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Original Article / *Özgün Makale*

The effect of clinical and pathological characteristics on central neck metastasis in early stage papillary thyroid carcinomas

Erken evre papiller tiroid karsinomalarında klinik ve patolojik özelliklerin santral boyun metastazı üzerine etkisi

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ABSTRACT

Objectives: This study aims to investigate the relationship between clinical and pathological characteristics and central neck metastasis in early stage papillary thyroid carcinoma (PTC).

Patients and Methods: The retrospective study included 50 patients (11 males, 39 females; mean age 42.9 years; range, 12 to 77 years). Patients were divided into two groups according to pathology results as metastasis positive (n=24) and metastasis negative (n=26). Clinical and pathological characteristics of both groups were compared statistically. BRAF mutation was studied in patients' deparaffinized tissues.

Results: There was no difference between both groups in terms of gender, mean age, risky age, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, mean platelet volume, mean tumor size, formation of capsule, or lymphocytic thyroiditis. There were significant differences in terms of histological subtype, multicentricity and capsular invasion. BRAF mutation was studied with polymerase chain reaction and appropriate band could be obtained in only 19 patients. BRAF mutation was positive in 11 of these. Nine of the 11 patients were in metastasis positive group. BRAF mutation was statistically more in metastasis positive group.

Conclusion: If a PTC is larger than 20 mm, non-classical variant, multicentric, and has BRAF mutation, it has higher risk for central metastasis. Close follow-up of patients with such characteristics is advised if they were not performed neck dissection. Further studies with larger sample sizes are needed in this area.

Keywords: BRAF mutation, lymphocyte, platelet, thyroid cancer.

ÖZ

Amaç: Bu çalışmada erken evre papiller tiroid karsinomunda (PTK) klinik ve patolojik özellikler ile santral boyun metastazı arasındaki ilişki araştırıldı.

Hastalar ve Yöntemler: Retrospektif çalışmaya 50 hasta (11 erkek, 39 kadın; ort. yaş 42.9 yıl; dağılım, 12-77 yıl) dahil edildi. Hastalar patoloji sonuçlarına göre metastaz pozitif (n=24) ve metastaz negatif (n=26) olarak iki gruba ayrıldı. İki grubun klinik ve patolojik özellikleri istatistiksel açıdan karşılaştırıldı. Hastaların deparafinize dokularında BRAF mutasyonu araştırıldı.

Bulgular: İki grup arasında cinsiyet, ortalama yaş, riskli yaş, nötrofil/lenfosit oranı, trombosit/lenfosit oranı, ortalama trombosit hacmi, ortalama tümör boyutu, kapsül oluşumu ve lenfositik tiroidit açısından farklılık yoktu. Histolojik alt tip, multisentrik olma ve kapsüler invazyon açısından anlamlı farklılıklar vardı. BRAF mutasyonu polimeraz zincir reaksiyonu ile çalışıldı ve yalnız 19 hastada uygun bant elde edildi. Bunların 11'inde BRAF mutasyonu pozitifti. On bir hastanın dokuzu metastaz pozitif gruptaydı. BRAF mutasyonu metastaz pozitif grupta istatistiksel olarak daha fazlaydı.

Sonuç: Eğer bir PTK 20 mm'den büyük ise, klasik dışı varyant ise, multisentrik ise ve BRAF mutasyonuna sahip ise santral metastaz açısından daha yüksek riski vardır. Bu özelliklere sahip hastaların boyun diseksiyonu yapılmamışsa yakından takip edilmesi önerilir. Bu alanda daha büyük örneklemler ile ileri çalışmalar gereklidir.

Anahtar sözcükler: BRAF mutasyonu, lenfosit, trombosit, tiroid kanseri.

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Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy and its frequency has increased. Patients have long survival rates and this feature makes it different from other malignancies. However, one of the most common problems in poor prognosis is neck recurrency, which develops from untreated occult metastatic lymph nodes, particularly in the central neck area.[1] Central neck dissection (CND) is already performed in metastasis-proven patients. Also, the American Thyroid Association (ATA) recommends prophylactic CND in late-stage patients (larger than 4 cm). Prophylactic CND, however, is controversial in early-stage patients[2] because of the presence of important anatomic structures. Thus, operations have the injury risk of recurrent nerve paralysis and hypoparathyrodism in this area, making the choice of patient particularly important for CND.

