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# The Impact of Noninvasive Follicular Variant of Papillary Thyroid Carcinoma on Rates of Malignancy for Fine-Needle Aspiration Diagnostic Categories

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***Background:*** Increased recognition of the indolent nature of noninvasive follicular variant of papillary thyroid carcinoma (NFVPTC) along with greater insight into the molecular alterations of these tumors has prompted endocrine pathologists to question whether these tumors warrant a diagnosis of carcinoma. However, a change in terminology would affect the rates of malignancy of fine-needle aspiration (FNA) diagnostic categories. Therefore, the aim of this study was to determine the percentage decrease in associated risk of malignancy for each FNA diagnostic category if NFVPTCs were no longer termed carcinomas.

***Methods:*** We evaluated a cohort of 655 FNAs with subsequent resection specimens over a 22-month time period. The diagnoses of the preceding FNAs were recorded according to the Bethesda System for Reporting Thyroid Cytopathology. For cases with more than one preceding FNA, the FNA diagnosis associated with the highest risk of malignancy was identified. Slides for all resection specimens with a diagnosis of FVPTC were reviewed to identify noninvasive tumors. By definition, all of these tumors were encapsulated, partially encapsulated, or well circumscribed and lacked any indication of infiltrative growth, capsular penetration, or lymphovascular invasion.

***Results:*** Our cohort of 655 FNAs with subsequent resection specimens included 53 (8.1%) nondiagnostic (ND), 167 (25.5%) benign, 97 (14.8%) atypia/follicular lesion of undetermined significance (AUS/FLUS), 88 (13.4%) suspicious for follicular neoplasm (SFN), 94 (14.4%) suspicious for malignancy (SUS), and 156 (23.8%) malignant cases (POS). Surgical resections demonstrated benign findings in 309 (47.2%) and malignant tumors in 346 (52.8%), including 85 NFVPTCs accounting for 24.6% of malignancies. Our rates of malignancy for ND, benign, AUS/FLUS, SFN, SUS, and POS were 18.9%, 13.2%, 39.2%, 45.5%, 87.2%, and 98.7%, respectively. If NFVPTC were no longer termed carcinoma, these rates would drop to 17.0% (10% decrease), 5.4% (59% decrease), 21.6% (45% decrease), 37.5% (18% decrease), 45.7% (48% decrease), and 93.6% (5% decrease), respectively.

***Conclusion:*** Our findings demonstrate that if terminology were changed and NFVPTCs were not considered carcinomas, the rates of malignancy for FNA diagnostic categories would be substantially decreased, with the most clinically significant decrease seen in the SUS category, which demonstrated a relative decrease of nearly 50%.

## Introduction

The incidence of papillary thyroid carcinoma (PTC) has nearly tripled in the United States since the 1970s, but in this same time period there has been virtually no change in disease-specific mortality, indicating that many of these tumors are indolent (1). Identifying which tumors are indolent is important to prevent overtreatment. In the past decade, it has been shown that FVPTC can be further subclassified based on growth pattern and molecular alterations. FVPTCs that demonstrate infiltrative growth have a significant rate of lymph node metastases, a potential to recur, and have a $BRAF^{V600E}$ mutation frequency of roughly 25% (2–4). In contrast, encapsulated, partially-encapsulated, or well-circumscribed FVPTCs without capsular penetration or lymphovascular invasion (i.e., noninvasive tumors) have very little, if any, metastatic potential or recurrence risk (3,5,6). Additionally, most groups have shown that the noninvasive follicular variant of

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papillary thyroid carcinoma (NFVPTC) harbors *RAS* and *PAX8/PPARγ* mutations but lacks the $BRAF^{V600E}$ mutation that is often associated with high-risk histopathologic features (7,8). The indolent nature of NFVPTCs along with a molecular profile that is more in keeping with follicular adenomas and follicular thyroid carcinomas (FTCs), i.e. tumors in malignancy has prompted endocrine pathologists to question whether NFVPTCs warrant a designation of carcinoma.

