

An Evaluation of Clinicopathological Factors Effective in the Development of Central and Lateral Lymph Node Metastasis in Papillary Thyroid Cancer

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Abstract: Introduction and Aim: Papillary thyroid cancer (PTC) constitutes more than 90% of newly emerging differentiated thyroid cancers. Lymph node metastasis is often seen in PTC. There is a high risk of central metastasis in the presence of clinicopathological factors such as extrathyroidal extension, multifocality and lymphovascular invasion. The aim of this study is to evaluate the clinicopathological features that are effective in the development of lymph node metastasis.

Material and Method: A retrospective examination was made of the records of patients diagnosed with papillary thyroid cancer and followed up in our clinic. Patients with and without lymph node metastasis were compared in respect of demographic features such as age, gender, pathology, histopathology, tumor size, lymph node metastasis, lymphovascular invasion, multifocality, capsule invasion, extrathyroidal extension and bilaterality.

Results: Lymph node metastasis was determined in 52 of 419 papillary thyroid cancers. In the logistic regression analysis, a statistically significant relationship was determined between cervical lymph node metastasis and age <45 years ($p < 0.001$, OR:4.193), lymphovascular invasion ($p < 0.001$, OR:7.762), capsule invasion ($p < 0.002$, OR:3.054), extrathyroidal extension ($p < 0.001$, OR:6.450) and bilaterality ($p < 0.001$, OR: 0.217).

Conclusion: The risk of cervical lymph node metastasis was determined to be high in the presence of clinicopathological factors such as extrathyroidal extension, multifocality and lymphovascular invasion. Although lymph node metastasis does not clinically develop in all patients, knowing the risk factors related to lymph node metastasis can contribute to the evaluation of prophylactic central neck dissection in high-risk patients and follow-up of the patient in respect of recurrence.

Keywords: Papillary thyroid carcinoma ■ Lymph node metastasis ■ Extrathyroidal extension ■ Multifocality ■ Lymphovascular invasion

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INTRODUCTION

Thyroid cancers constitute approximately 1% of all tumors and a third of all head and neck tumors.¹ Papillary thyroid cancer (PTC) is the most frequently seen histological type and constitutes 80%-85% of all thyroid malignancies.²⁻³ PTC is encountered incidentally in the examination of specimens of thyroidectomy applied for primary or other reasons.⁴ Lymph node

metastasis is often seen in PTC and while macroscopic lymph node metastasis is determined in approximately 35% of adult patients, this rate increases to 80% microscopically.⁵⁻⁶ Lymph node metastasis in PTC is generally seen in a sequential pattern.⁷ Lymph node metastasis shows extension first to the central area then to the ipsilateral lateral cervical lymph nodes and this is followed by extension to the contralateral lateral lymph nodes.² As the thyroid gland shows variations in intensity of lymphatic drainage, the extension pattern may not always be in this sequence and sometimes there can be lateral metastases without central metastasis.⁸ However, the most frequently seen metastasis is in the lymph nodes of the central area because of this sequential pattern.^{9,10}

The effect of lymph node metastasis on mortality is controversial. Although some studies have reported that lymph node metastasis has no effect on prognosis,¹¹ more recent studies have shown that lymph node metastasis is related to mortality, especially in patients aged over 45 years.¹² Rather than mortality, lymph node metastasis has also been reported as a risk factor for local recurrence and distant metastasis.¹³ After the first treatment for PTC, distant disease specific survival can be obtained. It has been seen that 20%-30% of recurrences occur in a few decades associated with the first treatment and tumor stage and two thirds of these are in the first decade after treatment.¹⁴ In a study in Ohio, USA, with a median 16,6 year follow-up, the total recurrence rate was 23,5%, of which 17,8% was local recurrence and lymph node recurrence constituted 74% of this.⁵ Therefore, lymph node metastasis is an important factor in the follow-up of patients in respect of the development of recurrence.

