Clinical Research

Comparison of the Classical and Follicular Variants of Papillary Thyroid Carcinomas in Terms of the Clinicopathological Prognostic Parameters

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ABSTRACT

Objective: The aim of the study was to evaluate the differences between the classical and follicular variants of papillary thyroid carcinoma (CVPTC and FVPTC) in terms of the clinicopathological prognostic parameters.

Material and Method: The study included 84 cases consisting of 37 CVPTC and 47 FVPTC. Patient age, gender and pathological prognostic parameters including multifocality, tumour size, tumour capsule, extrathyroidal extension, intratumoural and non-tumoural lymphocytic infiltration, tumoural stage, lymph node metastasis and distant metastasis were recorded for each case by using the pathology reports. Two variants were statistically compared in terms of these parameters.

Results: FVPTC cases were older than CVPTC cases (p= 0.016). There was no difference in terms of gender. Although the median tumour size was similar in two groups, the tumours over 4 cm were significantly more common in FVPTC (p= 0.044). Encapsulation was significantly higher in the FVPTC (p= 0.010). Multifocality and extrathyroidal extension were more frequent in CVPTC but these results were not statistically significant. Non-tumoural lymphocytic infiltration was significantly higher in CVPTC (p= 0.027), but there was no difference in terms of intratumoural lymphocytic infiltration. CVPTC and FVPTC were similar for the tumour stage and the lymph node metastasis. We had only one case with distant metastases and it was FVPTC.

Conclusion: Two PTC variants appear to exhibit some different prognostic features from each other and this may require different management of them. However, more studies with larger series are needed for this decision.

Keywords: *Papillary Thyroid Carcinoma, Classical Variant, Follicular Variant, Prognosis.*

ÖZ

Klasik ve Foliküler Varyant Papiller Tiroit Karsinomlarının Klinikopatolojik Prognostik Parametreler Açısından Karşılaştırılması

Amaç: Çalışmanın amacı, klinikopatolojik prognostik parametreler açısından, papiller tiroit karsinomunun klasik ve foliküler varyantları (KVPTK ve FVPTK) arasındaki farklılıkları değerlendirmektir.

Gereç ve Yöntem: Çalışmaya 37 KVPTK ve 47 FVPTK'den oluşan 84 olgu dahil edildi. Patoloji raporları kullanılarak her olgu için, hasta yaşı, cinsiyet, multifokalite, tümör boyutu, tümör kapsülü, ekstratiroidal yayılım, intratümöral ve non-tümöral lenfosittik infiltrasyon, tümör evresi, lenf nodu metastazı ve uzak metastaz gibi patolojik prognostik parametreler kaydedildi. İki varyant bu parametreler açısından istatistiksel olarak karşılaştırıldı.

Bulgular: FVPTK olguları KVPTK olgularına göre daha yaşlıydı (p= 0.016). Cinsiyet açısından fark görülmedi. Her iki grupta medyan tümör boyutu benzer olmasına rağmen 4 cm'nin üzerindeki tümörler FVPTK grubunda anlamlı olarak daha yaygındı (p= 0.044). Kapsül varlığı, FVPTK'de anlamlı olarak daha fazlaydı (p = 0.010). Multifokalite ve ekstratiroidal yayılım KVPTK'de daha sıktı ancak bu sonuçlar istatistiksel olarak anlamlı değildi. KVPTK'de non-tümöral lenfositik infiltrasyon anlamlı olarak daha fazlaydı (p= 0.027), ancak intratümöral lenfositik infiltrasyon açısından fark yoktu. KVPTK ve FVPTK, tümör evresi ve lenf nodu metastazı açısından benzerdi. Uzak metastazlı sadece bir olgumuz vardı ve FVPTK grubundaydı.

Sonuç: İki PTK varyantı birbirinden farklı bazı prognostik özellikler sergiliyor gibi görünmektedir ve bu durum onların farklı yönetimini gerektirebilir. Ancak bu karar için daha geniş serili daha fazla çalışmaya ihtiyaç vardır.

