Am J Transl Res 2019;11(9):6262-6270
www.ajtr.org /ISSN:1943-8141/AJTR0100682

Original Article

Columnar cell papillary thyroid carcinoma prognosis: findings from the SEER database using propensity score matching analysis

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Received July 18, 2019; Accepted August 29, 2019; Epub September 15, 2019; Published September 30, 2019

Abstract: Background: Columnar cell papillary thyroid carcinoma (CCPTC) is a rare variant of papillary thyroid carcinoma (PTC), whose prognosis, as defined by the American Thyroid Association (ATA) guidelines, is considered poor, although available evidence is insufficient for reliable assessment. This study aimed to investigate the CCPTC prognosis using the Surveillance, Epidemiology, and End Results (SEER) database. Methods: Data of thyroid cancer patients, recorded from 2004 to 2013, were extracted to assess the CCPTC prognosis. All-cause and cancer-specific mortality rates associated with thyroid cancer types were evaluated using the Kaplan-Meier method and Cox proportional hazards regression. Propensity score matching analysis was used to adjust for potential confounders. Results: Cancer-specific mortality per 1000 person-years was higher for CCPTC than for classic papillary thyroid cancer (CPTC) and follicular thyroid cancer (FTC). The multivariate Cox regression model revealed that the cancer-specific and all-cause mortality rates were higher for CCPTC than for CPTC but not FTC. However, propensity score matching analysis demonstrated a significantly lower survival for CCPTC than for both CPTC and FTC. Conclusions: Our findings provide evidence to support the poor prognosis associated with CCPTC. These findings may serve to improve the diagnosis of CCPTC, provide reliable reference data for clinical use, and increase the comprehensiveness of current guidelines.

Keywords: Columnar cell, papillary thyroid carcinoma, SEER database, mortality, propensity score matching analysis

Introduction

The increasing incidence of thyroid cancer has attracted considerable attention [1-4]. Currently, papillary thyroid cancer (PTC) and follicular thyroid cancer (FTC) account for approximately 80% and 10-15% of all thyroid cancers, respectively [5, 6]. These tumors are generally associated with a good prognosis. In contrast, rare thyroid cancer subtypes, such as the tall cell, diffuse sclerosing, solid, hobnail, and columnar cell (CCPTC) variants, may lead to poor outcomes [7-9].

PTC comprises a group of several morphologically heterogeneous variants. One of these, namely CCPTC, is characterized by pseudostratified columnar cells [10]. This entity was first described by Evans in 1986, and several case reports on it have been published since. CCPTC is rare and accounts for 0.15-0.4% of all PTC cases; it is usually defined by the histologic presence of papillary or gland-like structures lined by columnar cells, demonstrating prominent nuclear stratification [11-15]. Certain reports have proposed that CCPTC is an aggressive cancer, likely to invade the surrounding extrathyroidal tissue and progress to distant metastasis; however, other studies have reported a better prognosis for encapsulated tumors [15-17].

To-date, most reports on CCPTC are case reports and literature reviews that focus mainly on the pathologic characteristics of the cancer. Nevertheless, the relatively small number of reported cases allows for limited conclusions regarding this aggressive variant, particularly,

its likely behavior and prognosis. To address this issue, we obtained data of a large number of patients from the Surveillance, Epidemiology, and End Results Program (SEER) database and evaluated the prognosis of CCPTC and its treatment.

Materials and methods

Ethics statement

This study was conducted in accordance with the ethical standards of the Declaration of Helsinki, and national and international guidelines. The review board of the Wuhan Union Hospital approved this study.

Study population

For this study, we obtained records of patients with differentiated thyroid cancer (DTC) from the SEER project, the United States population-based cancer registry, initiated in 1973 and supported by the National Cancer Institute and the Centers for Disease Control and Prevention. This database, which covers multiple geographic regions, is the largest publicly available and authoritative source of information on cancer incidence and survival. It contains data on incidence, prevalence, mortality, population-based variables, and clinical tumor characteristics, among other parameters.

