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Original Article

Serum TSH levels are associated with postoperative recurrence and lymph node metastasis of papillary thyroid carcinoma

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Abstract: Objective: To explore the relationship between thyroid-stimulating hormone (TSH) levels in the serum and postoperative recurrence and lymph node metastasis (LNM) in papillary thyroid cancer (PTC) patients after surgery. Methods: We selected 272 patients diagnosed with PTC from June 2011 to July 2014. The clinical and pathological data of 272 PTC patients were collected at the First Affiliated Hospital of Wenzhou Medical University and analysed retrospectively. All PTC patients were tested for the $BRAF^{V600E}$ gene mutation before surgery by fine-needle aspiration (FNA) cytology, and TSH levels in the serum were determined one month after surgery. The optimal cut-off value of thyroid-stimulating hormone (TSH) for predicting the recurrence or metastasis of PTC after surgery was determined by the establishment of a receiver operating characteristic (ROC) curve. Kaplan-Meier and Cox regression analyses were used to evaluate the correlation between the optimal cut-off value of TSH and disease-free survival rate and prognosis. Results: Of 272 patients, only 182 (73 $BRAF^{V600E+}$, 109 $BRAF^{V600E-}$) met the final study criteria. Among them, 60 cases had recurrence or metastasis, and 122 cases were controls. The optimal cut-off value of TSH for the prediction of recurrence or metastasis of PTC after surgery was 2.615 mIU/L. In our study, a high TSH level (> 2.615 mIU/L) was correlated with the $BRAF^{V600E}$ mutation, multifocality, lymph node metastasis, recurrence, and metastasis. In all 182 patients, those with high TSH levels had worse disease-free survival. This result was more obvious in the 73 $BRAF^{V600E+}$ patients. The univariate analysis showed that lymph node metastasis, multifocality, lymph node dissection, tumour size, sex, $BRAF^{V600E}$ mutation, and a high postoperative TSH level were all significantly correlated with recurrence or metastasis in PTC patients (all $P < 0.05$). In addition, the Cox multivariate analysis showed that lymph node metastasis, $BRAF^{V600E}$ mutation, and high postoperative TSH levels were independent risk factors for PTC recurrence or metastasis (all $P < 0.05$). Conclusion: PTC patients with high TSH levels (> 2.615 mIU/L) have worse disease-free survival, which is more obvious in the $BRAF^{V600E+}$ population.

Keywords: Papillary thyroid cancer, recurrence, metastasis, $BRAF^{V600E}$, thyroid-stimulating hormone

Introduction

Thyroid carcinoma is one of the most malignant diseases of the endocrine system. As reported by the U.S. National Cancer Institute, there were estimated 53,990 newly diagnosed cases and 2,060 deaths in 2018 [1]. Similarly, in China, the estimated number of cases was 90,000, and the number of estimated deaths was 6,800 [2]. With regard to well-differentiated thyroid cancer, papillary thyroid carcinoma (PTC) accounts for approximately 80% of all types of thyroid cancers [3]. Improvements in assisted diagnostic technology and an increased understanding of the pathological characteristics of PTC have led to a high early diagnosis rate, high cure rate, and relatively good prognosis [4-6]. However, some PTC patients still die due to recurrence or metastasis after surgery. Therefore, the discovery of biomarkers

for predicting recurrence or metastasis after surgery has become an urgent clinical need.

Thyroid-stimulating hormone (TSH) is a hormone secreted by the pituitary gland that promotes the growth and function of the thyroid gland. Previous studies demonstrated that the level of TSH is correlated with the progression of PTC [7-9]. Zeng Q et al. discovered that patients with malignancy had a greater mean value of TSH than patients with benign tumours. Zhou Q et al. discovered that LncPVT1 might modulate thyroid cancer cell proliferation by recruiting EZH2 and regulating thyroid-stimulating hormone receptors [7]. With advancements in biotechnology, research on the molecular mechanisms of PTC has led to significant discoveries related to PTC. The principal BRAF mutation detected in thyroid carcinoma is a thymine-to-adenine transversion (c.1799T > A), in which valine 600 is replaced by glutamic acid (p.V600E) [10]. Shi et al. discovered the correlation between BRAF gene mutations and the clinicopathologic features of papillary thyroid carcinoma and central LNM [11]. Ren et al. verified that coexistence of $BRAF^{V600E}$ and TERT promoter mutations in papillary thyroid carcinoma is related to cancer aggressiveness [12].

