Follicular Variant of Papillary Thyroid Carcinoma Differences From Conventional Disease in Cytologic Findings and High-Risk Features

Patrick Sheahan, MB, FRCPI (ORL-HNS); Mohamed Mohamed, MB; Carmel Ryan, MB; Linda Feeley, MB, FRCPath; Brendan Fitzgerald, MB, FRCPath; Julie McCarthy, MB, FRCPath; Antoinette Tuthill, MB, MRCP; Matthew S. Murphy, MB, MRCP

**IMPORTANCE** The follicular variant (FV) of papillary thyroid carcinoma (PTC) is an important subtype that can be difficult to diagnose using preoperative cytologic analysis.

**OBJECTIVE** To compare conventional and FV PTC with regard to preoperative cytologic diagnosis using a tiered thyroid cytologic reporting system, tumor size at diagnosis, presence of invasion, and implications on prognostic scores.

**DESIGN, SETTING, AND PARTICIPANTS** This retrospective study was conducted in an academic teaching hospital and included 99 patients with conventional (n = 65) or FV (n = 34) PTC.

**INTERVENTIONS** Preoperative thyroid cytologic findings, originally reported using the tiered British Thy system, were recategorized according to the Bethesda classification system. Pathologic features recorded included tumor size, presence of extrathyroid extension (ETE), and metastases. Prognostic scores were calculated according to the MACIS system.

**MAIN OUTCOMES AND MEASURES** Differences in patient demographics, preoperative cytologic findings, tumor pathologic features, and prognostic risk categories between conventional and FV PTC were studied.

**RESULTS** There were no differences in patient age or sex. Cytologic findings from FV PTC were significantly more likely to be reported in a lower-risk category than those from conventional PTC for (1) malignant vs lower-risk category (22 [56%] vs 2 [8%]); (2) suspected malignant or malignant vs lower-risk category (26 [66%] vs 6 [23%]); and (3) follicular neoplasm or higher-risk category vs lower-risk category (34 [87%] vs 10 [38%]) (P < .001 for all 3 comparisons). There was also a significantly higher likelihood of false-negative cytologic findings among FV PTC cases (5 [19%] vs 1 [3%]) (P = .03). The mean size of FV PTC lesions (25.9 mm) at the time of pathologic diagnosis was significantly greater than that of conventional PTC lesions (15.5 mm) (P = .02). Even after exclusion of “coincidental” carcinomas, FV PTC tumors were significantly larger than conventional PTC tumors (31.7 vs 22.4 mm; P = .03). In contrast, FV PTC was significantly less likely to show ETE (0 of 34 vs 10 of 65; P = .01). There were no significant differences between FV PTC and conventional PTC in proportion of patients in intermediate- and high-risk prognostic groups combined (21 [62%] vs 38 [58%]) (P = .83) or in mean MACIS scores (4.68 and 4.38, respectively; P = .18).

**CONCLUSIONS AND RELEVANCE** Preoperative cytologic findings from FV PTC were more likely than those from conventional PTC to indicate a lower risk category, and FV PTC tumors were larger at time of diagnosis. On the other hand, owing to a lower incidence of ETE in conventional PTC, there was no difference in prognostic score at diagnosis.
Cancer of the thyroid gland is the most common endocrine malignant neoplasm, and well-differentiated papillary thyroid carcinoma (PTC) accounts for the vast majority of cases. Most cases of PTC have a favorable prognosis, with long-term survival rates in excess of 95% in many series.1 Risk factors for less favorable disease include patient age 45 years or older, tumor size greater than 4 cm, extrathyroid extension (ETE), and distant metastases.2 Over the last few decades, there has been a substantial increase in the incidence of thyroid cancer.3-4 Much of this increase has been made up of smaller PTC tumors with favorable prognoses.3

The follicular variant (FV) of PTC is an important subtype that was first described in the 1960s and 1970s.5,6 This variant is characterized by the presence of nuclear features of PTC together with a follicular growth pattern. In recent years, FV PTC has been increasingly recognized.7,8 It is currently reported to make up 11.8% to 53.3% of all PTC cases.7-9 Besides having a different growth pattern than conventional PTC, FV PTC has a different genetic profile, with a lower prevalence of B-type Raf kinase (BRAF) mutations10 and a higher incidence of RAS mutation,11 similar to follicular adenoma and follicular carcinoma.

Diagnosis of FV PTC can present a greater challenge than diagnosis of conventional PTC. The follicular variant has been reported to be a cause of false-negative results in thyroid cytologic findings,12-14 and in some cases, differentiation between a benign follicular lesion and FV PTC can be difficult.

