Do aggressive variants of papillary thyroid carcinoma have worse clinical outcome than classic papillary thyroid carcinoma?

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Abstract

Objective: Evidence for unfavorable outcomes of each type of aggressive variant papillary thyroid carcinoma (AV-PTC) is not clear because most previous studies are focused on tall cell variant (TCV) and did not control for other major confounding factors contributing to clinical outcomes.

Design: Retrospective cohort study.

Methods: This study included 763 patients with classical PTC (cPTC) and 144 with AV-PTC, including TCV, columnar cell variant (CCV) and hobnail variants. Disease-free survival (DFS) and dynamic risk stratification (DRS) were compared after two-to-one propensity score matching by age, sex, tumor size, lymph node metastasis and extrathyroidal extension.

Results: The AV-PTC group had significantly lower DFS rates than its matched cPTC group (HR=2.16, 95% CI: 1.12–4.16, $P=0.018$). When TCV and CCV were evaluated separately, there was no significant differences in DFS and DRS between patients with TCV ($n=121$) and matched cPTC. However, CCV group ($n=18$) had significantly poorer DFS than matched cPTC group (HR=12.19, 95% CI: 2.11–70.33, $P=0.005$). In DRS, there were significantly more patients with structural incomplete responses in CCV group compared by matched cPTC group ($P=0.047$). CCV was an independent risk factor for structural persistent/recurrent disease in multivariate analysis (HR=4.28; 95% CI: 1.66–11.00, $P=0.001$).

Conclusions: When other clinicopathological factors were similar, patients with TCV did not exhibit unfavorable clinical outcome, whereas those with CCV had significantly poorer clinical outcome. Individualized therapeutic approach might be necessary for each type of AV-PTCs.

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Introduction

Papillary thyroid carcinoma (PTC) is well known for its excellent prognosis with a 10-year survival rate of >95% (1). However, approximately 10–15% of patients with PTC develop recurrence after the initial surgery (1, 2, 3) and approximately 35% of them die due to PTC (4, 5), indicating that PTC comprises a heterogeneous group of tumors with wide variability in macroscopic and microscopic features resulting in various clinical prognoses. Patient factors, such as age and sex, as

well as tumor factors, such as size, multifocality, extrathyroidal extension (ETE), lymph node (LN) and distant metastasis, radioiodine (RAI) avidity and genetic mutation, all differ in various ranges. The importance of pathological subtype as one of the major factors contributing to the diverse clinical manifestation of PTC has been acknowledged since 1970s (6) and is currently receiving more attention from numerous actively ongoing studies.

Classic type of PTC is composed of papillary epithelial cells arranged in papillae with fibrovascular cores without excessive height compared to cell width (7). To date, more than 10 pathological variants of PTC have been documented in addition to this classic type: tall cell, columnar cell, diffuse sclerosing, follicular, insular, hobnail, solid, trabecular, oncocytic, cribriform-morular, PTC with fibromatosis/fasciitis-like stroma, spindle cell, Warthin-like and clear cell (8). Some of them are reported to exhibit indolent behavior, whereas others are believed to exhibit more aggressive behavior. The current American Thyroid Association (ATA) guidelines defined three subtypes as AV-PTC: tall cell, columnar cell, and hobnail (9). The tall cell variant (TCV) is the most common subtype among them, with an incidence of 3.2–19% (10, 11, 12). The other two subtypes are rare entities, with the columnar cell variant (CCV) accounting for 0.15–0.4% of the reported cases of PTC (13, 14) and the hobnail variant with only small number of case reports (15, 16). Despite their rarity, attention to these AV-PTCs is rising because of their prognostic significance.

According to the ATA guidelines, AV-PTCs are classified as an at least intermediate risk group, thereby suggesting the need for total thyroidectomy and subsequent radioactive iodine (RAI) therapy (9). However, evidence suggesting that the association of AV-PTCs with unfavorable outcomes is limited because most previous studies enrolled only small numbers of patients with AV-PTC due to its rarity and focusing mainly on TCV (17, 18, 19). In fact, to our knowledge, there are no clinical studies comparing the prognosis of CCV and hobnail variant with classical PTC (cPTC). More importantly, most previous studies did not control for major confounding factors contributing to clinical outcomes (17, 18, 19, 20, 21). These limitations led us to these certain questions: Do each type of aggressive variants of PTC have worse clinical outcomes than classical PTC, even when their clinicopathological factors are similar? If so, should patients receive more aggressive treatment and more exhaustive follow-up depending on the presence of an aggressive pathological subtype?

