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Original Article

Prognosis of FTC compared to PTC and FVPTC: findings based on SEER database using propensity score matching analysis

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Abstract: The significance of prognosis of follicular thyroid cancer (FTC) compared to other subtypes of thyroid cancer, based on large cohort data has only been addressed in a few studies, and the results remain controversial. In this study, we investigated the prognosis of FTC compared to papillary thyroid carcinoma (PTC) and follicular variant PTC (FVPTC) based on Surveillance, Epidemiology, and End Results database (SEER) Program data using propensity score matching. We evaluated data from 128,703 patients with thyroid cancer who were included in the SEER database between 2004 and 2013. Patient mortality was evaluated using Cox proportional hazards regression analyses and Kaplan-Meier analyses with log-rank tests. The average prognosis of FTC was poorer than both PTC and FVPTC. The multivariate Cox regression analysis revealed that the cancer-specific survival rate for FTC was lower than that for PTC and FVPTC without adjusting for risk factors. Furthermore, after propensity score matching analysis for relevant factors, the cancer-specific mortality rate for FTC was higher than that for PTC and FVPTC. These results based on a large population cohort database provide a benefit reference for individual and precise treatment and management of patients with FTC.

Keywords: Prognosis, follicular thyroid cancer, SEER, propensity score matching, cancer-specific survival

Introduction

The incidence of thyroid cancer has surged globally over the previous four decades [1-9]. Follicular thyroid cancer (FTC), which accounts for about 10% of all thyroid cancers, is the second most common thyroid cancer subtype after papillary thyroid cancer (PTC), which accounts for more than 80% of all thyroid cancer [2, 10].

The importance of prognostic factors and prognostic classifications for predicting the survival of patients with PTC has been demonstrated extensively [2, 11-14]. On the other hand, the prognosis of FTC, which has rather increased metastasis, recurrence compared to PTC has only been addressed by few studies and the outcome of such studies is rather controversial. In a recent review, Grani et al., 2017, suggested that FTC has a unique biological behavior with less favorable outcomes [10], which is in contrast to the other study that draws the opposite conclusion [15].

To further advance our understanding and significance of FTC prognosis, we investigated the prognosis of FTC compared to those of PTC and follicular variant PTC (FVPTC) by analyzing a cohort database from the Surveillance, Epidemiology, and End Results (SEER) Program using propensity score matching (PSM).

Materials and methods

Ethical considerations, study population and data collection

Our study's retrospective protocol was approved by Zhongnan Hospital of Wuhan University's ethical review board (approval number: 20131001PTMC) and complied with the ethical standards of the Declaration of Helsinki, as well as the relevant national and international guidelines.

The present study evaluated SEER data (2004-2013) from patients with thyroid cancer accord-

