



Comparison of Papillary Thyroid Carcinoma and Papillary Microcarcinoma in Terms of Clinical Features and Prognostic Factors

Papiller Tiroid Karsinom ve Papiller Mikrokarsinomun Klinik Özellikler ve Prognostik Faktörler Açısından Karşılaştırılması

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Abstract

Purpose: In this study, we compared papillary thyroid carcinoma (PTC) and papillary microcarcinoma (PMC) in terms of the clinical features and prognostic factors. For the choice of appropriate treatment method, we researched differences between PTC and PMC retrospectively.

Material and Method: A total 714 patients 486 with PTC (68%) and 228 with PMC (32%) who were followed in our hospital were enrolled into the study. Age, sex, background, tumour variants, pathologic features, surgical procedure and postoperative surgical complications were collected from archival records and were analysed.

Results: The average follow-up time was 33.7±24.7 months in patients with PTC and 34.2±29.1 months in those with PMC. 82% of patients with PTC and 81% of PMC patients were women. The mean age at diagnosis was 45.4±11.0 years. The mean age at diagnosis in male patients was (48.2±10.4 years) which was significantly higher compared to that in women (40.3±12.0 years) (p<0.001). There were also no significant differences in terms of prognostic factors, such as capsule invasion, vascular invasion, distant metastasis, bilaterality, multicentricity, age, sex, and tumour variants between PTC and PMC patients. Lymph node metastasis was more frequent in bilateral and multicentric tumours (p=0.010).

Discussion: We found no significant difference between PTC and PMC in terms of poor prognostic factors, such as capsule invasion, vascular invasion, distant metastasis, bilaterality and multicentricity. These findings suggest that follow-up and treatment of patients with bilateral and multicentric PMC is appropriate for patients with PTC.

Keywords: Papillary thyroid carcinoma, papillary microcarcinoma, prognostic factors

Öz

Amaç: Bu çalışmada klinik özellikler ve prognostik faktörler açısından papiller tiroid karsinom (PTK) ve papiller mikrokarsinomu (PMK) karşılaştırdık. Uygun tedavi metodu seçimi için PTK ve PMK arasındaki farklılıkları retrospektif olarak araştırdık.

Gereç ve Yöntem: Çalışmaya hastanemizde takip edilen 486 (%68) PTK ve 228 (%32) PMK olmak üzere toplam 714 hasta alındı. Yaş, cinsiyet, özgeçmiş, tümör alt tipi, patolojik özellikler, cerrahi yöntem ve operasyon sonrası cerrahi komplikasyonlar arşiv kayıtlarından kaydedildi ve analiz edildi.

Bulgular: Ortalama takip süresi PTK olan hastalarda 33,7±24,7 ay, PMK olan hastalarda ise 34,2±29,1 ay idi. PTK olan hastaların %82'si ve PMK olan hastaların %81'i kadındı. Hastalarımızın ortalama tanı yaşı 45,4±11,0 yıl idi. Erkek hastalarda ortalama tanı yaşı (48,2±10,4 yıl) kadın hastalarda göre (40,3±12,0 yıl) anlamlı derecede yüksekti (p<0,001). PTK ve PMK'lı hastaları arasında kapsül invazyonu, vasküler invazyon, lenf nodu metastazi, uzak organ metastazi, bilateralite, multisentrisite, yaş, cinsiyet ve tümör alt tipi gibi prognostik faktörler açısından önemli farklılık saptanmadı. Lenf nodu metastazi multisentrik ve bilateral tümörlerde daha sıkı (p=0,010).

Tartışma: Kapsül invazyonu, vasküler invazyon, uzak organ metastazi, bilateralite ve multisentrisite gibi kötü prognostik faktörler açısından PTK ve PMK arasında önemli bir farklılık saptamadık. Bu bulgulara göre özellikle bilateral veya multisentrik olan PMK olgularının izlem ve tedavisi PTK gibi yapılmalıdır.

Anahtar kelimeler: Papiller tiroid kanseri, papiller mikrokanser, prognostik faktörler

Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid cancer responsible for about 80% of thyroid cancer cases. PTC is defined as papillary microcarcinoma (PMC) when the tumor size is 1 cm or less (1,2,3). In recent years, thyroid cancer has been diagnosed at an early stage using ultrasonography and fine-needle aspiration biopsy. These developments have increased the incidence of patients diagnosed with PMC (4,5). The prognosis for thyroid cancer can be estimated based on clinical and pathological features (6). The prognostic factors are age, gender, distant metastasis, lymph node metastasis, histological subtype, primary tumor size, multifocality, tumor non-invasion, family history, and oncogenes (6). PMC is known to have a better prognosis, although some PMCs may have an aggressive course. Prognostic factors are important in the treatment of PMC (3,7,8). In this study, we retrospectively investigated patients diagnosed with PTC and PMC and compared them in terms of clinical characteristics and prognostic factors. In addition, we investigated the characteristics that may have influenced the choice of method for follow-up and treatment.

