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Null Association between *BRAF* V600E Mutation and Tumor Recurrence in Patients with Papillary Thyroid Microcarcinoma in South Korea

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Background and Objectives: The clinical implications of the *BRAF* V600E mutation in papillary thyroid microcarcinoma (PTMC), defined as ≤1.0 cm of tumor size, remain controversial. We investigated the association between the *BRAF* V600E mutation and PTMC recurrence in a retrospective cohort of patients with thyroid cancer. **Materials and Methods:** This study included 2319 patients with PTMC (median age, 50 years [interquartile range (IQR), 41-57 years]) who underwent thyroid surgery from 2010 to 2019 at a single tertiary medical center. The median follow-up time was 75 months (IQR, 30-98 months). Tumor recurrence was confirmed by histological, cytological, radiographic, and biochemical criteria, combined with persistent and recurrent disease. **Results:** A total of 60.2% (1395/2319) patients with PTMC had the *BRAF* V600E mutation. The tumor recurrence rate was 2.1% (19/924) in *BRAF* mutation-negative patients and 2.9% (41/1395) in *BRAF* mutation-positive patients, with a hazard ratio (HR) of 1.05 (95% confidence interval [CI], 0.61-1.84) after adjusting for clinicopathological risk factors. Similar results were found in patients with high-risk PTMC (adjusted HR, 1.09; 95% CI, 0.56-2.11) who had lymph node metastasis (LNM), extrathyroidal extension (ETE), or distant metastasis (DM) at diagnosis and in patients with low-risk PTMC (adjusted HR, 1.00; 95% CI, 0.35-2.83) who had no LNM, ETE, or DM. **Conclusion:** The finding that the *BRAF* V600E mutation was not associated with tumor recurrence in our cohort of Korean patients with PTMC, especially in patients with low-risk PTMC, suggests that its value in the prediction of disease progression is limited.

Key Words: Papillary thyroid microcarcinoma, *BRAF* V600E mutation, Active surveillance, Tumor recurrence

Introduction

Papillary thyroid microcarcinoma (PTMC), defined as a tumor that is not greater than 1 cm in its greatest dimension, accounts for approximately 50% of differentiated thyroid cancer (DTC) cases.[1-3] Moreover, previous studies have shown a robust increase in PTMC incidence, with an average annual increase of 9.3%.[3,4]

Despite the clinical importance of PTMC, controversies over its treatment have not been clearly resolved since active surveillance (AS) has been endorsed by the American Thyroid Association (ATA) and Korean Thyroid Association (KTA) guidelines.[5,6] The crux of this debate is whether very low-risk PTMC,

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with no clinical evidence of metastasis and local invasion, is indeed indolent and whether a novel approach including genetic markers can predict poor prognosis in this group.

In the past decades, the *BRAF* V600E mutation has been widely investigated as a prognostic marker in DTC, suggesting that *BRAF* mutation is related with tumor recurrence as well as aggressive clinicopathological characteristics.[7,8] However, there have been limited and discordant results on the clinical significance of *BRAF* mutation in PTMC. Chen et al.[9] have demonstrated that *BRAF* mutation correlates with tumor recurrence in PTMC using multi-institutional data and meta-analysis. Choi et al.,[10] in contrast, did not find a significant association between *BRAF* mutations and aggressive clinicopathological factors in PTMC. These inconsistent results can be explained by differences in sample size, ethnicity, length of follow-up, and *BRAF* mutation prevalence, leaving this issue open to further debate. Moreover, the prognostic importance of *BRAF* mutations in low-risk PTMC cases considered candidates for non-surgical AS has not been clearly elucidated, particularly in areas where the *BRAF* mutation is prevalent.

In this context, we investigated the prognostic implication of *BRAF* V600E for tumor recurrence in PTMC, especially for low-risk PTMC, in South Korea, where the *BRAF* mutation is highly prevalent.

