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Original Research

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

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ABSTRACT

Objectives: Lateral lymph node metastasis (LLNM) in papillary thyroid cancer (PTC) determines the extent of surgery to be performed and the prognosis of the disease. In this study, we aimed to evaluate the clinicopathological risk factors affecting the development of LLNM.

Methods: We retrospectively evaluated the demographic and clinicopathological data of 346 cases with PTC who were operated in our clinic between May 2012 and September 2020. The patients were divided into 2 groups as patients with LLNM (Group 1) and without LLNM (Group 2).

Results: Thirty-six (10.4%) patients out of 346 patients with PTC had LLNM. A statistically significant difference was found between Group 1 and Group 2 regarding the male gender (M/F: 38.9% vs. 21.6%; p=0.020), tumor size (2.30±1.99 cm vs. 1.31±1.40 cm; p=0.000), lymphovascular invasion (69.4 vs. 20.6%; p=0.000), multicentricity (69.4% vs. 35.5%; p=0.000), multifocality (p=0.000), aggressive variant (22.2% vs. 9.4%; p=0.000), extrathyroidal extension (50% vs. 16.1% p=0.000), central lymph node metastasis (CLNM) rates (75% vs. 6.5%; p=0.000), and ≥3 cm lymph node metastasis (48.5% vs. 0%, p=0.000), distant metastasis (2.1% vs. 0%, p=0.000), respectively. Multivariance analysis determined the presence of CLNM as an independent risk factor for the development of LLNM.

Conclusion: The presence of CLNM in patients with PTC was determined as an independent risk factor for the development of LLNM. Although there has been increasing debate about prophylactic central neck dissection (pCND) in LLNM, pCND should still be considered in these patients as the rate of CLNM is high in patients with LLNM. CLNM might be a reference for surgeons to determine the extent of surgery. In addition, the presence of CLNM is important for close follow-up for the early detection of LLNM recurrence.

Keywords: Central lymph node metastasis, lateral lymph node metastasis, papillary thyroid cancer, risk factors

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Thyroid cancer is a common endocrine malignancy with an increasing incidence over the years.[1] Among all diagnosed thyroid carcinomas, papillary thyroid carcinoma (PTC) is the most common subtype, accounting for 80–90% of thyroid carcinomas. Although the prognosis of PTC patients is good; it may present with a lymph node metastasis at a rate of 30–80%.[2-4]

In the literature, the prevalence of lateral lymph node metastasis (LLNM) in patients with PTC ranged from 6.5% to 27.5%.[5,6] PTC patients with LLNM have a higher incidence of disease recurrence and distant metastases than PTC patients with or without central lymph node metastasis (CLNM).[7] Therefore, an adequate assessment of the lateral lymph node status before surgery is very important in determining the surgical strategy and predicting the patient's survival.

Recent advances in ultrasound (US) allow accurate recognition of the involved cervical compartments. In the literature, the sensitivity and specificity of the US in detecting LLNM of PTC were found to be high, respectively.[8] ATA guideline recommends therapeutic selective lateral neck dissection in patients with lateral neck metastases proven by fine needle aspiration biopsy and/or thyroglobulin washout from the suspected lymph node.[2] However, the incidence of occult LLNM has been reported to be as high as 30.4% in PTC patients.[9] Selectively dissection of the group or groups with metastasis is the basic principle to reduce recurrence in the case of LLNM.[10,11]

Currently, the extent of therapeutic lateral neck dissection (tLND) and the necessity of prophylactic unilateral /bilateral central neck dissection (BCND) in patients with LLNM are still debatable.[12-14]

Therefore, determining the risk factors for LLNM has a great importance for the treatment. The aim of this study is to determine risk factors for LLNM in PTC and to provide further evidence for indications of lateral lymph node dissection. We summarized the clinicopathological risk factors affecting the development and characteristics of LLNM to make the most appropriate surgical plan for achieving the best treatment efficacy in PTC.

