Original Research

Predictive Factors Affecting the Development of Central Lymph Node Metastasis in Papillary Thyroid Cancer

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Abstract

Objectives: The most common subtype of thyroid cancer is papillary thyroid cancer (PTC); lymph node metastases are common in this disease. Factors affecting the development of central lymph metastasis of PTC determine the treatment modality and prognosis of the disease. In this study, we aimed to evaluate the clinicopathologic features affecting the development of central lymph node metastasis.

Methods: The data of a total of 346 PTC patients who were operated between May 2012 and September 2020 in our clinic and whose follow-up could be reached were evaluated retrospectively. Demographic data, surgical treatment modalities, and histopathological data of all patients were evaluated as a result of at least 6 months of follow-up. Patients age, sex, body mass index, pre-operative TSH levels, anti-TPO, and anti-Tg values at the time of diagnosis, whether lymph node dissection is performed, presence of lymph node metastasis, presence of distant metastasis, stage at the time of diagnosis (TNM 8th edition), ATA risk group at the time of diagnosis, multifocal and/or multicentric (bilaterality), largest tumor size, aggressive histological subtype, lymphovascular invasion of the tumor, extrathyroidal invasion, presence of lymphocytic thyroiditis, and surgical margin positivity were evaluated retrospectively.

Results: In the development of PTC central metastasis, distant metastasis, tumor size, multifocality, multicentricity, presence of lymphovascular invasion, aggressive tumor subtype, presence of lateral metastasis, nodular goiter, and extrathyroidal spread were found to be effective. Among these factors, T stage, presence of lymphovascular invasion, and multicentricity were identified as independent risk factors for the development of central metastasis.

Conclusion: Today, the investigation of predictive factors for the development of nodal metastasis in PTC does not seem to be out of date anytime soon. In our study, T stage, presence of lymphovascular invasion, and multicentricity were identified as independent risk factors for the development of central metastasis from the histopathological features of the tumor in PTC and of these features, T stage and multicentricity can be predicted by pre-operative imaging in many patients and can be used to decide whether to perform prophylactic SLN dissection in patients. However, new studies are still needed on this issue, in the literature.

Keywords: Central lymph node metastasis, central neck dissection, papillary thyroid cancer

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Thyroid diseases are one of the most common endocrinological pathologies and it could be occurred in very large spectrum from benign structural changes to metastatic cancers.[1] The incidence of thyroid malignancy has increased in all regions, especially in the past 3–5 decades. Thyroid malignancies currently have the most common malignancy rate among head and neck endocrine organs.[2]

Malign tumors of thyroid gland are derived from follicular cells, parafollicular cells, or lymphoid cells in generally.[3] Although the most common type among these malignancies is differentiated thyroid cancer, approximately 85% of differentiated thyroid cancers are papillary type thyroid cancer (PTC).[4] Although the survival rates in PTC are satisfactory and there is no significant increase in mortality, nodal metastases are detected more frequently than in the past with the developing technology and imaging methods. In the literature, it has been reported that the rate of macroscopic metastases is 35% and the rate of microscopic metastasis is up to 80%.[5-7] Although, the effect of nodal metastasis to the mortality in differentiated thyroid cancers is still debatable, it has been demonstrated as a risk factor for locoregional recurrence and distant metastasis.[8]

Therapeutic central neck dissection is accepted as part of the treatment for clinical central lymph node metastasis (CLNM) in PTC. However, although micrometastases are thought to have a role in recurrences after therapeutic central lymph node dissection, the approach for micrometastases and whether prophylactic central neck dissection is still a controversial issue.[9,10] The higher incidence of complications such as hypoparathyroidism and recurrent laryngeal nerve (RLN) paralysis after central lymph node dissection leads surgeons to be more selective for this operation.[11] In the other hand, the effect of micrometastasis for survive is getting more questionable due to there is no significant rising in locoregional recurrens and distant metastasis although, the rate of nodal micrometastasis is up to 80% in studies.[6] For these reasons, it is important to determine the extent of the surgery, taking into account the complication rates that may develop, in the selection of appropriate and adequate treatment methods for the surgery to be performed for thyroid malignancies. Undoubtedly, knowing the factors that have a role in the development of central nodal metastases has great importance in terms of surgery and follow-up.[6]

In the present, there are too many studies about determination of predictive factors for central nodal metastasis in PTC patients. Controversies on this issue have come from the past up to present and are still controversial. In our study, we aimed to evaluate the clinical and pathological factors that affect the development of central nodal metastases, which are still controversial and current in the literature.

