A population-based study of the three major variants of papillary thyroid carcinoma

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Abstract

Objective: To explore the clinicopathological features and relative prognostic risks of the three major variants of papillary thyroid carcinoma (PTC).

Methods: We retrospectively analyzed the clinicopathological characteristics and prognoses of patients with the three major PTC variants, conventional papillary thyroid carcinoma (CPTC), follicular-variant papillary carcinoma (FVPTC), and tall-cell papillary thyroid carcinoma (TCPTC), based on data from the Surveillance, Epidemiology, and End Results database from 2005 to 2009.

Results: A total of 29,555 patients were enrolled. In terms of their demographic and clinicopathological characteristics, TCPTC had the highest prevalence of older patients, men, patients with locally advanced stage (T stage and N stage), and mortality, while FVPTC had the lowest prevalence in relation to these factors. The three variants differed significantly in terms of 5-year overall survival and 5-year disease-specific survival. Cox regression analysis identified male sex, age ≥45 years, and higher American Joint Committee on Cancer and TNM stage as independent factors predicting a poor prognosis in relation to both overall and disease-specific survival.

Conclusions: CPTC, FVPTC, and TCPTC have different clinicopathological characteristics and prognoses, indicating the need for different treatment strategies for these three variants of PTC.

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Introduction

The incidence of thyroid carcinoma has been growing rapidly over the past few decades, making it the most prevalent endocrine malignant tumor.[1,2] The most common histologic subtype of thyroid carcinoma is papillary thyroid carcinoma (PTC), accounting for 80% to 90% of cases.[3–5]

Although most PTCs show indolent behavior, some are associated with an aggressive clinical course. PTCs have been subdivided histologically into a conventional type and other histological variants, including some aggressive variants.[6] Some parameters, including histological and molecular features, have been introduced to characterize the different subtypes of PTC, and extensive research has been conducted in this field. Kakudo et al.[7] revealed that loss of cellular polarity and loss of cellular cohesiveness were useful characteristics for identifying aggressive PTC subtypes. In addition, increasing numbers of molecular markers, such as BRAF and RAS, have been suggested to aid risk stratification.[8] The concept of stratifying PTC into high-risk and low-risk groups has attracted increasing recent attention because of its potential to predict prognosis and optimize the surgical and postsurgical management of patients with PTC. It is therefore important to define the histological criteria used to distinguish between high-risk and low-risk lesions within the broad framework of PTC.

Several subtypes of PTC have been reported, of which conventional PTC (CPTC), follicular-variant PTC (FVPTC), and tall-cell PTC (TCPTC) are the three main variants. Each histologic variant shows specific tumor cell and stromal features. CPTC, as the classical variant, is characterized by papillary architecture with fibrovascular cores and typical overlapping, grooved, clear nuclei. FVPTC includes small lining follicles comprising cells with irregular enlarged nuclei with cytological features of PTC. In TCPTC, the cells are two to three times as tall as they are wide, and show cytological features of PTC.[9,10] The different variants are also associated with different prognoses, with TCPTC being relatively aggressive with a high recurrence rate.[11,12] However, the relative prognoses of CPTC and FVPTC remain debatable.[13,14] Most previous studies have involved small sample sizes and have therefore lacked the statistical power required to reach a definitive conclusion. The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute is considered to be the largest public and authoritative database of information on the incidence and survival rate of cancers. The SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases includes population-based cancer registries for 18 geographical regions, covering almost 30% of the population of the USA, including about 100 million people. We hypothesized that the different subtypes of PTC

might have specific characteristics and long-term prognoses. We therefore investigated the differences in clinicopathological characteristics and prognoses among the three major PTC variants using data from the large-scale SEER database, to provide a reliable rationale for individual-based treatment for PTC.

Materials and Methods

### Database and patient selection

Data were collected from SEER 18 Regs Research Data + Hurricane Katrina impacted Louisiana Cases, Nov 2016 sub [2000–2014] <Katrina/Rita Population Adjustment>. The stepwise cohort ascertainment is shown in Figure 1. We included patients diagnosed with thyroid carcinoma between 2005 and 2009. We identified the three major PTC variants using the ICD-O-3 code (International Classification of Diseases for Oncology third edition) as follows: Papillary carcinoma of thyroid = 8260; Papillary carcinoma, Follicular variant = 8340/3; Papillary carcinoma, tall cell = 8344. Patients with unknown American Joint Committee on Cancer (AJCC) stage, T stage, N stage, or M stage, and patients without surgery were excluded. Information on age, sex, race, tumor size, AJCC stage, T stage, N stage, M stage, and follow-up status were extracted.

