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Clinical and Pathological Characteristics Associated with *BRAF* V600E Mutation in Vietnamese Patients with Papillary Thyroid Carcinoma

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Abstract

Background: Papillary thyroid carcinoma is the most common type of malignant thyroid tumor. A mutation frequently found in papillary thyroid carcinoma is *BRAF* V600E. This study aimed to determine the prevalence of the *BRAF* V600E mutation and to analyze the association between the *BRAF* V600E mutation and clinicopathological parameters in patients with papillary thyroid carcinoma.

Methods and Results*:* An analytical descriptive study was conducted in 88 patients with thyroid cancer at Nghe An Provincial Endocrinology Hospital. All patients were tested for the *BRAF* V600E mutation using polymerase chain reaction. Clinical and pathological variables, including age, sex, tumor size, multifocality, lymph node metastasis, and thyroid cancer stage, were compared between the *BRAF* V600E (+) and *BRAF* V600E (-) patient groups.

The *BRAF* V600E mutation was detected in 23 cases, accounting for 26.2%. Our study showed that the *BRAF* V600E mutation was statistically associated with tumor size, lymph node metastasis, N stage, and more advanced TNM stage.

Conclusion*:* The *BRAF* V600E mutation is common in papillary thyroid carcinoma and is associated with clinical and pathological factors such as tumor size, lymph node metastasis, N stage, and more advanced TNM stage of papillary thyroid carcinoma. **(International Journal of Biomedicine. 2026;16(4):462-468.)**

Keywords: papillary thyroid carcinoma • mutation • lymph node metastasis • thyroid cancer

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Introduction

Thyroid cancer is the most common endocrine malignancy, and its incidence has increased rapidly worldwide over the past several decades. The incidence of thyroid cancer increased threefold from 4.9 to 14.3 per 100,000 persons during the period from 1975 to 2009.[1] Thyroid cancer includes three main pathological types: differentiated thyroid cancer (DTC), anaplastic thyroid cancer (ATC), and medullary thyroid cancer (MTC). More than 90% of thyroid cancers are DTC. DTC is further divided into two types: papillary thyroid carcinoma (PTC) and follicular thyroid cancer (FTC). Among the four pathological types, papillary thyroid carcinoma is the most common, accounting for 89-90% of all thyroid malignancies.[2] Thyroid cancer has a good prognosis, with a 10-year survival rate of 80-95%. However, 10-20% of thyroid cancer cases develop more severe disease, leading to frequent recurrence and higher mortality rates.[3]

Currently, clinical guidelines have been developed to classify patients into different risk groups. This allows clinicians to adjust treatment more aggressively and to monitor more closely patients considered at high risk. Clinical guidelines are based on pathological risk factors including patient age, sex, comorbidities, tumor size, histological type, lymph node invasion, and extrathyroidal metastasis.[4]

However, risk stratification is often inaccurate, with 15% of tumor recurrences and 10% of thyroid cancer deaths occurring in patients considered to be at low risk. Therefore,

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clinicians have attempted to develop better prognostic algorithms, and recently molecular tumor biomarkers have received widespread attention.[5]

Many studies have demonstrated a strong association between the *BRAF* V600E mutation (B-Raf proto-oncogene serine/threonine kinase) and advanced tumor characteristics, extrathyroidal extension, lymph node metastasis, and advanced disease stage (III and IV) in papillary thyroid carcinoma.[6] In contrast, some studies have not demonstrated a significant association between the *BRAF* V600E mutation and clinicopathological characteristics.[7] This controversy has been addressed by larger studies with meta-analyses. These studies have confirmed the association between *BRAF* V600E and advanced tumor characteristics, particularly extrathyroidal extension, lymph node involvement, advanced TNM stages (III and IV), and a higher risk of recurrence.[8,9]

However, the question of whether the *BRAF* V600E mutation represents a poorer prognosis for papillary thyroid carcinoma patients in all regions of the world remains unanswered. This issue has been investigated by only a few authors and with very short follow-up periods. Therefore, the purpose of our study was to analyze *BRAF* V600E mutation status and clarify the association between the *BRAF* V600E mutation and clinicopathological parameters in patients with papillary thyroid carcinoma in Nghe An, Vietnam.

