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Context: Individualized management, incorporating papillary thyroid cancer (PTC) variant-specific risk, is conceivably a useful treatment strategy for PTC, which awaits comprehensive data demonstrating differential risks of PTC variants to support.

Objective: To establish the differential clinicopathological risk of major PTC variants—conventional PTC (CPTC), follicular-variant PTC (FVPTC), and tall-cell PTC (TCPTC).

Methods: Retrospective study of clinicopathological outcomes of 6,282 PTC patients (4,799 females and 1,483 males) from 26 centers and The Cancer Genome Atlas in 14 countries with a median age of 44 years (interquartile range [IQR], 33–56) and median follow-up time of 37 months (IQR 15–82).

Results: The cohort consisted of 4,702 (74.8%) CPTC, 1,126 (17.9%) FVPTC, and 239 (3.8%) TCPTC. The prevalence of high-risk parameters was significantly different among the three variants, including extrathyroidal invasion, lymph node metastasis, stages III/IV, disease recurrence, mortality and the use (need) of radioiodine treatment (all $P < 0.001$), being highest in TCPTC, lowest in FVPTC, and intermediate in CPTC, following an order of TCPTC>CPTC≫FVPTC. Recurrence and mortality in TCPTC, CPTC, and FVPTC were 27.3% and 6.7%, 16.1% and 2.5%, and 9.1% and 0.6%, corresponding to events per 1000 person-years (95% confidence interval-CI) of 92.47 (64.66–132.26) and 24.61 (12.31–49.21), 34.46 (30.71–38.66) and 5.87 (4.37–7.88), and 24.73 (18.34–33.35) and 1.68 (0.54–5.21), respectively. Mortality hazard ratios of CPTC and TCPTC over FVPTC were 3.44 (95% CI 1.07–11.11) and 14.96 (95% CI 3.93–56.89), respectively. Kaplan-Meier survival analyses showed the best prognosis in FVPTC, worst in TCPTC, and intermediate in CPTC in disease recurrence-free probability and disease-specific patient survival. This was particularly the case in patients ≥ 45 years old.

Conclusion: This large multicenter study demonstrates differential prognostic risks of the three major PTC variants and establishes a unique risk order of TCPTC > CPTC ≫ FVPTC, providing important clinical implications for specific variant-based management of PTC.

Papillary thyroid cancer (PTC) is the most common endocrine malignancy, accounting for 85% to 90% of all thyroid cancers, with an incidence continuing to rise globally in recent decades (1–3). This cancer consists of several histological variants, the most common of which are conventional PTC (CPTC), follicular-variant PTC (FVPTC), and tall-cell PTC (TCPTC), which collectively account for the vast majority of PTCs (4). CPTC is a classical PTC variant, characterized by papillary architecture and characteristic nuclear features of nuclear enlargement, crowding, clearing, and irregular nuclear contours that result in formation of nuclear grooves and, in extreme cases, nuclear pseudoinclusions. FVPTC, initially described by Lindsay (5) and then by Chem and Rosai (6), has now been widely recognized as a unique PTC variant characterized by nuclear features of classical PTC and follicular cell growth patterns (7, 8). TCPTC, initially described by Hawk and Hazard (9) and now a widely accepted variant, consists predominantly of tall cells that have height at least three times their width, eosinophilic cytoplasm, and basally oriented nuclei (7, 8, 10). All these three PTC variants are formally included in the World Health Organization Classification of Tumors (11).

The prognosis of PTC varies with different histological

variants. Individualized management, taking into consideration PTC variant-specific risk, is an important treatment strategy for PTC (12, 13); yet this practice is often hindered by the current lack of solid data concerning the differential clinicopathological risk and prognostic patterns of PTC variants, particularly the major variants. An exception is TCPTC, which, albeit uncommon—accounting for a small percentage of PTCs—is well established as a variant with relatively aggressive behaviors, such as invasion, metastasis and recurrence (14–20). It is therefore recommended that TCPTC be more aggressively treated (12, 13). In contrast, no variant-based recommendation is made for differential treatments of the far more common CPTC and FVPTC, as no distinction in prognostic risk has been established between the two variants. Although these two PTC variants likely behave differently, no recommendation can be made currently on whether the two should be treated differently (12, 13). This challenging dilemma is due to the fact that previous comparative studies on the clinicopathological characteristics of CPTC and FVPTC were mostly in relatively small cohorts and single-institution-based, yielding inconsistent and sometimes even conflicting results (21–27).

The aim of this study was to take advantage of a large international multicenter PTC cohort to characterize and compare the clinical and pathological characteristics of the three major PTC variants to establish a solid clinicopathological landscape, which can help determine the feasibility of variant-based management strategies for PTC.

Patients and Methods

Data were from 27 medical centers in 14 countries (Table 1), including the Johns Hopkins Medical Institution[1] (with the superscript number here and hereafter denoting the corresponding center number in Table 1), University of Pittsburgh Medical Center[8], Yale University[12], Massachusetts General Hospital[24], and University of California at San Francisco[25] in the United States; medical centers at the University of Pisa[2, 19], University of Perugia[3], University of Milan[4], University of Padua[7], and University of Bologna[13] in Italy; Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology[5] in Poland; medical centers at Griffith University[6] and University of Sydney[10] in Australia; Hospital La Paz Health Research Institute[9] in Spain; the Institute of Endocrinology in Prague[11], Czech Republic; University of Ulsan[14] in South Korea; King Faisal Specialist Hospital and Research Center[16] in Saudi Arabia; Gutenberg University Mainz[17] in Germany; Center for Endocrine Surgery, Kiev in Ukraine[18]; Federal University of São Paulo[20] in Brazil; University Health Network, Toronto[21] in Canada; the First Hospital of China Medical University[22], Qingdao University Affiliated Hospital[26], Shanghai Tenth People's Hospital[27], and Shanghai Changzheng Hospital[28] in China; and University of Porto[23] in Portugal. The study also included data on PTC from The Cancer Genome Atlas (TCGA) database[15] (28).

