

Associations of BRAF V600E, clinical pathology and imaging factors with the recurrence rate of papillary thyroid microcarcinoma

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Abstract. In the present study, the recurrence rate of papillary thyroid microcarcinoma (PTMC) was assessed by analyzing postoperative follow-up data of affected patients and its associations with BRAF V600E, clinical pathology and imaging factors were explored. A total of 506 patients with PTMC were selected who underwent surgery from January 2014 to March 2016. The maximal diameter of thyroid nodules was ≤ 1 cm and all patients who underwent BRAF V600E testing and evaluation for lymph node metastasis. Postoperatively, each patient was regularly followed up to detect recurrence. Categorical variables were comparatively analyzed using univariate Cox linear regression analysis to screen for protective and adverse factors influencing recurrence of PTMC. A stepwise Cox proportional hazards regression model analysis was performed to explore risk factors affecting recurrence. Among the 506 patients, 477 were followed up, 29 were lost to follow-up and 26 patients experienced recurrence. The 5-year recurrent rate of PTMC was 5.45%. The univariate Cox regression analysis indicated that PTMC recurrence was influenced by BRAF V600E, sex, multifocality, capsular invasion and lateral cervical lymph node metastasis ($P < 0.05$), but not by age, tumor location on the thyroid, size, single central lymph node metastasis, distant metastasis and operative approach ($P > 0.05$). The significant factors associated with recurrent PTMC were subjected to stepwise multivariate Cox proportional hazards regression model analysis and the results indicated that BRAF V600E, sex, multifocality and lateral cervical lymph node metastasis were independent factors influencing recurrence in patients with PTMC, with a statistically significant difference ($P < 0.05$). In conclusion, BRAF V600E, sex, multifocality and

lateral cervical lymph node metastasis are independent risk factors for recurrent PTMC.

Introduction

Thyroid carcinoma is the most common type of malignant tumor of the endocrine system; in recent years, there has been a gradual rise in associated morbidity and this has been increasingly studied by clinicians and researchers (1), and exhibits the fastest increase in incidence among all types of malignant tumors. The soaring rate of thyroid carcinoma is primarily due to papillary carcinoma, particularly in its earliest stages (i.e. microcarcinoma) (2). According to the latest Surveillance, Epidemiology and End Results data, nearly 90% of thyroid carcinomas are of the papillary type (3), indicating the particular importance of studying thyroid papillary microcarcinoma (PTMC). In addition, PTMC has a cervical lymph-node metastasis rate that is as high as 30-70% (4-6). Certain patients experience early postsurgical local recurrences or even initially present with distant metastases to the lungs or bone (4,5).

The BRAF V600E mutation is the most common mutation identified in papillary thyroid carcinoma (PTC) (6), corresponding to 28-83% of all gene mutations observed and accounting for ~90% of all BRAF mutations (7-9), but it has not been detected in normal thyroid tissues or benign lesions (10-14). The presence of the BRAF V600E mutation is closely associated with papillary carcinoma recurrence and patient mortality. In addition, numerous patients choose surgical treatment for PTMC due to the high morbidity rate (15). However, certain patients develop recurrent PTMC postoperatively (16). This study focused on BRAF V600E, clinical pathology and imaging factors to explore their associations with PTMC recurrence. According to the definition by the World Health Organization, PTC with a maximal diameter of tumor ≤ 1 cm is considered PTMC (17).

Patients and methods

Research subjects. The independent ethics committee of China Medical University (Shenyang, China) approved this study. In total, 506 patients were included who underwent

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surgery for a thyroid nodule (maximal diameter ≤ 1.0 cm) and underwent preoperative BRAF V600E testing at the Department of Thyroid Surgery of the First Affiliated Hospital of China Medical University between January 2014 and March 2016. The cohort comprised 420 females and 86 males with an age range of 17-73 years (mean age, 39.6 ± 2.6 years). All patients were pathologically diagnosed with PTMC, including 359 patients diagnosed with a single nodule and 147 patients with two and more nodules. The mean and median diameters of nodules were 0.63 cm [standard deviation (SD), 0.21 cm] and 0.6 cm (range, 0.41-1.00 cm). Partial thyroidectomy was performed for unilateral nodules and total thyroidectomy for bilateral nodules. None of the patients included had any contraindications for surgery and signed informed consent forms. Patients with a history of other tumors were excluded.