Statistical analysis

Demographic and clinicopathological characteristics were compared using non-parametric tests for continuous data and Pearson's χ^2 test for categorical variables. Median and 25% and 75% quartiles were reported. The 5-year overall survival (OS) and 5-year disease-specific survival (DSS) were investigated by Kaplan–Meier analyses. DSS was defined as death due to thyroid carcinoma, and OSS was defined as death from any cause. Survival curves were calculated and log-rank tests were performed. We also performed subgroup analyses with cut-off ages of 45 and 55 years. Independent predictors of poor survival were identified by Cox proportional hazards regression model analysis. All analyses were conducted using SPSS version 21.0 (IBM Corp, Armonk, NY, USA). $P < 0.05$ was considered statistically significant, and 95% confidence intervals were used to indicate confidence levels.

This study was conducted in accordance with the Declaration of Helsinki and its later amendments or comparable ethical standards and approved by the independent ethics committee/institutional review board of Shanghai General Hospital, Shanghai
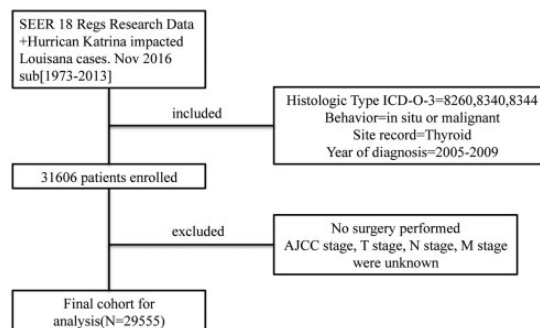
Figure 1. Stepwise cohort ascertainment from the Surveillance, Epidemiology, and End Results database for this study.

Jiaotong University School of Medicine. Informed consent was not required as the data in this study were collected from a public database.

Results

Demographic and clinicopathological characteristics

A total of 29,555 cases were enrolled in this study, including 19,445 CPTC cases (65.8%), 9776 FVPTC cases (33.1%), and 334 TCPTC cases (1.1%) (Table 1). The distributions of age, sex, race, tumor size, AJCC stage, T, N, and M stage, and survival status differed significantly among the three variants. TCPTC had the highest prevalence of locally-advanced disease (T stage and N stage) and mortality, while FVPTC had the lowest prevalence of these features. Notably, patients with TCPTC were older and more likely to be male.

OS and DSS

The median and average follow-up times were 60 and 57.51 months, respectively. We performed Kaplan–Meier analyses for 5-year OS and 5-year DSS among the three variants in the whole group, and stratified according to age (cut-off ages 45 and 55 years). The three variants differed significantly in terms of OS (log-rank test $\chi^2 = 86.427$, P<0.001) and DSS (log-rank test $\chi^2 = 157.896$, P<0.001) in both overall and pairwise comparisons (Figure 2). Survival was highest among patients with FVPTC, followed by CPTC and TCPTC. The differences in OS and DSS among the three variants were more obvious in older patients ($\geq$45 years; overall log-rank test $\chi^2 = 76.459$, P<0.001, disease-specific log-rank test $\chi^2 = 138.368$, P<0.001) compared with younger patients (<45 years; overall log-rank test $\chi^2 = 7.028$, P = 0.03, disease-specific log-rank test $\chi^2 = 12.25$, P = 0.002)

(Figure 3). The results were similar, but less significant, using a cut-off age of 55 years (log-rank test $\chi^2 = 5.933$ vs 7.028 for OS by younger age; $\chi^2 = 11.643$ vs 12.25 for DSS for younger age; $\chi^2 = 60.191$ vs 76.495 for OS by older age; $\chi^2 = 120.353$ vs 138.368 for DSS by older age) (Figure 4).

Multivariate analysis of OS and DSS

Multivariate analysis using a Cox proportional hazards regression model (Table 2) identified male sex, age $\geq$45 years, higher AJCC stage, and higher T, N, and M stages as independent prognostic factors for poorer OS and DSS. Race only affected OS, with a hazard ratio for Black > White > Asian of 1.543:1:0.765.

