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The Prognostic Importance of Bilaterality in Patients with Papillary Thyroid Cancer

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ABSTRACT:

The prognostic importance of bilaterality in patients with papillary thyroid cancer

Objective: Despite the high frequency of bilateral disease in patients with papillary thyroid cancer (PTC), the importance of bilaterality in the prognosis of the disease is still unclear. In this study, we aimed to figure out the effects of bilaterality in the prognosis of the disease.

Material and Method: A total of 113 patients with PTC, who were treated in our clinic with total thyroidectomy between 2011 and 2014, were divided into three groups: Group 1, patients with unilateral disease with single focus; Group 2, patients with unilateral disease with multiple foci; Group 3, patients with bilateral disease with multiple foci.

Results: There was a statistically significant difference between the presence of bilateral disease, compared to unilateral disease, in terms of lymphovascular invasion (p=0.001), the diameter of the tumor (p=0.028), extra- thyroidal disease (p=0.012), T stage of the disease (p=0.042) and lymph node metastasis (p=0.001).

Conclusion: Patients with bilateral papillary thyroid cancer are more likely to have larger tumors, higher extra- thyroidal dissemination rates, advanced T stages, lymph node metastasis and more aggressive tumors when compared to unilateral disease. Due to these considerations, the surveillance of the patients with bilateral papillary thyroid disease should be done more carefully and effectively.

Keywords: Bilaterality, multifocality, papillary thyroid cancer, prognostic factor

ÖZET:

Tiroid papiller kanserli hastalarda bilateralitenin prognostik önemi

Amaç: Papiller tiroid kanserli (PTK) olgularda bilateral hastalık sık görülmesine karşın, bu durumun hastalığın prognozu üstündeki etkileri hakkındaki bilgiler yetersizdir. Bu çalışmada bilateralitenin prognoz üzerindeki etkilerinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: 2011- 2014 yılları arasında hastanemizde total tiroidektomi ile tedavi edilen 113 hasta; Grup 1, tek lobda ve tek odakta tümör saptanan hastalar; Grup 2, tek lobda fakat birden fazla odakta kanser saptanan hastalar; Grup 3, her iki tiroid lobunda birden fazla tümör saptanan hastalar olacak şekilde gruplandırılarak kötü prognostik faktörler açısından incelendi.

Bulgular: Bilateral hastalık varlığının lenfovasküler invazyon (p=0.001), tümör çapı (p=0.028), tiroid dışı yayılım (p=0.012), hastalığın T evresi (p=0.042) ve lenf nodu metastazı varlığı (p=0.001) açısından tek taraflı hastalık ile karşılaştırıldığında istatistiksel olarak anlamlı farklılıklar gösterdiği saptandı.

Sonuç: Papiller tiroid kanserli hastalarda bilateral tümör varlığında tümör çapı daha yüksek, tiroid dışı yayılım, ileri T evresi oranı ve lenf bezi metastazı varlığı tek odaklı tümörlere göre daha sık olup, daha agresiv seyirli olabilirler. Bu nedenle bu hastalar ameliyat sonrası dönemde daha yakın ve etkin şekilde takip edilmelidir.

Anahtar kelimeler: Bilateralite, multifokalite, papiller tiroid kanseri, prognostik faktör

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INTRODUCTION

Although thyroid cancer constitutes 1% of all cancers, it accounts for 90% of endocrine cancers and is the most common one (1). According to the American Cancer Society (ACS), in the year 2017, a total of 56,870 new patients (42,470 female and 14,400 male) will be diagnosed with thyroid cancer in the USA. The number of deaths due to thyroid cancer for the year 2017 is estimated to be 2010, with 1090 female and 920 male patients (2). The most common subtype of thyroid cancers is papillary thyroid carcinoma (PTC) (3).

Papillary thyroid cancer is among the slow-onset cancers and the expected 30-year survival is over 90% independent of the administration of radioactive iodine ablation therapy after total thyroidectomy (4). Despite the fact that some PTC cases are treated with the most effective methods, an aggressive clinical course is observed (5,6). Therefore, it is thought that tumor characteristics which are thought to have an influence on the prognosis have important effects on the treatment and follow-up processes of the patients.

Papillary thyroid cancers may be solitary or multifocal/multicentric. Multifocality in general terms can be defined as the spreading of the single focus tumor through the thyroid tissue via lymphatic channels and resulting in multiple foci, and multicentricity can be defined as the onset and development of each tumor focus in the thyroid independently of the other (7).