This study included patients and institutions from recent studies (29, 30) and additional subjects and institutions as indicated above. Briefly, patients treated with total or near-total thyroidectomy for PTC were consecutively selected at each center over different time periods spanning 1978–2011. Neck dissection at the initial surgery and postsurgical radioiodine ablation were pursued as clinically indicated. Pathological diagnoses of PTC variants were established following the World Health Organization criteria and documented in our peer-reviewed publications (14, 31–51). Tumor recurrence referred to recurrent or persistent disease per standard histological/cytological/radiographical/biochemical criteria (12, 13). Mortality referred to thyroid cancer-specific patient death. Follow-up time of the patient was defined as the time period from the initial surgical treatment to the discovery of tumor recurrence or patient death or, in the case of no recurrence, to the most recent clinic visit and was censored in the survival analyses.

As described recently (29, 30), this was a retrospective study which was approved by the institutional review board (IRB) of each center. Informed patient consent was obtained where required and waived in some cases as approved by IRB because the study only involved the use of thyroid tumor tissues and collection of clinicopathological information. The American Joint Committee on Cancer staging system was used to define disease stages. Clinicopathological information was obtained from the medical records using a uniform protocol designed for this study at all the centers. Data pooled from the 26 centers and the TCGA database were analyzed to compare the clinicopathological characteristics of the three variants of PTC.

Frequencies and percents were used to summarize categorical data. Continuous variables in this study were found to not be normally distributed on distribution assessment and were therefore summarized using medians and interquartile ranges (IQR). χ^2 test was used to perform group comparisons of the categorical variables. Nonparametric statistics were used to compare the continuous variables— Wilcoxon rank sum test for comparisons of two groups and Kruskal-Wallis test for comparisons of three groups. Disease recurrence and patient survival were examined by Kaplan-Meier analyses and differences between survival curves were analyzed by the log-rank test. The Cox proportional hazards models were used to compare disease-specific recurrence and survival by PTC subtypes using hazard ratios (HR). Data were analyzed using SPSS version 16.0 (SPSS, Inc. Chicago, IL, USA). All P values were two-sided and a $P < .05$ was considered to be significant.

Results

The number, age at diagnosis and male sex of patients from individual medical centers and countries are sum-

Table 1. Demographic characteristics by medical center and country

Center or Country	No. of patients	Age at diagnosis, years*	Male sex, No. (%)
By Medical Center:			
1. Johns Hopkins Hospital (USA)	682	45 (34–56)	191 (28.0)
2.Department of Clinical and Experimental Medicine, WHO Collaborating Center, University of Pisa (Italy)	189	38 (28–51)	47 (24.9)
3. University of Perugia (Italy)	117	49 (37–59)	32 (27.4)
4. University of Milan (Italy)	265	45 (36–58)	63 (23.8)
5. Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology (Poland)	253	47 (35–59)	30 (11.9)
6. Griffith University (Australia)	76	40 (34–56)	20 (26.3)
7. University of Padua (Italy)	135	48 (39–57)	32 (23.7)
8. University of Pittsburgh (USA)	169	52 (38–63)	42 (24.9)
9. Hospital La Paz Health Research Institute, Madrid (Spain)	66	42 (32–54)	11 (16.7)
10. University of Sydney (Australia)	95	44 (34–59)	20 (21.1)
11. Institute of Endocrinology, Prague (Czech Republic)	222	47 (31–60)	39 (17.6)
12. Yale University (USA)	18	36 (32–49)	4 (22.2)
13. University of Bologna (Italy)	35	40 (32–55)	8 (22.9)
14. University of Ulsan (Korea)	197	43 (35–52)	34 (17.3)
15. TCGA data (The Cancer Genome Atlas) (mainly USA)**	304	46 (35–59)	77 (25.3)
16. King Faisal Specialist Hospital and Research Centre (Saudi Arabia)	296	39 (30–55)	73 (24.7)
17. Johannes Gutenberg University Mainz (Germany)	301	47 (34–62)	97 (32.2)
18. Center for Endocrine Surgery, Kyiv (Ukraine)	15	40 (38–46)	2 (13.3)
19. Department of Surgery, Pathology, University of Pisa (Italy)	1158	43 (35–55)	286 (24.7)
20. Federal University of São Paulo (Brazil)	120	44 (34–55)	19 (15.8)
21. University Health Network, Toronto (Canada)	195	44 (34–56)	41 (21.0)
22. China Medical University Program (China)***	559	41 (34–51)	96 (17.2)
23. University of Porto (Portugal)	219	34 (22–49)	33 (15.1)
24. Massachusetts General Hospital (USA)	71	52 (40–64)	40 (56.3)
25. University of California, San Francesco (USA)	259	44 (31–56)	72 (27.8)
26. The Affiliated Hospital of Qingdao University (China)	125	43 (33–57)	28 (22.4)
27. Shanghai Tenth People's Hospital (China)	96	49 (39–56)	27 (28.1)
28. Shanghai Changzheng Hospital (China)	45	42 (24–53)	19 (42.2)
By Country:			
United States****	1503	46 (34–58)	426 (28.3)
Italy	1899	44 (35–55)	468 (24.6)
Poland	253	47 (35–59)	30 (11.9)
Australia	171	43 (34–57)	40 (23.4)
Spain	66	42 (32–54)	11 (16.7)
Czech Republic	222	47 (31–60)	39 (17.6)
South Korea	197	43 (35–52)	34 (17.3)
Saudi Arabia	296	39 (30–55)	73 (24.7)
Germany	301	47 (34–62)	97 (32.2)
Ukraine	15	40 (38–46)	2 (13.3)
Brazil	120	44 (34–55)	19 (15.8)
Canada	195	44 (34–56)	41 (21.0)
China	825	42 (34–53)	170 (20.6)
Portugal	219	34 (22–49)	33 (15.1)
Overall	**6282**	**44 (33–56)**	**1483 (23.6)**

