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Original Research Article

Immunohistochemical Expression of BRAF V600E in Papillary Thyroid Carcinoma: Correlation with Clinicopathological Parameters and Adverse Prognostic Factors

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Abstract: ***Background*:** Papillary thyroid carcinoma (PTC) is the most prevalent thyroid malignancy, and BRAF V600E represents its most common genetic alteration. Immunohistochemistry (IHC) using the VE1 antibody offers a cost-effective alternative to molecular methods for mutation detection, particularly in resource-limited settings. ***Aims*:** To estimate the immunohistochemical expression of BRAF V600E in all histological types of PTC and determine its association with adverse prognostic factors. ***Methods*:** This cross-sectional analytical study included 67 histopathologically confirmed PTC cases from a tertiary care center over 18 months. BRAF V600E IHC was performed using the VE1 clone. Expression was correlated with clinicopathological parameters including tumor size, histological subtype, lymph node metastasis, extrathyroidal extension, and capsular status. Receiver operating characteristic (ROC) curve analysis evaluated predictive performance. ***Results*:** BRAF V600E positivity was observed in 37.3% of cases. The cohort demonstrated female predominance (89.6%) with mean age of 44.9±14.7 years. Significant associations were identified between BRAF V600E expression and classic variant histology ($p<0.0001$), larger tumor size (4.6 versus 2.6 cm; $p<0.001$), lymph node metastasis (69.2% versus 8.1%; $p<0.0001$), extrathyroidal extension (30.8% versus 5.4%; $p=0.014$), and capsular involvement (53.8% versus 8.1%; $p=0.001$). ROC analysis demonstrated excellent predictive performance for lymph node invasion (AUC=0.83; sensitivity 81.8%; specificity 84.1%) and classic PTC histology (AUC=0.837; specificity 96.9%). ***Conclusion*:** BRAF V600E immunohistochemical expression significantly correlates with adverse clinicopathological features in PTC, supporting its utility as a cost-effective tool for risk stratification and treatment planning.

Keywords: BRAF V600E, Papillary Thyroid Carcinoma, Immunohistochemistry, Prognostic Factors.

INTRODUCTION

Papillary thyroid carcinoma (PTC) constitutes the predominant histological subtype of thyroid malignancy, accounting for 80–90% of all thyroid cancer diagnoses worldwide [1, 2]. Global epidemiological data indicate a progressive increase in thyroid cancer incidence over the past three decades, with annual rates documented at 5.4 per 100,000 in males and 6.5 per 100,000 in females, reflecting an estimated yearly rise of 6.2% [3]. In India, thyroid cancer represents approximately 1–2% of all malignancies, with notable regional heterogeneity; a recent analysis of 96 hospital-based cancer registries (2012–2019) revealed that 57.5% of PTC cases are concentrated in the South region, whereas 15.3% originate from Western India [4]. Despite rising incidence, PTC generally carries a favorable prognosis, with five-year survival rates exceeding 95% when appropriately managed [5]. However, a subset of patients develops recurrent disease, locoregional lymph node involvement, extrathyroidal extension, or distant metastases, necessitating identification of molecular biomarkers capable of predicting aggressive tumor behavior and guiding therapeutic intensity [6, 7].

The BRAF V600E mutation represents the most prevalent genetic alteration in PTC, occurring in 38–86% of cases depending on geographic region, histological subtype, and detection methodology [8, 9]. This somatic missense mutation involves a thymine-to-adenine transversion at nucleotide position 1799 within exon 15, resulting in substitution of valine with glutamic acid at codon 600 [10]. The resultant mutant protein exhibits constitutive kinase activity approximately 300–500 fold above wild-type levels, driving ligand-independent activation of the mitogen-activated protein kinase (MAPK) signaling cascade [11]. Extensive literature demonstrates robust associations between BRAF V600E positivity and adverse clinicopathological features, including increased lymph node metastasis, extrathyroidal extension, advanced pathological stage, multifocal disease, and radioiodine refractoriness [12–14]. A landmark prospective multicenter study encompassing 1849 patients across 13 institutions in seven countries reported BRAF V600E positivity in 45.7% of cases, with mortality rates of 5.3% in mutation-positive versus 1.1% in mutation-negative patients, establishing its role as an independent adverse prognosticator [15]. Current American Thyroid Association guidelines accordingly incorporate BRAF V600E status into risk stratification algorithms for PTC management [16].

Traditional molecular approaches for BRAF V600E detection, including Sanger sequencing and polymerase chain reaction-based techniques, require advanced laboratory infrastructure, specialized technical expertise, and substantial financial resources, thereby limiting accessibility in resource-constrained settings [17]. Immunohistochemistry (IHC) utilizing the VE1 monoclonal antibody, which specifically recognizes the mutant BRAF protein epitope spanning amino acids 596–606, offers a practical and cost-effective alternative [18]. This technique enables direct visualization of mutated BRAF expression through cytoplasmic staining within routine histopathological sections, obviating the need for specialized molecular equipment. Meta-analytic data from 4079 cases across 23 studies demonstrated excellent diagnostic performance of VE1 immunohistochemistry, with 100% sensitivity and 84% specificity compared to DNA sequencing, and 98% sensitivity with 89% specificity compared to polymerase chain reaction [19]. A validation study of 514 specimens further corroborated these findings, reporting 99.3% sensitivity, 100% specificity, and positive and negative predictive values of 100% and 96.4%, respectively [20].