Materials and Methods

Study Design and Patients

This retrospective study initially analyzed patients from the Korea University Anam Hospital Thyroid Cancer Cohort, which included 6256 patients treated for papillary thyroid cancer at the Korea University Anam Hospital in Seoul, Korea since 2010. This database contains information on treatment modalities, tumor recurrence, and basic clinicopathological and demographic characteristics. This study was approved by the Institutional Review Board (IRB) of the Korea University Anam Hospital (IRB No. 2021AN0297). The requirement for informed consent was waived due to the retrospective study design, and all patient data were anonymized and de-identified. From the original cohort, we selected 2319 patients with *BRAF* V600E mutation status who had been confirmed to have PTMC by surgical resection. Fig. 1 shows a schematic diagram of the study flow.

Definition of Low- and High-Risk PTMC and Tumor Recurrence

Low-risk PTMC was defined as PTMC with no extrathyroidal extension (ETE), cervical lymph node metastasis (LNM), and distant metastasis (DM), while high-risk PTMC was defined as PTMC with at least one of these features. All patients underwent hemithyroidectomy or total thyroidectomy. Cervical lymph node dissection and radioactive iodine ablation (RAI) were performed when clinically indicated. The primary outcome was tumor recurrence defined as persistent or recurrent disease, confirmed by histological, cytological, radiographic, and biochemical criteria.[5,6,11] All patients were followed up until the earliest occurrence of tumor recurrence, death, or the end of the study period (December 31, 2020). For *BRAF* V600E mutation analyses, we amplified exon 15 of the *BRAF* gene using the PNAClamp *BRAF* Mutation Detection Kit (Panagene Ltd., Daejeon, Korea) based on a peptide nucleic acid (a synthetic DNA analog)-mediated PCR clamping technique. This approach has shown high sensitivity and specificity with a small amount of DNA,

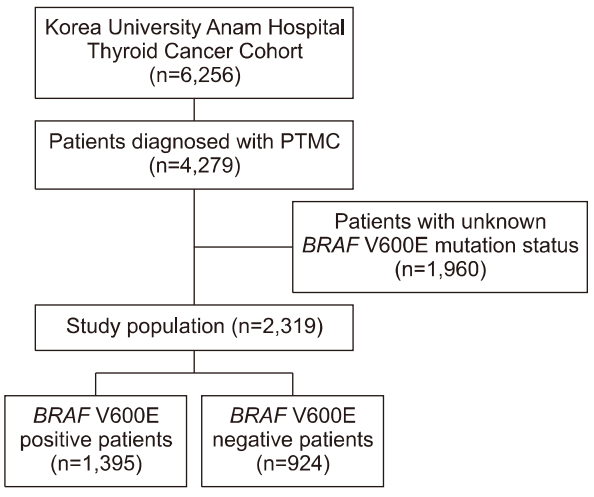

Fig. 1. Flow diagram of the study subject selection process.

and the details of the procedures have been described previously.[12,13] The physician was informed of the patient's *BRAF* mutation status after surgery.

Statistical Analysis

Continuous data of non-normally distributed variables are presented as medians and interquartile ranges (IQR), using the Wilcoxon-Mann-Whitney test, and categorical data are presented as numbers and percentages, using a chi-square test or Fisher's exact test. For tumor recurrence, we calculated the hazard ratios (HRs) with 95% confidence intervals (CIs) using Cox proportional hazard regression models. These analyses were performed according to the *BRAF* mutation status and further adjusted for patient age at diagnosis, sex, tumor size, LNM, ETE, multifocality, surgery type, and RAI treatments. To analyze recurrence-free survival, Kaplan-Meier survival curves with log-rank tests were used.

All statistical analyses were performed using SPSS version 23 (IBM SPSS Inc. New York, NY, USA) and R version 4.0.2 (R Foundation for Statistical Computing, www.R-project.org). Graphs were generated using GraphPad Prism version 9 (GraphPad Software, San Diego, CA, USA). Statistical significance was set at a two-sided p-value of <0.05.