Data collection and analysis

To identify patients in the SEER database diagnosed with DTC between 2004 and 2013, we searched the database using a combination of the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3), site code C73.9 (i.e., thyroid) and the key words "papillary" and/or "follicular histology". The following diagnostic codes were included in the study: "papillary carcinoma", "papillary adenocarcinoma", "follicular adenocarcinoma", "papillary & follicular adenocarcinoma", and "papillary cyst-adenocarcinoma".

To compare survival rates between different histological types of PTC, we identified 67144 patients using the ICD-O-3 histology codes. Among them, 8344 (columnar cell variant); 8330, 8332, and 8335 (FTC); and 8050, 8260, 8342, and 8343 (classic PTC). The following data were extracted for patients with different histologic subtypes: age, sex, race, T/N/M stage, presence of multifocality, extension, radiation therapy (none or refused, external beam radiation therapy, or radioactive I-131 ablation), and surgical treatment (biopsy, lobectomy, subtotal or near-total thyroidectomy, or total thyroidectomy).

Statistical analyses

The follow-up period was until December 2013. Patient survival (thyroid cancer-specific and all-cause mortality) was evaluated using the Kaplan-Meier method and log-rank tests. To further adjust for potential baseline confounders, we performed propensity score matching analysis. We additionally used Cox proportional hazards regression analyses to estimate hazard ratios (HRs), which represented the magnitude of the effect of histologic subtype on cancer-specific and all-cause mortality with 95% confidence intervals (CIs) and indicated the significance of the hazards [29]. All *P* values were 2-sided, and a value<0.05 was considered statistically significant. All analyses were performed using the SPSS version 22.0 (IBM, Armonk, NY, USA), Stata/SE version 14 (Stata Corp, College Station, TX, USA), and GraphPad Prism, version 6 (GraphPad Software Inc. San Diego, CA, USA) software packages.

Results

Demographic and clinical features

Among the 67144 patients with various histological types of PTC, 986, 60739, and 5419 were diagnosed with CCPTC, CPTC, and FTC, respectively. The clinical and pathologic characteristics of the cohort are presented in **Table 1**. The average survival for CCPTC, CPTC, and FTC was 44.06±33.01, 48.99±33.40, and 49.21±33.48 months, respectively, with a *p*-value<0.001. Notably, the survival rate was significantly lower among patients with CCPTC than among those with CPTC and FTC.

Cancer-specific and all-cause mortality per 1000 person-years according to histological type

Among patients with PTC, the rates of cancer-specific mortality per 1000 person-years for CCPTC, CPTC, and FTC were 16.85 (95% CI: 13.11-21.65), 2.51 (95% CI: 2.32-2.72), and