Ultrasound-guided fine-needle aspiration (FNA) is widely accepted as the diagnostic standard of care for preoperative evaluation of nontoxic thyroid nodules. In an effort to improve accuracy and facilitate communication of FNA results, the National Cancer Institute (NCI) organized the ''NCI Thyroid Fine Needle Aspiration State of the Science Conference,'' which led to the subsequent Bethesda System for reporting thyroid cytopathology (9,10). This classification scheme includes six diagnostic categories for thyroid FNA results: nondiagnostic (ND), benign, atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS), suspicious for follicular neoplasm (SFN), suspicious for malignancy (SUS), and malignant (POS). An important objective of this system is for each category to have an implied risk of malignancy to direct appropriate clinical management. Based upon a prior review of the literature, the rate of malignancy has been cited as 1%–4% for ND, 0%–3% for benign, 5%–15% for AUS/FLUS, 15%–30% for SFN, 60%–75% for SUS, and 97%–99% for POS (9).

Our group evaluated the preceding FNA diagnoses of a cohort of 72 NFVPTCs and found that the diagnosis associated with the highest risk of malignancy was POS in 7%, SUS in 49%, SFN in 10%, AUS/FLUS in 18%, benign in 13%, and ND in 4% of cases (11). These findings suggest that if NFVPTC were no longer termed carcinoma, this would not only impact the rate of malignancy for AUS and SFN, but also the rate for the SUS and even the malignant category. In order to determine the magnitude of that decrease, it is necessary to establish the percentage of malignant cases NFVPTCs account for within each Bethesda diagnostic category. Therefore, the aim of the current study was to evaluate a cohort of consecutive FNAs with subsequent resection specimens to assess the percentage of NFVPTCs in each diagnostic category and thus determine the percentage decrease in associated risk of malignancy for each FNA diagnostic category if NFVPTCs were no longer termed carcinomas.

## Materials and Methods

### *Study population and data acquisition*

Approval from the Brigham and Women's Hospital Investigation Review Board was obtained. A search of the pathology database at Brigham and Women's Hospital was performed to identify all thyroidectomy specimens resected between August 2010 and May 2012. For each case all surgical pathology reports were reviewed, and the surgical pathology diagnosis was recorded as indicated in the pathology report. For cases with a reported diagnosis of FVPTC, all available hematoxylin and eosin slides of the tumor for each case were reviewed by two pathologists at a multi-headed microscope (BEH and JAB, both thyroid pathology subspecialists at the staff surgical pathology level), and NFVPTCs were identified. NFVPTCs included tumors that were encapsulated or partially encapsulated/well circumscribed. Encapsulated tumors had a complete fibrous capsule delineating the tumor from the benign thyroid parenchyma. Encapsulated tumors with either lymphovascular invasion (present within the capsule or beyond) or complete capsular penetration were categorized as invasive and excluded from the NFVPTC group. Partially-encapsulated/well-circumscribed tumors had either a partial capsule or entirely lacked a capsule; however, there was a discrete interface between the tumor and benign parenchyma with no tumor infiltrating between benign glands. Cases with any indication of an infiltrative edge were excluded from the NFVPTC group. All tumors in this group had an entirely or almost entirely follicular architecture (i.e., ≤1% papillary architecture) along with nuclear features of PTC. Retrospectively, JAB re-reviewed tumor slides to compare histopathologic features of tumors with a preceding FNA diagnosis of SUS and those with a preceding FNA diagnosis of benign, AUS/FLUS, or SFN. Tumors were scored for the presence or absence of overt nuclear features of PTC. Tumors with overt nuclear features showed nuclear crowding, nuclear enlargement, nuclear contour irregularities, nuclear grooves, and nuclear clearing, while tumors that were scored as lacking overt nuclear features of PTC had only some of these characteristics. Additionally, the nuclear features were characterized as diffuse if >70% of the tumor demonstrated nuclear features of PTC. Additional clinical and pathologic characteristics obtained from the pathology report included sex, age at resection, type of surgery (hemithyroidectomy; lobectomy; near-total, total, or completion thyroidectomy), lymph node resection status, presence of lymphovascular invasion, presence of extrathyroidal extension, and presence of lymph node metastases. For the completion thyroidectomies, only those with a preceding FNA of a nodule in the remaining thyroid were included in the study.

