	**170 (100%)**
	Case	**90**	**80**	**170**	**184**

*Values are given as percentages in all columns
DC: Diagnostic Category; PTC: Papillary Thyroid Carcinoma, PTM: Papillary Thyroid Microcarcinoma; NIPTM: Non-incidental Thyroid Microcarcinoma; IPTM: Incidental Papillary Thyroid Microcarcinoma; NH: Nodular Goiter/Nodular Hyperplasia; AUS: Atypia of Indeterminate Significance; FLUS: Follicular Atypia of Uncertain Significance; FN: Follicular Cell Neoplasia, HCN: Hurthle Cell Neoplasia; FNAB: Fine-needle Aspiration Biopsy

Table V presents the histopathological features of the cases included in the study. The rate of cases diagnosed with PTM without capsular invasion was higher than in the PTC group (72.94% vs. 53.26%), and the difference was statistically significant (p<0.001). Although extrathyroidal spread was observed at a proportionally higher rate in the PTC group than in the PTM group (11.95% vs 3.53%), the difference was not statistically significant (p=0.695).

Lymphovascular invasion (LVI) was observed at a higher rate in the PTC group than in the PTM group (29.35% vs. 20%), but the difference was not statistically significant (p=0.117). Although there was a higher rate of LVI in the NIPTM group compared to the IPTM group (26.7% versus 12.5%), the difference was not statistically significant (p=0.595). Perineural invasion was observed at a higher rate in the PTC group than in the PTM group (9.78% vs. 2.35%) (p=0.947) (Table V).

When evaluated in terms of laterality, although bilaterality was seen at a higher rate in the PTM group than in the PTC group (25.88% vs. 21.74%), there was no statistically significant difference between the two (p=0.127). Bilaterality was detected at a higher rate in the IPTM group compared to the NIPTM group (32.5% vs. 20%), but the difference did not reach statistical significance (p=0.453) (Table V).

Table V. Evaluation of histopathological features

Diagnosis/ Pathological Features		PTM			PTC n (%)
		NIPTM n (%)	IPTM n (%)	Total n (%)	
Capsule Invasion	Not present	64 (71.2%)	60 (75.0%)	124 (72.94%)	98 (53,26%)
	Present	22 (24.4%)	18 (22.5%)	40 (23.52%)	64 (34,78%)
	Extrathyroidal spread (+)	4 (4.4%)	2 (2.5%)	6 (3.53%)	22 (11,95%)
LVI	Present	24 (26.7%)	10 (12.5%)	34 (20%)	54 (29,35%)
	Not present	66 (73.3%)	70 (87.5%)	136 (80%)	130 (70,65%)
Perineural Invasion	Present	2 (2.2%)	2 (2.5%)	4 (2.35%)	18 (9,78%)
	Not present	88 (97.8%)	78 (97.5%)	166 (97.65%)	166 (90,22%)
Laterality	Unilateral	72 (80%)	54 (67.5%)	126 (74.12%)	144 (78,26%)
	Bilateral	18 (20%)	26 (32.5%)	44 (25.88%)	40 (21,74%)
Tumor Size	Mean	6.19 ± 2.8	5.48 ± 2.46	5.86 ± 2.66	18,71 ± 12,03
	0-5 mm	36 (40%)	40 (50%)	76 (44.7%)	0
	5-10 mm	54 (60%)	40 (50%)	94 (55.3%)	0
	10-20 mm	0	0	0	110 (59,78%)
	≥20 mm	0	0	0	74 (40,22%)
Total		**90 (100%)**	**80 (100%)**	**170 (100%)**	**184 (100%)**

*Values are given as percentages in all columns

PTC: Papillary Thyroid Carcinoma; PTM: Papillary Thyroid Microcarcinoma; NIPTM: Non-incidental Papillary Thyroid Microcarcinoma; IPTM: Incidental Papillary Thyroid Microcarcinoma; LVI: Lymphovascular Invasion

In the PTC group, 59.78% of the cases had a tumor size in the range of 10-20 mm and 40.22% >20 mm, and the difference was statistically significant (p<0.001). While 60% of the NIPTMs cases had a tumor size of 5-10 mm, 50% of the IPTMs had a tumor size in this range, and the difference was not statistically significant (p=0.087) (Table V).