Results

Clinicopathological Characteristics of PTMC Based on the *BRAF* V600E Mutation Status

Table 1 presents the baseline characteristics of all patients with PTMC (n=2319). The median age of patients was 50 years (IQR, 41-57 years), and 82.2% (1907/2319) were women. The overall prevalence of the *BRAF* V600E mutation was 60.2% (1395/2319). The median tumor size was 0.6 cm for *BRAF* mutation-positive cases and 0.5 cm for *BRAF* mutation-negative cases ($p<0.001$). *BRAF* mutations were significantly associated with LNM (23.3% vs. 31.0%, $p<0.001$ for *BRAF* mutation-negative and -positive cases, respectively). However, *BRAF* mutations were not significantly associated with gross ETE, vascular invasion, or multifocality. Total thyroidectomy and RAI therapy were performed in 60.9% (n=1412) and 37.6%

Table 1. Clinicopathological demographic characteristics of papillary thyroid microcarcinoma according to *BRAF* genotype

	All patients	*BRAF* V600E-negative patients	*BRAF* V600E-positive patients	p value
Total cases, n (%)	2319	924 (39.8)	1395 (60.2)	
Age, median (IQR), years	50 (41-57)	50 (41-58)	49 (40-57)	0.062
Female sex, n (%)	1907 (82.2)	773 (83.7)	1134 (81.3)	0.144
Tumor size, median (IQR), cm	0.6 (0.4-0.8)	0.5 (0.4-0.7)	0.6 (0.5-0.8)	<0.001
Extrathyroidal extension, n (%)	23 (1.0)	11 (1.2)	12 (0.9)	0.432
Lymph node metastasis, n (%)	648 (27.9)	215 (23.3)	433 (31.0)	<0.001
Vascular invasion, n (%)	6 (0.3)	1 (0.1)	5 (0.4)	0.412*
Multifocality, n (%)	899 (38.8)	351 (38.0)	548 (39.3)	0.531
Distant metastasis, n (%)	1 (0.04)	0 (0.0)	1 (0.1)	1.00*
Stage (the AJCC 8th), n (%)				0.238*
I	2126 (91.7)	851 (92.1)	1275 (91.4)	
II	190 (8.2)	71 (7.7)	119 (8.5)	
III	2 (0.1)	2 (0.2)	0 (0.0)	
IV	1 (0.04)	0 (0.0)	1 (0.1)	
Total thyroidectomy, n (%)	1412 (60.9)	530 (57.4)	882 (63.2)	0.005
^{131}I treatment, n (%)	873 (37.6)	306 (33.1)	567 (40.6)	<0.001
^{131}I dose, median (IQR), mCi	100 (30-150)	100 (30-150)	100 (30-150)	0.635
Follow time, median (IQR), months	75 (30-98)	75 (33-99)	75 (27-97)	0.222
Tumor recurrence, n (%)	60 (2.6)	19 (2.1)	41 (2.9)	0.190

AJCC: American Joint Committee on Cancer, IQR: interquartile range
*Calculated using Fisher's exact test.

(n=873) of the total number of patients, respectively. Patients with *BRAF* mutations underwent total thyroidectomies and RAI treatment more frequently than those without *BRAF* mutations.

Effect of *BRAF* V600E Mutation on PTMC Recurrence

During the median follow-up period of 75 months (IQR, 30-98 months), tumor recurrence occurred in 2.6% (n=60) patients. The recurrence rate was 2.9% (41/1395) and 2.1% (19/924) for *BRAF* mutation-positive and -negative patients, respectively (Table 2), with an unadjusted HR of 1.48 (95% CI, 0.86-2.55). After adjustments for age, sex, tumor size, LNM, ETE, multifocality, surgical type, and RAI treatments, the effect of the *BRAF* mutation on tumor recurrence remained insignificant, with an HR of 1.05 (95% CI, 0.61-1.84). The Kaplan-Meier survival curve also showed no significant difference between *BRAF* mutation-positive and -negative patients in regard to recurrence-free survival (log-rank, p=0.157; Fig. 2A).

