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The effect of BRAF^{V600E} mutation on lymph node involvement in papillary thyroid cancer

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ABSTRACT

Objective: Papillary thyroid cancer (PTC) is the most common well-differentiated thyroid cancer. Lymph node (LN) metastasis is frequently seen in PTC. The effect of BRAF^{V600E} mutation on PTC-associated LN metastasis has not been clearly established. Therefore, we aimed to evaluate the effect of the BRAF^{V600E} mutation in patients with PTC on regional LN metastasis.

Material and Methods: Between January 2013 and 2017, sixty-three PTC patients who underwent central lymph node dissection were included into the study. The patients were divided into two groups according to the pathology results of the LN dissection, and these groups were compared for positive BRAF^{V600E} mutations and other clinicopathological findings.

Results: BRAF^{V600E} mutation was found to be more significant in the pLN1 group (p= 0.005). Multivariate analysis revealed that nodule size, microcalcifications, and BRAF^{V600E} mutation were associated with lymph node metastasis independent of other parameters. ROC analysis also evaluated the adequacy of the BRAF^{V600E} mutation in predicting the presence of LN involvement. AUC: 0.738 (95% CI: 0.6110.866, p: 0.002).

Conclusion: In our study, independent of other parameters, BRAF^{V600E} gene mutation was found to be effective on lymph node involvement.

Keywords: BRAF, Lymph node, involvement, papillary thyroid cancer

INTRODUCTION

Well-differentiated thyroid cancers are the most common endocrine malignancies and are among the world's most common cancers (1). Papillary thyroid cancer (PTC), the most common well-differentiated thyroid cancer, constitutes 80% of all endocrine malignancies (2). Lymph node metastasis, which is directly associated with increased local recurrence (3), is frequently seen in PTC, and its incidence varies between 20% and 90% (4). However, there are opposing views regarding the effect of lymph node metastasis on survival in well-differentiated thyroid cancers. Some previous studies have shown that regional lymph node metastasis has no effect on survival in PTC (5). Other studies, with a sufficiently long follow-up period, for example, 30-year survival in patients with cervical metastases, have shown survival rates to be significantly lower compared to those for patients without cervical metastasis (6).

BRAF^{V600E} is a major oncogenic mutation that promotes PTC development by activating the MAP kinase pathway (7). BRAF^{V600E} mutation, which is an activating mutation of the B isoform of the Raf kinase gene in exon 15, is the most common mutation in PTC, leading to the conversion of valine to glutamic acid at position 600 (8). RAF proteins are serine/threonine protein kinases and play an important role in cell proliferation, differentiation, and programmed cell death (9). RAF proteins act on cell proliferation and differentiation via this pathway by activating the mitogen-activated protein kinase (MAPK) pathway (10). Many studies have demonstrated the association of BRAF^{V600E} mutation with aggressive clinicopathological features of PTC (11). However, the effect of this mutation on PTC-associated lymph node metastasis has not been clearly established. In this study, we aimed to evaluate the effect of BRAF^{V600E} mutation in patients with PTC on regional lymph node metastasis known to be associated with poor prognosis in PTC.

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MATERIAL and METHODS

Between January 2013 and January 2017, patients whose postoperative pathology specimens indicated PTC at our General Surgery Clinic and who underwent therapeutic or prophylactic central lymph node dissection (CLND) were included into the study. Permission for the study was obtained from Ankara Numune Training and Research Hospital Ethics Committee. The study followed the guidelines and principles of the Declaration of Helsinki. All patients signed informed consents for the use of their clinical data and for genetic analysis.

Our study was organized with the support of medical pathology and medical genetics departments based on surgical approaches. A retrospective examination of the patients showed that total thyroidectomy (TT) was performed for patients whose fine-needle aspiration cytology (FNAC) preoperative results indicated that their specimens fell into one of the following categories: "PTC", "atypia of undetermined significance", "follicular lesion of undetermined significance (FLUS)" or "non-diagnostic" (two times). Fine needle aspiration cytology was performed for patients with lateral pathologic lymph nodes revealed by an ultrasound of the neck. Patients with lymph node metastasis indicated by FNAC and thyroglobulin measurements in the washout of the needle (FNAB-Tg) underwent therapeutic lymph node dissection. Therapeutic CLND was performed on patients with palpable lymph nodes found during TT. Based on the risk factors and tumor characteristics, prophylactic CLND was performed on patients suspected of having a malignancy although pathological lymph nodes were not detected in neck ultrasonography (US). The patients were divided into two groups according to the pathology results of the lymph node dissection, the pLN0 group (patients with no lymph node involvement) and the pLN1 group (patients with one or more lymph node involved). These groups were compared for positive BRAF^{V600E} mutations.