Materials and Methods

Study Design

The study design was analytical and descriptive, and included patients with thyroid cancer from Nghe An Endocrinology Hospital, Vietnam. Data on patient characteristics were collected from individuals undergoing thyroid cancer screening who were subsequently confirmed to have thyroid cancer.

This study was conducted from September 2023 to September 2025. This study was approved by the Ethics Committee of the Institute of Malariology and Parasitology (approval number 1178/QD-VSR dated day 8 month 12 year 2023). All patients provided written consent for all surgical procedures and mutation analyses.

Study Participants

Inclusion criteria: All individuals who attended thyroid disease screening at Nghe An Provincial Endocrinology Hospital, totaling 2,164 patients. Patients were confirmed to have thyroid cancer after clinical examination, diagnostic imaging, preoperative thyroid ultrasonography (US), fine needle aspiration biopsy (FNAB), and other tests. When preoperative findings suggested lymph node metastasis, computed tomography (CT) was performed. The location of the thyroid tumor was divided into four regions: upper third, middle third, lower third, or thyroid isthmus according to ultrasonographic findings.

From the initial group of patients attending thyroid cancer examination and screening, we selected 88 patients who were confirmed to have thyroid cancer. A total of 88 patients with a confirmed diagnosis of thyroid cancer were included in the study based on the following criteria: (1) postoperative gene analysis: *BRAF* V600E mutation; (2) preoperative ultrasonography: ultrasonography was performed at the hospital's ultrasonography department within 1 month before surgery, with complete ultrasonographic descriptions and clear images; and (3) tumor characteristics: diameter ≤ 10 mm and > 10-40 mm. Patients with thyroid cancer agreed to participate in the study and had complete medical records.

Exclusion criteria: Patients were excluded if they refused mutation analysis, had missing clinical data, or had a previous history of another cancer.

Study Variables

Demographic factors (age, sex) and clinicopathological parameters, including tumor size, tumor multifocality, unifocality, lymph node metastasis, location of lymph node metastasis, thyroid cancer stage, and the presence of the *BRAF* V600E mutation, were included in the analysis.

Data Collection

DNA extraction

Tumor tissue and corresponding adjacent normal tissue from thyroid cancer specimens were obtained by thyroidectomy. Tumor DNA was extracted from sections of formalin-fixed paraffin-embedded tissue. DNA purification was performed using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Tumor areas were manually dissected with a DNA-free scalpel under a microscope to obtain the important portion of the tumor. DNA extraction for PCR analysis was completed.

Detection of the BRAF V600E mutation

BRAF gene mutation analysis was performed on thyroid tumors from paraffin-embedded tissue blocks. Tissue samples were obtained from surgical cases at the Department of Pathology, Nghe An Provincial Endocrinology Hospital.

In cases of unilateral multifocal papillary thyroid carcinoma, analysis was performed on the tumor with the largest diameter, defined as the primary lesion. In patients with bilateral nodules classified as Bethesda V (suspicious for malignancy) or VI (malignant), mutation analysis was performed on tumors from both lobes. The larger tumor was designated as the primary lesion, and the remaining tumor in the contralateral lobe was referred to as the contralateral tumor.

Quantitative real-time PCR technique for BRAF mutation analysis

BRAF V600E mutation analyses were performed by pathologists after surgical treatments of patients. The primers used were: 5'-TCATAATGCTTGCTCTGATAGGA-3' (forward primer) and 5'-GGCCAAAAATTT-ATCAGTGGA-3' (reverse primer). The following steps were performed in the amplification reaction: (1) initial denaturation for 15 seconds at 95°C, (2) annealing for 30 seconds at 57°C, (3) extension for 30 seconds at 72°C, and (4) holding at 4°C. A 2 µL aliquot of the PCR product was electrophoresed on 1% Tris-borate-EDTA (TBE) agarose. The appearance of a band indicated the presence of *BRAF* amplification.