In the histopathological examination of the 354 cases included in the study, the total number of metastatic lymph nodes (MLNs) was 642. The number of MLNs per case was 2.56 in the PTC group and 1.06 in the PTM group. This number was higher in the NIPTM group than in the IPTM group (1.44 versus 0.625) (Table VI). Although the number of metastatic LNs in the central region was similar, when evaluated in terms of metastasis to their cervical LNs, it was seen that the IPTM group metastasized to their LNs in this anatomical region at a proportionally higher rate compared to the NIPTM group (52% versus 36.9%). While no metastases were observed in the jugular and Delphian LNs in the IPTM group, there was metastasis to the LNs of this region in the NIPTM diagnosis group, albeit at a low rate (jugular: 3.07%; Delphian: 6.15%) (Table VI).

Table VI. Evaluation of Metastatic Lymph Nodes According to Histopathological Diagnoses

Diagnosis/ MLN		PTM			PTC n (%)
		NIPTM n (%)	I-PTM n (%)	Total n (%)	
Anatomical Localization n (%)	Ct	70 (53.8%)	24 (48.0%)	94 (52.2%)	256 (55.4%)
	C	48 (36.9%)	26 (52%)	74 (41.1%)	190 (41.1%)
	J	4 (3.07%)	0	4 (2.2%)	14 (3.1%)
	D	8 (6.15%)	0	8 (4.4%)	2 (0.4%)
Total MLN		**130**	**50**	**180**	**462**
Total Number of Cases		**90**	**80**	**170**	**184**
MLN/Number of Cases		**2.56**	**1.44**	**0.625**	**1.06**

*%'s are given throughout the columns.

PTC: Papillary Thyroid Carcinoma; PTM: Papillary Thyroid Microcarcinoma; NIPTM: Non-Incidental Papillary Thyroid Microcarcinoma; IPTM: Incidental Papillary Thyroid Microcarcinoma; MLN: Metastatic Lymph Node; Distribution: Anatomical Distribution of Metastatic Lymph Nodes; Ct: Central, C: Cervical, J: Jugular, D: Delphian

DISCUSSION

PTC constitutes 80-85% of thyroid cancers, and the rates of PTM and IPTM cancer diagnoses among all PTC cases are increasing rapidly with the emergence and widespread use of advanced diagnostic techniques (18). In a study conducted in a region with a high prevalence of goiter, Lombardi et al. reported the rate of PTM as 42%, of which 75.5% was coincidental (19). Although there are studies in the literature indicating the prevalence of IPTM as 7.1-16.3%, Pagni et al. (12) found an incidental PTC in 45.2% of the patients. In another study conducted in an endemic region, it was shown that the rate of PTM in all PTC cases was 47%, and the majority (78.7%) had coincidental diagnoses (4). In our study, although 48.02% of the PTC cases were found to be PTM, 47.06% of the PTMs were diagnosed with IPTM. Although our PTM rate was consistent with the literature, our IPTM rate was lower. We consider that the reason for our lower rate of IPTM cases may be due to the approach of the endocrine council in our hospital to follow up benign cases rather than performing surgery.

In a study by Gürleyik et al. (4), 74.7% of all thyroidectomies and 86.5% of cases with IPTM were reported to be female. Maturo et al. (20) detected IPTM in 84.33% of the cases and noted that 5% were female and 15.67% were male. In our study, the rate of the female patients was 77.97% in the PTC group and 82.5% in the IPTM group. Although similar rates are seen in relation to the literature, it is noteworthy that as the tumor size decreases, the female ratio increases.

In the literature, the mean age of the cases diagnosed with IPTM was reported as 44.1 (4), which is similar to the mean age of the cases diagnosed with IPTM in our study (43.6±12.59 years). In addition, according to our results, the age range with the highest number of cases was 41-60 years. On the other hand, while the mean age of the male patients was higher than that of the female patients in all diagnostic groups, we observed that the mean age of the women was higher compared to men in the IPTM group. Sharon et al. (21) found that an age younger than 20 years was not associated with a worse survival. In another study, 2.7% of the IPTM cases were observed to be under the age of 19 years and 5.4% over 60 (4). In our study, consistent with the literature, 5% of the cases with IPTM were aged under 20 years and 7.32% were in the above 60 group. According to our results, a higher rate of NIPTM cases were in the 21-40 years range compared to the IPTMs (44.4% versus 37.5%).