Patients who had their first operation at another center and underwent complementary thyroidectomy and regional lymph node dissection at our clinic and patients who underwent regional lymph node dissection at our clinic after TT at another center were excluded from the study. Patients whose clinical information could not be obtained and patients whose pathology specimens could not be acquired were also excluded from the study. Gaps in information were addressed by contacting the patients by telephone.

One hundred and twenty-three patients were operated on with the diagnosis of PTC and performed right, left or bilateral modified radical neck dissection in addition to TT and prophylactic or therapeutic CLND. A total of 19 patients were excluded since pathology specimens of eight patients could not be reached and clinicopathological data of the remaining eleven patients could not be reached either from them or hospital information management system. The remaining 104 patients were subjected to further processing. From the paraffin blocks of the thyroidectomy material of 104 patients, tumoral tissue sections were obtained. DNA isolation was performed in 104 tissues, and the purity/concentration ratios of 75 patients were seen in the appropriate range. DNA isolation materials of 75 patients were subjected to further treatment. Ten out of the 75 patients were excluded from the study until the sequence analysis due to improper banding on gel electrophoresis and primary duplication and DNA fractures during ExoSAP-cycle step. Two patients were excluded from the study during sequence analysis since one had "forward repeat", and the other had a "reverse repeat". Ultimately, sixty-three patients were included into the study. Hospital records indicating age, sex, thyroid and neck US results (number of nodules, nodule size, echogenicity status, cystic or solid state of the nodule, the presence of microcalcifications, increase in nodal blood flow, border irregularity in nodules), FNAC results regarding malignancy (the presence of nuclear elongation, discohesive cells, nuclear notching, irregular nucleus, cytoplasmic clarification, inclusion body, oncocytoid morphology, histiocytic giant cells), postoperative pathology specimen results (tumor size, multicentricity status, the presence of capsule invasion or neurovascular invasion), the number of metastatic and total lymph nodes removed during neck dissection, and the results of BRAF^{V600E} mutation data analysis were obtained and evaluated.

Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS), version 20 (SPSS, Inc., IBM, Armonk, NY, USA). Continuous variables were evaluated for normality using the Kolmogorov–Smirnov test. Normally distributed variables expressed as mean ± standard deviation were compared using the Student's t test. Non-parametric variables expressed as median (interquartile range) were compared using the Mann–Whitney U test. Nominal variables were compared using the Pearson's chi-squared test or Fisher's exact test. Univariant and multivariant analyses were conducted to determine if any of the variables were associated with lymph node involvement. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic ability of BRAF in determining lymph node involvement. $P < 0.05$ was determined as being significant.

RESULTS

Mean age of the 63 patients was 42.9 ± 13.3 years. Of these, 45 were females (71.4%) and 18 were males (28.6%). TT and CLND were performed on 38 patients (60.3%), 29 (46%) for prophylactic purposes and 9 (14.3%) for therapeutic purposes. TT, CLND, and modified radical neck dissection (MRND) were performed on 25 (39.6%) patients (Table 1). Based on the postoperative pathology specimens, fifty of the 63 patients had classic PTC (79.4%), 12 had follicular variant (FV) of PTC (19.1%), and 1 had the tall cell variant

Table 1. Numerical distribution of operations according to FNAB results

	TT + CLND		TT + MRND
	Prophylactic	Therapeutic	
Non-diagnostic	4	1	6
AUS	3	6	3
FLUS	-	-	1
Malignancy Suspicion	3	2	5
PTC	19	0	10

N: Number, PTC: Papillary thyroid cancer, AUS: Atypia of undetermined significance, FLUS: Follicular lesion of undetermined significance, TT: Total thyroidectomy, CLND: Central lymph node dissection, MRND: Modified radical neck dissection.

Table 2. Lymph node metastasis according to post-operative pathology results

	pLN0	pLN1
Classic type PTC	23 (46%)	27 (54%)
FV-PTC	6 (50%)	6 (50%)
TCV-PTC	-	1

LN: Lymph node, PTC: Papillary thyroid cancer, FV-PTC: Follicular Variant Papillary thyroid cancer, TCV-PTC: Tall Cell Variant Papillary thyroid cancer, pLN0: patients without lymph node involvement, pLN1: Patients with lymph node involvement.