Papillary thyroid cancer is often seen as multifocal / multicentric (8). This can be attributed to the natural behavior of the tumor, as well as the intra-gland metastasis independently (9). The characteristics of bilateral multifocal PTC and the effects on prognosis are still controversial (10,11). In this retrospective study we aimed to evaluate the characteristics of multifocal PTC and the relationship between the presence of bilateral multifocal disease and histopathologic features of the tumor.

MATERIAL AND METHOD

The data of 113 patients with PTC diagnosis who underwent total thyroidectomy between 2011 and 2014 were evaluated retrospectively in the electronic database Panates (Panates Informatics and Technology Inc. Co., Turkey, ver.3.7.24.2010). The patients were divided into three groups. The first group (G1) consisted of patients with tumor at single lobe and with single focus; the second group (G2) of patients with tumor at single lobe but with multiple foci; and the third group (G3) of patients with multiple tumors in both thyroid lobes. In these groups, the incidence of papillary microcarcinoma, lymphovascular invasion, tumor diameter, extra-thyroidal spread, T-stage, presence of lymph node metastasis, number of metastatic lymph nodes and presence of lymph node capsular invasion were investigated. Tumors smaller than 1 cm in diameter are defined as micropapillary carcinoma (7).

IBM SPSS Statistics 22 (IBM SPSS, Turkey) program was used for statistical analyses. The normal distribution relevance of the parameters was assessed by the Shapiro-Wilk test. One-way ANOVA test was used for comparison of parameters with normal distribution between groups in comparing the quantitative data, as well as descriptive statistical methods (mean, standard deviation, frequency). The Kruskal-Wallis test was used for the comparison of parameters with non-normal distribution and the Mann-Whitney U test was used to determine the group causing the difference. Chi-square test was used for comparison of qualitative data. Significance was assessed at $p<0.05$ level.

RESULTS

A total of 113 cases were included in this study between the years of 2011 and 2014, with 82 (72.6%) women and 31 (27.4%) men, aged between 18 and 80 years. The mean age of the patients was 48.36±13.14 years. Tumor with single focus affecting one lobe was detected in 64 (56.6%) of 113 patients (G1), multi foci tumor at single lobe was detected in in 21 (18.6%) patients (G2), and multi foci tumor affecting both lobes was detected in 28 (24.8%) patients (G3) (Table-1).

No statistically significant difference was found between age groups and gender distributions in the patient groups (p=0.549, p=0.195, respectively).

Table-1: Demographic characteristics of patients according to groups

	Group I n (%)	Group II n (%)	Group III n (%)	p
Age Mean±SS	47.86±12.24	46.86±13.5	50.64±14.95	0.549
Gender				
Female	44 (68.8%)	14 (66.7%)	24 (85.7%)	0.195
Male	20 (31.3%)	7 (33.3%)	4 (14.3%)	
Type of cancer				
Papillary microcarcinoma	40 (62.5%)	8 (38.1%)	8 (28.6%)	0.006
>1 cm Papillary carcinoma	24 (37.5%)	13 (61.9%)	20 (71.4%)	
Lymphovascular invasion	13 (20.3%)	7 (33.3%)	18 (64.3%)	0.001
Tumor diameter (mm) Mean±SS (Median)	10.95±10.93 (8)	12.57±7.79 (11)	14.68±12.95 (12)	0.028
Extra-thyroidal spread	18 (28.1%)	8 (38.1%)	17 (60.7%)	0.012
T-stage				
T1	42 (65.6%)	11 (52.4%)	11 (39.3%)	0.042
T2	2 (3.1%)	2 (9.5%)	0 (0%)	
T3	20 (31.3%)	8 (38.1%)	17 (60.7%)	
Lymph node metastasis	4 (6.3%)	7 (35%)	12 (42.9%)	0.001

There was a statistically significant difference between the patient groups, in terms of papillary cancer greater than 1 cm in diameter and papillary microcarcinoma distributions (p=0.006). As a result of the binary comparisons to determine which group originated the difference, the incidence of papillary cancer greater than 1 cm in G3 (71.4%) was found to be significantly higher than that of G1 (37.5%) (p=0.006). No statistically significant differences were found between G1 and G2, and G2 and G3 in terms of cancer types (p=0.088, p=0.692, respectively).

There was a statistically significant difference in the incidence of lymphovascular invasion between the groups (p=0.001). The incidence of lymphovascular invasion was 64.3% in G3, 30.3% in G2 and 20.3% in G1. Binary comparisons between the groups revealed that the incidence of lymphovascular invasion was significantly higher in G3 than in G1 (p<0.001), and there was no significant difference between G1 and G2 and G2 and G3 (p=0.245, p=0.063, respectively).

