VIA MEDICA

REVIEW ARTICLE

Nur Qodir[1], Bima Indra[2], Afifah Zulfa Salsabila[2]

[1]Department of Surgery, University of Sriwijaya/Mohammad Hoesin General Hospital, Palembang, Indonesia
[2]Faculty of Medicine, University of Sriwijaya, Palembang, Indonesia

Relationship between *BRAF V600E* mutation and recurrence of differentiated thyroid cancer — a systematic review

Address for correspondence:
Bima Indra, MD
Faculty of Medicine, University of Sriwijaya
Sudirman Street, 30126 Palembang, Indonesia
e-mail: bimaindra26@gmail.com

Oncology in Clinical Practice
DOI: 10.5603/ocp.104554

ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Introduction. The *BRAF V600E* mutation is implicated in the tumorigenesis of differentiated thyroid cancer, and its role in cancer recurrence remains debated. This systematic review aims to assess the relationship between *BRAF* mutations and the recurrence of DTC and its impact on lymph node metastasis and mortality.

Methods. Following PRISMA 2020 guidelines, a comprehensive search was performed across PubMed and ScienceDirect databases covering studies published up to September 2024. Eligible studies reported on the association between *BRAF V600E* mutation and recurrence in DTC. Data on patient characteristics, recurrence rates, metastasis, and mortality were extracted for synthesis.

Results. A total of seven studies with 4660 patients were included. Most of the patients had papillary thyroid carcinoma, and the mean age ranged from 40 to 54 years. Three studies found no significant association between *BRAF V600E* mutation and DTC recurrence, while two studies reported a significant association. Lymph node metastasis was associated with *BRAF* mutation in three studies, without contradictory findings. Regarding mortality, two studies found no significant association, whereas one study reported an increased mortality risk with *BRAF* mutation.

Conclusions. The relationship between *BRAF V600E* mutation and recurrence in DTC is inconclusive, with mixed findings across the studies. *BRAF V600E* mutation is more consistently linked to lymph node metastasis, though its role in predicting recurrence and mortality remains uncertain. Further research with standardized methodologies is required to better understand the clinical implications of *BRAF V600E* mutations in DTC.

Keywords: *BRAF* mutation, differentiated thyroid cancer, recurrence, metastasis, mortality.

Oncol Clin Pract

Introduction

Thyroid cancer particularly differentiated thyroid cancer (DTC), which includes papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), represents the majority of thyroid cancer cases, accounting for over 90% [1, 2]. The incidence of thyroid cancer has significantly increased over recent decades, partly due to advancements in diagnostic imaging [3]. Despite its rising incidence, DTC generally has a favorable prognosis, with 10-year survival rates exceeding 90% for PTC and FTC [4, 5]. Treatment typically involves surgery and radioactive iodine therapy, contributing to high survival rates [6].

Despite the overall positive prognosis, recurrence in DTC can occur in a subset of patients, influenced by

Received: 19.01.2025 Accepted: 17.03.2025 Early publication: 25.04.2025

several factors. Extrathyroidal extension, lymph node metastasis (LNM), and larger tumor size have been shown to significantly increase recurrence risk [7, 8]. Multifocality and bilaterality of tumors, particularly in certain populations, also contribute to recurrence [9]. Molecular markers, such as *BRAF* and *RAS* mutations, are associated with a more aggressive disease and higher recurrence rates [10]. Postoperative treatment, especially the effectiveness of radioactive iodine (RAI) ablation, further influences recurrence, with inadequate treatment linked to higher risks [11].

The *BRAF V600E* mutation is a common genetic alteration in PTC, activating the mitogen-activated protein kinase (MAPK) signaling pathway, which drives tumor growth and progression [12]. It is associated with aggressive features, such as lymph node metastasis, extrathyroidal extension, and recurrence [13]. The mutation also contributes to the hypermethylation of tumor suppressor genes, promoting malignancy [14]. Clinically, the presence of the *BRAF* mutation is a marker of poor prognosis, influencing treatment strategies and risk stratification. Targeted therapies, including BRAF inhibitors, have shown promise in treating BRAF-mutant DTC, particularly in cases resistant to standard treatments [15].

