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# Classic and Follicular Variants of Papillary Thyroid Carcinoma: A Comparative Clinicopathological Analysis

## Papiller Tiroid Karsinomunun Klasik ve Foliküler Varyantları: Karşılaştırmalı Klinikopatolojik Analiz

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## Abstract

**Objectives:** Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, accounting for approximately 70% of all thyroid cancers, and its prevalence has been increasing steadily. Although the prognosis is generally favorable, disease recurrence may occur in approximately 10% of patients, and disease-related mortality has been reported in nearly 5% of cases. The most frequently observed histopathological subtypes of PTC are the classic variants (CV) and follicular variants (FV). However, it has been suggested that clinical behavior and prognosis may differ among the histopathological subtypes, and studies directly comparing these variants remain limited. Pathological features such as capsular invasion, lymphatic invasion, and extrathyroidal extension have been reported to play a critical role in predicting the biological behavior and prognosis of the disease.

The aim of this study was to compare the CV and FV of PTC with respect to clinical and histopathological characteristics and to identify potential differences between these variants.

**Material and Methods:** This retrospective study involved reviewing the medical records and final pathology reports of patients who underwent thyroid surgery at a tertiary referral center between 2012 and 2023. Pathology reports for 401 patients were screened. Among these, 98 patients with a final pathological diagnosis of PTC were identified. Those with tall-cell variant, anaplastic carcinoma, and other rare histopathological variants were excluded; a total of 77 patients diagnosed with CV-PTC or FV-PTC were included in the analysis. Demographic data, clinical presentation, surgical and adjuvant treatments, and pathological features, including capsular invasion, lymphatic invasion, and extrathyroidal extension, were evaluated. Tumors were staged according to the AJCC/TNM 8$^{th}$ edition staging system. Survival analyses were performed using the Kaplan-Meier method.

**Results:** Of the 77 patients, 48 were in the FV-PTC group and 29 were in the CV-PTC group. The age at diagnosis was significantly higher in the FV-PTC group compared with the CV-PTC group (51.6±12.9 vs. 44.8±13.5 years; p=0.031). No significant differences were observed between the groups in clinical presentation, surgical management, or rates of radioactive iodine therapy. Capsular invasion was significantly more frequent in the CV-PTC group (p=0.029). Lymphatic invasion was also higher in the CV-PTC group (p=0.017). Extrathyroidal extension was significantly more frequent in the CV-PTC group (p<0.001). No significant differences were detected between the groups in terms of stage distribution or overall survival (log-rank p=0.921).

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**Conclusion:** This study demonstrates marked differences in histopathological aggressiveness between the CV and FV of PTC, with capsular invasion, lymphatic invasion, and extrathyroidal extension observed more frequently in the CV. However, these differences did not translate into significant disparities in stage distribution or survival outcomes between the two groups. Histopathological variants should therefore be considered alongside other clinical and pathological risk factors when making clinical decisions for PTC.

**Keywords:** Classic variant, follicular variant, papillary thyroid carcinoma, clinicopathological features, prognosis

## Öz

**Giriş / Amaç:** Papiller tiroid karsinomu (PTK), tüm tiroid kanserlerinin yaklaşık %70'ini oluşturan en sık görülen tiroid malignitesidir ve prevalansı istikrarlı bir şekilde artmaktadır. Prognoz genel olarak olumlu olmakla birlikte, hastaların yaklaşık %10'unda hastalık nüksü gelişebilmekte ve olguların yaklaşık %5'inde hastalığa bağlı mortalite bildirilmektedir. PTK'nın en sık gözlenen histopatolojik alt tipleri klasik varyant (KV) ve foliküler varyanttır (FV). Bununla birlikte, histopatolojik alt tipler arasında klinik davranış ve prognozun farklılık gösterebileceği öne sürülmüş olup bu varyantları doğrudan karşılaştıran çalışmalar sayıca sınırlı kalmıştır. Kapsül invazyonu, lenfatik invazyon ve ekstratiroidal uzanım gibi patolojik özelliklerin, hastalığın biyolojik davranışını ve prognozunu öngörmede kritik bir rol oynadığı bildirilmiştir.