Based on these findings, this study aims to determine serum TSH levels that might predict postoperative relapse or metastasis of PTC.

Patients and methods

Patients

This study included 272 patients diagnosed with papillary thyroid carcinoma who were admitted to the First Affiliated Hospital of Wenzhou Medical University from June 2012 to July 2014 and aged 20-80 years. These patients were tested for the $BRAF^{V600E}$ mutation before surgery by fine-needle aspiration (FNA) cytology, and their serum TSH levels were determined one month after surgery. Patients who met all of the following inclusion criteria were enrolled: (1) Between 20 and 80 years of age. (2) Presented with the classical types of PTC. (3) No history of thyroid or neck surgery or other cancer. (4) No family history of PTC. (5) Agreed to participate in the study.

Ninety patients were excluded from the study. Ethics approval was granted by the First Affiliated Hospital of Wenzhou Medical University Institutional Review Board (approval no. 2018-40). In addition, the medical directors' offices at the hospital authorized the use of patient data for this report. The data contained no personal identifiers and were maintained as confidential; as a result, informed consent was not required.

Methods

All patients were initially admitted to the hospital for bilateral thyroid cancer at which point cervical lymph node ultrasonography and thyroid function tests were performed. For B-ultrasound finding of patients with cervical lymph node metastasis, the neck was swept and enhanced CT was performed; for suspected thyroid malignancy, the suspicious thyroid nodule was sampled by fine-needle aspiration biopsy. According to the above results and cervical lymph node metastasis, different surgical methods were selected. Fifty-five patients underwent bilateral total thyroidectomy, 55 patients underwent subtotal thyroidectomy (both sides of the affected gland plus isthmus plus contralateral side), and 72 patients underwent ipsilateral glandular lobe and isthmus resection. When preoperative B-ultrasound and cervical CT revealed lateral lymph node metastasis or when focus on the middle of the neck revealed metastasis in more than 3 central lymph nodes of the neck, cervical lymph node dissection was performed. Fifty cases underwent lymph node dissection in the cervical region. All specimens were tested for the $BRAF^{V600E}$ gene mutation before surgery by fine-needle aspiration (FNA) cytology, while the serum TSH level was determined one month after surgery.

The follow-up period ranged from 40 to 79 months, and the average follow-up time was 60.82 months. Thyroid function, serum TSH and colour Doppler ultrasound of the thyroid and cervical lymph nodes were reviewed every 3 months for two years in patients with thyroid cancer. After two years and within 5 years, patients were followed-up every six months, while after 5 years, patients were followed-up every year. The endpoint of follow-up was recurrence or metastasis. Recurrence was defined as regional recurrence (including recurrence due to residual tumour in the thyroid and surrounding tissues and cervical lymph node metastasis), while metastasis was defined as distant metastasis.

Table 1. Characteristics of PTC patients and tumours

Characteristics	Data (%)
Total no. of patients	182
Age (y)	
Mean	48.23
Range	23-79
Gender	
Female	136 (74.7)
Male	46 (25.3)
Tumour size	1.37±0.89
< 3 cm	168 (92.3)
≥3 cm	14 (7.7)
Surgical approach	
Total bilateral thyroidectomy	55 (30.2)
Subtotal thyroidectomy	54 (29.7)
Ipsilateral glandular lobe plus isthmus resection	72 (40.1)
Lymph node dissection	
No	36 (19.8)
VI	96 (52.7)
VI + lateral	45 (24.7)
lateral	5 (2.8)
$BRAF^{V600E}$ mutation	
Yes	73 (40.1)
No	109 (59.9)
Multifocal	
Yes	50 (27.5)
No	132 (72.5)
Hashimoto's thyroiditis	
Yes	42 (23.1)
No	140 (76.9)
Lymph node metastasis	
Yes	84 (46.2)
No	98 (53.8)
Recurrence or metastasis	
Yes	60 (33.0)
No	122 (67.0)
Serum TSH level	
≤2.615 mIU/L	116 (63.7)
> 2.615 mIU/L	66 (36.3)