(TCV) of PTC (1.5%) (Table 2). $BRAF^{V600E}$ mutation was detected in 21 (33.3%).

Lymph node metastasis was found in 34 patients (53.9%), based on post-operative pathology results. In classic type PTC, 23 of 50 the patients, in FV-PTC, 6 of the 12 patients and 1 TCV-PTC patient had lymph node involvement.

Mean age of the pLN0 group was 43.9 ± 12.9 years, and mean age of the pLN1 group was 42 ± 13.8 years, and there was no significant difference between the two groups (p= 0.583). Lymph node involvement was higher in males than in females (p= 0.005) (Table 3).

When preoperative US parameters were compared between the groups, only the nodule size (p = 0.004) and the presence of microcalcifications (p= 0.009) were found to be more significant in the pLN1 group (Table 3).

The results of fine needle aspiration cytology showed no significant difference between the two groups (p> 0.05 for both) (Table 3).

When the $BRAF^{V600E}$ result was compared between the groups, BRAF mutation was found to be more significant in the pLN1 group (p= 0.005) (Table 3).

Multivariate analysis revealed that nodule size, the presence of microcalcifications, and the presence of the $BRAF^{V600E}$ mutation were associated with lymph node metastasis independent of other parameters, which were significantly higher in the pLN1 group according to the univariate analyses (Table 4).

$BRAF^{V600E}$ mutation was detected in 3 (10.3%) of the 29 patients in the pLN0 group, while gene mutation positivity was found in 18 (52.9%) of the 34 patients in the pLN1 group (p< 0.001). ROC analysis to assess the adequacy of $BRAF^{V600E}$ mutation in predicting the presence of pathologic lymph node involvement was calculated as AUC: 0.738 (95% CI: 0.611-0.866, p: 0.002) (Figure 1).

DISCUSSION

In this study, the effect of $BRAF^{V600E}$ mutation on lymph node metastasis in PTC was evaluated, and lymph node mutation was found to be significantly higher in individuals with the gene mutation. $BRAF^{V600E}$ mutation was detected in 31.7% of our patients. In addition to being the most common mutation in PTC, the incidence of $BRAF^{V600E}$ has also increased (12,13). According to the literature, the frequency of $BRAF^{V600E}$ mutation in patients with PTC ranges from 18%-87% (14,15). In a study by Kurtulmuş et al. (16), $BRAF^{V600E}$ mutation rate has been found to be 36.4%, and the rate in our study was similar. The frequency of lymph node metastasis in PTC also ranges widely from 30%-90%) (17-19). In our study, lymph node metastasis was observed in 34 patients (53.9%) according to postoperative pathology results, which is consistent with the literature.

Although preoperative ultrasonographic evaluation is routine in the management of thyroid diseases and is a valuable examination on PTC, its adequacy in predicting lymph node involvement is limited, and there are opposing views in the literature. According to Schlumberger et al. (20), US is the most sensitive test to detect metastatic lymph nodes. However, Kim et al. (21) have found that the sensitivity of US during the preoperative period is lower when not combined with other imaging methods. In evaluating the relation between preoperative US findings and lymph node involvement in our patient group, the presence of microcalcification in the thyroid nodule and increased nodule size indicated a significant increase in lymph node involvement, but no difference was found between other ultrasonographic findings and lymph node metastasis. While 11 of the 26 patients with lymph node involvement were not identified based on US, lymph node involvement was observed in the specimens. However, there was no lymph node involve-

Table 3. Comparison of preoperative demographic, ultrasonographic parameters, FNAC and sequence results of the groups

