Journal of Infectious Diseases & Therapy
ISSN: 2332-0877

Research Article Open Access

BRAF V600E Gene Testing Combined with Serum TSH, TGAb and TPOAb Testing for the Diagnosis of Malignancy in TI-RADS 4 Nodules

Ya Jun Ying[1], Lin Zheng[2] and Yan Lin[3*]

[1]Department of Pathology, Taizhou Cancer Hospital, Zhejiang, China
[2]Department of Radiation Oncology, Taizhou Cancer Hospital, Zhejiang, China
[3]Department of Laboratory Medicine, Taizhou Cancer Hospital, Zhejiang, China

Abstract

Background: To evaluate the diagnostic value of *BRAF V600E* gene testing combined with serum Thyroid Stimulating Hormone (TSH), Thyroid Peroxidase Antibody (TPOAb) and Thyroglobulin Antibody (TGAb) testing for malignancy in Thyroid Imaging Reporting and Data System (TI-RADS) 4 nodules.

Methods: This was a retrospective study of patients who were diagnosed with TI-RADS 4 nodules via ultrasound examination during an outpatient or inpatient visit who underwent *BRAF V600E* gene testing and who had histopathological results from June 2020 to June 2022 at Taizhou Cancer Hospital. We compared the baseline characteristics, namely, age, sex, presence of lymph node metastasis, tumour size, cytological results and *BRAF V600E* gene testing results, of the two patient groups according to their postoperative pathological results. Using postoperative pathology as the gold standard, the sensitivity and specificity of serum TSH, TGAb and TPOAb and *BRAF V600E* gene testing alone for diagnosing malignant TI-RADS 4 nodules and the Area Under The Curve (AUC) were calculated. The four indicators were then combined to diagnose TI-RADS 4 nodule malignancy and the sensitivity, specificity and AUC were calculated.

Results: Among 112 patients with TI-RADS 4 nodules, 89 had malignant nodules and 23 had benign nodules. The proportions of patients with TI-RADS 4 nodules aged ≥ 50 years and aged <50 years were 89.9% (71/79) and 54.5% (18/33), respectively (p=0.000). The proportion of malignant TI-RADS 4 nodules >1 cm was significantly greater (86.8% (33/38)) than that of nodules ≤ 1 cm (75.7% (56/74), p=0.003). None of the benign modules were positive for the *BRAF V600E* gene mutation, but 73.0% of malignant nodules had this mutation (p=0.000). Among patients with and without the *BRAF V600E* gene mutation, 30.8% and 12.8%, respectively, had cervical lymph node metastasis (p=0.026). The sensitivity and specificity of *BRAF V600E* gene testing for diagnosing malignancy in TI-RADS 4 nodules were 100% and 48.94%, respectively. However, when the *BRAF V600E* gene was combined with the serum TSH, TGAb and TPOAb levels, the specificity and AUC of the combined indicators were 100% and 0.891, respectively.

Conclusion: The combination of *BRAF V600E* gene testing and serum TSH, TPOAb and TGAb testing has good clinical value for diagnosing malignancy in TI-RADS 4 nodules.

Keywords: TI-RADS 4 nodules; *BRAF V600E* ; Diagnostic test; Thyroid cancer

Abbervations: ROC: Receiver-Operator Characteristic Curve; TI-RADS: Thyroid Imaging-Reporting and Data System; FNAC: Fine Needle Aspiration Cytology; TSH: Thyroid-Stimulating Hormone; TGAb: Thyroid Globulin Antibody; TPOAb: Thyroid Peroxidase Antibodies.

Introduction

Among endocrine tumours, Thyroid Cancer (TC) is the most common. The increasing occurrence of TC is related to lifestyle, environmental or genetic factors [1,2]. It is one of the most common cancers in women with a threefold greater incidence in women than in men, which may be related to hormone secretion. TC especially Papillary Thyroid Carcinoma (PTC), has a high overall survival rate and good prognosis [3,4]. Superaudible-introductory Fine Needle Aspiration Cytology (FNAC) is traditionally used to assess the nature of all types of high-venture thyroid tumours. However, due to restrictions in cytological judgement, such as false-negative results, indeterminate meaning, or suspicion of malignancy, the use of molecular producers and serology for judgement is needed to increase the inspection rate of thyroid cancer. Researchers have studied the value of several molecular producers in the judgement of PTC and venture stratification and discovered that *BRAF V600E* gene aberrance is the most accurate diagnostic marker for PTC [5]. However, there are few reports on the diagnostic value of the *BRAF V600E* gene combined with serum TSH, TGAb and TPOAb for determining whether TI-RADS 4 tumours are bad. Therefore we aimed to explore the value of *BRAF V600E* gene expression combined with serum TSH, TGAb and TPOAb levels for diagnosing malignancies in TI-RADS 4 tumours.