We aimed to identify the difference in long-term clinical outcome between AV-PTC and cPTC and to evaluate whether AV-PTC is an independent risk factor for structural recurrent/persistent disease when controlling for other risk factors by propensity score matching. We also aimed to evaluate the clinical outcomes of patients with TCV and CCV separately compared to their propensity score-matched patients with cPTC.

Patients and methods

Study design and patients

This single-center, retrospective cohort study included patients with PTC who underwent total thyroidectomy with subsequent RAI therapy from 2009 to 2012 at Asan Medical Center, Seoul, Korea. We selected patients with tumors larger than 1 cm in longest diameter to exclude all cases of micro-PTC and also excluded patients with synchronous distant metastasis. In total, 763 patients with cPTC and 144 with AV-PTC were enrolled. Of the patients with AV-PTC, 123 had TCV, 19 had CCV and 2 had hobnail variants. Data collection and subsequent analysis were approved by the Institutional Review Board of Asan Medical Center.

Propensity score matching process

Using propensity score matching method, patients with cPTC and AV-PTC were matched by age, sex, tumor size, cervical LN metastasis and ETE in a two-to-one ratio. Propensity score matching is a method to control for covariate imbalance that produces selection bias. In this study, propensity score was defined as the probability of being assigned to the AV-PTC group based on the aforementioned five covariates, ranging from 0 to 1. Patients with a similar propensity score between the two groups were matched by caliper matching method. With this method, all units within a certain range of the propensity score of the treated units get matched, and others beyond the certain range are excluded, allowing the distribution of observed baseline covariates to be similar. This left 141 patients out of initial 144 patients with AV-PTC (121 with tall cell, 18 with columnar and 2 with hobnail variants; three patients were excluded with no matching propensity score with cPTC patients) and 282 with cPTC for the final study.

Pathologic examination

The entire submitted specimens of removed thyroid were thoroughly reevaluated by one experienced endocrine pathologist to determine the TCV, CCV and hobnail variants before enrollment. Any proportion of aggressive variants was recorded, and final definition of each aggressive variant was based on newly published World Health Organization (WHO) classification of tumors of endocrine organs (8). For the diagnosis of TCV, a height-to-width ratio at least >3 and >30% of tall cells were

applied and for the CCV and hobnail variants, minimal of 30% of each type of cells within the neoplasm was applied. After reevaluation, a total of 75 patients who were originally diagnosed as classic PTC were reclassified as aggressive variant PTC (61 were tall cell variant, 13 were columnar cell variant and 1 was hobnail variant). Entire tumor was pathologically examined in cases with less than 2 cm in the greater dimension, and representative more sections were submitted in cases with more than 2 cm in the greatest dimension. Extent of ETE was defined microscopically on pathological examination.

Clinical outcomes

The primary outcome of this study was structural persistent/recurrent disease, defined as the appearance of metastatic lesions after initial treatment and was confirmed by cytological or histopathological examination and/or by imaging studies with a positive serum thyroglobulin (Tg), as described previously (22). Disease-free survival (DFS), the interval from initial surgery to the detection of structural persistent/recurrent disease, was compared between the two groups. The secondary outcome was dynamic risk stratification (DRS) (9). Patients were classified into four response groups according to the DRS system ('excellent', 'indeterminate', 'biochemical incomplete' and 'structural incomplete' responses) by means of serum Tg levels, serum Tg antibody (TgAb) levels and imaging findings (neck ultrasound with or without diagnostic whole-body scan) during the first 2 years of follow-up (22, 23, 24).

Statistical analysis

R version 3.03 software and the R libraries survival, car and Cairo were used for data analysis (R Foundation for Statistical Computing, Vienna, Austria; available at <http://www.R-project.org>). Continuous variables are presented as medians with interquartile ranges (IQRs) using the Wilcoxon rank-sum test, and categorical variables are presented as numbers with percentages using Pearson's χ^2 test. Variables associated with clinical outcomes were evaluated using both unconditional and conditional Cox proportional hazard regression models and results from the unconditional models are reported in detail. DFS curves were constructed using the Kaplan–Meier method and drawn by Prism. Log-rank tests were used to compare DFS between patients with AV-PTC and those with cPTC. Differences with P values <0.05 were regarded as statistically significant.

Results

Clinicopathological characteristics

Patients with AV-PTC and those with cPTC had similar rates for age (more than 55 years), female sex and cervical LN metastasis. However, patients with AV-PTC presented with significantly larger tumor size and a higher rate of microscopic ETE (Table 1). After propensity score matching, no difference was observed in age, sex, tumor size, microscopic ETE and LN metastasis between the two groups (Table 1, right column). Postoperative RAI dose also was similar between the two groups.