Fine-needle aspiration (FNA) biopsy is widely regarded as a first-line diagnostic tool in the assessment of thyroid nodules. To improve the consistency of reporting thyroid cytologic findings, researchers have devised several tiered classification systems, including the British Thy system15 and the American Bethesda system.16 One of the major roles for these classification systems is to facilitate triage of cases into those that require surgery and those that may be clinically observed over time. To optimize thyroid cancer outcomes, physicians must recognize FV PTC, particularly in the setting of possible risk factors for more aggressive thyroid cancer.

The purpose of the present study was to compare the clinicopathologic features of conventional PTC and FV PTC. In particular, we wished to compare (1) findings of preoperative cytologic studies, when these were reported according to a tiered thyroid cytologic findings reporting system, and (2) presence of established risk factors for aggressive disease (patient age, large tumor size, ETE, and metastases) at the time of pathologic diagnosis. We also wished to investigate whether any such differences were associated with any prognostic implications.

Methods

The Cork clinical research ethics committee approved this retrospective review of medical records of all patients with thyroid cancer who underwent surgery at the South Infirmary Victoria University Hospital, Cork, Ireland, an academic teaching hospital and tertiary referral center for patients with thyroid diseases. All procedures were performed by the senior author (P.S.) between March 2009 and October 2013. Cases were identified by review of a prospectively maintained thyroid cancer database, which included demographic and clinical details, reasons for surgery, types of surgery performed, intraoperative findings, and postoperative course and outcome. All included cases had been subtyped as conventional or FV PTC.

Preoperative cytologic findings were reported according to the British Thy system,17 which is directly analogous to the American Bethesda system for thyroid cytology reporting.17 Table 1 lists the British Thy categories and corresponding Bethesda categories. For the purpose of the present study, the Thy cytologic diagnoses were reclassified according to the Bethesda system. Cases with a Thy-3a classification were additionally re-reviewed by a specialist cytopathologist (J.M.C.) for designation as either atypia of undetermined significance (AUS) or follicular neoplasm of undetermined significance (FLUS). In patients who underwent more than 1 preoperative FNA biopsy, the highest-risk cytologic findings were considered to constitute the final preoperative diagnosis.

All cases with thyroid cytologic findings reported as AUS, FLUS, follicular neoplasm (FN), suspect for malignancy, or malignant were discussed at thyroid or head and neck multidisciplinary meetings, with re-review of cytologic findings and radiology results. Indications for surgery included any case with malignant or suspect for malignant cytologic findings as well as most cases of FN. Cases of AUS or FLUS without suspect sonographic or clinical features were generally recommended for follow-up with interval ultrasonography-FNA biopsy, with surgery recommended for cases with persistent indeterminate cytologic findings. In addition, surgery was generally offered to patients with a dominant nodule larger than 4 cm, nodules smaller than 4 cm but with suspect sonographic features, local symptoms, or other causes of clinical concern.

Malignant thyroid disease was reported according to a specific thyroid cancer reporting protocol based on the RCPPath Thyroid Cancer Data set,18 with systematic reporting of salient pathologic data, including tumor type and subtype, tumor size, presence of multifocality, presence of ETE, and lymph node involvement. In addition, all cases of thyroid cancer were discussed at thyroid or head and neck multidisciplinary meetings, with re-review of pathology slides, including verification of all data reported in the original protocol. In cases where there were any changes in the pathology interpretation after...
the re-review, a supplementary report was issued. Pathologic data for the present study was extracted from the final histopathology reports.

Follicular variant PTC was considered to be present in cases of PTC showing a follicular growth pattern with virtually no papillary structures along with nuclear features of papillary carcinoma. In cases of FV PTC where the nuclear features diagnostic of cancer were only focal or multifocal within the nodule, the total nodule size was used for staging purposes. The histologic sections from all FV PTCs were further reviewed by 2 consultant histopathologists (L.F. and B.F.) and were subclassified as encapsulated, infiltrative, or partially encapsulated/well-circumscribed variants.19 Cases were designated as encapsulated when the tumor had a complete capsule with or without capsular or vascular invasion. The infiltrative variant was diagnosed when the tumor was not encapsulated and demonstrated an infiltrative growth pattern into the surrounding thyroid parenchyma. Cases lacking a complete capsule but remaining well circumscribed and without an infiltrative growth pattern were designated partially encapsulated/well circumscribed.

Cases of conventional PTC and FV PTC were compared with respect to patient demographics, preoperative cytologic findings, and histologic findings. Preoperative cytologic findings were correlated with histologic findings only in those cases where the preoperative FNA biopsy specimen had been taken from the cancerous nodule. In other words, cases of carcinoma occurring outside the biopsied nodule, where the biopsied nodule was found to be benign, were not included in the analysis of preoperative cytologic findings.