Despite recognition of BRAF V600E positivity for enhanced risk assessment in international guidelines, standardized immunohistochemical protocols and consistent scoring criteria remain variable across institutions [16]. Furthermore, comprehensive characterization of the correlation between BRAF V600E immunohistochemical expression and pathological staging parameters across all PTC subtypes remains inadequately defined, particularly within the Indian population where region-specific epidemiological data are limited [4-21]. Therefore, this study was undertaken at a tertiary care center to systematically estimate the prevalence of BRAF V600E expression via immunohistochemistry across all PTC histological variants and to determine its association with established adverse prognostic factors in our patient population.

MATERIALS AND METHODS

Study Design and Setting

This cross-sectional analytical study was conducted at Bharati Vidyapeeth Deemed to Be University, Medical College, Hospital and Research Centre, a tertiary care institution, over a period of 18 months.

Sample Size and Selection Criteria

A total of 67 cases were included based on sample size estimation. Surgical specimens from patients who underwent total thyroidectomy, near-total thyroidectomy, or hemithyroidectomy with histopathologically confirmed papillary thyroid carcinoma (PTC), including all classical and variant subtypes, were included. Cases diagnosed as follicular adenoma, medullary carcinoma, and other papillary-like lesions were excluded.

Clinical Data Collection and Specimen Processing

Relevant demographic and clinical data including age, sex, and preoperative imaging findings were retrieved from patient medical records. Data collection was performed both retrospectively from archived records and prospectively for recent cases. All thyroidectomy specimens underwent systematic gross examination with documentation of specimen type, tumor size (maximum dimension in centimeters), tumor site, focality, extrathyroidal extension, and lymph node involvement. Representative sections from tumor, adjacent thyroid parenchyma, surgical margins, and all identified lymph nodes were processed for histopathological examination.

Histopathological Evaluation and Staging

Hematoxylin and eosin (H&E) stained sections were evaluated and reported according to the College of American Pathologists (CAP) protocol for thyroid carcinoma, documenting histological type and subtype, tumor size, focality, extrathyroidal extension, lymphovascular invasion, surgical margin status, and lymph node metastasis. All cases were assigned pathological TNM staging according to the American Joint Committee on Cancer (AJCC) 8th edition criteria [22].

Immunohistochemistry for BRAF V600E

Immunohistochemical staining was performed on 4-µm thick sections from selected formalin-fixed paraffin-embedded tissue blocks using poly-L-lysine coated slides. Heat-induced epitope retrieval was

performed using citrate-based buffer (Dako Target Retrieval Solution, 1:50 dilution) at 97°C for two cycles of 10 minutes each. Endogenous peroxidase activity was blocked with hydrogen peroxide for 30 minutes. Sections were incubated with primary antibody against BRAF V600E (clone VE1) for 2 hours at room temperature, followed by biotinylated secondary antibody for 1 hour. Detection was performed using the avidin-biotin complex (ABC) technique with 3,3'-diaminobenzidine (DAB) as chromogen. Sections were counterstained with Harris hematoxylin. Known BRAF V600E-positive PTC tissue served as positive control, while normal thyroid tissue served as negative control.

Interpretation of Immunohistochemistry

BRAF V600E immunohistochemical expression was categorized as: positive (unequivocal dark brown cytoplasmic staining in tumor cells), negative (absence of cytoplasmic staining), or equivocal (focal or weak cytoplasmic staining). All slides were independently reviewed by two pathologists, with consensus achieved through joint evaluation in discordant cases.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics Version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequencies and percentages; continuous variables were presented as mean ± standard deviation. Chi-square test or Fisher's exact test (when expected cell frequency <5) was employed for categorical variables. One-way ANOVA was used to compare means of continuous variables among BRAF V600E-positive, equivocal, and negative groups. Receiver operating characteristic (ROC) curve analysis was conducted to evaluate diagnostic performance of BRAF V600E expression in predicting adverse prognostic features, with area under the curve (AUC) and 95% confidence intervals calculated. A p-value <0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

A total of 67 patients with histopathologically confirmed papillary thyroid carcinoma were included in this study. BRAF V600E immunohistochemical expression was positive in 25 cases (37.3%), equivocal in 4 cases (6.0%), and negative in 37 cases (55.2%). The overall prevalence of BRAF V600E positivity in this cohort was 37.3%, which aligns with previously reported frequencies from the Indian subcontinent ranging between 33% and 58% [21].

The study cohort demonstrated a marked female predominance, with 60 females (89.6%) and 7 males (10.4%), yielding a female-to-male ratio of approximately 8.6:1. No statistically significant association was observed between gender and BRAF V600E expression status (p=0.592). The mean age of the entire cohort was 44.9 ± 14.7 years. Patients with BRAF V600E-positive tumors exhibited a higher mean age (49.3 ± 15.1 years) compared to those with negative expression (41.2 ± 14.0 years), though this difference did not attain statistical significance (p=0.081). The majority of patients were distributed in the 41–60 years age group (40.3%), followed by 21–40 years (35.8%), consistent with the typical age distribution of PTC reported in literature.

Histopathological Characteristics

The classic variant of papillary thyroid carcinoma was the predominant histological subtype, accounting for 35 cases (52.2%), followed by the follicular variant in 25 cases (37.3%). A highly significant association was observed between BRAF V600E expression and histological subtype (p<0.0001). Among BRAF V600E-positive cases, 96.2% (24/25) were of the classic variant, whereas only 3.8% (1/25) represented the follicular variant. Conversely, among BRAF V600E-negative cases, the follicular variant predominated at 62.2% (23/37), while the classic variant constituted only 18.9% (7/37). These findings corroborate the established molecular-morphological correlation wherein BRAF V600E mutations demonstrate preferential association with the classic papillary architecture [23, 24].