Methods

Approval for the study was obtained from our Local Ethics Committee (date: December 22, 2020 and no: 3081). The data of 346 PTC patients operated in our clinic between May 2012 and September 2020 were evaluated retrospectively. Patients under 16 years of age, patients with a primary surgery in another institute and those whose follow-up data could not be reached, and patients with thyroid malignancies other than PTC were excluded from the study. The written consent of the patients was obtained.

Patients demographical profile and clinicopathological characteristics such as, age, gender, body mass index (BMI), pre-operative thyroid stimulating hormone levels, anti-TPO, and anti-Tg values at diagnosis, presence of lymph node metastasis and distant metastasis, stage at diagnosis (TNM 8th edition), and ATA risk group at the time of diagnosis, the multifocality an/or multicentricity (bilaterality) of the tumor, largest tumor size, histological subtype, lymphovascular invasion, extrathyroidal invasion, presence of lymphocytic thyroiditis, and surgical margin positivity characteristics were obtained retrospectively. Detection of two or more tumoral foci in both thyroid lobes during the pathological examination was defined as multicentric (bilaterality).[15] Multifocality was defined as the presence of more than one tumor focus in a single lobe.[16] The pathological examination revealed the aggressive subtypes as tall cell, hobnail, solid, and diffuse sclerosing variants. The diameter of the dominant tumor was accepted as tumor size, in multifocal and/or multicentric tumors. Extrathyroidal extension (ETE) was divided into two categories; minor (ETE 1) tumor with perithyroidal extension or extension to strap muscles; and gross (ETE 2) with invasion of strap muscles and/or subcutaneous soft tissue, recurrent laryngeal nerve, esophagus, trachea, larynx, carotid artery or mediastinal vessels.[17]

Patients with pre-operative FNAB results of suspected PTC (Bethesda 5) or PTC (Bethesda 6) were evaluated through pre-operative US for lymph node metastasis by an experienced radiologist. In patients with suspected LLNM on US, FNAB, including cytological examination and thyroglobulin washout, was performed. In patients with a result of suspected PTC after FNAB, the diagnosis was confirmed by performing an intraoperative frozen section examination.

PTC patients with LLNM proven by pre-operative FNAB were applied tLND. Considering the extent of lymph node metastasis, compartmental neck dissection was performed. LND including at least 3, 4 or 2A, 3, 4 compartments was performed. 2B dissection was performed in the presence of diffuse and lateral conglomerated metastatic lymph nodes, metastasis in 2A, and suspected metastasis in 2B. In patients with suspected metastasis in 5B by palpation/or US, 5B was added to the dissection. If there is metastasis in 5A, this region was added to the dissection. BCND was applied to the patients who underwent LND, even if it was prophylactic.

Intraoperative nerve monitoring was used in all patients. All patients underwent vocal cord examination with fiber optic laryngoscopy by an independent otolaryngologist in the pre-operative period and in the first 2 days postoperatively. Follow-up examinations were planned for the pa-

tients with vocal cord paralysis at post-operative 15th day, 1st, 2nd, 4th, and 6th months.

The SPSS (Statistical Packages for the Social Sciences, software, edition 21, SPSS Inc. Chicago, USA) was used for the statistical analysis. Descriptive statistical methods (mean, standard deviation, percentage, minimum, and maximum) were used to evaluate the study data. The "MannWhitney U"-test was used to compare the quantitative variables that did not show normal distribution between the two groups. "The Pearson Chi-square test" and "Fisher's Precision Test" were used to compare the qualitative data. Logistic regression analysis was performed by the 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 $p<0.05$.

Results

The demographical profile of the patients and clinicopathological characteristics of the 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/m^2 (17.9–48). Eighty-five (24.6%) patients underwent lobectomy/hemithyroidectomy, while 261 (75.4%) patients underwent total thyroidectomy. In the present study, prophylactic central neck dissection (pCND) was performed in 29 (8.3%) patients; therapeutic central neck dissection (tCND) was performed in 16 (4.6%) patients; and tLND was performed in 36 (10.4%) patients. Prophylactic lateral neck dissection is not performed in our clinic. Skip metastasis was detected in eight (2.3%) patients.