Histopathological diagnosis

The histopathological diagnosis of thyroid cancer was confirmed by experienced physicians based on the current diagnostic criteria of the World Health Organization.[10]

Tumor-node-metastasis (TNM) staging was performed using the eighth edition of the American Joint Committee on Cancer (AJCC) staging system.[11]

Data Analysis

For qualitative variables, data were presented as frequencies and percentages (%).To evaluate associations between variables, bivariate analysis was performed using the Chi-square test when its conditions were met or Fisher's exact test as an alternative. Data analysis was performed using SPSS version 20. Results were presented as p-values. A p-value of less than 0.05 for each test was considered statistically significant. Logistic regression analysis was used to determine whether clinicopathological and ultrasonographic characteristics were independent variables.

Results

Patient Demographic Information

A total of 8 (9%) patients were male, and 80 (91%) patients were female. Age is considered a risk factor in the prognosis of patients with thyroid cancer. According to the TNM staging criteria of the American Thyroid Association, patients were divided at the age of 55 years. Of the 88 patients, 61 (70%) were younger than 55 years, and 27 (30%) were 55 years or older. While 73% of patients had a tumor size ≤ 10 mm, 27% had a tumor size of 10-40 mm. Our study showed that 23 patients with thyroid cancer had the *BRAF* gene mutation, whereas 65 patients were negative for the mutated gene.

Among the 88 patients with thyroid cancer, 35 patients were confirmed to have lymph node metastasis by histopathological results, giving a lymph node metastasis rate of 40%. The status of lymph node metastasis in the central compartment, lateral neck, or both was confirmed by postoperative histopathological results for each patient.

Nineteen patients underwent thyroid lobectomy. While 13 patients underwent total thyroidectomy, 56 patients underwent total thyroidectomy with lymph node dissection.

There were 49 (56%) patients classified as stage I. The remaining patients were classified as stage II and stage III, accounting for 41% and 3%, respectively. Most patients were diagnosed with papillary thyroid carcinoma (94%; 83/88), while the remaining patients were diagnosed with the follicular variant of papillary thyroid carcinoma (5%; 4/88) and follicular thyroid carcinoma (1%; 1/88). Clinical and pathological information from the 88 patients was collected and is presented in Table 1.

Association between the *BRAF* V600E Mutation and Clinicopathological Characteristics in Papillary Thyroid Carcinoma

The clinical and pathological characteristics of thyroid cancers with the *BRAF* mutation were separately compared with those without the mutation (Table 2).

There were 23 cases of the *BRAF* V600E gene mutation in the specimens, yielding a mutation rate of 26.2%. Among patients carrying gene mutation, 18 patients were younger than 55 years, and 5 patients were aged ≥ 55 years. Among

Table 1.

Demographic and clinicopathological characteristics of patients with thyroid cancer.

Variables	Patients' parameters	Total n (%)	Variables	Patients' parameters	Total n (%)
Sex	Male	8 (9)	T stage	T1	68 (77)
	Female	80 (91)		T2	3 (3)
Age	< 55 years	61 (70)		T3b	14 (16)
	≥ 55 years	27 (30)		T4a	3 (3)
Tumor size	≤ 10 mm	64 (73)	N stage	N0	50 (57)
	10-40 mm	24 (27)		N1	35 (40)
Histological variant	Papillary thyroid carcinoma	83 (94)		Nx	3 (3)
	Follicular thyroid carcinoma	1 (1)	M stage	M0	88 (100)
	Follicular variant of papillary thyroid carcinoma	4 (5)		M1	
Lymph node metastasis	Yes	35 (40)	AJCC stage	I	49 (56)
	No	53 (60)		II	36 (41)
Location of lymph node metastasis	Central compartment	25 (67)		III	3 (3)
	Lateral neck	1 (4)	Type of surgery	Thyroid lobectomy	19 (22)
	Both	9 (29)		Total thyroidectomy	13 (15)
Tumor focality	Unifocal	67 (76)		Total thyroidectomy with lymph node dissection	56 (63)
	Multifocal	21 (23)	BRAF V600E	Yes	23 (26)
				No	65 (74)

these patients, 52% had a tumor size ≤ 10 mm and 48% had a tumor size of 10-40 mm. Among the 23 cases with the *BRAF* V600E gene mutation, 91% had lymph node metastasis, with central, lateral neck, and both locations accounting for 67%, 4%, and 29%, respectively. Among the 23 patients, 17 had a single focus, and the remainder had multifocal disease.