Discussion

PTC accounts for 80% to 90% of all thyroid carcinomas, and for most of the increases in thyroid cancer in recent decades. The increases were considered as over-diagnoses by most oncologists,[15,16] leading to the question of whether or not all PTC patients should be treated equally.[17] The appropriate medical treatment for PTC relies on accurate stratification of the disease, allowing more aggressive treatments for aggressive subtypes of PTC and less aggressive treatments for less-aggressive subtypes. PTC has several variants, including CPTC, FVPTC, TCPTC, oncocytic PTC, columnar cell PTC, diffuse sclerosing PTC, solid PTC, and clear cell PTC, of which the first three account for most cases of PTC.[18,19] However, the relative clinicopathological characteristics and prognostic risks of these three subtypes remain controversial, especially for CPTC and FVPTC. Burningham et al. and Lang et al.[13,20] suggested that FVPTC was the more aggressive subtype, whereas Hagag et al., Yu et al., and Shi et al.[21–23] found the opposite result. The current study thus

Table 1. Demographic and clinicopathological characteristics of different papillary thyroid carcinoma variants.

| Characteristic	All variants	CPTC (%)	FVPTC (%)	TCPTC (%)	P value
N (%)	29,555 (100)	19,445 (65.8)	9776 (33.1)	334 (1.1)	
Age, years, median (quartiles)	47 (37,57)	46 (36,56)	49 (38,58)	53 (39,65)	<0.001
Sex					<0.001
Male	6338	4328 (22.3)	1919 (19.6)	91 (27.2)	
Female	23,217	15,117 (77.7)	7857 (80.4)	243 (72.8)	
Race					<0.001
White	24,276	15,922 (81.9)	8070 (82.5)	284 (85.0)	
Black	1730	920 (4.7)	796 (8.1)	14 (4.2)	
Asian	3258	2406 (12.4)	819 (8.4)	33 (9.9)	
Unknown	292	197 (1.0)	91 (0.9)	3 (0.9)	
Age, years					<0.001
Age <45	12,943	9008 (46.3)	3825 (39.1)	110 (32.9)	
Age ≥45	16,612	10,437 (53.7)	5951 (60.9)	224 (67.1)	
Tumor size, cm					<0.001
≤1	11,084	7389 (38.0)	3634 (37.2)	61 (18.3)	
>1	18,471	12056 (62.0)	6142 (62.8)	273 (81.7)	
AJCC stage					<0.001
I	22105	14,642 (75.3)	7310 (74.8)	153 (45.8)	
II	2181	1080 (5.6)	1083 (11.1)	18 (5.4)	
III	3382	2304 (11.8)	1004 (10.3)	74 (22.2)	
IV	1887	1419 (7.3)	379 (3.9)	89 (26.6)	
T stage					<0.001
T1	17,561	11,680 (60.1)	5793 (59.3)	88 (26.3)	
T2	5155	3031 (15.6)	2079 (21.3)	45 (13.5)	
T3	5521	3753 (19.3)	1634 (16.7)	134 (40.1)	
T4	1318	981 (5.0)	270 (2.8)	67 (20.1)	
N stage					<0.001
N0	22,689	13,869 (71.3)	8645 (88.4)	175 (52.4)	
N1	6866	5576 (28.7)	1131 (11.6)	159 (47.6)	
M stage					<0.001
M0	29234	19,228 (98.9)	9689 (99.1)	317 (94.1)	
M1	321	217 (1.1)	87 (8.9)	17 (5.1)	
Status					<0.001
Disease-specific death	352	272 (1.4)	55 (0.6)	25 (7.5)	
Other cause death	676	427 (2.2)	234 (2.4)	15 (4.5)	
Alive	26726	17,531 (90.2)	8686 (88.9)	259 (77.5)	
Untraced	2478	1642 (8.4)	801 (8.2)	35 (10.5)	

CPTC, conventional papillary thyroid carcinoma; PVPTC, follicular-variant papillary carcinoma; TCPTC, tall-cell papillary thyroid carcinoma.