Bu çalışmanın amacı, PTK'nın KV ve FV'lerini klinik ve histopatolojik özellikler açısından karşılaştırmak ve bu varyantlar arasındaki olası farklılıkları ortaya koymaktır.

**Gereç ve Yöntem:** Bu retrospektif çalışma, 2012-2023 yılları arasında üçüncü basamak bir referans merkezde tiroid cerrahisi uygulanan hastaların tıbbi kayıtları ve nihai patoloji raporlarının incelenmesiyle gerçekleştirildi. Toplam 401 hastanın patoloji raporları tarandı. Bu hastalar arasından nihai patolojik tanısı PTK olan 98 hasta belirlendi. Uzun boylu hücreli varyant, anaplastik karsinom ve diğer nadir histopatolojik varyantlara sahip hastalar dışlandı ve KV-PTK veya FV-PTK tanısı alan toplam 77 hasta analize dahil edildi. Demografik veriler, klinik başvuru bulguları, cerrahi ve adjuvan tedaviler ile kapsül invazyonu, lenfatik invazyon ve ekstratiroidal uzanım dahil olmak üzere patolojik özellikler değerlendirildi. Tümörler AJCC/TNM 8. baskıya göre evrelendi. Sağkalım analizleri Kaplan-Meier yöntemi ile gerçekleştirildi.

**Bulgular:** Çalışmaya dahil edilen 77 hastanın 48'i FV-PTK grubunda, 29'u KV-PTK grubunda yer almaktaydı. Tanı yaşı FV-PTK grubunda KV-PTK grubuna kıyasla anlamlı olarak daha yüksek bulundu (51,6±12,9'a karşı 44,8±13,5 yıl; p=0,031). Klinik başvuru bulguları, cerrahi yaklaşım ve radyoaktif iyot tedavisi oranları açısından gruplar arasında anlamlı fark saptanmadı. Kapsül invazyonu KV-PTK grubunda anlamlı olarak daha sık izlendi (p=0,029). Lenfatik invazyon da KV-PTK grubunda daha yüksek oranda gözlendi (p=0,017). Ekstratiroidal uzanım KV-PTK grubunda belirgin olarak daha sık saptandı (p<0,001). Evre dağılımı ve genel sağkalım açısından gruplar arasında anlamlı fark tespit edilmedi (log-rank p=0,921).

**Tartışma / Sonuç:** Histopatolojik agresiflik açısından PTK'nın KV ve FV arasında belirgin farklılıklar bulunmakta olup kapsül invazyonu, lenfatik invazyon ve ekstratiroidal uzanım klasik varyantta daha sık gözlenmektedir. Bununla birlikte, bu farklılıklar evre dağılımı ve sağkalım sonuçları açısından anlamlı bir ayrışmaya yol açmamıştır. Bu nedenle histopatolojik varyantların, PTK'da klinik karar alma süreçlerinde diğer klinik ve patolojik risk faktörleriyle birlikte değerlendirilmesi önerilmektedir.

**Anahtar Kelimeler:** Klasik varyant, foliküler varyant, papiller tiroid karsinomu, klinikopatolojik özellikler, prognoz

## Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, accounting for approximately 70% of thyroid cancers, and its incidence has been increasing steadily, with epidemiological data showing a rise from 9.9 to 16.1 per 100.000 between 2003 and 2017 (1). Although the prognosis is generally favorable, certain clinical features such as a history of rapid nodule growth, invasion into surrounding tissues, new-onset hoarseness, or ipsilateral cervical lymphadenopathy are important indicators of an increased likelihood of malignancy. Surgical treatment followed by radioactive iodine (RAI) therapy is curative for the majority of patients. Nevertheless, disease recurrence may occur in approximately 10% of patients, and disease-related mortality has been reported in nearly 5% of cases; a comprehensive appraisal of recurrence risk factors has highlighted the importance of identifying high-risk patients at disease onset to guide personalized management (2,3).