We also evaluated whether *BRAF* V600E mutation affected tumor recurrence differently in low-risk and high-risk groups. The overall recurrence rates were 1.0% (16/1662) for low-risk PTMC and 6.7% (44/657) for high-risk PTMC. The *BRAF* V600E mutation did not significantly affect tumor recurrence in either low-risk or high-risk PTMC (Table 2). For low-risk PTMC, the recurrence rates were 0.9% (6/703) in *BRAF* mutation-negative patients and 1.0% (10/959) in *BRAF* mutation-positive patients, with an adjusted HR of 1.00 (95% CI, 0.35-2.83). For high-risk PTMC, the recurrence rates were 5.9% (13/221) and 7.1% (31/436) in *BRAF* mutation-negative and -positive patients, respectively, with an adjusted HR of 1.09 (95% CI, 0.56-2.11). Similar results were obtained using Kaplan-Meier analyses (Fig. 2B, C). In both groups, the *BRAF* V600E mutation had no significant effect on recurrence-free survival (log-rank p=0.611 for low-risk PTMC and log-rank p=0.606 for high-risk PTMC).

Effect of Other Clinicopathological Factors on PTMC Recurrence

Univariate and multivariate Cox proportional analyses were performed to investigate the risk factors for tumor recurrence (Table 3). Conventional risk factors such as male sex, LNM, ETE, tumor size and multifocality affected tumor recurrence in univariate analysis, and especially male sex (adjusted HR, 2.25; 95% CI, 1.25-4.10), LNM (adjusted HR, 5.62; 95% CI, 2.88-10.99) and multifocality (adjusted HR, 2.43; 95% CI, 1.33-4.44) remained significant in multivariate analysis.

Table 2. Hazard ratios of the *BRAF* V600E mutation for PTMC recurrence

	Recurrence, n (%)	Unadjusted		Adjusted	
		HR (95% CI)	p value	HR (95% CI)	p value
All PTMCs					
BRAF V600E-negative	19/924 (2.1)	1 (reference)		1 (reference)	
BRAF V600E-positive	41/1395 (2.9)	1.48 (0.86-2.55)	0.159	1.05 (0.61-1.84)	0.850*
Low-risk PTMC					
BRAF V600E-negative	6/703 (0.9)	1 (reference)		1 (reference)	
BRAF V600E-positive	10/959 (1.0)	1.30 (0.47-3.60)	0.612	1.00 (0.35-2.83)	0.999†
High-risk PTMC					
BRAF V600E-negative	13/221 (5.9)	1 (reference)		1 (reference)	
BRAF V600E-positive	31/436 (7.1)	1.19 (0.62-2.27)	0.607	1.09 (0.56-2.11)	0.802†

CI: confidence interval, HR: hazard ratio, PTMC: papillary thyroid microcarcinoma

*Adjusted for patient age at diagnosis (analyzed as a continuous variable), sex (male/female), tumor size (analyzed as a continuous variable), cervical lymph node metastasis (present/absent), extrathyroidal extension (present/absent), multifocality (multifocal/single), surgery type (total thyroidectomy/hemithyroidectomy), and radioactive iodine treatment (received/not received).

†Adjusted for patient age at diagnosis, sex, tumor size, multifocality, surgery type, and radioactive iodine treatment.