Recently, there has been significant research on the relationship between inflammatory response and cancer stage, prognosis and survival. Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are easy to use and generally examined in every patient.[3] In this regard, Kim et al.[4] report that higher NLR is related to poor prognosis in late stage PTC patients. Another study found that higher PLR is significant for lateral neck metastasis in PTC patients.[5]

Mean platelet volume (MPV) is a variable in thrombopoiesis. It increases with new platelets and can be a marker of inflammation. Mean platelet volume was found to be higher in PTC patients than in goiter patients.[6] The BRAF mutation is a point mutation on the seventh chromosome. It encodes the B-Raf protein, which is involved in the mitogen activated protein kinase pathway, cell growth and differentiation. The most common mutation form is $BRAF^{V600E}$. In this mutation, thymine changes to adenine at nucleotide 1799, changing valine to glutamate and altering the B-Raf protein structure. The BRAF mutation is related to poor prognosis in PTC.[7] Papillary thyroid carcinoma has excellent prognosis even in recurrent diseases. Therefore, it introduces debate on the extent of surgery. A balance must be established between effective surgery and potential morbidities brought by surgery.[8] Therefore, in this study, we aimed to investigate the relationship between clinical and pathological characteristics and central neck metastasis in early stage PTC.

PATIENTS AND METHODS

A total of 50 patients (11 males, 39 females; mean age 42.9 years; range, 12 to 77 years) who underwent total thyroidectomy and CND between January 2012 and June 2015 at Erciyes University, Faculty of Medicine were enrolled in this retrospective study. All patients had early stage PTC. Patients who had benign disease, late-stage disease, extra-thyroid extension and malignancy different from PTC were excluded. Their age, gender, laboratory findings and pathological results were recorded retrospectively. Neutrophil/lymphocyte ratio, PLR and MPV values were estimated preoperatively. The patients were divided into two groups according to their lymphadenectomy specimens as metastasis negative and metastasis positive. The study protocol was approved by the Erciyes University, Ethical Committee of Clinical Researchs. The study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients had total thyroidectomy and prophylactic/therapeutic CND, according to their preoperative or intraoperative findings, performed by experienced head and neck surgeons. It was attempted to protect bilateral recurrent nerves by direct vision and to protect all parathyroid glands. Ischemic parathyroid glands were implanted into sternocleidomastoid muscle after frozen section.

For nucleic acid extraction, the pathologist used 5 mm sections of patient specimens from the tumor area. The sections were placed in xylene and 96% ethanol three times for 8 minutes to remove paraffin and left in the air to dry. Tumor cells that were detected by the pathologist were placed in an Eppendorf tube and 180 µL ATL (Animal Tissue Lysis) buffer (Qiagen GmbH, Hilden, Germany) and 20 µl proteinase K were added to remove proteins. QIAamp deoxyribonucleic acid (DNA) FFPE kit (Qiagen, California, USA) was used to obtain DNA. Polymerase chain reaction (PCR) amplification of the exon 15 segment of the BRAF gene was performed. Primers (forward, 5'- TCTCACCTCATCCTAACACAT-3'; reverse, 5'-GTTTGAAATACACTGAAACTGGT-3') were used to amplify a 224 bp fragment of exon 15 of BRAF containing the site in which the T1799A mutation occurs. Polymerase chain reaction were performed in 25 µL of 1.5 mM magnesium chloride, with 200 mM deoxynucleoside triphosphates, 50–100 ng genomic DNA, 0.5 mM of each primer and 2.5 U polymerase (Qiagen PCR purification kit, Qiagen GmbH, Hilden, Germany). Amplification products were separated on 1.2% agarose gel and visualized by ethidium bromide staining. All samples were re-examined for the BRAF mutation at least three times. Electrophoresis was carried out on the AB 3130 Genetic Analyzer device (Hitachi Ltd, Tokyo, Japan) at 15.8 C, 650 V, 30 mA and 15 W for 120 minutes. Sequences were compared with the Sequencing Analysis Software 6 and SeqSpace Software 3 (Thermo Fisher Scientific, Massachusetts,

USA) programs. If there was adenine instead of thymine at nucleotide 1799, this was identified as the $BRAF^{V600E}$ mutation.