The most frequently observed histopathological subtypes of PTC are the classic variant (CV) and the follicular variant (FV). These variants are referred to as the CV-PTC and the FV-PTC, respectively. In the literature, the CV has been reported to constitute approximately 55-65% of all PTC, whereas the FV accounts for 23-41% (3-5). However, it has been suggested that clinical behavior and prognosis may differ among the histopathological subtypes of PTC, with recent large-scale data indicating that extrathyroidal extension and lymph node metastasis are significantly more common in the CV compared with the FV (6). Furthermore, the introduction of the 2022 World Health Organization (WHO) classification has brought important reclassifications regarding follicular-patterned tumors, underscoring the need for updated comparative analyses between these subtypes (7). A clearer

delineation of these differences is important for prognostic assessment and for guiding patient management.

Numerous studies have aimed to identify clinical and pathological markers that may be associated with long-term adverse clinical outcomes among PTC variants (3,5). These markers include histological subtypes, tumor invasion characteristics, and genetic mutation profiles (5,6). Pathological features such as capsular invasion, lymphatic invasion, and microscopic and macroscopic extrathyroidal extension have been reported to play a critical role in predicting the biological behavior and prognosis of the disease (6,7); recent evidence further confirms that the degree and extent of these invasion parameters are independently associated with lymph node metastasis and disease recurrence (8). However, the number of studies evaluating these clinical and histopathological markers in a comparative manner between the classic and FV remains limited, and their relative prognostic significance within each variant warrants further investigation in light of contemporary classification criteria (9).

The aim of this study was to compare the classic and FV of PTC with respect to clinical and histopathological characteristics and to identify potential differences between these variants. Within this framework, the distribution of clinical and pathological parameters reported to be important for prognostic prediction was evaluated across the variants. Through this approach, our study aimed to contribute to a better understanding of variant-specific clinical and pathological features in PTC.

## Materials and Methods

This retrospective study involved reviewing the medical records and final pathology reports of patients who underwent thyroid surgery in the department of general surgery of a tertiary referral center between 2012 and 2023. During the study period, pathology reports from 401 patients who underwent thyroid surgery were screened. Among these, 98 patients with a final pathological diagnosis of PTC were identified. Thyroid pathologies other than PTC were excluded from the study. Of the 98 patients diagnosed with PTC, those with the tall-cell variant, anaplastic carcinoma, and other rare histopathological variants were excluded, and a total of 77 patients diagnosed with the classic or FV of PTC who met the study criteria were included in the analysis.

Histopathological subtype classification was performed based on the diagnoses reported in the archived pathology reports. Diagnoses were based on the histopathological criteria defined in the 2017 WHO classification of tumours of endocrine organs, which was in effect during the study period. Cases were divided into two groups according to the pathology reports: the CV-PTC and the FV-PTC. Pathological evaluations were performed by the department of pathology at the same institution as part of routine diagnostic practice and based on the histopathological diagnostic criteria valid during the respective period. As the study period preceded the 2022 WHO classification, a systematic retrospective reclassification of non-invasive encapsulated FV cases (NIFTP) could not be performed. Therefore, cases were evaluated according to the terminology reported in the archived pathology reports.

Demographic data (age, sex), presenting complaints and symptoms (asymptomatic status, neck swelling, dyspnea), surgical procedures performed, pathological findings, RAI therapy, staging, and survival data were obtained retrospectively from patients' records. Preoperative thyroid functional status was classified as hyperthyroidism, hypothyroidism, or euthyroidism based on thyroid-stimulating hormone (TSH) levels measured during anesthesia preparation.

The surgical approach was planned according to preoperative evaluation and clinical indications. The surgical technique was determined on an individual basis, taking into account tumor size, location, and extent; patients underwent lobectomy, total thyroidectomy, or completion thyroidectomy as indicated. The application of neck dissection was recorded in the patients' files. Postoperative RAI therapy administration was recorded, and indications for RAI and treatment decisions were determined by the radiation oncology department.

Pathological parameters reported as prognostically significant were extracted from pathology reports. The presence of capsular invasion and lymphatic/lymphovascular invasion was classified as "present" or "absent" as reported in the pathology findings. The presence of extrathyroidal extension was recorded as reported; in cases where microscopic or macroscopic distinction was not specified in the report, extrathyroidal extension was evaluated as "present" or "absent." Tumor staging was determined according to the American Joint Committee on Cancer (AJCC)/tumor-node-metastasis (TNM) 8$^{th}$ edition criteria based on data obtained from medical records.