Gross ETE was determined by intraoperative findings of grossly invasive tumor as recorded in the prospective database. Information regarding operative management of lymph nodes was also obtained from the prospective database (no formal nodal dissection; formal unilateral or bilateral central compartment neck dissection).

Patients were classified into low-, intermediate-, or high-risk groups using the Memorial Sloan Kettering risk stratification system.2 The MACIS score (metastasis, age, completeness of resection, invasion, size) for patients 40 years or older was calculated according to the following formula: [age × 0.08] + [size (mm) × 0.03] + 1 (if incomplete resection) + 1 (if local invasion) + 3 (if distant metastases). For patients younger than 40 years, the same formula was used, but the age term was constant, 3.1,20

Statistical analysis was performed using XLSTAT (Addinsoft Software, version 2013,5,05). A Fisher exact test was used for analysis of 2 × 2 contingency tables.

Results

During the study period, 124 patients underwent thyroid surgery at our institution and received a final diagnosis of thyroid cancer, including 105 diagnoses of PTC. Histologic findings of the remaining cases included follicular carcinoma (n = 12), medullary carcinoma (n = 4), poorly differentiated thyroid carcinoma (n = 2), and anaplastic carcinoma (n = 1).

Among the 105 patients with PTC, 65 patients (62%) had conventional PTC, and 34 (32%) had FV PTC. Six patients (6%) had other variants (1 diffuse sclerosing variant, 2 solid variants, and 3 oncocytic variants). These 6 cases were excluded.

Among the 34 cases of FV PTC, slides were available for review in 31 cases. Of these, 5 had an infiltrative growth pattern, 21 were well partially encapsulated/well circumscribed, and 5 were completely encapsulated. Angioinvasion was seen in 2 cases (1 infiltrative, 1 encapsulated).

There were 4 patients with simultaneous conventional PTC and FV PTC. One of these had a 2.2-cm FV PTC lesion within the index nodule and 3 additional foci of papillary microcarcinoma. For the purpose of this study, this patient was considered to have FV PTC. Three patients had conventional PTC within the index nodule and additional foci of micro-PVT that were considered coincidental. For the purpose of this study, these patients were included in the conventional PTC group.

Among the 99 cases included in the study, tumor sizes ranged from smaller than 1 mm to 85 mm. Forty-three tumors measured less than 1 cm. Of these, 30 were considered to have been incidental carcinomas discovered on histologic examination where the indication for surgery was for diagnosis of a different nodule, which turned out to be benign (n = 27), or where malignancy was otherwise not suspected (n = 3). Among the remaining 13 cases that measured less than 1 cm, surgery had been performed for definitive management of the cancerous nodule (5 after FNA biopsy of the thyroid nodule measured at 1 cm or larger on preoperative sonography, but with final pathologic size measured at less than 1 cm; 5 after FNA biopsy of a thyroid node measured at less than 1 cm on preoperative sonography; and 3 after FNA biopsy of a lateral cervical lymph node only).

Demographic and clinicopathologic features of patients with conventional PTC and FV PTC are listed in Table 2. There were no significant differences between the groups in age or male-female ratio.

Preoperative FNA biopsy of the nodule that turned out to be papillary cancer was performed on 65 patients. Among the 34 patients without preoperative cytologic findings from the cancer, 3 (1 with FV PTC and 2 with conventional PTC) underwent preoperative biopsy of a lateral cervical node with diagnosis made of thyroid cancer, but they did not undergo FNA biopsy of the thyroid. Four patients underwent thyroid surgery without preoperative FNA biopsy. Indications for surgery in these patients were compressive goiter without suspect dominant nodule (n = 2), Graves disease (n = 1), and intraoperative findings of suspect thyroid nodule during parathyroid surgery (n = 1). Finally, 27 patients (6 with FV PTC and 21 with conventional PTC) had undergone preoperative FNA biopsy of a dominant nodule that was found to be benign on histologic examination, and the thyroid cancer was an incidental finding outside the biopsied nodule. Indications for surgery in these cases were FN or other high-risk cytologic findings of the dominant nodule (n = 19), large size of the dominant nodule (n = 5), local symptoms (n = 2), and patient concern (n = 1). Table 3 summarizes the preoperative cytologic findings correlated with
Conventional PTC was significantly more likely than FV PTC to have a malignant cytologic diagnosis (P < .001) or FLUS or AUS cytologic findings vs those with lower-risk cytologic findings. P value is for comparison of cases with malignant, suspect for malignant, or FN cytologic findings vs those with lower-risk cytologic findings.