In a study by Uhliarova and Hajtman (22), CLT coexistence was reported in 15% of the TC cases, and this association was found to be associated with an increased risk of developing PTM. Evranos et al. (23) determined that the frequency of CLT coexistence in the histopathological evaluation of the specimens was similar in the IPTM and NIPTM case groups (IPTM: 34.2%; NIPTM: 35.6%). In our study, although the incidence of CLT coexistence was similar to the literature, it observed to be higher in the PTM cases than in the PTC cases (41.12% vs 36.96%). In addition, the presence of CLT was seen at a higher rate in the NIPTM group than in the IPTM group (46.7% versus 35%).

In the literature, it is stated that a high serum TSH concentration is associated with the emergence and spread of PTC, and the growth of well-differentiated malignant cells in PTC is due to TSH-controlled thyrotropin receptors (24). There are studies suggesting that the TSH signaling pathway may predispose thyroid cells to BRAF-induced transformation (25). In our study, when the cases were evaluated according to the mean TSH values, it was observed that these values were generally higher in all groups, but in the evaluation made according to the diagnostic groups, the mean TSH value was proportionally higher in the PTM group than in the PTC group (4.67 versus 2.98). As for the NIPTM group, the mean TSH value was proportionally higher than in the IPTM group (7.03 versus 2.03). When the TSH values were divided into levels as described in the study of Lun et al. (26), although the PTC and PTM groups had similar TSH rates of patients with a TSH range of 1.36-1.90, the number of cases in the IPTM group was proportionally higher than those in the NIPTM group (25.0% versus 11.1%). In both NIPTM and IPTM groups, there was a high number of patients with a TSH value of >1.35 at high rates (60-67.5%). Our results suggest that high TSH values, even within normal limits, may contribute to an increased tendency to develop malignancy.

The probability of malignancy is reported to vary between 77.4 and 82.8% in thyroid nodules smaller than 1 cm that show suspicious features in terms of TCA on USG (27). Fabio et al. (12) found that 68.6% of the TC cases were associated with multiple nodules. The presence of palpable nodules in the physical examination of the cases in our study was found to be statistically significantly higher in the PTC group than in the IPTM group (79.35% versus 37.5%; p<0.01). The rate of palpable nodules was proportionally higher in the NIPTM group than in the IPTM group (46.6% vs 37.5%). We consider that this higher rate was due to the higher incidence of nodules in the NIPTM group compared to the IPTM group (86.7% vs 80%). In the literature, it has been reported that hypoechoic nodules carry a higher risk of malignancy than hyperechoic nodules (28). In our study, while 48.9% of the cases in the NIPTM group presented with hypoechoic features, this rate was seen to be 65% in the IPTM group. The risk of malignancy increases as the solid part inside the nodules increases on USG (29). In our study, we observed that the presence of solid nodules was higher in the IPTM group than in the NIPTM group (51.1% versus 60%). These results suggest that in patients followed up for the benign diseases of the thyroid, the presence of a hypoechoic and solid nodule on USG may be an important warning sign for TC.

Although the rapidly increasing incidence of TC has been associated with many thyroid nodules, ultrasound guided FNAB is considered the gold standard in the presence of normal or increased TSH levels (30). Pagni et al. (12) stated that the sensitivity of FNAB was 31.8% in the microcarcinoma group, and it was strongly correlated with tumor size.

In the literature, it has been reported that the coexistence of CLT makes the diagnosis of PTC very difficult, since thyroid follicle epithelial cells in FNAB have an appearance similar to the papillary nucleus (31). When we compared the PTC and PTM groups in our study, we observed that the rate of DC-1 (non-diagnostic-inadequate) cytological diagnoses was statistically significantly higher in the latter (49.4% versus 60.2%, (p<0.001). This difference can be attributed to the lesions being smaller and the CLT rate being higher in the PTM group, which negatively affects the success of diagnosis based on the FNAB of the lesion. The most significant difference for the rate of DC-2 (benign) cytological diagnoses was found between the PTC and IPTM groups (2.4% vs. 5.4%; p=0.894). We consider that this may be related to the IPTM cases being mostly detected incidentally during surgery due to the presence of nodules. In addition, in our study, DC-5 (suspicion of malignancy) cytological diagnoses were seen at a higher rate in the PTC group (11.76%) compared to of the PTM group (7.2%). DC-6 (malignant) cytological diagnoses were mostly seen in the NIPTM group at a rate of 41.3%. Although the number of FNABs per case was similar between the PTC and PTM groups, the reason for the highest cytological diagnosis success in the NIPTM group can be attributed to the evaluation of those who could not be diagnosed cytologically in the PTM group in the IPTM group, and the evaluation of those who could be diagnosed in the NIPTM group.