Materials and Methods

In this study, medical records of 714 patients diagnosed with PMC and PTC at our hospital were evaluated. The following data were gathered for each patient:

1. Demographic characteristics: Age at diagnosis, gender, medical history of radiation, and family history of thyroid disease (benign or malignant).
2. Tumor characteristics at the time of diagnosis: The tumor type and sub-type according to the World Health Organization classification, tumor size, number of tumor foci, bilateral tumors, vascular invasion, capsular invasion, lymph node metastasis, tumor invasion, and distant metastasis.
3. Preoperative diagnosis: Solitary nodule, euthyroid multinodular goiter (EMNG), toxic nodular goiter, and Graves' disease.
4. Tumor staging: According to the tumor node metastasis system proposed by the American Joint Committee on Cancer published in 2002.
5. Features related to the Therapy: Only primary surgery, adjunct thyroidectomy, radioactive iodine therapy.
6. Complications of surgical treatment: Temporary and permanent vocal cord paralysis, permanent hypocalcemia.
7. Follow-up: Thyroglobulin levels, I-131 whole body scan scintigraphy, neck ultrasonography, chest computed tomography and bone scintigraphy, magnetic resonance imaging, and fluorodeoxyglucose-positron emission tomography, when needed, due to metastases.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) 16.0 for Windows was used for the statistical analysis. Parametric tests were used to analyze the data with a normal distribution. For the statistical evaluation, the chi-square test, the Student's t-test and the Fisher's exact chi-square test were used. A p value of less than 0.050 was considered statistically significant.

Results

Of the 714 patients who were included, 486 (68%) patients were diagnosed with PTC and 228 (32%) had PMC. The mean clinical follow-up in patients with PTC was 33.7 ± 24.7 months, while patients with PMC were followed up for 34.2 ± 29.1 months.

The ratio of female PTC and PMC was significantly higher than that of men ($p < 0.001$ and $p = 0.010$). However, there was no statistically significant difference in the prevalence of PTC and PMC in females ($p = 0.459$).

None of the patients had a medical history of radiation exposure. The overall mean age at diagnosis was 45.4 ± 11.0 years. The age at diagnosis in patients with PTC and PMC were 41.4 ± 14.6 years and 43.3 ± 11.6 years, respectively. There was no statistically significant difference between patients with PTC and PMC in terms of average age at diagnosis ($p = 0.070$). The mean age at diagnosis in males was 48.2 ± 10.4 years, whereas that in females was 40.3 ± 12.0 years. The mean age at diagnosis was significantly higher in men than in women ($p = 0.040$). According to the findings in Table 1, although a family history of malignant thyroid disease was more frequent in patients with PMC compared to patients with PTC, the difference was not statistically significant ($p = 0.288$). However, a family history of benign or malignant thyroid disease was significantly more common in patients with PMC than in patients with PTC ($p = 0.020$).

According to the findings in Table 1, in both patients with PMC and PTC, the most frequently encountered preoperative diagnosis was EMNG, and the least observed preoperative diagnosis was Graves' disease. There was no statistically significant difference between the groups of PTC and PMC in the distribution of the patients with respect to the preoperative diagnosis ($p = 0.224$).

In the entire group, the mean tumor size was 2.2 ± 1.7 cm. The mean tumor size was 2.8 ± 1.5 cm in patients with PTC, whereas the average tumor size in patients with PMC was 0.6 ± 0.3 cm.

According to the findings in Table 1, there was no statistically significant difference between patients with PTC and PMC in terms of the histopathological subtypes. The combined type ($n = 98$, 41.1%) was the most frequent type. The combined type was relatively more frequent in patients with PTC.

In both PTC and PMC, follicular variant + classical type was most frequently observed, although it was not statistically significant (Table 1).

As seen in Table 1, between the patients with PTC and PMC, there was no statistically significant difference with regard to capsular invasion, vascular invasion, distant metastases, multicentricity, and bilateral tumors. The frequency of lymph node metastasis was significantly higher in patients with PTC compared to patients with PMC ($p < 0.001$). In our study, twelve patients had distant metastases. All were diagnosed with PTC. None of them had a bilateral tumor. Two of them had multifocal tumor.

