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Original Article

Association between *BRAF*^{V600E} Mutations and Clinicopathological Features of Papillary Thyroid Microcarcinoma (PTMC)

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Purpose: In this study, the relationship between the *BRAF*^{V600E} mutation and the clinicopathological features of papillary thyroid microcarcinoma (PTMC) was examined in a single center.
Methods: From January 2011 to December 2012, a total of 911 patients with PTMC who underwent thyroidectomy at Severance Hospital, Korea were enrolled in this study. The status of *BRAF*^{V600E} mutation was assessed in thyroid fine-needle aspiration specimens by real-time polymerase chain reaction amplification prior to thyroidectomy. The associations between *BRAF*^{V600E} mutation status and clinicopathological features of PTMC were examined.
Results: The overall prevalence of the *BRAF*^{V600E} mutations was 78.8% (717/911). Chi-square analysis revealed that *BRAF*^{V600E} mutations were significantly associated with the male sex, lateral neck node metastasis, and several risk factors. And the age, tumor size, extent of surgery, multiplicity, bilaterality, central node metastasis, and distant metastasis were not associated with *BRAF*^{V600E} mutation. Multivariate analysis showed that capsular invasion and lateral neck node metastasis were significantly associated with *BRAF*^{V600E} mutations. In particular, lateral neck node metastasis showed negative correlation with *BRAF*^{V600E} mutations. And the recurrence rate and disease-free survival were not associated with *BRAF*^{V600E} mutation status.
Conclusion: *BRAF*^{V600E} mutations in PTMC was associated with presence of capsular invasion and absence of lateral neck node metastasis. However, *BRAF*^{V600E} mutations could not serve as a prognostic factor that affected the recurrence of PTMC in our study.

Keywords: Papillary thyroid cancer; Mutation; Prognosis

INTRODUCTION

Papillary thyroid microcarcinoma (PTMC) is defined by the World Health Organization as a papillary thyroid carcinoma (PTC) measuring ≤ 1 cm in diameter (1). The clinical significance of PTMC remains variable and controversial, because these tumors generally have a clinically indolent course with excellent clinical prognosis. However, some cases of PTMC have aggressive clinicopathological characteristics and poor clinical outcomes (2). Therefore, determination of markers capable of identifying these aggressive tumors,

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Author Contributions

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especially in the phase before surgery, would be very useful in guiding appropriate clinical management of PTMCs. The revised American Thyroid Association (ATA) guidelines indicate that thyroid cancer should be treated based on risk stratification and genetic testing, and should be assessed on the basis of the disease stage (3). Therefore, correct risk stratification is important in clinical decision-making.

The activating somatic point mutation, BRAF results in substitution of valine to glutamate (^{V600E}), leading to the constitutive activation of the BRAF kinase and consequent uncontrolled activation of the mitogen-activated protein kinases signaling pathway (4). It is the most common genetic alteration observed in PTC. *BRAF*^{V600E} mutation occurs in approximately 45%–80% of PTC cases and 25% of anaplastic thyroid cancer, depending on the population examined and the geographical region (5). However, it does not occur in other thyroid cancers and benign tumors (6). Many studies have indicated that *BRAF*^{V600E} is significantly associated with the aggressive clinicopathological characteristics of PTC, such as capsular invasion, multifocality, lymph node metastases (LNMs), and advanced clinical stage (6-8). However, the role of *BRAF*^{V600E} as a prognostic marker in PTMC is not clear, although PTMC also belongs to the well-differentiated PTC group. Some individual and meta-analysis studies have revealed that *BRAF*^{V600E} is significantly correlated with more aggressive characteristics of PTMCs; however, other studies do not show such a relationship (9-13).

Thus, in this study, we examined the percentage of *BRAF*^{V600E} mutation and the relationship between *BRAF*^{V600E} mutation and the clinicopathological features of PTMC in a group of single centers.

MATERIALS AND METHODS

1. Patients

Patients who underwent initial thyroidectomy at our institution between January 2011 and December 2012 were included in this study. During this period, 911 consecutive patients who underwent thyroidectomy for treatment of PTMC were enrolled and follow-up over the study period. In all 911 patients, pre-operative fine needle aspiration biopsy (FNAB) was used to confirm the diagnosis of well-differentiated PTMC and *BRAF*^{V600E} mutation analysis was performed on FNAB or post-thyroidectomy tissue samples. Median follow-up duration was 61.2 months (range 13–78.3 months).

