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RESEARCH

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BRAF V600E mutation in thyroid carcinoma: a large-scale study in Han Chinese population

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Abstract

Background The prevalence of genetic mutations in thyroid cancer varies significantly among different ethnic backgrounds. The present study aimed to investigate the clinical potential of BRAF V600E in a large group of homogenous Han Chinese patients.

Methods From 2018 to 2021, 6232 thyroid disease patients who underwent thyroidectomy at our hospital were enrolled. We measured the diagnostic value of BRAF and plotted ROC curves. Patients with full clinical-pathological data were selected and divided into the BRAF mutation and wild type groups. We conducted univariate and multivariate analyses to quantify the differences in potential predictive factors of papillary thyroid carcinoma (PTC) patients between the groups. Kaplan–Meier survival analysis was used to estimate overall recurrence and recurrence rate.

Results The prevalence of BRAF V600E mutation was 86.0% in PTCs. The sensitivity and specificity of BRAF mutation for diagnosing PTC from suspicious lesions were 85.5% and 100%, respectively. The sensitivity and specificity of BRAF analysis in the indeterminate cytology group were 72.5% and 100%, respectively. BRAF mutation showed an independent association with older age, negative HT, larger tumor size, extrathyroidal extension, and multifocality in PTCs. In micro-PTCs (tumor size ≤ 1), the mutation was also positively correlated with progressive phenotypes of extrathyroidal extension and multifocality. BRAF mutation was associated with poorer recurrence-free probability in Kaplan–Meier survival analysis.

Conclusions This large single-center study reveals that BRAF V600E is highly prevalent in the Han Chinese population and demonstrates BRAF V600E mutation testing has high diagnostic accuracy and its strong association with the progress of aggressiveness in PTCs and a higher probability of recurrence. BRAF mutation can serve as an accurate marker for diagnosis and decision-making with great value.

Keywords Thyroid carcinoma, BRAF V600E, Chinese population, Prevalence

Introduction

Thyroid cancer has become one of the top ten cancers posing a significant health threat to the Chinese population, exhibiting an average annual increase of 14.51% [1–3]. Over the past two decades, extensive research has delved into the molecular mechanisms of thyroid cancer, aiming to address the rapid surge in its incidence. Numerous genetic alterations in the carcinogenesis process have been scrutinized for their clinical implications in managing patients with thyroid cancers [4]. Notably, the B-type Raf kinase (BRAF) V600E mutation stands out as the most prevalent molecular target, frequently identified in papillary thyroid carcinoma (PTC), as well as PTC-derived poorly or anaplastic differentiated carcinoma. However, BRAF

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V600E was rarely detected in benign nodules, follicular tumors or medullary carcinomas [5, 6].

Various studies have consistently indicated the widespread prevalence of the BRAF V600E mutation, ranging from 33.2% to 88% in PTC cases globally [7–9]. The discrepancies in these figures, as reported in the literature, can be attributed to variations in geographic locations and ethnicities, potentially influenced by differences in etiology or study methodologies [10].

It is a challenge facing clinicians to distinguish thyroid cancers from benign nodules to ensure that each patient receives timely and appropriate treatment [11]. The fine needle aspiration cytology (FNAC) has proven useful in assessing the likelihood of malignant tumors [12, 13]. However, the sample collection and interpretation of thyroid smears can be intractable and require experience. With the development of molecular analysis, the BRAF V600E test has been widely proposed as an auxiliary diagnostic tool with a confirmed high specificity for thyroid cancer [14, 15]. Notably, its sensitivity correlates with the mutation rate, thereby substantially enhancing the accuracy of molecular analysis in BRAF prevalent areas [16, 17].

BRAF V600E has emerged as a promising prognostic factor in the risk stratification of PTC in recent years [18]. Accumulating studies have suggested the BRAF mutation is strongly associated with poorer clinical course and more aggressive tumor behavior such as older age, male gender, multifocality, lymph node metastasis, extrathyroidal extension, advanced disease stages III and IV [19, 20]. However, persistent controversies surround this correlation, casting doubt on whether the mutation can unequivocally serve as a prognostic factor in clinical practice [21, 22]. The conflicting results across different study populations contribute to an ongoing debate regarding the qualification of BRAF alteration as a novel dimension in the assessment and management of thyroid cancers. Therefore, it is imperative to ascertain the prevalence and clinical significance of this mutation within specific patient cohorts, with the aim to reduce the systematic deviation observed across diverse regions or ethnicities.

Ethnic Han population constitutes the majority of the Chinese demographic. However, the prevalence and clinical implications of BRAF V600E mutation in this population have not yet well-documented. Accordingly, we conducted a large-cohort research using patient data from a single Chinese medical institution to investigate the mutation rate, diagnostic and prognostic efficacy of BRAF V600E in patients of thyroid cancers.

Methods

Patients

From 2018 to 2021, all participants were patients of Han ethnicity who were pathologically diagnosed as PTC and tested for the BRAF V600E mutation following thyroid resection at the Department of General Surgery, Xiangya Hospital, Central South University. Inclusion criteria: 1. Patients of Han ethnicity who underwent thyroid resection; 2. Pathological diagnosis of PTC; 3. Availability of BRAF V600E mutation test results. Exclusion criteria: 1. Patients with a previous history of thyroidectomy; 2. Patients who refused BRAF V600E mutation analysis; 3. Patients with inconclusive clinicopathological diagnoses. As a result, a total of 6232 patients were enrolled in this study. Clinical and pathological data were retrieved. The procedure of patients enrollment of the study is shown in Fig. 1. This study was conducted according to the STROBE statement and written consent was obtained from all the patients for the use of the clinical samples for research purposes.

