Suggesting the Cytologic Diagnosis of Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features (NIFTP): A Retrospective Analysis of Atypical and Suspicious Nodules

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BACKGROUND: The term “noninvasive follicular thyroid neoplasm with papillary-like nuclear features” (NIFTP) has replaced a subset of follicular variant of papillary thyroid carcinoma due to the indolent behavior of such tumors. NIFTPs are most often classified in an “indeterminate” diagnostic category. In the current study, the authors sought to identify cytologic features helpful in distinguishing NIFTP from other entities in these categories, particularly benign nodules.

METHODS: The authors retrospectively evaluated a consecutive cohort of 130 thyroid fine-needle aspiration (FNA) specimens with an indeterminate diagnosis and available histopathologic follow-up. All FNA specimens were evaluated using the ThinPrep method. Each FNA was blindly reviewed by 2 board-certified cytopathologists, who assessed overall cellularity; architectural parameters; and nuclear features, including nuclear pallor and fine chromatin, distinct nucleoli, and irregular nuclear membranes. Each case received a score of 0 to 3, based on the presence or absence of these 3 nuclear features.

RESULTS: Nuclear but not architectural features appeared to distinguish NIFTP from benign nodules. Ninety-one percent of the NIFTPs (32 of 35 NIFTPs) received a score of ≥2, compared with 35% of benign nodules (23 of 66 benign nodules) (P < .0001). In contrast, NIFTP could not be differentiated from the invasive/infiltrative follicular variant of papillary thyroid carcinoma using these criteria (P ≥ 1.000). Nuclear scoring was found to be especially useful in atypia of undetermined significance/follicular lesion of undetermined significance (AUS); a score ≥2 enriched for NIFTP (39% vs 3% of AUS cases with a score < 2), whereas a score < 2 was more likely benign (85% vs 50% of AUS cases with a score ≥ 2).

CONCLUSIONS: In indeterminate FNA specimens, the distinction of a possible NIFTP from a benign thyroid nodule can be suggested using a simple nuclear scoring system that is most valuable in AUS aspirates. Cancer Cytopathol 2017;000:000-000. © 2017 American Cancer Society.

KEY WORDS: Bethesda; fine-needle aspiration; follicular neoplasm; follicular variant; noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP); papillary carcinoma; thyroid cancer; thyroid cytology.

INTRODUCTION

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) comprises a substantial subset of thyroid tumors previously classified as malignant. This terminology was proposed by Nikiforov et al for many tumors previously classified as encapsulated or noninvasive follicular variant of papillary thyroid carcinoma (FVPTC) to recognize the extremely low risk of adverse outcomes for patients with these tumors and to reduce the psychological and clinical consequences of a cancer diagnosis for these individuals.1 Surgical management by lobectomy or hemithyroidectomy is warranted for patients with NIFTP for 2 main reasons: 1) histologic...
evaluation is necessary to exclude an invasive/infiltrative FVPTC (IFVPTC) or other type of thyroid carcinoma; and 2) NIFTP may represent a significant precursor lesion to thyroid malignancy. In addition, more experience with the long-term follow-up of patients diagnosed with NIFTP is needed to confirm and further characterize the indolent behavior of these tumors.

Ultrasound-guided fine-needle aspiration (FNA) is the preoperative test of choice for the diagnosis of nontoxic thyroid nodules, and The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) is the most widely accepted terminology for reporting results. Although retrospective studies have shown that NIFTP can be preceded by any of the 6 categories of TBSRTC, NIFTP most often is associated with the 3 so-called “indeterminate” categories: 1) atypia of undetermined significance/follicular lesion of undetermined significance (AUS); 2) suspicious for follicular neoplasm/follicular neoplasm (SFN); and 3) suspicious for malignancy (SUS). In a recently published prospective study, we demonstrated that NIFTP and FVPTC can be reliably distinguished from classic papillary thyroid carcinoma (PTC) based on a novel evaluation of cytologic features such as microfollicular predominance, nuclear pseudo-inclusions, psammomatous calcifications, and papillae. The distinguishing features between NIFTP and classic PTC typically are appreciated in aspirates that are classified either as SUS or malignant by cytologic assessment. We anticipate that identifying NIFTP in FNA specimens with less concerning features for PTC overall, such as those in the AUS and SFN categories, may require a different set of cytologic criteria.