Table 1. Characteristics of patients according to histological types

Covariate	level	Histological types				
		CCPTC (n=986)	CPTC (n=60739)	*P* value	FTC (n=5419)	*P* value
Age (years)		53.43±16.28	48.37±15.36	<0.001	50.79±17.29	<0.001
Sex	Female (%)	709 (71.9)	46786 (77.0)	<0.001	3843 (70.9)	0.528
	Male (%)	277 (28.1)	13953 (23.0)		1576 (29.1)	
Race	White (%)	832 (85.7)	49651 (82.8)	0.060	4186 (78.3)	<0.001
	Black (%)	45 (4.6)	3159 (5.3)		640 (12.0)	
	Other (%)	94 (9.7)	7133 (11.9%)		517 (9.7)	
T-stage	T1 (%)	277 (28.4)	37974 (63.8)	<0.001	1240 (23.7)	<0.001
	T2 (%)	116 (11.9)	8062 (13.6)		2110 (40.4)	
	T3 (%)	412 (42.2)	10845 (18.2)		1682 (32.2)	
	T4 (%)	171 (17.5)	2599 (4.4)		191 (3.7)	
N-stage	N0 (%)	519 (54.9)	44102 (74.9)	<0.001	5114 (96.9)	<0.001
	N1 (%)	427 (45.1)	14744 (25.1)		161 (3.1)	
M-stage	M0 (%)	944 (95.7)	59951 (98.7)	<0.001	5093 (94.0)	0.029
	M1 (%)	42 (4.3)	788 (1.3)		326 (6.0)	
Multifocality	No (%)	488 (51.3)	35549 (60.1)	<0.001	4464 (85.7)	<0.001
	Yes (%)	463 (48.7)	23591 (39.9)		742 (14.3)	
Extension	No (%)	458 (46.9)	49129 (82.1)	<0.001	4795 (90.4)	<0.001
	Yes (%)	518 (53.1)	10744 (17.9)		512 (9.6)	
Radiation	None or refused (%)	300 (31.3)	30701 (51.7)	<0.001	2303 (83.8)	<0.001
	Radiation beam or radioactive implants (%)	66 (6.9)	1105 (1.9)		163 (5.9)	
	Radioisotopes I-131 ablation (%)	592 (61.8)	27548 (46.4)		282 (10.3)	
Surgery	Biopsy (%)	13 (1.3)	1513 (2.5)	<0.001	183 (3.4)	<0.001
	Lobectomy (%)	69 (7.0)	7750 (12.9)		1207 (22.5)	
	Subtotal or near-total thyroidectomy (%)	22 (2.2)	2116 (3.5)		277 (5.2)	
	Total thyroidectomy (%)	875 (89.5)	48771 (81.1)		3696 (68.9)	
Survival (months)		44.06±33.01	48.99±33.40	<0.001	49.21±33.48	<0.001

CCPTC: columnar cell papillary thyroid carcinoma; CPTC: classic papillary thyroid cancer; FTC: follicular thyroid carcinoma.

Table 2. Hazard ratios for cancer-specific and all-cause mortality in thyroid cancer per histological type

Histological type	Cancer-Specific Deaths, No.	%	Cancer-Specific Deaths per 1,000 Person-Years	95% CI	All Cause Deaths, No.	%	All Cause Deaths per 1,000 Person-Years	95% CI
CCPTC	64	6.49	16.85	13.11-21.65	130	13.18	35.08	29.08-41.74
CPTC	659	1.08	2.51	2.32-2.72	2722	4.48	10.54	10.14-10.95
FTC	178	3.28	6.68	5.72-7.81	474	8.75	18.58	16.93-20.40

CCPTC: columnar cell papillary thyroid carcinoma; CPTC: classic papillary thyroid cancer; FTC: follicular thyroid carcinoma.

6.68 (95% CI: 5.72-7.81), respectively (**Table 2**). The corresponding rates of all-cause mortality per 1000 person-years were 35.08 (95% CI: 29.08-41.74), 10.54 (95% CI: 10.14-10.95), and 18.58 (95% CI: 16.93-20.40), respectively (**Table 2**).

Risk factors for thyroid cancer-specific and all-cause mortality

In univariate Cox regression analysis, age, male sex, other race (American Indian/AK Native, and Asian/Pacific Islander), TNM stage, tumor extension, radiation therapy, and surgical treatment were identified as significant risk factors for thyroid cancer-specific mortality.

In multivariate Cox regression, the CCPTC subtype was associated with a significantly higher risk of cancer-specific mortality relative to CPTC after adjusting for all other relevant risk factors; however, no significant difference was observed between CCPTC and FTC (**Table 3**).

For all-cause mortality, univariate Cox regression analysis identified age, male sex, African

Table 3. Risk factors for survival based on all-cause and thyroid cancer-specific mortality