BRAF V600E testing

Assays were performed at the Molecular Pathology Laboratory of our institution. The BRAF V600E mutation was detected by amplification-blocking mutation system polymerase chain reaction (ARMS-PCR). All testing procedures were performed in compliance with quality control standards.

Fine needle aspiration analysis

Not all patients had FNA (fine needle aspiration) or FNA-based BRAF testing, as a result, 3915 thyroid nodules were aspirated and yielded FNA samples. The FNA procedure was conducted under ultrasound guidance by an experienced thyroid surgeon, endocrinologist, or radiologist following a standardized protocol. The operator held the ultrasound probe to ensure precise needle positioning within the nodule or lymph node. The needle was inserted and withdrawn multiple times within the lesion to collect an adequate tissue sample. An assistant managed the syringe to extract the cellular fluid, with each drainage period lasting approximately 15 s. For patients with multiple lesions, each lesion was aspirated using a new needle, and the specimens were separately labeled for processing by a cytotechnician.

The cytopathology of FNA was read by two pathologists and the 'indeterminate' cytology was reviewed by another pathologist. The cytology results were categorized according to The Bethesda System for Reporting Thyroid Cytology (TBSRTC) stages I–VI.

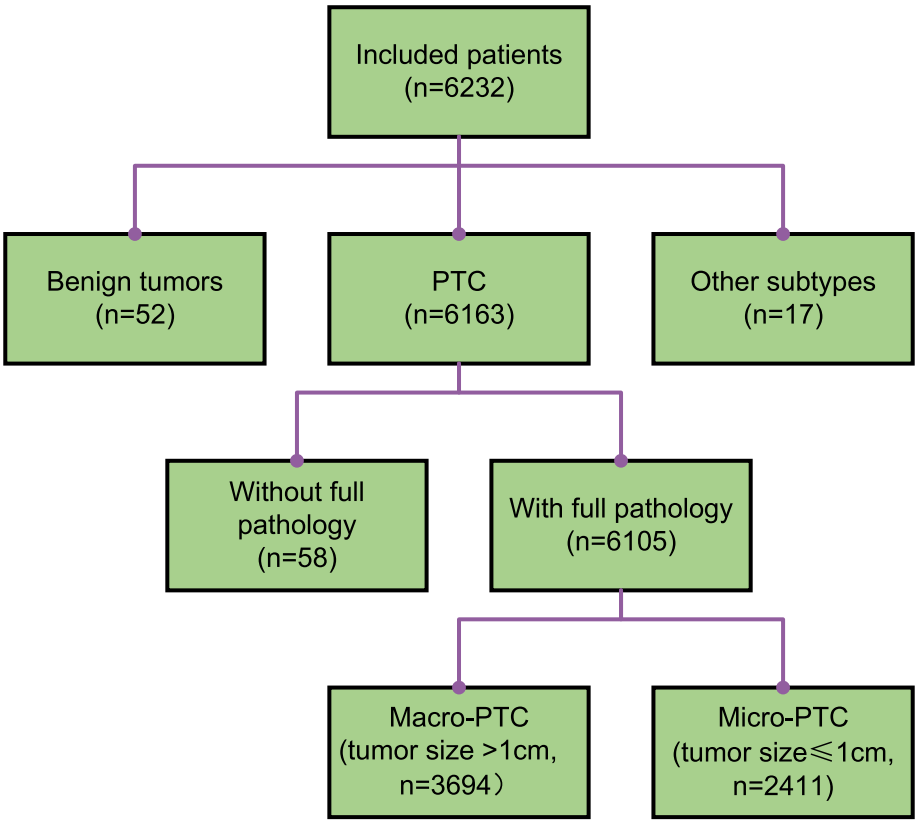

Fig. 1 A comprehensive flow chart showing the selection of patients throughout the study

Follow-up

The follow-up time was 25–73 months. Recurrence was defined as radiological evidence of recurrent disease, visualized on CT or ultrasound or PET scan, with confirmation on cytological analysis of FNAB or on histopathological analysis of re-operative surgical specimens.

Statistical analysis

All data were analyzed by the statistical software SPSS 26.0. Qualitative variables were presented with frequencies and percentages, whereas continuous variables were presented as mean values and standard deviation (SD). Diagnostic characteristics (sensitivity and specificity) were calculated, with the postoperative histopathological diagnoses set as the gold standard. A receiver-operating characteristic (ROC) curve was plotted with sensitivity against 1-specificity where sensitivity is on the y-axis and 1-specificity is on the x-axis.

An independent t-test was used to compare the mean values of continuous variables and a chi-square test to compare the frequencies of qualitative variables. Multivariate logistic regression analysis was performed to evaluate the associations between clinical and pathological parameters of PTC and the BRAF V600E mutation. Variables distinguished by the univariate analysis were included in the multivariate binary logistic regression analysis. Values of odds ratio (OR) were determined to measure the strength of the associations. Kaplan–Meier survival analysis was used to estimate the overall recurrence and recurrence rate. The log-rank test was used to compare differences in recurrence outcomes by BRAF V600E mutation status. The statistical significance of all the tests was based on two-tailed p-value < 0.05 and 95% confidence intervals (CI).