Procedures. Phillip iu22 and EPIQ7 color Doppler ultrasonic (US) diagnosis systems (Philips Medical Systems, Inc.) with a probe frequency of 5-12 MHz were used. Patients were placed in a supine position. The thyroid glands were scanned preoperatively to determine the size, number, position, border, shape and internal echo of thyroid nodules and the presence or absence of lymph node metastasis. Surgical treatment was performed after the diagnosis was confirmed by cytopathological evaluation. Prior to surgical resection of the thyroid nodules, BRAF V600E testing was performed using the Amplification Refractory Mutation System method with the human BRAF gene V600E mutation detection kit (Shanghai Yuanqi Biological Co., Ltd.) and the manufacturer's protocol was strictly followed. During the test, 5 μ l of the standardized DNA template was pipetted into 35 μ l of the reaction mixture containing Taq enzyme (40 μ l of the PCR reaction system). Nodule positions were classified as being in the central area or marginal area; the marginal area included anterior, posterior, lateral and medial borders and the isthmus of the thyroid gland and the central area consisted of the remaining parts of the thyroid gland.

Follow-up. All patients underwent thyroid-stimulating hormone (TSH)-suppressive therapy with levothyroxine postoperatively. At 3, 6, 12, 18, 24, 36, 48 and 60 months after the operation, each patient was followed up, and US scan, thyroglobulin (TG) and thyroid function tests (including serum TSH, FT4, FT3, and anti-TG antibody) were performed to detect recurrence and metastasis. For patients with suspected or proven elevation of TG, enhanced CT and cytopathological examinations were performed to evaluate metastasis, and emission computed tomography (ECT) or positron emission tomography-CT (PET-CT) examination was performed as necessary.

To assess serum TG levels, electrochemiluminescence immunoassay using the Cobas e601 immunoassay analyzer (Roche Diagnostics) was used. Functional sensitivity is defined as the lowest analyte concentration that can be reproducibly measured with a precision coefficient of variation (CV) of 20%; the functional sensitivity was 0.1 ng per milliliter. Using a chemiluminescence immunoassay with an automated immunoassay analyzer (Architect i2000; Abbott Laboratories; reference range, 0.35-4.94 μ IU/ml; functional sensitivity, 0.01 μ IU/ml), serum thyroid-stimulating hormone (TSH) levels were measured.

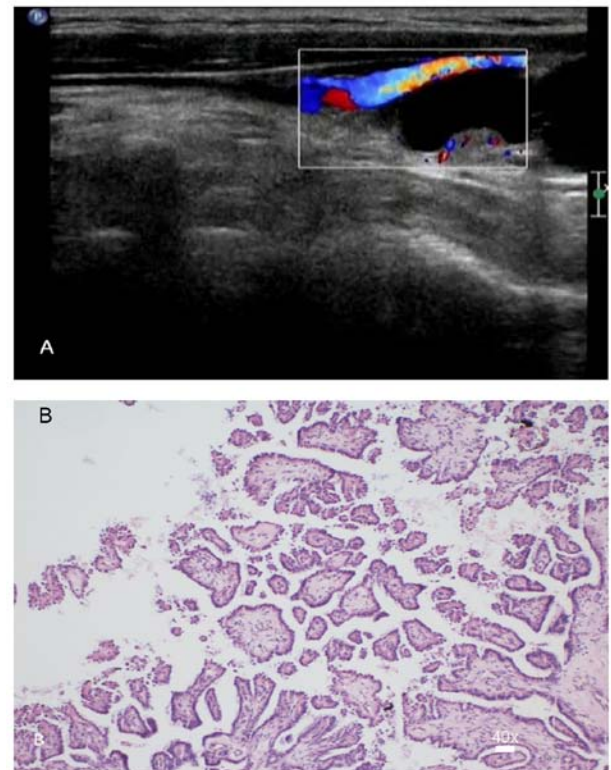


Figure 1. Female, 43 years old, recurrence 36 months after surgery. Structural recurrence of papillary thyroid microcarcinoma in a lymph node. (A) Ultrasound indicates that the lymph node is cystic. (B) Pathological examination reveals cancer cells in the lymph node (magnification, x100).