CLNM was detected in 47 (13.6%) patients while LLNM in 36 (10.4%) patients. The mean tumor size was 1.41±1.50 cm (0, 1–±12), including <1 cm in 195 (56.4%) patients and ≥1 cm in 151 (45.6%) patients. Multicentricity was detected in 132 (38.2%) patients, and multifocality was in 98 (28.3%) patients. Lymphovascular invasion was found in 89 (25.7%) patients and extrathyroidal spread in 68 (29.7%) patients. In addition, an aggressive variant was found in 68 (29.7%) patients lymphocytic thyroiditis in 168 (48.6%) patients, and surgical margin positivity in 10 (2.9%) patients (Table 1).

In PTC patients, the rate of male patients with lateral metastases was higher than those without lateral metastases (38.9% vs. 21.6%; p=0.020). The mean age of patients with and without lateral metastases was similar, and also there was no difference when the patients were categorized as <55 or >55 years of age (p=0.814, p=0.254; respectively) (Table 2).

Table 1. Demographical profile and clinicopathological characteristics of the patients

Features	%	Patient number
Gender		
Male	23.4	81
Female	76.6	265
Age (year)		
Mean±SD	47.31±13.92	
Min-Max	16–85	
<55	72	249
≥55	28	97
BMI (kg/m2)		
Mean±SD	27.23±5.11	346
Min-Max	17.9–48	
Tumor size (cm)		
Mean±SD	1.41±1.50	346
Min-Max	0.1–12	
<1	56.4	195
≥1	45.6	151
Extrathyroidal extension		
Positive	29.7	68
Negative	70.9	272
Lymphocytic thyroiditis		
Positive	48.6	168
Negative	51.4	196
Surgical margin positivity		
Positive	2.9	10
Negative	97.1	336
Lymphovascular ınvasion		
Positive	25.7	89
Negative	74.3	257
Multicentricity		
Positive	38.2	132
Negative	61.8	214
Multifocality		
Positive	28.3	98
Negative	71.7	248
Aggressive histological subtype		
Positive	10.7	37
Negative	89.3	309
Central lymph node metastases		
Positive	13.6	47
Negative	86.4	299
Lateral lymph node metastases		
Positive	10.4	36
Negative	89.6	310

SD: Standard deviation; Min: Minimum; Max: Maximum; cm: Centimeter; kg: Kilogram; m^2: Square meter; BMI: Body mass index.