Materials and Methods

This anamnestic research of patients diagnosed with TI-RADS 4 tumours who underwent surgery, with postoperative histopathological results as the gold standard, from June 2020 to June 2022 at TCH. This research was approved by the ECTCH.

Inclusion criteria

1) Single or multiple tumours; 2) indication for FNAC (patients diagnosed with TI-RADS 4 tumours by superaudible examination, with the largest lesion diameter exceeding 0.5 cm and no systemic organic or haemorrhagic diseases; 3) no history of other bad tumours or collar surgery; 4) complete clinical data and 5) ability to communicate independently.

Exclusion criteria

1) The absence of serum TSH, TPOAb and TGAb serological indicators; 2) the absence of *BRAF V600E* gene experimental results; 3)

***Corresponding author:** Yan Lin, Department of Laboratory Medicine, Taizhou Cancer Hospital, Zhejiang, China, E-mail: ly-1015@163.com

Received: 28-Oct-2024, Manuscript No. JIDT-24-156121; **Editor assigned:** 30-Oct-2024, PreQC No. JIDT-24-156121 (PQ); **Reviewed:** 13-Nov-2024, QC No. JIDT-24-156121; **Revised:** 20-Nov-2024, Manuscript No. JIDT-24-156121 (R); **Published:** 27-Nov-2024, DOI: 10.4173/2332-0877.24.8.617

Citation: Ying YJ, Zheng L, Lin Y (2024) *BRAF V600E* Gene Testing Combined with Serum TSH, TGAb and TPOAb Testing for the Diagnosis of Malignancy in TI-RADS 4 Nodules. J Infect Dis Ther 12:617.

nonsurgical patients.

The cytological pathological results were categorized as next

1) Nondiagnostic; 2) initiation; 3) atypia of dubious meaning; 4) turgid cancer; 5) dubious for cancer and 6) bad.

Patients with TI-RADS 4 tumours endured the *BRAF V600E* gene experiment and the rescopents served were obtained from Xiamen Ed Bio-Pharmaceutical Technology Co., Ltd. A human *BRAF V600E* gene aberrance inspection kit (fluorescent PCR method) was used for *BRAF V600E* somatic gene aberrance inspection (i.e., 1799T>A). Each patient was placed in an upturned position with the collar gently extended and sterile tissue was placed over the collar. The skin was disinfected with 0.5% iodine solution and local anaesthesia was administered. The physician used a 22-gauge needle to puncture the nodule under superaudible guidance, aspirating multiple points and evenly smearing the aspirate on 3-4 microscope slides, which were quickly fixed in 95% ethanol for the preparation of pathological sections. Another needle was inserted into the *BRAF V600E* gene experiment preservation solution.

Patients underwent thyroid function experiments. Before surgery, 3 ml of fasting blood was collected from each patient and the TSH, TGAb and TPOAb concentrations were measured using a Roche fully automated chemiluminescence analyser. The following criteria were used for energetic thyroid function indicators: TSH>5 μIU/ml, TPOAb>34 IU/ml and TGAb>115 IU/ml.

Total methods

The Kolmogorov-Smirnov (KS) experiment was used to simulate natural conditions. Classified shifts are used as a scale and persistent shifts are expressed as the mean ± standard deviation for ordinarily parted shifties. The chi-square test was used to compare the differences between teams for classified shifties. For diagnostic experiments, perception and excellence were computed, Receiver Operating Characteristic (ROC) curves were plotted and the Area Under The Curve (AUC) was computed. A two-tailed $p<0.05$ was considered to indicate total significance. IBM SPSS 25 total software was used to summarize the results.