Follow-up duration and survival data were obtained from clinical records. Overall survival was defined as the time interval (months) from the date of surgery to death or last follow-up. Survival analysis was performed using the Kaplan-Meier method, and differences in survival between groups were compared using the log-rank test.

### Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics software (version 25.0). The distribution of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables with normal distribution were expressed as mean ± standard deviation, whereas non-normally distributed variables were expressed as median (interquartile range). Comparisons of

continuous variables between the two groups were performed using the Student's t-test or the Mann-Whitney U test, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test when appropriate. A two-sided p-value of <0.05 was considered statistically significant.

Ethics committee approval was obtained for the study from Çukurova University Faculty of Medicine (approval no: 26, date: 09.01.2026). Due to the retrospective study design, the requirement for individual informed consent was waived by the ethics committee.

## Results

Of the 77 patients included in the study, 48 were in the FV-PTC group and 29 were in the CV-PTC group. When demographic characteristics were compared between the groups, the age at diagnosis was found to be significantly higher in the FV-PTC group compared with the CV-PTC group (51.6±12.9 vs. 44.8±13.5 years; p=0.031). No significant difference in sex distribution was observed between the two groups (Table 1).

With a focus on the clinical presentation, a similar distribution was observed between the two variants. In both groups, the most common presenting complaint was a palpable neck mass, whereas asymptomatic cases and patients presenting with dyspnea were observed less frequently. When preoperative thyroid functional status was evaluated, the majority of patients in both groups were euthyroid, and no significant difference in TSH-based classification was detected between the groups (Table 1).

**Table 1. Demographic, clinical, and treatment characteristics of the patients**

| Variable | FV-PTC (n=48) | CV-PTC (n=29) | p-value |
|---|---|---|---|
| Age (years) | 51.6±12.9 | 44.8±13.5 | 0.031 |
| Sex | | | |
| Male | 9 (18.8%) | 8 (27.6%) | 0.365 |
| Female | 39 (81.3%) | 21 (72.4%) | |
| Symptomatic presentation | 39 (81.2%) | 26 (89.7%) | 0.324 |
| Preoperative TSH status | 0.926 | | |
| Hyperthyroid | 2 (4.2%) | 1 (3.4%) | |
| Hypothyroid | 1 (2.1%) | 1 (3.4%) | |
| Euthyroid | 45 (93.8%) | 27 (93.1%) | |
| Neck dissection | 6 (12.5%) | 3 (10.3%) | 0.775 |
| Radioactive iodine therapy | 32 (68.1%) | 23 (79.3%) | 0.288 |

Data are presented as mean ± standard deviation or n (%). P-values were calculated using the Student's t-test, chi-square test, or Fisher's exact test, as appropriate

FV-PTC: Follicular variant papillary thyroid carcinoma, CV-PTC: Classic variant papillary thyroid carcinoma, TSH: Thyroid-stimulating hormone

No marked difference was observed between the FV-PTC and CV-PTC groups with regard to surgical procedures. Neck dissection rates were similar in the two variants. Likewise, the rates of postoperative RAI therapy administration were comparable between the groups (Table 1).

When pathological features were compared, findings reflecting invasion and tumor spread were more pronounced in the CV-PTC group. Capsular invasion was significantly more frequent in the CV-PTC group than in the FV-PTC group (p=0.029). Similarly, lymphatic invasion occurred more frequently in the CV-PTC group (p=0.017), and extrathyroidal extension occurred markedly more frequently in the CV-PTC group than in the FV-PTC group (p<0.001) (Table 2).

No significant differences in stage distribution were observed between the groups. The mean overall survival was 97.3 months in the FV-PTC group and 93.6 months in the CV-PTC group. According to Kaplan-Meier analysis, no statistically significant difference in survival was detected between the groups (log-rank p=0.921). During the follow-up period, one death related to primary thyroid malignancy was recorded in the CV-PTC group, while one death due to a non-thyroid-related cause was recorded in the FV-PTC group (Table 3, Figure 1).