For each surgical specimen, the preceding FNA reports were identified. The FNA diagnoses were recorded from the pathology reports generated by staff cytopathologists using a six-tiered diagnostic system essentially identical to that elucidated in the 2007 National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference and the subsequent Bethesda System for Reporting of Thyroid Cytopathology. The diagnostic categories were ND, benign, AUS/FLUS, SFN, SUS, and POS. For patients with FNAs of multiple nodules, only the nodule and corresponding FNA associated with the highest risk of malignancy was evaluated, with the risk of malignancy based on statistics quoted for the Bethesda System (9). Cases in which the FNA specimen could not be matched to a specific nodule in the thyroidectomy specimen were excluded from the study. For cases with multiple FNAs of the same nodule, the preceding FNA diagnosis associated with the highest risk of malignancy was recorded.

### *Statistical analysis*

Fisher's exact test was used to evaluate the statistical significance of categorical variables, and an unpaired *t*-test was used to compare continuous variables. All *p*-values are two-sided, and a level of 0.05 was considered statistically significant. GraphPad Instat (GraphPad Software, San Diego, CA) was used to analyze the data.

## Results

### *Clinical and histopathologic characteristics*

Our cohort included 655 consecutive patients who underwent FNA of a thyroid nodule and a subsequent surgical resection. Overall, there were 510 (77.9%) women and 145 (22.1%) men with a mean age of 50 years at the time of surgical resection (range 16–89 years). There were 241 (36.8%) lobectomies or hemithyroidectomies, 409 (62.4%) near-total or total thyroidectomies, and five (0.8%) completion thyroidectomies. Of the 655 resections, 346 (52.8%) were malignant, including 304 (87.6%) PTCs, 31 (8.9%) FTCs, 5 (1.4%) medullary thyroid carcinomas, two (0.6%) anaplastic thyroid carcinomas, and four (1.2%) other types of malignancy. The four other malignancies included a poorly differentiated thyroid carcinoma, a biphasic synovial sarcoma, a low-grade B-cell lymphoproliferative disorder, and a metastatic breast carcinoma. Of the 304 PTCs, 135 (44.4%) were classical type, 119 (39.1%) were follicular variant, 23 (7.6%) were tall cell variant, and 27 (8.9%) were other variants. The mean size of malignant nodules was 2.2 cm (range 0.4–7.8 cm), with 307 (88.5%) ≥1 cm in size. The majority of the tumors that were <1 cm in size appeared over a 1 cm at time of ultrasound, though measured smaller upon histopathologic analysis. Of the 346 malignant cases, 85 (24%) of the tumors had lymphovascular invasion, 66 (19%) had extrathyroidal extension, and 212 (61.3%) had lymph nodes sampled. Sixty (28.3%) of those cases had positive lymph nodes and 152 (71.7%) had negative lymph nodes. Histologic review of all 119 FVPTCs revealed a total of 85 NFVPTCs, indicating that NFVPTCs accounted for 71.4% of FVPTCs (with FVPTCs that were either infiltrative or invasive accounting for 28.6%) and 24.6% of malignancies overall. In the NFVPTC subgroup there were 67 (78.8%) women and 18 (21.2%) men, with a mean age of diagnosis of 52 years at resection. The mean tumor size was 2.4 cm (range 0.5–6.5 cm), with 79 (92.9%) ≥1 cm in size. Of 85 NFVPTC cases, 39 (45.9%) had lymph nodes sampled, with 38 (97.4%) cases with negative nodes and only one (2.6%) case with positive lymph nodes. The one case with positive lymph nodes harbored a separate classical PTC in the other lobe that was not diagnosed on FNAs preceding the thyroidectomy. The lymph node metastases had a classical morphology similar to the separate classical PTC and morphologically distinct from the NFVPTC. The lack of lymph node metastases associated with NFVPTC corroborates previous findings that these are indolent tumors that do not metastasize.