Footnotes:

*Median (interquartile range)

**To avoid potential overlap, 304 cases from TCGA were included in the present study, excluding the 50 cases from Johns Hopkins and the 41 cases from University of Pittsburgh used in the TCGA database. The cases from the University Health Network, Toronto used in the present study were not overlapped with the TCGA data.

***This program included samples from Bingzhou and Heze, China.

****The TCGA data, containing mainly USA cases and also a cohort from Canada, were included in this group.

marized in Table 1. We studied a total of 6282 patients (4,799 females and 1483 males) from these centers. The median patient age was 44 years (IQR, 33–56 years), with

a median follow-up time of 37 months (IQR 15–82 months).

Among the total of 6282 cases of PTC, the most common three variants were CPTC (4,702 cases, 74.8%), FVPTC (1,126 cases, 17.9%), and TCPTC (239 cases, 3.8%), collectively accounting for 96.6% of the entire PTC cohort. Other variants (eg, diffuse sclerosing variant, insular variant, and cribriform-morular variant) were rare (collectively 215 cases, 3.4%). Information on some clinicopathological parameters was not provided by all centers. As indicated in Table 2, we analyzed each specific clinicopathological parameter on the pooled patients only from the centers that provided such information on all or nearly all the study subjects.

Comparisons of the clinicopathological characteristics of the three PTC variants were summarized in Table 2. All the classical clinicopathological parameters except for patient sex (male) showed significant difference among the three variants in the three-way comparison. In most parameters, FVPTC had the lowest prevalence of occurrence, including extrathyroidal invasion, lymph node metastasis, advanced stages III/IV, clinically indicated radioiodine-131 therapy (treatment and dosage), tumor recurrence, and patient mortality. In contrast, TCPTC had the highest prevalence for these aggressive clinicopathological param-eters, while CPTC showed a generally intermediate aggressiveness.

These patterns were further confirmed on pair-wise comparison (Table 3). Specifically, the prevalence of most of the classical risk parameters was significantly higher in CPTC than FVPTC and in TCPTC than CPTC, including extrathyroidal invasion, lymph node metastasis and advanced tumor stages III/IV; it was all significantly higher in TCPTC than in FVPTC (Table 3). The overall risk was thus highest in TCPTC, lowest in FVPTC, and intermediate in CPTC. The prevalence of patient age $\geq$ 45 years was significantly higher in TCPTC than FVPTC and in FVPTC than CPTC. Patient sex distribution showed no difference between CPTC and TCPTC, but male patients were significantly more commonly seen with CPTC and TCPTC than FVPTC. Tumor size was similar between FVPTC and TCPTC and both were larger than CPTC. The prevalence of multifocality and distant metastasis were similar between CPTC and FVPTC and significantly higher in TCPTC. The clinically indicated use (need) of radioiodine-131 treatment was similar between CPTC and FVPTC and significantly more common in TCPTC. A significantly higher radioiodine dose was used (needed) in TCPTC than CPTC and FVPTC.

As shown in Table 2, tumor recurrence rate occurred in 290/1800 (16.1%) CPTC, 43/473 (9.1%) FVPTC, and 30/110 (27.3%) TCPTC, being highest in TCPTC, lowest in FVPTC, and intermediate in CPTC. On the pair-wise analysis (Table 3), this recurrence rate was significantly higher in CPTC than FVPTC and in TCPTC than either CPTC or FVPTC. As shown in Table 2, patient mortality occurred in 44/1792 (2.5%) CPTC, 3/523 (0.6%) FVPTC, and 8/119 (6.7%) TCPTC, being also highest in TCPTC, lowest in FVPTC, and intermediate in CPTC. Like tumor recurrence rate, on pair-wise analysis (Table 3), the mortality rate was significantly higher in CPTC than FVPTC and in TCPTC than either CPTC or FVPTC.

Similar distribution patterns of tumor recurrence and patient mortality among the three PTC variants were observed when events per 1000 person-years and HR were analyzed (Table 4). For patients of all ages, recurrences per 1000 person-years were 34.46 (95% confidence interval (CI) [CI], 30.71–38.66), 24.73 (95% CI 18.34–33.35), and 92.47 (95% CI 64.66–132.26) for CPTC, FVPTC, and TCPTC, respectively. Mortality per 1000 person-years were 5.87 (95% CI 4.37–7.88), 1.68 (95% CI 0.54–5.21), and 24.61 (95% CI 12.31–49.21) for CPTC, FVPTC, and TCPTC, respectively. CPTC and TCPTC both displayed significant higher HRs for tumor recurrence and patient mortality compared with FVPTC. As an example, compared with FVPTC, HRs of mortality for CPTC and TCPTC were 3.44 (95% CI 1.07–11.11) and 14.96 (95% CI 3.93–56.89), respectively. After adjustment for patient age and sex, these HRs for recurrence and mortality mostly remained significant. In patients $\geq$ 45 years old, similarly significant differences among the three PTC variants were observed for disease recurrences per 1000 person-years, patient mortality per 1000 person-years, percent rates of the events, and HRs, again showing clearly an aggressiveness order of TCPTC $>$ CPTC $\gg$ FVPTC (Table 4). In patients $<$ 45 years old, recurrence was not significantly different among the three PTC variants and the few deaths made it impossible to compare the three variants (Table 4).