Table 1. Characteristics for Patients with different histological types

Covariate	Level	Histological types				
		FTC (n=5865)	PTC (n=92963)	*P* value	FVPTC (n=29875)	*P* value
Age (year)		51.33±17.20	49.36±15.29	<0.001	51.03±15.15	0.175
Sex	Female	4137 (70.5%)	71785 (77.2%)	<0.001	23269 (77.9%)	<0.001
	Male	1728 (29.5%)	21178 (22.8%)		6606 (22.1%)	
Race	White	4529 (78.3%)	76038 (82.9%)	<0.001	24512 (82.9%)	<0.001
	Black	695 (12.0%)	5704 (6.2%)		2498 (8.5%)	
	Other	558 (9.7%)	9987 (10.9%)		2546 (8.6%)	
T stage	T1	1283 (23.8%)	55606 (62.2%)	<0.001	16344 (60.7%)	<0.001
	T2	2174 (40.2%)	13811 (15.5%)		5342 (19.8%)	
	T3	1747 (32.4%)	16407 (18.4%)		4600 (17.1%)	
	T4	194 (3.6%)	3463 (3.9%)		662 (2.4%)	
N-stage	N0	5370 (97.0%)	69465 (79.0%)	<0.001	23581 (88.6%)	<0.001
	N1	168 (3.0%)	18460 (21.0%)		3030 (11.4%)	
M-stage	M0	5377 (94.2%)	89658 (98.8%)	<0.001	26846 (98.9%)	<0.001
	M1	329 (5.8%)	1132 (1.2%)		296 (1.1%)	
Multifocality	No	4735 (85.6%)	52324 (58.3%)	<0.001	14747 (54.6%)	<0.001
	Yes	797 (14.4%)	37350 (41.7%)		12264 (45.4%)	
Extension	No	5027 (88.9%)	75994 (83.7%)	<0.001	24207 (88.6%)	0.455
	Yes	626 (11.1%)	14847 (16.3%)		3121 (11.4%)	
Radiation	None or refused	2573 (45.0%)	46761 (51.5%)	<0.001	14734 (50.6%)	<0.001
	Radiation Beam or Rdioactive implants	177 (3.1%)	1705 (1.9%)		611 (2.1%)	
	Radioisotopes or Radiation beam plus isotopes or implants	2970 (51.9%)	42296 (46.6%)		13792 (47.3%)	
Surgery	Lobectomy	1300 (23.6%)	12688 (14.2%)	<0.001	4803 (16.9%)	<0.001
	Subtotal or near-total thyroidectomy	303 (5.5%)	3337 (3.7%)		1175 (4.1%)	
	Total thyroidectomy	3911 (70.9%)	73162 (82.1%)		22456 (79.0%)	
Survival months (month)		53.12±34.33	49.09±33.76	<0.001	49.92±34.86	<0.001

FTC: follicular thyroid cancer; PTC: papillary thyroid cancer; FVPTC: follicular variant papillary thyroid cancer.

ing to their subtype (FTC, PTC, and FVPTC) using code C73.9 from the International Classification of Diseases for Oncology (i.e., thyroid, papillary, and/or follicular histology). The eligible diagnostic codes were: "papillary carcinoma", "papillary adenocarcinoma", "follicular adenocarcinoma", "papillary carcinoma, follicular variant", and "papillary & follicular adenocarcinoma". Cases without American Joint Committee on Cancer staging information (version 6) were excluded to ensure accurate analyses. Cases without information of follow up time were also excluded. The three histological subtypes were compared according to age, sex, race, TNM stage, multifocality, extension, radiation treatment (i.e., none or refused, external beam radiation therapy, or RAI) and surgical approaches (lobectomy, subtotal or near-total thyroidectomy and total thyroidectomy).

Statistical analyses

All included patients were followed-up until December 2013. The quantitative variables were expressed as mean ± standard deviation (SD), while the categorical ones were presented as percentages. Patient survival curves for thyroid cancer-specific mortality and all-cause mortality were examined by Kaplan-Meier analyses with the log-rank test. Cox proportional hazard regression analyses were using to estimate hazard ratios and 95% CIs, in order to quantify the effects of the different histological subtypes on cancer-specific and all-cause mortality. PSM was also used to further adjust for potential baseline confounding factors (demographic data, clinicopathological characteristics and treatment approaches). All *p*-values were 2-sided, and *p*-values <.05 were considered significant. Analyses were performed using SPSS version 23.0, Stata/SE version 12 (Stata Corp.), and GraphPad Prism version 6 (GraphPad Software Inc.).

Results

Demographic and clinical features

This study extracted and assessed data from 128,703 patients (PTC, n=92,963; FTC, n=

Table 2. Hazard Ratios of different histological types for the cancer specific deaths and all cause deaths of thyroid cancer

Histological types	Cancer-Specific Deaths	%	Cancer-Specific Deaths per	95% CI	All Cause Deaths	%	All Cause Deaths per	95% CI
	No.		1,000 Person-Years		No.		1,000 Person-Years	
FTC	190	3.24	6.509	5.598-7.569	538	9.17	19.337	17.717-21.104
PTC	966	1.04	2.403	2.252-2.564	4388	4.72	11.068	10.739-11.408
FVPTC	510	1.71	3.990	3.654-4.357	2779	9.30	21.611	20.809-22.444

FTC: follicular thyroid cancer; PTC: papillary thyroid cancer; FVPTC: follicular variant papillary thyroid cancer.