### *FNA diagnoses, correlation with histologic findings, and rates of malignancy for each FNA diagnostic category*

The FNA diagnoses, correlation with histologic findings, and rates of malignancy for each FNA diagnostic category are summarized in Tables 1 and 2. Of the 655 FNAs, 53 (8.1%) were ND, 167 (25.5%) were benign, 97 (14.8%) were AUS/FLUS, 88 (13.4%) were SFN, 94 (14.4%) were SUS, and 156 (23.8%) were POS. The risk of malignancy calculated for each FNA diagnostic category was as follows: ND, 18.9%; benign, 13.2%; AUS/FLUS, 39.2%; SFN, 45.5%; SUS, 87.2%; and POS, 98.7%. NFVPTVs accounted for one (11.1%) of the malignant tumors in the ND category, 13 (59.1%) in the benign category, 17 (43.6%) in the AUS/FLUS category, seven (17.5%) in the SFN category, 39 (47.6%) in the SUS category, and eight (5.2%) in the POS category. The risk of malignancy for each FNA diagnostic category if NFVPTCs were not considered malignant would be as follows: ND 17.0% (a 10% relative decrease), benign 5.4% (a 59% relative decrease), AUS/FLUS 21.6% (a 45% relative decrease), SFN 37.5% (an 18% relative decrease), SUS 45.7% (a 48% relative decrease), and POS 93.6% (a 5% relative decrease).

In order to further evaluate the high rate of malignancy for the benign category, we determined the total number of FNAs diagnosed as benign during our study period. There were 2279 benign FNAs during the study period, 167 (7.3%) of which were followed by resection. Twenty-two of these cases were malignant at resection, resulting in a 0.97% (22/2279) rate of malignancy, a number well within the 0%–3% accepted rate of malignancy for the benign category. The malignancies that were preceded by a benign FNA diagnosis

Table 1. Histologic Versus Fine-Needle Aspiration Diagnoses

| *Histologic diagnosis* | *Nondiagnostic* | *Benign* | *AUS/FLUS* | *SFN* | *SUS* | *POS* | *Total* |
|---|---|---|---|---|---|---|---|
| Benign | 43 | 145 | 59 | 48 | 12 | 2 | 309 |
| Anaplastic thyroid carcinoma | 0 | 0 | 0 | 0 | 0 | 2 | 2 |
| Medullary thyroid carcinoma | 0 | 0 | 0 | 0 | 1 | 4 | 5 |
| Follicular carcinoma | 2 | 2 | 8 | 18 | 0 | 1[a] | 31 |
| Other malignancies | 0 | 1 | 0 | 0 | 1 | 2 | 4 |
| Papillary thyroid carcinoma | 8 | 19 | 30 | 22 | 80 | 145 | 304 |
| Classical variant | 2 | 1 | 5 | 3 | 20 | 104 | 135 |
| Follicular variant | 4 | 17 | 21 | 11 | 50 | 16 | 119 |
| Invasive/infiltrative FVPTC | 3 | 4 | 4 | 4 | 11 | 8 | 34 |
| NFVPTC | 1 | 13 | 17 | 7 | 39 | 8 | 85 |
| Tall cell variant | 0 | 0 | 1 | 2 | 3 | 17 | 23 |
| Other variants | 2 | 1 | 3 | 6 | 7 | 8 | 27 |

[a]The one follicular carcinoma that was diagnosed as positive on FNA was an oncocytic follicular carcinoma that was diagnosed as positive for papillary thyroid carcinoma on the preceding FNA.

AUS/FLUS, atypia/follicular lesion of undetermined significance; FNA, fine-needle aspiration; POS, malignant; FVPTC, follicular variant papillary thyroid carcinoma; NFVPTC, noninvasive follicular variant of papillary thyroid carcinoma; SFN, suspicious for follicular neoplasm; SUS, suspicious for malignancy.