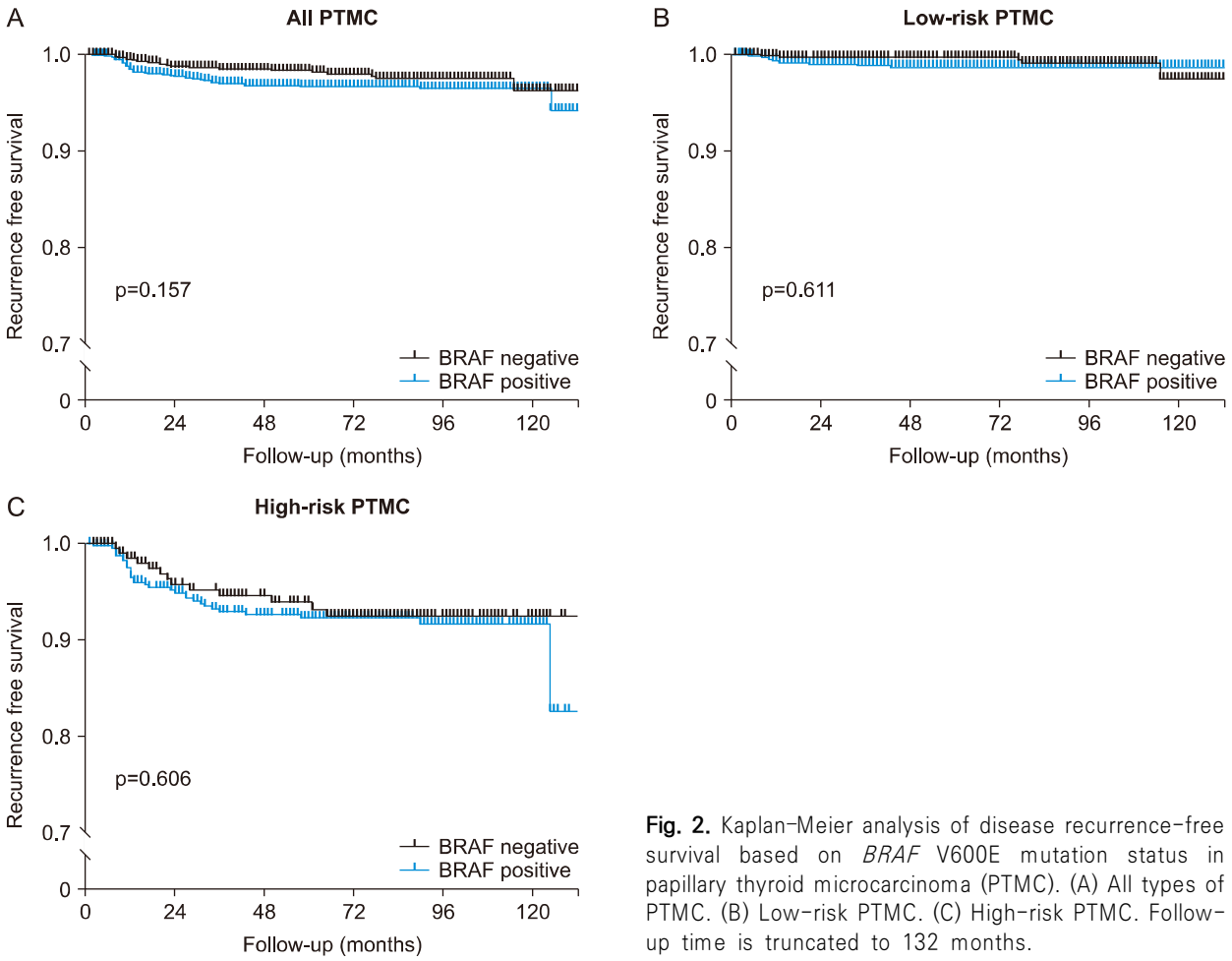

Fig. 2. Kaplan-Meier analysis of disease recurrence-free survival based on *BRAF* V600E mutation status in papillary thyroid microcarcinoma (PTMC). (A) All types of PTMC. (B) Low-risk PTMC. (C) High-risk PTMC. Follow-up time is truncated to 132 months.

Table 3. Univariate and multivariate analyses of clinicopathological factors and PTMC recurrence

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age ≥55 years	0.73 (0.41-1.31)	0.288	0.78 (0.41-1.47)	0.443
Male sex	2.19 (1.26-3.81)	0.006	2.25 (1.25-4.10)	0.007
Tumor size >0.5 cm	3.26 (1.74-6.15)	<0.001	1.63 (0.84-3.17)	0.148
LNM	7.06 (3.98-12.51)	<0.001	5.62 (2.88-10.99)	<0.001
ETE	6.59 (1.60-27.16)	0.009	1.58 (0.21-11.64)	0.656
Multifocality	2.70 (1.60-4.57)	<0.001	2.43 (1.33-4.44)	0.004
BRAF mutation	1.48 (0.86-2.55)	0.159	1.33 (0.71-2.49)	0.366

CI: confidence interval, ETE: extrathyroidal extension, HR: hazard ratio, LNM: cervical lymph node metastasis, PTMC: papillary thyroid microcarcinoma, RAI: radioactive iodine ablation
All variables were analyzed as categorical values: age (≥55/<55 years), sex (male/female), tumor size (>0.5/≤0.5 cm), LNM (present/absent), ETE (present/absent), multifocality (multifocal/single), and *BRAF* mutation (positive/negative).