Statistical analysis

All statistical analyses were performed using SPSS 23.0 software (IBM Corp., Armonk, NY, USA). The receiver operating characteristic curve (ROC) was used to determine the optimal cut-off value for TSH. Kaplan-Meier and Cox regression analyses were used to assess the correlation of serum TSH levels with disease-free survival and prognosis. Data are presented as the mean ± standard deviation. The differences in characteristics between the two groups were assessed by Student's t-test. Clinicopathological features were evaluated using the χ^2 test. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Of the 272 patients diagnosed with PTC, only 182 met the final study criteria. The baseline characteristics of these PTC patients are presented in **Table 1**. The clinicopathological features of the 182 PTC patients were: 46 males and 136 females aged 23-79 years, with a median age of 48 years. In all, 73 cases (40.1%) were positive for the $BRAF^{V600E}$ mutation and 109 cases were negative; 84 PTC patients had cervical lymph node metastasis at the first surgery, and 98 patients did not have cervical lymph node metastasis. The average tumour size was 1.37±0.89 cm. The baseline serum TSH level was 2.69±0.85 mIU/L. We found that patients with recurrence and metastasis had higher TSH levels than patients without recurrence and metastasis (**Figure 1**).

Then, we analysed follow-up data of 182 PTC patients. According to the results of the ROC curve, 2.615 mIU/L was taken as the optimal cut-off value of TSH. At that value, the sensitivity for the postoperative recurrence and metastasis of papillary thyroid carcinoma was 68.3%, and the specificity was 77.9% (**Figure 2**). Then, we divided these patients into two groups: 116 in the low-TSH group (TSH 1 2.615) and 66 in the high-TSH group (TSH > 2.615). Among them, 39 patients with recurrence had high TSH levels, and 27 patients without recurrence had high TSH levels. To demonstrate whether the optimal cut-off value is correlated with recurrence of PTC, we tested the relationship between TSH and clinical features. As shown in **Table 2**, higher TSH expression was correlated with the $BRAF^{V600E}$ mutation, multifocality, LNM, and recurrence or metastasis (all $P < 0.05$).

To determine the prognostic value of the optimal cut-off value, univariate logistic analysis

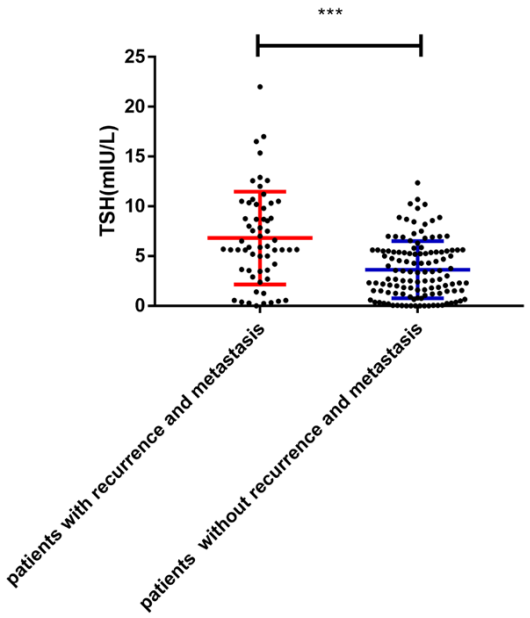

Figure 1. Patients with recurrence and metastasis had higher TSH levels than patients without recurrence and metastasis.