In the current study, we retrospectively examined a consecutive series of indeterminate thyroid FNA specimens with known histologic outcome, including NIFTP, to characterize cytologic features that could be useful in distinguishing NIFTP from other entities with indeterminate cytologic diagnoses, particularly benign thyroid nodules.

MATERIALS AND METHODS

Case Selection

As previously described, the pathology database at Brigham and Women’s Hospital was searched to identify all consecutive thyroidectomy specimens resected between August 2010 and May 2012. For each case, all surgical pathology reports were reviewed, and the surgical pathology and cytologic diagnoses were recorded. All hematoxylin and eosin-stained slides for specimens diagnosed as FVPTC were reviewed by 2 pathologists (J.A.B. and B.E.H.) at a multihheaded scope to identify cases of NIFTP. Tumors in this group fulfilled all published criteria for NIFTP, with the entire capsule of the lesion having been examined histologically.

Cytologic Review and Data Acquisition

Cytologic diagnoses were matched to each surgical pathology diagnosis, and cases with a preceding cytologic diagnosis of AUS, SFN, or SUS were identified. All such cases from this time period were reviewed if material was available. Liquid cytology preparations (ThinPrep; Hologic, Marlborough, Massachusetts) from these thyroid FNA specimens were re-reviewed by 2 board-certified cytopathologists with expertise in thyroid FNA, each with >20 years of experience (E.S.C. and J.F.K.). The reviewing cytopathologists were blinded to both the original cytologic diagnosis (albeit aware that the diagnosis was one of AUS, SFN, or SUS) and the surgical pathology findings. For each case, the pathologists semi-quantitatively scored the specimen for overall cellularity (<20, 20-50, or >50 groups), architectural characteristics, and cytologic features. Architectural characteristics included an evaluation of the percentage architectural change/atypia (0%, 1%-25%, 25%-50%, or >50%), which was an estimate of the amount of microfollicular, trabecular, or crowded 3-dimensional groups within the specimen. Cytologic characteristics included an assessment of pseudo-inclusions (none, 1-2, or ≥3 in total), pale nuclei with fine chromatin (0%, 1%-25%, 25%-50%, or >50%), distinct nucleoli (0%, 1%-25%, 25%-50%, or >50%), and irregular nuclear membranes (0%, 1%-25%, 25%-50%, or >50%). Other assessments included Hurthle cell change, cyst-lining cells, hemosiderin-laden macrophages, background lymphocytes, and multinucleated giant cells. The pathologists provided an overall impression that the nodule was or was not a potential NIFTP. A composite numerical score of 0 to 3 was assigned to each case based solely on the presence or absence of nuclear features (ie, pale nuclei, distinct nucleoli, and irregular nuclear membranes). For each feature, a score of 1 was given if both cytopathologists recorded it as present in at least 1% to 25% of nuclei.

Statistical Analysis

The Pearson chi-square test was used to evaluate sets of categorical data, and a significance level of .05 was considered...
to be statistically significant. SPSS statistical software (version 24; IBM Corporation, Armonk, New York) was used to analyze the data.

RESULTS

Patient Demographics
The study cohort included 130 FNA specimens with indeterminate cytology and subsequent surgical resection obtained from 112 patients (87 women and 25 men) with 115 nodules. The average age of the patients was 52 years. Lymph nodes were sampled in 8 cases, and 2 positive lymph node metastases were recorded (1 from a case of tall cell variant of PTC with 2 NIFTPs in the contralateral lobe, and the other associated with multifocal IFVPTC).

Cytologic and Histologic Diagnoses
During the study period, there were 2523 thyroid FNA specimens, with 403 (16.0%) classified as nondiagnostic, 1603 (63.5%) classified as benign, 234 (9.3%) classified as AUS, 57 (2.3%) classified as SFN, 39 (1.5%) classified as suspicious for a Hurthle cell neoplasm, 76 (3.0%) classified as SUS, and 110 (4.4%) classified as malignant diagnoses. A single case was termed “neoplastic cells present.” Cytologic diagnoses with surgical follow-up included 62 AUS cases (48%), 30 SFN cases (23%), and 38 SUS cases (29%). The 62 AUS diagnoses included 15 nodules that were aspirated twice, with an AUS diagnosis reached for both the initial and repeat specimens. Pathologic evaluation of 115 nodules demonstrated benign histology in 56 cases (49%), NIFTP in 31 cases (27%), follicular carcinoma in 9 cases (8%), IFVPTC in 8 cases (7%), and other types of PTC in 11 cases (10%; including 7 classic, 1 solid, 1 tall cell, and 2 variant not otherwise specified). Benign histologic diagnoses included nodular hyperplasia (29 cases), adenomatous nodule (15 cases), follicular adenoma (8 cases), hyperplastic nodule (3 cases), and lymphoepithelial cyst (1 case). The distribution of cytologic diagnoses for each histologic category is summarized in Table 1.