Results

Prevalence of the BRAF V600E mutation

A total of 6232 consecutive patients were included in this study. The BRAF V600E mutation was observed in 85.8% (5300/6180) of all malignancy, with a specific prevalence of 86.0% (5299/6163) in papillary thyroid carcinomas and one case in anaplastic thyroid cancer. The mutation was negative in all benign nodules ($n=52$), follicular thyroid cancer ($n=3$), medullary thyroid cancer ($n=12$), and poorly differentiated thyroid cancer ($n=1$), which was consistent with previous studies.

Diagnostic performance

To evaluate the diagnostic performance, the postoperative histopathology was set as the gold standard. With the limited sample size of other subtypes, we only evaluated the diagnostic accuracy of BRAF or FNAC analysis for diagnosing PTC.

In 3915 patients who received both BRAF test and FNAC, the distribution of the BRAF V600E mutational status in different FNAC groups is shown in Table 1. The BRAF molecular analysis yielded a negative test result in 591 (15.1%) samples and a positive result in 3324 (84.9%) samples.

The statistical diagnostic performance of BRAF V600E and FNAC was calculated and presented in Table 2. Additionally, we explored a parallel diagnostic modality where the results were considered positive if either BRAF or FNAC analysis showed positivity. The indeterminate results accounted for 2.2% (88/3915) of the cytological analysis. Therefore, we specifically tested the performance of BRAF mutation in the indeterminate (Bethesda III and IV) nodules to determine whether BRAF testing could serve as an accurate marker to complement FNAC in guiding thyroid surgery. Furthermore, we trained a predictive model based on logistic regression, in which the coefficients of BRAF and FNAC were 19.74 and 4.47, respectively.

Table 1 The distribution of the BRAF V600E mutational status in different FNAC groups

FNA Bethesda category	BRAF mutation		Total
	Positive	Negative	
Inadequate (I)	6 (60%)	4	10
Benign (II)	12 (63.2%)	7	19
Indeterminate (III, IV)	50 (56.8%)	38	88
Suspicious for malignant or malignant (V, VI)	3256 (85.7%)	542	3798
Total	3324	591	3915

FNA Fine needle aspiration

The sensitivity of BRAF and FNA analysis were 85.5% (95% CI 84.3–86.6%) and 97.6% (95% CI 97.0–98.0%), respectively. The specificity of BRAF and FNA were 100% (95% CI 84.5–100%) and 81.5% (95% CI 61.3–93.0%), respectively. Additionally, the sensitivity and specificity of BRAF analysis in the indeterminate cytology group were 72.5% (95% CI 60.2–82.2%), 100 (95% CI 79.1–100%). Moreover, the sensitivity and specificity of parallel analysis were 99.3% (95% CI 99.0–99.5%) and 81.5% (95% CI 61.3–93.0%). We plotted the ROC curves using sensitivity against 1-specificity (Fig. 2). The areas under the ROC curves (AUC) of BRAF testing, FNAC analysis, BRAF testing in the indeterminate cytology group, parallel analysis were 0.927 (95% CI 0.910–0.945), 0.895 (95% CI 0.809–0.982), 0.862 (95% CI 0.809–0.915), 0.904 (95% CI 0.817–0.991), respectively. In the multivariate predictive model, the AUC was 0.983 (95% CI 0.970–0.996). The positive predictive value (PPV) and negative predictive value (NPV) were also presented in Table 2.

Correlation between BRAF V600E and progressiveness of PTC

To investigate the relationship between BRAF V600E and clinical-pathological features of PTC, we only retained and analyzed those samples of 6105 patients with detailed descriptions of the lesions in the pathological reports. The relationships between the BRAF V600E mutation and the clinicopathological characteristics of the PTC patients are shown in Table 3 and Fig. 3. We found that the BRAF V600E mutation was associated with age, the mean age in the BRAF V600E mutation group was significantly higher than in the wild type group (42.17 ± 10.85 vs 40.14 ± 11.10; $P < 0.001$). Men were more subjective to BRAF mutation than women ($P = 0.041$). The data analysis presented Hashimoto's thyroiditis (HT) was less common among the BRAF positive patients ($P < 0.001$). And BRAF V600E were significantly associated with larger tumor size ($P = 0.008$), extrathyroidal extension ($P = 0.001$),

Table 2 Performance characteristics of cytology, molecular, and parallel analysis in definitive diagnosis of malignancy from thyroid nodules

Diagnostic modality	Sensitivity, %	Specificity, %	Positive predictive value,%	Negative predictive value,%	AUC
BRAF testing	85.5 (84.3–86.6)	100 (84.5–100)	100 (99.9–100)	4.6 (3.1–6.7)	0.927 (0.910–0.945)
FNA analysis	97.6 (97.0–98.0)	81.5 (61.3–93.0)	99.9 (99.7–100.0)	18.8 (12.4–27.3)	0.895 (0.809–0.982)
BRAF testing in FNA indeterminate cytology	72.5 (60.2–82.2)	100 (79.1–100)	100 (91.1–100)	50 (33.7–66.3)	0.862 (0.809–0.915)
Parallel analysis	99.3 (99.0–99.5)	81.5 (61.3–93.0)	99.9 (99.7–100.0)	44.9 (30.9–59.7)	0.904 (0.817–0.991)