Regarding tumor staging, among the 23 patients with the gene mutation, 2 were stage I, 19 were stage II, and 2 were stage III.

Gene sequence data were collected from 88 thyroid tissue samples; we identified *BRAF* V600E mutation status in 22 (96%) patients with papillary thyroid carcinoma and 1 (4%) patient with the follicular variant of papillary thyroid carcinoma.

There was no significant association between *BRAF* V600E positivity and multifocality. Multifocality was slightly higher in the *BRAF* (+) group than in the *BRAF* (-) group; however, the difference was not statistically significant (p=0.771). In our study, females accounted for the majority (91%); however, there was no statistically significant difference between males and females in relation to the *BRAF* V600E mutation.

A notable finding in our study was that the *BRAF* V600E mutation was significantly associated with tumor size, lymph node metastasis, N stage, and a more advanced stage of papillary thyroid carcinoma.

The proportion of *BRAF* V600E-positive patients with tumor sizes of 10-40 mm was higher than that in the negative

Table 2.

Comparison of clinical and pathological parameters according to detection of the BRAF V600E mutation in patients with papillary thyroid carcinoma.

Patients' parameters		BRAF V600E positive n=23 (%)	BRAF V600E negative n=65 (%)	p-value
Sex	Male	3 (13)	5 (8)	0.426
	Female	20 (87)	60 (92)	
Age	< 55 years	18 (78)	43 (66)	0.279
	≥ 55 years	5 (22)	22 (34)	
Tumor size	≤ 10 mm	12 (53)	52 (80)	0.010
	10-40 mm	11 (47)	13 (20)	
Histological variant	Papillary thyroid carcinoma	22 (96)	61 (94)	1.000
	Follicular thyroid carcinoma	0 ()	1 (2)	
	Follicular variant of papillary thyroid carcinoma	1 (4)	3 (4)	
Lymph node metastasis	Yes	21 (91)	14 (22)	<0.001
	No	2 (9)	51 (78)	
Location of lymph node metastasis	Central compartment	14 (67)	11 (79)	0.822
	Lateral neck	1 (4)	0 (0)	
	Both	6 (29)	3 (21)	
Tumor focality	Unifocal	17 (74)	50 (77)	0.771
	Multifocal	6 (26)	15 (23)	
T stage	T1	16 (70)	52 (80)	0.192
	T2	0 (0)	3 (5)	
	T3b	5 (22)	9 (14)	
	T4a	2 (8)	1 (1)	
N stage	N0	2 (9)	48 (74)	<0.001
	N1	21 (91)	14 (22)	
	Nx	0 (0)	3 (4)	
M stage	M0	23 (100)	65 (100)	—
	M1			
AJCC stage	I	2 (9)	47 (72)	<0.001
	II	19 (83)	17 (26)	
	III	2 (8)	1 (1)	
Type of surgery	Thyroid lobectomy	4 (17)	15 (23)	0.882
	Total thyroidectomy	3 (13)	10 (15)	
	Total thyroidectomy with lymph node dissection	16 (70)	40 (62)	

group (p=0.01). Among 24 patients with tumor sizes of 10-40 mm, the *BRAF* V600E gene mutation occurred in 47% of patients, whereas patients without the mutation accounted for only 20%. *BRAF* V600E positivity was associated with lymph node metastasis (p<0.001). Specifically, among 35 patients with lymph node metastasis, 21 (91%) carried the *BRAF* V600E mutation, and 14 (22%) did not.

TNM staging was performed in 88 patients. Among 49 patients with stage I disease, the gene mutation was detected in 2 (9%) patients, and no mutation was detected in 47 (72%) patients. The proportion of *BRAF* V600E-positive patients with stage II and III papillary thyroid carcinoma was higher than that in the negative group (p<0.001). Among 36 patients with stage II disease, the gene mutation was detected in 19 (83%), and no mutation was detected in 17 (26%). Among 3 patients with stage III disease, 2 had the *BRAF* V600E mutation.