Clinical outcomes: DFS and DRS

During a median follow-up of 4 years (IQR, 2.1–5.9 years), overall recurrence rates for AV-PTC and cPTC were 13.5% (19 of 141 patients) and 6.0% (17 of 282), respectively ($P=0.017$). Figure 1A presents the DFS rates of patients in the two groups. The AV-PTC group had a significantly lower DFS than its matched cPTC group (HR: 2.16, 95% CI: 1.12–4.16, $P=0.018$).

However, on comparing the proportion of patients belonging to each of the four categories of DRS, no significant difference was observed between patients with AV-PTC and those with cPTC ($P=0.086$; Fig. 2A).

Subgroup analysis: TCV and CCV

Subgroup analyses of each group of patients with TCV ($n=121$) and CCV ($n=18$) were performed. Hobnail variant was not feasible for subgroup analysis since there were only two patients. There was no significant difference in clinicopathological features of patients with TCV and cPTC after propensity score matching (Supplementary Table 1, see section on supplementary data given at the end of this article). No significant differences in DFS (HR: 1.50, 95% CI: 0.74–3.02, $P=0.253$; Fig. 1B) and in DRS ($P=0.547$; Fig. 2B) between patients with TCV and matched cPTC were found.

After propensity score matching, there were no differences in clinicopathological factors between patients with CCV and those with cPTC (Supplementary Table 2). In the subgroup analysis with patients with CCV, DFS were significantly poorer in CCV group than its matched cPTC group (HR: 12.19, 95% CI: 2.11–70.33, $P=0.005$; Fig. 1C). Proportion of patients according to DRS categories was also significantly different between the two groups ($P=0.047$; Fig. 2C). There were more patients with

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Table 1 Clinicopathological characteristics of patients with AV-PTC and cPTC before and after propensity score matching.

	AV-PTC (n=144)	cPTC (n=763)	P value	After matching		
				AV-PTC (n=141)	cPTC (n=282)	P value
Age (years)	54.5 (42.0–62.0)	54.0 (45.0–62.0)	0.666	54.0 (41.0–61.0)	53.5 (44.0–60.0)	0.941
≥55	66 (45.8%)	363 (47.6%)	0.412	65 (46.1%)	130 (46.1%)	0.999
Sex (female)	109 (75.7%)	579 (75.9%)	0.999	108 (76.6%)	227 (80.4%)	0.421
Primary tumor size (cm)	1.7 (1.3–2.6)	1.5 (1.3–2.2)	0.015	1.6 (1.3–2.4)	1.7 (1.3–2.5)	0.390
>2 cm	52 (36.1%)	214 (28.0%)	0.064	50 (35.5%)	89 (31.6%)	0.487
Extrathyroidal extension (Yes)	129 (89.58%)	616 (80.73%)	0.015	126 (89.4%)	253 (89.7%)	0.999
Cervical LN metastasis			0.098			0.942
N0	19 (13.2%)	62 (8.1%)		18 (12.7%)	35 (12.4%)	
N1a	73 (50.7%)	440 (57.7%)		72 (51.1%)	149 (52.8%)	
N1b	52 (36.1%)	261 (34.2%)		51 (36.2%)	98 (34.8%)	
TNM stage			0.756			0.856
I	82 (56.9%)	438 (57.4%)		79 (56.0%)	155 (55.0%)	
II	61 (42.4%)	322 (42.2%)		61 (43.3%)	126 (44.7%)	
III	1 (0.7%)	3 (0.4%)		1 (0.7%)	1 (0.4%)	
IV	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
RAI dose (mCi)	150 (80–150)	150 (80–150)	0.099	150 (80–150)	150 (80–150)	0.133

Categorical variables are presented as numbers with percentages and were analyzed by Pearson's χ^2 test. Continuous variables are presented as median with IQR and were analyzed by Wilcoxon rank-sum test. Cervical LN metastasis and TNM stage categories were according to Eighth American Joint Committee on Cancer Tumor, Nodes, and Metastasis (AJCC TNM) staging system.

AV-PTC, aggressive variants of papillary thyroid carcinoma; cPTC, classical papillary thyroid carcinoma; LN, lymph node; mCi, millicurie; RAI, radioactive iodine.

structural incomplete response in CCV group (16.7%) compared to cPTC group (0%).