FNA Fine needle aspiration

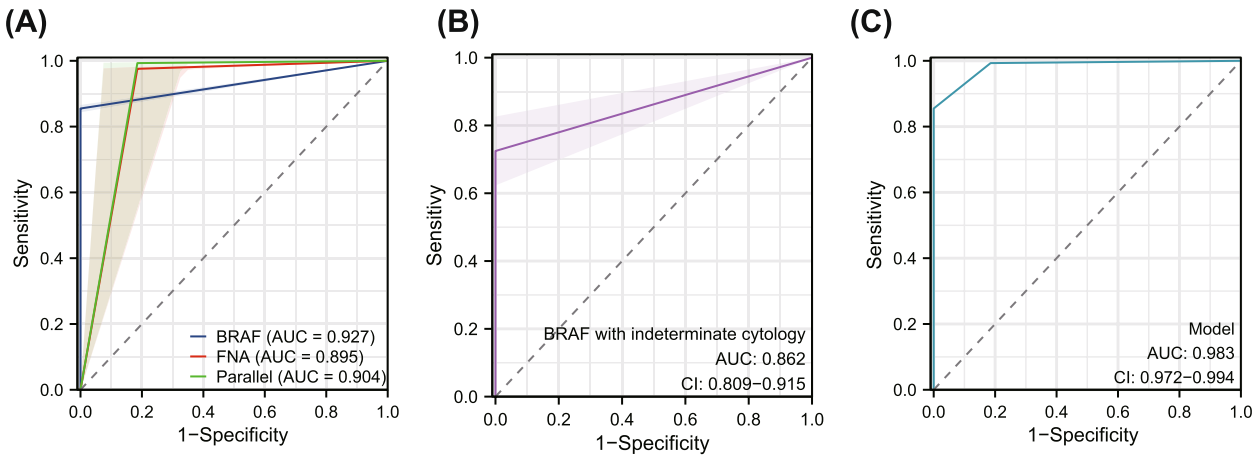

Fig. 2 ROC curves for the diagnosis of papillary thyroid cancer. **A** The areas under the ROC curves (AUC) for the BRAF mutation testing, FNAC analysis, parallel analysis were 0.927 (95% CI 0.910–0.945), 0.895 (95% CI 0.809–0.982), 0.904 (95% CI 0.817–0.991), respectively. **B** AUC for the BRAF testing in the indeterminate cytology group was 0.862 (95% CI 0.809–0.915). **C** AUC for the predictive model was 0.983 (95% CI 0.970–0.996)

Table 3 Correlations of BRAF mutation with clinicopathologic characteristics of 6105 PTC patients from 2018 to 2021

Characteristics	Wild type *n* = 783	BRAF mutation *n* = 5322	*P*
Age (years, mean ± SD)	40.14 ± 11.10	42.17 ± 10.85	< 0.001*
Gender			0.041*
Male	179 (22.9%)	1399 (26.3%)	
Female	604 (77.1%)	3923 (73.7%)	
HT			< 0.001*
No	524 (66.9%)	4179 (78.5%)	
Yes	259 (33.1%)	1143 (21.5%)	
Tumor size[a] (cm, mean ± SD)#	1.25 ± 0.82	1.33 ± 0.65	0.008*
Extrathyroidal extension			0.001*
None	683 (87.2%)	4356 (81.8%)	
Minimal extension	72 (9.2%)	657 (12.3%)	
Gross extension	28 (3.6%)	309 (5.8%)	
Multifocality			< 0.001*
No	604 (77.1%)	3649 (68.6%)	
Yes	179 (22.9%)	1673 (31.4%)	
Lymph node metastasis			0.095
No	429 (54.8%)	2746 (51.6%)	
Yes	354 (45.2%)	2576 (48.4%)	
Primary tumor stage			0.002*
T1	675 (86.2%)	4628 (87.0%)	
T2	73 (9.3%)	344 (6.5%)	
T3	15 (1.9%)	105 (2.0%)	
T4	20 (2.6%)	245 (4.6%)	
Recurrence	12	71	

P-values were determined by independent t-test and χ2

* *P*-value < 0.05; HT, Hashimoto thyroiditis

[a] Greatest tumor diameter

Patients with censored data were excluded

multifocality ($P < 0.001$) and primary tumor stage ($P = 0.002$). There were no significant associations found for lymph node metastasis ($P = 0.095$).

We performed a multivariate regression logistic analysis for the debatable clinical variables in order to investigate whether these features could be considered as independent predictors of the BRAF V600E mutation (Fig. 4). We chose to exclude the parameter of advanced T stage on account of its close clinical connection with tumor size and extrathyroidal invasion, which may render the advanced T stage of minimal statistical significance. We found that older age at diagnosis (OR: 1.016; 95% CI: 1.008–1.023; p value < 0.001), negative HT (OR: 0.559; 95% CI: 0.474–0.660; p value < 0.001), larger tumor size (OR: 1.172; 95% CI: 1.023–1.342; p value 0.022), extrathyroidal extension (OR: 1.221; 95% CI: 1.032–1.445; p value 0.02) and multifocality (OR: 1.463; 95% CI:1.222–1.752; p value < 0.001) were still significantly associated with the BRAF V600E mutation. No significant differences were found for gender and lymph node metastasis.

In light of its strong correlation with tumor size, we investigated whether the BRAF V600E presence was associated with increased tumor invasiveness also in micro-PTCs (tumor size ≤ 1). We conducted univariate and multivariate regression logistic analyses for micro-PTCs and the results are presented as follows (Fig. 5). The parallel conclusions were drawn that BRAF mutation was significantly associated with negative HT, extrathyroidal extension, and multifocality. In contrast, age was not found significant among micro-PTC patients. Notably, the significance of lymph node metastasis (OR: 1.261; 95% CI: 1.011–1.573; p value 0.040) related to the BRAF mutation in the univariate regression logistic analysis disappeared after adjusted for other variables.