Covariate	level	Thyroid cancer-specific mortality				All-cause mortality			
		Univariate Cox regression		Multivariate Cox regression		Univariate Cox regression		Multivariate Cox regression	
		Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value	Hazard Ratio (95% CI)	*p*-value
Age		1.096 (1.091-1.101)	<0.001	1.061 (1.055-1.067)	<0.001	1.087 (1.084-1.089)	<0.001	1.071 (1.068-1.074)	<0.001
Sex	Female	ref		ref		ref		ref	
	Male	2.648 (2.322-3.020)	<0.001	1.154 (0.981-1.358)	0.083	2.443 (2.280-2.616)	<0.001	1.599 (1.479-1.730)	<0.001
Race	White	ref		ref		ref		ref	
	Black	1.085 (0.7823-1.430)	0.511	0.885 (0.610-1.285)	0.643	1.304 (1.145-1.486)	<0.001	1.173 (1.008-1.365)	0.040
	Other	1.372 (1.114-1.648)	0.002	0.925 (0.735-1.164)	0.506	0.921 (0.822-1.031)	0.151	0.806 (0.708-0.919)	0.001
histological types	CCPTC	ref		ref		ref		ref	
	CPTC	0.156 (0.121-0.202)	<0.001	0.731 (0.536-0.996)	0.047	0.309 (0.259-0.368)	<0.001	0.719 (0.588-0.881)	0.001
	FTC	0.452 (0.340-0.602)	<0.001	1.042 (0.719-1.509)	0.829	0.565 (0.465-0.686)	<0.001	0.834 (0.662-1.050)	0.834
T-stage	T1	ref		ref		ref		ref	
	T2	3.568 (2.540-5.013)	<0.001	3.199 (2.236-4.577)	<0.001	1.145 (1.022-1.282)	<0.001	1.203 (1.064-1.361)	0.003
	T3	9.015 (6.843-11.876)	<0.001	4.439 (2.995-6.577)	<0.001	1.712 (1.560-1.879)	<0.001	1.252 (1.069-1.467)	0.005
	T4	98.406 (76.325-128.875)	<0.001	16.021 (10.214-25.131)	<0.001	8.525 (7.790-9.329)	<0.001	2.715 (2.204-3.346)	<0.001
N-stage	N0	ref		ref		ref		ref	
	N1	4.463 (3.872-5.146)	<0.001	1.858 (1.540-2.242)	<0.001	1.709 (1.584-1.843)	<0.001	1.429 (1.292-1.580)	<0.001
M-stage	M0	ref		ref		ref		ref	
	M1	48.278 (42.206-55.225)	<0.001	5.729 (4.703-6.981)	<0.001	15.146 (13.794-16.630)	<0.001	3.328 (2.885-3.839)	<0.001
Multifocality	No	ref		ref		ref		ref	
	Yes	0.992 (0.856-1.150)	0.915	0.874 (0.741-1.031)	0.109	0.907 (0.842-0.978)	0.011	0.956 (0.881-1.038)	0.283
Extension	No	ref		ref		ref		ref	
	Yes	14.018 (11.966-16.422)	<0.001	1.500 (1.062-2.120)	0.022	2.908 (2.706-3.126)	<0.001	1.180 (0.991-1.404)	0.063
Radiation	None or refused	ref		ref		ref		ref	
	Radiation Beam or radioactive implants	16.365 (13.813-19.388)	<0.001	2.173 (1.726-2.736)	<0.001	4.452 (3.952-5.015)	<0.001	1.236 (1.056-1.4472)	0.008
	Radioisotopes I-131 ablation	0.937 (0.804-1.091)	0.403	0.743 (0.613-0.900)	0.002	0.615 (0.571-0.663)	<0.001	0.669 (0.611-0.732)	<0.001
Surgery	Biopsy	ref		ref		ref		ref	
	Lobectomy	0.040 (0.031-0.052)	<0.001	0.477 (0.331-0.688)	<0.001	0.092 (0.082-0.104)	<0.001	0.323 (0.274-0.381)	<0.001
	Subtotal or near-total thyroidectomy	0.085 (0.062-0.117)	<0.001	0.579 (0.382-0.876)	0.010	0.098 (0.082-0.117)	<0.001	0.336 (0.271-0.416)	<0.001
	Total thyroidectomy	0.051 (0.044-0.060)	<0.001	0.476 (0.361-0.629)	<0.001	0.072 (0.066-0.079)	<0.001	0.297 (0.257-0.344)	<0.001

CCPTC: columnar cell papillary thyroid carcinoma; CPTC: classic papillary thyroid cancer; FTC: follicular thyroid carcinoma.