**Table 2. Comparison of tumor and pathological characteristics**

| Pathological feature | FV-PTC (n=48) | CV-PTC (n=29) | p-value |
|---|---|---|---|
| Capsular invasion | 13 (27.1%) | 15 (51.7%) | 0.029 |
| Lymphatic/lymphovascular invasion | 8 (16.7%) | 12 (41.4%) | 0.017 |
| Extrathyroidal extension | 10 (20.8%) | 17 (58.6%) | <0.001 |

Data are presented as n (%). P-values were calculated using the chi-square test or Fisher's exact test, as appropriate

FV-PTC: Follicular variant papillary thyroid carcinoma, CV-PTC: Classic variant papillary thyroid carcinoma

**Table 3. Staging and survival outcomes**

| AJCC TNM stage distribution | | |
|---|---|---|
| **AJCC stage** | **FV-PTC (n=48)** | **CV-PTC (n=29)** |
| Stage 0 | 1 (2.1%) | 0 |
| Stage I | 7 (14.6%) | 1 (3.4%) |
| Stage II | 27 (56.3%) | 17 (58.6%) |
| Stage III | 9 (18.8%) | 8 (27.6%) |
| Stage IV | 4 (8.3%) | 3 (10.3%) |

Staging was performed according to the AJCC/TNM 8th edition criteria. P-value for stage distribution comparison: p=0.478 (chi-square test). Mean overall survival: 97.3 months (FV-PTC) vs 93.6 months (CV-PTC); log-rank p=0.921

FV-PTC: Follicular variant papillary thyroid carcinoma, CV-PTC: Classic variant papillary thyroid carcinoma, AJCC: American Joint Committee on Cancer, TNM: Tumor-node-metastasis

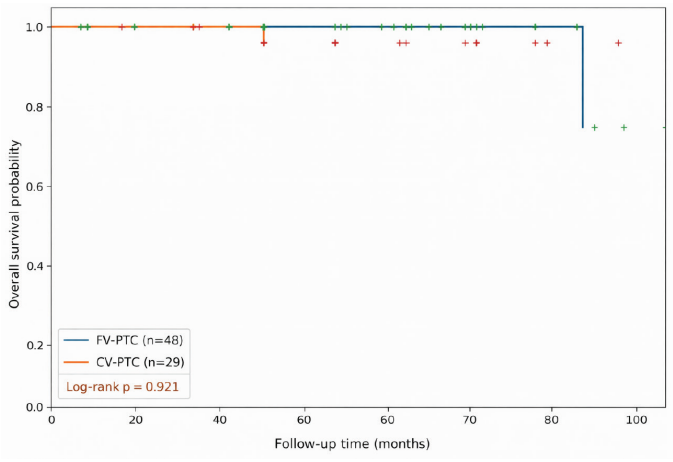


**Figure 1.** Survival outcomes

Kaplan-Meier overall survival curves for follicular variant papillary thyroid carcinoma (FV-PTC) and classic variant papillary thyroid carcinoma (CV-PTC). The x-axis represents follow-up time in months; the y-axis represents cumulative survival probability. No statistically significant difference in overall survival was detected between the two groups (log-rank p=0.921). One disease-specific death was recorded in the CV-PTC group and one non-thyroid-related death in the FV-PTC group during the follow-up period

## Discussion

In this study, the classic and FV of PTC were compared with respect to clinical, surgical, and histopathological characteristics. Our findings demonstrated that the CV of PTC exhibited higher rates of pathological indicators of aggressiveness, including capsular invasion, lymphatic invasion, and extrathyroidal extension, compared with the FV. These findings are consistent with the existing literature suggesting that CV-PTC tends to display a more infiltrative growth pattern, potentially reflecting its BRAF-like molecular profile and associated downstream effects on tumor invasiveness (10). In contrast, no significant differences were identified between the two variants in terms of stage distribution, surgical and adjuvant treatments administered, or survival duration. Although these results suggest that the CV may, histopathologically, display a more aggressive biological behavior they indicate that this aggressiveness does not translate into a marked difference in mid- to long-term survival outcomes, a finding that has similarly been reported in other comparative series (11).