Regarding tumor dimensions, BRAF V600E-positive tumors exhibited significantly larger mean tumor size (4.6 ± 1.8 cm) compared to negative cases (2.6 ± 1.2 cm), with equivocal cases demonstrating the largest mean size (5.3 ± 2.5 cm). This difference was statistically significant (p<0.001), consistent with previous reports demonstrating BRAF V600E-driven constitutive MAPK pathway activation promoting accelerated tumor growth kinetics [25]. Multifocal disease was observed in 45 cases (67.2%) overall. Although a higher proportion of BRAF V600E-positive cases demonstrated multifocality (73.1%) compared to negative cases (59.5%), this difference did not reach statistical significance (p=0.186).

Association with Adverse Prognostic Factors

BRAF V600E expression demonstrated significant associations with several established adverse prognostic parameters. Lymph node metastasis was present in 22 cases (32.8%) overall, with a highly significant association with BRAF V600E status (p<0.0001). Among BRAF V600E-positive cases, 69.2% demonstrated lymph node involvement compared to only 8.1% among negative cases. Regional lymph node staging analysis revealed that N1a disease (central compartment metastasis) was present in 53.8% of BRAF V600E-positive tumors versus 8.1% of negative tumors (p=0.007). These findings are concordant with meta-analyses demonstrating odds ratios of 1.5 to 2.8 for nodal involvement in BRAF-mutated cases [12-26].

Capsular status analysis revealed significant differences across BRAF expression categories (p=0.001). Capsular involvement was observed in 53.8% of BRAF V600E-positive cases compared to only 8.1% of negative cases. One case (3.8%) in the positive group demonstrated frank capsular invasion.

Extrathyroidal extension, a critical prognostic determinant affecting pathological staging, was present in 10 cases (14.9%) overall. A statistically significant association was identified between BRAF V600E positivity and extrathyroidal extension (p=0.014), with 30.8% of positive cases demonstrating this feature compared to 5.4% of negative cases. This finding supports previous observations reporting two- to three-fold higher rates of capsular breach in BRAF-mutated tumors [13-27].

Angioinvasion was identified in 19 cases (28.4%) but did not demonstrate significant association with BRAF V600E status (p=0.34). Similarly, surgical margin involvement was observed in 8 cases (11.9%) without significant correlation to BRAF expression (p=0.177). Associated lymphocytic thyroiditis was documented in 8 cases (11.9%). Although a higher proportion of BRAF V600E-positive cases demonstrated associated thyroiditis (23.1%) compared to negative cases (5.4%), this difference approached but did not attain statistical significance (p=0.078).

Diagnostic Performance of BRAF V600E IHC Expression

Receiver operating characteristic curve analysis was performed to evaluate the discriminatory capacity of BRAF V600E immunohistochemical expression for predicting adverse clinicopathological parameters (Table 2). BRAF V600E expression demonstrated excellent predictive performance for lymph node invasion with an area under the curve (AUC) of 0.83 (95% CI: 0.717–0.942; p<0.001), sensitivity of 81.8%, and specificity of 84.1%. For prediction of classic papillary thyroid carcinoma histology, the AUC was 0.837 (95% CI: 0.735–0.940; p<0.0001) with 70.6% sensitivity and notably high specificity of 96.9%.

Good discriminatory performance was observed for capsular invasion prediction (AUC=0.788; 95% CI: 0.662–0.915; p<0.0001) with sensitivity and specificity both approximating 79%. Extrathyroidal extension prediction yielded an AUC of 0.748 (95% CI: 0.586–0.910; p=0.013) with 80% sensitivity and 69.6% specificity. In contrast, BRAF V600E expression demonstrated poor predictive capacity for angioinvasion (AUC=0.583; p=0.3) and margin involvement (AUC=0.64; p=0.2). The prediction of associated thyroiditis yielded an AUC of 0.711 (95% CI: 0.522–0.900) but did not achieve statistical significance (p=0.054).

RESULTS AND OBSERVATIONS

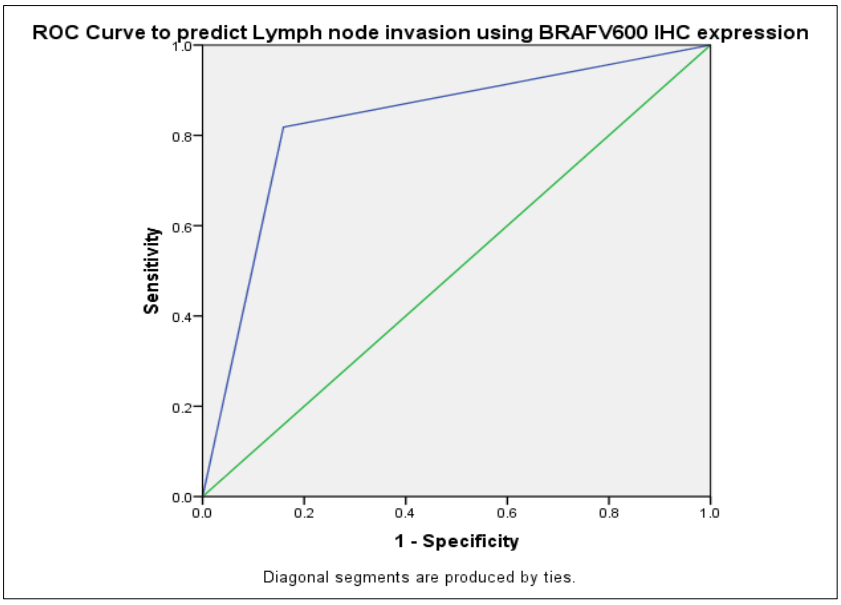
Table 1: Clinicopathological Characteristics in Relation to IHC BRAFV600 Status