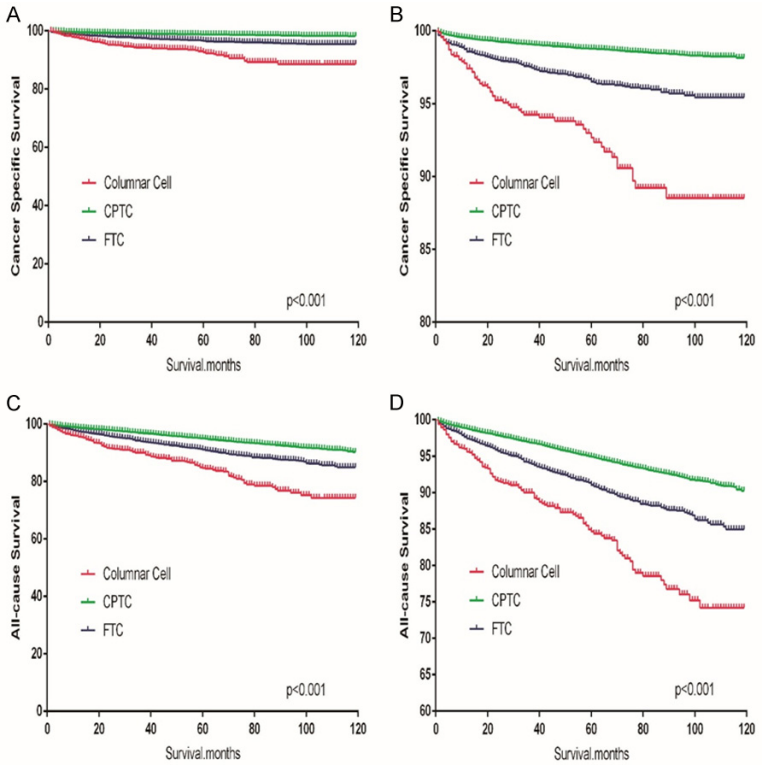

Figure 1. Kaplan-Meier curves among patients stratified by subtype for cancer-specific mortality (A, B: Log rank test P<0.001) and all-cause mortality (C, D: Log rank test P<0.001).

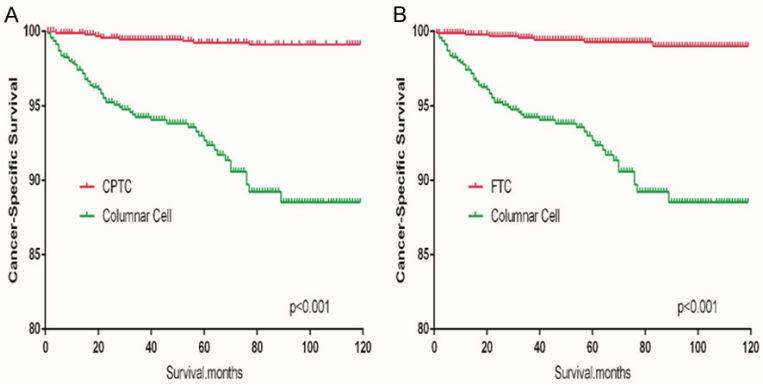

Figure 2. Kaplan-Meier curves for cancer-specific mortality among subtype-matched pairs, matching for age, sex, and race: CCPTC and CPTC (A), and CCPTC and FTC (B).

with CPTC but not FTC (**Table 3**).