Abbreviations: FN, follicular variant; PTC, papillary thyroid carcinoma.

* Unless otherwise noted, data are reported as number (percentage) of patients.

**p value is for comparison of cases with malignant or suspect for malignant histologic findings for those cases with FNA biopsy of the cancerous nodule.

Conventional PTC was significantly more likely than FV PTC to have a malignant cytologic diagnosis (P < .001) or preoperative malignant or suspect for malignant cytologic findings (P < .001). Conventional PTC was also significantly more likely to have an FN or higher-risk cytologic diagnosis (P < .001) and more likely to have FLUS, AUS, or higher-risk cytologic diagnosis (P = .002). In contrast, FV PTC was significantly more likely to have false-negative benign preoperative cytologic findings (P = .03).

From cases ultimately determined to be FV PTC, Figure 1 shows cytologic atypia of undetermined significance, and Figure 2 shows follicular neoplasm.

The mean size of the tumor in FV PTC was, by pathologic examination, 26.3 mm. This was significantly greater than that of conventional PTC (14.8 mm) (P = .002) (Table 1).

To exclude bias in the comparison of nodule size between conventional and FV PTC introduced by possible inclusion of more cases of incidental microcarcinoma in the conventional than in the FV PTC group, the analysis was repeated after excluding cases of incidental carcinoma, where the preoperative FNA biopsy specimen had been taken from an index nodule that was found to be benign on final histologic analysis or where preoperative FNA biopsy had not been performed. Among the remaining (non INCIDENTAL) cases, the mean size of the cancer lesion by pathologic examination was 31.7 mm in patients with FV PTC and 22.4 mm in those with conventional PTC. The difference was statistically significant (P = .03). The mean size of the cancer lesion by sonographic examination was 32.9 mm in FV PTC and 24.9 mm in conventional PTC, which was outside the 5% level of significance (P = .07).

In the conventional vs FV PTC group, there appeared to be a trend toward a higher incidence of tumor multifocality (n = 29 [45%] vs n = 9 [27%]) and bilaterality (n = 17 of 56 [30%] vs n = 5 of 30 [17%]), but the differences were not significant (P = .09 and P = .20, respectively) (Table 1). There was a significant difference in incidence of microscopic ETE (conventional PTC, n = 10 [15%] vs FV PTC, n = 0) (P = .01). All 5 cases of grossly invasive carcinoma occurred in the conventional PTC group, although the number of grossly invasive cancers was too small to show a significant difference from FV PTC (P = .15) (Table 1).

Twenty-six patients (26%) underwent formal central lymph node dissection. Fifteen (58%) of these were positive for metastatic carcinoma. In addition, 2 patients not undergoing central neck dissection in the conventional PTC group had metastatic carcinoma.
static carcinoma in an incidentally removed lymph node, and 1 patient with a negative finding on a central neck dissection specimen had positive lateral cervical nodes. The incidence of lymph node metastases was lower in FV PTC (10%; n = 3) than conventional PTC (23%; n = 15), but the difference was not significant ($P = .10$). Among patients undergoing formal central neck dissection, the incidence of metastatic disease was 50% (3 of 6) in the FV PTC group, and 60% (12 of 20) in the conventional PTC group ($P > .99$). Of note, all 3 cases with lymph node metastases in the FV PTC group occurred in cases with infiltrative growth patterns.

Among patients with FV PTC, there were 13 patients classified as low risk, 20 as intermediate risk, and 1 as high risk, according to the Memorial Sloan Kettering risk grouping system. Among patients with conventional PTC, there were 27 patients classified as low risk, 34 as intermediate risk, and 4 as high risk. There was no significant difference in proportion of intermediate to high-risk cases between the groups ($P = .83$). The mean MACIS score was 4.68 among patients with FV PTC and 4.38 among patients with conventional PTC, which was not significantly different ($P = .18$).

### Discussion

The purpose of the present study was to investigate differences in clinicopathologic features between FV PTC and conventional PTC, with particular emphasis on preoperative cytologic diagnosis, when this is reported according to a standardized tiered cytologic reporting system, and risk factors for more aggressive disease. We found some important differences in relation to preoperative cytologic findings, mean tumor size at diagnosis, and incidence of ETE; but not in patient age or sex, incidence of tumor multicentricity or bilaterality, incidence of lymph nodes metastases, or prognostic grouping or MACIS scores.