Statistical analysis

Data were compared with the IBM SPSS version 21.0 program (IBM, Corp., Armonk, NY, USA). Distributions of normality were evaluated by the Shapiro-Wilks test. Normally distributed values were compared with independent groups t-test and non-normally distributed data were compared by Mann-Whitney U test. Cross-tables were prepared for nominal data and Fisher's exact test was used to compare groups. Receiver operator characteristics (ROC) curve was used to find cut-off values and sensitivity and specificity rates. P<0.05 was accepted as statistically significant.

RESULTS

Fifty patients who met the inclusion criteria were included, 39 of whom were women and 11 men. The minimum and maximum ages were 12 and 77 respectively, the mean age being 42.88. Fifteen patients were aged between 30 and 40 years, eleven of whom were females. Patients were divided into two groups: metastasis negative (n=26) and metastasis positive (n=24). There was no significant difference between the two groups in terms of gender (p>0.05) (Table 1).

The mean age was 45.5±1.3 in the metastasis negative group and 40.4±1.5 in the metastasis positive group, and the age difference was not statistically significant (p>0.05) (Table 1). The number of patients in the high-risk group (under 20 years and over 60 years for PTC) was four and six in the metastasis negative and metastasis positive groups, respectively. There was no significant difference in age for high risk between the two groups (p>0.05) (Table 1). Fifty-five was accepted as the new cut-off for staging of thyroid cancer.[9] Two groups had no statistically significant difference in terms of the new cut-off value (p>0.05) (Table 1). There were no significant differences between mean NLR, PLR and MPV values (p>0.05) (Table 1). In ROC analysis, when NLR was larger than 2.13, it gave 65.4% sensitivity and 58.3% specificity for central metastasis. When PLR was larger than 125.47, it gave 65.4% sensitivity and 50% specificity. When MPV was larger than 9.15, it gave 88.5% sensitivity and 83.3% specificity for central metastasis.

When the groups were compared in terms of tumor size and stage, there was no significant difference in terms of mean size (p>0.05). But there was a significant difference for the number of patients who had T_1 and T_2 stage tumors (p<0.05).

When the groups were evaluated in terms of pathological subtypes, all patients in the metastasis negative group had the classical variant. On the other hand, there were four follicular variants and one Hurthle cell variant in the metastasis positive group. Non-classical variants were more susceptible to central neck metastasis. The difference between them was statistically significant (p<0.05) (Table 2).

Table 1
Comparison of demographic and clinical data of two study groups

	Metastasis negative group		Metastasis positive group		
Variables	n	Mean±SD	n	Mean±SD	*p*
Gender					0.064
Female	23		16		
Male	3		8		
Mean age (year)		45.5±1.33		40.4±1.55	0.186
Risky age (Under 20 years and over 60 years)	4		6		0.31
Patient number					0.848
Under	20		19		
Under/over 55 years	6		5		
Neutrophil/lymphocyte ratio		2.46±0.77		3.48±.77	0.19
Platelet/lymphocyte ratio		147.6±51		160.7±98	0.74
Mean platelet volume		7.98±1.05		8.16±1.04	0.55

SD: Standard deviation.

Table 2
Comparison of pathological features and BRAF mutation of two study groups

	Metastasis negative group		Metastasis positive group		
Variables	n	Mean±SD	n	Mean±SD	*p*
Mean tumor size (mm)		14.12±5.94		19.67±9.95	0.061
Tumor					0.048
T_1	20		12		
T_2	6		12		
Classical/non-classical subtype	26/0		19/5		0.031
Capsular formation	5		3		0.399
Multicentricity	5		12		0.046
Lymphocytic thyroiditis	6		5		0.84
BRAF mutation					0.022
+	2		9		
-	6		2		

SD: Standard deviation.

There were five and three specimens with capsular formation in the metastasis negative and metastasis positive groups, respectively, while there was no statistically significant difference in between (p>0.05) (Table 2).

In terms of lymphatic invasion, there was only one patient and he was in the metastasis positive group. However, the difference was not statistically significant (p>0.05) (Table 2). There was no patient with vascular invasion in either group.