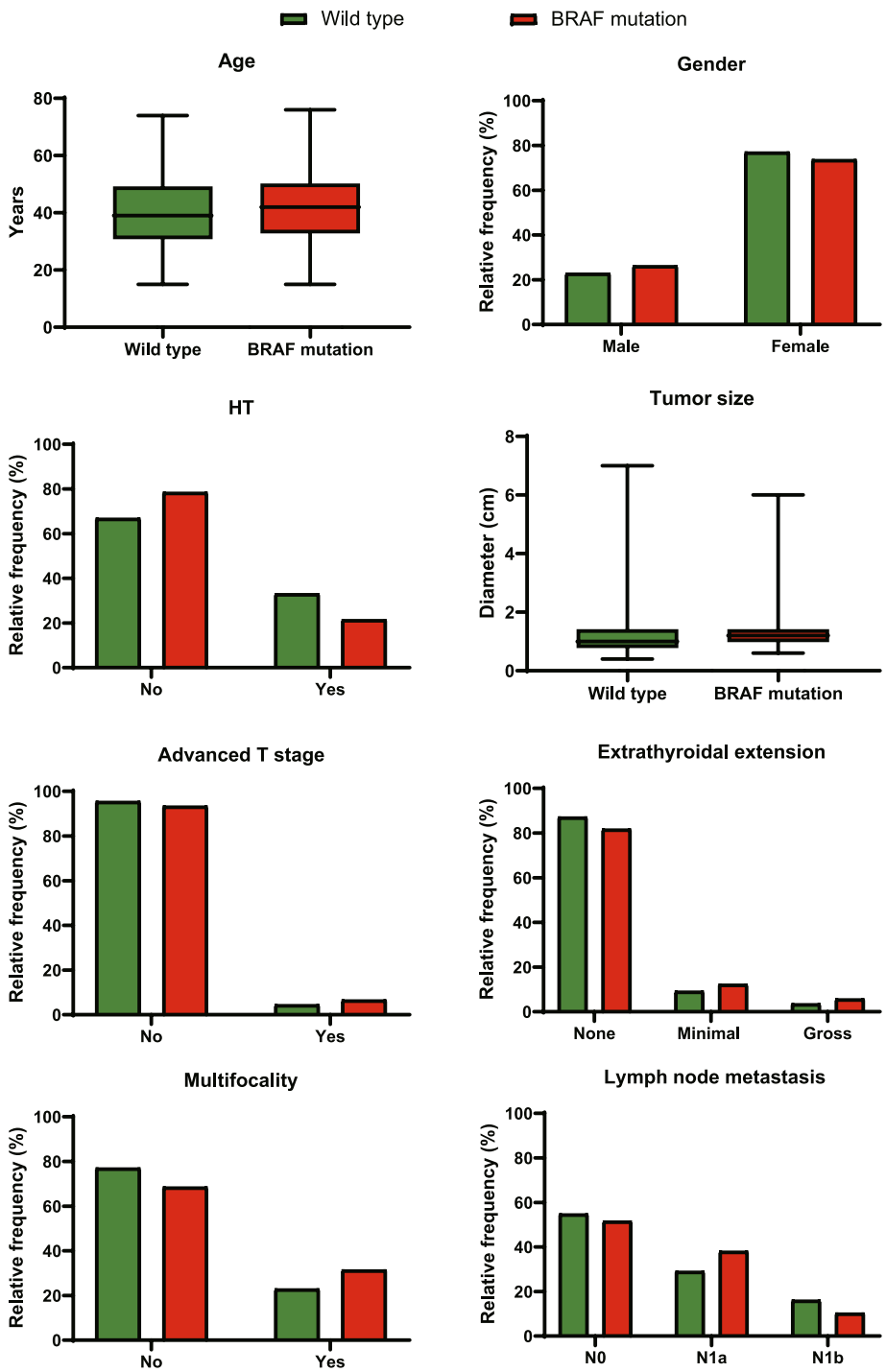

Fig. 3 BRAF testing of 6105 papillary thyroid cancer patients with detailed information on demographic, clinical, and pathological features

To investigate the relationship between BRAF V600E mutation and recurrence of PTC, the prognostic data of 6059 patients, who completed follow-up at the time of data cutoff, were analyzed and are presented in Table 4 and Fig. 6. All patients remained alive and free from distant recurrence at the last follow-up. Recurrence rates were significantly higher for BRAF mutation positive versus negative patients (5.2% vs 3.3%, $P=0.011$), with the medium time of no significant differences ($P=0.052$).