High-resolution staging ultrasonography and computed tomography of the neck were performed in all cases for pre-operative staging. The extent of surgical resection was determined based on the ATA guidelines. A less than total thyroidectomy was performed If the following criteria were met by preoperative evaluation: a single lesion, no definite capsular invasion, no clinical lymph node metastasis, and no personal history of radiation therapy to the head or neck. A bilateral total thyroidectomy was performed if there were multiple lesion or bilateral lesions, or if a definite capsular invasion or a clinical lymph node metastasis was discovered during surgery. Prophylactic ipsilateral central compartment node dissection (CCND) was performed in all cases.

Details of the patient presentations, surgical and pathological findings, adjunctive treatments, and follow-up data were obtained from our Thyroid Cancer Database. This study was conducted after obtaining approval from the Institutional Review Board (IRB) of the Severance Hospital (IRB No.4-2015-0615).

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2. *BRAF*^{V600E} mutation analysis

Real-time polymerase chain reaction for *BRAF*^{V600E} was performed using the real-Q *BRAF*^{V600E} detection kit (BioSewoom, Seoul, Korea).

3. Statistical analysis

Continuous outcomes were analyzed using independent t-test between 2 groups. And the *BRAF*^{V600E}-positive status and *BRAF*^{V600E}-negative status groups and dichotomous outcomes were analyzed using the χ^2 test. A binary logistic regression analysis was performed to assess the correlation between *BRAF*^{V600E} and clinical factors. All statistical analyses were performed using IBM SPSS version 23.0 (IBM Co., Armonk, NY, USA). A P value less than 0.05 (P<0.05) was considered significant.

RESULTS

The clinicopathological characteristics according to *BRAF*^{V600E} mutation status are shown in **Table 1**. Of the 911 enrolled patients, 717 (78.8%) patients were *BRAF*^{V600E}-positive and 194 (21.3%) were *BRAF*^{V600E}-negative. There were more male patients in the *BRAF*^{V600E}-positive status group than in the negative status group. In the *BRAF*^{V600E}-negative status group, LNMs were higher. The mean age, family history, tumor size, extent of surgery, capsular invasion, multicentricity, bilaterality, central LNMs, distant metastases, and recurrence rate were the same in both groups. Subgrouping with a number of risk factors (capsular invasion, multifocality, central node metastasis, LMNs, distant metastasis) revealed that 2 risk factors were more prevalent in the *BRAF*^{V600E}-positive group and three or more risk factors were more prevalent in the negative group. Disease-free survival (DFS) was not significantly different between the 2 groups (P=0.350) (**Fig. 1**). There was no mortality during the study period.

We analyzed the clinicopathological characteristics according to the surgical extent (less than total thyroidectomy and bilateral total thyroidectomy) and *BRAF*^{V600E} mutation status. A total of 507 patients received less than total thyroidectomy with CCND and 404 patients received bilateral total thyroidectomy with CCND. In patients that underwent less than total thyroidectomy, there were more male patients in the *BRAF*^{V600E}-positive status group in than the negative status group (P=0.014). Other factors, such as family history, tumor size,

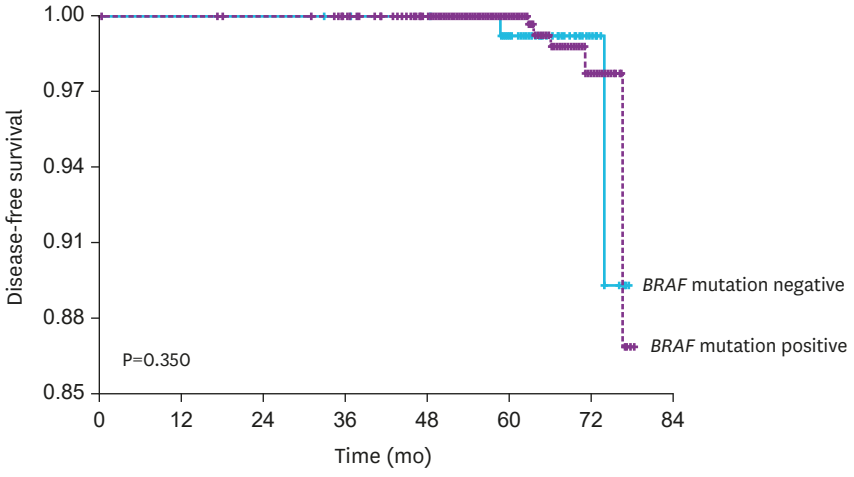

Fig. 1. Disease-free survival according to the *BRAF* mutation status(P=0.350).