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

Features	Lateral lymph node metastases (+) (%)	Lateral lymph node metastases (–) (%)	p
Gender (n, %)			
Male	14 (38.9)	67 (21.6)	0.020
Female	22 (61.1)	243 (78.4)	
Age (year) (Mean±SD) (Min-Max)	47.03±18.47 (19–81)	47.35±13.33 (16–85)	0.814
≥55 age (n+%)	13 (36.1)	84 (27.1)	0.254
<55 age (n+%)	23 (63.9)	226 (72.9)	
BMI (kg/m^2) (mean±SD) (min-max)	25.89±4.42 (18.90–36.90)	27.39±5.16 (17.90–48.00)	0.150
TSH (uIU/Ml) (mean±SD) (min-max)	2.68±4.06 (0.01–24.6)	2.17±2.78 (0.01–28.04)	0.360
Anti-TPO (IU/mL) (mean±SD) (min-max)	34.88±106.62 (0.10–561)	58.45±136.22 (0.10–1083)	0.151
(n+%)	3 (9.1)	62 (23.6)	0.061
Anti-TG (IU/mL) (mean±SD) (min-max)	175.43±708.80 (0.90–4000)	95.04±374.43 (0.90–4000)	0.833
(n+%)	6 (17.6)	49 (18.4)	0.913
Tumor Size (cm) (mean±SD) (min-max)	2.30±1.99 (0.6–8.5)	1.31±1.40 (0.1–12)	0.000
ETE (n+%)			
ETE 0 (none)	18 (54.5)	260 (83.1)	0.000
ETE 1 (minor)	11 (30.6)	43 (13.9)	
ETE 2 (major)	7 (14.9)	7 (3)	
Lymphocytic thyroiditis (n+%)	13 (36.1)	155 (50)	0.115
Surgical margin positivity (n+%)	2 (5.6)	8 (2.6)	0.313
Lymphovascular ınvasion (n+%)	25 (69.4)	64 (20.6)	0.000
Multicentricity (n+%)	25 (69.4)	107 (34.5)	0.000
Multifocality (n+%)	20 (55.6)	78 (25.2)	0.000
Aggressive histological subtype (n+%)	8 (22.2)	29 (9.4)	0.018
Central lymph node metastases (n+%)	27 (75)	20 (6.5)	0.000
Extranodal extension in lymph nodes (n+%)	2 (5.7)	5 (15.6)	0.185
≥3 cm lymph node (n+%)	9 (48.5)	0	0.002
ATA risk stratification (n+%)			
Low	5 (13.9)	271 (87.4)	0.000
Intermediate	21 (58.3)	39 (12.6)	
High	10 (27.8)	0	
Stage (TNM) (n+%)			
Stage 1	29 (80.6)	291 (93.9)	0.001
Stage 2	6 (16.7)	19 (6.1)	
Stage 3	0	0	
Stage 4	1 (2.8)	0	
T Stage (n+%)			
T1	16 (44.4)	230 (74.2)	0.001
T2	5 (13.9)	27 (8.7)	
T3	14 (38.9)	52 (16.8)	
T4	1 (2.8)	2 (0.3)	
M stage (n+%)	1 (2.1)	0	0.003

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; BMI: Body mass index.

Table 3. Factors affecting the development of lateral metastasis according to logistic regression

	Odds ratio (95%CI lower-upper)	p
T stage		0.194
T1	1 (Reference)	
T2	2.5 (1.189–500)	
T3	34.483 (1.307–1000)	
T4	28.57 (1.212–1000)	
Lymphovascular invasion		0.102
Negative	1 (Reference)	
Positive	2,577 (0.829–8.000)	
Multicentricity		0.863
Negative	1 (Reference)	
Positive	1.129 (0.286–4.451)	
Multifocality		0.448
Negative	1 (Reference)	
Positive	1.186 (0.455–2.817)	
Aggressive histological subtype		0.710
Negative	1 (Reference)	
Positive	1.274 (0.355–4.569)	
Central lymph node metastases		0.000
Negative	1 (Reference)	
Positive	3.333 (1.149–100)	

T: Tumor.

Tumor size (2.30±1.99 cm vs. 1.31±1.40; p=0.000), lymphovascular invasion rate (69.4% vs. 20.6%; p=0.000), multicentricity rate (69.4% vs. 35.5%, p=0.000), multifocality (55.6% vs. 25.2%; p=0.000), aggressive variant rate (22.2% vs. 9.4%); p=0.000) was significantly higher in the LLNM positive group. While the absence of ETE rate is lower in patients with LLNM (54.5% vs. 83.1%), the rates of patients with ETE 1 (30.6% vs. 13.9%), and ETE 2 (16.7% vs. 1.9%) were significantly higher (p=0.000) in the LLNM positive group. T stage was significantly different between patients with and without LLNM (p=0.001). T1 tumor rate is lower in patients with LLNM (44.4% vs. 74.2%), while T2 (13.9% vs. 8.7%), T3 (38.9% vs. 16.8%), and T4 (2.8% vs. 0.3%) tumor rates were significantly higher (p=0.001) in the LLNM positive group. Distant metastasis was detected in 1 patient (2.1%) at the time of diagnosis in the LLNM-positive group, and the difference was significant (p=0.003). TNM stage was also different between the groups with and without lateral metastases (p=0.001). Stage 2 tumor rate was higher (16.7% vs. 6.1%), while stage 1 tumor rate was lower in the group with LLNM (80.6% vs. 93.9%). The rate of CLNM was also higher in patients with LLNM (75% vs. 6.5%; p=0.000). In the group with LLNM, according to the ATA risk stratification; the rate of low-risk patients was found lower (80.6% vs. 93.9%), while the rates of medium-risk (16.7% vs. 6.1%), and high-risk (27.8% vs. 0%) patients were found significantly higher (p=0.000). In patients with LLNM, ≥3 cm lymph node metastasis was found significantly higher than in patients without LLNM (48.5% vs. 0%; p=0.000) (Table 2).