We also performed Kaplan-Meier analyses of tumor recurrence and PTC-specific patient survival among the three PTC variants. As shown in Figure 1A, on the analysis of patients of all ages, tumor recurrence-free probability among the three PTC variants was significantly different on three-way comparison (log-rank test $P < .001$). In pair-way comparison, tumor recurrence-free probability was significantly lower in CPTC than FVPTC (log-rank test $P = .025$) and in TCPTC than either CPTC or FVPTC (log-rank test both $P < .001$). As shown in Figure 1B,

Table 2. Three-way comparison of the clinicopathological characteristics among the three common variants of papillary thyroid cancer

Characteristic	All variants	Conventional	Follicular-variant	Tall-cell	*P* value
n	6282	4702 (74.8%)	1126 (17.9%)	239 (3.8%)	
Age at diagnosis (yr)[1]	6255	4686	1118	238	
	44 (33–56)	43 (33–55)	45 (35–56)	51 (39–64)	<0.001
Age ≥ 45 yr[1] *	3054/6255 (48.8%)	2223/4686 (47.4%)	569/1118 (50.9%)	153/238 (64.3%)	<0.001
Sex (male)[1]	1483/6282 (23.6%)	1118/4702 (23.8%)	236/1126 (21.0%)	65/239 (27.2%)	0.049
Tumor size (cm) [2]	5303	3896	1010	225	
	1.7 (1.0–3.0)	1.5 (1.0–2.7)	2.0 (1.3–3.2)	1.8 (1.3–2.7)	<0.001
Tumor size ≥ 1.0 cm [2]	4215/5303 (79.5%)	2942/3896 (75.5%)	905/1010 (89.6%)	209/225 (92.9%)	<0.001
Extrathyroidal invasion[2]	1638/5407 (30.3%)	1265/3967 (31.9%)	171/1023 (16.7%)	144/229 (62.9%)	<0.001
Lymph node metastasis[3]	1747/4716 (37.0%)	1347/3315 (40.6%)	209/992 (21.1%)	116/225 (51.6%)	<0.001
Multifocality[4]	1802/4664 (38.6%)	1277/3320 (38.5%)	348/946 (36.8%)	103/223 (46.2%)	0.034
Tumor stage[3]	4802	3381	1013	225	
I	3270 (68.1%)	2378 (70.3%)	685 (67.6%)	100 (44.4%)	<0.001
II	475 (9.9%)	257 (7.6%)	159 (15.7%)	36 (16.0%)	<0.001
III	640 (13.3%)	454 (13.4%)	110 (10.9%)	52 (23.1%)	<0.001
IV	417 (8.7%)	292 (8.6%)	59 (5.8%)	37 (16.4%)	<0.001
Tumor stage III/IV[3]	1057/4802 (22.0%)	746/3381 (22.1%)	169/1013 (16.7%)	89/225 (39.6%)	<0.001
Distant metastasis[5]	182/3025 (6.0%)	112/2183 (5.1%)	38/588 (6.5%)	15/123 (12.2%)	<0.001
I-131 treatments[6]	1917/2407 (79.6%)	1388/1748 (79.4%)	333/433 (76.9%)	98/110 (89.1%)	<0.001
Total I-131 dose (mCi)[6]	2388	1735	432	107	
	100 (30–108)	100 (30–109)	100 (30–103)	100 (55–150)	<0.001
Tumor recurrence[7]	383/2499 (15.3%)	290/1800 (16.1%)	43/473 (9.1%)	30/110 (27.3%)	<0.001
Follow-up time (months)[7]	2499	1800	473	110	
	37 (15–82)	41 (16–87)	29 (9–68)	25 (12–37)	<0.001
Mortality[8]	57/2553 (2.2%)	44/1792 (2.5%)	3/523 (0.6%)	8/119 (6.7%)	<0.001

Footnotes:

1. Age at diagnosis, sex (male): data from medical centers 1~28, total 6282 cases, missing 27 and 0 cases respectively.

2. Tumor size, extrathyroidal invasion: data from medical centers 1~22, total 5,467cases, missing 164 and 60 cases respectively.

3. Lymph node metastasis, tumor stage: data from medical center 1~21, total 4908 cases, missing 192 and 106 cases respectively.

4. Multifocality: data from medical centers 1~20, total 4713 cases, missing 49 cases.

5. Distant metastasis: data from medical centers 1~11, 14 and 16~18, total 3078 cases, missing 53 cases.

6. I-131 treatments, I-131 dosage: data from medical centers 1~5 and 7~14, total 2443 cases, missing 36 and 55 cases respectively.

7. Tumor recurrence, follow-up time: data from medical centers 1~14, total 2519 cases, missing 20 and 20 cases respectively.