Results

Clinicopathological characteristics

A total of 112 patients with TI-RADS 4 tumours including 21 males with a middling scope of 42.56 ± 13.33 years and 91 females with a middling scope of 41.83 ± 9.65 years, were included in the explanation (Figure 1). Among the 112 patients with TI-RADS 4 tumours, 89 had poor tumours, including 15 males (16.9%) and 84 females (83.1%). The proportion of patients aged ≥ 50 years with poor TI-RADS 4 tumours was 89.9% (71/79), while that of patients aged <50 years with poor tumours was 54.5% (18/33); this difference was significant (p=0.000). In the nodule size group, 86.8% (33/38) of the patients had poor TI-RADS 4 tumours >1 cm, while 75.7% (56/74) had TI-RADS 4 tumours ≤ 1 cm (p=0.003). Among the cytological types, there were 2 undiagnosed cases due to insufficient quantity, but the postoperative pathology of these 2 cases was initiated. There were 7 cases that were indeterminate, in which 2 tumours were initiated and 5 were bad on postoperative pathology. Among the poor tumours 80.9% were PTCs and 19.1% were other malignancies. The *BRAF V600E* gene experiment revealed that all 23 patients whose initiation tumours were negative for *BRAF V600E* gene aberrance while 73% of the 89 patients whose tumours were bad were energetic this difference was significant (p=0.000). Table 1 for details on *BRAF V600E* gene aberrance.

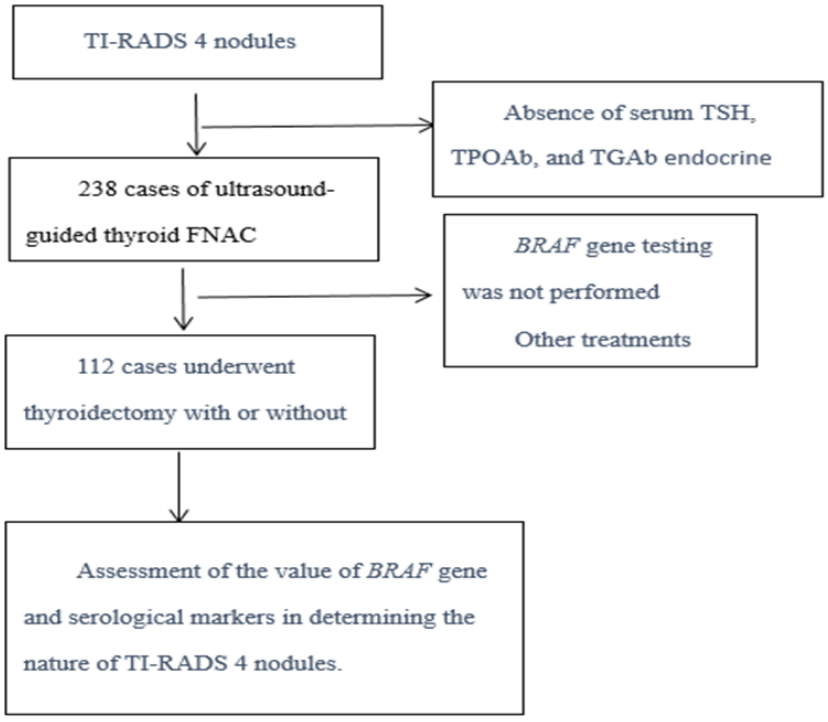

Figure 1: Flowchart of case selection. A total of 112 patients met the inclusion criteria. **Note:** TI-RADS: Thyroid Imaging Reporting and Data System; PTC: Papillary Thyroid Carcinoma; TSH: Thyroid-Stimulating Hormone; TPOAb: Thyroid Peroxidase Antibody; TGAb: Thyroglobulin Antibody; FNAC: Fine Needle Aspiration Cytology.