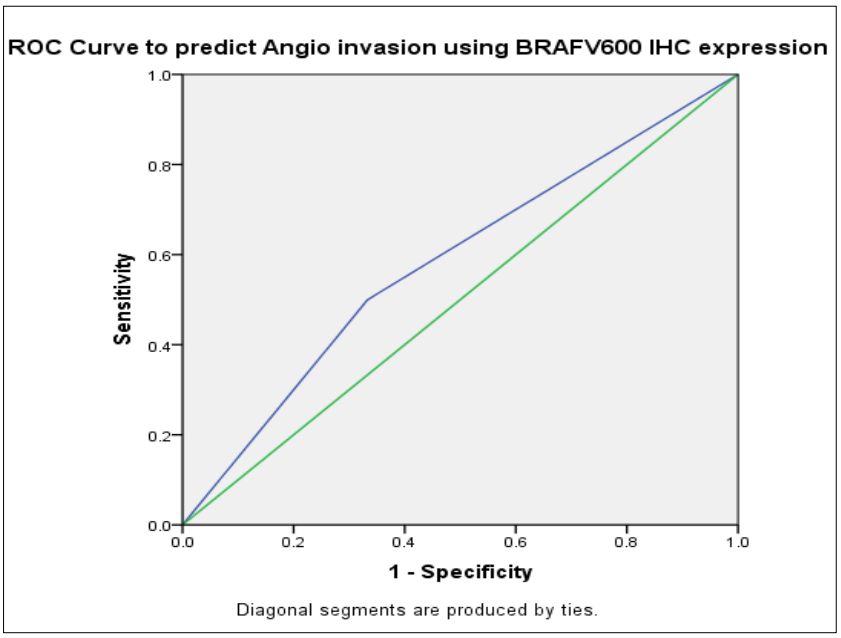
Characteristic	Category	BRAF V600E Expression				
		Positive (N=25) n (%)	Equivocal (N=4) n (%)	Negative (N=37) n (%)	Total n (%)	P value
Age distribution	≤20 years	0 (0.0)	1 (25.0)	4 (10.8)	5 (7.5)	0.272
	21–40 years	9 (34.6)	1 (25.0)	14 (37.8)	24 (35.8)	
	41–60 years	10 (38.5)	2 (50.0)	15 (40.5)	27 (40.3)	
	61–80 years	7 (26.9)	0 (0.0)	4 (10.8)	11 (16.4)	
Age (years)	Mean ± SD	49.3 ± 15.1	49.3 ± 11.1	41.2 ± 14.0	44.9 ± 14.7	0.081
Gender	Female	24 (92.3)	4 (100.0)	32 (86.5)	60 (89.6)	0.592
	Male	2 (7.7)	0 (0.0)	5 (13.5)	7 (10.4)	
Tumour focality	Multifocal	19 (73.1)	4 (100.0)	22 (59.5)	45 (67.2)	0.186
	Unifocal	7 (26.9)	0 (0.0)	15 (40.5)	22 (32.8)	
Lymph node invasion	No	3 (75.0)	34 (91.9)	8 (30.8)	45 (67.2)	<0.0001
	Yes	1 (25.0)	3 (8.1)	18 (69.2)	22 (32.8)	
Angioinvasion	No	16 (61.5)	3 (75.0)	29 (78.4)	48 (71.6)	0.34
Margins	Yes	10 (38.5)	1 (25.0)	8 (21.6)	19 (28.4)	
	Free	21 (80.8)	3 (75.0)	35 (94.6)	59 (88.1)	0.177
	Involved	5 (19.2)	1 (25.0)	2 (5.4)	8 (11.9)	
Capsular status	Capsular invasion	1 (3.8)	0 (0.0)	0 (0.0)	1 (1.5)	0.001
	Free	11 (42.3)	3 (75.0)	34 (91.9)	48 (71.6)	
	Involved	14 (53.8)	1 (25.0)	3 (8.1)	18 (26.9)	
Extrathyroidal extension	No	18 (69.2)	4 (100.0)	35 (94.6)	57 (85.1)	0.014
	Yes	8 (30.8)	0 (0.0)	2 (5.4)	10 (14.9)	
Nodal status	N1a	14 (53.8)	1 (25.0)	3 (8.1)	18 (26.9)	0.007
	N1b	1 (3.8)	0 (0.0)	0 (0.0)	1 (1.5)	
	NA	9 (34.6)	3 (75.0)	32 (86.5)	43 (64.2)	
	NE	0 (0.0)	0 (0.0)	1 (2.7)	1 (1.5)	
	NFM	0 (0.0)	0 (0.0)	1 (2.7)	1 (1.5)	
	YA	2 (7.7)	0 (0.0)	0 (0.0)	2 (3.0)	
	No	20 (76.9)	4 (100.0)	35 (94.6)	59 (88.1)	0.078