The detection of higher rates of capsular invasion, lymphatic invasion, and extrathyroidal extension in the CV of PTC suggests that this variant may exhibit more aggressive histopathological features than the FV. The CV is predominantly associated with the BRAF V600E mutation, which activates the MAPK signaling pathway and has been shown to upregulate VEGF-C expression, thereby promoting lymphangiogenesis and facilitating lymphatic invasion (12). The more frequent presence of papillary architecture in the CV, combined with its infiltrative growth pattern and associated stromal reaction, may allow tumor cells to establish earlier and more pronounced contact with stromal and lymphatic structures (10). In contrast, the FV-particularly its encapsulated form-is more commonly associated with RAS-like molecular alterations and tends to exhibit a less-infiltrative phenotype, which may account for the lower rates of invasion-related findings observed in our FV-PTC cohort (capsular invasion: 27.1% vs. 51.7%; lymphatic invasion: FV-PTC vs. CV-PTC, p=0.017; extrathyroidal extension: 20.8% vs. 58.6%, p<0.001) (7). In this context, the invasion-related pathological findings observed in the CV in our study support the presence of biologically distinct behaviors among the subtypes of PTC, consistent with their divergent molecular landscapes.

Although more pronounced features of invasion and dissemination were identified in the CV of PTC in our study, these findings did not translate into significant differences in stage distribution (stage I-II: 79.2% vs. 79.3%, p=0.478) or in survival outcomes between the two groups. This pattern is consistent with prior large-scale series demonstrating that, despite higher-risk histopathological features in CV-PTC, both variants carry similarly favorable long-term prognoses when treated according to current guidelines. Henke et al. (11) reported that even when pathologically aggressive FV-PTC tumors were selected for comparison, FV-PTC remained a more favorable diagnosis, while disease recurrence and disease-specific deaths were rare and occurred late in both subtypes. The predominance of early-stage disease in our cohort and the comparable application of total thyroidectomy and RAI treatment across groups may have attenuated the prognostic impact of histopathological differences between variants. The uniform treatment of patients, according to institutional guidelines, has been highlighted as a key factor limiting outcome divergence between CV-PTC and FV-PTC in single-institution series (11). Furthermore, the limited number of adverse events during the follow-up period-a recognized challenge in PTC outcome research given the indolent nature of the disease-reduces statistical power to detect differences in survival between subtypes. These observations collectively suggest that, while CV-PTC and FV-PTC differ in their local aggressiveness, this distinction may not independently drive survival outcomes within a uniformly treated, predominantly early-stage cohort.

In a large series by Sebastian et al. (3) evaluating the clinicopathological characteristics of histological variants, the incidence of the CV was 46%, whereas the FV accounted for 17.6%. Sparano et al. (6) also reported rates of 62% for the CV and 37% for the FV. In our center, however, 62.3% of the cases included in the study were classified as FV-PTC and 37.7% were classified as CV-PTC. This distribution differs from series in the literature that report a higher prevalence of the CV and suggests a possible influence of either the patient population at our

center or the histopathological reporting approach during the study period. In addition, the reliance of our study on pathology reports predating the 2022 WHO classification and the inability to systematically perform NIFTP differentiation should be considered factors that may complicate comparisons with the literature in the classification of follicular-patterned lesions (7).

In our study, invasion-related pathological findings were more frequently detected in the CV-PTC group. These findings are consistent with series that report that the CV is associated with higher rates of capsular invasion, lymphovascular invasion, and extrathyroidal extension than the FV (6,13). In our cohort, capsular invasion was observed in 27.1% (n=13) of FV-PTC cases and in 51.7% (n=15) of CV-PTC cases (p=0.029); lymphatic invasion was also significantly higher in the CV-PTC group, at 41.4% (n=12), compared with the FV-PTC group (p=0.017). These proportions are broadly consistent with published series of encapsulated variants, in which capsular invasion rates of 18-26% for FV-PTC and lymphovascular invasion rates of 4-17% for CV-PTC have been reported (13). Raffaelli et al. (14) reported that the CV may be associated with increased local lymph node metastasis. Because our study did not include a systematic analysis of variables related to lymph node metastasis, direct comparison of this finding is limited. Nevertheless, similar rates of neck dissection between the groups (p=0.775) suggest no marked difference in surgical approach based on clinical lymph node assessment.