Table 2. Fine-Needle Aspiration Diagnostic Categories

| *FNA diagnosis* | *Total cases (%)* | *Benign diagnoses* | *Malignant diagnoses* | *NFVPTC diagnoses* | *% ROM* | *% ROM if NFVPTCs nonmalignant* | *% Absolute decrease in ROM* | *% Relative decrease in ROM* |
|---|---|---|---|---|---|---|---|---|
| Nondiagnostic | 53 (8.1) | 43 | 10 | 1 | 18.9 | 17.0 | 1.9 | 10 |
| Benign[a] | 167 (25.5) | 145 | 22 | 13 | 13.2 | 5.4 | 7.8 | 59 |
| AUS/FLUS[b] | 97 (14.8) | 59 | 38 | 17 | 39.2 | 21.6 | 17.6 | 45 |
| SFN | 88 (13.4) | 48 | 40 | 7 | 45.5 | 37.5 | 8.0 | 18 |
| SUS | 94 (14.4) | 12 | 82 | 39 | 87.2 | 45.7 | 41.5 | 48 |
| POS | 156 (23.8) | 2 | 154 | 8 | 98.7 | 93.6 | 5.1 | 5 |
| Total | 655 | 309 | 346 | 85 | 52.8 | 39.8 | 13.0 | 25 |

The table includes the number of benign, malignant, and NFVPTC cases in each FNA diagnostic category, the risk of malignancy (ROM) given the current characterization of NFVPTC as carcinoma, the ROM if NFVPTC was not considered carcinoma, the resulting absolute decrease in ROM, and the resulting relative decrease in ROM.

[a]Referred for surgery because of large nodule size, compressive symptoms or suspicious clinical or sonographic findings.

[b]Referred for surgery because of persistent AUS/FLUS cytology, or suspicious clinical or sonographic findings.



included 17 FVPTCs (including 13 NFVPTCs), two FTCs, one classical PTC, one solid variant of PTC, and one poorly differentiated thyroid carcinoma. While it is not surprising that a small number of FVPTCs and FTCs may appear benign on cytology (due to a variable distribution of nuclear features of PTC in the case of FVPTCs and due to areas of macrofollicular architecture in the case of FTCs), the benign FNA diagnoses preceding the solid and classical PTCs and the poorly differentiated thyroid carcinoma were unexpected. Review of the slides of the classical PTC (measuring 5.0 cm) revealed that although the tumor had over 1% papillary architecture, the architecture was predominantly follicular including large macrofollicular areas (Supplementary Figure S1; Supplementary Data are available online at www.liebertpub.com/thy). Thus, the preceding benign FNA likely sampled these macrofollicular areas. The poorly differentiated carcinoma was a large (6.0 cm) tumor with a poorly differentiated component arising in a background of a well-differentiated thyroid carcinoma. Again, the result of the preceding FNA likely represents a sampling error within a large heterogeneous tumor. The explanation for the preceding benign cytology for the solid variant of PTC is less clear, though sampling error is still the most likely explanation.

Due to the high number of cases of NFVPTC that were diagnosed as SUS on preceding cytology, we retrospectively compared the histopathologic features of the group of NFVPTCs preceded by a SUS diagnosis and those preceded by a benign, AUS/FLUS, or SFN diagnosis. While we found no difference in the size of tumor for the two groups ($p = 0.45$), significantly more NFVPTCs preceded by a SUS diagnosis on FNA had overt nuclear features of PTC compared with NFVPTCs preceded by a benign, AUS/FLUS, or SFN diagnosis ($p = 0.0271$). Additionally, there was a trend for NFVPTCs with a preceding SUS diagnosis to have more diffuse nuclear features of PTC ($p = 0.1046$).

