



Editorial

# Significance and Implications of BRAF-V600E mutation in Thyroid Neoplasm

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The incidence of thyroid cancer has increased worldwide over last few decades and it accounts for the most common endocrine tumor. This increased incidence of thyroid cancer is attributed to radiological detection of small thyroid lesions. In the last decade, there has been an unprecedented advancement in the molecular information of thyroid neoplasms, which has revolutionized the histological classification, prognostication, and evidence-based management of thyroid neoplasm.<sup>1–3</sup>

The recent World Health Organization classification of thyroid neoplasm has enlisted new categories based on histological features, molecular classification, and biological behavior. Overall follicular cell-derived neoplasms have been classified into benign tumors, low-risk neoplasm, and malignant neoplasm. Malignancies derived from thyroid follicular cells are categorized at the molecular level and majority of well differentiated thyroid carcinoma are grouped into two categories. The first, with predominantly expansile pattern of growth, often with clear encapsulation and follicular architecture are classified as RAS-like tumors due to associated high incidence of RAS mutations. These are the most differentiated carcinoma based on histomorphology, iodine metabolism, and functional thyroid differentiation expression profiles. The second important group with histological abnormalities including papillary architecture, infiltrative growth pattern have associated high frequency of BRAF-V600E mutation like tumors.<sup>1</sup>

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy (~85%). BRAF-V600E mutation is the most common underlying genetic alteration which leads to activation of downstream mitogen-activated protein kinase pathway, which eventually upregulates extracellular signal-regulated kinases pathway, causing tumorigenesis. This mutation is not only involved in tumorigenesis but also involved in transformation to aggressive high-grade differentiated

and nondifferentiated cancer. The frequency of BRAF-V600E mutation varies among the histological subtypes of PTC with highest frequency (80%) seen in tall cell variant. Some other subtypes of PTC also show BRAF-V600E mutations, like infiltrating follicular variant [FV-PTC], oncocytic variant, and some cases of warthin-like PTC. Hobnail PTC is clinically aggressive subtype of PTC that also shows BRAF-V600E mutation with concomitant TP53 mutations, TERT promoter mutations, and PIK3CA mutation, attributing to aggressive clinical course.<sup>1,4–6</sup>

The prognostic significance of BRAF-V600E mutations in PTC is still contentious. Many published studies have reported aggressive clinical outcome associated with this mutation, but this was predicted in univariate analysis. Moreover, high prevalence of this mutation is seen in papillary thyroid microcarcinoma (PTMC), which is associated with excellent prognosis.<sup>3–5,7,8</sup>

Silver et al<sup>9</sup> underscores the prognostic significance of BRAF-V600E mutation in determining the aggressiveness of PTC measuring  $\leq 1.5$ cm. In a retrospective study of 121 patients who were subjected to thyroid surgery for small PTC (1–1.5cm) or PTMC ( $\leq 1$ cm), BRAF-V600E mutations were detected in 42.4 and 43.6% of small PTC and PTMC, respectively. Among the PTMC cases with detected mutation, 54.1% demonstrated aggressive characteristics (extrathyroid extension, lymph node metastasis) in comparison to 19.4% of the nonmutated tumors. In the category of small PTC, aggressive pathological features were seen in 82.1% of mutated and 28.9% of non-mutated tumors. The authors suggested that performing the molecular testing for BRAF-V600E mutation can guide for appropriate patient care and management.<sup>9</sup>

Studies have shown that PTC with coexistent BRAF-V600E and TERT genetic mutations have poor disease-specific survival than those with either individual mutation alone.<sup>1,9</sup>

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The significance of detecting BRAF-V600E mutation in clinical management of thyroid lesion is more established as a diagnostic modality, especially in the fine-needle aspiration cytology (FNAC) of thyroid lesion under evaluation.<sup>2,6</sup>

Qi et al<sup>2</sup> retrospectively analyzed 252 patient who underwent thyroid surgery. All these patients underwent preoperative cytological examination, and thyroid puncture cell fluid was also analyzed for BRAF-V600E mutation by molecular testing: polymerase chain reaction (PCR). Postoperatively, 242 cases were diagnosed as PTC on histopathology examination that was used as gold standard diagnostic modality. In FNAC sample reporting, 57% of benign, 80% of indeterminate, and 88.9% of malignant cases shows BRAF-V600E mutation. The diagnostic sensitivity of BRAF-V600E mutation in samples from FNAC for diagnosing PTC was 91.7% in benign, 82.8% in indeterminate, and 89.4% in malignant cases; while the specificity was 100% in all the three categories. The authors found BRAF-V600E mutation analysis in samples from FNAC procedures as a highly effective supplementary diagnostic modality. However, prognostic significance of the mutation was not established.

Several other studies found BRAF-V600E mutation analysis as a useful adjuvant for detecting malignancy (PTC) in the cytological specimens of the thyroid lesion undergoing evaluation preoperatively, which helps in guiding the extent of operative procedure including regional lymph node dissection. Regarding the testing modality for detection of BRAF-V600E mutations, there has been a good concordance among gene sequencing, PCR, and IHC. In a study by Zhao et al,<sup>6</sup> the concordance for all the above mentioned three methods was seen in 92.4% of cases. The sensitivity and specificity for IHC was 98.6 and 97.6%, respectively. Hence, it can be utilized as the most convenient and reliable method in routine clinical workup of the cases. Immunostaining for BRAF-V600E using the clone VE1 is highly specific and sensitive for the detection of mutation in PTC. The staining should be diffuse and cytoplasmic ( $\geq 90\%$  of tumor cells) to be considered as positive test.