8. Mortality: data from medical centers 1~11 and 15, total 2573 cases, missing 20 cases.

Table 3. Pair-wise comparison of clinicopathological characteristics among the three common variants of papillary thyroid cancer (*P* values)

Characteristic	Conventional *vs.* Follicular-variant	Tall-cell *vs.* Conventional	Tall-cell *vs.* Follicular-variant
Age at diagnosis (yr)	0.011	<0.001	<0.001
Age ≥ 45 yr	0.038	<0.001	<0.001
Sex (male)	0.044	0.227	0.035
Tumor size (cm)	<0.001	<0.001	0.304
Tumor size ≥ 1.0 cm	<0.001	<0.001	0.134
Extrathyroidal invasion	<0.001	<0.001	<0.001
Lymph node metastasis	<0.001	0.001	<0.001
Multifocality	0.349	0.022	0.009
Tumor stage			
I	0.099	<0.001	<0.001
II	<0.001	<0.001	0.910
III	0.032	<0.001	<0.001
IV	0.004	<0.001	<0.001
Tumor stage III/IV	<0.001	<0.001	<0.001
Distant metastasis	0.205	0.001	0.028
I-131 treatments	0.254	0.014	0.005
Total I-131 dose (mCi)	0.308	<0.001	<0.001
Tumor recurrence	<0.001	0.002	<0.001
Follow-up time (months)	<0.001	<0.001	0.185
Mortality	0.004	0.006	<0.001

disease-specific patient survival probability among the three PTC variants was also significantly different on three-way comparison (log-rank test $P < .001$). In the pair-way comparison, patient survival probability was significantly lower in CPTC than FVPTC (log-rank test $P = .028$) and in TCPTC than either CPTC or FVPTC (log-rank test both $P < .001$). These differential risk patterns of disease recurrence and patient mortality among the three PTC variants were similarly observed when the analysis was performed only on patients ≥ 45 years old (Figure 2A and 2B). In patients < 45 years old, recurrence was not significantly different among the three PTC variants (Figure 2C), but mortality associated with TCPTC was significantly higher than that associated with CPTC ($P = .001$) or FVPTC ($P = .012$) (Figure 2D). There were very few deaths associated with CPTC or FVPTC and no statistical difference in mortality could be appreciated between the two PTC variants in this younger patient group (Figure 2D).

Discussion

Conventional management of thyroid cancer is guided by clinicopathological risk stratification of the disease, which has proven to be effective for many decades and is currently the mainstream of the practice of thyroid cancer medicine (12, 13). The general principle in this practice is that aggressive thyroid cancers are more aggressively treated whereas treatment of less aggressive thyroid cancer can be relatively limited in appropriate clinical settings. Success of this practice relies on accurate clinicopatholog-

Table 4. Comparison of tumor recurrence and patient mortality among various papillary thyroid cancer variants

Patient age	Event type	PTC variants	Percent rates, no./total (%)	*P* value, compared with FVPTC	Events per 1000 person-years (95% CI)	HR (95% CI), compared with FVPTC		
						Unadjusted	Adjusted[a]	
All ages	Tumor recurrence	FVPTC	43/473 (9.1)	–	24.73 (18.34–33.35)	1.00	1.00	
		CPTC	290/1800 (16.1)	<0.001	34.46 (30.71–38.66)	1.44 (1.05–1.98) [b]	1.44 (1.05–1.99) [c]	
		TCPTC	30/110 (27.3)	<0.001	92.47 (64.66–132.26)	3.52 (2.20–5.63) [d]	3.09 (1.90–5.01) [e]	
	Patient mortality	FVPTC	3/523 (0.6)	–	1.68 (0.54–5.21)	1.00	1.00	
		CPTC	44/1792 (2.5)	0.004	5.87 (4.37–7.88)	3.44 (1.07–11.11) [f]	2.55 (0.80–8.41) [g]	
		TCPTC	8/119 (6.7)	<0.001	24.61 (12.31–49.21)	14.96 (3.93–56.89) [h]	10.28 (2.59–40.81) [i]	
≥ 45 yr	Tumor recurrence	FVTC	19/249 (7.6)	–	21.73 (13.86–34.06)	1.00	1.00	
		CPTC	145/910 (15.9)	0.001	35.54 (30.20–41.83)	1.71 (1.06–2.76) [j]	1.62 (1.01–2.62) [k]	
			25/73 (34.2)		<0.001	126.32 (85.35–186.94)	5.33 (2.91–9.76) [l]	3.68 (1.94–6.97) [m]
	Patient mortality	FVPTC	3/284 (1.1)	–	3.26 (1.05–10.10)			
		CPTC	42/927 (4.5)	0.004	11.22 (8.29–15.19)	3.36 (1.04–10.86) [n]	2.55 (0.79–8.29) [o]	
		TCPTC	7/82 (8.5)	0.002	34.74 (16.56–72.87)	10.75 (2.75–42.01) [p]	8.50 (2.09–34.60) [q]	
<45 yr	Tumor recurrence	FVPTC	24/224 (10.7)	–	27.77 (18.62–41.43)	1.00	1.00	
		CPTC	145/890 (16.3)	0.038	33.43 (28.41–39.34)	1.23 (0.80–1.89) [r]	1.24 (0.80–1.91) [s]	
		TCPTC	5/37 (13.5)	0.616	39.53 (16.45–94.96)	1.45 (0.55–3.80) [t]	1.49 (0.57–3.93) [u]	
	Patient mortality	FVPTC	0/239 (0.0)	–	0	–	–	
		CPTC	2/865 (0.2)	1.000	0.53 (0.13–2.13)	– [v]	– [v]	
		TCPTC	1/37 (2.7)	0.134	8.09 (1.14–57.44)	– [v]	– [v]	