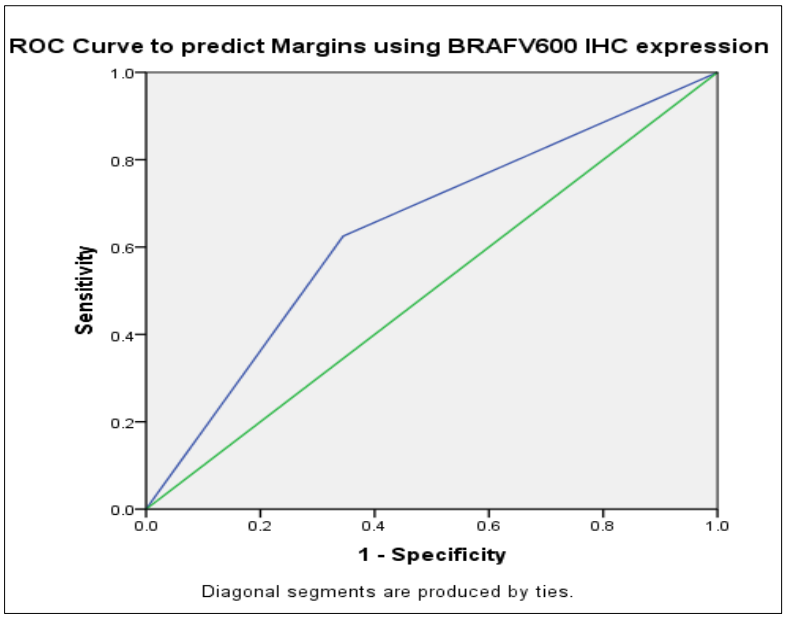
Associated thyroiditis	Yes	6 (23.1)	0 (0.0)	2 (5.4)	8 (11.9)	
Histological subtype	Anaplastic	0 (0.0)	0 (0.0)	1 (2.7)	1 (1.5)	<0.0001
	Classic	25 (96.2)	3 (75.0)	7 (18.9)	35 (52.2)	
	Follicular hyperplasia	0 (0.0)	0 (0.0)	3 (8.1)	3 (4.5)	
	Follicular nodular disease	0 (0.0)	0 (0.0)	3 (8.1)	3 (4.5)	
	Follicular variant	1 (3.8)	1 (25.0)	23 (62.2)	25 (37.3)	
Tumour size (cm)	Mean ± SD	4.6 ± 1.8	5.3 ± 2.5	2.6 ± 1.2	3.6 ± 1.9	<0.001

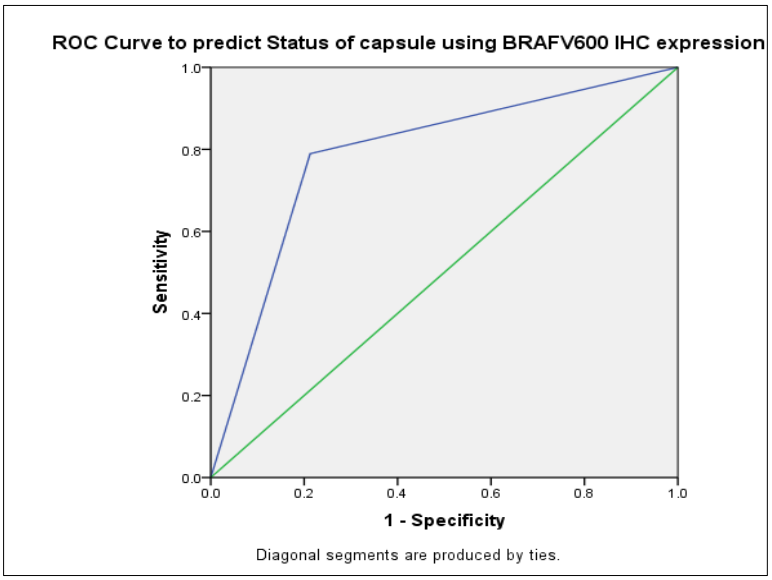
Table 2: ROC Curve Analysis for Prediction of Clinicopathological Parameters Using BRAFV600 IHC Expression

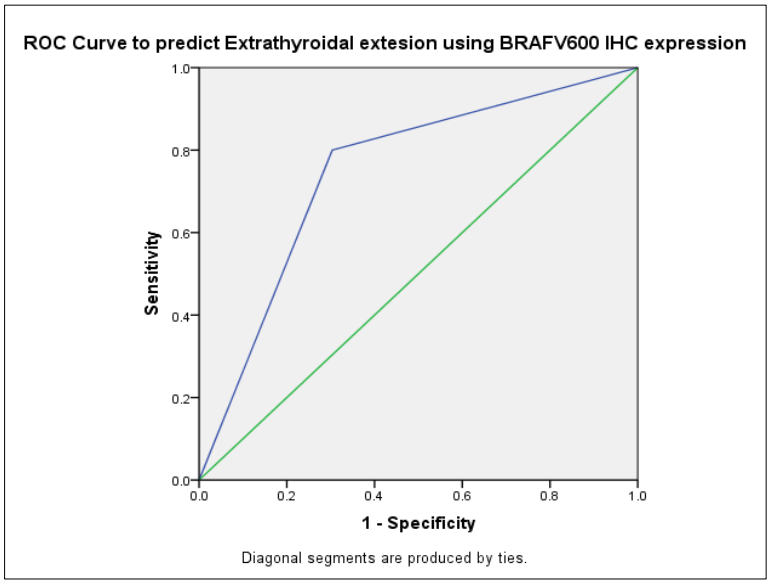
Predicted Outcome	AUC	95% CI (Lower–Upper)	Sensitivity (%)	Specificity (%)	P value
Lymph node invasion	0.83	0.717–0.942	81.8	84.1	<0.001
Angioinvasion	0.583	0.426–0.741	50	66.6	0.3
Margin involvement	0.64	0.432–0.848	62.5	65.5	0.2
Capsular invasion	0.788	0.662–0.915	78.9	78.8	<0.0001
Extrathyroidal extension	0.748	0.586–0.910	80	69.6	0.013
Associated thyroiditis	0.711	0.522–0.900	75	67.2	0.054
Classic papillary thyroid carcinoma	0.837	0.735–0.940	70.6	96.9	<0.0001