There were five and 12 patients who had multicentric tumors in the metastasis negative and metastasis positive groups, respectively. This difference was statistically significant (p<0.05) (Table 2). Multicentric tumors were more susceptible to central neck metastasis.

There were also some additional pathological features in specimens. There were 11 specimens (22%) with lymphocytic thyroiditis in the study group. Six of them were in the metastasis negative group. There was no statistically significant difference in terms of lymphocytic thyroiditis (p>0.05) (Table 2).

The BRAF mutation was scanned by PCR on the seventh chromosome at nucleotide 1799. Fifty kits were used. DNA amplification was not successful in 31 patients. There were 19 specimens with successful DNA amplification. The BRAF mutation was positive in 11 specimens (11/19) (57%). Nine of them were in the metastasis positive group. Tumors that had the BRAF mutation were more prone to central metastasis (p<0.05). V600E was detected in all BRAF mutations.

DISCUSSION

Papillary thyroid carcinoma is the most common endocrine malignancy and, though it is more common in females, its incidence is becoming higher worldwide, particularly in males.[10] The incidence of PTC increased 2.9 fold from 1988 to 2002 and 88% of these were under 2 cm. The development of new imaging methods has made a large contribution to this increase.[11] There were more females in the study group (78%) and one third of them were between the ages of 30 and 40 years.

Papillary thyroid carcinoma is more common in the premenopausal period. However, it has better prognosis in female patients with non-recurrent disease.[12] When comparing the relationship between central neck metastasis and gender, there was no significant difference in the study group.

Clinical course and prognosis of PTC are closely related to age. Fifty-five years old is accepted new cut-off value for risk groups in PTC.[9] No significant difference was found in terms of mean age and central neck metastasis. When groups were compared in terms of the old cut-off value of 45 years, there was also no significant difference between the high-risk age and central neck metastasis.

Neutrophil/lymphocyte ratio is an easy-to-use and inexpensive test used recently, particularly in oncology and cardiology. It is related to the inflammatory reaction to cancer. Although it is not used as a prognostic factor in PTC, studies evaluating it are increasing.[13] Liu et al.[14] reported that higher NLR is related to tumor size and

recurrence risk in PTC patients. In a study by Seretis et al.,[15] NLR was found to be a variable to predict the difference of goiter and micropapillary carcinoma. Neutrophil/lymphocyte ratio and PLR are related to poor prognosis and their relationship to central neck metastasis was examined in the present study. Although they were higher in the metastasis positive group, this difference was not statistically significant.

Mean platelet volume is also commonly used now as a marker of inflammation. Mean platelet volume was found to be higher in PTC patients than in goiter patients.[16] Mean platelet volume was evaluated as a marker for central neck metastasis in the present study. However, there was no statistically significant difference between the metastasis negative and metastasis positive groups. To our knowledge, this is the first study in the literature evaluating this relationship.

Tumor size is a very important feature for cancer and the first used variable in all classification systems. Studies reported that tumors larger than 20 mm are more susceptible to distant metastasis. A cut-off value 4 cm is accepted for high-risk classification.[17] There was no statistically significant difference between the two groups in terms of mean age in this study. When the two groups were compared in terms of tumor stage, there were more patients in the metastasis positive group and this difference was statistically significant.

Papillary thyroid carcinoma has different pathological subtypes. Some of these are classical: follicular, tall cell, columnar cell, oncocytic, Warthin-like, solid and diffuse sclerosis.[18] Tall cell, columnar cell and diffuse sclerosis variants have poor prognosis.[19] There were many classical variants in the present study group. Five patients with central metastasis had different subtypes. When classical and non-classical variants were compared in terms of metastasis, non-classical subtypes were more susceptible to central metastasis statistically.

Papillary thyroid carcinoma generally grows invasively and rarely forms a capsule. In addition, capsuled tumors have better prognosis.[20] A significant relationship was not detected in the two study groups in terms of central metastasis and capsular formation.

Lymphatic or vascular invasion can be detected in malignant histology. McHugh et al.[21] reported a strong relationship between lymphovascular invasion and recurrence in PTC patients. In both of our study groups, there was no patient with vascular invasion and one patient had lymphatic invasion with central metastasis.