	pLN 0	pLN 1	p
Age	43.9 ±12.9	42 ±13.8	0.583*
Sex			**0.005**
Female	26 (89.7%)	19 (55.9%)	
Male	3 (10.3%)	15 (44.1%)	
Ultrasonographic parameters			
Number of nodule	2 (1-3)	3 (2-3)	0.132ǂ
Nodule size (mm)	13 (7.5-18)	18 (13.8-22.3)	**0.004ǂ**
Echogenicity			0.154†
Hypoechogenous	20 (69%)	16 (47.1%)	
Isoechogenous	2 (6.9%)	7 (20.6%)	
Mixed	7 (24.1%)	11 (32.4%)	
Cystic-solid construction			0.861†
Cystic	2 (6.9%)	2 (5.9%)	
Solid	17 (58.6%)	18 (52.9%)	
Mixed	10 (34.5%)	14 (41.2%)	
Microcalcification			**0.009†**
(-)	18 (62.1%)	10 (29.4%)	
(+)	11 (37.9%)	24 (70.6%)	
Blood supply of nodule			0.268†
(-)	13 (44.8%)	20 (58.8%)	
(+)	16 (55.2%)	14 (41.2%)	
Border regularity			0.251†
Regular	17 (58.6%)	15 (44.1%)	
Irregular	12 (41.4%)	19 (55.9%)	
LN metastasis			0.097†
(-)	15 (51.8%)	11 (32.3%)	
(+)	14 (48.2%)	23 (67.7%)	
FNAC results			
Nuclear elongation			0.681†
(-)	8 (27.6%)	11 (32.4%)	
(+)	21 (72.4%)	23 (67.6%)	
Discohesive cell			0.859†
(-)	13 (44.8%)	16 (47.1%)	
(+)	16 (55.2%)	18 (52.9%)	
Nuclear notching			0.758†
(-)	10 (34.5%)	13 (38.2%)	
(+)	19 (65.5%)	21 (61.8%)	
Irregular nucleus			0.231†
(-)	7 (24.1%)	13 (38.2%)	
(+)	22 (75.9%)	21 (61.8%)	
Cytoplasmic clarification			0.080†
(-)	9 (31%)	18 (52.9%)	
(+)	20 (69%)	16 (47.1%)	
Intranuclear inclusions			0.512†
(-)	8 (27.6%)	12 (35.3%)	
(+)	21 (72.4%)	22 (64.7%)	
Oncocytic morphology			0.233†
(-)	11 (37.9%)	18 (52.9%)	
(+)	18 (62.1%)	16 (47.1%)	
Multinuclear histiocytic giant cell			0.572†
(-)	15 (51.7%)	20 (58.8%)	
(+)	14 (48.3%)	14 (41.2%)	
BRAF^{V600E}			**0.005†**
(-)	25 (86.2%)	18 (52.9%)	
(+)	4 (13.8%)	16 (47.1%)	

*: mean ± SD and Student's t test
†: number and Fisher's exact test or Pearson chi square test
ǂ: median (IQR) and Mann Whitney U test
LN: Lymph node, pLN0: Patients with lymph node involvement, pLN1: Patients with lymph node involvement.

Table 4. Multivariate analysis of the factors associated with the pLN1 group

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Male sex	6.48 (1.73-27.02)	0.006	6.12 (0.89-42.1)	0.066
Microcalcification (US)	3.93 (1.37-11.25)	0.011	1.16 (1.05-1.29)	0.004
Nodule size, mm (US)	1.10 (1.02-1.18)	0.013	10.11 (1.97-51.85)	0.006
$BRAF^{V600E}$	9.75 (2.48-38.44)	0.001	6.41 (1.25-32.8)	0.026

OR: Odd ratio, CI: Confidence interval, US: Ultrasonography.

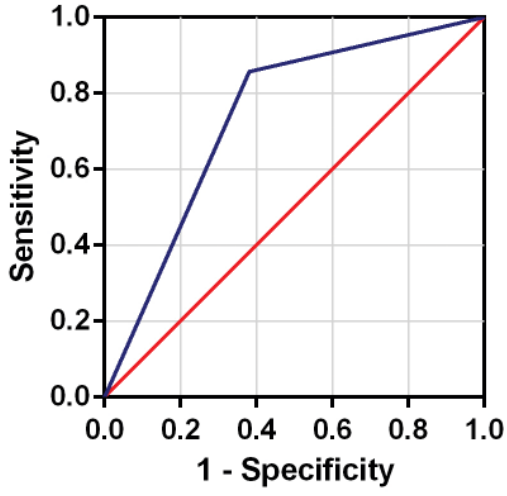

Figure 1. Revised roc curve for the ability of $BRAF^{V600E}$ mutation to demonstrate lymph node metastasis.

ment in the specimens of 14 of the 37 patients with pathologic lymph nodes identified using US. This result shows that US is not sufficient to predict lymph node metastasis in the preoperative period and that the evaluation of lymph node involvement should be supported by non-subjective preoperative data.

Although FNAC is a gold standard method for detecting the presence of malignancy in thyroid nodules (22,23), our study concluded that none of the cytopathological parameters in FNAC were different in patients with or without lymph node metastasis. Each of the cytopathological parameters evaluated in our study are diagnostic findings for PTC. From this point of view, it is noteworthy that FNAC was not associated with lymph node metastasis in the diagnosis of PTC.