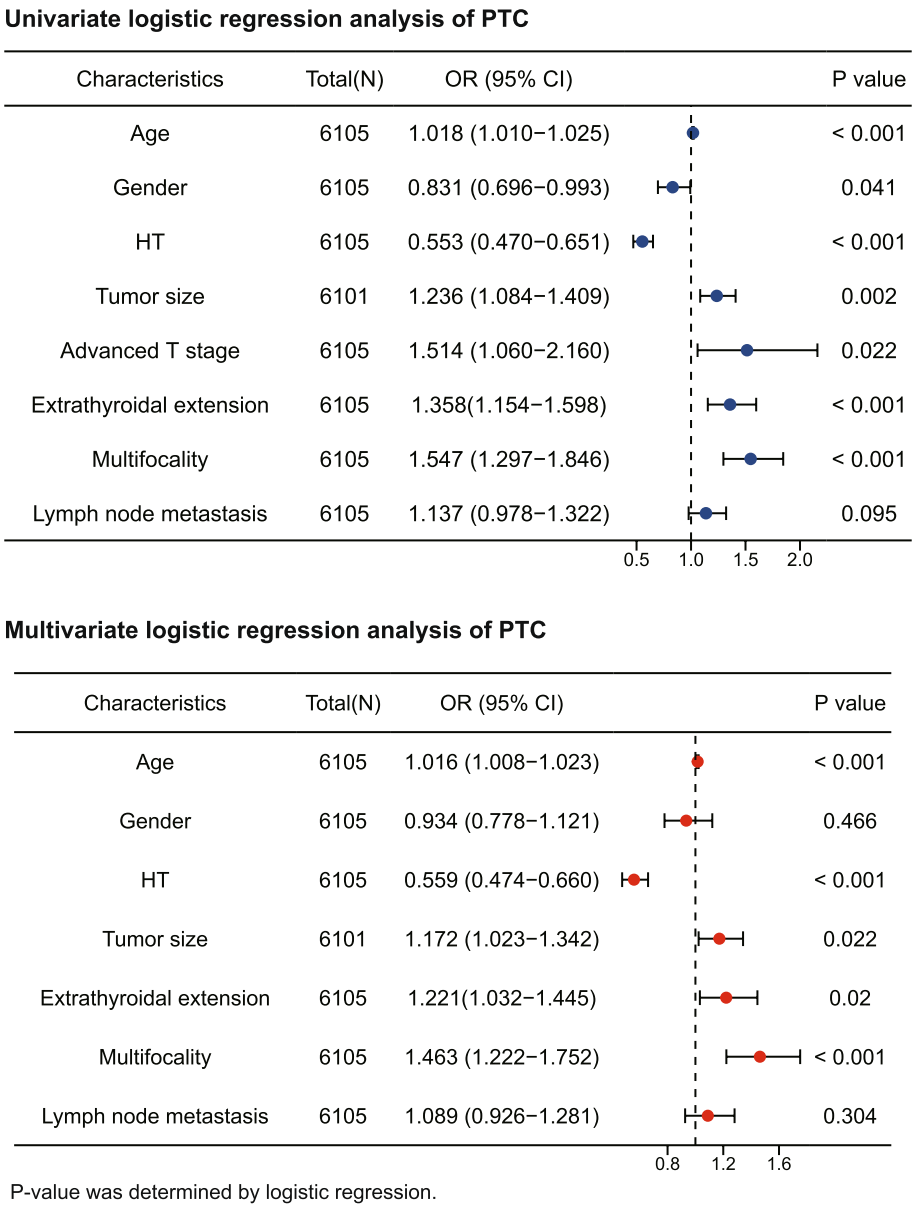

Fig. 4 Correlation between BRAF V600E and progressiveness of papillary thyroid carcinoma (PTC). Univariate and multivariate logistic regression analysis of the association of BRAF V600E with various clinicopathological parameters in 6105 patients with PTC

Discussion

Evidence has confirmed that there are considerable differences between the Western and Asian series, with a much higher prevalence of BRAF V600E in the latter. The prevalence ranges from 32–49% in the United States of America and Europe [21]. In addition, the heterogeneity of the BRAF rate has been addressed in Asian countries and regions, with the highest prevalence in East Asian countries (>70%), followed by Southeast Asia (57%), and a region encompassing South Asia, Central Asia, and the Middle East (<50%) [23]. Moreover, the within-country discrepancy has been discovered in China, ranging from 31 to 87% [24]. Therefore, it is of necessity to verify the role of BRAF V600E in specific population in an effort to adjust medical strategies appropriately rather than simply followed by contemporary international guidelines, which predominantly reflect western perspectives [25]. To our knowledge, We reported the largest prospective study aimed at investigating the BRAF mutation of PTC in homogenous population of Han Chinese, with detailed analyses on its prevalence, diagnostic performance and prognostic value. In our studied cohort, BRAF V600E