5,865; FVPTC, n=29,875) with thyroid cancer. The patients' mean age and follow-up duration according to different histological subtypes are shown in **Table 1**. Patients with FTC had longer follow up time compared to patients with PTC or FVPTC (both P<0.001).

Cancer-specific and all-cause mortality rates of different histological subtypes

During the follow-up period to December 2013, cancer-specific mortality was noted in 190 patients in the FTC group, 996 patients in the PTC group, and 510 patients in the FVPTC group. The cancer-specific mortality rates per 1,000 person-years for patients with FTC, PTC, and FVPTC were 6.509 (95% CI: 5.598-7.569), 2.403 (95% CI: 2.252-2.564), and 3.990 (95% CI: 3.654-4.357) respectively (**Table 2**). In addition, during the follow-up period, all-cause mortality was noted in 538 patients in the FTC group, 4,388 patients in the PTC group, and 2,779 patients in the FVPTC group. The all-cause mortality rates per 1,000 person-years for patients with FTC, PTC, and FVPTC were 19.337 (95% CI: 17.717-21.104), 11.068 (95% CI: 10.739-11.408), and 21.611 (95% CI: 20.809-22.444) respectively (**Table 2**).

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

The univariate Cox regression analyses demonstrated that cancer-specific mortality was associated with significant risk factors such as age, sex, race, histological type, T/N/M stage, multifocality, tumor extension, radiation treatment, and surgical approach. The multivariate Cox regression model illustrated that PTC had a significant better cancer-specific survival with a hazard ratio of 0.573 (95% CI [0.451-0.727]) compared to FTC. Further, FVPTC also had a better cancer-specific survival with a hazard ratio of 0.482 (95% CI [0.361-0.644]) compared to FTC (**Table 3**). The univariate Cox regression analyses revealed that all-cause mortality was associated with age, race, sex, histological type, T/N/M stage and radiation treatment. The multivariate Cox regression model illustrated that PTC had a significant better cancer-specific survival with a hazard ratio of 0.8 (95% CI [0.708-0.904]) compared to FTC and a hazard ration of 0.801 (95% CI [0.702-0.914]) compared to but for FVPTC (**Table 3**).

Adjusting for patient characteristics using PSM

The cancer-specific rate of mortality was significantly different when compared to FTC to PTC and FVPTC (FTC was higher than PTC or FVPTC), without matching for any confounders (both P<0.001, **Figure 1A-C**). Whereas, the all-cause mortality rate of patients with FTC was significantly higher/lower when compared to PTC (P<0.001), but there was no significant difference in all-cause mortality rate of patients between the FTC and FVPTC group (P=0.233, **Figure 1D-F**). To minimize selection bias, PSM was performed for age, sex, race, TNM stage, multifocality, tumor extension, radiation and surgical treatment. PSM analysis performed for demographic data such as age, sex, and race, revealed that cancer-specific mortality rates between both FTC and PTC group and FTC and FVPTC group were significantly different (P< 0.001, P<0.001 respectively; **Figure 2A**, **2B**). Furthermore, PSM analysis for age, sex, race, and clinicopathologic features (T/N/M stage, multifocality, and extension), also showed significant differences in cancer-specific mortality rates between FTC and PTC, and FTC and FVPTC groups (both P<0.001; **Figure 3A**, **3B**). PSM analysis performed for all relevant factors and radiation and surgical treatment, demonstrated that the cancer-specific mortality rate for FTC group remained still significantly higher compared to PTC and FVPTC group (both P< 0.001; **Figure 4A**, **4B**).