Propensity score matching adjustment of patient characteristics

Analysis of the original data showed that compared with patients with CPTC and FTC, patients with CCPTC had a poorer prognosis in terms of both cancer-specific and all-cause mortality (**Figure 1A-D**). Propensity score matching analysis was performed based on age, sex, race, T/N/M stage, histologic subtype, multifocality, extension, surgical treatment, and radiation therapy to minimize selection bias. On survival analysis conducted after propensity score matching by age, sex, and race, the prognosis of CCPTC in terms of cancer-specific mortality remained poorer than that of CPTC and FTC (both P≤0.001, **Figure 2A**, **2B**). Compared with CPTC and FTC, CCPTC also had a poorer prognosis in terms of thyroid cancer-specific mortality after propensity score matching for age, sex, race, T/N/M stage, multifocality, and extension (both P≤0.001, **Figure 3A**, **3B**). This difference in thyroid cancer-specific mortality remained significant after matching for all influential factors, including surgical treatment and radiation therapy (P<0.001 for CCPTC vs. CPTC and FTC, **Figure 4A**, **4B**).

origin, TNM stage, multifocality, and tumor extension as significant risk factors. In contrast, radiation therapy and surgical treatment emerged as protective factors. Multivariate Cox regression revealed that, after adjusting for all other influential risk factors, the CCPTC subtype was associated with a significantly higher risk of all-cause mortality than that associated

On survival analysis of all-cause mortality, CCPTC also exhibited a poorer prognosis relative to CPTC and FTC after propensity matching for age, sex, and race (both P<0.001, **Figure 5A**, **5B**). Similar results were observed after matching for age, sex, race, T/N/M stage, multifocality, and extension (**Figure 6A**, **6B**). The poorer all-cause mortality of CCPTC than that

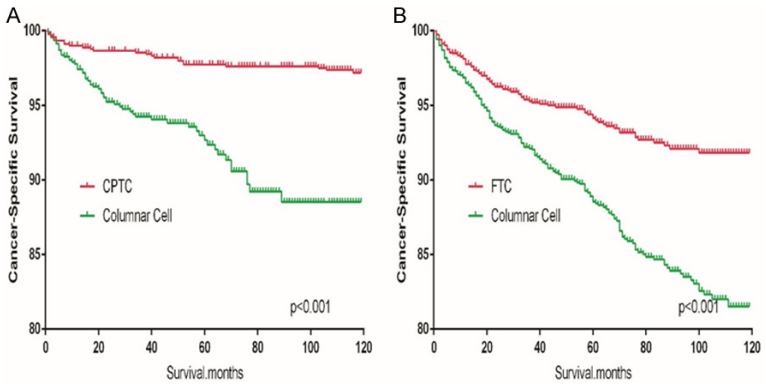

Figure 3. Kaplan-Meier curves of cancer-specific mortality for subtype-matched pairs, matching for age, sex, race, T/N/M stage, and multifocality: CCPTC and CPTC (A), and CCPTC and FTC (B).

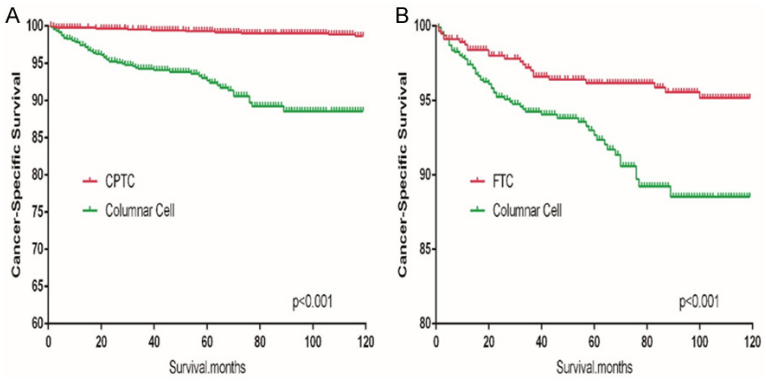

Figure 4. Kaplan-Meier curves of cancer-specific mortality for subtype-matched pairs, matching for age, sex, race, T/N/M stage, multifocality, extension, surgery, and radiation treatment: CCPTC and CPTC (A), and CCPTC and FTC (B).