Anahtar Sözcükler: *Papiller Tiroit Karsinomu, Klasik Varyant, Foliküler Varyant, Prognoz.*

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Papillary thyroid carcinoma (PTC) is the most common thyroid carcinoma and it accounts for 80-90% of the cases (1, 2).

It has been reported that PTC had a good prognosis with a 10-year survival rate of over 93% (2). However, some poor clinicopathological prognostic parameters as older age, male gender, larger tumour size, absence of

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tumour capsule, extrathyroidal extension, multifocality, lymph node metastasis and advanced stage have been defined in the literature (1-4).

A relationship was reported between the intra and/or peri-tumoural inflammatory activation which is mainly assessed by the lymphocytic infiltration and the favorable outcome (5). Hashimoto's thyroiditis (HT) which is an autoimmune disease characterized with parenchymal damage and the lymphocytic infiltration in the histological samples was reported to have a favorable prognostic impact on PTC (5, 6).

Several PTC subtypes have been described (4, 7). Classical (CVPTC) and follicular variants (FVPTC) are the most common subtypes which account for more than 50% and 23-41%, respectively (2, 3). CVPTC is characterized by papillary structures with fibrovascular cores and the cells with overlapping, grooved, clear nuclei that are typical for PTC (1). In contrast, well-formed papillae should not be seen in the FVPTC (7). In this variant, the tumour is commonly well circumscribed or encapsulated and it is composed of follicles lined by cells that have typical nuclear features of PTC (7). The rarer tall cell variant PTC (TCVPTC) is characterized by cells that are two or three times as tall as their width, and has been usually reported as the most aggressive variant (1, 7). However, the relative prognoses of CVPTC and FVPTC remain controversial (1, 3, 4).

Giani et al. (3) reported that FVPTC patients were older and more frequently capsulated than CVPTC. On the other hand, multifocality, perithyroidal soft tissue invasion and the lymph node metastasis were higher in CVPTC. In multivariate analysis, they also showed that CVPTC was an independent risk factor for the persistence of the disease (3). Tunca et al. (2) found that extrathyroidal extension, lymph node metastasis and the local recurrence were more frequent in CVPTC, while the multifocality was more frequent in FVPTC. In another study, FVPTC was associated with lower T and N stage, but higher metastasis rate (1).

In this study, we aimed to evaluate the differences between 37 CVPTC and 47 FVPTC cases in terms of the clinicopathological prognostic parameters.

MATERIAL AND METHOD

This study is in accordance with the Helsinki Declaration. The study protocol was accepted by the Clinical Research Ethics Committee of a local university (Date: 06-01-2022, Decision Number: 03).

Eighty-four thyroidectomy materials which were diagnosed as PTC (37 CVPTC and 47 FVPTC) in a university hospital between 2010 and 2013 were included in the study. Clinicopathological parameters including age, gender, multifocality, tumour size, capsule presence or absence, extrathyroidal extension, intratumoural and non-tumoural lymphocytic infiltration, tumoural stage, lymph node metastasis, distant metastasis were recorded for each case by using the pathology reports. The tumours were classified according to World Health Organization (WHO) 2017 classifications (8). A tumour was considered as multifocal when there were more than one tumour focus in the same lobe and in these cases the prognostic parameters were determined according to which tumour had the largest size. AJCC/TNM 8th edition was used to determine the tumour stage (9).

Two PTC variants were statistically compared in terms of age, gender and the pathological prognostic parameters. Statistical analyses were done by using the SPSS Statistics software package programme, Version 21 (IBM Corp. NY, USA). The statistical distributions of the groups were analyzed using the Kolmogorov Smirnov test. Normally distributed continuous variables were analyzed with the Independent samples t test, and those outside the normal distribution were analyzed with the Mann-Whitney U-test. The Chi-square test or Fisher's exact test, as appropriate, was performed for comparison of categorical variables. A p-value <0.05 was considered statistically significant.

RESULTS

Patients

The study included 84 PTC cases which consisted of 37 CVPTC and 47 FVPTC (Figure 1).