The role of *BRAF V600E* as a predictor of recurrence and mortality in DTC remains controversial. Some studies report a strong association between *BRAF* mutation and worse outcomes, including higher recurrence rates and mortality [14]. However, other studies have found no significant link between *BRAF* mutation and recurrence, suggesting that its prognostic value may be limited [10]. The coexistence of other genetic mutations, such as Telomerase Reverse Transcriptase (TERT), may also influence the impact of *BRAF*, complicating its role as an independent prognostic marker [16].

Despite numerous studies exploring the role of the *BRAF V600E* mutation in DTC, there is no clear consensus on its impact on recurrence and mortality. While some research highlights a strong association between *BRAF* mutation and aggressive tumor behavior, others find no significant link, leading to confusion regarding its prognostic value. Given these conflicting findings, a systematic review is necessary to synthesize available evidence, providing a clearer understanding of the relationship between *BRAF* mutation and DTC recurrence. This will aid in improving risk stratification and guiding clinical decision-making. The objective of this systematic review is to evaluate the association between the *BRAF V600E* mutation and the recurrence, lymph node metastasis, and mortality in patients with differentiated thyroid cancer. By compiling and analyzing existing studies, this review aims to provide clarity on the prognostic significance of *BRAF* mutation in DTC and its potential role in clinical management.

Methods

According to the PRISMA 2020 guidelines, a systematic literature search was conducted to identify studies examining the relationship between *BRAF* mutation and the recurrence of DTC. PubMed, ScienceDirect, CINAHL, Web of Science, and Trip Database were searched to find all relevant articles published until September 2024. The reviewers independently searched for combinations of "*BRAF V600E* mutation", "differentiated thyroid cancer", "recurrence", "metastasis", and "mortality." Any disagreements were resolved through discussion.

The criteria were set to include original studies published in English between the inception to September 2024 examining *BRAF V600E* mutations as indicators of recurrence, metastasis, and mortality in patients with DTC. The studies included both PTC and FTC. Studies without relevant outcomes, case reports, and reviews were excluded. The full-text articles were evaluated after initial screening of titles and abstracts.

Each study was assessed for bias using the ROBANS-2 (A Revised Risk of Bias Assessment Tool for Nonrandomized Studies of Interventions) tool. Confounders, selection bias, and outcome measurement were evaluated using this tool. The data extraction was performed independently by the reviewers. Data extracted included study design, patient characteristics, recurrence rates, lymph node metastasis, and mortality outcomes. Discrepancies were resolved through discussion. A meta-analysis was not possible due to heterogeneity across studies. This review summarizes the association between *BRAF* mutations and key outcomes in DTC. Mendeley References Manager's web version was used to manage references.

Results

In total, 1,140 articles were identified through database searches, with 372 articles from PubMed, 751 articles from ScienceDirect, and 17 articles from other sources. Following the removal of duplicates and screening of titles and abstracts, 10 articles were determined to be potentially relevant. Seven articles met the inclusion criteria for this systematic review after full-text reviews. PRISMA flowchart depicting identification, screening, and eligibility stages is shown in Figure 1.

ROBANS-2 was used to assess bias risk. Two studies were judged to have a high level of bias due to concerns about confounders and comparability of target groups. Four studies had a moderate bias risk, while one study had a low bias risk. All studies showed low risks of bias in blinding, outcome measurement, and outcome data, with confounding factors and group selection as the most common sources of bias. Table 1 shows the risk of bias assessment.