## Discussion

Not only has there been an increase in PTC in recent decades, but there has been an increase in the percentage of PTCs that are FVPTC (12). Jung and colleagues reported that FVPTCs accounted for 10% of all PTCs diagnosed at the University of Pittsburgh between 1974 and 1985 (with classical PTC accounting for 52%), but for 25% of PTCs diagnosed in 2009 (with classical PTCs accounting for 19%, and the bulk of the remaining tumors classified as microcarcinomas) (12).

FVPTC has been found to have clinical and molecular characteristics intermediate between classical type PTC and FTC. In a population-based study of roughly 36,000 cases of thyroid carcinomas over 1 cm recorded in the Surveillance, Epidemiology and End Results (SEER) database between 1988 to 2007, Yu *et al*. (13) found that there were approaching 22,000 classical type PTCs, 11,000 FVPTCs, and 4000 FTCs. When they compared the behavior of the three groups, they found that extrathyroidal extension and lymph node metastases were more common in FVPTC than in FTC, but significantly less frequent than in classical type PTC. Thus, they concluded that FVPTC has features between that of classical type PTC and FTC. Molecular evaluation of FVPTC has demonstrated similar findings. The $BRAF^{V600E}$ mutation is the most common mutation in classical PTC with *RET/PTC* rearrangements seen at a lower frequency; in contrast, *RAS* mutations and *PAX8/PPARγ* rearrangements are the most frequent alterations associated with FTC (14–17). While FVPTCs have frequent *RAS* mutations and can harbor *PAX8/PPARγ* rearrangements, some have the $BRAF^{V600E}$ mutation or a *RET/PTC* rearrangement, albeit at a much lower frequency than classical type PTC (6,14,18–22). In the past decade it has become clear that not all FVPTCs are biologically alike. FVPTCs with an infiltrative growth pattern, which account for roughly 20% of FVPTCs, are associated with frequent lymph node metastases and a risk of recurrence (2,3,23). Additionally, about a quarter of infiltrative FVPTCs harbor the $BRAF^{V600E}$ mutation and a small percentage have a *RET/PTC* rearrangement (6). In contrast, encapsulated or partially-encapsulated/well-circumscribed FVPTCs with no associated capsular penetration or lymphovascular invasion (i.e., NFVPTCs) have virtually no metastatic potential or risk of recurrence, and most groups have shown that they are associated with *RAS* mutations and *PAX8/PPARγ* rearrangements, but lack the $BRAF^{V600E}$ mutation (2,3,5,6). Thus, it is likely that infiltrative FVPTCs are contributing to the classical PTC-like clinical and molecular features of FVPTC; whereas the NFVPTCs are more akin to follicular adenomas and FTCs, with invasion determining the clinical course.

Due to the large number of PTCs being diagnosed, the high percentage of PTCs that are FVPTCs, and the fact that most

FVPTCs are NFVPTCs, identifying these tumors as indolent has significant clinical implications. As a result, endocrine pathologists are currently questioning whether these tumors warrant a diagnosis of carcinoma. If NFVPTCs are no longer termed carcinomas, this will impact the rates of malignancy for FNA diagnostic categories. The aim of this study was to determine the magnitude of that impact.