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Table 1. The clinicopathologic characteristics of papillary thyroid microcarcinoma comparing according to the *BRAF*^{V600E} mutation status

Characteristics	Total	BRAF positive	BRAF negative	P value
Number	911	717 (78.8)	194 (21.3)	
Age(yr)	47.7±11.1	47.6±11.2	48.3±10.3	0.082
<55	361 (39.6)	293 (40.9)	68 (35.1)	
≥55	550 (60.4)	424 (59.1)	126 (64.9)	
Sex				0.039
Male	163 (17.9)	137 (19.1)	26 (13.4)	
Female	748 (82.1)	580 (80.9)	168 (86.6)	
Family history	83 (9.1)	66 (9.2)	17 (8.8)	0.489
T size (cm)	0.60±0.21	0.60±0.21	0.60±0.23	0.848
≤0.5 cm	239 (26.2)	188 (26.2)	51 (26.3)	
>0.5 cm	672 (73.8)	529 (73.8)	143 (73.7)	
Extent of surgery				0.075
Less than total thyroidectomy	507 (55.7)	414 (57.9)	93 (48.0)	
Total thyroidectomy	404 (44.3)	303 (42.1)	101 (52.0)	
Capsular invasion				0.107
No	516 (56.6)	398 (55.5)	118 (60.8)	
Yes	395 (43.4)	319 (44.5)	76 (39.2)	
Multiplicity				0.441
Yes	227 (24.9)	180 (25.1)	47 (24.2)	
No	684 (75.1)	537 (74.9)	147 (75.8)	
Bilaterality				0.231
Yes	142 (15.6)	108 (15.1)	34 (17.5)	
No	769 (84.4)	609 (84.9)	160 (82.5)	
Central node metastases				0.188
No	641 (70.4)	499 (69.6)	142 (73.2)	
Yes	270 (29.6)	218 (30.4)	52 (26.8)	
Lateral node metastasis				0.001
No	885 (97.1)	704 (98.2)	181 (93.3)	
Yes	26 (2.9)	13 (1.8)	13 (6.7)	
Distant metastases (initial)				0.787
No	910 (99.9)	716 (99.9)	194 (100)	
Yes	1 (0.1)	1 (0.1)	0	
Radioactive iodine treatment				0.039
No	632 (69.4)	508 (70.8)	124 (63.9)	
Yes	279 (30.6)	209 (29.2)	70 (39.1)	
Dose				
Low-dose	240 (86.2)	188 (80.0)	52 (74.3)	
High-dose	39 (13.8)	21 (10.0)	18 (25.7)	
No. of risk factor*				0.020
None	404 (44.3)	315 (43.9)	89 (45.9)	
One	378 (41.5)	298 (41.6)	80 (41.2)	
Two	111 (12.2)	95 (13.2)	16 (8.2)	
Three or more	18 (2.0)	9 (1.2)	9 (4.7)	
Recurrence				0.459
No	904 (99.2)	712 (99.3)	192 (99.0)	
Yes	7 (0.8)	5 (0.7)	2 (1.0)	

Data are shown as mean±standard deviation or number (%).
*Ristk factors: capsular invasion, multifocality, central node metastases, lateral node metastases, distant metastasis.

capsular invasion, multiplicity, bilaterality, node metastases, and recurrence rate were the same in both groups. In patients who received bilateral total thyroidectomy, only LNMs were higher in *BRAF*^{V600E}-negative group (P=0.004) and the other factors were not different between the 2 groups (**Table 2**).

We performed univariate and multivariate analyses for evaluating the correlation between *BRAF*^{V600E} mutation and clinicopathological factors. Capsular invasion showed a positive

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Table 2. The clinicopathologic characteristics of papillary thyroid microcarcinoma comparing according to the surgical range analysis

Characteristics	Less than total				Bilateral total			
	Total	BRAF+	BRAF−	P value	Total	BRAF+	BRAF−	P value
Number	507	414 (81.7)	93 (18.3)		404	303 (75.0)	101 (25.0)	
Age (yr)								
Sex				0.014				0.873
Male	102 (20.1)	92 (22.2)	10 (10.8)		61 (15.1)	45 (14.9)	16 (15.8)	
Female	405 (79.9)	322 (77.8)	83 (89.2)		343 (84.9)	258 (85.1)	85 (84.2)	
Familiy histroy	45 (8.9)	37 (8.9)	8 (8.6)	0.553	38 (9.4)	29 (9.6)	9 (8.9)	0.511
T size (cm)				0.905				0.193
≤0.5 cm	180 (35.5)	148 (35.7)	32 (34.4)		59 (14.6)	40 (13.2)	19 (18.8)	
>0.5 cm	327 (64.5)	266 (64.3)	61 (65.6)		345 (85.4)	263 (86.8)	82 (81.2)	
Capsular invasion	178 (35.1)	149 (36.0)	29 (31.2)	0.403	217 (53.7)	170 (56.1)	47 (46.5)	0.107
Multiplicity	61 (12.0)	50 (12.1)	11 (11.8)	0.555	166 (41.4)	130 (42.9)	36 (35.6)	0.243
Bilaterality	11 (2.2)	7 (1.7)	4 (4.3)	0.124	131 (32.4)	101 (33.3)	30 (29.7)	0.541
Central node metastases	128 (25.2)	109 (26.3)	19 (20.4)	0.291	142 (35.1)	109 (36.0)	33 (32.7)	0.630
Lateral node metastases	0				26 (6.4)	13 (4.3)	13 (12.9)	0.004
Recurrence	6 (1.2)	4 (1.0)	2 (2.2)	0.304	1	1 (0.2)	0	0.750