Discussion

In this retrospective, large, single-center study, we confirmed that patients with PTMC usually have an excellent prognosis, with a tumor recurrence rate of 2.6% over a median follow-up period of 75 months. Although patients with *BRAF* mutation-positive PTMC had numerically higher tumor recurrence rates, when separated into high- and low-risk groups as well as overall, HRs were not statistically significant after ad-

justing for clinicopathological factors in each group. On the other hand, conventional risk factors such as male sex, LNM, and multifocality were significantly associated with tumor recurrence in PTMC. These results suggest that the *BRAF* mutation has a limited prognostic value regarding tumor recurrence in PTMC, particularly for low-risk PTMC in Korea, a representative *BRAF* mutation-prevalent area.

According to the KTA guidelines, PTMC can be observed without immediate surgical treatment if the tumor has no aggressive cytologic features and shows no local/distant metastasis.[6] However, all PTMC cases may not consistently have a good prognosis in real practice, and these recommendations are based on a few observational studies conducted in the same country.[14,15] Hence, there is an increasing need for a prognostic marker to facilitate decision making on the AS of PTMC, and the *BRAF* V600E mutation can potentially play a decisive role in risk stratification. Several studies have reported that *BRAF* mutation is associated with tumor recurrence in patients with PTMC,[9] especially in those with low-risk PTMC.[16] In contrast, studies have shown that the *BRAF* mutation alone has no independent prognostic effect in PTMC cases.[10,17,18] Hence, clinical guidelines on the management of DTC have defined all intrathyroidal PTMCs as a low-risk group, regardless of the *BRAF* mutation status.[5,6] The discrepancy between the results of previous studies may be mainly attributed to the differences in the prevalence of *BRAF* mutations in each region, ranging from 30% to 80% of all PTMCs.[5,10,16,17,19-22] In particular, Korea, where our study was conducted, has a higher prevalence of *BRAF* mutations than most Western countries.[10,18,22-24] Two important questions need to be addressed in this regard—the first is why the prevalence of *BRAF* mutation varies by geographical region, and the second is why the prognostic effect of *BRAF* mutation seems to be less powerful in areas where *BRAF* mutation is prevalent. Although these questions remain unresolved, previous studies have reported that high iodine intake is associated with a high prevalence of *BRAF* mutation,[25,26] therefore, we speculate that high iodine intake may influence the negative effects of *BRAF* mutation on the iodine metabolism.[27,28] Further investigations are needed to answer these questions.

This study has several limitations to be mentioned. First, this was a single-center study, and this study type often requires external validity; however, we included a large number of patients (n=2319) with PTMC. Second, considering the good prognosis of PTMC,[14,29,30] relatively short follow-up periods inevitably led to a low disease recurrence rate and reduced the power to conclude firm results. Third, other genetic mutations, such as rat sarcoma mutations and telomerase reverse transcriptase promoter mutations were not analyzed due to a lack of relevant data. Lastly, since the mutation analyses were performed after the surgical treatment and reported to the physician, RAI treatment may have been influenced by the *BRAF* mutation results.

In summary, this study investigated the prognostic role of the *BRAF* V600E mutation in PTMC, including low-risk PTMC considered for conservative surveillance instead of immediate surgical treatment, using a large, retrospective, single-center database. An excellent prognosis was observed in PTMC, and the *BRAF* V600E mutation was not associated with disease recurrence in PTMC, suggesting that the *BRAF* mutation has limited value as a deciding factor for AS in an area where the mutation is prevalent. Our results would require further investigation into prognostic factors that determine AS in appropriate low-risk PTMC.

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Conflicts of Interest

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

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