Clinical characteristics	Postoperative pathology		X^2 value	p-value
	Malignant (n=89)	Benign (n=23)		
Sex				
Men	15 (16.9%)	6 (26.1%)	1.553	0.213
Women	74 (83.1%)	17 (73.9%)		
Age				
<50	18 (20.2%)	15 (65.2%)	17.802	0
≥ 50	71 (79.8%)	8 (34.8%)		
Tumour size				
≤ 1 cm	56 (62.9%)	18 (78.3%)	8.54	0.003
>1 cm	33 (37.1%)	5 (21.7%)		
Cervical lymph node metastasis				
Yes	7 (7.9%)	0 (0.0%)	1.912	0.167
No	82 (92.1%)	23 (100%)		
Number of lesions				
Single	41 (46.1%)	7 (30.4%)	1.809	0.179
Multiple	48 (53.9%)	16 (69.6%)		
Sand granular calcification				
Yes	5 (5.6%)	0 (0.0%)	1.34	0.247
No	84 (94.4%)	23 (100%)		
Cytology results				
Lower puncture volume	0 (0.0%)	2 (8.7%)	103.246	0
Benign lesions	0 (0.0%)	19 (82.6%)		
Indeterminate lesions	5 (5.6%)	2 (8.7%)		
Other malignant lesions	12 (13.4%)	0 (0.0%)		
PTC	72 (81.0%)	0 (0.0%)		
Histopathology				
Benign	0 (0.0%)	23 (100.0%)	90.25	0
Other malignant lesions	17 (19.1%)	0 (0.0%)		
PTC	72 (80.9%)	0 (0.0%)		
Test indicators				
TSH (+)	45 (50.6%)	11(47.8%)	0.078	0.318
TPOAb (+)	35 (39.3%)	9 (39.1%)		
TGAb (+)	32 (36.0%)	9 (39.1%)		
***BRAF V600E* gene**				
Positive	65 (73.0%)	0 (0.0%)	40.029	0
Negative	24 (27.0%)	23 (100.0%)		

Note: TI-RADS: Thyroid Imaging Reporting and Data System; PTC: Papillary Thyroid Carcinoma; TSH: Thyroid-Stimulating Hormone; TPOAb: Thyroid Peroxidase Antibody; TGAb: Thyroglobulin Antibody

Table 1: Baseline characteristics of the patients with nodules (N=112) classified as TI-RADS 4.

Among the 112 patients with TI-RADS 4 tumours, 65 had *BRAF V600E* gene aberrance. Among patients with gene aberrances, 30.8% of those with a bad tumour had cervical lymph node metastasis, while among those without an aberrance, 12.8% of those with a bad tumour had cervical lymph node metastasis; the difference was significant (p=0.026). Among the 65 patients with *BRAF V600E* gene aberrance all had a bad nodule (100%); however, among the 47 patients without an aberrance, 23 had an initiation nodule and 24 had a bad nodule (51.1%). Among the 72 PTC patients 61 had a gene aberrance (84.7%) (Table 2).

Diagnostic experiment results

Although the prevalence of *BRAF V600E* gene aberrance alone for diagnosing malignancy in TI-RADS 4 tumours was 100%, the prevalence was low at only 48.94%. However, when the *BRAF V600E* mutation was combined with serum TSH, TGAb and TPOAb the detection rate was greater than that of TSH, TGAb and TPOAb alone. The increase in *BRAF V600E* gene aberrance in combination with serum TSH, TGAb and TPOAb was greater than that of each of the four indicators alone. The AUC of the four indicators combined was the highest, reaching 0.891 (95% CI, 0.832-0.949) (Figure 2 and Table 3).

Clinical characteristics	*BRAF V600E* gene		X^2 value	p-value
	Positive (n=65)	Negative (n=47)		
Sex				
Men	17 (26.1%)	12 (25.5%)	0.005	0.941
Women	48 (73.9%)	35 (74.5%)		
Age				
<50	18 (27.7%)	11 (23.4%)	0.261	0.609
≥ 50	47 (72.3%)	36 (76.6%)		
Tumour size				
≤1 cm	42 (64.6%)	37 (78.7%)	2.612	0.108
>1 cm	23 (35.4%)	10 (21.3%)		
Cervical lymph node metastasis				
Yes	20 (30.8%)	6 (12.8%)	4.96	0.026
No	45 (69.2%)	41 (87.2%)		
Number of lesions				
Single	31 (47.7%)	22 (46.8%)	0.009	0.926
Multiple	34 (52.3%)	25 (53.2%)		
Sand granular calcification				
Yes	4 (6.1%)	1 (2.1%)	1.027	0.311
No	61 (93.9%)	46 (87.9%)		
Cytology results				
Lower puncture volume	0 (0.0%)	2 (4.2%)	62.147	0
Benign lesions	0 (0.0%)	19 (40.4%)		
Indeterminate lesions	1 (1.5)	6 (12.8%)		
Other malignant lesions	0 (0.0%)	12 (25.5%)		
PTC	64 (98.5%)	8 (17.0%)		
Histopathology				
Benign lesions	0 (0.0%)	23 (48.9%)	61.174	0
Other malignant lesions	4 (6.1%)	13 (27.7%)		
PTC	61 (93.9%)	11 (23.4%)		
Test indicators				
TSH (+)	29 (44.6%)	27 (57.4%)	2.291	0.318
TPOAb (+)	28 (43.1%)	16 (34.0%)		
TGAb (+)	25 (38.5%)	16 (34.0%)		