Data are shown as mean±standard deviation or number (%).

correlation and LNMs showed negative correlation with *BRAF*^{V600E} mutation (**Table 3**). Both factors were significantly correlated with *BRAF*^{V600E} mutation.

DISCUSSION

According to the 2016 annual report of cancer statistics in Korea, thyroid cancer is the third most common cancer in all populations and the second most common cancer in women (14). Although the incidence decreased after the controversy regarding the overdiagnosis of thyroid cancer, it is still a cancer with high prevalence in Korea. The prevalence of thyroid cancer has been increasing at a quite rate in recent decades, especially PTC. It is still debated as to whether improved detection is the only reason for the increase in the diagnosis of PTCs or whether the tumorigenesis of thyroid cancer has changed (15). Additionally, the rate of PTMCs is consistently diagnosed and treated at a level of over 50% in all PTCs. PTC, especially PTMC has low mortality and comparably good prognosis and clinically favorable results. The *BRAF*^{V600E} mutation is a common mutation in PTMC and active research has been

Table 3. The univariate and multivariate analyses of the BRAF mutation and clinicopathological features of papillary thyroid microcarcinoma

Variable (n=911)	Univariate analysis		Multivariate analysis	
	OR	P value	OR	P value
Sex (male/female)	0.655 (0.416–1.031)	0.067	0.705 (0.479–1.040)	0.078
Family history (yes/no)	0.947 (0.542–1.656)	0.849	-	-
Age* (yr)	0.882 (0.620–1.255)	0.485	-	-
Tumor size† (mm)	1.004 (0.700–1.439)	0.985	-	-
Extent of surgery (less than total vs. total)	0.674 (0.069–6.551)	0.054	-	-
Capsular extension (yes/no)	1.402 (1.058–1.857)	0.019	1.491 (1.112–1.999)	0.008
Multifocality (multiple/single)	1.048 (0.725–1.517)	0.802	1.172 (0.843–1.629)	0.345
Bilaterality (bilateral/single)	0.835 (0.547–1.274)	0.402	-	-
Central node metastases (yes/no)	0.838 (0.588–1.196)	0.330	0.198 (0.874–1.643)	0.262
Lateral node metastases (yes/no)	0.257 (0.117–0.564)	0.001	0.399 (0.231–0.689)	0.001
No. of risk factors	1.050 (0.899–1.227)	0.539	-	-
Recurrence (yes/no)	0.674 (0.130–3.502)	0.639	-	-

OR = odds ratio.
*≥55 vs. <55; †5< and ≤10 vs. ≤5.

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conducted since the early 2000s on the prognosis of the mutation. In recent years, *BRAF*^{V600E} has emerged as a highly specific biomarker and useful prognostic factor associated with high-risk clinicopathological factors in PTMCs. Some studies have reported that the *BRAF*^{V600E} mutation is associated with poor clinicopathological outcomes in PTMC such as the high incidence of capsular invasion, metastasis of the tumor, advanced clinical stage, and high recurrence rate. Other studies have shown that the *BRAF*^{V600E} mutation is not associated with age, sex, or multicentricity (11,12,16,17).

The high distribution (78.8%) of *BRAF*^{V600E} among patients with PTMC observed in our study, was similar to that observed in other studies (incidence rate, 27.3%–87.1%) (5,9,18). These findings are consistent with the significantly higher prevalence of PTMC in Asia, especially in Korea relative to Western countries (5,19,20). However, the mechanisms underlying the difference in PTMC prevalence among various countries are not well understood. A recent theory suggests that the difference originates from the intake of iodine, Korea and other Asian countries have a higher intake of iodine, and the geographic differences are made apparent by the change in prevalence over time (18,19,21,22). There has been an increase in *BRAF*^{V600E}-associated thyroid cancers from 62.2% to 73.7% over the last two decades in Korea (23). Similarly, the overall prevalence of PTC had remained stable for an extended period of time, but has increased rapidly from 50.0% to 76.9% over the last four decades in the United States (24). More in-depth research on changes in mutational variation and their clinical outcomes are needed.