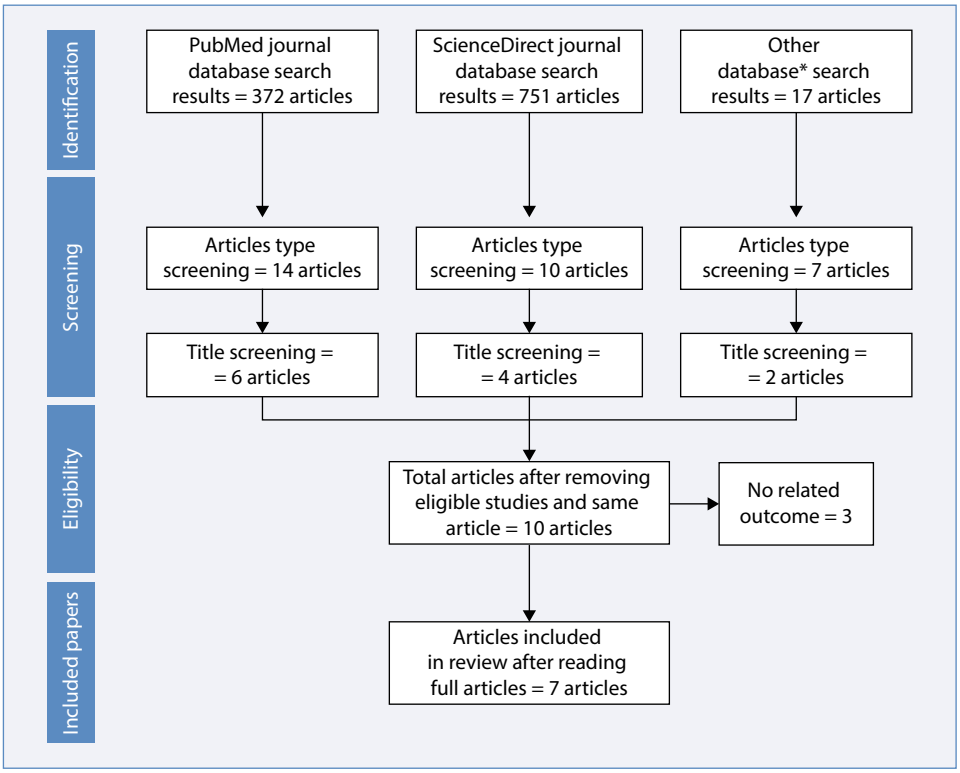

Figure 1. PRISMA flowchart; *CINAHL, Web of Science, Trip Database

Table 1. Risk of bias assessment using ROBANS-2

No.	Domain	Study index number						
		1	2	3	4	5	6	7
1	Comparability of the target group	Low	Low	High	Low	High	High	High
2	Target group selection	Low	High	Low	Low	Low	Low	Low
3	Confounders	Low	High	High	High	Low	Low	Low
4	Measurement of exposure	Low	Low	Low	Low	Low	Low	Low
5	Blinding of assessors	Low	Low	Low	Low	Low	Low	Low
6	Outcome assessment	Low	Low	Low	Low	Low	Low	Low
7	Incomplete outcome data	Low	Low	Low	Low	Low	Low	Low
8	Selective outcome reporting	Low	Low	Low	Low	Low	Low	Low
Overall results		**Low**	**High**	**High**	**Moderate**	**Moderate**	**Moderate**	**Moderate**

Table 2 summarizes the studies included. A total of 4,660 patients were included in the seven studies, 3,462 of whom were women and 1,178 of whom were men. PTC was the most common type of cancer, accounting for 4,640 cases, while FTC was rare. Study participants ranged in age from 40 to 54 years. Studies were conducted in a variety of countries, including China (2 studies), Indonesia, Vietnam, India, Brazil, and one multicenter study from the United States. Six studies used cohort designs while one used a case-control design.

A variety of studies included in the analysis showed inconsistent results regarding *BRAF V600E* mutations and DTC recurrences. There was no significant association between *BRAF V600E* mutation and thyroid cancer recurrence in three studies [10, 17, 18]. The *BRAF V600E* mutation, however, was associated with higher recurrence rates in three studies [19–21]. Even though a high proportion of patients in these studies carried the *BRAF* mutation, no recurrence was reported in the remaining study.

Regarding lymph node metastasis, two studies reported a significant association with the *BRAF* mutation [20, 21], and one study presented evidence contradicting this finding [17]. One study found a higher mortality rate among patients with the *BRAF* mutation [14],