Methods

Patients

Approval for the study was obtained from the in our Local Ethics Committee with the date of December 22, 2020 and decision number 3081. The data of a total of 346 PTC patients who were operated between May 2012 and September 2020 in our clinic and whose follow-up could be reached were evaluated retrospectively. Patients under 16 years of age, whose files could not be reached, whose first surgical treatment was performed in another institution, whose post-operative follow-up could not be reached, and patients with thyroid malignancies other than PTC were excluded from the study. Patient's consents were obtained for this study.

Evaluated Clinopathological Features

Patients age, gender, body mass index (BMI), pre-operative TSH levels, anti-TPO, and anti-Tg values at diagnosis, whether lymph node dissection was performed, presence of lymph node metastasis, presence of distant metastasis, stage at diagnosis (TNM 8th edition), and ATA risk group at the time of diagnosis, whether the tumor is multifocal and/or multicentric (bilaterality), largest tumor size, histological subtype, lymphovascular invasion in the tumor, extra thyroidal invasion, and presence of lymphocytic thyroiditis, whether surgical margin positivity characteristics were obtained retrospectively. In pathological examinations, multicentrity (bilaterality) was defined as the detection of two or more than two foci in both thyroid lobes of the tumor. Multifocality was defined as the presence of more than one tumor focus in a single lobe. In the pathology results, the subtypes that were evaluated as aggressive subtypes are high cylindrical cell (Tall Cell) variant, hobnail variant, solid (trabecular) variant, and diffuse sclerosing variant. The diameter of the dominant tumor was accepted as tumor size, in multifocal and/or multicentric tumors. Extrathyroidal extension (ETE) was divided in two categories; minor (ETE 1) tumor with perithyroidal extension or extension to strep muscles; and gross (ETE 2) was considered as invasion of strep muscles and/or invasion of subcutaneous soft tissue, RLN, esophagus, trachea, larynx, carotid artery, or mediastinal vessels.

Operation Approach

Lobectomy was performed in patients with Bethesda 3, Bethesda 4 cytological findings in pre-operative FNAB, in patients with suspected unifocal papillary thyroid cancer (PTC) (Bethesda 5), and PTC (Bethesda 6) <1 cm in diameter. According to the post-operative pathology, some patients underwent completion thyroidectomy. In patients with suspected multifocal papillary cancer or proven multifocal papillary cancer, even if below 1 cm; in patients with suspected papillary cancer or proven papillary cancer, greater than 1 cm; and in patients with clinical central metastases regardless of tumor size, total thyroidectomy was performed. Prophylactic or therapeutic central neck dissection

was applied to the patients. Prophylactic central neck dissection was performed on selected patients according to ATA guidelines. Before 2015, in T3–T4 tumors according to the 2009 version of the guideline; after 2015, according to the 2015 version of the guidelines, in T3–T4 tumors; in patients with lateral metastases; and in patients whose post-surgical treatment is thought to be affected; prophylactic central neck dissection was performed.[6,12] Therapeutic central neck dissection was performed bilaterally, prophylactic central neck dissection was performed unilaterally (UCND), except for bilateral tumors. Therapeutic selective lateral neck dissection was performed in patients who were detected by ultrasonography on the lateral neck and proved to have metastasis by fine-needle aspiration biopsy and/or thyroglobulin washout.

According to the pathological evaluation, the patients were divided into two groups as with and without central metastasis, and their data were evaluated.

Statistical Analysis

SPSS (Statistical Packages for the Social Sciences, software, edition 21, SPSS Inc. Chicago, USA) was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, first quarter, third quarter, frequency, percentage, minimum, and maximum) were used to evaluate the study data. The "Mann–Whitney U"-test was used to compare the quantitative variables that did not show normal distribution between the two groups. "Pearson Chi-square test" and "Fisher's Precision Test" were used to compare the qualitative data. Logistic regression analysis was performed by Binary method to examine the effects of independent variables (gender, age, tumor diameter, non-thyroid capsule soft-tissue invasion, etc.,) that were predicted to be related to the risk of lymph node metastasis according to the results of univariate analysis. The statistical significance was accepted as $p<0.05$.

Results

The data of a total of 346 patients diagnosed with PTC in our clinic were evaluated retrospectively. The demographic and clinical characteristics of the patients and the pathological characteristics of tumor are summarized in Table 1.