Yang et al. (32) stated that the capsular invasion of PTCs was 33%. They reported that the risk of central lymph node metastasis was less when the tumor invaded the capsule but did not spread extrathyroidally. In another study, Sharon et al. reported extracapsular spread in 8% of patients in well-differentiated carcinomas, including PTCs (22). In our study, there was no capsular invasion in 53.26% of the cases in the PTC group and 72.94% of the cases in the PTM group. We found no significant difference between the IPTM and NIPTM groups in terms of capsular invasion. While there was extrathyroidal spread in 11.95% of the cases in the PTC group, this rate was 3.53% in the PTM group. Our results suggest that tumor size has an effect on capsular invasion.

The presence of LVI has been reported to be a pathological feature indicating the metastatic ability of the malignancy (4). In our study, LVI was seen at a higher rate in the PTC group than in the PTM group (29.35% vs. 20%). The rate of LVI was also higher in the NIPTM group than in the IPTM group (12.5% versus 26.7%). In an invasive cancer series, Nakao et al. reported that the recurrent laryngeal nerve was affected in 61% of the patients, vagus nerve in 13%, phrenic nerve in 10%, and spinal accessory nerve in 6% (33). In our study, there was a higher rate of invasion in the PTC group than in the PTM group (9.78% vs. 2.35%). These results suggest that lesion size and suspicious appearance on USG are important in terms of a high LVI rate and nerve invasion.

One of the important features of PTC is multifocality and bilaterality. Gürleyik et al. reported the rate of bilateralism to be 20% in cases with IPTM (4). In our study, bilaterality was seen at a higher rate in the IPTM group than in the NIPTM group (32.5% vs. 20%).

Studies indicate that tumor focal diameter is an independent risk factor for IPTM (34). Wang et al. reported the mean size of tumor foci as <5 mm in patients with IPTM (35). In our study, the mean size of the IPTM tumors was 5.48 mm, which represented the smallest mean tumor size among all the diagnostic groups. It was also determined that 44.7% of the PTM tumors were <5 mm. In addition, while 60% of the NIPTM tumors were 5-10 mm in size, 50% of the IPTM tumors were in this size range. The small tumor size of cases with IPTM seems to be compatible with the good prognosis-tumor size relationship reported in the literature in terms of both spread and prognosis.

Clinical studies report that PTCs have a high incidence of lymph node metastasis and recurrence (36). In our study, the rate of MLNs per case was 2.56 in the PTC group and 1.06 in the PTM group. In addition, it was seen that this rate was higher in the NIPTM group than in the IPTM group (1.44 versus 0.625). Although similar rates were observed in all groups in terms of central LN metastasis, the lowest rate was observed in the IPTM group. When cervical LN was evaluated in terms of metastasis, it was determined that a proportionally higher rate of cases in the IPTM group showed metastasis to LNs in this anatomical region compared to the NIPTM group (52% versus 36.9%). These results suggest that tumor size is one of the most important factors in terms of extracapsular and lymph node metastasis in cases with PTC.

CONCLUSION

In our study, we observed that the IPTM cases were detected at a higher rate in younger patients, female gender, patients with a lower level of hypothyroidic hormone, and surgical procedures performed for thyroid nodules compared to the PTC group. In these cases, especially if there is a coexistence of CLT, cytological diagnosis seems to have a lower chance of success, and there is a higher risk of malignancy. We consider that IPTMs have a lower metastasis ability due to their small tumor diameter, and therefore they have a good prognosis. Our study suggests that even if the cytology result is negative for malignancy, patients with findings on USG together with tumor size should be followed up closely.

Conflict of interest

No conflict of interest was declared by the authors.

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