Table 3. Risk factors for survival: outcome of thyroid cancer specific mortality and all-cause 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		1.092 (1.088-1.096)	<0.001	1.069 (1.064-1.075)	<0.001	1.082 (1.080-1.084)	<0.001	1.078 (1.075-1.080)	<0.001
Sex	Female	Ref		Ref		Ref		Ref	
	Male	2.801 (2.543-3.085)	<0.001	1.510 (1.305-1.749)	<0.001	2.404 (2.297-2.516)	<0.001	1.683 (1.581-1.792)	<0.001
Race	White	Ref		Ref		Ref		Ref	
	Black	1.134 (0.942-1.365)	0.185	1.220 (0.901-1.651)	0.198	1.311 (1.211-1.419)	<0.001	1.472 (1.320-1.641)	<0.001
	Other	1.519 (1.322-1.744)	<0.001	0.925 (0.747-1.147)	0.478	0.954 (0.882-1.030)	0.230	0.790 (0.706-0.885)	<0.001
Histological types	FTC	Ref		Ref		Ref		Ref	
	PTC	0.341 (0.292-0.399)	<0.001	0.573 (0.451-0.727)	<0.001	0.559 (0.511-0.611)	<0.001	0.800 (0.708-0.904)	<0.001
	FVPTC	0.544 (0.461-0.643)	<0.001	0.482 (0.361-0.644)	<0.001	1.062 (0.968-1.165)	0.201	0.801 (0.702-0.914)	<0.001
T-stage	T1	Ref		Ref		Ref		Ref	
	T2	2.529 (1.945-3.289)	<0.001	2.006 (1.469-2.738)	<0.001	1.041 (0.961-1.129)	0.323	1.087 (0.991-1.191)	0.077
	T3	7.346 (5.971-9.038)	<0.001	3.694 (2.681-5.089)	<0.001	1.492 (1.390-1.601)	<0.001	1.141 (1.010-1.289)	0.035
	T4	81.543 (67.445-98.588)	<0.001	14.264 (9.883-20.586)	<0.001	6.979 (6.487-7.508)	<0.001	2.666 (2.259-3.146)	<0.001
N-stage	N0	Ref		Ref		Ref		Ref	
	N1	4.880 (4.332-5.498)	<0.001	1.946 (1.641-2.307)	<0.001	1.661 (1.562-1.767)	<0.001	1.483 (1.362-1.614)	<0.001
M-stage	M0	Ref		Ref		Ref		Ref	
	M1	51.522 (45.896-57.838)	<0.001	7.299 (6.133-8.686)	<0.001	12.860 (11.886-13.914)	<0.001	4.052 (3.588-4.576)	<0.001
Multifocality	No	Ref		Ref		Ref		Ref	
	Yes	0.865 (0.765-0.978)	0.021	0.746 (0.643-0.865)	<0.001	0.882 (0.835-0.932)	<0.001	0.967 (0.907-1.031)	0.305
Extension	No	Ref		Ref		Ref		Ref	
	Yes	13.025 (11.495-14.758)	<0.001	1.456 (1.087-1.952)	0.012	2.501 (2.362-2.647)	<0.001	1.094 (0.952-1.257)	0.206
Radiation	None or refused	Ref		Ref		Ref		Ref	
	Radiation Beam or Rdioactive implants	13.670 (11.982-15.596)	<0.001	3.046 (2.435-3.809)	<0.001	3.164 (2.896-3.456)	<0.001	1.455 (1.260-1.680)	<0.001
	Radioisotopes or Radiation beam + isotopes/implants	0.989 (0.885-1.106)	0.849	0.837 (0.702-0.997)	0.046	0.599 (0.570-0.628)	<0.001	0.699 (0.652-0.748)	<0.001
Surgery	Lobectomy	Ref		Ref		Ref		Ref	
	Subtotal or near-total thyroidectomy	1.795 (1.326-2.429)	<0.001	1.057 (0.712-1.570)	0.782	1.023 (0.906-1.155)	0.713	0.999 (0.859-1.162)	0.989
	Total thyroidectomy	1.486 (1.230-1.795)	<0.001	1.032 (0.803-1.326)	0.804	0.808 (0.756-0.863)	<0.001	0.983 (0.903-1.070)	0.691

FTC: follicular thyroid cancer; PTC: papillary thyroid cancer; FVPTC: follicular variant papillary thyroid cancer.