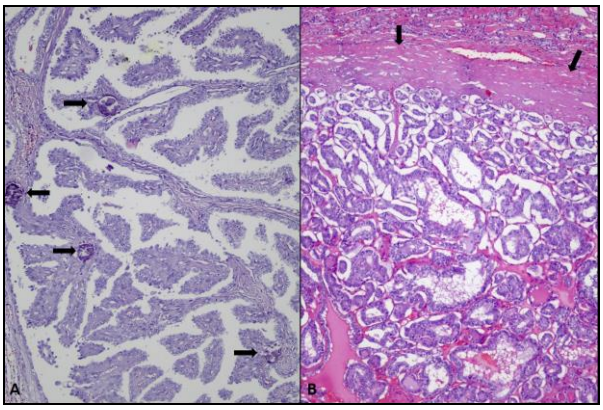

Figure 1. *A: Classical variant papillary thyroid carcinoma characterized by papillary structures with fibrovascular cores. It is accompanied by Psammomatous calcified structures (arrows) (H&Ex100). B: Folicular variant papillary thyroid carcinoma composed of follicles. The tumour is well circumscribed and encapsulated. Arrows show the tumour capsule (H&Ex100).*

Female: male ratio was 5:1. The mean age was 46.40±12.96 (14-83). Considering the literature, when the cases were divided into two groups based on the cut-off value of 45 years old, 35 (41.67%) cases were <45 years and 49 (58.33%) cases were ≥45 years (1, 4).

Pathological Prognostic Parameters

Multifocality was seen in 24 (28.57%) of the cases. The tumour size range was between 0.3-8 cm. The tumour size was ≤1 cm in 37 (44.05%) cases, between >1 cm and ≤4 cm in 43 (51.19%) cases, and >4 cm in 4 (4.77%) cases.

The tumour was non-capsulated in 58 (69%) cases and encapsulated in 26 (31%) cases. There was extrathyroidal extension in 11 (13.10%) cases.
Intratumoural lymphocytic infiltration and non-tumoural lymphocytic infiltration were seen in 6 (7.14%) cases and 16 (19.05%) cases, respectively.
The tumour stages were as follows: 70 (83.33%) pT1, 7 (8.33%) pT2, 4 (4.76%) pT3 and 3 (3.57%) pT4. There was lymph node metastasis in 6 (7.14%) cases and distant metastasis in 1 (1.19%) case.

Comparison of CVPTC and FVPTC

Comparison of CVPTC and FVPTC in terms of clinicopathological prognostic parameters were summarized in table 1.

Table 1. *Comparison of CVPTC and FVPTC in terms of clinical and pathologic prognostic parameters.*

Parameters		**CVPTC**		**FVPTC**		**p value***
		n	**%**	**n**	**%**	
Age (years)	mean±SD	42.62±10.56		49.40±13.98		**0.016**
	<45	19	51.35	16	34.04	0.110
	≥45	18	48.65	31	65.96	
Gender	female	33	89.19	37	78.72	0.201
	male	4	10.81	10	21.28	
Multifocality	absent	25	67.57	35	74.47	0.487
	present	12	32.43	12	25.53	
Tumour size (cm)	median (min-max)	1.10 (0.50-3.70)		1 (0.30-8.00)		0.243
	≤1	13	35.14	24	51.06	0.159
	>1	24	64.86	23	48.94	
	≤4	37	100	43	91.49	**0.044**
	>4	0	0	4	8.51	
Tumour growth pattern	non-capsulated	31	83.78	27	57.45	**0.010**
	encapsulated	6	16.22	20	42.55	
Ekstrathyroidal extension	absent	31	83.78	42	89.36	0.524**
	present	6	16.22	5	10.64	
Intratumoural lymphocyte infiltration	absent	33	89.19	45	95.74	0.398**
	present	4	10.81	2	4.26	
Non-tumoural lymphocyte infiltration	absent	26	70.27	42	89.36	**0.027**
	present	11	29.73	5	10.64	
Tumour stage	pT1	30	81.08	40	85.11	0.628
	pT2	4	10.81	3	6.38	
	pT3	1	2.70	3	6.38	
	pT4	2	5.41	1	2.13	
Lymph node metastasis	absent	35	94.59	43	91.49	0.690**
	present	2	5.41	4	8.51	
Distant metastasis	absent	37	100	46	97.87	***
	present	0	0	1	2.13	
TOTAL		37	100	47	100	