In a study by Dong et al. (24), the authors have found that $BRAF^{V600E}$ gene mutation is not associated with all PTC subgroups with regional lymph node metastasis but with lymph node metastasis in patients with classic PTC. In a study in which the factors affecting cervical lymph node metastasis in patients with Delphian lymph node metastasis were examined, tumor size, multifocality, extrathyroidal spread, and $BRAF^{V600E}$ mutation in pathology specimens have been found to be independent risk factors related to each metastasis (25). In another study in which patients with metastatic thyroid cancer but no primary tumor were evaluated, it has been observed that the patients with metastatic thyroid cancer had a statistically significant $BRAF^{V600E}$ mutation than the patients without metastatic thyroid cancer (26). In a study by Kurtulmuş et al., the presence of the gene mutation has been associated with regional lymph node metastasis (16). In our study, the presence of $BRAF^{V600E}$ mutation was found to be effective in predicting lymph node involvement using ROC curve analysis.

According to the American Thyroid Association (ATA), $BRAF^{V600E}$mutation was identified for the first time in 2002 even though it was not described in the 2009 guidelines. The first time this mutation was described as being useful in risk classification is in the 2015 guidelines (19). The role of gene mutation has been better elucidated by means of systematic meta-analyzes published in subsequent years (27,28). In the 2009 ATA guidelines, TT without the need for SLND was recommended if no lymph node metastasis was clinically detected in T1-2 tumors (29). Also, according to the 2015 ATA guidelines, BRAF review is not routinely recommended in the first postoperative risk classification of the DTK, since knowing the BRAF mutation contributes a very small prognostic contribution to the clinico-pathological staging system (weak suggestion, moderate evidence) (19). However, in our study, $BRAF^{V600E}$ mutation was found to be associated with lymph node metastasis independent of other pre-operative clinicopathological findings. The high cost of the genetic kit we used in our study had an impact on the limited number of patients. This situation is seen as the limitation of our study. Further studies involving mostly patient groups are needed to support the routine use of BRAF gene mutation analysis in predicting lymph node metastasis.

Ethics Committee Approval: Ethics committee approval was received for this study from Ankara Numune Training and Research Hospital Ethics Committee 2015/649.

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Papiller tiroid kanserli hastalarda BRAF^{V600E} mutasyonunun bölgesel lenf nodu tutulumuna etkisi

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ÖZET

Giriş ve Amaç: Papiller tiroid kanseri (PTK) iyi diferansiye tiroid kanserleri içinde en sık görülen tiptir. Lenf nodu (LN) metastazı PTK'de sıklıkla görülür. BRAF^{V600E} mutasyonunun PTK ile ilişkili LN metastazı üzerindeki etkisi kesin olarak belirlenememiştir. Bu nedenle çalışmamızın amacı PTK'li hastalarda BRAF^{V600E} mutasyonunun bölgesel LN metastazı üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntem: Ocak 2013-2017 arasında santral lenf nodu diseksiyonu yapılan 63 hasta çalışmaya dahil edildi. Hastalar LN diseksiyonunun patoloji sonuçlarına göre pLN0 ve pLN1 olmak üzere iki gruba ayrıldı. Gruplar BRAF^{V600E} mutasyon varlığı açısından ve diğer klinikopatolojik bulgular ile karşılaştırıldı.

Bulgular: BRAF^{V600E} mutasyonu, pLN1 grubunda anlamlı yüksek saptandı. (p= 0,005). Yapılan çok değişkenli analizde nodül büyüklüğü, mikrokalsifikasyon ve BRAF^{V600E} mutasyonunun diğer parametrelerden bağımsız olarak lenf nodu metastazı ile ilişkili olduğunu ortaya koyuldu. ROC analizi ile BRAF^{V600E} mutasyonunun LN tutulumunun varlığını öngörmedeki yeterliliği de anlamlı olarak saptandı [AUC: 0,738 (%95 CI: 0,61-0.86, p= 0,002)].

Sonuç: Çalışmamızda diğer parametrelerden bağımsız olarak BRAF^{V600E} gen mutasyonunun lenf nodu tutulumu üzerinde etkili olduğu bulundu.

Anahtar Kelimeler: Braf, lenf nodu tutulumu, papiller tiroid kanser

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