Perhaps the most clinically important difference we found was in preoperative cytologic diagnosis. While most cases of conventional PTC in the present series were correctly identified by preoperative cytologic analysis as malignant, aspirates from cases of FV PTC were significantly more likely to be reported in a lower-risk cytologic category and also significantly more likely to have had a false-negative (benign) cytologic result. This is an important issue because cases belonging to low-risk cytologic categories may be more likely to be recommended for nonsurgical follow-up, which may lead to increased risk of delayed diagnosis or failure to diagnose cases of FV PTC.

Reasons for the reduced sensitivity of FNA biopsy in the diagnosis of malignant FV PTC may include the absence of prominent nuclear changes in cytologic specimens, the frequent presence of abundant colloid, and the absence of papillary formations and psammoma bodies. Furthermore, nuclear changes in FV PTC can be multifocal and randomly distributed within a single nodule, increasing the risk of false-negative cytologic findings owing to sampling error. Follicular variant PTC has been previously reported by other authors, including our own research team, to account for a large proportion of false-negative cases in thyroid cytologic findings. In the present series, we demonstrate that in addition to a higher likelihood of false-negative cytologic findings, preoperative FNA biopsy results from FV PTC are significantly more likely to fall into a lower risk category than those from conventional PTC when thyroid cytologic findings are reported according to a standardized tiered classification system.

In the future, it is possible that the diagnosis of FNA biopsy samples may be improved by molecular analysis. However, the utility in FV PTC may be hindered by the lower incidence of BRAF mutations, whereas RAS mutations may also be found in benign follicular lesions.

The mean size of FV PTC tumors in the present study was significantly greater than that of conventional PTC tumors. This held true even after we excluded cases of incidentally discovered carcinomas. A larger size for FV PTC was also reported by Ertek et al and Ozdemir et al. We believe that the most likely
Follicular Variant of Papillary Thyroid Carcinoma

Follicular variant PTC is an important subtype of the disease. Compared with conventional PTC, the cytologic findings from FV PTC are more likely to belong to a lower-risk cytologic category. The FV variant appears to have a larger mean tumor size at diagnosis than conventional PTC. This larger size may be related to overrepresentation of larger FV PTCs in surgical series. On the other hand, this policy may have minimized the risk of delayed diagnosis of larger cancers and averted any trend for more high-risk tumors in the FV PTC group.

Finally, given that FV PTC is a relatively recently recognized entity, it is likely that the Memorial Sloan Kettering risk stratification and MACIS scoring systems are mostly based on patients with classic PTC, and there are few data regarding their specific applicability to FV PTC. It is assumed that these systems are probably applicable, since the survival outcomes are not significantly different between conventional and FV PTC. What is less certain is whether infiltrative FV PTC variants may have a significantly poorer prognosis and, if so, whether such variants should be upstaged to higher risk categories or scores.

**Conclusions**

Follicular variant PTC is an important subtype of the disease. Compared with conventional PTC, the cytologic findings from FTV PTC are more likely to belong to a lower-risk cytologic category. The FV variant appears to have a larger mean tumor size at diagnosis than conventional PTC. This larger size may be related to overrepresentation of larger FV PTCs in surgical series resulting from failure to capture smaller FV PTC tumors, owing to lack of definitive cytologic cancer diagnosis. On the other hand, cases of FV PTC are less likely to show micro-
scopric or gross ETE and are no more likely to fall into a higher-risk prognostic category at diagnosis than conventional PTC. Preoperative diagnosis of FV PTC presents a greater challenge than conventional PTC, which may lead to increased tumor size at time of diagnosis, but this does not appear to have prognostic implications.

ARTICLE INFORMATION

Submitted for Publication: May 31, 2014; final revision received August 3, 2014; accepted September 2, 2014.


Author Contributions: Dr Sheahan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Sheahan, Murphy.

Acquisition, analysis, or interpretation of data: Sheahan, Mohamed, Ryan, Feeley, Fitzgerald, McCarthy, Tuthill, Murphy.

Drafting of the manuscript: Sheahan, Mohamed, Ryan, Feeley, McCarthy.

Critical revision of the manuscript for important intellectual content: Sheahan, Feeley, Fitzgerald, McCarthy, Tuthill, Murphy.

Statistical analysis: Sheahan, Feeley, Fitzgerald, McCarthy, Tuthill, Murphy.

Administrative, technical, or material support: Mohamed, Ryan, Fitzgerald, Tuthill, Murphy.

Study supervision: Feeley, Fitzgerald, McCarthy, Murphy.

Conflict of Interest Disclosures: None reported.

Previous Presentation: This study was presented at the Fifth World Congress of the International Federation of Head and Neck Oncologic Societies and the Annual Meeting of the American Head & Neck Society; July 29, 2014; New York, New York.

REFERENCES