aimed to establish the relationships among the three major variants of PTC. TCPTC is usually accepted as the most aggressive variant of PTC. This was confirmed in our study, which showed that TCPTC had the highest prevalence of cases with advanced AJCC and locally-advanced stage (T stage and N stage), and the poorest 5-year prognoses in terms of both OS and DSS.[6,24,25] Notably, patients with TCPTC were also
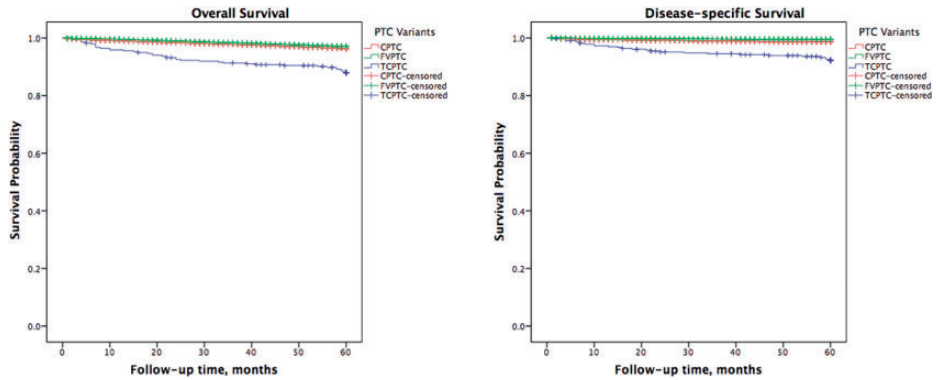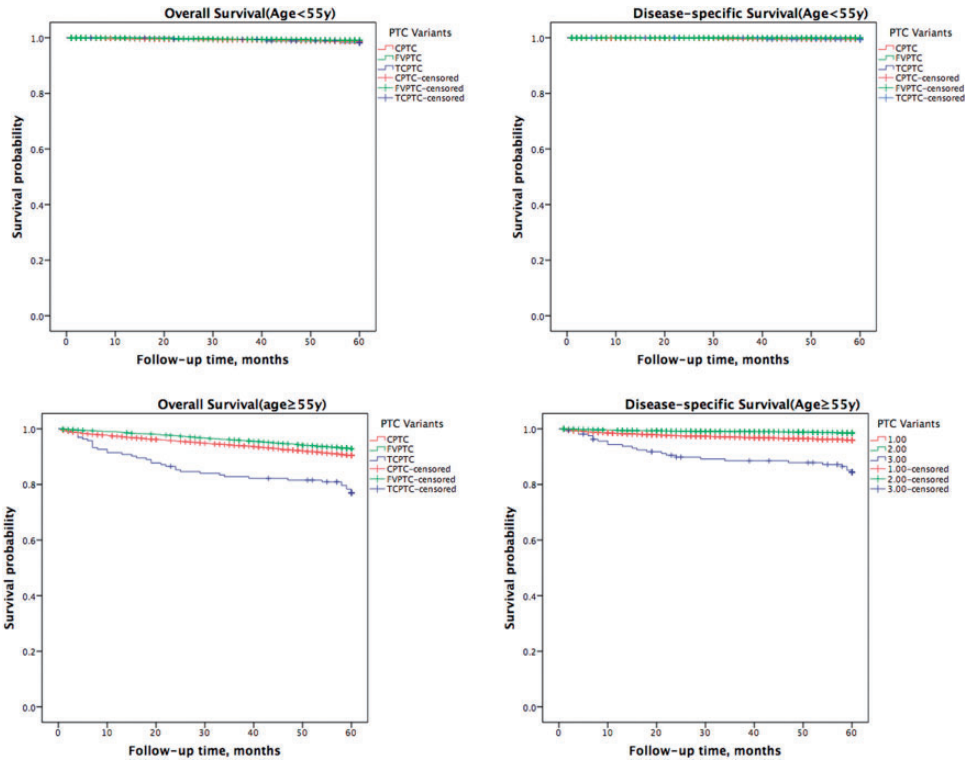
Figure 2. Kaplan–Meier analyses of 5-year overall survival (OS) and disease-specific survival (DSS) for patients with conventional papillary thyroid carcinoma (CPTC), follicular-variant papillary thyroid carcinoma (FVPTC), and tall-cell papillary thyroid carcinoma (TCPTC). Log-rank values and P values for OS comparisons among the three variants: 86.427 and <0.001; between FVPTC and CPTC: 8.339 and 0.004; between CPTC and TCPTC: 66.243 and <0.001; and between FVPTC and TCPTC: 87.538 and <0.001. Log-rank values and P values for DSS comparisons among the three variants: 157.896 and <0.001; between FVPTC and CPTC: 42.274 and <0.001; between CPTC and TCPTC: 84.883 and <0.001; and between FVPTC and TCPTC: 208.574 and <0.001.
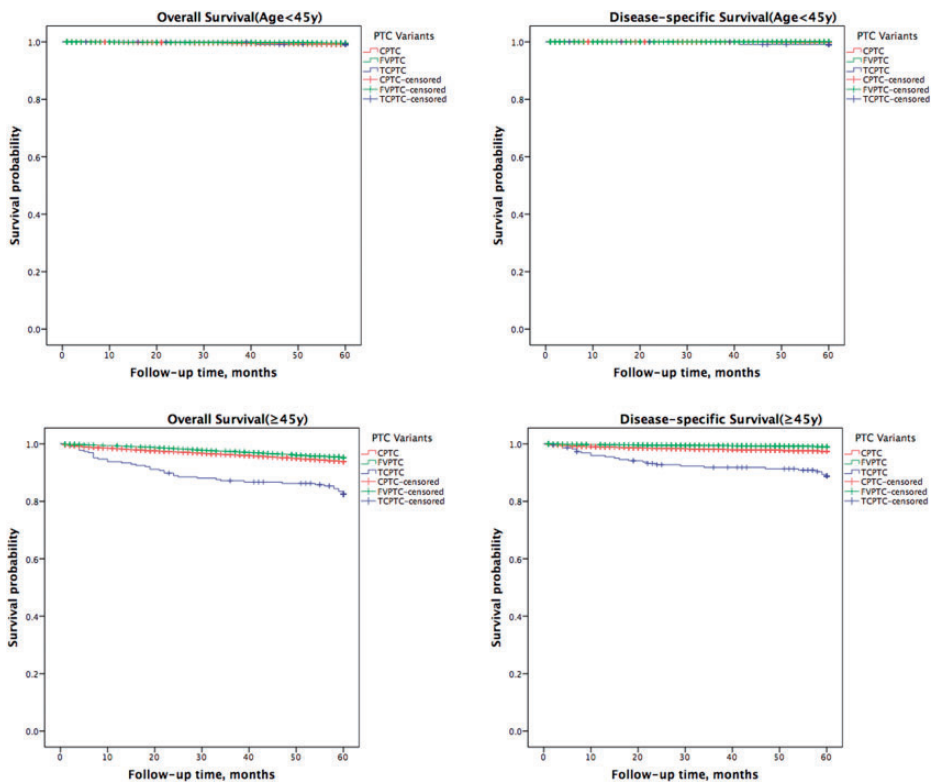
Figure 3. Kaplan–Meier analyses of 5-year overall survival (OS) and disease-specific survival (DSS) for patients with conventional papillary thyroid carcinoma (CPTC), follicular-variant papillary thyroid carcinoma (FVPTC), and tall-cell papillary thyroid carcinoma (TCPTC) in younger (age <45 years) and older patients (age ≥45 years). Log-rank values and P values for OS comparisons among the three variants in the younger age group: 7.028 and 0.03; and for DSS: 12.25 and 0.002. Log-rank values and P values for OS comparisons among the three variants in the older age group: 76.459 and <0.001; and for DSS: 138.368 and <0.001.

