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Factors Affecting the Risk of Lymph Node Metastasis in Papillary Thyroid Cancer

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ABSTRACT

Aim: Papillary thyroid cancer is the most common type of differentiated thyroid carcinoma and lymph node metastasis is common. Lymph node metastasis is an important prognostic factor for disease recurrence. The aim of this study was to evaluate the predictive factors affecting lymph node metastasis.

Materials and Methods: The files of 34 patients who underwent central and / or lateral neck dissection with the diagnosis of papillary thyroid cancer (PTC) between June 2017 and June 2020 were retrospectively analyzed from the hospital database. The relationship of age, gender, thyroid function tests and antibodies, tumor size, lymphovascular invasion and multicentricity factors with lymph node metastasis was evaluated.

Results: The most common surgery performed according to the clinical conditions of the 34 patients included in the study was central neck dissection with total thyroidectomy (64.7%), and a total of 12 (35.3%) patients underwent lateral neck dissection in addition to central dissection. In the central node positive patient group, statistically significantly more multicentric tumors and lymphovascular invasion were observed ($p = 0.033$; $p = 0.050$). In the lateral lymph node positive patient group, statistically significantly more central metastases and lymphovascular invasion were observed ($p = 0.007$; $p = 0.007$). Regardless of the lymph node regions, statistically significantly more LVI positivity was observed in node-positive patients compared with node-negative patients ($p = 0.025$).

Conclusion: In PTC patients, preoperative lymph node metastasis status should be staged by clinical and imaging methods, taking into account predictive risk factors, and the lymph node dissection method and the method should be determined in order to prevent recurrence and reduce re-operations.

Key Words: Papillary thyroid carcinoma, lymph node metastasis, predictive factors

Introduction

Differentiated thyroid carcinoma (DTC) is a malignancy with increasing worldwide incidence in recent years. DTC originating from follicular epithelial cells is classified in two separate subgroups as well differentiated thyroid cancer and poorly differentiated thyroid cancer in terms of pathological appearance, clinical course and prognosis. Papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) are in the IDTC group and constitute more than 95% of thyroid cancers. Although PTC, which constitutes 80-85% of IDTCs, is a relatively inactive tumor, it frequently spreads to the central and lateral cervical lymph nodes (LN) (Cabalinnas 2016:2783;Davidson 2008:2161;Gillanders 2018:286;Ito 2010:28;Roh 2008:2482). While macrometastases are seen in 35-40% of cases, LN micrometastases are seen in up to 90% (Sherman 2003:501;Trimpoli 2006:1151; McHenry 2014:529). In PTC, LN metastasis presents a gradual spread pattern, which is first typically central and then lateral cervical LN, while in some cases it spreads directly to the lateral cervical area without central metastasis, which is known as skip metastasis (Roh 2008:1177;Haugen 2016:1;Viola 2015:1316;Lee 2014:887). There is considerable consensus among endocrinologists and endocrine surgeons on the role of total thyroidectomy (TT) and Thyroid Stimulating Hormone (TSH) suppression therapy in the treatment of the disease. Prophylactic or therapeutic treatment of LN dissection is still a matter of controversy. Although there are studies stating that LN dissection has no effect on mortality (Shaha 1996:534), there are also studies showing that it has an impact on recurrence and mortality, especially over the age of 45 years (Noguchi 1998:276; Zaydfudim 2008:1070). The presence of prominent macroscopic neck metastasis is

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associated with a higher risk of recurrence than subclinical microscopic nodal metastasis (Randolph 2012:1144). While therapeutic dissection is recommended in cases of macroscopic neck LN involvement, prophylactic neck dissection is not currently recommended in cases of subclinical LN, but only in selected high-risk cases (Haugen 2016:1). Therefore, accurate detection and prediction of neck LN metastasis, and the presence of predictive factors that can predict LN metastasis may improve treatment planning and risk stratification in PTC patients. Therefore, the aim of ths study was to evaluate the clinical and pathological factors affecting LN metastasis in PTC.

Materials and Methods

The files of 34 patients who underwent central and / or lateral neck dissection with the diagnosis of papillary thyroid cancer (PTC) between June 2017 and June 2020 were retrospectively analyzed from the hospital database. Patients who were diagnosed with PTC but did not undergo neck dissection and those who were operated on for a diagnosis of non-PTC thyroid malignancy were not included in the study.