**p< 0.050 was considered statistically significant. **Fisher's exact test. ***Due the small case number for the "present" group, statistical analysis could not be done. CVPTC: Classical variant papillary thyroid carcinoma, FVPTC: Follicular variant papillary thyroid carcinoma.*

Female: male ratio was 33:4 in CVPTC and 37:10 in FVPTC. There was no difference between two variants in terms of gender (p= 0.201). The mean age was 42.62±10.56 (14-62) in CVPTC and 49.40±13.98 (23-83) in FVPTC. When two variants were compared in terms of the mean age, FVPTC cases were older than CVPTC cases (p= 0.016). According to groups based on the cut-off value of 45 years, there was no statistical significance between two variants (p= 0.110).
Multifocality was more common in CVPTC (32.43%) than FVPTC (25.53%) cases, but this result was not statistically significant (p= 0.487). The median tumour size was 1.10 (0.5-3.7) cm in CVPTC and 1 (0.3-8) cm in FVPTC. Two groups were similar in terms of the median size (p= 0.243). Then, we grouped the cases according to 1 and 4 cm cut-off values. There was no significant difference between two variants in terms of the groups based on 1cm cut-off value (p= 0.159). When we divided the cases according to 4 cm cut-off value, the difference between two variants was statistically significant (p= 0.044). The tumours over 4 cm were more common in FVPTC.
Encapsulation was significantly higher in the FVPTC than in the CVPTC group (p= 0.010). Extrathyroidal extension was more frequent in CVPTC but this result was not statistically significant (p= 0.524).
Non-tumoural lymphocytic infiltration was significantly higher in CVPTC than in the FVPTC group (p= 0.027). There was no difference in terms of intratumoural lymphocytic infiltration (p= 0.398).
CVPTC and FVPTC were similar for tumour stage and lymph node metastasis (p= 0.628, p= 0.690, respectively). We had only one case with distant metastases and

it was FVPTC. So, we couldn't compare the groups in terms of this parameter.

DISCUSSION

Several variants have been described for PTC including classical, follicular, tall cell, oncocytic, columnar cell, diffuse sclerosing, solid and clear cell variants (1, 4, 7). CVPTC and FVPTC account for the majority of the cases (2, 4).

Some poor clinicopathological prognostic parameters as older age, male gender, larger tumour size, absence of tumour capsule, extrathyroidal extension, multifocality, lymph node metastasis and advanced stage have been defined in the literature (1, 4). TCVPTC is the most aggressive variant with more frequent extrathyroidal extension, higher recurrence and mortality rate (1, 3, 7). However, it is still controversial whether two variants behave differently (1, 3, 4, 10).

Giani et al. (3) found that male gender was one of the prognostic factors for the persistence of the disease in PTC cases. In a study, it was reported that the male gender was more common in CVPTC and TCVPTC than FVPTC (11). However, in some other studies, it was reported that female gender was more common in both variants and there was no significant difference between CVPTC and FVPTC (3, 4, 12). In our study, the frequency of females was higher in both variants; and there was not statistically significant difference between two groups in terms of gender.

Age ≥45 years was reported as an independent poor prognostic factor in association with both overall and the disease specific survival (1). Yang et al. (4) found that the mean age was similar in both CVPTC and FVPTC cases. However, FVPTC cases were more likely to be ≥45 years old. In another study, it was found that the patients with FVPTC were older in terms of both the mean age and the 45 years old cut-off value (3). In our study, according to mean age, FVPTC cases were significantly older than CVPTC cases (p= 0.016). However, there was no significant difference, when we grouped the cases according to the cut-off value of 45 years old.