In addition, in our study, the *BRAF* V600E mutation was associated with the extent of cancer spread (N stage) to regional lymph nodes (p<0.001).

Discussion

In Vietnam, in recent years thyroid cancer has increased markedly and has become one of the 10 most common cancers.[12] Recent studies have shown that gene mutations are important factors in tumorigenesis. In 2002, Davies et al. first reported the *BRAF* V600E mutation in the MEK-ERK pathway in human malignancies. The *BRAF* V600E mutation is considered one of the key genes in papillary thyroid carcinoma and initiates the process of tumor formation. Recent studies have found that the frequency of the *BRAF* mutation ranges from 25-83% of papillary thyroid carcinoma cases, depending on the study population and geographic region.[13] Furthermore, the association between the *BRAF* V600E mutation and clinical prognostic factors of papillary thyroid carcinoma remains controversial. Some authors have demonstrated an association between the *BRAF* V600E mutation and poor prognostic factors such as advanced TNM stage, bilaterality, multifocality, extrathyroidal tumor invasion and lymph node metastasis, distant metastasis, higher tumor stage, and recurrence of papillary thyroid carcinoma.[8,9] On the other hand, some other studies have not confirmed the prognostic value of the *BRAF* V600E mutation in PTC.[7] To clarify these apparently contradictory results, we evaluated the association between the gene mutation and clinical factors of papillary thyroid carcinoma.

According to these results, among 88 patients with thyroid cancer, the mutation prevalence was 26%, whereas no mutation was detected in 74%. The results of this study are consistent with several previous reports from Italy, Korea, and Singapore.[14-16] In contrast, a recent study in Korea reported the *BRAF* V600E mutation in 60% of patients with small papillary thyroid carcinoma, and two studies in China reported mutation rates of 83.33% and 82.28%.[17-18] The reason that the *BRAF* V600E mutation rates in China and Korea were higher than in our study may be that access to health examination services is easier, providing more opportunities for mutation testing. Furthermore, mutation analysis in our study was performed in a relatively small number of patients (88 patients); therefore, the mutation prevalence may have been underestimated. In addition, differences in mutation prevalence may be due to differences in study populations, geographic regions, and racial factors.

In our study, papillary thyroid carcinoma accounted for the majority of thyroid cancer cases. PTC is a slowly progressing cancer with favorable long-term survival with standard treatments such as total thyroidectomy and radioactive iodine-131 treatment for residual thyroid tissue after surgery.

In our study, thyroid cancer occurred more frequently in women than in men. This result is also consistent with several previous studies; Changjiao Yan et al. reported that papillary thyroid carcinoma frequently occurs in women at a ratio of 3:1.[19] In our study, we found that the gene mutation was more common in female patients, but the difference was not statistically significant (p=0.426).

Lymph node metastasis was confirmed histopathologically in 35 patients, representing 40% of patients. Because lymph node metastasis is a risk factor for local recurrence and increases the mortality rate in papillary thyroid carcinoma,[20] these patients need to be stratified by lymph node metastasis and evaluated for its association with the *BRAF* V600E mutation. It has been reported that the rate of lymph node metastasis ranges from 24.1% to 64.1% in papillary thyroid carcinoma.[21] The lymph node metastasis results in our study were like those reported in the literature.

In our study population, we found that the age distribution, sex ratio, multifocality, and T stage of thyroid cancer did not differ significantly between patients with and without the *BRAF* V600E mutation. These findings indicate that the presence of the mutation was not associated with age, sex, multifocality, or T stage among patients with papillary thyroid carcinoma in our study population.