Note: PTC: Papillary Thyroid Carcinoma; TSH: Thyroid-Stimulating Hormone; TPOAb: Thyroid Peroxidase Antibody; TGAb: Thyroglobulin Antibody.

Table 2: Baseline characteristics of the patients with nodules (N=112) according to *BRAF V600E* mutation status.

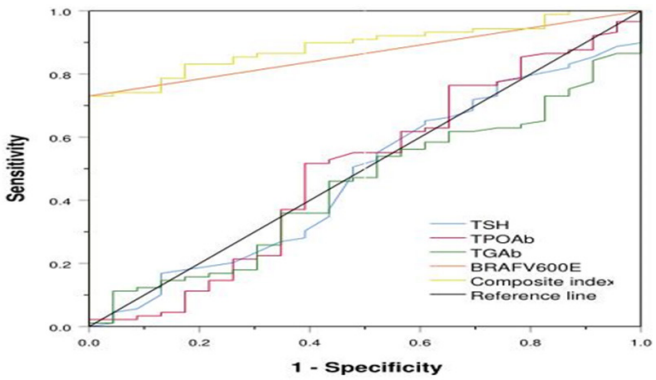

Figure 2: Receiver Operating Characteristic (ROC) curve analysis of the diagnostic performance of *BRAF V600E* gene testing combined with serum TSH, TPOAb and TGAb marker testing in distinguishing the nature of TI-RADS 4 nodules. **Note:** TSH: Thyroid-Stimulating Hormone; TPOAb: Thyroid Peroxidase; TGAb: Thyroglobulin; TI-RADS: Thyroid Imaging Reporting and Data System.

Index	AUC	SE	P	95% CI	Sensitivity	Specificity
TSH	0.476	0.068	0.727	0.343-0.610	65.17	39.13
TPOAb	0.496	0.073	0.948	0.353-0.638	51.69	60.87
TGAb	0.445	0.063	0.414	0.321-0.568	11.24	95.65
BRAF V600E	0.865	0.033	0	0.801-0.930	100	48.94
Composite index	0.891	0.03	0	0.832-0.949	73.03	100

Note: Composite indices: *BRAF V600E*, TSH, TPOAb and TGAb; TSH: Thyroid-Stimulating Hormone; TPOAb: Thyroid Peroxidase; TGAb: Thyroglobulin; TI-RADS: Thyroid Imaging Reporting and Data System.

Table 3: Comparison of the diagnostic value of *BRAF V600E* with TSH, TPOAb and TGAb testing of thyroid nodules classified as TI-RADS 4.

Discussion

Superaudible-introductory fine needle aspiration cytology is widely used as a minimally invasive examination for assessing thyroid lesions [6]. However, there is still uncertainty in 20% to 30% of cases with a pathological judgement [7]. For example among the 112 patients with TI-RADS 4 tumours in this research 2 were nondiagnostic due to insufficient quantity and 7 had indeterminate results. With the rapid progress in tumour molecular diagnostic technology it is now clear that aberrantly activated signalling pathways play a partial role in the occurrence and progression of thyroid tumours among which *BRAF* gene dysregulation is a partial event in the abnormal activation of the thyroid tumour pathway. BRAF leads to cellular abnormalities through the MAPK/ERK pathway and several studies have shown that aberrant *BRAF V600E* gene expression is related to pathological invasion, recurrence and mortality in primary tumours [8-10]. The *BRAF V600E* gene aberrance experiment may be clinically valuable especially for cases where cytology is inconclusive and is important for the early determination of PTC. Among *BRAF*gene aberrances, *BRAF V600E* gene aberrances are the most common in PTC and the rate of such aberrance is lower in other pathological types of thyroid cancer [11]. According to our diagnosis of PTC, 84.7% of the patients had *BRAF V600E* gene aberrance which is in accordance with the findings of Jing Zhang et al., [12,13]. Recent research has shown that *BRAF V600E* gene aberrance detection contributes to the clinical judgement, handling decisions and foreboding assessment of PTC [14]. However, there are few reports on the diagnostic value of *BRAF V600E* gene aberrance combined with serum TSH, TGAb and TPOAb for detecting the malignancy of TI-RADS 4 tumours. Our research revealed that the combined indicators have good clinical value for diagnosing malignancy in TI-RADS 4 tumours, with an AUC of 0.891.