Table 2. Summary of the included studies

No	Study Details	Subject characteristics	Results
1	Harahap et al. [10] Indonesia, 2022 Case control	N = 20 cases (15 women, 5 men) with recurrence of well-differentiated thyroid cancer and 20 controls (no recurrence). Mean age: 42.9–44.3 years	No significant difference between *BRAF V600E* expression intensity and thyroid cancer recurrence
2	Minh et al. [19] Vietnam, 2023 Cohort	N = 102 patients (18 women, 84 men) with thyroid carcinoma confirmed by histopathology. Mean age: 45.1 years	The recurrence rate was significantly higher in *BRAF V600E* mutation patients. Recurrence time: 12.39 ± 7.44 months (mutation) *vs.* 18.71 ± 7.44 months
3	Yan et al. [21] China, 2019 Cohort	N = 2,048 patients (1,556 women, 492 men) with PTC who underwent surgery. Mean age: 43.14 ± 11.01 years	*BRAF* mutation was higher in patients > 45 years. No significant association was found between *BRAFV600E* mutation and PTC persistence or recurrence, extrathyroidal invasion, vascular invasion, lymph node metastasis, and distant metastasis.
4	Barreno et al. [17] Brazil, 2022 Cross-sectional	N = 85 PTC samples (73 women, 12 men) from patients > 45 years. Mean age: 54 years	No significant association with recurrence or lymph node metastasis. Associated with tumors > 1 cm and extrathyroidal extension (p = 0.034)
5	Ramshankar et al. [20] India, 2017 Cohort	N = 53 patients (33 women, 20 men) with PTC. Median age: 40 years	*BRAF V600E* mutation is linked to poorer disease-free survival, regional lymph node metastasis, and recurrence
6	Xing et al. [14] Multicenter, 2013 Cohort	N = 1,849 patients (1,411 women, 438 men) treated with total thyroidectomy and neck dissection. Median age: 46 years	Prevalence of *BRAF V600E* was 45.7%. The mortality rate higher in BRAF-positive patients, but significance was reduced when metastasis was included
7	Huang et al. [18] China, 2019 Cohort	N = 483 patients (356 women, 127 men) with PTC. Mean age: 43.15 years	No recurrence or mortality was observed despite 90% *BRAF* mutation prevalence. Lymph node metastasis was higher in the non-BRAF mutation group

PTC — papillary thyroid carcinoma

whereas two studies found no significant association between the *BRAF V600E* mutation and mortality [18, 21]. However, when adjusting for other factors such as lymph node metastasis and extrathyroidal invasion, the association between *BRAF* mutation and mortality was no longer significant. According to the evidence, there is a complex relationship between *BRAF V600E* mutation and DTC outcomes, especially recurrence and metastasis, with findings varying across populations and study designs.

Discussion

Based on the findings of this review, *BRAF V600E* mutation is significantly associated with lymph node metastasis and recurrence in DTC patients. In DTC, particularly in PTC, *BRAF V600E* mutations play a critical role. Several interconnected mechanisms explain its role in DTC recurrence and lymph node metastasis. *BRAF V600E* activates the MAPK pathway, which contributes to recurrence through one of its primary pathways. *BRAF* is constantly activated by this mutation, resulting in uncontrolled proliferation and survival of cells via the MEK and ERK pathways [22, 23]. The mutation also facilitates the epithelial-mesenchymal transition (EMT), which enables cancer cells to become more invasive and metastatic, increasing the risk of recurrence [24]. Additionally, the *BRAF V600E* mutation is associated with the downregulation of genes involved in iodine metabolism, such as the sodium-iodide symporter (NIS), reducing the efficacy of RAI therapy, a key treatment for DTC. This resistance to RAI therapy allows cancer cells to survive, further elevating the risk of recurrence [25].

The coexistence of *BRAF V600E* with other genetic mutations, particularly *TERT promoter* mutations, exacerbates the aggressiveness of the disease. This combination enhances tumor growth, invasiveness, and recurrence potential [6]. Moreover, *BRAF V600E* increases the production of pro-tumorigenic factors like vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs), which facilitate tumor angiogenesis and invasion [14]. These factors contribute to a more aggressive tumor phenotype, increasing the likelihood of both local recurrence and metastasis. In terms of lymph node metastasis, *BRAF V600E* plays a crucial

role through similar mechanisms. The mutation activates the MAPK pathway, leading to increased expression of proteins involved in cell motility and invasion, such as MMPs, which degrade the extracellular matrix and enable cancer cells to migrate to lymph nodes [26]. Furthermore, BRAF V600E-induced EMT enhances the invasive capabilities of thyroid cancer cells, making them more likely to metastasize to lymph nodes [27]. Tumors harboring this mutation often exhibit aggressive features like larger size, multifocality, and extrathyroidal extension, all of which are associated with higher rates of lymph node metastasis [28]. Additionally, the *BRAF V600E* mutation creates a pro-inflammatory tumor microenvironment, increasing the production of cytokines and growth factors that promote lymphangiogenesis, further facilitating the spread of cancer cells to regional lymph nodes [29]. Studies have consistently shown that the *BRAF V600E* mutation is correlated with a higher incidence of both central and lateral lymph node metastasis in PTC [30].