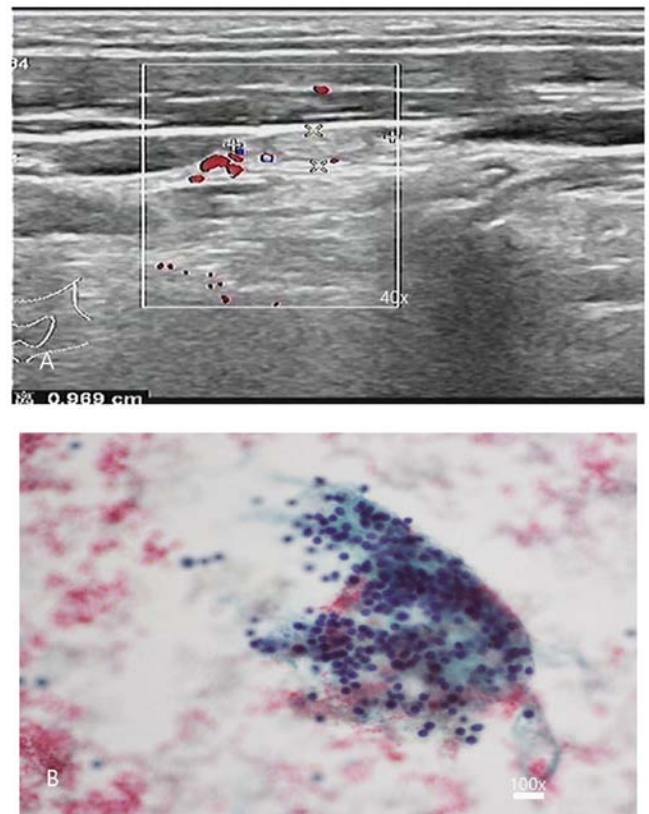


Figure 2. Female, 36 years old, appeared 24 months after surgery. Lymph node structural persistence. (A) Ultrasound indicates the loss of fatty hilum of the lymph node. (B) Cytopathological examination reveals lymphocytes and no malignant cells are observed (magnification, x200).

Table I. The recurrence time and number of cases of papillary thyroid microcarcinoma.

Recurrence time (month)	3	6	12	18	24	36	48	60	Total
N	0	0	1	1	3	5	8	8	26

A lymph node is defined as abnormal on ultrasonography if it meets any of the following criteria (12): i) Loss of fatty hilum, ii) diffuse or focal hyperechogenicity, iii) cystic changes, iv) microcalcifications, v) round shape, or vi) disorganized or peripheral vascularity. Any lymph nodes classified as abnormal underwent cytopathological examination; those in which cancer cells were detected were considered metastatic.

Recurrence. It was determined that there was no clinical evidence of disease if the following criteria were satisfied: i) Suppressed thyroglobulin (TG) <1 ng/ml, ii) stimulated TG <2 ng/ml, iii) no detectable anti-TG antibody, or iv) no evidence of disease on ultrasonography, computed tomography (CT), MRI, positron emission tomography-CT (PET-CT) or ECT at the final follow-up. Persistence was defined as suppressed TG ≥1 ng/ml, stimulated TG ≥2 ng/ml, or any evidence of disease on ultrasonography, CT, MRI, PET-CT or ECT after initial surgery and remnant ablation therapy with radioiodine. Recurrence was defined as malignancy diagnosed based on cytology results, elevated serum TG, or PET-CT, ECT in patients with no clinical evidence of disease (18). For a suspected recurrent mass detected on ultrasound, ultrasound-guided fine-needle aspiration (FNA) was usually performed. Cytopathological results were then obtained from the samples taken from the FNA and surgical excision.