The role of thyroid hormones in the occurrence of thyroid cancer is not completely clear but research has shown that TSH can bind to human TSH receptors stimulate the activity of adenylate cyclase and lead to thyroid cancer [15]. TSH can serve as a guiding serum factor in the screening of thyroid tumours and thyroid cancer and an elevated TSH level in patients with nodular thyroid disease is closely related to the development of differentiated thyroid cancer [16]. Fan et al., also reported that an increase in serum TSH manifests as an increase in thyroid cancer [17]. This finding suggests that TSH has diagnostic value in the screening of thyroid cancer. TPOAb and TGAb are two vital thyroid autoantibodies generally detected in patients with thyroid disease and have been confirmed to be vital thyroid autoantibodies for evaluating the development of thyroid tumours [18,19]. In this research, the perception and accuracy of TGAb for diagnosing poor thyroid tumours were 11.24% and 95.65%, respectively. In addition, Parham et al., showed that high levels of TPOAb may also be related to thyroid cancer [20]. Therefore, we combined serum TSH, TPOAb and TGAb with *BRAF V600E* gene aberrance inspection to diagnose the malignancy of TI-RADS 4 tumours and discovered that the AUC was greater than that of each indicator alone.

Although this study revealed that *BRAF V600E* gene aberrance combined with serum TSH, TGAb and TPOAb levels has good clinical value for diagnosing the malignancy of TI-RADS 4 tumours, there are still some limitations. First this was a single-centre anamnestic study with a small sample size, which may infuse the option principle and restrict the universality of the results. Moreover, although *BRAF V600E* gene aberrance experiments were combined with serum indicator experiments in this research, other potential molecular producers, such as RAS gene aberrations, which may also have an impact on the judgement of thyroid tumours, were not deemed. In addition, there may be controversy over the threshold values for serum indicators, as different studies may use different criteria, affecting the comparability of the results. Future research directions should include conducting larger-scale, multi-centre prospective research, considering the presence of more potential molecular producers, optimizing the threshold values of serum indicators and exploring new diagnostic methods, such as the application of artificial intelligence-assisted diagnostic technology in the judgement of thyroid tumours, to improve diagnostic accuracy.

Conclusion

In conclusion, this research revealed that *BRAF V600E* gene aberrance combined with serum TSH, TGAb and TPOAb levels has good clinical value for diagnosing the malignancy of TI-RADS 4 tumours. Future research should focus on conducting larger-scale, multi-centre prospective research and considering the presence of more potential molecular producers to further validate and refine this conclusion.

Ethics Approval and Consent to Participate

This retrospective study's protocol was approved by the Independent Ethics Committee of Taizhou Cancer Hospital (NO: SL-2023-037), patient records were anonymized and deidentified before analysis. We confirm that all methods were performed in accordance with the relevant guidelines and regulations.

Availability of Data and Materials

The datasets generated and/or analysed during the current study are not publicly available due privacy but are available from the the first author by reasonable request. At this point, we are not sharing the code publicly in order not to compromise potential commercialization of our system.

Competing Interests

The authors declare no competing interests.

Funding

This work was supported by the Wenling Science and Technology

Plan Project (2022S00031).

Authors Contributions

Yan Lin conceived and designed the study. Lin Zheng were responsible for data correction and interpretation, image data analysis. Ya Jun Ying were responsible for statistical analysis. Yan Lin did a major contributor in writing the manuscript. Lin Zheng and Ya Jun Ying were responsible for manuscript reviewing and editing. All authors read and approved the final manuscript.