When the groups were evaluated in terms of tumor diameters, a statistically significant difference was found between the groups (p=0.028). As a result of the tests carried out to determine which group originated the difference, the tumor diameter of G3 (14.68±12.95 mm) was found to be statistically significantly higher than G1 (10.95±10.93 mm) (p=0.013). There was no statistically significant difference between the tumor diameters in G1 and G2 and G2 and G3 (p=0.103, p=0.693, respectively).

There was a statistically significant difference between the rates of extrathyroidal spread according to patient groups (p=0.012). In binary group comparisons, the incidence of extrathyroidal spread in G3 (60.7%) was found to be statistically significantly higher than G1 (28.1%) (p=0.001). There was no statistically significant difference between G1 and G2, and G2 and G3, in terms of extra-thyroidal spread (p=0.557, p=0.201, respectively).

There was a statistically significant difference between the T-stages according to patient groups (p=0.042). In binary group comparisons; the incidence of T3 stage in G3 (60.7%) was statistically significantly higher than in G1 (31.1%) (p=0.024). There is no statistically significant difference between G1 and G2, and G2 and G3 in terms of stage distributions (p=0.360, p=0.115, respectively).

There was a statistically significant difference in the rate of lymph node metastasis according to patient groups (p=0.001). As a result of the binary comparisons to determine which group originated the difference, the rate of lymph node metastasis in G1 (6.3%) was statistically significantly lower than in G2 (35%) and G3 (42.9%) (p=0.003, p=0.001, respectively). There was no statistically significant difference between lymph node metastasis rates in G2 and G3 (p=0.803).

In patients with lymph node metastasis, there was

Table-2: Evaluation of parameters according to patient groups in patients with lymph node metastasis

	Group I n (%)	Group II n (%)	Group III n (%)	p
Number of metastatic lymph nodes				
Less than 5	2 (50%)	3 (42.9%)	6 (54.6%)	0.682
Between 6-10	0 (0%)	2 (28.6%)	1 (9.1%)	
More than 10	2 (50%)	2 (28.6%)	4 (36.4%)	
Lymph node capsular involvement	0 (0%)	4 (57.1%)	3 (30%)	0.147

no statistically significant difference between the number of metastatic lymph nodes and lymph node capsular involvement rates according to patient groups (p>0.05) (Table-2).

DISCUSSION

Although bilateral multifocal PTC is not uncommon, its histopathologic characteristics and biological behavior are still unclear (12). When the pathogenesis of bilateral multifocal cancer is examined, it is not clear whether the disease is originated from the spread within the same gland (intraglandular metastasis) or a secondary lesion that develops from a different focus. The clonal analysis of Wang et al. (13) shows that most of the bilateral multifocal cancers have the same biological structure, supporting the idea that the bilaterality develops more in the form of intra-gland metastases. Sugg et al. (14) found the same ret/PTC rearrangement in different foci in only 2 cases in the study performed in 17 multifocal PTC patients, whereas in the other 15 cases, they detected different ret/PTC rearrangements in different foci. This suggests that different foci develop separately as "de nova" depending on environmental and genetic factors.

Papillary thyroid carcinoma prognosis has been shown to be associated with factors such as lymphovascular invasion, tumor diameter, extrathyroidal spread, T-stage of the tumor and presence of lymph node metastasis (15-17). In our study, it was seen that bilaterally evaluated with these factors showed a worse clinical course than unilateral cancer cases. Wang et al. (18) have shown that bilateral tumors are associated with more advanced stage tumors and shorter disease-free survival. This finding supports our current study.

Multifocal thyroid carcinoma was detected between 23% and 40% in performed studies and has been associated with aggressive tumor behavior in many of them (19-21). Kim et al. (22) observed that multifocality was a more determinative prognostic factor than bilaterality in their study. Kim et al. concluded that, although both bilaterality and multifocality have aggressive pathological features, only multifocality is effective in tumor recurrence. Suh et al. (23) concluded that bilaterality is an independent factor in the development of local recurrence.

Qu et al. (24) reported that the disease coursed with worse prognosis as the number of tumor foci increased, in their study performed with 496 patients in 2014, and in the study they published in 2016 (25), bilateral disease affected prognosis worse than multifocal disease.

The limitations of our study are not only its retrospective design, but also assessing only histopathologic features predictive of aggressiveness and not having local recurrence, disease-free survival and PTC-related mortality data as there is no long-term follow-up results.

In conclusion, we believe that bilateral disease should be considered as a poor prognostic factor independent of age and sex in patients with papillary thyroid carcinoma and that these cases should be followed up more closely in the postoperative period and their treatment should be planned in the light of this information.

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