A formula including T stage, lymphovascular invasion, multicentricity, multifocality, aggressive histological subtype, and presence of CLNM, which are among the anatomical factors that are significant in the pairwise comparison regarding the development of lateral metastasis, was formed and evaluated with logistic regression analysis. As a result, only the presence of CLNM was determined as an independent risk factor for the development of LLNM (p=0.000). The presence of CLNM increases the risk of developing LLNM approximately 3.3 times (Table 3).

Discussion

Thyroid gland cancer is the most common endocrine system malignancy with an increasing incidence, especially in recent years.[18] The most common subtype among thyroid cancers is PTC, and the increased incidence is associated with PTC.[18] PTC, with a 10-year survival rate of over 90%, usually metastasizes through the lymphatics and cervical lymph node metastases are frequently involved.[19,20] The extension pattern of lymph node metastases in PTC is from the central to the lateral compartments, except for skip metastasis.[21] PTC has high morbidity and low mortality. LLNM is frequently associated with local recurrence in PTC patients.[22]

In the present study, the rate of clinical lateral metastasis in patients was 10%, and in the literature, the prevalence of LLNM in patients with PTC ranged from 6.5% to 27.5%.[5,6] In the literature, the male sex ratio is reported to be higher in patients with LLNM.[6] In a comprehensive meta-analysis, including 18741 patients of 23 studies, by So et al., [23] male gender is found to be an effective factor in the development of LLNM. In this study, LLNM developed in 17.3% of male patients and 8.3% of female patients. Although it was detected approximately 2 times higher in males, the difference was not statistically significant. This statistical result may be related to the number of cases in the present study.

In the present study, tumor diameter, multifocality, multicentricity, lymphovascular invasion, aggressive tumor subtype, CLNM, presence of ≥3 cm lymph nodes, and ETE were determined to have a significant effect on the development of lateral metastasis in patients with PTC, in a pairwise comparison. Among these anatomical factors, a formula including T stage, lymphovascular invasion, multicentricity, multifocality, aggressive histological subtype,

and presence of CLNM was created and these risk factors were evaluated with logistic regression analysis. Considering the number of patients with LLNM, the T stage was only put into the formula since it included both the features of tumor diameter and ETE. According to this evaluation, only the presence of CLNM was determined as an independent risk factor for the development of LLNM. The presence of CLNM increases the risk of developing LLNM approximately 3.3 times (OR: 3.333 (1.149–100; p=0.000).

The effect of tumor size in the development of LLNM is a long-known factor, as in the development of CLNM. In the literature, there is a common opinion that the increase in tumor size is a significant risk factor for the development of LLNM.[24,25] In the study of Ito et al., [26] a tumor size of >4 cm was detected to be a significant risk factor for the development of LLNM. In another study, including 1587 patients with papillary microcarcinoma by Zheng et al., [27] a tumor in size of >0.6 cm was detected to be significant for LLNM development. In the study of Wang et al., [22] it was stated that the incidence of LLNM increased above the tumor size of 1–2 cm.

In our study, as in the development of CLNM, tumor size was calculated according to this tumor in patients with a single focus and according to the dominant tumor size in patients with more than one tumor focus. Consistent with the literature, the mean tumor diameter was found to be higher in patients with LLNM (2.30±1.99 vs. 1.31±1.40 cm, p=0.000). Although tumor diameter was greater in patients with LLNM, the T stage was not detected as an independent risk factor.