This systematic review is the first to specifically focus on the relationship between the *BRAF V600E* mutation and recurrence in DTC. By synthesizing current evidence from diverse studies, this review provides valuable insights into the mutation's role in DTC progression, particularly in recurrence and lymph node metastasis. One strength of this review is its inclusion of studies from various geographical regions and different study designs, offering a broad and nuanced perspective on the prognostic implications of the *BRAF* mutation. Additionally, the use of PRISMA guidelines ensures a systematic, transparent, and unbiased approach, further enhancing the credibility of the findings. The risk of bias assessment across included studies also strengthens the reliability of the conclusions drawn.

While this systematic review offers important insights into the relationship between *BRAF V600E* mutation and recurrence in DTC, several limitations must be noted. First, there is significant heterogeneity across the included studies in terms of study design, population characteristics, and assessment methods for recurrence and metastasis, which may limit the comparability of results, and a meta-analysis could not be performed, limiting the ability to quantitatively assess the overall impact of the *BRAF* mutation on recurrence and mortality in DTC. Additionally, most of the included studies were assessed as having a moderate to high risk of bias. This raises concerns about the reliability of the findings in some cases. Another limitation is the possibility of publication bias, as studies with negative or inconclusive findings may be underreported. Despite these limitations, this review identifies key trends and areas for future research to better understand the clinical implications of *BRAF* mutations in DTC.

In terms of clinical practice, the findings have significant implications. While the *BRAF V600E* mutation is consistently associated with more aggressive features, such as lymph node metastasis, its predictive value for recurrence remains uncertain. Clinicians should therefore be cautious in using *BRAF* status as a sole prognostic marker and consider it in conjunction with other factors, including tumor size, extrathyroidal extension, and additional mutations like TERT. Moreover, the findings suggest that BRAF-positive tumors may demonstrate resistance to RAI therapy, highlighting the potential for targeted therapies to improve outcomes in this patient subgroup. As molecular testing becomes more common in thyroid cancer management, this review underscores the need for a comprehensive, individualized approach to risk stratification and treatment, particularly for patients with BRAF V600E-positive DTC.

Given the mixed findings regarding the relationship between *BRAF V600E* mutation and DTC outcomes, further research is crucial. Future studies should focus on addressing the limitations identified in this review, including the need for larger, multicenter trials with standardized methodologies to reduce heterogeneity. Consistent patient selection criteria, uniform follow-up periods, and comprehensive data on coexisting mutations are essential to clarify the true prognostic significance of *BRAF V600E*. Additionally, the role of *BRAF* in resistance to RAI therapy should be explored more thoroughly, as this has important implications for treatment strategies. Studies incorporating the latest targeted therapies and their effects on BRAF-positive patients are also needed to determine the best approaches to managing this mutation. Ultimately, well-designed, large-scale research will help refine risk stratification models, enabling clinicians to make more personalized and effective treatment decisions for patients with DTC.

Conclusions

Differentiated thyroid cancer recurrence and *BRAF V600E* mutations are inconsistently linked in this systematic review. *BRAF V600E* mutation has been associated with recurrence in some studies, but not in others. Although its role in predicting mortality is unclear, *BRAF V600E* mutation is more consistently linked to lymph node metastasis. The mixed findings suggest that further large-scale, well-designed studies are needed to determine the exact clinical impact of *BRAF V600E* mutation on DTC prognosis. The standardization of study methodologies will be crucial to clarifying these associations and guiding future clinical practice.

Article Information and Declarations

Author contributions

N.Q.: design, validation, supervision, writing — original draft preparation, project administration; B.I.: design, methodology, software, formal analysis, investigation, resources, data curation, writing — original draft preparation, writing — review and editing, project administration; A.S.: methodology, formal analysis, investigation, resources, data curation, writing — original draft preparation, writing — review and editing, project administration.

All authors have read and agreed to the published version of the manuscript.

Funding

No funding was received for this review by the authors.

Acknowledgements

This manuscript has been greatly improved by the valuable insight and suggestions provided by the peer reviewers.

Conflicts of interest

This systematic review is free of conflict of interest on the part of the authors. No financial or personal relationships have influenced the work presented by the authors in any way.

Supplementary material

None.