In a study, multifocality was found to be higher in CVPTC (3). In another study, it was more frequent in FVPTC (2). In our study, multifocality was higher in CVPTC, but in the statistical study, two groups were similar for this parameter as some studies in the literature (10, 11).

In PTC, the tumour size ≥4 cm was reported to be an independent factor for persistence of disease (3). In many studies, the tumour size was found to be larger in FVPTC (11, 12, 13, 14). It was thought that the larger size of FVPTC might be related to the understanding of its clinical importance only after reaching certain sizes due to its benign ultrasonographic features (12). In contrast, in a study that included only papillary microcarcinoma cases, Sparano et al. found that FVPTC had a smaller mean size than CVPTC which was partially due to the higher proportion of incidental cases (15). In our study, the median tumour size was similar in two groups. When we divided the cases according to 1 cm cut-off value, so as the micropapillary PTC and the others, there was also no difference between two PTC variants. However, the tumours over 4 cm were significantly more common in FVPTC compared to CVPTC (p= 0.044).

Giani et al. (3) found that the tumour capsule was much more frequent in FVPTC compared to CVPTC. Consistently, in our study, encapsulation was significantly higher in the FVPTC group (p= 0.010). Compared to FVPTC, it was reported that extrathyroidal extension was more frequent in CVPTC (2, 3, 12, 13, 16). In our study, extrathyroidal extension was also higher in CVPTC but this result was not statistically significant.

A relationship was reported between the intra-and/or peri-tumoural inflammatory activation which is mainly assessed by the lymphocytes and the favorable outcome (5). Coexisting Hashimoto's thyroiditis (HT) and thyroid carcinoma is a common entity and following surgery, in histological samples, HT presents with parenchymal damage and the lymphocytic infiltration (6). In a study, compare to the carcinomas without HT, the thyroid carcinomas with HT were reported to be associated with papillary histological type, multifocality and reduced frequency of lymphatic metastasis (6). In another study, PTC with HT were found to be associated with smaller tumour size, lower rate of aggressive PTC variants and longer recurrence free survival (5).

Therefore, in our routine practice, we have been reported the absence/presence and the degree of the tumoural and non-tumoural lymphocytic infiltration in PTC cases, even though we could not give the exact diagnosis of HT. In this study, when we compared the CVPTC and FVPTC in terms of non-tumoural lymphocytic infiltration, it was significantly higher in the CVPTC group (p= 0.027). However, there was no difference in terms of intra-tumoural lymphocytic infiltration between two groups.

Xu et al. (14) reported that FVPTC was associated with a lower T stage than CVPTC (1). In other study, it was found that the tumour stage was higher in FVPTC. It was reported that lymph node metastasis was more frequent in CVPTC, while FVPTC was associated with lower N stage (1-3, 16). In our series, two variants were similar in terms of both T stage and the lymph node metastasis.

In a study, two variants were found to be similar in terms of the distant metastasis (11). In another study, it was reported that FVPTC had a higher metastasis rate than CVPTC (1). It was thought that this might be due to the late diagnosis by fine needle aspiration because of the pathological features of the tumour, or its tendency to invade the tumour capsule and spread into blood vessels such as follicular carcinomas (1). In our small series, there was only one case with distant metastasis and it was FVPTC. We could not statistically compare the two variants in terms of this parameter.

Xu et al. found that FVPTC had better overall and disease specific survival and this difference was more obvious in older patients (1). In other studies, it was reported that long term outcome was similar in both variants (2, 10). Since this is a retrospective archive study and the data on the survival are not available, the two groups could not be compared in this respect.

In conclusion, in our study, FVPTC cases were found significantly older and more frequently encapsulated than CVPTC cases, in accordance with the literature. On the other hand, the non-tumoural lymphocytic infiltration was significantly more frequent in CVPTC. Although the results were not statistically significant, the frequency of multifocality and extrathyroidal extension were also higher in CVPTC. The tumours over 4 cm were significantly more common in FVPTC. These two variants of the PTC appear to exhibit some different prognostic features from each other and this may require different management of the patients with them. However, more studies with larger series are needed for this decision.

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