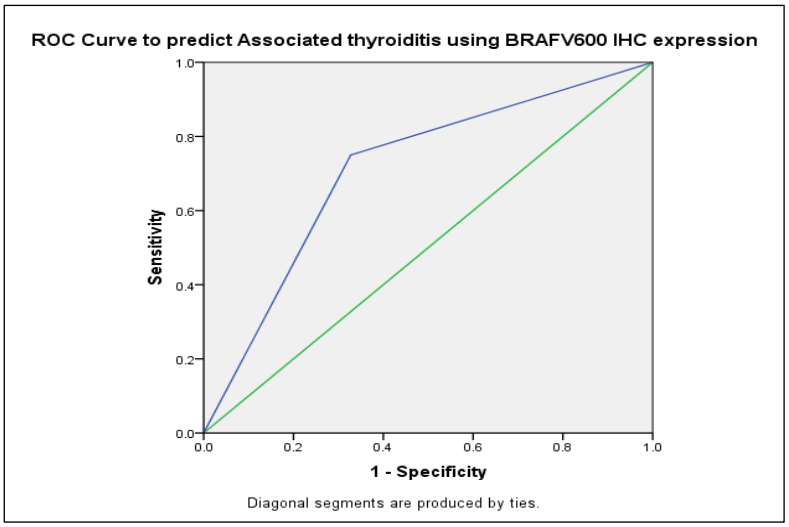





ROC Curve to predict Margins using BRAFV600 IHC expression
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0
Diagonal segments are produced by ties.


ROC Curve to predict Status of capsule using BRAFV600 IHC expression
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0
Diagonal segments are produced by ties.


ROC Curve to predict Extrathyroidal extesion using BRAFV600 IHC expression
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0
Diagonal segments are produced by ties.