The prevalence of the *BRAF* V600E mutation was higher in the group of patients with multifocal tumors confirmed by postoperative histopathology, but the difference was not statistically significant (p=0.771). This differs from the meta-analysis by Li et al., which reported that the *BRAF* V600E mutation was significantly associated with multifocality, cervical lymph node metastasis, and higher TNM stage. They demonstrated that the *BRAF* V600E mutation leads to more aggressive characteristics.[22]

The results of our study showed an association between the *BRAF* V600E mutation and tumor size > 10-40 mm in patients with papillary thyroid carcinoma (p=0.01). This means that the proportion of patients positive for the mutated gene with tumor size > 10-40 mm was higher than that in the negative group. Virk et al. reported results similar to those of our study. They demonstrated that tumor size greater than 5 mm was associated with papillary thyroid microcarcinoma.[23] In contrast, another study demonstrated no association between the mutation and large tumor size.[24] Therefore, the association between the BRAF V600E mutation and tumor size remains controversial.

According to the Eighth Edition of the American Joint Committee on Cancer (AJCC) staging system, patients with stage II and III disease accounted for 44% and 4%, respectively.

Our study showed that the *BRAF* V600E mutation was highly associated with more advanced disease stages II and III ($p<0.001$). The proportion of patients positive for the mutated gene at stages II and III was higher than that in the negative group. Furthermore, we found that the rate of lymph node metastasis in patients with the *BRAF* V600E mutation was significantly higher than in those without the mutation. We found that the *BRAF* V600E mutation was associated with lymph node metastasis ($p<0.001$). Several studies have reported that lymph node metastasis was significantly higher in patients with papillary thyroid carcinoma carrying the mutation.[25]

Our analyses showed a significant association between the presence of *BRAF* V600E and tumor size, lymph node metastasis, N stage, and more advanced TNM stage ($p<0.05$). Our analysis is consistent with previous reports. Liu et al. demonstrated that the mutation was associated with advanced TNM stage (III/IV), lymph node metastasis, and tumor recurrence.[26] In contrast, Mai Trong Khoa reported in a study of Vietnamese patients with differentiated thyroid cancer that 75.8% had the *BRAF* V600E mutation. The authors also reported that the mutated gene was not associated with age, sex, histopathological characteristics, disease stage, T classification, lymph node metastasis, or distant metastasis.2[7]However, the sample size in our study was relatively small. Therefore, the sample size should be expanded to further study the association between the *BRAF* V600E mutation and clinicopathological parameters in papillary thyroid carcinoma.

The present study has several limitations. First, the sample size was relatively small, with 2,164 patients screened for thyroid cancer, after which 88 cases were diagnosed with thyroid cancer and included in our study. The results showed that the *BRAF* V600E gene mutation is common in papillary thyroid carcinoma and is associated with tumor size, lymph node metastasis, and thyroid cancer stage. A larger number of patients in our study could help confirm our findings. Second, these results are due to the short follow-up period. Therefore, oncological outcomes such as recurrence, metastasis, and survival could not yet be observed. Future studies with larger patient groups and longer follow-up periods are needed to evaluate oncological outcomes.

Conclusion

This study showed that the prevalence of the *BRAF* V600E mutation was 26% among 88 patients with thyroid cancer at Nghe An Provincial Endocrinology Hospital. Furthermore, our study initially demonstrated the relationship between the *BRAF* V600E gene mutation and clinical and pathological characteristics in patients with papillary thyroid carcinoma. The results showed that the *BRAF* V600E gene mutation is common in papillary thyroid carcinoma. Our study showed that the gene mutation was associated with tumor size ($p=0.01$), lymph node metastasis ($p<0.001$), N stage ($p<0.001$), and more advanced TNM stage ($p<0.001$) in patients with papillary thyroid carcinoma.

Ethical Considerations

This study was approved by the Ethics Committee under Decision No 1178/QD-VSR of the National Institute of Malariology, Parasitology and Entomology.

Authorship Contributions

Conceptualization: Nguyen Thanh Hai, Tran Quang Phuc; Data curation: Cao Ba Loi. Formal analysis: Nguyen Thanh Hai, Nguyen Van Chuyen; Nguyen Thi Thu Trang; Methodology and Research: Cao Ba Loi, Nguyen Huu Le, Tran Quang Phuc; Supervision: Cao Ba Loi. Drafting - Revision and editing: Cao Ba Loi, Nguyen Van Chuyen.

Disclosure and Conflicts of Interest

The authors declare that they have no potential conflicts of interest relevant to this article.

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