References

1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, et al. (2016) American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. Thyroid 26:1-133.
2. Xu J, Ding K, Mu L, Huang J, Ye F, et al. (2022) Hashimoto's thyroiditis: A "double-edged sword" in thyroid carcinoma. Front Endocrinol 24:13-19.
3. Chen P, Pan L, Huang W, Feng H, Ouyang W, et al. (2020) *BRAF V600E* and lymph node metastases in papillary thyroid cancer. Endocr Connect 9:999-1008.
4. Yuan MW, Wang HH, Duan RF, Xu KP, Hu SY, et al. (2022) Analysis on cancer incidence and mortality attributed to Human papillomavirus infection in China, 2016. Chinese Journal of Epidemiology 43:702-708.
5. Li F, Chen G, Sheng C, Gusdon AM, Huang Y, et al. (2015) *BRAF V600E* mutation in papillary thyroid micro carcinoma: A meta-analysis. Endocr Relat Cancer 22:159-168.
6. Mayson SE, Haugen BR (2019) Molecular diagnostic evaluation of thyroid nodules. Endocrinol Metab Clin North Am 48:85-97.
7. Keutgen XM, Filicori F, Crowley MJ, Wang Y, Scognamiglio T, et al. (2012) A panel of four miRNAs accurately differentiates malignant from benign indeterminate thyroid lesions on fine needle aspiration. Clin Cancer Res 18:2032-2038.
8. Zhou B, Zhai YF, Zhang DY, Wang DQ, Wei L, et al. (2020) The role of combined *BRAF V600E* gene detection in the diagnosis of thyroid nodule determined as Bethesda III by fine-needle aspiration. Chinese Journal of Otolaryngology-Head and Neck Surgery 55:1057-1062.
9. Yan C, Huang M, Li X, Wang T, Ling R (2019) Relationship between *BRAF V600E* and clinical features in papillary thyroid carcinoma. Endocr Connect 8:988-996.
10. Walczyk A, Kowalska A, Kowalik A, Sygut J, Wypiórkiewicz E, et al. (2014) The *BRAF V600E* mutation in papillary thyroid micro carcinoma: Does the mutation have an impact on clinical outcome. Clin Endocrinol 80: 899-904.
11. Zhang J, Zhang J, Han J (2022) Advantages and clinical significance of enhanced CT combined with *BRAF V600E* gene detection in the diagnosis of papillary thyroid carcinoma. Med Eng Phys 28:110:103862.
12. Rashid FA, Munkhdelger J, Fukuoka J, Bychkov A (2020) Prevalence of *BRAF V600E* mutation in Asian series of papillary thyroid carcinoma-a contemporary systematic review. Gland Surg 9:1878-1900.
13. Su A, Zhao W, Wu W, Wei T, Ruan M, et al. (2020) The association of preoperative thyroid-stimulating hormone level and the risk of differentiated thyroid cancer in patients with thyroid nodules: A systematic review and meta-analysis. Am J Sung 220:634-641.
14. Xiang Y, Xu Y, Bhandari A, Sindan N, Hirachan S, et al. (2021) Serum TSH levels are associated with postoperative recurrence and lymph node metastasis of papillary thyroid carcinoma. Am J Transl Res 13:6108-6116.
15. Fan XY, You W, Chen Y, Nie CC, Wang XL, et al. (2024) A meta-analysis of the value of serum TSH concentration in the diagnosis of differentiated thyroid cancer in patients with thyroid nodules. Heliyon 10:e24391.
16. Wu X, Lun Y, Jiang H, Gang Q, Xin S, et al. (2014) Coexistence of thyroglobulin antibodies and thyroid peroxidase antibodies correlates with elevated thyroid-stimulating hormone level and advanced tumor stage of papillary thyroid cancer. Endocrine 46:554-560.
17. Udovcic M, Pena RH, Patham B (2017) Hypothyroidism and the heart. Methodist Debakey Cardiovasc J 13:55-59.
18. Parham M, Aminorroaya A, Amini M (2009) Prevalence of palpable thyroid nodule in Isfahan, Iran, 2006: A population based study. Exp Clin Endocrinol Diabetes 117:209-213.