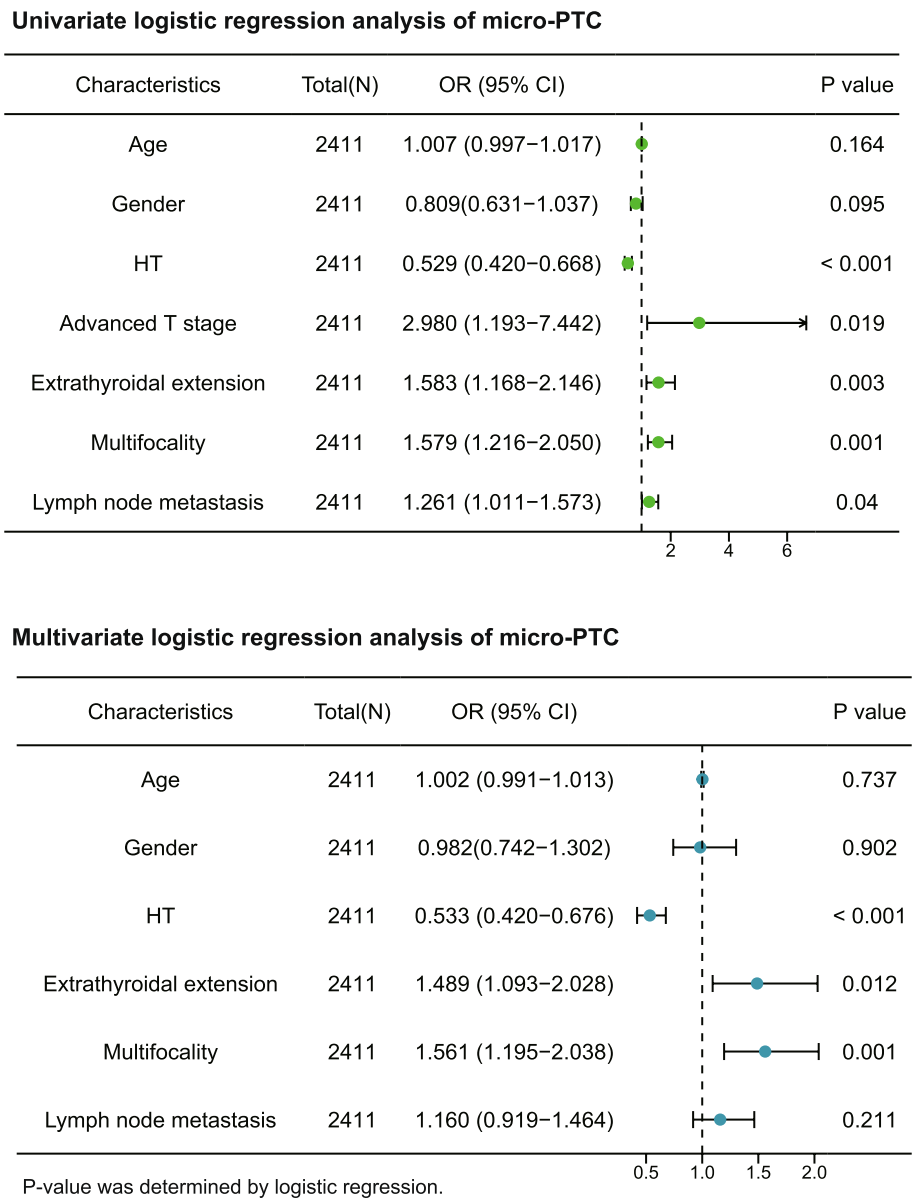

Fig. 5 Univariate and multivariate logistic regression analysis of the association of BRAF V600E with various clinicopathological parameters in 2411 patients with micro- papillary thyroid cancer (tumor size ≤ 1)

Table 4 Relationship between BRAF mutation and PTC recurrence

	BRAF mutation	Wild type	Total
Tumor recurrence	276/5276	26/783	302
Recurrence rate*(%)	5.2	3.3	5.0
Medium time of recurrence (months, mean ± SD)	22 ± 13	27 ± 13	23 ± 13

* *p* value < 0.05

was highly and predominantly detected in PTCs, which may result in robust sensitivity of diagnosis and solid connection with prognosis.

It is widely recognized that the most effective approach to curbing unnecessary thyroid surgeries involves improving the sensitivity and specificity of diagnosing thyroid nodules [26, 27]. Nikiforov et al. [28] conducted a large prospective study and illustrated that the BRAF test can enhance the accuracy of FNAC, especially in cases of indeterminate lesions, which account for

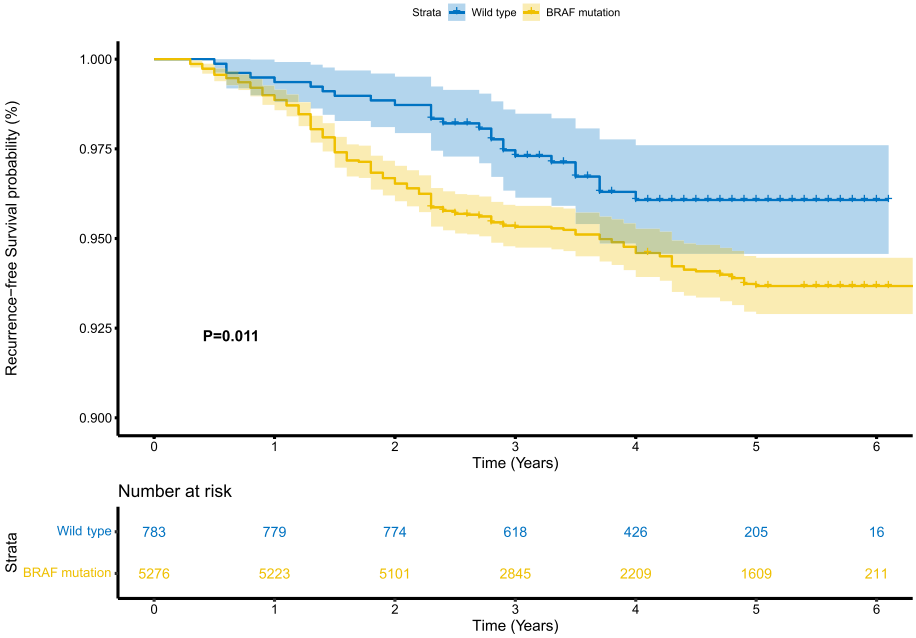

Fig. 6 Kaplan–Meier survival curve of effect of BRAF V600E mutation status on disease recurrence–free probability in patients with papillary thyroid cancer. Comparison of recurrence-free survival of patients, represented by indicated log-rank and *P* values in the panel, was performed between BRAF mutation and wild type groups. Follow-up time truncated at 6 years