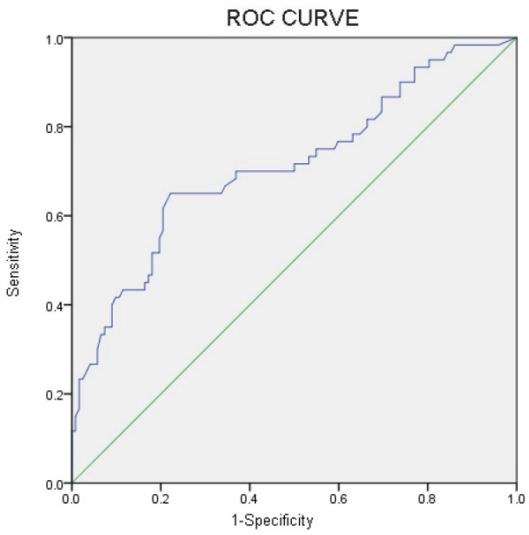

Figure 2. ROC curve for the ability of TSH expression to predict PTC in 182 patients. The AUC was 72.3%, with 68.3% sensitivity and 77.9% specificity.

was conducted to adjust for clinical features. High levels of TSH (hazard ratio [OR] 4.363, 95% CI 2.519-7.555, P = 0.000), lymph node metastasis (OR 4.815, 95% CI 2.638-8.788, P = 0.000), multifocality (OR 2.163, 95% CI 1.279-3.658, P = 0.004), lymph node dissection (OR 1.342, 95% CI 1.062-1.694, P = 0.014), tumour size (OR 2.226, 95% CI 1.091-4.541, P = 0.028), gender (OR 2.340, 95% CI 1.363-4.015, P = 0.002), and the $BRAF^{V600E}$ mutation (OR 4.873, 95% CI 2.760-8.605, P = 0.000) were distinctively linked with the risk of recurrence or metastasis of PTC (**Table 3**). Multivariate logistic analysis indicated that the significant variables of high TSH level (odds ratio [OR] 2.661, 95% CI 1.481-4.779, P = 0.001), lymph node metastasis (OR 3.215, 95% CI 1.762-5.867, P = 0.000), and $BRAF^{V600E}$ mutation (OR 3.621, 95% CI 1.942-6.752, P = 0.000) were positively associated with the risk of recurrence or metastasis of PTC (**Table 4**).

Disease-free survival was used to evaluate the prognostic effect of TSH in PTC patients. As shown in **Figure 3**, the variance between the disease-free survival curves of the two groups was statistically significant (P < 0.0001). We divided patients in the $BRAF^{V600E+}$ group into high TSH and low TSH subgroups, and the disease-free survival curves of the two groups were still statistically significant (**Figure 4**). This same phenomenon was also observed in the $BRAF^{V600E-}$ group (**Figure 5**). As shown in **Table 5**, in the $BRAF^{V600E+}$ group, the high TSH subgroup had more lymph node metastasis (P = 0.028) and a higher rate of recurrence or metastasis (P = 0.000). We found that the combination of $BRAF^{V600E}$ (+) and TSH > 2.615 mIU/L had better predictability of the recurrence of papillary thyroid carcinoma after surgery (**Table 6**).

Discussion

Thyroid cancer is a common endocrine malignancy, and the incidence of thyroid cancer worldwide has increased more rapidly than any other cancer type [1, 13]. Some experts believe that the incidence of thyroid cancer will become the fourth most commonly diagnosed cancer by 2030 [14]. Papillary thyroid carcinoma (PTC), the most common type of thyroid malignancy, accounts for 85-90% of all thyroid cancers [15]. With improvements in auxiliary diagnostic technology, such as extensive use of neck ultrasonography, some PTCs can be found in the primary stage and can be prevented from developing into critical clinical disease [16, 17]. The preferred treatment for PTC is surgery, which leads to good clinical outcomes and long-term survival in most patients. According to the literature, the 10-year survival rate of

Table 2. Clinicopathological features of first-time postoperative patients with papillary thyroid carcinoma