Regarding prognostic factors, the literature reports that distant metastasis is the strongest predictor of disease-specific mortality in PTC, followed by extrathyroidal extension, vascular invasion, and advanced age at diagnosis (11). In our series, the significantly higher frequency of extrathyroidal extension in the CV-PTC group compared with the FV-PTC group [58.6% (n=17) vs. 20.8% (n=10); p<0.001] supports the notion that indicators of local aggressiveness may be more pronounced in the CV (4,5). Notably, the prognostic significance of extrathyroidal extension in PTC remains a subject of ongoing debate; while gross extrathyroidal extension is consistently associated with worse outcomes, the AJCC/TNM 8$^{th}$ edition staging system no longer incorporates minimal extrathyroidal extension into T-stage classification, reflecting uncertainty about its independent impact on survival (15). In contrast, no significant difference in staging according to the AJCC/TNM 8$^{th}$ edition (p=0.478) was detected between the two groups, and patients in both groups were predominantly classified as stage II. Survival analysis also revealed no significant difference between the groups (Kaplan-Meier, log-rank p=0.921). This finding may be related to the low number of events in our cohort and the similarity of treatment approaches; therefore, rather than directly confirming or refuting the recurrence and cancer-related mortality differences reported in some series, we believe our results should be validated by larger cohorts with standardized pathological classification.

Among the strengths of the study are the evaluation of a homogeneous patient population who underwent standardized surgical and pathological assessment at a single center, and the detailed comparison of clinical and histopathological features of the two variants. The findings indicate that the CV of PTC is associated with greater histopathological aggressiveness-including higher rates of capsular and lymphatic invasion and extrathyroidal extension-suggesting the need for closer postoperative surveillance and risk-based assessment in these patients. Nevertheless, these differences did not result in significant changes in stage distribution or survival when treatment approaches were comparable, implying that histopathological subtype alone may not be sufficient to determine prognosis. Accordingly, the variant should be evaluated comprehensively alongside other clinical and pathological risk factors in therapeutic decision-making.

### Study Limitations

The retrospective design, single-center nature, and limited sample size represent the main limitations of this study. Histopathological classification was based on archived reports predating the 2022 WHO classification, preventing systematic reclassification of NIFTP and potentially complicating direct comparison with contemporary literature. Furthermore, the low number of oncologic events during follow-up reduced the statistical power to detect potential survival differences between variants. Prospective, multicenter studies with larger cohorts and standardized pathological classification, ideally incorporating molecular profiling, are warranted to better clarify the prognostic implications of histopathological variants in PTC.

## Conclusion

This study demonstrates that there are marked differences in histopathological aggressiveness between the CV and FV of PTC, with capsular invasion, lymphatic invasion, and extrathyroidal extension being observed more frequently in the CV. However, these differences did not translate into significant disparities in stage distribution or survival outcomes between the two groups. While our findings provide important insights into the biological behavior of PTC across histopathological variants, they suggest that variant subtype alone may not independently determine prognosis. Therefore, histopathological variants should be considered holistically alongside other clinical and pathological risk factors in clinical decision-making for PTC.

### Ethics

**Ethics Committee Approval:** Ethics committee approval was obtained for the study from Çukurova University Faculty of Medicine (approval no: 26, date: 09.01.2026).

**Informed Consent:** Due to the retrospective study design, the requirement for individual informed consent was waived by the ethics committee.

### Footnotes

### Authorship Contributions

Concept/Design: A.Y., B.A., Y.K., A.G.S., K.D., Data Collection or Processing: A.Y., Analysis or Interpretation: A.Y., B.A., Y.K., Literature Review: A.Y., B.A., Y.K., Writing, Reviewing and Editing: A.Y., S.G., İ.A., Y.K., A.G.S., K.D., G.S.

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