Statistical analysis. SPSS v21.0 software (IBM Corp.) was used for data analysis. Measurement data are presented as the mean ± SD and numerical data are expressed as n (%). The categorical variables associated with the recurrent rate were compared among different groups using univariate Cox linear regression analysis to screen for protective and adverse factors influencing recurrence of PTMC. Survival rates were calculated using the Kaplan-Meier method and compared using a log-rank test. A multivariate Cox proportional hazard regression model was used to estimate the mortality risk. Subsequently, stepwise multivariate co-variant analysis of the recurrence rates in different groups was performed using the Cox proportional hazards regression model to explore risk factors of recurrence. P<0.05 was considered to indicate statistical significance.

Results

Follow-up findings. During the study, there was no case of death; 477 patients were followed up, 29 patients were lost to follow-up and 26 patients experienced recurrence; the 5-year recurrent rate was 5.45%. The follow-up time from initial treatment to final clinical follow-up was 49.7 months (SD, 11.6 months; median, 48.5 months; range, 36.0-60.0 months). During follow-up, there was no case of recurrence at 3 and 6 months, 1 case of recurrence each at 12 and 18 months, 3 new

Table II. The follow-up of lymph node structural persistence.

Types of follow-up	Lymph node structural persistence
No recurrence after surgery (N)	2
No change without undergoing surgery (N)	4
Total	6

cases of recurrence at 24 months, 5 new cases of recurrence at 36 months and 8 new cases of recurrence at 48 and 60 months (Table I).

Recurrence parameters. Cases of structural recurrence accounted for 5.45% (26/477) and all were lymph node metastasis without secondary thyroid nodule or distant metastasis (Fig. 1); 1.26% (6/477) of cases exhibited structural persistence (Fig. 2) and biochemical recurrence accounted for 2.73% (13/477). Among the 26 patients with structural recurrence, 13 and 13 cases presented with increased serum TG levels and normal serum TG levels, respectively; all of these patients underwent surgery, including 2 cases (increased TG) who underwent surgery for secondary recurrence (The patient relapsed after undergoing a second operation following the first recurrence) and were not indicated to have recurrence at the second follow-up (Follow-up after the second operation). Out of the 6 patients with structural persistence, 2 cases underwent surgery without apparent metastasis and recurrence at the last visit, and 4 cases were observed and determined to be without significant enlargement of lymph nodes at the last follow-up (Table II).

Influencing factors of recurrence. Table III presents details of the patients with PTMC, including the presence of BRAF V600E, clinical pathology and imaging factors (e.g., sex, age, lesion location, size and number, capsular invasion, metastasis location, distant metastasis and operative approach). Univariate Cox regression analysis indicated that recurrence of PTMC was affected by BRAF V600E, sex, multifocality, capsular invasion and lateral cervical lymph node metastasis (P<0.05), but not by age, lesion location, size, single central lymph node metastasis, distant metastasis and operative approach (P>0.05; Figs. S1 and S2).

As indicated by the stepwise multivariate Cox proportional hazards regression model analysis of the significant influencing factors for recurrent PTMC, sex, BRAF V600E, multifocality and lateral cervical lymph node metastasis were independent influencing factors for recurrence in patients with PTMC, with a statistically significant difference (P<0.05; Table IV).

Table III. Analysis of the association of BRAF V600E, clinical pathology and imaging factors with recurrence of papillary thyroid microcarcinoma.