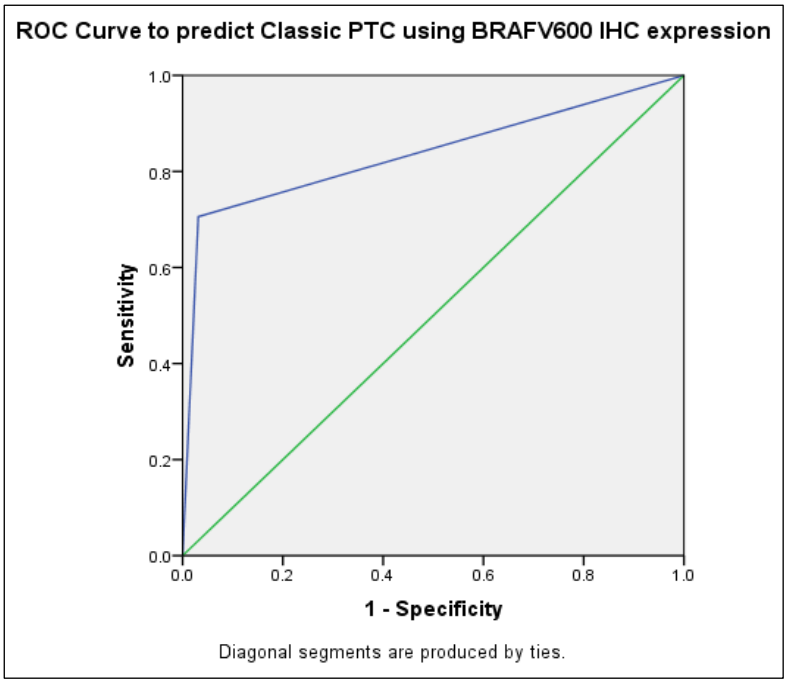


IMAGE GALLERY

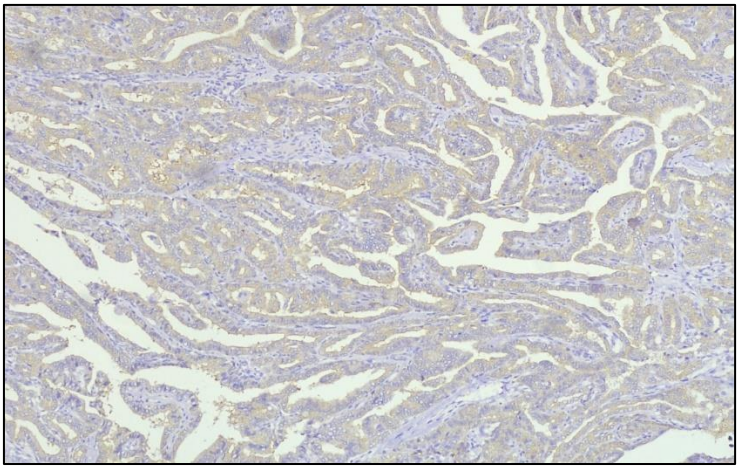


Figure 3: 6850/23 IHC positive for PTC

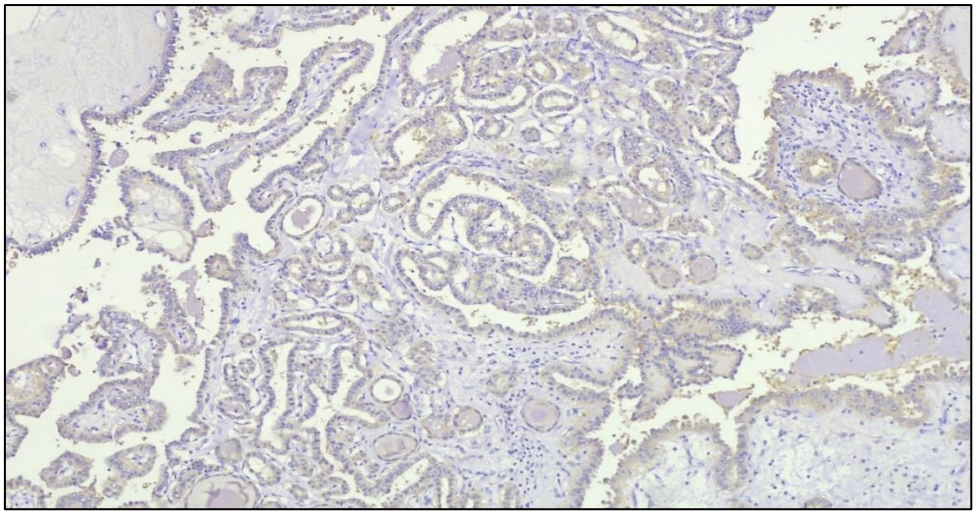


Figure 4: 6056/24 IHC positive for PTC

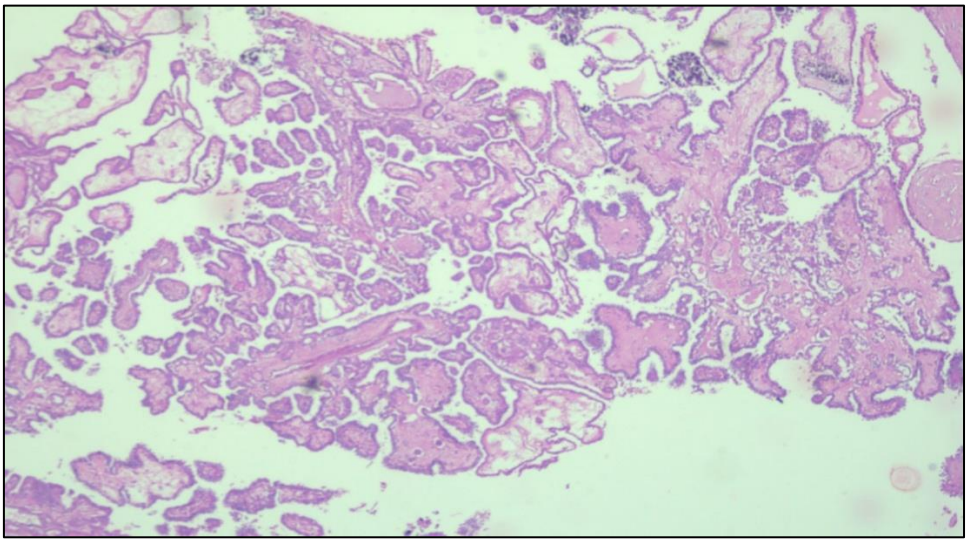


Figure 5: 5604/25 H&E of classic PTC

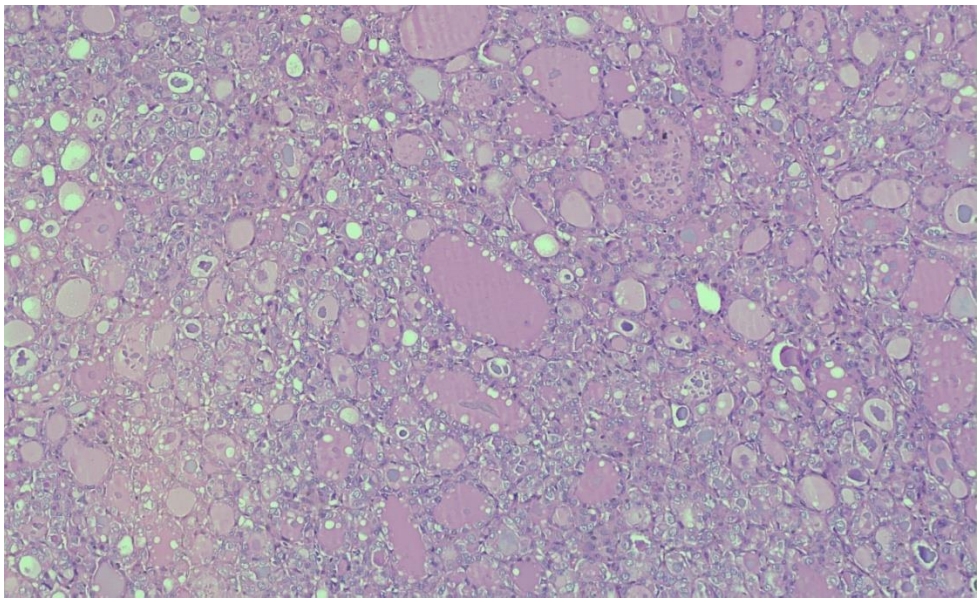


Figure 6: 4654/25 - H&E of Follicular nodular disease

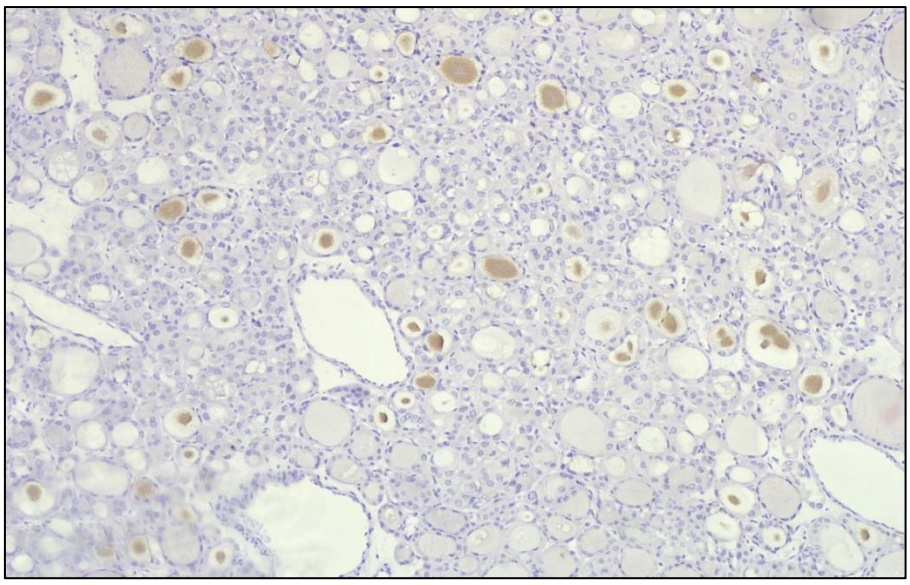


Figure 7: 4654/25 IHC negative for Follicular nodular disease

DISCUSSION

The present study evaluated immunohistochemical expression of BRAF V600E in papillary thyroid carcinoma at a tertiary care center in Western India, revealing an overall prevalence of 37.3%. This finding aligns with the lower end of the spectrum reported in Indian studies, which ranges between 33% and 58% [21-28]. The observed prevalence is comparable to that reported by Kristiani *et al*., (34%) and Kocheri *et al*., (38%), though lower than the 60–80% frequencies documented in certain Asian and Western cohorts [29, 30]. This variability likely reflects differences in histological subtype distribution, detection methodologies, and population-specific genetic factors influencing BRAF mutation frequency across geographic regions.

The demographic profile of our cohort demonstrated a marked female preponderance (89.6%) and mean age of 44.9 years, consistent with established epidemiological patterns of PTC [2]. Although BRAF V600E-positive cases exhibited higher mean age compared to negative cases (49.3 versus 41.2 years), this difference did not attain statistical significance, corroborating findings from several prior investigations that reported inconsistent age-mutation correlations [26]. Similarly, the absence of significant gender-based differences in mutation status aligns with the majority of published literature, though some studies have suggested marginally higher mutation frequencies in males [15].

A striking finding of this study was the near-exclusive association of BRAF V600E positivity with the classic variant of PTC, wherein 96.2% of positive cases demonstrated this histology compared to only 18.9% of negative cases. Conversely, the follicular variant predominated among BRAF-negative tumors (62.2%). This robust molecular-morphological correlation has been consistently documented across diverse populations and reflects the distinct oncogenic pathways operative in different PTC subtypes, with follicular variants characteristically harboring RAS mutations or gene fusions rather than BRAF alterations [23, 24]. The significant association between BRAF V600E expression and larger tumor size (4.6 versus 2.6 cm; $p<0.001$) observed in our study supports the biological premise that constitutive MAPK pathway activation drives accelerated cellular proliferation and tumor growth kinetics [25].