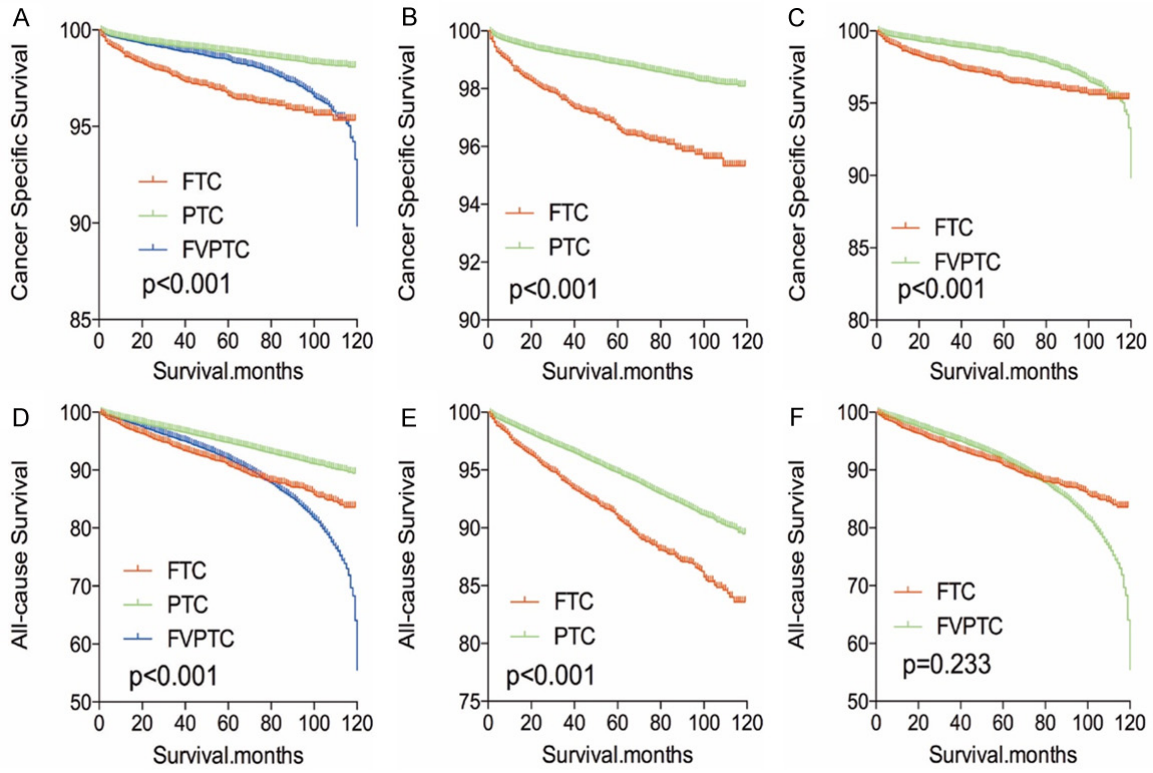

Figure 1. Kaplan Meier curves among patients stratified by subtype for cancer-specific mortality (A-C) and all cause mortality (D-F).