Notes: PTC, papillary thyroid cancer; FVPTC, follicular-variant papillary thyroid cancer; CPTC, conventional papillary thyroid cancer; TCPTC, tall-cell papillary thyroid cancer; HR, hazard ratios; CI, confidence internal. [a] Adjusted for patient age and sex, [b] $P = 0.026$, [c] $P = 0.025$, [d] $P < 0.001$, [e] $P < 0.001$, [f] $P = 0.039$, [g] $P = 0.118$, [h] $P < 0.001$, [i] $P = 0.001$, [j] $P = 0.028$, [k] $P = 0.047$, [l] $P < 0.001$, [m] $P < 0.001$, [n] $P = 0.043$, [o] $P = 0.119$, [p] $P = 0.001$, [q] $P = 0.003$, [r] $P = 0.350$, [s] $P = 0.333$, [t] $P = 0.455$, [u] $P = 0.419$, [v] HR could not be calculated due to the zero death in FVPTC.

ical risk stratifications of thyroid cancer. Among the three major PTC variants—CPTC, FVPTC and TCPTC, it is recommended and widely accepted that the rarely encountered TCPTC be generally more aggressively treated because of its known more aggressive clinicopathological behaviors demonstrated in previous studies and confirmed in the present study (12, 13). In contrast, there is no general agreement or recommendation on differential treatments of CPTC and FVPTC based on their distinct risk behaviors; they are usually clinically lumped together without differentiation in variant-related risk (12, 13). This is because, unlike TCPTC, the relative risk levels of CPTC and FVPTC have not been clearly established, making impossible a fine risk assessment and hence differentiated treatments of the two most common PTC variants. The relative clinicopathological and prognostic risks of CPTC and FVPTC have remained controversial with inconsistent and sometimes conflicting results in previous studies (21–27). These studies often suffered from such drawbacks as relatively small series, lack of complete information and long-term clinical follow-up, and single institutional selection bias.

In the present study, we took advantage of the largest ever international multicenter cohort of PTC from 26 medical centers and the TCGA database in North America, South America, Asia, Middle East, and Europe to comprehensively characterize and compare the clinicopathological characteristics of the three PTC variants. The results in the present study establish a clinicopathological landscape for the three PTC variants. This large study

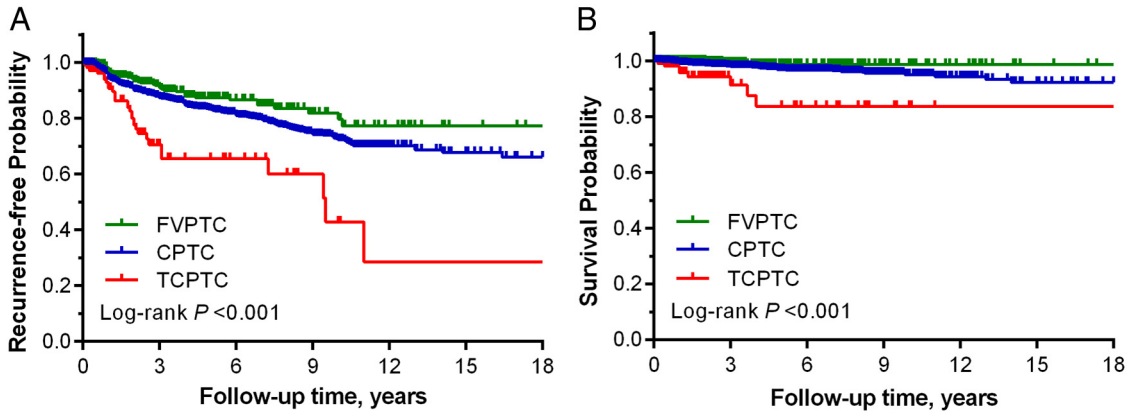

Figure 1. **Kaplan-Meier analyses of recurrence–free probability and disease-specific survival of patients with follicular-variant papillary thyroid cancer (FVPTC), conventional papillary thyroid cancer (CPTC), and tall-cell papillary thyroid cancer (TCPTC)—analysis on the entire cohort of patients of all ages. Panel A: Disease recurrence–free probability.** Data were from medical centers 1~14, with 1820 CPTC, 473 FVPTC and 110 TCPTC. Log-rank tests: $P < .001$, among FVPTC, CPTC and TCPTC; $P = .025$, between FVPTC and CPTC; $P < .001$, between CPTC and TCPTC; and $P < .001$, between FVPTC and TCPTC. **Panel B: Disease-specific patient survival.** Data were from medical centers 1~11 and 15, with 1812 CPTC, 523 FVPTC and 119 TCPTC. Log-rank tests: $P < .001$, among CPTC, FVPTC and TCPTC; $P = .028$, between CPTC and FVPTC; $P < .001$, between CPTC and TCPTC; $P < .001$, between FVPTC and TCPTC.

particularly demonstrates that TCPTC is the most aggressive among the three major variants and, in contrast, FVPTC is the least aggressive and CPTC has an intermediate aggressiveness. For example, the occurrence rate was the highest in TCPTC and lowest in FVPTC and intermediate in CPTC for the major conventional high-risk clinicopathological parameters, including extrathyroidal invasion, lymph node metastasis, and advanced stages III/IV. All these differences among the three PTC variants were significant. With the highest aggressiveness of TCPTC, it is not surprising that in the present study, TCPTC patients most commonly received clinically indicated radioiodine treatments with the highest doses. Clinical outcomes, including tumor recurrence and patient mortality, followed exactly this distribution pattern among the three PTC variants. It is particularly worth noting that the overall patient mortality in FVPTC was extremely low in this large cohort, being only 0.6%, in contrast to the 2.5% in CPTC and 6.7% in TCPTC, with HR of 3.44 and 14.96 for CPTC and TCPTC, respectively, when compared with FVPTC. These results establish a unique aggressiveness order of TCPTC > CPTC ≫ FVPTC. Interestingly, this risk pattern among the different PTC variants was particularly prominent in patients ≥ 45 years old, but less so in younger patients.