Of the patients with PTC and PMC, in those with bilateral tumors, the frequency of lymph node metastasis was significantly higher than in patients who had no bilateral tumors ($p = 0.030$ and $p = 0.010$). Of the patients with PTC and PMC, in those with multifocality, the frequency of lymph node metastasis was significantly higher than in patients who had no multifocality ($p = 0.040$ and $p = 0.030$; Table 2). The frequency

of lymph node metastasis was not significantly different in patients without family history, compared to patients with a family history ($p=0.430$).

As seen in Table 2, in patients with multifocal and bilateral tumors, the frequency of lymph node metastasis was significantly higher

than in patients who had no multifocal and bilateral tumors ($p=0.010$). In patients with only multifocal tumors, the frequency of lymph node metastasis was significantly higher than in patients who had no multifocal and bilateral tumors ($p=0.010$).

Of the patients with PTC, 72 had lymph node metastases, 54 of whom had positive capsular invasion. The frequency of lymph node metastasis was significantly higher in PTC patients with capsule invasion compared to patients without capsule invasion ($p<0.001$). Of the patients with PMC, 12 had lymph node metastases, 6 of whom had positive capsular invasion. The frequency of lymph node metastasis was not significantly different between the PTC patients with and without capsular invasion ($p=0.154$).

Of all the patients included in the study, 318 (44.5%) underwent bilateral total thyroidectomy (BTT), 312 (43.6%) underwent bilateral subtotal thyroidectomy (BSTT), and BTT with cervical neck dissection (CND) was performed in 84 (11.7%) patients. Of the 486 patients diagnosed with PTC, 216 underwent BBT, 198 underwent BSTT, and 72 underwent BTT + CND. Of the 228 patients diagnosed with PMC, 102 underwent BBT, 114 BSTT and 12 BTT + CND. Of the 486 patients diagnosed with PTC, 222 (45.7%) patients, in whom surgical treatment was insufficient, underwent completion thyroidectomy. Of the 228 patients diagnosed with PMC, 126 (55.3%) underwent completion thyroidectomy due to the presence of one or more factors, such as multicentricity, detection bilateral tumors, capsular invasion and lymph node metastases. The rate of postoperative complications was significantly lower in patients with PMC, compared to patients with PTC ($p=0.030$). Regarding the complications of surgical treatment, a total of 66 cases had complications. The most common complication was permanent hypoparathyroidism secondary to hypoparathyroidism.

Of the 714 patients included in the study, 612 received radioactive iodine therapy. Of those patients, 468 were diagnosed with PTC, whereas 144 patients had PMC.

There was no statistically significant difference between the two groups with respect to tumor node metastasis stages ($p=0.104$). On the other hand, when "T" was considered alone, tumors with a T2 stage and higher were significantly more frequent in patients with PTC ($p<0.001$). As to the frequency of "n" positivity at the time of diagnosis, there was no significant difference between patients with PTC and PMC ($p=0.530$).

No mortality was observed in patients with PMC, while two patients with PTC died due to lung metastasis. TSH suppressed thyroglobulin levels in patients who underwent BTT were 0.8 ng/mL in patients with PTC and 0.2 ng/mL in patients with PMC. The difference was not statistically significant ($p=0.116$). Thyroglobulin levels were higher in patients with lymph node metastasis ($p=0.120$).

Discussion

The PTC/PMC ratio of the patients included in our study was 2/1, which is high compared to previous research studies (9). We have detected that PMC occurs more frequently. The female/male ratio of the patients included in our study was 4.6/1. This value is similar to the results in the literature (10,11,12,13). In

Table 1. Comparison of the demographic characteristics and prognostic factors in patients with papillary microcarcinoma and papillary thyroid carcinoma at diagnosis