Of the patients, 265 (23.4%) were female, 81 (76.6%) were male; the mean age was 47.31±13.92 years (16–85); and the mean BMI was 27.23±5.11 kg/m² (17.9–48) 85 patients (24.6%) underwent lobectomy/hemitiroidectomy; 261 patients (75.4%) underwent total thyroidectomy. In our study, prophylactic central neck dissection was performed in 29 cases (8.3%); therapeutic central neck dissection was performed in 16 cases (4.6%); and therapeutic lateral neck dis-

Table 1. Characteristics of patients

Features	Patient number	(%)
Gender		
Male	81	23.4
Female	265	76.6
Age(year)		
Mean + SD		47.31±13.92
Min-Max		16–85
<55	249	72
≥55	97	28
BMI (kg/m²)		
Mean + SD	346	27.23±5.11
Min-Max		17.9–48
Tumor size (cm)		
Mean + SD	346	1.41±1.50
Min-Max		0.1–12
<1	195	56.4
≥1	151	45.6
ETE		
Positive	68	29.7
Negative	272	70.9
Lymphocytic thyroiditis		
Positive	168	48.6
Negative	196	51.4
Surgical margin positivity		
Positive	10	2.9
Negative	336	97.1
Lymphovascular ınvasion		
Positive	89	25.7
Negative	257	74.3
Multicentricity		
Yes	132	38.2
No	214	61.8
Multifocality		
Yes	98	28.3
No	248	71.7
Aggressive histological subtype		
Yes	37	10.7
No	309	89.3
Central lymph node metastases		
Yes	47	13.6
No	299	86.4

SD: Standard deviation; min: Minimum; max: Maximum; cm: Centimeter; kg: Kilogram; m²: Square meter.

section was performed in 36 cases (10.4%). Prophylactic lateral neck dissection is not performed in our clinic. Patients with central lymph node metastases, patients who underwent prophylactic, and therapeutic central neck dissection were also included in patients with incidental central lymph node metastases. Skip metastasis was detected in eight patients (2.3%).

CLNM was detected in 47 patients (13.6%). The mean tumor size of the patients included in the study was 1.41±1.50 cm (0.1–12 cm); tumor size was <1 cm in 195 patients (56.4%); ≥1 cm in 151 patients (45.6%). Multicentricity was detected in 132 patients (38.2%), multifocality in 98 patients (28.3%), lymphovascular invasion in 89 patients (25.7%), and ETE in 68 patients (29.7%). In addition, aggressive histological subtype was detected in 68 patients (29.7%), lymphocytic thyroiditis in 168 patients (48.6%), and surgical margin pos-

itivity in ten patients (2.9%) (Table 1).

The mean age of patients with PTC was significantly lower in patients with central metastasis at first admission compared to those without central metastasis (41.77±16.79 vs. 48.18±13.2; p=0.008, respectively). On the other hand, when the patients under 55 years of age and over were categorized as TNM staging criteria, the distribution of patients with and without central metastases to age categories was found to be similar (p=0.217) (Table 2).