This risk pattern is interestingly well consistent with the results in the TCGA study, showing that FVPTC has a high Thyroid Differentiation Score, with CPTC being intermediate and TCPTC at the lowest end of this scale (28). Indeed, it has recently been suggested that FVPTC is more akin to minimally invasive follicular thyroid cancer, a lesion that is known to be of low risk, than to CPTC (52). This molecular understanding of FVPTC combined with the outcome data from the present study should facilitate decision making in its clinical management. In this context, the present study will be useful in helping clinically

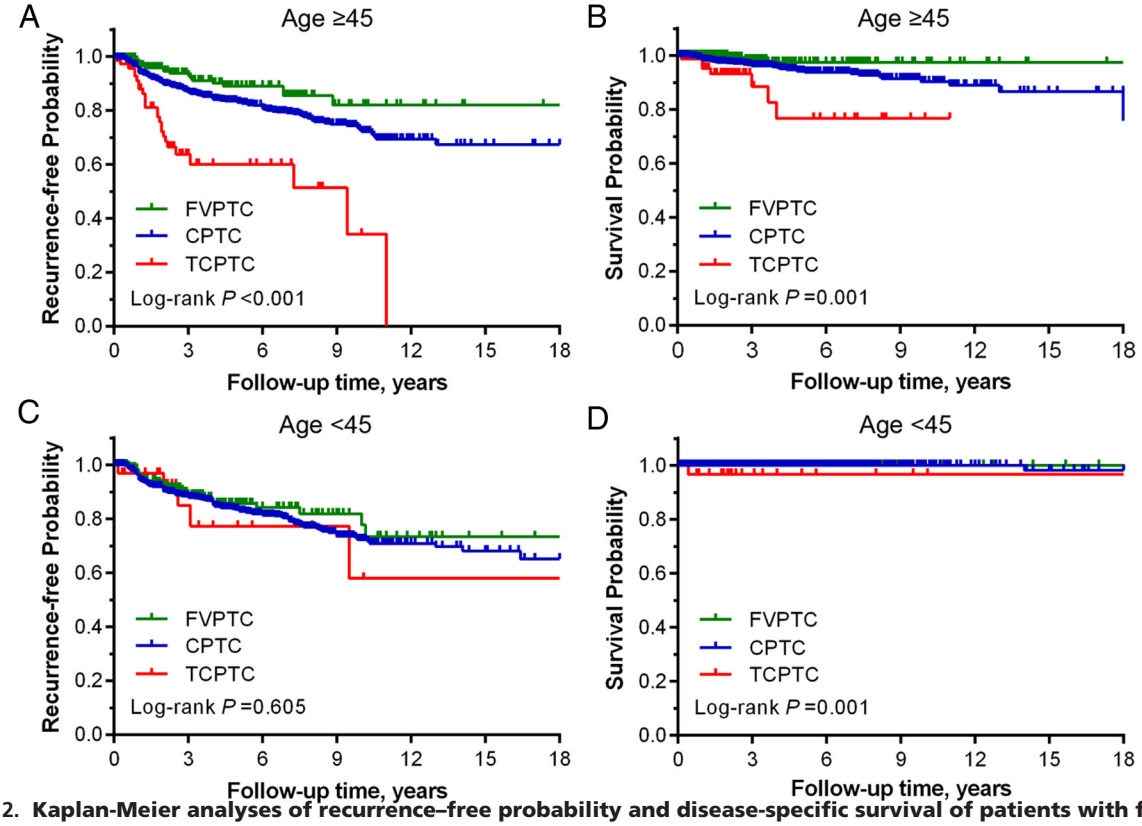

Figure 2. Kaplan-Meier analyses of recurrence–free probability and disease-specific survival of patients with follicular-variant papillary thyroid cancer (FVPTC), conventional papillary thyroid cancer (CPTC), and tall-cell papillary thyroid cancer (TCPTC)—analysis in the young (< 45 years old) and older (≥ 45 years old) patient age groups. **Panels A** and **B** show the results on disease recurrence and patient survival, respectively, in patients aged at or older than 45 years. **Panels C** and **D** show the results on disease recurrence and patient survival, respectively, in patients < 45 years old. **Panels A** and **C:** Disease recurrence data were from medical centers 1∼14, with 1820 CPTC, 473 FVPTC and 110 TCPTC. **Panels B** and **D**: Patient survival data were from medical centers 1∼11 and 15, with 1812 CPTC, 523 FVPTC and 119 TCPTC. **Panel A**: Log-rank tests— $P < .001$, among FVPTC, CPTC and TCPTC; $P = .025$, between FVPTC and CPTC; $P < .001$, between CPTC and TCPTC; $P < .001$, between FVPTC and TCPTC. **Panel B**: Log-rank tests— $P = .001$, among CPTC, FVPTC and TCPTC; $P = .032$, between CPTC and FVPTC; $P = .005$, between CPTC and TCPTC; $P < .001$, between FVPTC and TCPTC. **Panel C**: Log-rank tests— $P = .605$, among CPTC, FVPTC and TCPTC; $P = .348$, between CPTC and FVPTC; $P = .772$, between CPTC and TCPTC; $P = .451$, between FVPTC and TCPTC. **Panel D**: Log-rank tests— $P = .001$, among CPTC, FVPTC and TCPTC; $P = .761$, between CPTC and FVPTC; $P = .001$, between CPTC and TCPTC; $P = .012$, between FVPTC and TCPTC.

separate FVPTC from CPTC and avoid overtreatment of the largely nonaggressive tumors in the former group. This may particularly be the case in patients ≥ 45 years old. The study has important clinical relevance also given the fact that FVPTC is the second most common PTC variant in many series with a still rising incidence (21–27).