	PTC (n=486)	PMC (n=228)	p
Age			
≥45	174 (35.8%)	84 (36.8%)	
<45	312 (64.2%)	144 (63.2%)	
Gender			
Woman	402 (82.7%)	186 (81.5%)	
Man	84 (17.3%)	42 (18.5%)	
Radiation exposure	0	0	
Family history			
No history	420 (86.4%)	156 (68.4%)	
Positive history (benign)	60 (12.4%)	54 (23.7%)	
Positive history (malignant)	6 (1.2 %)	18 (7.9%)	
Preoperative diagnosis			
ENG	90 (18.5%)	24 (10.5%)	
EMNG	324 (66.6%)	138 (60.6%)	
TNG	48 (9.8%)	48 (21.0%)	
Graves disease	24 (4.9%)	18 (7.9%)	
Lymph node metastasis	72 (14.8%)	12 (5.2%)	
Distant metastasis	12(2.4%)	0	
Pathological characteristics			p=0.280
Capsular invasion	144 (29.7%)	60 (26.3%)	
Vascular invasion	24 (4.9%)	0	
Multicentricity	192 (39.5%)	72 (31.4%)	
Bilaterality	126 (25.9%)	60 (26.3%)	
Type of tumor			p=0.342
Follicular variant	138 (28.5%)	84 (36.8%)	
Classical type	60 (12.3%)	18 (7.8%)	
Oncocytic	18 (3.7%)	0	
Combine	216 (44.6%)	84 (36.8%)	
Diffuse sclerosing variant	0	12 (5.4%)	
Columnar	6 (1.2%)	0	
Trabecular	12 (2.4%)	0	
Tall cell	0	6 (2.7%)	
Cystic	6 (1.2%)	0	
Type undetermined	30 (6.1%)	24 (10.5%)	
Radioiodine therapy			p<0.001
Received	468 (96.2%)	144 (63.2%)	
Unreceived	18 (3.8%)	84 (36.8%)	

PTC: Papillary thyroid carcinoma, PMC: Papillary microcarcinoma, TNG: toxic nodular goiter, EMNG: Euthyroid multinodular goiter, ENG: Euthyroid nodular goiter

terms of gender distribution, there was no statistically significant difference between patients with PMC and PTC. This result is also in accordance with other clinical trials comparing patients with PTC and PMC (9,14,15,16).

In terms of age at diagnosis, there was no statistically significant difference between patients with PMC and PTC ($p>0.05$). Similar to other studies, the age at diagnosis in men appeared to be higher than in women (13,17,18). The diagnosis of women at an earlier age may be related to hormonal factors. Age is a prognostic factor in papillary thyroid cancer. In patients diagnosed with PTC, an age of <45 years is an indicator of a better prognosis (19). In our study, 63.8% of patients were under 45 years of age and the rate of patients who were <45 years was similar in both groups ($p>0.05$).

Some histological types (tall cell, columnar cell, diffuse sclerosing, solid-trabecular, and insular type) are characterized with an aggressive course compared to the classic type (20). In our study, the prevalence of tall cell PTC was found to be 1.6%, and this rate was higher than in previous studies (21,22). The increasing number of diagnosed cases may change these rates. The columnar type, which is a rare type of PTC, comprises 0.15-0.2% of all cases of PTC (23). In our study, of the 714 patients diagnosed with PTC, only two (0.84%) patients had columnar-type PTC.

In a study of 21 patients diagnosed with asymptomatic PMC, Sugitani and Fujimoto (7) followed the patients with conservative treatment, and no recurrence was observed within a three-year follow-up period. On the other hand, in another study conducted with 203 patients diagnosed with PMC, Chow et al. (8) observed recurrence and mortality after 10 years in some patients. Furthermore, Usluogullari et al. (24) found recurrence in 10 patients (4%) out of 248 patients with PMC at the end of a five-year follow-up period. In addition, they showed that lymph node metastases were independent predictors of recurrence. In a meta-analysis that included 3,523 patients, Mehanna et al. (25) found that the recurrence rate was 7.9% in patients with non-incident PMC and 0.5% in patients with incident PMC. In our study, the mean follow-up time was 33 months, and we observed recurrence in 76 patients with a diagnosis of PMC. We did not encounter any mortality.

In a study in which 102 patients diagnosed with PMC were compared with 382 patients diagnosed with PTC, Cappelli et al. (10) did not observe any difference between the two groups in terms of lymph node metastasis, extrathyroidal invasion, and multifocality. In another study in which 66 patients diagnosed with PMC were compared with 136 patients diagnosed with PTC, Arora et al. (16) also demonstrated that there were no differences between the two groups in terms of lymph node metastasis, extrathyroidal invasion, vascular invasion, multifocality, and distant metastasis.

In our study, in patients with both PMC and PTC, there was a significant increase in the incidence of lymph node metastasis in the presence of bilateral tumors and multifocality. Chow et al. (8) also found a correlation between multifocality and lymph node metastasis. As the number of patients with distant metastasis is small in our study, the relationship between lymph node metastasis and distant metastasis could not be assessed. However, in our study, the four patients who had lymph node metastasis had distant metastasis as well. Sugino et al. (26) examined 112 patients diagnosed with PMC between the years 1992 and 1995 and found the rate of lymph node metastasis to be 63.8% in the presence of multifocality. These rates may change with the increasing number of cases.