All patients were evaluated with preoperative clinical examinations and imaging methods. The PTC diagnosis and the presence of central and lateral metastasis were confirmed by neck ultrasound, tomography or magnetic resonance imaging as required, fine needle aspiration biopsy, and washing cytology. Patients with no metastases determined preoperatively were re-evaluated perioperatively. Suspected LN was examined by frozen examination. Unilateral central neck dissection (USBD) or bilateral central neck dissection (BSND) was performed with TT in the presence or suspicion of metastasis, and lateral neck dissection (LND) in the presence of lateral LN involvement. LBD included level II, III, IV and V lymph nodes.

Clinical and pathological data included age, gender, serum thyroid function tests at the time of diagnosis (thyroid stimulating hormone (TSH), free triiodothyronine (T3), free Thyroxine (T4), Thyroglobulin, Anti-thyroglobulin, Anti-TPO (Thyroid Peroxidase), pathological tumour size according to the 8th Edition TNM staging system (T1a: ≤1, 1 <T1b≤2, 2 <T2≤4, T3a> 4, T3b: any diameter and invasion of non-thyroid strep muscles), multicentricity, lymphovascular invasion (LVI) and central / lateral contained the status of LNs.

Statistical analysis

Data obtained in the study were analyzed statistically using IBM Statistics software vn. 23.0. All numerical data were stated as mean ± standard deviation values or percentages. Histogram graphs and the Kolmogorov-Smirnov test were used to analyze the normal distribution of numerical data. In the comparison of clinicopathological characteristics of patient groups with and without LN positive and negative, central node positivity, with and without lateral node positivity, and with and without both central and lateral node positivity, the Student's t-test or Mann-Whitney U test were used for numerical data, and the Chi-square test or Fisher Exact test for categorical data. A value of $p<0.05$ was considered statistically significant.

Results

The clinicopathological characteristics of the patients included in the study are summarized in Table 1. The mean age was 42.71 ± 9.16 years, and the male to female ratio was 10/24. The most common surgery performed according to the clinical conditions of the patients was TT + BSBD (64.7%) and a total of 12 (35.3%) patients underwent LND in addition to central dissection. When T stages were examined, it was seen that most of the patients (67.6%) had T3 stage. When the pathology results were examined, a total of 15 patients (44.1%) were LN positive, 13 patients (38.2%) had central, 7 patients (20.5%) had lateral, and 5 patients (14.7%) had both central and lateral LN metastasis. Lateral skip metastasis was detected in two patients (5.8%). While no distant metastases were detected in the patients, it was observed that 9 (26.5%) patients had LVI + and 21 (61.8%) patients had multicentric tumors in the thyroid gland.

When patients with and without central metastases were compared, no difference was found in terms of age, gender, T stage and preoperative thyroid function test results, while statistically significant more multicentric tumors and LVI were observed in the central LN positive patient group ($p = 0.033$; $p = 0.050$) (Table 2).

When the patients with and without lateral metastases were compared, no difference was found in terms of age, gender, T stage, presence of multicentric tumor and preoperative thyroid function test results, while statistically significant more LVI was observed in the lateral LN positive patient group ($p = 0.007$). The central LN positivity rate was found to be statistically significantly higher in lateral LN positive patients than in lateral LN negative patients (85.7%; 25.9% $p = 0.007$) (Table 3).

When the patients were divided into two groups as LN positive and LN negative independently of LN regions, there was no difference between the groups in terms of age, gender, T stage, presence of multicentric tumor and preoperative thyroid function test results, and statistically significantly more LVI positivity was observed in LN positive patients compared to LN negative patients (46.7%; 10.5% $p = 0.025$) (Table 4).

Discussion

It is important to determine predictive factors for LN metastasis in patients with PTC. The American Thyroid Association (ATA) recommends therapeutic LN dissection when there is macroscopic LN involvement, and does not recommend prophylactic dissection in the absence of clinical LN involvement due to possible complications and increased morbidity. However, prophylactic lymph node dissection is recommended in selected cases of T3, T4 tumor stage and

high-risk patient groups (Haugen 2016:1; Haugen 2017:372). Therefore, determination of high-risk patient groups is important in terms of the recurrence risk of the disease.