Clinicopathologic characteristics	TSH≤2.615 mIU/L (%)	TSH > 2.615 mIU/L (%)	X^2	P
Age			1.807	0.179
< 45	41 (35.3)	30 (45.5)		
≥45	75 (64.7)	36 (54.4)		
Gender			0.905	0.341
Female	84 (72.4)	52 (78.8)		
Male	32 (27.6)	14 (21.2)		
Tumour size			2.861	0.091
< 3 cm	110 (94.8)	58 (87.9)		
≥3 cm	6 (5.2)	8 (12.1)		
Surgical approach			1.001	0.606
Total bilateral thyroidectomy	33 (28.4)	22 (33.3)		
Subtotal thyroidectomy	34 (29.3)	21 (31.8)		
Ipsilateral glandular lobe plus isthmus resection	49 (42.3)	23 (34.9)		
Lymph node dissection			4.385	0.223
No	25 (21.6)	11 (16.7)		
VI	65 (56)	31 (47)		
VI + lateral	2 (1.7)	3 (4.5)		
lateral	24 (20.7)	21 (31.8)		
$BRAF^{V600E}$ mutation			13.150	0.000
Yes	35 (30.2)	38 (57.6)		
No	81 (69.8)	28 (42.4)		
Multifocal				
Yes	25 (21.6)	25 (37.9)	5.628	0.018
No	91 (78.4)	41 (62.1)		
Hashimoto's thyroiditis				
Yes	26 (22.4)	16 (24.2)	0.079	0.778
No	90 (77.6)	50 (75.8)		
Lymph node metastasis			4.427	0.035
Yes	48 (41.4)	38 (57.6)		
No	68 (58.6)	28 (42.4)		
Recurrence or metastasis			31.979	0.000
Yes	21 (18.1)	39 (59.1)		
No	95 (81.9)	27 (40.9)		

Table 3. Univariate logistic regression analysis for recurrence or metastasis risk

Clinicopathologic features	OR	95% CI	P
TSH level (mIU/L)	4.363	2.519-7.555	0.000
Lymph node metastasis	4.815	2.638-8.788	0.000
Multifocal	2.163	1.279-3.658	0.004
Lymph node dissection	1.342	1.062-1.694	0.014
Tumour size	2.226	1.091-4.541	0.028
Gender	2.340	1.363-4.015	0.002
$BRAF^{V600E}$ mutation	4.873	2.760-8.605	0.000

patients with PTC is 98%, but the recurrence rate ranges from 0% to 35%. Eighty percent of patients relapse within 10 years after surgery [18]. However, 10% of PTC patients experience recurrent disease and death because the tumor becomes poorly differentiated or dedifferentiated [13]. If early recurrence and metastasis can be detected, clinicians can perform surgery or administer radioactive iodine therapy for early effective intervention. These treatments can prevent tumour progression and invasion of important tissues in the neck or dis-

Table 4. Multivariate logistic regression analysis for recurrence or metastasis risk

Clinicopathologic features	OR	95% CI	P
TSH level (mIU/L)	2.661	1.481-4.779	0.001
$BRAF^{V600E}$ mutation	3.215	1.762-5.867	0.000
Lymph node metastasis	3.621	1.942-6.752	0.000

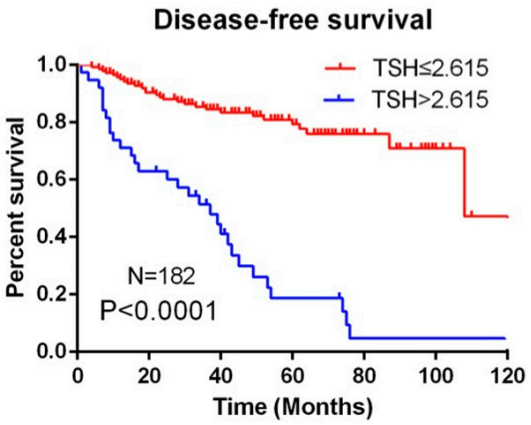

Figure 3. Kaplan-Meier analysis of the disease-free survival of 182 PTC patients with different TSH expression levels. Patients with higher TSH expression had a shorter disease-free survival than those with lower expression.