Figure 4. Kaplan–Meier analyses of 5-year overall survival (OS) and disease-specific survival (DSS) for patients with conventional papillary thyroid carcinoma (CPTC), follicular-variant papillary thyroid carcinoma (FVPTC), and tall-cell papillary thyroid carcinoma (TCPTC) in younger (age <55 years) and older patients (age ≥55 years). Log-rank values and P values for OS comparisons among the three variants in the younger age group: 5.933 and 0.051; and for DSS: 11.643 and 0.003. Log-rank values and P values for OS comparisons among the three variants in the older age group: 60.191 and <0.001; and for DSS: 120.353 and <0.001.

older (median age, 53 years) at diagnosis and were the most likely to be male (27.2%), which were considered to be unfavorable prognostic factors. However, TCPTC only accounted for 1.1% of patients with PTC in the current analysis, while CPTC and FVPTC comprised the majority of cases (29,221 cases, 98.9%). FVPTC was associated with lower AJCC, T, and N stages than CPTC, but higher M stage and better OS and DSS. The higher rate of metastasis in FVPTC may be because its pathological features make it difficult to use fine needle aspiration, resulting in late diagnosis. It also tends to spread by invading through the capsule into the blood vessels, similar to follicular thyroid carcinoma.[26,27] However, despite its high metastasis prevalence, FVPTC demonstrated the best prognosis among the three variants, reflecting its indolent biological features. Analysis of the different clinicopathological characteristics and progression of three histological variants of PTC indicated that FVPTC and CPTC should be included in a low-risk group while TCPTC should be in a high-risk group, with aggression based on clinicopathological characteristics and prognosis decreasing in the order TCPTC > CPTC > FVPTC.