The rate of PTC in females is approximately three times higher than in males. The onset of PTC is at a younger age in females, but males tend to have more aggressive disease at the time of diagnosis. It has been stated that aggressive subtypes are observed at the same rate in both genders. In most studies, male gender has been associated with lower disease-free survival and higher mortality rates (Kilfoy 2009:1092; Rahbari 2010:1771; Gilliland 1997:564). Similar to the literature, the number of female patients in the current study was higher than the number of male patients. In terms of LN metastasis, no statistically significant difference was found between the genders.

In a meta-analysis by Wang et al., the LN metastasis rate was found to be statistically significantly higher in young patients aged ≤30 years than in older PTC patient groups. (Wang 2018;3867). In the current study, although the mean age was younger in the groups with central and lateral LN metastases compared to the groups without metastasis, no statistically significant difference was found.

In the literature, there are studies evaluating central LN metastasis due to the association of chronic lymphocytic thyroiditis (CLT) with PTC. In those studies, it has been stated that central LN metastasis was found at a lower rate in PTCs with CLT compared to PTCs without CLT (Kim 2011:1272; Paulson 2012:444; Jara 2013:1272). Nam et al. found that preoperative high serum antithyroglobulin level and PTC combined with CLT were associated with good prognosis indicators (Nam 2016:358). In the current study, there was no statistically significant difference between those with and without CLT antibodies with central and lateral metastasis.

Serum thyroglobulin level is one of the main markers frequently used in postoperative metastasis and recurrence follow-up (Giovanella 2008:1067; Alzahrani 2002:443). In the current study, although the preoperative serum thyroglobulin level was higher in the group with both central and lateral LN metastases compared to the group without metastases, no statistically significant difference was found. It has been shown in many studies that the prognosis of PTC developing on a hyperthyroid background is poor (Pellegriti 2013:1014; Pellegriti 1998:2805; Belfiore 1990:830). In the current study, no statistically significant difference was determined for serum TSH, T3 and T4 levels in terms of LN metastasis.

Meta-analyses have shown that there is increased risk of LN metastasis if there is increased tumor diameter, lymphovascular invasion and in multicentric tumors (Ma 2016:153; Qu 2015:124; Sun 2015:10). Ma et al. (Ma 2016:153) reported that the diameter for PTC was> 1 cm, and Sun et al. (Sun 2015:10) stated that diameter of > 2 cm for PTC, and for papillary microcarcinoma, lesions > 5 mm in diameter were independent risk factors for central LN metastasis in both studies. When the tumor sizes were examined according to the TNM staging system, it was seen that the majority of the patients (67.6%) in the current study had T3 stage. There was no statistically significant difference in terms of LN metastasis risk. For central LN metastasis, LVI and multicentric tumor risk factors were found to be statistically significant. For lateral LN metastasis, central metastasis and the presence of LVI were found to be statistically significant risk factors.

The main limitations of this study were possible selection bias due to the retrospective nature of the study and the limited adaptability of the results to the general population due to the relatively low sample size.

In conclusion, in order to prevent recurrence and reduce morbidity in PTC patients, preoperative LN metastasis status should be staged by clinical and imaging methods, taking into account predictive risk factors, and LN dissection method and the methods should be determined. However, there remains a need for predictive factors to be confirmed with further, prospective, randomized studies.

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Tables

Table 1. Clinicopathological characteristics of the patients included in the study

Patient Characteristics	**n=34 (mean ± standard deviation /%)**
Age (years)	47.03±13.47
Gender (male/female)	10/24
Operation Type	
TT+UCND	0(0)
TT+BCND	22(64.7)
TT+UCND+LND	1(2.9)
TT+BCND+LND	11(32.4)
T stage	
T1a	1(2.9)
T1b	2(5.9)
T2	8(23.5)
T3a	6(17.6)
T3b	17(50)
T4a	0(0)
T4b	0(0)
N stage	
Nod –	19 (55.9)
Nod +	15 (44.1)
Central +	13 (38.2)
Only central +	8 (23.5)
Lateral +	7 (20.5)
Central and lateral +	5 (14.7)
Only lateral + (skip)	2 (5.8)
M stage	
M0	34(100)
M1	0(0)
TNM stage	
I	30(88.2)
II	4(11.8)
III	0(0)
IVa	0(0)
IVb	0(0)
LVİ (+)	9(26.5)
Multicentricity (+)	21(61.8)

Numerical values are given as mean ± standard deviation or percentages. TT: Total Thyroidectomy UCND: Unilateral Central Neck Dissection, BCND: Bilateral Central Neck Dissection, LND: Lateral Neck Dissection, TNM: Tumor, Node, Metastasis, LVI: Lymphovascular Invasion.