Multicentricity is a well-known feature of PTC ever since Black et al.[22] found that 20% of PTC were multicentric. It is seen in 30% of patients in routine histological sections. When sections are reduced, this rate reaches 85%.[23] In the present study, there were 17 patients with multicentric tumor (34%) and there was a statistically significant difference between multicentricity and central metastasis.

Lymphocytic thyroiditis is an autoimmune disease with lymphocyte infiltration, fibrosis and parenchymal atrophy in the thyroid gland.[24] Chronic inflammation and development of malignancy is a well-known entity.[25] Larson et al.[26] reported that patients who have Hashimoto thyroiditis are three times more at risk than normal in terms of PTC. Lun et al.[27] found that Hashimoto thyroiditis has better prognosis in PTC even though it is a risk factor. There were 11 patients who had lymphocytic thyroiditis in the study group. Although it is a risk factor for PTC, it was not related to central neck metastasis.

The BRAF mutation is the most common mutation in PTC and makes it more resistant to radioactive iodine (RAI) treatment. BRAF mutations has been used as a diagnostic and prognostic factor in PTC.[28] Lee et al.[29] reported, in a meta-analysis in 2007, that the BRAF mutation is related to extra-thyroid extension and late stage disease, but not related to tumor size, gender or race. Although some reports on that issue suggested that BRAF mutations is related to a more aggressive clinical course, other reports found no relationship.[28] Li et al.[28] reported in a 6,372-case meta-analysis that the BRAF mutation is a poor prognostic factor and prophylactic central neck dissection can be offered to patients who are diagnosed with the BRAF mutation preoperatively.

The BRAF mutation was investigated in tumor cells by PCR. There were 19 patients who had successful amplification of the appropriate gene. Eleven of them had the BRAF mutation (57%) and nine were in the metastasis positive group. There was a significant relationship between having the BRAF mutation and metastasis. Because the BRAF mutation was analyzed in old tissues, PCR did not always work properly. The BRAF mutation is therefore best studied in fresh tissues.

Central neck metastasis is usually not determined in preoperative ultrasonography (USG) and intraoperative inspection.[30,31] Papillary thyroid carcinoma patients who have clinically proven metastasis must have neck dissection performed. Occult lymph node metastasis, however, is determined at a rate of 70-90% in non-metastatic patients.[32] This is a very high recurrence rate and if left untreated; it may cause local recurrence and lower survival rate.[33] Pai and Tufano[34] reported that local recurrence is seen in 5-20% of patients who undergo only total thyroidectomy for PTC. When

patients with local recurrence are examined, the central neck compartment is seen as the place of origin of local recurrence in 60-75% of recurrent disease.[35] Leboulleux et al.[36] reported that all local recurrences originated from the central neck and 73% patients had central neck activity in total body scan after RAI ablation. In addition, treatment of local recurrence is more complicated and these patients have a more aggressive clinical course.

A balance must be established between risk of disease and treatment in PTC patients. There is no test at present to diagnose micrometastasis preoperatively. Even studies that used high resolution USG could not obtain definitive results.[37] Prophylactic CND is still controversial in the treatment of early stage PTC and performed according to intraoperative palpation findings.[33] The ATA does not recommend prophylactic CND in early-stage PTC patients and advises that studies on this issue in the future should examine surgical risks and benefits provided to patients.[38]

Today, prognostic factors for PTC are more related to postoperative histological findings. Some preoperative variables, however, must be used to form a high-risk group for prophylactic CND, which is a very controversial issue. This study aimed to find high-risk preoperative variables for central neck metastasis.

The limitations of the present study were its retrospective nature and small sample size. The broader and more positive achievement of the study was to prove the presence or absence of metastasis pathologically. There is not yet any preoperative test or radiological method to identify occult central neck metastasis in PTC patients. The debate about prophylactic CND in early-stage PTC patients is not likely to be completed in the near future.

In conclusion, if the tumor is larger than 20 mm, it presents a higher risk for central neck metastasis. Statistically, the metastasis positive group had higher NLR, PLR and MPV, although these findings were not found to be significant. Therefore, we can recommend prophylactic CND for patients who have higher NLR, PLR and MPV and a tumor larger than 20 mm. Studies are needed in this area in larger patient groups using CND for every patient.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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