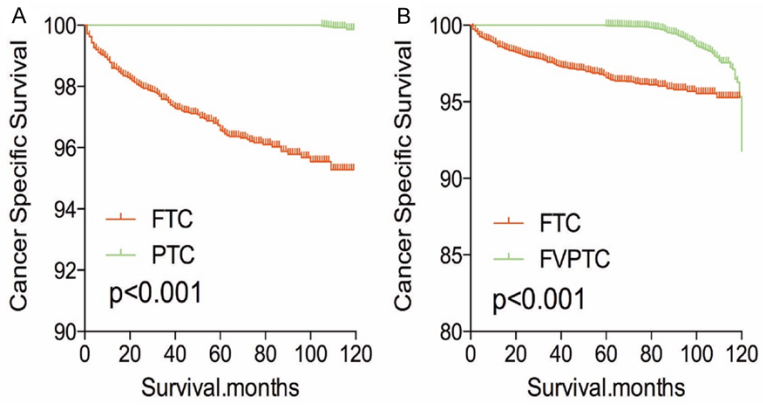

Figure 2. Kaplan Meier curves of cancer-specific mortality for matched subtype pairs. Age, sex and race matching between FTC and PTC (A), FTC and FVPTC (B).

After PSM analysis was performed for demographic data (age, sex, and race), all-cause mortality rate for FTC was worse compared to PTC and FVPTC (both P<0.001, **Figure 5A**, **5B**). Similar results were obtained when PSM analysis for age, sex, race and clinicopathologic factors (T/N/M stage, multifocality, and extension; **Figure 6A**, **6B**), and PSM analysis for all relevant factors and radiation and surgical treatment (**Figure 7A**, **7B**) were performed.

Discussion

According to World Health Organization classification, FTC is a malignant epithelial tumor showing follicular cell differentiation, without the nuclear features of papillary thyroid carcinoma [10]. The histological definitions of PTC, FTC and FVPTC are based on the predominant papillary or follicular growth pattern, and alterations in nuclear morphology [10, 16]. Many thyroid cancers which were previously diagnosed as FTC were later labeled as FVPTC after Chem and Rosai defined the FVPTC in 1977 [17]. In addition, follicular adenomas cannot be distinguished from follicular thyroid cancer cytologically because the distinction between them is based on capsular and vascular invasion, neither of which can be seen in the cytology specimens [10].

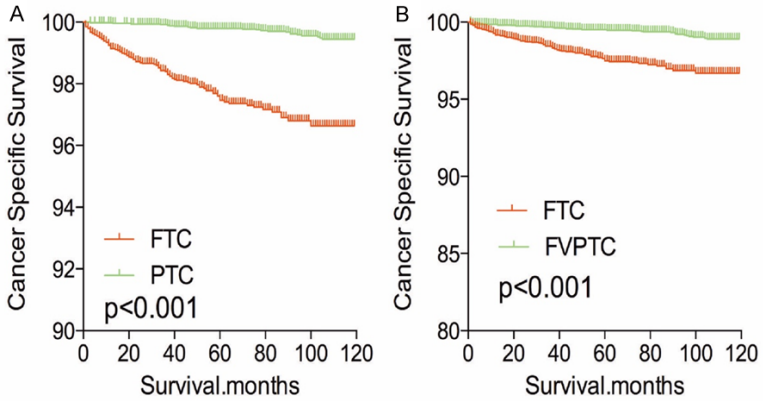

Figure 3. Kaplan Meier curves of cancer-specific mortality for matched subtype pairs. Age, sex, race, T/N/M stage, multifocality, extension matched between FTC and PTC (A), FTC and FVPTC (B).