Tablo 2. Comparison of clinicopathological variables of patients with and without central metastasis.

Patient Characteristics	Central Metastasis+ (n=13)	Central Metastasis- (n=21)	p value
Age (years)	44.38±13.09	48.67±13.75	0.376
Gender (male/female)	5/8	5/16	0.298
T stage			0.465
T1	1(7.7)	2(9.5)	
T2	2(15.4)	6(28.6)	
T3	10(76.9)	13(61.9)	
LVI (+)	6(46.2)	3(14.3)	**0.050**
Multicentricity (+)	5(38.5)	16(76.2)	**0.033**
TSH	1.81±0.78	2.26±1.56	0.583
T3	3.20±0.37	3.14±0.52	0.727
T4	1.21±0.13	1.27±0.38	0.589
Thyroglobulin	44.83±20.70	33.73±22.37	0.158
Anti-Thyroglobulin	27.19±25.86	27.51±23.22	0.468
Anti-TPO	15.68±11.82	18.68±11.12	0.228

Numerical values are given as mean ± standard deviation or percentages. LVI: Lymphovascular Invasion. TSH: Thyroid Stimulating Hormone, TPO: Thyroid Peroxidase.

Table 3. Comparison of clinicopathological variables of patients with and without lateral metastasis.

Patient Characteristics	Lateral Metastasis + (n=7)	Lateral Metastasis - (n=27)	P value
Age (years)	42.71±9.16	48.15±14.30	0.350
Gender (male/female)	3/4	7/20	0.644
T stage			0.069
T1	0(0)	3(11.1)	
T2	0(0)	8(29.6)	
T3	7(100)	16(59.3)	
LVİ (+)	5(71.4)	4(14.8)	**0.007**
Multicentricity (+)	5(71.4)	16(59.3)	0.682
Central Metastasis	6(85.7)	7(25.9)	**0.007**
TSH	1.96±0.61	2.13±1.46	0.782
T3	3.28±0.41	3.13±0.48	0.463
T4	1.21±0.12	1.26±0.34	0.713
Thyroglobulin	50.67±18.35	34.68±22.10	0.088
Anti-Thyroglobulin	24.49±22.64	28.14±24.54	0.915
Anti-TPO	11.61±4.08	19.07±12.11	0.084

Numerical values are given as mean ± standard deviation or percentages. LVI: Lymphovascular Invasion. TSH: Thyroid Stimulating Hormone, TPO: Thyroid Peroxidase.

Table 4. Comparison of clinicopathological variables of node positive and node negative patients.

Patient Characteristics	Nod + (n=15)	Nod - (n=19)	p value
Age (years)	44.64±12.62	48.70±14.71	0.385
Gender (male/female)	5/10	5/14	0.718
T stage			0.271
T1	1(6.7)	2(10.5)	
T2	2(13.3)	6(31.6)	
T3	12(80)	11(57.9)	
LVİ (+)	7(46.7)	2(10.5)	**0.025**
Multicentricity (+)	6(40)	15(78.9)	0.160
TSH	1.90±0.81	2.23±1.59	0.808
T3	3.23±0.37	3.12±0.53	0.683
T4	1.23±0.13	1.27±0.39	0.496
Thyroglobulin	45.84±20.25	32.46±22.17	0.103
Anti-Thyroglobulin	26.35±25.05	28.12±23.65	0.591
Anti-TPO	15.85±11.37	18.71±11.41	0.323

Numerical values are given as mean ± standard deviation or percentages. LVI: Lymphovascular Invasion. TSH: Thyroid Stimulating Hormone, TPO: Thyroid Peroxidase.