Table 2. Factors affecting the development of central lymph node metastases

Features	Central lymph node metastases (+)	Central lymph node metastases (-)	p
Gender (n+%)			
Male	16 (19.8)	65 (80.2)	0.064
Female	31 (21.7)	234 (78.3)	
Age(year) (mean ± SD) (min-max)	41.77±16.79 (16–81)	48.18±13.24 (18–85)	0.008
≥55 age(n+%)	10 (21.3)	87 (29.1)	0.217
<55 age(n+%)	37 (78.7)	212 (70.9)	
BMI (kg/m^2) (mean ± SD) (min-max)	25.65±4.52 (18.30–34.70)	27.48±5.16 (17.90–48.00)	0.470
TSH (uIU/Ml) (mean ± SD) (min-max)	2.67±3.67 (0.01–24.6)	2.15±2.80 (0.01–28.04)	0.117
Anti TPO (IU/mL) (mean ± SD) (min-max)	54.05±119.93 (0.10–561)	56.05±135.39 (0.10–1083)	0.775
(n+%)	8 (20)	57 (22.1)	0.776
Anti TG (IU/mL) (mean ± SD) (min-max)	186.61±659.97 (0.90–4000)	89.33±365.69 (0.90–4000)	0.907
(n+%)	8 (20)	47 (18.1)	0.770
Tumor Size (cm) (mean ± SD) (min-max)	2.38±2.14 (0.4–10)	1.26±2.14 (0.1–12)	0.000
ETE (n+%)			
ETE 0(Yok)	22 (46.8)	256 (85.6)	0.000
ETE 1(Minör)	16 (34)	38 (12.7)	
ETE 2(Gross)	9 (19.2)	5 (1.7)	
Lymphocytic Thyroiditis (n+%)	28 (59.6)	140 (46.8)	0.104
Surgical Margin Positivity (n+%)	3 (6.4)	7 (2.3)	0.770
Lymphovascular Invasion (n+%)	34 (72.3)	55 (18.4)	0.000
Multicentricity (n+%)	35 (74.5)	97 (32.4)	0.000
Multifocality (n+%)	26 (55.3)	72 (24.1)	0.000
Aggressive histological subtype (n+%)	13 (27.7)	24 (8)	0.000
Lateral Lymph Node Metastases (n+%)	27 (57.4)	9 (3)	0.000
Stage (TNM) (n+%)			
Stage 1	37 (78.7)	283 (94.6)	0.000
Stage 2	9 (19.1)	16 (5.4)	
Stage 3	0	0	
Stage 4	1 (2.1)	0	
ATA risk stratification (n+%)			
Low	8 (17)	268 (89.6)	0.000
Intermediate	31(66)	29 (9.7)	
High	8 (17)	2 (0.7)	
T Stage (n+%)			
T1	18 (38.3)	228 (76.3)	0.000
T2	9 (19.1)	23 (7.7)	
T3	20 (42.6)	46 (15.4)	
T4	0	2 (0.7)	
M stage (n+%)	1 (2.1)	0	0.000

SD: Standard deviation; min: Minimum; max: Maximum; cm: Centimeter; kg: kilogram; m^2: Square meter; n: Number; TSH: Thyroid-stimulating hormone; Anti TPO: Antithyroid peroxidase; Anti TG: Anti: Antithyroglobulin; ETE: Extrathyroidal extension; T: Tumor; N: Node; M: Metastasis; ATA: American thyroid association.

Of the histopathological features of the tumor, tumor size (2.38±2.14 cm vs 1.26±2.14; p=0.000), lymphovascular invasion rate (72.3% vs. 18.4%; p=0.000), multicentricity rate (74.5 % vs. 32.4%; p=0.000), multifocality (55.3% vs. 24.1%; p=0.000), and aggressive histological subtype rate (27.7% vs. 8%; p=0.000) were significantly higher in CLNM developed patients than those without CLNM, respectively.

T stage was significantly different between patients with and without central metastases (p=0.000). T1 tumor rate was lower in patients with central metastases (38.3% vs. 76.3%, respectively), compared to patients without central metastases, while T2 (19.1% vs. 7.7%, respectively) and T3 (42.6% vs. 15.4%, respectively) tumor rate was significantly higher. In the central metastasis group, distant metastasis was detected in one patient (2.1%) at the time of diagnosis, but there was no distant metastasis in the group without central metastases and the difference was significant (p=0.000).

The TNM stage was found also different between the groups with and without central metastases. The Stage 2 tumor rate (19.1% vs. 5.4%, respectively) was higher in the group with central metastasis compared to the group without central metastasis. In addition, the Stage 1 tumor rate was lower (78.7% vs. 94.6%, respectively) in the group with central metastasis compared to the group without central metastasis. The rate of clinical lateral metastasis was also higher in patients with central metastasis (57.4% vs. 3%, respectively, p=0.000). In the group with central metastases, the rate of low-risk patients was significantly lower (17% vs. 89.6%, respectively). Although, the rate of medium-risk (66% vs. 9.7%, respectively) and high-risk (17% vs. 0.7%, respectively) patients were higher in the group with central metastases. Apart from this, there was no significant difference in terms of demographic, clinical, biochemical, and histopathological features (Table 2).

A formula, including T stage, lymphovascular invasion, multicentristy, multifocality, and aggressive histological subtype features, which are significant anatomical factors in the bilateral comparison regarding the development of central metastasis, was formed and evaluated by logistic regression analysis. According to this evaluation, T stage, presence of lymphovascular invasion, and multicentricity were determined as independent risk factors for the development of central metastasis (p=0.048; p=0.000; and p=0.019, respectively). When T1 stage is taken as reference, T2 tumor increases the risk of developing central metastasis approximately 4.2 times compared to T1. The presence of lymphovascular invasion increases the risk of developing central metastasis approximately 6.2 times, and multicentricity increases the risk of developing central metastasis approximately 3.5 times (Table 3).