10–40% of cytological results. We confirmed the molecular test alone had remarkably high specificity of 100%, which implicates BRAF V600E to be one of the decisive drivers in the process of tumorigenesis. Furthermore, the sensitivity is markedly increased due to the elevated prevalence of the BRAF mutation compared to the result reported by Jinih et al. [29], where only 44.5% of thyroid cancers tested positive for the mutation. Especially, BRAF analysis represents a suitable candidate for cytological indeterminate samples, being a cost effective procedure with a high accuracy for PTC with virtually no false-positive results, which can eliminate the need for repeated aspiration, diagnostic hemithyroidectomy and intraoperative pathology consultation. However, the discrepancy of BRAF mutation prevalence limited its potential to substitute FNAC in clinical practice. As proposed by Xing et al. [30], while the BRAF mutation test alone may not suffice as a highly sensitive diagnostic tool for evaluating thyroid nodules in general, all patients with cytologically diagnosed papillary thyroid carcinoma (PTC) should undergo preoperative BRAF mutation testing on their FNA specimens for prognostic purposes.

The association between patient age and the presence of the BRAF mutation has been a subject of controversy [31]. Although Basolo et al. [32] observed an inverse correlation, most investigators found a higher percentage of BRAF alterations in older patients [33, 34]. Our study supported the reciprocal trend and discovered that age was an independent risk factor for the BRAF V600E mutation. A study performed by Yokoyama et al. [35] demonstrated that remodeling of the normal epithelium by numerous driver-mutated clones was an inevitable consequence of normal aging. Consequently, the plausible explanation for this phenomenon could be that neoplastic transformation initiates more frequently in older individuals.

We found a significant and independent negative association between BRAF V600E and HT in PTC patients, aligning with findings from several prior studies [36]. The molecular associations between HT and PTC remain a subject of ongoing investigation [37]. Guerra et al. [38] proposed that the prevalence of the BRAF mutation in patients with HT has been underestimated by a dilution effect on the mutated alleles of infiltrating lymphocytes, which carried wild-type BRAF. Meanwhile, Pessôa-Pereira et al. [39] believed that the molecular circuits linking HT and PTC mostly did not involve the BRAF V600E mutation, but preferably RET/PTC rearrangements.

Both in vitro studies and transgenic models suggest that the BRAF V600E mutation promotes thyroid cancer progression and is associated with invasive thyroid cancer phenotype [40, 41]. While real-world studies exhibit some variability in their findings, a majority highlight a significant association between the BRAF mutation and one or more conventional adverse pathological features

of PTC [42–46]. Whereas the study performed by Guo et al. [42] did not identify a significant association in contrast to the prevailing trend. Our investigation, through multivariate analysis, reveals a positive and independent correlation between the BRAF mutation and key indicators of aggressive thyroid cancer, including larger tumor size, extrathyroidal extension, multifocality. To summarize, the BRAF V600E mutation is implicated in several high-risk clinical variables utilized in prognostic staging systems, indicating a heightened likelihood of disease recurrence and a poorer prognosis. In addition, we found the similar conclusion on micro-PTC that BRAF mutation was associated with negative HT, extrathyroidal extension and multifocality, except for age. Moreover, we demonstrated an unfavorable prognostic role of BRAF V600E based on large-sample follow ups for 6 years. The aggressive role and prognostic value of BRAF V600E mutation in PTC can be explained by several molecular mechanisms, including its aberrant regulation of various signaling pathways, such as the MAP kinase pathway, NF_kB pathway, and RASSF1A pathway; upregulation of various pro-oncogenic molecules; and downregulation of various tumor suppressor genes in thyroid cancer [47].

However, we could not confirm an independent prognostic role of BRAF V600E due to the lack of survival data, because the follow-up time was short in view of the natural course of thyroid cancer. In view of our results, it seems to be highly recommended to provide closer scrutiny and more intensive treatment to BRAF+patients of thyroid cancers, even of micro-PTCs which are generally biological indolent.

Conclusions

Our study underscores the clinical importance of the BRAF V600E mutation in PTC among Han Chinese patients. Our findings confirm a high prevalence of the mutation, particularly in PTCs, which is associated with aggressive tumor behavior, higher recurrence rates, and poorer prognosis. The mutation also demonstrates high specificity and sensitivity in diagnosing PTC, especially in cases of indeterminate cytology. These results emphasize the significance of BRAF V600E mutation testing in guiding treatment decisions and improving patient outcomes in PTC among Han Chinese patients. Although the results gained from this study alone is not sufficient to guide practice, follow-up data is necessary to validate the significance of BRAF mutation in terms of PTC survival.

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Authors' contributions
Y.L. onceptualized the study. R.C. and H.O. contributed to the methodology. R.C. conducted formal analysis. H.O. developed the software. F.X. provided supervision. D.Z. visualized the data. R.C. drafted the original manuscript, and R.C. and all authors reviewed and edited the manuscript.

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Availability of data and materials
The datasets generated and analyzed during the current study are not publicly available due privacy, but can be obtained by email (xiafada@csu.edu.cn) from the corresponding author on reasonable request

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Xiangya Hospital Central South University (No. 2022020377& 2023030424) and individual consent for this retrospective analysis was waived.

Competing interests
The authors declare no competing interests.

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