When the clinicopathological characteristics were compared to the *BRAF*^{V600E} mutation status, the aggressive factors, like tumor size, capsular invasion, multicentricity, bilaterality, central node metastases, distant metastasis were found to be similar in both *BRAF*^{V600E}-positive and -negative status patient groups. However, there were more male patients in the *BRAF*^{V600E}-positive group than in the *BRAF*^{V600E}-negative group (19.1% vs. 13.4%). These results were more prominent in the less than total thyroidectomy group compared to the patient group according to the surgical range (less than total vs. bilateral total thyroidectomy). Many studies have been published regarding whether male thyroid cancer patients have a poor prognosis or not. The results from a meta-analysis by Liu et al. revealed that the male sex is a poor, independent prognostic factor for all PTMCs. However, sex is not an independent prognostic factor for cause-specific survival in PTMC (25), and Kim et al. (26) reported that sex was not an independent prognostic factor for tumor recurrence. Although other factors involved in mediating the aggressiveness of PTMC and recurrence showed no significant difference, it is difficult to find an explanation for a higher *BRAF*^{V600E}-positive rate in male patients. A long-term follow-up study would be needed to investigate this further.

Most PTMCs have an indolent clinical course and an excellent prognosis, but early spread to the lymph nodes is not rare, and so, there is a high incidence of disease recurrence in the lymph nodes. The highest LNM rate is up to 50% (27), and lateral LNMs are found in 3.7%–45% of the patients with PTMC. Many studies have reported that patients with nodal metastasis have an increased rate of disease recurrence (28,29). In this study, there was no difference in the central lymph node metastasis between the 2 groups. However, lateral neck node metastases were detected more in the *BRAF*^{V600E}-negative status group. The overall lateral lymph node metastasis rate was only 2.9%; 6.7% in the *BRAF*^{V600E}-negative group and 1.8% in the positive group. In the subgroup analysis based on the surgical range of bilateral total thyroidectomy patients, the overall lateral lymph node metastasis rate was 6.4%; 4.3% in the BRAF-positive group and 12.9% in the negative group. Multivariate analysis to evaluate

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the factors significantly correlated with the *BRAF*^{V600E} mutation revealed that lateral neck node metastasis was negatively correlated with the *BRAF*^{V600E} mutation. Same in our result, other studies reported that higher lateral neck node metastasis rates were detected in the *BRAF*^{V600E}-negative group in PTMC. However, the lateral lymph node metastasis was not significantly associated with *BRAF*^{V600E} mutation in PTMC (11,30). Though we couldn't investigate the exact reason that the correlation of lymph node metastasis rate with the *BRAF*^{V600E} mutation status in our study, there was no difference in the recurrence rate and DFS based on the *BRAF*^{V600E} mutation status. Therefore, this suggests that *BRAF*^{V600E} mutation is not correlated with the poor prognostic factor.

The *BRAF*^{V600E} mutation analysis was performed in our institution in June 2015, on all patients who underwent surgery for differentiated thyroid cancer. However, due to the short duration of the follow-up, it is difficult to draw an accurate conclusion about the effect of the *BRAF*^{V600E} mutation on PTMCs. Long-term follow-up of *BRAF*^{V600E} mutations, disease recurrence, and mortality is therefore necessary.

There were some limitations in this study. Due to the retrospective nature of the study and single-center analysis, the registration information, patient volume, and inspection items could not be designed beforehand. As we mentioned, *BRAF*^{V600E} mutation analysis was performed on FNAB or post-surgery specimens from selected patients. This strategy may have created discrepancies in the results obtained from *BRAF*^{V600E} mutation testing. However numerous studies have demonstrated that a preoperative BRAF mutation analysis can be performed readily and reliably by the use of FNAB specimen (31-33). In addition, the indolent clinical course of PTMC implies that the follow-up duration would not be enough to verify the prognosis.

In conclusion, *BRAF*^{V600E} mutations in PTMC was associated with presence of capsular invasion and absence of lateral neck node metastasis. However, *BRAF*^{V600E} was not found to be a prognostic factor that affected the recurrence of PTMC in our study. It would be of great importance to identify the *BRAF*^{V600E} mutation status in PTMC patients who were treated in a large-scale institution. In addition, further investigation is needed to define the factors associated with *BRAF*^{V600E} and to correlate them as prognostic factors.

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