Evaluation of Thyroid Aspirates for Study Criteria
The histologic diagnosis of NIFTP is defined by the presence of a follicular patterned lesion with nuclear features of PTC, although prior experience has indicated that nuclear pseudoinclusions typically are absent or infrequent.4,5 Accordingly, we evaluated the presence and extent of the following nuclear characteristics associated with PTC: pale nuclei with fine chromatin, distinct nucleoli, nuclear membrane irregularity, and nuclear pseudoinclusions. Compared with FNA specimens from benign nodules, NIFTP was associated with the presence of pale nuclei (P < .0001), distinct nucleoli (P < .0001), and irregular nuclear membranes (P < .0001) (Figs. 1A-1C). FNA specimens of benign entities often demonstrated architectural atypia (Fig. 1D), and this feature did not aid in the distinction between a benign diagnosis and NIFTP (P = .301). Similarly, other parameters did not correlate with a diagnosis of NIFTP (P > .05), including cellularity; a noncohesive, isolated follicular cell pattern; clusters of ≥3 microfollicles; Hurthle cell change; noncohesive Hurthle cells; cyst-lining cells; hemosiderin-laden macrophages; lymphocytes; and multinucleated giant cells.

Benign nodules with indeterminate diagnoses frequently had architectural alterations but lacked nuclear atypia (Fig. 2A). Nuclear atypia was noted in a minority of benign cases (Fig. 2B), but was typically present to a lesser extent compared with NIFTP cases (Fig. 2C). Only a single case of NIFTP demonstrated a rare pseudoinclusion (Fig. 2D).

A Composite 3-Point Nuclear Score Segregates NIFTP From Benign Nodules
For each case, we assigned a 3-point composite score based on the presence of 3 nuclear features (ie, pale nuclei, nucleoli, or membrane irregularities). For each characteristic, a single point was assigned if both reviewers recognized the feature in as little as 1% of follicular groups. A summary of the nuclear score for each category of histologic diagnosis is

TABLE 1. Cytologic Diagnoses for Each Type of Histologic Diagnosis

<table>
<thead>
<tr>
<th>Histologic Diagnosis</th>
<th>AUS</th>
<th>SFN</th>
<th>SUS</th>
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<tbody>
<tr>
<td>Benign</td>
<td>43 (33%)</td>
<td>16 (12%)</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>NIFTP</td>
<td>12 (9%)</td>
<td>2 (2%)</td>
<td>21 (16%)</td>
</tr>
<tr>
<td>Follicular carcinoma</td>
<td>4 (3%)</td>
<td>5 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>IFVPTC</td>
<td>2 (2%)</td>
<td>5 (4%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Other PTC</td>
<td>1 (1%)</td>
<td>4 (3%)</td>
<td>6 (5%)</td>
</tr>
</tbody>
</table>

Abbreviations: AUS, atypia of undetermined significance/follicular lesion of undetermined significance; IFVPTC, invasive/infiltrative follicular variant of papillary thyroid carcinoma; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma; SFN, suspicious for a follicular neoplasm/follicular neoplasm; SUS, suspicious for malignancy.

*Includes 10 benign nodules, 4 NIFTP nodules, and 1 FVPTC nodule diagnosed as AUS on both an initial and repeat aspiration.
summarized in Table 2. NIFTP was associated with a higher nuclear score (Fig. 3A), with 32 of 35 of all NIFTP cases (91%) receiving a score of ≥2. In contrast, only 23 of 66 benign nodules (35%) had a score of ≥2. Using a score of ≥2 to segregate NIFTP from benign nodules was found to have a relatively high sensitivity (0.91) and negative predictive value (0.93), but demonstrated a low specificity (0.65) and positive predictive value (0.58). The correlation of nuclear score with NIFTP held even for sparsely cellular aspirates with <20 follicular groups (P < .001). It is interesting to note that NIFTP could not be differentiated from IFVPTC using the 3-point score criteria (P = 1.000). In contrast, the consensus impression of the reviewing cytopathologists regarding whether NIFTP was favored had greater specificity (0.97) but lower sensitivity (0.31) (Fig. 3B). The reviewers demonstrated fair agreement with regard to favoring NIFTP (kappa, 0.39).