Arora et al. (16) reported the rate of vascular invasion as 6% and the rate of distant metastasis as 1.8% in patients with PMC. In a study conducted with 300 patients diagnosed with PMC, Lee et al. (27) did not observe distant metastasis in any patient, whereas Chow et al. (8) found distant metastasis in two (1%) of 203 patients diagnosed with PMC. In our study, we did not find vascular invasion and distant metastasis. Further studies including a greater number of cases may provide more accurate information in this regard. We have found distant metastases in four patients diagnosed with PTC, which were all lung metastases in accordance with the literature. In all patients, tumor diameter was above 4 cm and there was capsule invasion and lymph node metastasis.

Pelizzo et al. (28) did not define capsule invasion as a prognostic factor. However, in contrast, there are also studies that identify

Table 2. The impact of bilateral tumors and multifocality on lymph node metastasis and distant metastasis in patients with Papillary microcarcinoma and papillary thyroid carcinoma

Metastasis	PTC (n=486)				PMC (n=228)			
	Bilaterality		Multicentricity		Bilaterality		Multicentricity	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
Lymph node metastasis (+)	36 (28.5%)	36 (10%)	48 (24.2%)	24 (8.3%)	12 (20%)	0	12 (16.6%)	0
Distant metastasis (+)	0	4 (3.3%)	2 (3.0%)	2 (2.0%)	0	0	0	0

PTC: Papillary thyroid carcinoma, PMC: Papillary microcarcinoma

capsule invasion as a prognostic factor (26,27,29,30). The presence of only thyroid capsule invasion has a prognosis similar to that of extrathyroidal invasion, even when there is no invasion of surrounding soft tissue (1). In our study, in patients with PMC there was no significant difference between the patients with capsule invasion and those without capsule invasion in terms of the frequency of lymph node metastasis. This was likely due to the small number of patients diagnosed with PMC and with lymph node metastases. In contrast, in patients with PTC, the frequency of lymph node metastasis was significantly higher in patients with capsular invasion compared to those without capsular invasion. In our study, it has been shown that in cases of bilateral tumors, there is a high rate of lymph node metastases, similar to the case of multifocality. Detection of tumors in patients with PMC bearing these risks may require different therapeutic and follow-up approaches. The American Thyroid Association guidelines propose bilateral total or near-total thyroidectomy due to a higher rate of recurrence when one of the following is present: tumor size >1-1.5 cm, contralateral lobe involvement, regional or distant metastasis, a history of head and neck irradiation, a history of differentiated thyroid cancer in first-degree relatives, and age >45 years. BTT is recommended, especially in children and young adults (31). In our study, it is noteworthy that the selected surgery was similar in patients with PTC and with PMC. BTT rates in the two groups were close to each other. In our series, CND was performed at a higher rate in patients with PTC. This is likely due to the fact that the type of surgery in cases with PTC was determined immediately after the preoperative diagnosis was established, whereas there were more incidental cases with PMC. Sahin et al. (32) suggested that more thyroid cancer could be detected in infracentrimetric nodules that hypoechoic or fine calcification on thyroid ultrasonography than supracentrimetric nodules. They found that malignancy rate was 21.4% in these infracentrimetric nodules. Therefore, that should be performed USG-guided fine needle aspiration biopsy from suspicious infracentrimetric nodules with findings of ultrasonography.

Conclusion

In conclusion, in our study, both in PTC and PMC cases, the lymph node metastases were found to be significantly more frequent in patients who had bilateral and multifocal tumors. The mean age at diagnosis was significantly higher in men than in women. There was no difference between patients with PTC and PMC with regard to poor prognostic factors (capsule invasion, vascular invasion, and distant metastases). These findings suggest that follow-up and treatment of patients with bilateral and multicentric PMC is appropriate for patients with PTC.

Ethics

Ethics Committee Approval: Gaziantep University Faculty of Medicine has received approval from the, Informed Consent: A retrospective study.

Peer-review: Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Hakan Korkmaz, Umut Elboğa, Avni Gökalp, Ersin Akarsu, Concept: Hakan Korkmaz, Umut

Elboğa, Design: Hakan Korkmaz, Ersin Akarsu, Data Collection or Processing: Hakan Korkmaz, Umut Elboğa, Mehmet Metin Sevim, Mesut Özkaya, Suna Erkiş, Analysis or Interpretation: Hakan Korkmaz, Ersin Akarsu, Mustafa Araz, Suzan Tabur, Literature Search: Hakan Korkmaz, Umut Elboğa, Writing: Hakan Korkmaz. Conflict of Interest: No conflict of interest was declared by the authors.

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