In addition, in the present study, multifocality, multicentricity, and ETE were found to have significant effects on the development of LLNM by pairwise comparison (p=0.000, p=0.000, and p=0.000, respectively). In the studies of Feng et al. [28] published in 2019, it was revealed that there is a significant relationship between ETE and LLNM. In the other study, by Zhang et al., [29] evaluating LLNM in 1066 patients with papillary microcarcinoma, it was found that multifocality, ETE, bilaterality, and CLNM had significant effects on the development of LLNM. On the other hand, there are a few studies in the literature reporting that bilaterality does not significantly effect the development of LLNM, although it is rare.[30] According to our data, although multifocality, multicentricity, and ETE were found to be significant factors in pairwise comparison for the development of LLNM, none of them were detected as independent risk factors in logistic regression analysis.

Lymphovascular invasion is considered another risk factor for the development of LLNM.[5] In the study of Lombardi et al., [31] the number of skip lateral metastases without metastases in the central compartments was reported to be significantly higher in patients with lymphovascular invasion. In another meta-analysis including 23 studies and 18741 patients evaluating LLNM in PTC; lymphovascular invasion was determined as a significant risk factor for the development of LLNM.[21] In our study, although lymphovascular invasion was significantly higher in patients with LLNM than patients without lateral metastasis (69.4% vs. 20.6%, respectively; p=0.000), it was not determined as an independent risk factor in the logistic regression analysis.

The presence of aggressive histological subtypes is considered one of the important risk factors in the development of LLNM as well as in the development of CLNM. In the study of Lombardi et al., [31] examining patients with tLND, it is stated that the presence of aggressive variants was significantly higher in patients with LLNM. In the literature, the number of studies evaluating the effects of PTC subtypes on the development of LLNM is not as much as the number of studies evaluating the effects of PTC on the development of CLNM. In the present study, despite the rate significantly higher rate of aggressive variants in the LLNM positive group (22.2% vs. 9.4%, respectively; p=0.018), it was not determined as an independent risk factor in logistic regression analysis. The effect of aggressive subtypes of PTC on the development of LLNM might be revealed more clearly with larger studies.

The diameter of the metastatic lymph node ≥3 cm is considered in the high-risk group of ATA risk classification. Our study found a significant relationship between the metastatic lymph node of ≥3 cm in size and LLNM was found as a different factor from the ATA risk classification (p=0.002).[2] In our study, the rate of ≥3 cm lymph node metastasis was significantly higher in patients with LLNM than in patients without metastasis (48.5% vs. 0; p=0.002). Thus, the presence of ≥3 cm metastatic lymph nodes may increase the development of LLNM. In our study, the rate of CLNM in patients with LLNM was significantly higher than in patients without LLNM (75% vs. 6.4%; p=0.000), and it was the only independent risk factor determined in logistic regression analysis. The presence of CLNM increases the risk of developing LLNM approximately 3.3 times (OR: 3.33; p=0.000). CLNM was suggested as an important risk factor for the development of LLNM, according to our results. Considering the anatomical extension pattern of PTC, it can be said that this is the expected result. There have been many studies on this subject in the literature and it has been revealed that the development of LLNM is significantly higher in the presence of CLNM.[23,32-35]

The limitations of our study are that it is a retrospective study with a limited number of cases. However, we think that the inclusion of only the cases with primary surgery and forming a homogeneous group is an important advantage in terms of the results of the study.

Conclusion

The presence of CLNM in patients with PTC was determined as an independent risk factor for the development of LLNM. Although there is an ongoing debate about performing pCND in LLNM, pCND should still be considered in these patients as the rate of CLNM is high in patients with LLNM. Although clinical LLNM is not common, if CLNM is detected preoperatively, the surgeon should comprehensively evaluate the patient for LLNM.

CLNM can guide surgeons to determine the extent of surgery. In addition, the presence of CLNM is important for close follow-up for the early detection of LLNM recurrence in patients with PTC who had total thyroidectomy and central neck dissection and have not been detected to have clinically LLNM at the beginning.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Sisli Hamidiye Etfal Training and Research Hospital (No: 3081, dated 22.12.2020).

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Conflict of Interest: None declared.

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