To further assess the usefulness of the nuclear scoring system, the data were evaluated according to both the original cytologic classification and the reviewers’ nuclear score in comparison with the histologic diagnosis (Table 3). Unsurprisingly, 37 of 38 SUS cases (97%) had a nuclear score of ≥2, reflecting the presence of features deemed suspicious for PTC by the original cytologic interpretation. In contrast, the majority of SFN cases had a nuclear score of <2 (25 of 30 cases; 83%). Unlike either the SUS or SFN specimens, aspirates originally diagnosed as AUS were nearly equally divided between those with nuclear scores of <2 (34 of 62 cases; 55%) and ≥2 (28 of 62 cases; 45%). The AUS cases with a nuclear score of ≥2 were more likely to be NIFTP (11 of 28 cases; 39%) compared with those with a nuclear score of ≤2 (1 of 34 cases; 3%). AUS aspirates with a nuclear score of <2 also were found to be more likely to be benign (29 of 34 cases; 85%) compared with those with a nuclear score of ≥2 (14 of 28 cases; 50%). In comparison with the SFN/SUS cases with a nuclear score of ≥2, the AUS cases with a nuclear score of ≥2 were significantly less cellular (P = .001). In general, cases with an AUS diagnosis had significantly less cellularity than cases with a diagnosis of SFN/SUS (P < .0001).

**DISCUSSION**

The proposed reclassification of a subset of thyroid tumors previously classified as FVPTC as NIFTP is based on the indolent clinical course of such neoplasms. Nevertheless, surgical resection, usually by lobectomy/hemithyroidectomy, remains the standard of care for such tumors. Just as
surgical pathology evaluation is needed to distinguish follicular carcinoma from follicular adenoma, so too is historical examination necessary to distinguish NIFTP from IFVPTC (or, less frequently, other thyroid malignancies).

To the best of our knowledge, criteria for recognizing potential NIFTP on cytologic material have not been established to date. Previously, we demonstrated that for aspirates with prominent nuclear features of PTC (those diagnosed as malignant or SUS), NIFTP usually can be distinguished from classic PTC in the preoperative setting. This is a potentially important distinction because total thyroidectomy often is the preferred management for patients with a malignant cytologic diagnosis, making it desirable to minimize classifying likely NIFTP cases as

### TABLE 2. Nuclear Scores of Each Category of Histologic Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Nuclear Score</th>
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<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Benign</td>
<td>29 (22%)</td>
</tr>
<tr>
<td>NIFTP</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Follicular carcinoma</td>
<td>7 (5%)</td>
</tr>
<tr>
<td>IFVPTC</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other PTC</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>38 (29%)</td>
</tr>
</tbody>
</table>

Abbreviations: IFVPTC, invasive/infiltrative follicular variant of papillary thyroid carcinoma; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma.

Figure 2. Cytologic features of benign nodules and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). (A) Histologically benign nodule. This follicular group illustrates a microfollicular pattern lacking the cytologic features of NIFTP. (B) Histologically benign nodule. In a few cases, histologically benign nodules exhibited groups with fine chromatin and irregular nuclear contours. (C) NIFTP. Groups tended to demonstrate pale nuclei with fine chromatin, nuclear membrane irregularities, and distinct nucleoli. (D) NIFTP. Only a single case of NIFTP demonstrated a rare nuclear pseudoinclusion (arrow).
malignant. Examination of liquid-based thyroid FNA preparations for papillae, psammomatous calcifications, and nuclear pseudoinclusions successfully distinguishes classic PTC from potential NIFTP in the majority of cases. Other authors have found that the cytologic overlap between NIFTP and IFVPTC precludes the reliable distinction of these entities on cytologic material alone, and the data from the current study support this conclusion.

Thyroid FNA specimens of NIFTP and benign lesions are similar in that they lack papillae, psammomatous calcifications, or frequent nuclear pseudoinclusions. Therefore, in the indeterminate categories (AUS, SFN, and SUS), in which the majority of NIFTP aspirates are identified, other criteria are needed to recognize NIFTP and distinguish it from benign lesions. The objective of the current study was to catalogue the features of indeterminate thyroid FNA specimens to assess whether criteria can be established to distinguish NIFTP reliably from other entities, particularly benign nodules, identified in these diagnostic categories.