The principal clinical significance of our findings lies in the demonstrated associations between BRAF V600E positivity and established adverse prognostic parameters. Lymph node metastasis was present in 69.2% of BRAF-positive tumors compared to only 8.1% of negative cases, yielding excellent predictive performance on ROC analysis (AUC 0.83; sensitivity 81.8%; specificity 84.1%). Similarly, extrathyroidal extension occurred in 30.8% of positive versus 5.4% of negative cases, and capsular involvement demonstrated comparable disparity (53.8% versus 8.1%). These findings substantiate meta-analytic data reporting odds ratios of 1.5–2.8 for nodal involvement and two- to three-fold increased rates of extrathyroidal extension in BRAF-mutated PTC [12-26]. Such associations underscore the clinical utility of BRAF V600E immunohistochemistry in preoperative risk stratification, potentially informing decisions regarding surgical extent and necessity for prophylactic central compartment lymph node dissection.

The absence of significant associations with angioinvasion, surgical margin involvement, and multifocality in our cohort merits consideration. While some investigators have reported correlations between BRAF status and vascular invasion, others, including Koperek *et al*., found no significant relationship between mutation presence and parameters of aggressiveness in

microcarcinomas, suggesting that BRAF V600E may not universally predict aggressive behavior across all tumor size categories [31].

This study has certain limitations, including the relatively modest sample size, single-institution design, and absence of molecular confirmation of immunohistochemically equivocal cases. Additionally, clinical outcome data including recurrence and survival were not evaluated. Nevertheless, the high specificity (96.9%) of BRAF V600E immunohistochemistry for identifying classic PTC histology and its strong predictive value for lymph node metastasis support its utility as a cost-effective screening tool in resource-limited settings where molecular testing facilities are unavailable.

CONCLUSION

BRAF V600E immunohistochemical expression demonstrates significant associations with adverse clinicopathological features in PTC, including lymph node metastasis, extrathyroidal extension, capsular involvement, and larger tumor size. These findings support incorporation of BRAF V600E immunohistochemistry into routine pathological evaluation to facilitate risk-adapted treatment planning and surveillance strategies.

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