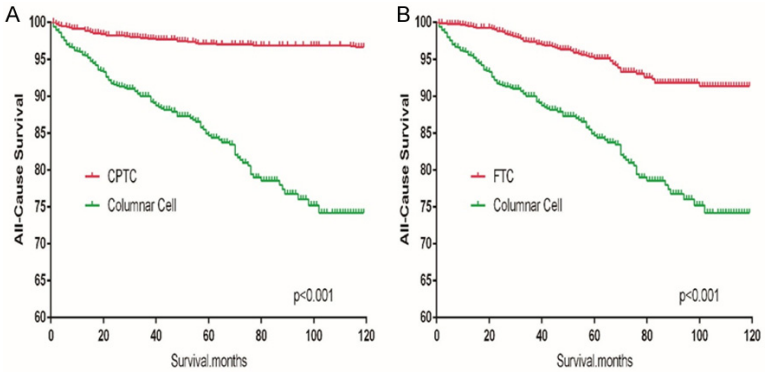

Figure 5. Kaplan-Meier curves of all-cause mortality for subtype-matched pairs, matching for age, sex, and race: CCPTC and CPTC (A), and CCPTC and FTC (B).

of CPTC and FTC persisted after matching for all influential factors, including surgical treatment and radiation therapy (**Figure 7A**, **7B**).

Discussion

In this study, the data obtained from the SEER database were evaluated using Cox regression analysis. The results showed histological subtype of thyroid cancer as an independent risk factor for cancer-specific and all-cause mortality. Specifically, CCPTC was associated with increased mortality compared with CPTC. In contrast, mortality rates associated with CCPTC and FTC were comparable. Furthermore, on non-risk variant-matched analysis, compared with CPTC and FTC, CCPTC was associated with a significantly poorer prognosis. After matching for different risk factors, including demographics (age, race, and sex), pathological features (T/N/M stage, multifocality, and extension), and surgery and radiation treatment, mortality rates associated with CCPTC remained higher compared to mortality rates associated with CPTC or FTC.

Characteristic cytological features, such as nuclear pseudostratifcation, rare nuclear grooves, intranuclear cytoplasmic inclusions, inconspicuous nucleoli, morphologically columnar cells, and wispy cytoplasm may be distinctive features of CCPTC [14, 18, 19]. However, fine-needle aspiration (FNA) biopsy-based diagnosis of CCPTC might be challenging because of the lack of standardized criteria applicable to these features or the patient's history of metastases or other malignancies (e.g., colonic or endometrial adenocarcinoma) [11, 12, 20, 21]. Furthermore, characteristic ultrasonographic or radiologic features have not been established for CCPTC [22-24].

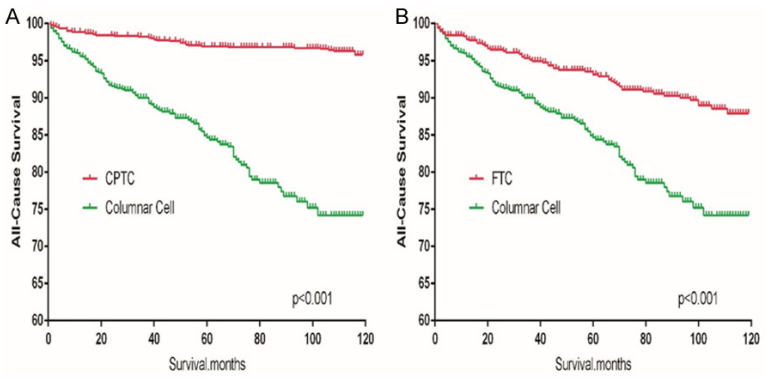

Figure 6. Kaplan-Meier curves of all-cause mortality for subtype-matched pairs, matching for age, sex, race, T/N/M stage, multifocality, and extension: CCPTC and CPTC (A), and CCPTC and FTC (B).