Overall, the results of the current study indicate that a limited set of cytologic features is associated with a likely histologic diagnosis of NIFTP. Architectural alterations, such as a predominantly microfollicular growth pattern, overlap significantly with follicular adenoma and other benign thyroid nodules and were not found to be helpful in identifying potential cases of NIFTP. In contrast, nuclear features typically associated with PTC were helpful in distinguishing potential NIFTP from benign nodules within the indeterminate categories. Using a 3-point nuclear scoring system, based on the features of nuclear pallor, distinct nucleoli, and nuclear membrane irregularities, NIFTP could be frequently distinguished from benign lesions. As a practical matter, nuclear features

**Figure 3.** The composite nuclear score is a more sensitive indicator of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) than the impression of cytopathologists. (A) NIFTP and benign lesions were scored using a 3-point composite nuclear scoring system. (B) Reviewers provided their overall impression of whether they favored a diagnosis of NIFTP (“yes” column) or not (“no” column). The consensus impression of the reviewers was specific but had low sensitivity (sensitivity of 0.31, specificity of 0.97, positive predictive value of 0.85, and negative predictive value of 0.73). In contrast, using a threshold of ≥2, the 3-point nuclear scoring system was found to be sensitive for identifying potential cases of NIFTP but with less specificity (sensitivity of 0.91, specificity of 0.65, positive predictive value of 0.58, and negative predictive value of 0.93).

**TABLE 3.** Cytologic Diagnoses and Nuclear Score With Respect to Histologic Diagnosis

<table>
<thead>
<tr>
<th>Original Cytologic Diagnosis</th>
<th>Nuclear Score</th>
<th>Benign</th>
<th>NIFTP</th>
<th>FC</th>
<th>IFVPTC</th>
<th>PTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUS</td>
<td>0-1</td>
<td>29 (85%)</td>
<td>1 (3%)</td>
<td>3 (9%)</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>14 (50%)</td>
<td>11 (30%)</td>
<td>1 (4%)</td>
<td>2 (7%)</td>
<td>0</td>
</tr>
<tr>
<td>SFN</td>
<td>0-1</td>
<td>14 (56%)</td>
<td>2 (8%)</td>
<td>5 (20%)</td>
<td>0</td>
<td>4 (16%)</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>2 (40%)</td>
<td>0</td>
<td>3 (60%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SUS</td>
<td>0-1</td>
<td>7 (19%)</td>
<td>21 (67%)</td>
<td>0</td>
<td>4 (11%)</td>
<td>1 (100%)</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5 (13%)</td>
</tr>
</tbody>
</table>

Abbreviations: AUS, atypia of undetermined significance/follicular lesion of undetermined significance; FC, follicular carcinoma; IFVPTC, invasive/infiltrative follicular variant of papillary thyroid carcinoma; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid carcinoma; SFN, suspicious for a follicular neoplasm/follicular neoplasm; SUS, suspicious for malignancy.
associated with PTC were nearly universally present in aspirates initially diagnosed as SUS in the current series and were uncommon in aspirates diagnosed as SFN. By contrast, using a nuclear score of ≥2 divided AUS cases nearly equally into those with cytologic atypia (nuclear score of ≥2), which were highly associated with NIFTP, and those cases lacking cytologic atypia (nuclear score of <2), which were highly associated with a benign histologic outcome. Therefore, it is within the setting of a potential AUS diagnosis in which nuclear scoring can be of the most use for subclassification and risk stratification purposes. Several studies have demonstrated that malignancy risk differs according to the nature of the pattern of AUS identified, with cytologic atypia having the highest risk of malignancy.10–18:1,2 These studies predate the introduction of NIFTP terminology, and the current study cohort of AUS cases with cytologic atypia suggests that many such cases would be reclassified as NIFTP.

We noted that the nuclear scoring system performed well in specimens with low cellularity and that the AUS specimens in the current study were less cellular overall than the SFN and SUS specimens. Therefore, the data from the current study suggest that in challenging specimens with overall low cellularity or infrequent atypical cells, emphasis should be placed on assessing the nuclear features outlined in the scoring system we have described to successfully separate aspirates with a high probability of being benign from those for which a diagnosis of NIFTP is more likely.