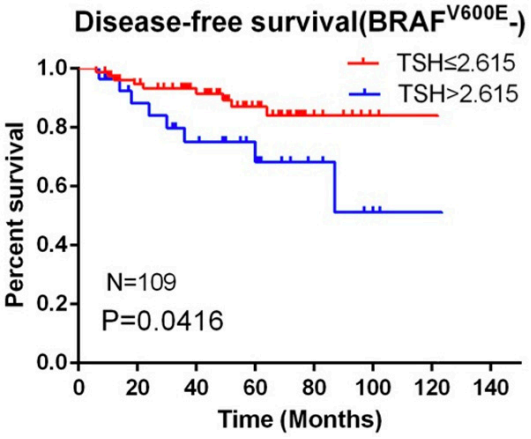

Figure 4. Kaplan-Meier analysis of the disease-free survival of PTC ($BRAF^{V600E+}$) patients with different TSH expression levels in 182 patients ($BRAF^{V600E+}$). Patients with higher TSH expression had a shorter disease-free survival than those with lower expression.

tant metastasis. Therefore, it is necessary to find candidate biomarkers of recurrence and metastatic PTC to avoid overtreatment or undertreatment.

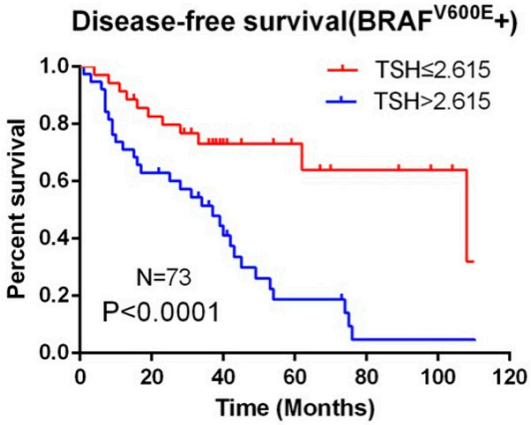

Figure 5. Kaplan-Meier analysis of the disease-free survival of 182 PTC ($BRAF^{V600E-}$) patients with different TSH expression levels. Patients with higher TSH expression had a shorter disease-free survival than those with lower expression.

TSH, a pituitary hormone, can induce thyroid hormone synthesis and thyroid cell growth. Excessive serum TSH levels after surgery can stimulate the recurrence and proliferation of thyroid cancer tissue, and thus, infrequent administration of levothyroxine sodium tablets after surgery may cause recurrence or metastasis of thyroid cancer. Elevated TSH also enhances the sensitivity of thyroglobulin detection. Many studies have demonstrated that the expression of TSH is related to thyroid cancer [19, 20]. Zeng et al. discovered that patients with malignancy had a higher mean value of TSH than patients with benign tumours [7]. Zhou et al. found that LncPVT1 could modulate thyroid cancer cell proliferation by recruiting EZH2 and regulating thyroid-stimulating hormone receptors [8]. Boelaert et al. verified that a high level of serum TSH in the presence of undiagnosed nodules may indicate cancer [21]. A positive association has been found between the levels of serum TSH and advanced tumour stage in PTC [22]. TSH receptor (TSHR) is expressed on the surface of thyroid cancer cells. TSH combined with TSHR can stimulate the recurrence and proliferation of thyroid cancer. Therefore, irregular administration of levothyroxine sodium tablets may lead to the recurrence of thyroid cancer [23]. In our study, 2.615 mIU/L was taken as the optimal cut-off value of TSH based on the results of the ROC curve in 182 PTC patients. Then, we divided these patients into two groups, and the rate of high TSH in patients with recurrence (65%) was