Although therapeutic central area neck dissection is an accepted procedure for patients with central lymph node metastasis which has been diagnosed with preoperative physical examination, imaging methods and intraoperative findings, the subject of extension continues to be controversial.¹⁰ When prophylactic lymph node dissection has been applied even in PTC with no clinical lymphatic metastasis, occult central lymph node metastasis has often

Table 1. Demographic characteristics of the patients.

Risk Factors	n	%
Gender		
Male	57	13.6
Female	362	86.4
Age (years)		
< 45	133	31.7
> 45	286	68.3
Histopathology		
Follicular variant	195	46.5
Classic variant	214	51.1
Oncocytic variant	10	2.4
T stage		
T1a	232	55.4
T1b	122	29.1
T2	55	13.1
T3	10	2.4
Lymphovascular invasion		
Present	24	5.7
Absent	395	94.3
Capsular invasion		
Present	104	24.8
Absent	315	75.2
Multifocality		
Present	151	36
Absent	268	64
Extrathyroidal extension		
Present	32	7.6
Absent	387	92.4
Lymph node metastasis		
Present	52	12.4
Absent	367	87.6
Bilaterality		
Present	84	20
Absent	335	80
Hashimoto Thyroiditis		
Present	101	24.1
Absent	318	75.9

been found.¹⁵ In the presence of clinicopathological factors such as extrathyroidal extension, multifocality and lymphovascular invasion, the risk of central metastasis is high.¹⁶ In clinically metastasis negative PTC cases, as there is no clear evidence related to the contribution to survival,

whether prophylactic central lymph node dissection should be applied or not and the width of the applied dissection are still controversial issues. While some schools of thought recommend prophylactic neck dissection of all cancers, some advocate prophylactic dissection in conditions negatively affecting the prognosis. These factors are T3 and T4 stage tumors according to the TNM classification, tumors with extra-capsular extension, tumors with lymphovascular invasion, multifocal tumors, those with aggressive histology, male patients, aged <15 years or >45 years, BRAF v600 mutation positive tumors, tumors involving the delphian node and tumors involving the lateral lymph node.¹⁷

Lymph node metastasis does not develop clinically in all patients and the knowledge of factors related to lymph node metastasis development may contribute to the evaluation of prophylactic central neck dissection in high-risk patients and the follow-up of patients in respect of recurrence. The aim of this study was to evaluate the clinicopathological features that have an effect on the development of lymph node metastasis.

MATERIAL AND METHOD

A retrospective evaluation was made of the data of patients diagnosed with papillary thyroid cancer in the Endocrinology Department of Eskişehir Osmangazi University Hospital between 1995 and 2016. Thyroidectomy had been performed together with central and when necessary, therapeutic lateral neck dissection. A total of 419 patients were included who had undergone a thyroid operation for a diagnosis of PTC. Patients were excluded if they had malignancies other than papillary thyroid cancer of the thyroid gland or if there was a history of other cancers. Age was evaluated as younger or older than 45 years. Tumor size was evaluated according to the T stage in the TNM system. In the tumor classification, T1a < 1 cm; T1b > 1 cm-≤2 cm; T2 >2 cm- ≤4 cm; T3 >4 cm. In the evaluation of extrathyroidal extension, if there was minimal extrathyroidal extension in tumors <4 cm, it was evaluated at the stage of the T stage of the tumor size. As there were no patients with tumors invasive to surrounding organs, T4 stage was not used in the evaluation. Histopathology was differentiated as follicular variant, classic variant and oncocytic variant. Patients were evaluated in respect of preoperative use of medication, euthyroid and thyroid autoantibody positivity. Those with the feature of multifocality were separated according to single lobe or both lobes (bilaterality). The effects of age, gender, T-stage, extrathyroidal extension, multifocality, lymphovascular invasion, capsular invasion, bilaterality and thyroid antibody were examined on the development of lymph node metastasis.

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