In our evaluation of 655 consecutive FNAs with subsequent resection specimens, we found that the rates of malignancy would drop for each FNA diagnostic category if NFVPTCs were no longer termed carcinomas, with a striking relative decrease of 45% and 48% seen in the AUS/FLUS and SUS categories, respectively. The rates of malignancy for many of the FNA diagnostic categories in our study may appear high compared to the rates initially put forth for the Bethesda classification system (9). In part, this is a reflection of selection bias since most nodules interpreted as ND or benign and many diagnosed as AUS/FLUS are not resected unless there are suspicious clinical or sonographic findings or there is a persistent ND or a repeat AUS/FLUS on FNA. Thus, it is not surprising that a substantially higher rate of malignancy was detected in these diagnostic categories. Due to the high rate of malignancy for the benign category, we evaluated the rate of malignancy based on the number of malignant resections following a benign FNA result and the total number of benign FNAs during our study period, including those that were not followed by surgery. There were a total of 2279 benign FNAs during our study period and only 22 cases diagnosed as malignant at resection, resulting in a 0.97% rate of malignancy, a number well within the 0%–3% accepted rate of malignancy for the benign category. The higher rates of malignancy, especially for the AUS/FLUS and SUS categories, likely also reflect the increase in diagnosis of FVPTC in the past three decades (12). For example, in two of the studies cited in determining risks of malignancy for the Bethesda diagnostic categories, the data were from1980–1997 and 1995–2004 (23,24). In the study by Jung *et al*. (12), the percentage of FVPTCs in 2000 was 13% (with classical at 38%) while in 2009 the percentage of FVPTCs was virtually double at 25% (with classical at 19%). The increase in diagnosis of FVPTC likely also occurred at our institution (and others) at roughly the same time. In fact, our rate of malignancy for the AUS/FLUS category is similar to that reported previously by our group (with data generated from patients evaluated between 2005 and 2009) (26) and reported by others including the groups at Memorial Sloan-Kettering Cancer Center (analyzing data from 2008 to 2011), Yale (with data from 2008), and Beth Israel Deaconess Medical Center (with data from 2006 to 2008) (27–29). Similarly, our rate of malignancy for the SUS category is also comparable to these groups (28,29).

While we acknowledge the selection bias reflected in some of our results, the results still have significant clinical implications. For example, for a nodule with an AUS/FLUS FNA diagnosis that has worrisome clinical and/or sonographic features (i.e., a nodule that would prompt surgical resection), the upper estimate of the risk of malignancy is approximately 40%. If NFVPTC was no longer considered malignant, the chance that this nodule would be malignant at resection would be expected to drop by half, to almost 20%. In other words, the results of our study are directly applicable to the select group of patients with an AUS/FLUS diagnosis that have been advised to undergo surgical resection. Because a diagnosis of SFN, SUS, or malignant on cytology results in surgical resection, our results for these categories lack the selection bias described for AUS/FLUS. For the malignant category, because the reported risk of malignancy is so high (97%–99%), a subsequent malignant diagnosis on surgical resection is expected. If NFVPTC was not considered malignant, while the vast majority (roughly 94%) of nodules with a malignant diagnosis on FNA would still be malignant at resection, a few would not. This is an important piece of data for clinicians and patients to have. Perhaps the most significant finding of our study concerns the SUS category. Many nodules with a SUS diagnosis on FNA go directly to total or near-total thyroidectomy. Because NFVPTC has been shown to be an extraordinarily indolent tumor, lobectomy only has been advised (2). We found that NFVPTC accounts for 48% of malignant cases in the SUS category. This means in almost half of cases with a SUS diagnosis on FNA, lobectomy and not total thyroidectomy might be the best surgical approach. Thus, this result has significant clinical implications that need to be further evaluated.

If the current terminology were changed and NFVPTCs were no longer termed carcinomas, the risk of malignancy for a SUS diagnosis on cytology in our cohort would decrease nearly 50%. Although this finding has significant implications, it must be noted that these findings are specific for our institution. Because the decrease in the risk of malignancy depends on the prevalence of the diagnosis of FVPTC, and FVPTC is known to be a diagnosis with low interobserver reproducibility (23,30), it is essential that additional studies are performed at other institutions. The magnitude of the impact will vary, and the biggest impact will be seen at institutions where the rate of diagnosis of FVPTC is the highest. Nonetheless, if NFVPTC were no longer termed carcinoma, the rates of malignancy for each Bethesda diagnostic category would universally drop to some extent. In this altered scenario, molecular testing to identify patients at greatest risk of clinically significant disease could become increasingly important. At the same time, reclassification of NFVPTCs could also prompt cytopathologists to refine cytologic criteria to shift these tumors into lower risk diagnostic categories that are treated with lobectomy only.

## Authors Disclosure Statement

No competing financial interests exist for any of the authors.

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