Table 3. Factors affecting the development of central metastasis according to logistic regression (T: Tumor)

	Odds ratio (95%CI lower-upper)	p
T Stage		0.048
T1	1 (Reference)	
T2	4.243 (1.491–12.072)	0.007
T3	0.125 (1.949 (0.821–4.569)	0.125
T4	0.000	0.999
Lymphovascular Invasion		0.000
Negative	1 (Reference)	
Positive	6.173 (2.770–13.700)	
Multicentricity		0.019
Negative	1 (Reference)	
Positive	3.472 (1.230–9.804)	
Multifocality		0.733
Negative	1 (Reference)	
Positive	1.186 (0.447–3.145)	
Aggressive histological subtype		0.109
Negative	1 (Reference)	
Positive	2.132 (0.845–5.376)	

Discussion

Thyroid gland carcinoma is the most common endocrine system malignancy and the incidence of this disease has been increasing in recent years.[4] The most common subtype of thyroid cancers is PTC and increasing of incidence is related with PTC.[13] The prognosis of PTC, recurrence rate, follow-up of the disease, and the extent of treatment for cure of PTC has been discussed for a long time.

PTCs, with a 10-year survival rate of over 90%, generally metastasize through the lymphatic route and cervical lymph node metastases are frequently seen.[7,14] If the spread pattern of lymph node metastasis in PTC is examined, it is seen that there is a central to lateral orientation, except for skip metastases, which are rarely seen.[15]

Lymph node metastasis is one of the important risk factors for recurrences in PTC. In addition, considering the increasing complication rates in recurrent surgeries, the necessity and extent of lymph node dissection in the first operation are one of the most important topics in PTC treatment today. For these reasons, factors affecting nodal metastases are important factors that can affect the width of lymph node dissection, and these are an important topic of discussion in present. In PTC patients, TNM classification is used for determining mortality and ATA classification is used for predicting recurrence, frequently.[6,16] Although these two guidelines are the most important guides in PTC surgery, they may be insufficient in some cases to determine the extent of the surgery to be performed and to predict the

prognosis. The development of CLNM is one of the most important issues in terms of adequate surgery and post-operative disease-free survival.

There are many studies in the literature evaluating risk factors for central lymph node metastases.[17-21] The prevalence of CLNM is seen in a wide range in the literature. The prevalence of CLNM, which is seen between 24.1% and 64.1%, may vary according to the methods of the studies, patient groups, and surgery performed[22-27] In this study, the rate of CLNM was demonstrated to be 13.6% in 346 patients. When compared with the literature, it is seen that the prevalence value found in our study is low. Since the rate of microscopic lymph node metastasis is high, microscopic central metastasis may not be rare, especially in patients who have not undergone central dissection. This low rate, we think that it is related to performing central dissection in selected patients in accordance with ATA 2009 and 2015 guidelines instead of routine prophylactic central dissection in PTC patients in our clinic and including incidentally detected papillary microcarcinomas in the study.

It is thought that many demographic, clinical, and molecular factors have an effect on the development of CLNM. The effect of gender among demographic findings is one of the factors frequently discussed in the literature. In the studies of Zhang et al. and Yan et al., it is seen that male gender is predominant in patients with central metastasis.[28,29] In the study of Lim et al. including 31,017 patients, male gender was determined as a risk factor for the development of CLNM in pairwise comparisons, but it was not detected as an independent risk factor.[30] In our study, no significant effect of gender on the development of CLNM was found. Although there are studies in the literature stating that male gender is a risk factor for the development of CLNM, there are not enough studies yet showing the effect mechanism of gender on CLNM. There is a need for more detailed studies involving more patients on this subject.

There are many studies in the literature examining the relationship between the mean age and the prognosis of PTC.[29] Age is one of the main determining criteria in the TNM staging system of differentiated thyroid cancers.[31] In two recent studies in the literature, it has been shown that the development of CLNM in PTC patients under the age of 45 is higher than in patients over the age of 45.[32,33] In our study, the mean age in the group with CLNM was found to be significantly lower than the group without nodal metastasis (41.77+16.79 vs. 48.18+13.24; p=0.008). However, in our study, as in the latest version of the TNM staging system (Edition 8), when we stratified patients according to 55 years of age, no significant difference was found in terms of CLNM development between in patients younger and

older than 55. These results may be due to the inclusion of papillary microcarcinoma patients in our study and the limited number of cases compared to other studies. In a meta-analysis by Liu et al., CLNM in papillary microcarcinoma was not found to be associated with age or gender.[34]

In our study, tumor diameter, multifocality, multicentricity (bilaterality), presence of lymphovascular invasion, aggressive tumor subtype, presence of lateral metastases, and ETE were found to have a significant effect on the development of central metastasis, in pair-wise comparisons of patients with PTC. However, T stage, presence of lymphovascular invasion, and multicentricity were determined as independent risk factors for the development of central metastasis (p=0.048, p=0.000, and p=0.019, respectively).