For the diagnosis of noninvasive follicular thyroid neoplasm with papillary-like-nuclear features (NIFTP), which is considered as low-risk thyroid neoplasm as per the recent WHO Classification (5<sup>th</sup> edition), the detection of BRAF-V600E mutation precludes the diagnosis of NIFTP. In the recent WHO classification of thyroid tumors update, molecular profiling data have revealed that infiltrative-FVPTC is a BRAF-like tumor (PTC family tumor), whereas encapsulated-FVPTC being a RAS-like neoplasm, aligns toward follicular thyroid carcinoma instead of PTC.<sup>1</sup>

In the recent WHO classification, two groups of high grade, nonanaplastic follicular derived carcinoma have emerged, that carries intermediate prognostic risk: poorly differentiated thyroid carcinoma (PDTC) and differentiated high-grade thyroid carcinoma (DHGTC). These tumors are large widely invasive and are associated with lymph node metastasis in about 30 to 50% of cases. Substantial proportion of DHGTC are BRAF-V600E driven and exhibit high proclivity for regional lymph node metastasis, while PDTC are enriched

in RAS mutations, and are commonly associated with regional and distant metastasis. In addition, both of these entities are associated with secondary mutations, of which TERT mutations are most frequent.<sup>1</sup>

Another diagnostic important implication of BRAF-V600E is in the correct categorization of squamous cell carcinoma of thyroid as a subtype of anaplastic thyroid carcinoma (ATC), which was considered as separate entity in previous WHO classification (4<sup>th</sup> edition).<sup>1,10,11</sup> Chen et al<sup>12</sup> has done analysis of multi-institutional data and found pure squamous cell carcinoma of thyroid with or without associated differentiated component, were associated with BRAF-V600E mutation in 87% of cases and had clinical outcome parallel to that of ATC. The diagnostic utility is more critical at the metastatic site like lung in which presence of squamous cell carcinoma with BRAF V600E mutation rules out a second primary etiology in lung and confirms it to be a metastasis from ATC with squamous morphology.

From a therapeutic point of view recently it has been emphasized to do prompt testing for BRAF-V600E in all ATC cases, as those with mutation associated ATC will respond to therapeutic target (BRAF plus MEK inhibitors).<sup>1</sup>

To conclude, BRAF-V600E mutation is the most common mutation seen in PTC, DHGTC, and ATC. IHC is an efficient and reliable modality for detection of this mutation. The clinical utility of detecting this mutation carries mainly diagnostic and therapeutic implications. In cytology specimen, the detection of this mutation is confirmatory of malignancy; whereas in ATC, this mutation offers a therapeutic avenue for targeted therapy.

#### Conflict of Interest

None declared.

#### References

- Baloch ZW, Asa SL, Barletta JA, et al. Overview of the 2022 WHO classification of thyroid neoplasms. *Endocr Pathol* 2022;33(01): 27–63
- Qi W, Shi C, Zhang P, Feng L, Wang J, Chen D. Effect of BRAF V600E mutation detection of fine-needle aspiration biopsy on diagnosis and treatment guidance of papillary thyroid carcinoma. *Pathol Res Pract* 2020;216(08):153037
- Kebebew E, Weng J, Bauer J, et al. The prevalence and prognostic value of BRAF mutation in thyroid cancer. *Ann Surg* 2007;246 (03):466–470, discussion 470–471
- Attia AS, Hussein M, Issa PP, et al. Association of BRAFV600E mutation with the aggressive behavior of papillary thyroid microcarcinoma: a meta-analysis of 33 studies. *Int J Mol Sci* 2022;23 (24):15626
- Kim WW, Ha TK, Bae SK. Clinical implications of the BRAF mutation in papillary thyroid carcinoma and chronic lymphocytic thyroiditis. *J Otolaryngol Head Neck Surg* 2018;47(01):4
- Zhao J, Liu P, Yu Y, et al. Comparison of diagnostic methods for the detection of a BRAF mutation in papillary thyroid cancer. *Oncol Lett* 2019;17(05):4661–4666
- Araque KA, Gubbi S, Klubo-Gwiedzinska J. Updates on the management of thyroid cancer. *Horm Metab Res* 2020;52(08): 562–577
- Cohen Y, Xing M, Mambo E, et al. BRAF mutation in papillary thyroid carcinoma. *J Natl Cancer Inst* 2003;95(08):625–627

- 9 Silver JA, Bogatchenko M, Pusztaszeri M, et al. BRAF V600E mutation is associated with aggressive features in papillary thyroid carcinomas  $\leq 1.5$  cm. *J Otolaryngol Head Neck Surg* 2021;50(01):63
- 10 Xu B, Fuchs T, Dogan S, et al. Dissecting anaplastic thyroid carcinoma: a comprehensive clinical, histologic, immunophenotypic, and molecular study of 360 cases. *Thyroid* 2020;30(10):1505–1517
- 11 Torrez M, Braunberger RC, Yilmaz E, Agarwal S. Primary squamous cell carcinoma of thyroid with a novel BRAF mutation and High PDL-1 expression: a case report with treatment implications and review of literature. *Pathol Res Pract* 2020;216(10):153146
- 12 Chen TY, Lorch JH, Wong KS, Barletta JA. Histological features of BRAF V600E-mutant anaplastic thyroid carcinoma. *Histopathology* 2020;77(02):314–320