Table 2. Cox proportional hazards regression model analysis of overall and disease-specific survival.

Variable	Overall survival		Disease-specific survival	
	HR(95% CI)	P value	HR(95% CI)	P value
Sex		<0.001		0.01
Male	Reference		Reference	
Female	0.628 (0.551,0.716)		0.748 (0.599,0.934)	
Age, years		<0.001		<0.001
<45	Reference		Reference	
≥45	8.016 (6.404,10.034)		18.522 (10.373,33.075)	
AJCC stage		<0.001		<0.001
I	Reference		Reference	
II	1.549 (1.244,1.928)		3.116 (1.791,5.42)	
III	1.374 (1.134,1.666)		3.562 (2.253,5.631)	
I	5.911 (5.042,6.929)		32.961 (22.751,47.752)	
T stage		<0.001		0.02
T1	Reference		Reference	
T2	1.172 (0.963,1.428)		1.786 (1.097,2.906)	
T3	1.503 (1.268,1.783)		4.05 (2.824,5.809)	
T4	4.784 (3.976,5.755)		20.307 (14.329,28.779)	
N stage		<0.001		<0.001
N0	Reference		Reference	
N1	1.371 (1.181,1.592)		1.808 (1.415,2.309)	
M stage		<0.001		<0.001
M0	Reference		Reference	
M1	5.692 (4.62,7.012)		8.451 (6.52,10.955)	
Race		<0.001		0.222
White	Reference		Reference	
Black	1.543 (1.224,1.944)		1.439 (0.911,2.272)	
Asian	0.765 (0.622,0.941)		0.822 (0.604,1.119)	
Unknown	0.138 (0.019,0.984)		0 (0,0.0000087)	

HR, hazard ratio; CI, confidence interval.

We also performed survival analysis stratified by age (cut-offs of 45 and 55 years), because the updated AJCC 8th edition raised the cut-off age from 45 to 55 years.[28–31] Both analyses revealed that differences among the PTC subtypes were greater in older patients. Interestingly, the difference using 55 years as the cut-off age, as suggested in the new edition, was less significant than that based on a cut-off age of 45 years, suggesting that some higher-risk patients aged 45 to 54 years were moved to a younger, lower-risk group by the switch in cut-off age. However, the differences in significance between the two cut-off ages were very small. Another international study showed that an increase in the cut-off age from 45 to 55 years at diagnosis down-staged 12% of patients and was associated with a 10-year DSS of 98% in the down-staged group. Only a very small number of patients (about 0.3% in that study) with higher risk (10-year DSS of 68%) transitioned from 7th edition stage IV to 8th edition stage II, with little impact on the stage group.[32]

After adjusting for other factors, Cox regression analysis identified male sex, age ≥45 years, higher AJCC stage, and higher T, N, and M stages as independent risk factors for a poor prognosis in patients with PTC. Race was a significant factor affecting OS and the distribution of PTC variants but did not influence DSS after adjusting for other factors.

This study had some limitations. Notably, information on cancer recurrence could not be obtained from the SEER database, and we could therefore not calculate disease-free survival. Furthermore, information on extrathyroid extension, neurovascular invasion, patient history, and immunohistochemistry results could not be obtained from the database, and these factors were therefore not included in our analysis. In addition, 5 years is a relatively short follow-up period for thyroid carcinoma, and further studies with a 10-year follow-up are required.

Conclusion

This study showed that the three main types of PTC decreased in aggressiveness in the order TCPTC > CPTC > FVPTC, based on clinicopathological characteristics and prognosis. Different treatment strategies should therefore be applied to the different variants of PTC. Male sex, age ≥45 years, higher AJCC stage, and higher T, N, and M stage may be independent risk factors for a poor prognosis in patients with PTC.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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