References

1. Cappellacci F, Canu GL, Piras S, et al. Technological Innovations in Thyroid Cancer Surgery. Oncologie. 2022; 24(1): 35–50, doi: 10.32604/oncologie.2022.020864.
2. Toraih EA, Hussein MH, Jishu JA, et al. Initial versus Staged Thyroidectomy for Differentiated Thyroid Cancer: A Retrospective Multi-Dimensional Cohort Analysis of Effectiveness and Safety. Cancers (Basel). 2024; 16(12), doi: 10.3390/cancers16122250, indexed in Pubmed: 38927955.
3. Zhang H, Li S, Li W. Development of a Prognostic Signature Based on Hypoxia-related Genes for Thyroid Cancer. Research Square. 2021, doi: 10.21203/rs.3.rs-438962/v1.
4. Wahba H, El-Hadaad H, Anter A, et al. Impact of Thyroglobulin on Survival and Prognosis of Differentiated Thyroid Cancer. J Cancer Ther. 2018; 09(09): 706–713, doi: 10.4236/jct.2018.99058.
5. Patrone R, Velotti N, Masone S, et al. Management of Low-Risk Thyroid Cancers: Is Active Surveillance a Valid Option? A Systematic Review of the Literature. J Clin Med. 2021; 10(16), doi: 10.3390/jcm10163569, indexed in Pubmed: 34441866.
6. Liu R, Bishop J, Zhu G, et al. Mortality Risk Stratification by Combining BRAF V600E and TERT Promoter Mutations in Papillary Thyroid Cancer: Genetic Duet of BRAF and TERT Promoter Mutations in Thyroid Cancer Mortality. JAMA Oncol. 2017; 3(2): 202–208, doi: 10.1001/jamaoncol.2016.3288, indexed in Pubmed: 27581851.
7. Amin SN, Shinn JR, Naguib MM, et al. Risk Factors and Outcomes of Postoperative Recurrent Well-Differentiated Thyroid Cancer: A Single Institution's 15-Year Experience. Otolaryngol Head Neck Surg. 2020; 162(4): 469–475, doi: 10.1177/0194599820904923, indexed in Pubmed: 32069184.
8. Anwar SL, Cahyono R, Suwardjo S, et al. Extrathyroidal extension and cervical node infiltration are associated with recurrences and shorter recurrence-free survival in differentiated thyroid cancer: a cohort study. Thyroid Res. 2022; 15(1): 13, doi: 10.1186/s13044-022-00131-7, indexed in Pubmed: 35883150.
9. Lo TE, Canto AUy, Maningat PD. Risk Factors for Recurrence in Filipinos with Well-Differentiated Thyroid Cancer. Endocrinol Metab (Seoul). 2015; 30(4): 543–550, doi: 10.3803/EnM.2015.30.4.543, indexed in Pubmed: 26485470.
10. Harahap WA, Tofrizal T, Oktahermoniza O. Relationship between the Expression of BRAF V600E and Ki-67 with the Recurrence of Well-Differentiated Thyroid Cancer. Asian Pac J Cancer Prev. 2022; 23(11): 3617–3622, doi: 10.31557/APJCP.2022.23.11.3617, indexed in Pubmed: 36444572.
11. Tsai CY, Lin SF, Chen ST, et al. Therapeutic Outcomes of Recurrent Well-Differentiated Thyroid Carcinomas. Int Surg. 2021; 104(7-8): 304–313, doi: 10.9738/intsurg-d-17-00132.1.
12. Kim TH, Park YJ, Lim JAh, et al. The association of the BRAF(V600E) mutation with prognostic factors and poor clinical outcome in papillary thyroid cancer: a meta-analysis. Cancer. 2012; 118(7): 1764–1773, doi: 10.1002/cncr.26500, indexed in Pubmed: 21882184.
13. Jafri S, Yaqub A. Redifferentiation of BRAF V600E-Mutated Radioiodine Refractory Metastatic Papillary Thyroid Cancer After Treatment With Dabrafenib and Trametinib. Cureus. 2021; 13(8): e17488, doi: 10.7759/cureus.17488, indexed in Pubmed: 34595070.
14. Xing M, Alzahrani AS, Carson KA, et al. Association between BRAF V600E mutation and mortality in patients with papillary thyroid cancer. JAMA. 2013; 309(14): 1493–1501, doi: 10.1001/jama.2013.3190, indexed in Pubmed: 23571588.
15. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer. J Clin Oncol. 2018; 36(1): 7–13, doi: 10.1200/JCO.2017.73.6785, indexed in Pubmed: 29072975.