Factor	Cases (n)	Recurrence, n (%)		HR (95% CI)	P-value
		Positive	Negative		
Location				0.451 (0.055-3.718)	0.460
Marginal region or near isthmus	286	16 (5.59)	270 (94.41)		
Central region	191	10 (5.24)	181 (94.76)		
Sex				1.689 (1.045-3.262)	0.004
Female	397	18 (4.53)	379 (95.47)		
Male	80	8 (10.00)	72 (90.00)		
Age (years)				1.065 (0.110-10.299)	0.956
≥45	204	14 (6.86)	190 (93.14)		
<45	273	12 (4.40)	261 (95.60)		
Anteroposterior nodule size (cm)				0.444 (0.058-3.402)	0.435
0.9-1.0	195	15 (7.69)	180 (92.31)		
<0.9	282	11 (3.90)	271 (96.10)		
Nodule number				2.462 (1.192-5.086)	0.015
Single	338	12 (3.55)	326 (96.45)		
Multifocal	139	14 (10.07)	125 (89.93)		
BRAF V600E testing				2.312 (1.254-4.074)	0.022
Positive	222	17 (7.66)	205 (92.34)		
Negative	255	9 (3.53)	246 (96.47)		
Capsular invasion				1.244 (1.013-2.115)	0.043
Yes	77	7 (9.09)	70 (90.91)		
No	400	19 (4.75)	381 (95.25)		
Single central lymph node metastasis				0.991 (0.863-1.137)	0.894
Yes	185	14 (7.57)	171 (92.43)		
No	292	12 (4.11)	280 (95.89)		
Lateral cervical lymph node metastasis				1.899 (1.308-2.966)	0.001
Yes	72	9 (12.50)	63 (87.50)		
No	405	17 (4.20)	88 (95.80)		
Distant metastasis				0.151 (0.009-2.529)	0.189
Yes	0	0 (0)	0 (0)		
No	477	26 (5.45)	451 (94.55)		
Operative approach				1.012 (0.954-1.074)	0.682
Total thyroidectomy	153	12 (7.84)	141 (92.16)		
Unilateral thyroidectomy	324	14 (4.32)	310 (95.68)		

HR, hazard ratio.

Table IV. Multivariate stepwise Cox proportional hazards regression model analysis of factors influencing the recurrence of papillary thyroid microcarcinoma.

Factor	HR (95% CI)	P-value
Sex (female vs. male)	2.340 (1.980, 5.585)	0.032
BRAF V600E testing	2.267 (1.311, 4.193)	0.027
Multifocality (yes vs. no)	3.043 (1.370, 6.759)	0.019
Capsular invasion (yes vs. no)	1.391 (0.702-3.906)	0.504
Lateral cervical lymph node metastasis (yes vs. no)	3.216 (2.393, 6.634)	0.009

HR, hazard ratio; CI, confidence interval.

Discussion

In recent years, the frequency of PTMC has rapidly risen and its morbidity has markedly increased (16). Although the requirement for surgery in the treatment of PTMC is debated, surgical management of nodal metastasis of PTMC is undisputed and the rate of nodal metastasis is high (16). For instance, the reported rates of central lymph node metastasis alone range from 24 to 64% and its occurrence is associated with recurrence and death rates (19,20). However, there is no expert consensus on the susceptibility of PTMC types to recurrence. In the present study, the risk of PTMC recurrence with respect to BRAF V600E, clinical pathology factors and imaging factors was analyzed; this analysis provided a detailed assessment of the biological behavior and relapse rate associated with the BRAF mutation status.

Various studies have completed multi-year postoperative follow-ups of patients with PTMC, but they have drawn different conclusions. Hay *et al* (21) reported on 900 patients with PTMC diagnosed and treated at the Mayo Clinic from 1945 to 2004, with an average follow-up duration of 17.2 years; the 20-year and 40-year tumor recurrence rates were 6 and 8%, respectively. Out of 281 patients with PTMC treated at the Gustave-Roussy Institute, 3.9% of cases experienced local recurrence and 1 case developed pulmonary metastasis (22). In a study on patients with low-risk thyroid carcinoma (stage I or II), the recurrence rate was 8.9% (23-28). However, Nixon *et al* (29) reported that PTMC had a low recurrence rate of only 0.6%. Durante *et al* (30), confirmed that none of their 312 patients with PTMC T1N0M0 experienced local recurrence during a median 6-year follow-up. These conflicting results may be due to different stages of primary carcinoma, different FNA diagnostic criteria and a difference in the size criterion of US-FNA used for suspected cervical lymph node lesions. The 5-year recurrence rate in the present study was 5.45%, which is similar to the 20-year follow-up results of the study by Hay *et al* (21) and close to those reported by the Gustave-Roussy Institute (22). However, the recurrence rate would certainly increase with the prolongation of follow-up. Despite slow growth, thyroid carcinoma has exhibited a high incidence rate in recent years. Furthermore, as tumor heterogeneity is observed, the importance of biological behaviors of PTMC should be recognized.