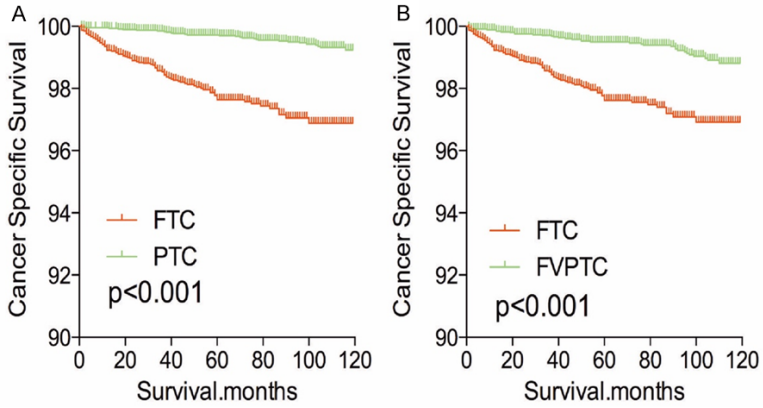

Figure 4. Kaplan Meier curves of cancer-specific mortality for matched subtype pairs. Age, sex, race, T/N/M stage, multifocality, extension, surgery and radiation treatment matched between FTC and PTC (A), FTC and FVPTC (B).

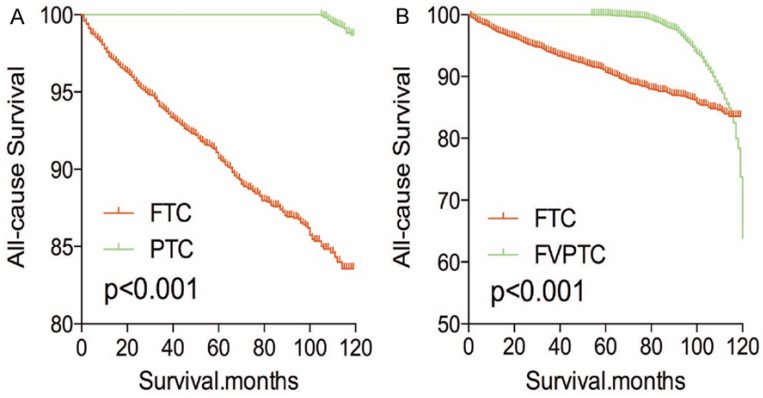

Figure 5. Kaplan Meier curves of all cause mortality for matched subtype pairs. Age, sex and race matching between FTC and PTC (A), FTC and FVPTC (B).

Verkooijen et al., 2003 found that almost 45% of thyroid nodules initially classified as FTC in the years 1970-80 were reclassified as PTC after pathological re-evaluation of specimens [18]. Many genetic alterations such as RAS mutation and rearrangements of *PPAR*-γ have been identified to have a fundamental role in follicular thyroid oncogenesis [10, 19-22]. Based on this insight, tumor histological features, recurrence, and cancer-specific mortality have been better illustrated now than before.

However, for a long time, the prognosis of FTC has been controversial. Nicole et al., 2016, demonstrated that FTC patients portends a worse outcome compared with that of the patients with FVPTC [15]. However, Verburg et al. hypothesized that patients with FTC were often diagnosed with advanced stage disease, older age and distant metastasis. They further identified that patients with FTC and PTC seemed to have similar prognosis when matched for age and stage of cancer [23].

In this study, however, we illustrated that the prognosis for FTC (both cancer-specific and all-cause mortality) is worse than both PTC and FVPTC, based on a large population: SEER database. Previous studies have shown that an increased age contribute to an increase in cancer-specific mortality for patients with thyroid cancer [24]. Englum et al., [25] suggested that the mean age for diagnosis of FTC was slightly higher than that for PTC and FVPTC. Also, the frequency of FTC diagnosis increased as the age of the patient from 45 years which is consistent with our study. On the other hand, the