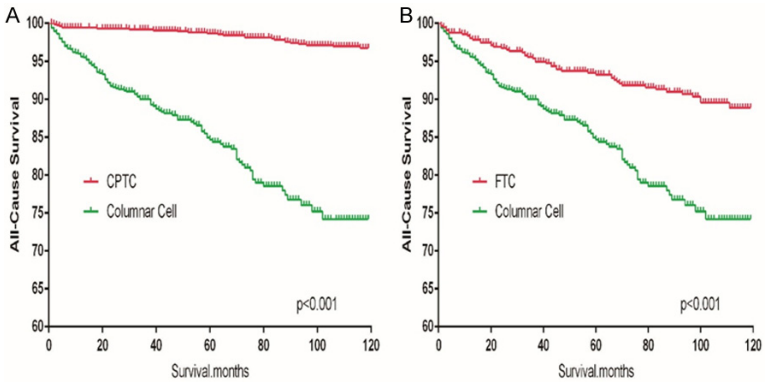

Figure 7. Kaplan-Meier curves of all-cause mortality for subtype-matched pairs, matching for age, sex, race, T/N/M stage, multifocality, extension, surgery, and radiation treatment: CCPTC and CPTC (A), and CCPTC and FTC (B).

Research has found that, overall, CCPTC tends to be more aggressive than CPTC. Although certain studies suggest that CCPTC is always aggressive, others have reported that encapsulated CCPTC is associated with better outcomes after complete surgical removal. Silver *et al.* suggested that, as an aggressive variant, CCPTC tends to confer a poorer prognosis and is associated with a higher risk. After comparing two cases of CCPTC, Yunta *et al.* also concluded that the presence of a capsule was associated with a favorable prognosis [11, 12, 14, 15, 25-27]. However, assessment of CCPTC prognosis requires further studies with large samples.

It should be noted that, in the SEER database, CCPTC cases had a relatively shorter follow-up period than CPTC and FTC cases, which is also evident from previous studies [12, 13, 16, 17]. As a result, the possibility that the prognosis of CCPTC was affected by shorter follow-up durations cannot be excluded. Nevertheless, our results may provide clinical guidance and serve to increase the comprehensiveness of the new American Thyroid Association guidelines. Previous studies, which mostly focused on pathological characteristics as applicable to the diagnostics of CCPTC, have suggested that detection of FNA and *BRAF*^{V600E} may help distinguish CCPTC from other types of thyroid cancer. Nevertheless, additional molecular and immunophenotypic research is required for further clarification [10, 12, 19, 28].

Biologically, CCPTC may exhibit considerably greater aggressive and invasive behavior. In a case of recurrent CCPTC, Sen *et al.* reported that the recurrent tumor invaded the capsule and extended into the larynx within 1 year after subtotal thyroidectomy. In our study, 53.1% of the patients with CCPTC had extrathyroidal tumor extension; this proportion was significantly greater than the corresponding rates for CPTC and FTC. In addition, 45.1% of patients with CCPTC had lymph node metastases; this was also considerably higher than the corresponding rates for patients with CPTC and FTC. Patients with CCPTC also presented with higher rates of metastasis and multifocality than those with CPTC. This evidence supports the hypothesis that CCPTC is an aggressive subtype of CPTC, which may account for its higher mortality rates.

Few effective, specific, and universal molecular targeted therapies are currently available for CPTC, and none have been developed for CCPTC. Furthermore, CCPTC is associated with shorter survival even following total thyroidectomy and radiation therapy. Given the aggressive behavior and poor prognosis of CCPTC, radical approaches should be explored when treating these tumors. New molecular tests or

alternative diagnostic methods that precisely identify and distinguish CCPTC would confer substantial benefit.

Our study has several limitations. First, the SEER dataset lacked information regarding recurrence. Accordingly, the cancer-specific and all-cause mortality rates may have been overestimated. Second, we did not include data on family history, vascular invasion, or other histologic findings, which may have affected the outcomes. Finally, we did not include molecular markers, such as the *BRAF* mutation, in the analysis.

Conclusions

Our findings suggest that patients with CCPTC have a greater risk of lymph node metastases and extrathyroidal extension as well as a poorer prognosis than do patients with CPTC or FTC. These findings may serve to improve the diagnosis of CCPTC, provide reliable reference data for clinical use in this PTC subtype, and increase the comprehensiveness of the new edition of the ATA guidelines. Further prospective studies are warranted to validate our findings.

Disclosure of conflict of interest

None.

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