16. Liu R, Xing MT. Promoter Mutations in Thyroid Cancer. Endocrine Related Cancer. 2016.
17. Barreno LR, Mello JB, Barros-Filho MC, et al. Characterization of BRAF mutation in patients older than 45 years with well-differentiated thyroid carcinoma. Braz J Otorhinolaryngol. 2022; 88(4): 523–528, doi: 10.1016/j.bjorl.2020.07.007, indexed in Pubmed: 32972866.
18. Huang M, Yan C, Xiao J, et al. Relevance and clinicopathologic relationship of BRAF V600E, TERT and NRAS mutations for papillary thyroid carcinoma patients in Northwest China. Diagn Pathol. 2019; 14(1): 74, doi: 10.1186/s13000-019-0849-6, indexed in Pubmed: 31300059.
19. Bui Dang Minh T, Nghiem Duc T, Phan Nguyen Thanh V, et al. Relationships of BRAF V600E Gene Mutation With Some Immunohistochemical Markers and Recurrence Rate in Patients With Thyroid Carcinoma. Clin Med Insights Oncol. 2023; 17: 11795549231203503, doi: 10.1177/11795549231203503, indexed in Pubmed: 37905233.
20. Yan C, Huang M, Li X, et al. Relationship between BRAF V600E and clinical features in papillary thyroid carcinoma. Endocr Connect. 2019; 8(7): 988–996, doi: 10.1530/EC-19-0246, indexed in Pubmed: 31252408.
21. Krishnamurthy A, Ramshankar V, Murherkar K, et al. Role and relevance of BRAF mutations in risk stratifying patients of papillary thyroid cancers along with a review of literature. Indian J Cancer. 2017; 54(1): 372–378, doi: 10.4103/ijc.IJC_182_17, indexed in Pubmed: 29199726.
22. Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014; 159(3): 676–690, doi: 10.1016/j.cell.2014.09.050, indexed in Pubmed: 25417114.
23. Mady LJ, Grimes MC, Khan NI, et al. Molecular Profile of Locally Aggressive Well Differentiated Thyroid Cancers. Sci Rep. 2020; 10(1): 8031, doi: 10.1038/s41598-020-64635-8, indexed in Pubmed: 32415114.
24. Li R, Hao J, Zhu Z, et al. Correlation between US-FNAC with BRAF V600E Mutation Analysis and Central Neck Lymph Node Metastasis in cN0 Papillary Thyroid Cancer. Biomed Res Int. 2021; 2021: 9937742, doi: 10.1155/2021/9937742, indexed in Pubmed: 34307677.
25. Liu J, Liu R, Shen X, et al. The Genetic Duet of V600E and Promoter Mutations Robustly Predicts Loss of Radioiodine Avidity in Recurrent Papillary Thyroid Cancer. J Nucl Med. 2020; 61(2): 177–182, doi: 10.2967/jnumed.119.227652, indexed in Pubmed: 31375570.
26. Sahin S, Daglar G, Menekse E, et al. The Effect of BRAF Mutation on Lymph Node Involvement in Papillary Thyroid Cancer. Turk J Surg. 2020; 36(3): 249–255, doi: 10.47717/turkjsurg.2020.4696, indexed in Pubmed: 33778379.
27. Wang X, Xu X, Peng C, et al. BRAF-induced KRT19 expression in thyroid cancer promotes lymph node metastasis via EMT. Oncol Lett. 2019; 18(1): 927–935, doi: 10.3892/ol.2019.10360, indexed in Pubmed: 31289571.
28. Fakhruddin N, Jabbour M, Novy M, et al. BRAF and NRAS Mutations in Papillary Thyroid Carcinoma and Concordance in BRAF Mutations

Between Primary and Corresponding Lymph Node Metastases. Sci Rep. 2017; 7(1): 4666, doi: 10.1038/s41598-017-04948-3, indexed in Pubmed: 28680105.
29. Lai Y, Gu Y, Yu M, et al. Younger Than 55 Years Old and V600E Mutation are Risk Factors for Lymph Node Metastasis in Papillary Thyroid Carcinomas ≤1.0 cm but Not in >1.0 cm. Int J Gen Med. 2023; 16: 1403–1414, doi: 10.2147/IJGM.S408588, indexed in Pubmed: 37155469.
30. Huang K, Gao N, Bian D, et al. Associations of BRAF V600E, clinical pathology and imaging factors with the recurrence rate of papillary thyroid microcarcinoma. Exp Ther Med. 2020; 20(6): 243, doi: 10.3892/etm.2020.9373, indexed in Pubmed: 33178341.