The effects of tumor size on the development of CLNM have been frequently investigated in the literature. Although different cutoff values have been demonstrated in different studies, the general opinion in the literature is that the increase in tumor size has significant effects on the development of CLNM.[35-37]

In a large meta-analysis including 8345 patients, it was determined that tumor size over 5 mm had significant effects on the development of CLNM.[38] In addition, it was reported that tumor size over 1 cm in the study of Ahn et al. and over 0.25 cm in the study of Yan et al. have significant effects on the development of CLNM.[29,39] Lin et al., on the other hand, found that CLNM development was significantly higher in microcarcinomas larger than 0.45 cm in papillary microcarcinomas.[30] In our study, the tumor diameter was found to be significantly larger in the patient group with CLNM compared to the group without nodal metastasis (2.38cm+2.14 cm vs. 1.26 cm+2.14 cm, respectively, p=0.000), and that supports the results of studies were mentioned above.

Another predictive factor found to have significant effects on the development of CLNM in our study is ETE. T stage, which was determined as an independent risk factor for the development of CLNM in our study, includes both tumor diameter and ETE. In our study, when T1 stage was taken as reference, it was found that T2 tumors increased the risk of developing CLNM approximately 4.2 times (Odds Ratio: 4.243 [1.491–12.072] p=0.048). Although the ratios of multifocality and multicentricity from histological tumor characteristics were significantly higher in the group with CLNM compared to the group without CLNM in the pairwise comparison (p=0.000 and p=0.000, respectively), only multicentricity was found to be as an independent risk factor for the development of CLNM in the logistic regression analysis (p=0.019). Multicentricity increases the risk of developing central metastasis approximately 3.5 times (Odds Ratio: 3.472 [1.230–9.804]).

In many studies in the literature, it has been reported that multifocality, multicentricity (bilaterality), and ETE were found to be significant risk factors for the development of CLNM.[40-43] In a meta-analysis by Liu et al., it was underlined that multifocality had a significant effect on the development of CLNM even in papillary microcarcinoma.[34] In a meta-analysis including four prospective and 21 retrospective studies and 7719 patients by Qu et al., lymphovascular invasion was also found to be a significant risk factor for the development of CLNM.[44] Similarly, Reddy et al. found that the presence of lymphovascular invasion significantly increased the development of CLNM.[18] In addition, in another study conducted in our clinic about the factors affecting the development of nodal metastases in patients with PTC in the past, it was determined that lymphovascular invasion is one of the significant risk factors for the development of CLNM.[40] In our current study, similar to our previous study, lymphovascular invasion was found to be an independent risk factor for the development of CLNM (p=0.000). It was determined that lymphovascular invasion increased the development of CLNM approximately 6.2 times (OR: 6,173 (2,770–13,700). As well as lymphovascular invasion is one of the main steps for the invasion of PTC into lymphatic pathways, we believe that this histological feature is one of the most important factors for the development of CLNM.

There are many studies in the literature investigating the subtypes of PTC. The effects of the more aggressive types of these subtypes or the more benign types on nodal metastases are one of the current controversial issues in PTC. Lin D et al. and Spinelli et al.'s studies on the factors affecting nodal metastases in PTC patients showed that different subtypes occur different risks and that aggressive subtypes of PTC are a significant risk factor for the development of CLNM.[30,45] In our study, although PTC aggressive subtypes were a significant risk factor for CLNM in pair-wise comparison (p=0.000), it was not detected as an independent risk factor in logistic regression analysis.

Conclusion

In the present, the investigation of predictive factors for the development of nodal metastases in PTC does not seem to lose its currency in the near future.

In our study, T stage, lymphovascular invasion, and multicentricity among the histopathological features of the tumor were determined as independent risk factors for the development of central metastasis in PTC. Among these features, T stage and multicentricity can be predicted in many patients by pre-operative imaging and can be used in the decision of whether to perform prophylactic central

lymph node dissection in patients. However, there is still a need for new studies in the literature on factors that may affect the treatment decision.

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