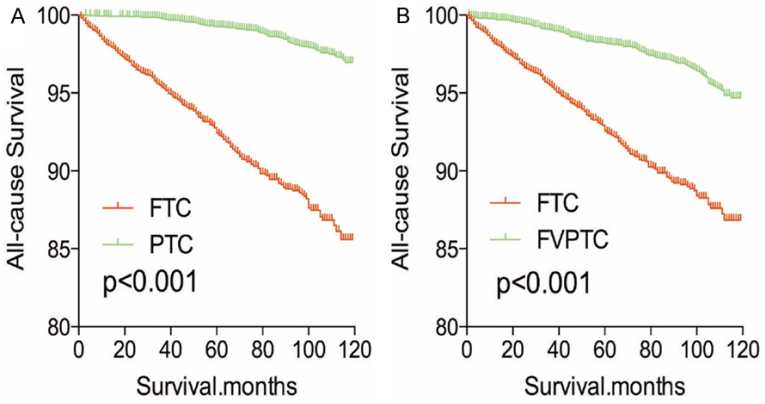

Figure 6. Kaplan Meier curves of all cause mortality for matched subtype pairs. Age, sex, race, T/N/M stage, multifocality, extension matching between FTC and PTC (A), FTC and FVPTC (B).

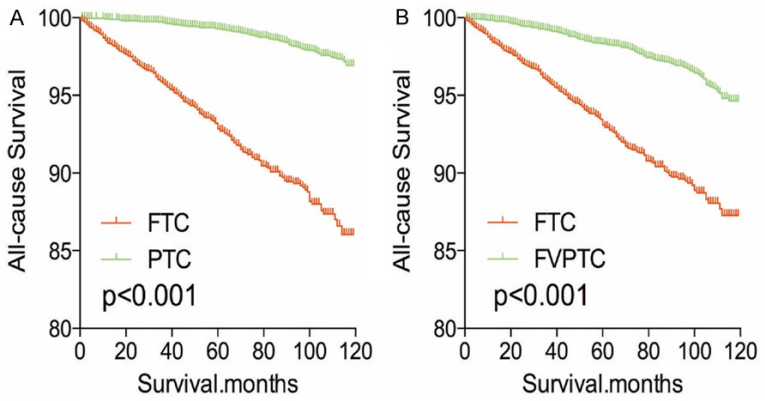

Figure 7. Kaplan Meier curves of all cause mortality for matched subtype pairs. Age, sex, race, T/N/M stage, multifocality, extension, surgery and radiation treatment matching between FTC and PTC (A), FTC and FVPTC (B).

age as a risk factor *per se* may impact the prognosis of thyroid cancer patients. Except patients' age, other confounders like gender, race, T/N/M stage and treatment may all affect the prognosis of thyroid cancer and therefore should be adjusted when analyzing the prognosis of different histological subtypes. In our study, however, after the PSM analysis for all the effect/confounder factors, the cancer-specific mortality and all-cause mortality were still worse for patients with FTC than both PTC and FVPTC. Thus, our finding may provide a reliable evidence for the worse outcome of patients with FTC compared to PTC and FVPTC.

Interestingly, it has been reported in previous studies that distant metastasis was observed in 15-27% patients with FTC most likely due to that fact that FTC spread haematogenously [26-29]. However, in this study, only 5.8% of patients showed distant metastasis of FTC, compared to 1.2% of patients with PTC and 1.1% of patients with FVPTC.

Although our findings show a worse prognosis of FTC, there are some limitations in this study. First of all, recurrence, which is another important indicator for prognosis, is not incorporated in SEER database as the SEER database only possesses reliable information during the diagnostic period, hence, it may introduce an overestimation bias when designating cancer-specific and all-cause mortality rates of different cancer subtypes. Furthermore, lack of molecular marker information such as RAS mutation and TERT mutation, which might help for a better adjustment and minimize selection bias, is other limitation in this study. In addition to this, vascular invasion, family history, number of lymph node metastases and other histological findings were also not included in our study.

Conclusion

In summary, we illustrated that the average prognosis of FTC is poorer than both PTC and FVPTC, even after adjustment for demographic characteristics, clinicopathologic data, and cancer treatment adjustment. Thus, this study provides a benefit reference for patients with FTC and a precise treatment and management of these tumors with better planning for future therapies in patients with FTC.

Disclosure of conflict of interest

None.

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