The univariate analysis using univariate Cox regression analysis indicated that BRAF V600E, sex, multifocality, capsular invasion and lateral cervical lymph node metastasis affected the recurrent rate of PTMC, according to the step-wise multivariate Cox proportional hazards regression model analysis, BRAF V600E, sex, multifocality and lateral cervical lymph node metastasis were independent influencing factors for recurrence in patients with PTMC (HR=2.267, 2.340, 3.043 and 3.216, respectively), which was consistent with the results of several previous studies (31-33). Li *et al* (34), reported a close association of BRAF V600E mutation with extracapsular infiltration of PTC, lymph node metastasis and high TNM tumor stage, and a subsequent higher capsular invasion rate (35). BRAF V600E-variant PTC has a relatively higher risk of invasion, easily invades the tissues surrounding the thyroid gland, and means that patients frequently present at an advanced clinical stage (31,36,37) and is associated with a worse prognosis (36,38,39). Therefore, for patients

with BRAF V600E-positive tumors, more attention should be paid to US reexamination and TG and thyroid function tests in order to avoid markedly elevated TSH levels. In addition, surgery should be performed as soon as possible when BRAF V600E-positive nodes are detected.

Sex, multifocality and lateral cervical lymph node metastasis, as independent clinical pathology and imaging factors influencing PTMC recurrence, are mainly associated with the characteristics of PTMC. The incidence rate of PTMC in females is markedly higher than that in males (up to 3.9-fold) (40), but the recurrence rate exhibits the opposite trend, being higher in males (10.00%) than in females (4.53%). However, a larger sample size is required to further validate the accuracy of results because of the small number of cases with recurrence. Multifocality, as an independent risk factor for recurrence, contributes to the high morbidity (up to 25.7%) of PTMC and is associated with BRAF V600E mutation (32). Therefore, regular US and TG monitoring are required for patients with multifocality. Wada *et al* (33), indicated that the recurrence rate of patients with lateral cervical lymph node metastasis was higher than that of patients with only central lymph node metastasis and the difference was statistically significant; this is comparable to the present results. The major cause for this is that central lymph nodes are located in the VI area, the first location of thyroid carcinoma metastasis, while lateral cervical lymph nodes are located at the II, III and IV areas and are usually the second location of metastasis; the lymph drainage generally reaches the second location in the middle and advanced tumor stages. In addition, patients with lateral cervical lymph node metastasis are frequently at least stage T1N1bM0, and they are more susceptible to recurrence and metastasis than patients with stage T1N1aM0. In addition, the cutoff criterion of the thyroid nodule size in the present study was 0.9 cm, mainly because if the nodule size is >9 mm, its risk of metastasis increases, compared with it risk decreasing if the size is <9 mm (41).

The present study has the following limitations. First, it was a retrospective analysis and the exclusion of certain cases was unavoidable. Furthermore, the sample size was relatively small and a larger sample size is required. In addition, the follow-up time was short and requires to be prolonged to further validate the conclusion of the present study. In addition, the imaging characteristics of nodules were not considered, which will be investigated in future studies by our group.

In conclusion, PTMC has a low recurrence rate after surgery; BRAF V600E, sex, multifocality and lateral cervical lymph node metastasis are independent risk factors for recurrent PTMC.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

KH conceived this article, revised it critically for important intellectual content and was responsible for the interpretation of data. NG and PY made substantial contributions to acquisition and analysis of data. DB and QZ constructed the figures and involved in the acquisition of data. YZ collected the data regarding the patients, drafted the manuscript and approved it for publication. The final version of the manuscript has been read and approved by all authors, and each author believes that the manuscript represents honest work.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the First Affiliated Hospital of China Medical University (Shenyang, Liaoning, China; no. AF-SOP-07-1.0-01).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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