The findings of the current study are in agreement with what to our knowledge are the limited studies regarding distinguishing the cytologic features of NIFTP from those of benign nodules.8,9 In a report of the cytologic parameters of NIFTP and benign follicular lesions, Maletta et al demonstrated that NIFTPs tend to demonstrate nuclear enlargement, nuclear membrane irregularities, ground-glass nuclei, and nuclear molding more often than benign lesions.8 Brandler et al found statistically significant differences in nuclear crowding, enlargement, and clearing in NIFTP compared with follicular adenomas.9 In the current study, we assessed nuclear crowding as a component of architectural atypia. Although we expected this parameter to act as a surrogate marker of nuclear enlargement, we did not observe a difference between NIFTP and benign nodules with regard to this characteristic. Similarly, the nuclear scoring system proposed for diagnosing NIFTP on histology by Nikiforov et al1 coincides to a large extent with the current study findings. There the criteria were based on: 1) nuclear size and shape (including nuclear enlargement and overlapping); 2) nuclear membrane irregularities; and 3) chromatin features.

Although not statistically significant, a strong trend toward prominent nucleoli in NIFTP (P = .077 per report) was observed by Maletta et al.8 In the current study, we asked the reviewers to document “distinct nucleoli,” which often were associated with NIFTP. Between our 2 reviewers, there often was disagreement regarding what constituted a distinct nucleolus (kappa, 0.16), which may explain the nonsignificant trend observed by Maletta et al.8 As shown in our example (Fig. 2C), nucleoli associated with NIFTP typically were diffusely present in the follicular cells and contrasted with the fine/pale nuclear chromatin.

The current study was a retrospective analysis performed at a single institution with several important limitations. Its findings were based on consensus review of liquid-based samples by 2 experienced cytopathologists at the same institution with particular interest in thyroid FNA. Other institutions and reviewers may have different thresholds for the criteria identified, and further studies may be necessary to assess the reliability of these parameters in both liquid-based and conventional smears. Similarly, it has been established that NIFTP cases are variably classified among the indeterminate categories in different laboratories.2,3,8 The original cytologic diagnoses in the current series predate the introduction of NIFTP, and it is possible that NIFTP could alter how the indeterminate categories are used in current clinical practice. Although surgical resections of FVPTC underwent slide review to generate the cohort of NIFTP cases in the current study, benign cases were not re-reviewed, and it is possible that some benign nodules would have been reclassified as NIFTP.

NIFTP often can be distinguished from benign nodules in indeterminate thyroid FNA specimens using the criteria of nuclear pallor, distinct nucleoli, and irregular nuclear membranes. Although any individual feature can be associated with benign nodules, the combined presence of these features favors NIFTP. Nevertheless, there remains some overlap of potential NIFTP cases with benign aspirates, and the criteria do not reliably distinguish NIFTP from IFVPTC or other PTCs. The findings of the current study indicate that close scrutiny of the nuclear features described above is most beneficial for subclassifying aspirates in the AUS category into those with cytologic atypia.
of greater concern for surgical disease (especially NIFTP) or those lacking cytologic atypia that are likely benign. The latter cases especially may benefit from molecular testing with the gene expression classifier test, which is more frequently benign in AUS cases lacking cytologic atypia. Conversely, although not all NIFTPs have been found to have molecular alterations, many are associated with RAS gene mutations, \textit{BRAF} \textit{K601E} mutations, and \textit{PPAR-\gamma} and \textit{THADA} gene fusions\textsuperscript{1,20–22} so that mutational testing may have added usefulness in AUS aspirates with cytologic atypia. In the future, as criteria for NIFTP are incorporated into \textit{TBSRTC}, it will be worthwhile to consider refinements to the indeterminate categories. Such refinements might help to distinguish among the risks associated with these differing patterns of atypia and thus help to risk stratify patients appropriately for management, whether it be surgery, molecular testing, repeat FNA, or clinical observation.

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**CONFLICT OF INTEREST DISCLOSURES**

The authors made no disclosures.

**AUTHOR CONTRIBUTIONS**

Kyle C. Strickland: Conceptualization, methodology, formal analysis, investigation, data curation, visualization, writing-original draft, writing-review and editing, and project administration. Brooke E. Howitt: Investigation, data curation, and writing-review and editing. Justine A. Barletta: Investigation, data curation, and writing-review and editing. Edmund S. Cibas: Conceptualization, methodology, investigation, writing-review and editing, and supervision. Jeffrey F. Krane: Conceptualization, methodology, investigation, writing-review and editing, supervision, and project administration.

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