There are several limitations in the present study. The involvement of the large number of medical centers around the world was inherently associated with patient and data inhomogeneity. For example, the extent of neck dissection and treatment with radioiodine-131 ablation were performed as clinically indicated and at the discretion of the treating physicians at the individual centers, which was not uniformly controlled. This weakness is minimized by the fact that the medical centers participating in this study are all major institutions where standard thyroid cancer treatment guidelines are normally followed. The intra- and interobserver diagnostic variability as commonly seen in the pathological diagnosis of tumors, including thyroid tumor, particularly follicular thyroid tumors (53), is potentially also an issue in the present study. These inhomogeneity issues were minimized by our research design requirement that the WHO criteria be used to make the histological diagnosis of PTC variants and a uniform protocol be used for data collection at all the participating centers. Also, by having the widest inclusion of the subjects around the world, the results on the differential risk patterns of PTC variants observed in this study are highly generalizable. As an attesting to the reliability of the study, it confirmed the prevalence order of CPTC > FVPTC ≫ TCPTC reported in most previous studies and the known aggressiveness of TCPTC (15–19). The compositional percentages of the three PTC variants in the entire pooled cohort in the present study were comparable with those reported in various geographical and ethnic populations around the world, including North America, Asia, Australia, and Europe (4, 15–19, 24–26, 54, 55). It should be noted, however, that some individual centers in the present study contributed selectively only certain PTC variants. Thus, one needs to be cautious in generalizing the compositional patterns of PTC variants observed here although this issue should not affect the conclusions on the differential risks of PTC variants, the focus of the present study. Also, although the total number of patient subjects was high at 6282, the number of subjects was reduced in the analysis of several specific clinicopathological parameters. Even in these cases, however, the number of subjects was still extremely large and the analyses were highly powered.

In conclusion, this is the largest comprehensive multicenter study to characterize the differential clinicopathological risk and prognosis of the three major PTC variants, which establishes a clinicopathological landscape for them. The unique aggressiveness order of TCPTC > CPTC ≫ FVPTC established in this study, particularly in patients aged ≥ 45 years, has important clinical implications for improved variant-based decision making in the management of PTC, which will likely have a significant impact on the current practice of thyroid cancer medicine.

Acknowledgments

This project was supported by U.S.A. National Institutes of Health (NIH) grants RO1CA113507 and R01CA189224 to M. Xing. In addition, the studies at individual centers were supported as follows: The National Science Centre Poland grants N N403 194 340 and N N401 612 440 to A. Czarniecka and B. Jarzab, respectively and Milestone Grant No 267 398 to both (Poland); Grants from Queensland Government Smart State Fellowship and Griffith Health Institute to A. K. Lam (Australia); grants RD12/0036/0030 FIS-ISCIII, S2011/BMD-2328 TIRONET and SAF2013–44 709-R to P. Santisteban (Spain); grants from Fondazione Cassa di Risparmio di Perugia and Associazione Italiana per la Ricerca sul Cancro (IG 9338) (Italy) and the Beadle Family Foundation (San Antonio, Texas, U.S.A.) to E. Puxeddu; grant IGA MH CR NT 13 901–4 to V. Sykorova and B. Bendlova (the Czech Republic); grants from the New South Wales Cancer Institute to C. J. O'Neill and from Cancer Council of New South Wales to R. Clifton-Bligh (Australia); Italian Government-Ministero della Salute grant RF-2011–02 350 857 to G. Tallini (Italy); NIH/NIA 5R03AG042334–02 to L. Yip (U.S.A.); grants from the Ministerodella Istruzione Universitaria e Ricerca Scientifica, the AssociazioneItaliana per la Ricerca sul Cancro, the Istituto Toscano Tumori, and the Ministero della Salute to D. Viola and R. Elisei (Italy); and grant CB-2011–03-02 from the Korean Foundation for Cancer Research to Y.K. Shong and T.Y. Kim (South Korea); Research grants 2012/02902–9 and 2013/03867–5 from The São Paulo State Research Foundation (FAPESP) to J.M. Cerutti (G. Oler is a FAPESP scholar and J.M. Cerutti is a Brazilian Research Council (CNPq) investigator (Brazil); AIRC grant IG 10 316 to F. Basolo (Italy); Grant SHDC 12 014 229 from Shanghai Hospital Development Center to H. Xu (China); Programa Operacional Regional do Norte (ON.2 – O Novo Norte), under the Quadro de Referência Estratégico Nacional (QREN), and through the Fundo Europeu de Desenvolvimento Regional (FEDER) to M. Sobrinho-Simões and P. Soares.

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This work was supported by **Funding Support:** This project was supported by U.S.A. National Institutes of Health (NIH) grants RO1CA113507 and R01CA189224 to M. Xing. The

studies at individual centers were additionally supported by specific funding as indicated in the Acknowledgment..

***These two authors contributed equally to this work**

Disclosure Summary: No authors reported disclosures of conflict of interest.

Précis: By investigating the differential clinicopathological characteristics and outcomes of the three major papillary thyroid cancer (PTC) variants—conventional (CPTC), follicular (FVPTC), and tall-cell (TCPTC)— in > 6000 patients, this multicenter study establishes a clinicopathological landscape for these PTC variants and a unique prognostic risk order of TCPTC>CPTC≫FVPTC, providing important clinical implications for variant-based management of PTC.

Conflicts of Interest: None of the authors has conflict of interest to disclose related to this study.

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