Table 5. Clinicopathological features of BRAF+ papillary thyroid carcinoma

Clinicopathologic characteristics	TSH≤2.615 mIU/L (%)	TSH > 2.615 mIU/L (%)	X^2	P
Age			0.096	0.756
< 45	16 (45.7)	16 (42.1)		
≥45	19 (54.3)	22 (57.9)		
Gender			0.988	0.32
Female	21 (60.0)	27 (71.1)		
Male	14 (40.0)	11 (28.9)		
Tumour size			0.878	0.349
< 3 cm	32 (91.4)	32 (84.2)		
≥3 cm	3 (8.6)	6 (15.8)		
Surgical approach			1.566	0.457
Total bilateral thyroidectomy	13 (37.1)	14 (36.8)		
Subtotal thyroidectomy	7 (20.0)	12 (31.6)		
Ipsilateral glandular lobe plus isthmus resection	15 (42.9)	12 (31.6)		
Lymph node dissection			0.457	0.928
No	8 (22.9)	7 (18.4)		
VI	13 (37.1)	14 (36.8)		
VI + lateral	1 (2.9)	2 (5.3)		
lateral	13 (37.1)	15 (39.5)		
Multifocal			0.000	0.995
Yes	12 (34.3)	13 (34.2)		
No	23 (65.7)	25 (65.8)		
Hashimoto's thyroiditis			0.570	0.450
Yes	5 (14.3)	8 (21.1)		
No	30 (85.7)	30 (78.9)		
Lymph node metastasis			4.836	0.028
Yes	15 (42.9)	26 (68.4)		
No	20 (57.1)	12 (31.6)		
Recurrence or metastasis			18.755	0.000
Yes	11 (31.4)	31 (81.6)		
No	24 (686)	7 (18.4)		

Table 6. The combination of $BRAF^{V600E}$ (+) and a TSH level > 2.615 mIU/L has better predictability of the recurrence of papillary thyroid carcinoma after surgery

	$BRAF^{V600E}$ (+)	$BRAF^{V600E}$ (+) and TSH > 2.615 mIU/L	X^2	P
			5.176	0.023
Number with recurrence (%)	44 (60.3)	31 (81.6)		
Number with no recurrence (%)	29 (39.7)	7 (18.4)		

greater than that in patients without recurrence (22.1%); this difference was statistically significant ($P < 0.05$). Univariate logistic and multivariate logistic analyses indicated that a postoperative TSH level > 2.615 is a risk factor that predicts postoperative recurrence and metastasis of PTC. During the postoperative follow-up of PTC patients, if the level of TSH is elevated, especially in those with cervical lymphadenopathy, attention should focus on whether local recurrence or distant metastasis has occurred. However, TSH inhibition treatment also has adverse side effects, and particularly, a supraphysiological dose of thyroxine has adverse effects on the cardiovascular and skeletal systems. A prospective observational study report-

ed that for postmenopausal women with differentiated thyroid cancer (DTC), TSH inhibition resulted in a decrease in bone density and a higher risk of osteoporotic fractures [24]. Similarly, other studies have found that TSH inhibition therapy is associated with tachyarrhythmia and decreased cardiac function [25].

With the development of gene sequencing technology, increasing numbers of underlying candidate markers have been discovered [26-28]. In addition, the MAPK pathway is regularly triggered by BRAF mutations, with a widespread rate of 45% in PTC patients [29]. BRAF is a prominent oncogene in PTC, and the $BRAF^{V600E}$ mutation has good specificity for PTC. The predominant BRAF mutation discovered in thyroid carcinoma is a thymine-to-adenine transversion (c.1799T > A), which results in the replacement of valine 600 with glutamic acid (p.V600E) [10]. Currently, biopsy by needle puncture is performed on suspected thyroid nodules before surgery. The combination of positive fine needle aspiration biopsy (FNAB) and positive $BRAF^{V600E}$ indicates a PTC diagnosis. Therefore, $BRAF^{V600E}$ is an important diagnostic marker of PTC, and $BRAF^{V600E}$ may also be a potential prognostic factor in PTC. In our study, univariate logistic and multivariate logistic analyses indicated that postoperative $BRAF^{V600E}$ mutation is a risk factor that can predict postoperative recurrence and metastasis of PTC. The combination of $BRAF^{V600E}$ (+) and TSH > 2.615 mIU/L has better predictability of the relapse of papillary thyroid carcinoma after surgery.

Conclusion

The patients with high TSH level (> 2.615 mIU/L) had worse disease-free survival, which was more obvious in $BRAF^{V600E+}$ patients.

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Disclosure of conflict of interest

None.

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