Impact of clinicopathological parameters on recurrence

Cox proportional hazard regression analysis for variables associated with structural persistent/recurrent disease, including TCV and CCV pathology, was performed (Table 2). Along with male sex, microscopic ETE and cervical LN metastasis, CCV pathology increased the risk of structural persistence/recurrence (HR: 4.28, 95% CI: 1.66–11.00, $P=0.003$) while TCV pathology showed insignificant result ($P=0.247$). Furthermore, multivariate analysis revealed that CCV was an independent risk factor for structural persistent/recurrent disease (HR: 5.04, 95% CI: 1.91–13.32, $P=0.001$) along with microscopic ETE. Conditional Cox regression analysis produced similar results.

Discussion

This study evaluated the prognostic implication of AV-PTC when other major risk factors are controlled for. AV-PTC exhibited more aggressive biologic behavior, such as larger tumor size and higher rate of ETE. In a propensity score-matched cohort, patients with AV-PTC exhibited poorer

DFS than their matched patients with cPTC. However, when TCV and CCV were evaluated separately, the clinical outcome of patients with TCV did not differ from that of patients with cPTC and only the patients with CCV had significant difference in DFS and DRS compared to their matched cPTC. This leads to the conclusion that CCV was mainly responsible for the poorer DFS rate in patients with AV-PTC. Also, multivariate analysis revealed that CCV pathology has an independent effect on structural persistence/recurrence while TCV did not.

It is generally accepted that AV-PTC has more aggressive biological features, such as larger tumor size, more frequent LN metastasis, or higher rate of ETE, than cPTC (10, 11, 17, 25, 26). However, in terms of long-term prognosis after initial surgical treatment and subsequent RAI therapy, controversies exist whether aggressive variant histology itself portends a poor prognosis. Previous studies comparing the clinical outcome of TCV with that of cPTC have revealed conflicting results, with some studies illustrating an independent role of TCV in poor prognosis (11, 17, 20, 25), whereas others reporting that the clinical stage of TCV, not the histological subtype, is associated with a poor prognosis (7, 19, 21, 27). Nevertheless, data on CCV and hobnail variants are limited, with most previous studies focusing only on TCVs. To our knowledge, Wenig *et al.* (14) have reported the largest study to date, which is mainly a description of 16 cases of CCV and lacked information about the clinical impact of this variant on

Figure 1

Kaplan-Meier survival curves to compare DFS of patients with AV-PTC (A), patients with TCV (B), and patients with CCV (C) to their matched cPTC cohort.

Figure 2

DRS of patients with AV-PTC (A), TCV (B), and CCV (C) compared with matched patients with cPTC.

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Table 2 Cox proportional hazard regression analysis for variables associated with recurrence.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (≥ 55 years)	0.93 (0.48–1.80)	0.820	–	–
Sex (male)	2.16 (1.09–4.28)	0.026	1.99 (0.98–4.05)	0.057
Primary tumor size (>2 cm)	1.59 (0.82–3.08)	0.171	–	–
Extrathyroidal extension (Y)	5.01 (1.23–20.42)	0.025	6.03 (1.42–25.66)	0.015
Cervical LN metastasis (Y)	1.75 (1.03–2.98)	0.039	1.45 (0.85–2.49)	0.175
Pathology (TCV)	1.49 (0.76–2.90)	0.247	–	–
Pathology (CCV)	4.28 (1.66–11.00)	0.003	5.04 (1.91–13.32)	0.001

CCV, columnar cell variant; CI, confidence interval; HR, hazard ratio; LN, lymph node; TCV, tall cell variant; Y, yes.

long-term outcome compared with the outcome of cPTC cases.

Furthermore, most of the previous studies evaluating the clinical outcomes of AV-PTCs did not control for other confounding factors contributing to clinical outcomes. There are various clinicopathological factors regarding PTC and although we cannot predict the prognosis of PTC apart from one another, defining the independent role of pathologic subtype in long term prognosis is worthwhile when deciding whether to perform more aggressive treatment and more frequent follow-up when final pathologic diagnosis was made as AV-PTC. One study involving 278 patients with TCV, which was conducted by Morris *et al.*, did control major risk factors and compared 5-year disease-specific survival between patients with TCV and cPTC (11). Age, sex, extent of ETE, regional and distant metastases, surgical and adjuvant therapy and year of diagnosis were matched between the two groups. Patients with TCV exhibited poorer 5-year disease-specific survival than matched cPTC patients, although the *P* value was marginally significant (81.9% vs 91.3%, *P*=0.049). The results of our subgroup analysis including patients with TCV only are contrary to those of this cited study with no significant differences in DFS or DRS compared to the matched patients with cPTC. Some differences in patient cohort may explain the discrepancy. Only half of the patients underwent RAI therapy and 8.3% exhibited distant metastases in the cited study, whereas our study selected only patients who underwent total thyroidectomy with subsequent RAI therapy to fully remove the confounding impacts of therapy. We also excluded all patients with synchronous distant metastasis because our primary outcome was DFS. Moreover, all patients with micro-PTC were initially excluded in our study since micro-PTC usually has an excellent prognosis regardless of other clinicopathological factors. With all the aforementioned efforts to minimize the confounding bias along with controlling for major prognostic factors by using propensity score matching method, the result of

our study supports that TCV alone is not associated with unfavorable clinical outcome.

CCV is far less characterized than TCV due to its rarity. Since the first description of CCV by Evans *et al.* (28), a few case reports have attempted to characterize the pathological features of this entity but to date, information about its clinical significance is very limited. In this context, the result of our subgroup analysis with patients with CCV, which revealed that both DFS and DRS were significantly poorer in patients with CCV compared to their matched patients with cPTC, is noteworthy. Our subgroup analysis of CCV includes 18 patients of CCV which, to our knowledge, exceeds the number of isolated cases published in previous studies. The result of our study may prompt the fact that CCV is worth much consideration solely for its clinical impact on prognosis. The fact that CCV has an independent role in increased risk of structural persistence/recurrence raises the necessity of more careful attention and perhaps more aggressive treatment or follow-up strategies. Because most diagnoses of AV-PTC could be made after initial surgery, it is important to determine the molecular markers to predict these aggressive variants, especially CCV, and guide the extent of initial surgical treatment.

Precise pathological sub-classification and accurate diagnosis of AV-PTC are mandatory prior to any modification in treatment or follow-up strategies. In the past, the histologic definition of AV-PTC had inter-observer variations causing heterogeneity in the AV-PTC cohort. For instance, in the TCV, some pathologists applied various height-to-width ratios, from over >2 to >3 , and a wide range of 30–75% of tall cells within the neoplasm to finally classify as the TCV (11, 12, 17, 20, 25, 29). Similarly, in the CCV, no clear consensus on the minimal percentage of columnar cells to define as CCV is made with range between 30 and 80% (14, 28, 30). In our study, a height-to-width ratio at least >3 and $>30\%$ of tall cells were applied consistently based on the newly published WHO classification of tumors

of endocrine organs for TCV (8). For columnar cell and hobnail variants, >30% of columnar cells and hobnail cells were applied respectively. There was no evidence of poorly differentiated or undifferentiated carcinoma transformation of AV-PTC during the follow-up in the present study. Furthermore, the pathological definition of each AV-PTC variant should be clearly standardized to avoid diagnostic disagreement and to thoroughly evaluate the prognostic impact of each AV-PTC.

The strength of our study is that relatively large numbers of patients with AV-PTC were enrolled covering all three variants of AV-PTC proposed in the ATA guidelines and defined on the basis of newly published WHO criteria. Subgroup analysis of TCV and CCV provided detailed data of separate subtypes and particularly, clinical outcomes of CCV add significantly to current literature. Secondly, our study applied propensity score matching method for five major risk factors to minimize the selection bias and is the first study to approve that clinical outcomes of TCV, based on the newly published WHO classification, did not differ from that of cPTC when other risk factors were controlled for. In addition, unlike other previous studies, comparison of DRS for clinical outcome was included, which is currently the most accurate system to predict risk of recurrence. Our study also has some potential limitations. First, this was a single-center study at a tertiary medical center, which may limit generalization on broader basis. Second, the median follow-up period was 4.4 years, which was relatively short for evaluating the recurrence of PTC and requires further follow-up. Third, we did not perform molecular level study for this study. Future study focusing on molecular genetics of AV-PTCs is expected to give more definite answers on why certain variants of PTC exhibit poor prognosis.

In conclusion, patients with AV-PTC exhibited poorer DFS than those with cPTC even when major prognostic factors were controlled for. However, when examined separately, only the CCV was associated with unfavorable clinical outcome and TCV was not. Furthermore, CCV had an independent influence on the prognosis of structural persistence/recurrence in multivariate analysis. Our results emphasize the need for accurate pathological identification of AV-PTC and further modification in therapeutic and follow-up strategies according to the individual type of AV-PTCs.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-17-0991>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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