Noninvasive Follicular Thyroid Neoplasm With Papillary-Like Nuclear Features (NIFTP): A Changing Paradigm in Thyroid Surgical Pathology and Implications for Thyroid Cytopathology

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INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common malignant tumor of the thyroid, and the most common subtypes of PTC are classic PTC and the follicular variant (FVPTC). Diagnosis of the former is based on the presence of papillary architecture and, later, on follicular growth pattern; both variants have diagnostic nuclear morphology. Two major subtypes of FVPTC have been described: infiltrative and encapsulated/well demarcated. When encapsulated FVPTC (EFVPTC) is invasive, it resembles follicular carcinoma (thick capsule, pushing invasion into the tumor capsule, and vascular invasion). In recent years, molecular profiling has indicated that indeed EFVPTC more closely resembles follicular adenoma/follicular carcinoma, whereas infiltrative FVPTC is similar to classic PTC.[1–4]

A subset of EFVPTC that lacks capsular or vascular invasion is still designated as cancer-based solely on its nuclear features; this "noninvasive" EFVPTC has proven to be the most controversial diagnosis in thyroid tumor pathology over the past few decades.[5,6] From its inception, equating this variant with other more overtly infiltrative thyroid cancers seemed counterintuitive. These tumors often exhibited borderline nuclear features, and there was considerable interobserver variability in diagnosis, even among thyroid pathology experts.[6] Emerging data documenting the indolent nature of noninvasive FVPTC have now lead some authors to propose that diagnosing these tumors as carcinoma does more harm than good, leading to excessive treatment, ie, total thyroidectomy radioiodine (RAI) ablation and thyroid-stimulating hormone suppression with levothyroxine.[2,7,8]

RENAMING NONINVASIVE FVPTC TO DEESCALATE TREATMENT—EVOLUTION OF A CONCEPT

Recently, a multidisciplinary endeavor, which included thyroid pathologists, endocrinologists, and an endocrine surgeon, was undertaken to address the important issue of over-diagnosing noninvasive FVPTC and to evaluate

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its current diagnosis. The pathology panel examined a total of 268 tumors that were diagnosed as EFVPTC based on current criteria. The case cohort was divided into 2 groups: group 1 included noninvasive EFVPTCs from patients who did not receive RAI treatment and had at least 10 years of follow-up (n = 138), and group 2 included EFVPTCs from patients who had vascular invasion and/or tumor capsule invasion and ≥1 year of follow-up (n = 130). Consensus diagnostic criteria for noninvasive EFVPTC were adopted after multiple reviews of the slides by the pathology panel and were applied to the contributed cases, producing an overall classification accuracy of 94%. Molecular analysis was performed on cases for which paraffin blocks were available.

After excluding cases that did not meet the consensus criteria, in group 1 (noninvasive EFVPTCs), 109 patients were followed for 10 to 26 years, and all were alive without evidence of disease. None of these patients received RAI ablation, and 67 underwent lobectomy only. In group 2 (invasive EFVPTCs), 101 patients were followed for 1 to 18 years, and 12% had adverse events, including 5 patients who developed distant metastases, 2 of whom died of disease. In the molecular analysis, none of the noninvasive EFVPTC cases harbored molecular alterations typically seen in classic PTC, such as *BRAF* v-Raf murine sarcoma viral oncogene homolog B (*BRAF*) valine-to-glutamic substitution at position 600 (V600E) mutations or Ret proto-oncogene tyrosine protein kinase receptor [*RET*] gene fusions. Rat sarcoma (*RAS*) gene mutations were present in 8 of 27 cases (30%), and peroxisome proliferated receptor receptor-γ (*PPARG*) or thyroid adenoma associated (*THADA*) gene fusions were present in additional 12 of 27 (44%) noninvasive tumors. These mutations are encountered in follicular-pattern thyroid tumors, including follicular adenoma, follicular thyroid carcinoma, and EFVPTC.

On the basis of the clinical outcome information for patients with noninvasive EFVPTC in this study, and after reviewing the literature, it is proposed that this tumor should be designated as "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP). This proposed reclassification will impact a large population of patients worldwide and result in significant reductions in the overtreatment and psychological and clinical consequences associated with the diagnosis of cancer.[9] This will also raise ethical issues of how to inform patients who have been rendered a malignant diagnosis based on a pathology that is now reclassified as NIFTP.

IMPACT ON CYTOPATHOLOGIC DIAGNOSIS

Fine-needle aspiration (FNA) is the commonly used modality for the preoperative testing of thyroid nodules. Currently, thyroid FNA specimens are classified into 6 diagnostic categories according to the The Bethesda System for Reporting of Thyroid FNA Cytology (TBSRTC): nondiagnostic, benign, atypia/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), suspicious for malignancy (SM), and malignant. Each diagnostic category is associated with a risk of malignancy (ROM) and a set of recommendations for clinical management.[10]

It is well known that thyroid FNA serves as a diagnostic test for the majority of benign nodules, most PTCs, and other carcinomas; however, for follicular-patterned lesions, FNA is best considered as a screening test. These lesions include follicular adenoma, follicular carcinoma, and an appreciable number of FVPTCs.[11] The limited accuracy of FNA cytology in this category of lesions is a result of similar and/or overlapping cytomorphologic features among these entities, particularly when the characteristic nuclear morphology of FVPTC is borderline or limited and, thus, subject to sampling error.[11,12] Various studies have demonstrated that the rate of a definitive diagnosis of FVPTC on thyroid FNA specimens is low, ranging from 9.8% to 37.5%.[11–16] During the past decade, it has been demonstrated that the implementation of molecular tests with high negative and/or positive predictive values enhance the identification of thyroid nodules that harbor malignancy.[17–19]

The ROM for each of the indeterminate categories in TBSRTC, with or without molecular refinement, has been predicated on the classification of noninvasive EFVPTC as malignancy. With the recently published NIFTP proposal, however, critical questions have been raised regarding how the change in terminology will impact the current practice of thyroid FNA cytology (specifically the ROM) and the management algorithm associated with each diagnostic category of TBSRTC. Data to address this issue are currently limited but have demonstrated a notable decrease in the ROM for the indeterminate diagnostic categories AUS/FLUS, FN/SFN, and SM but concurrently have demonstrated no appreciable change in the risk of malignancy for FNAs diagnosed as benign and malignant (Table 1).[20,21] These studies clearly indicate

TABLE 1. The Reported Impact of a Diagnosis of Noninvasive Follicular Tumor With Papillary-Like Nuclei on the Risk of Malignancy for Diagnostic Categories of The Bethesda System for Reporting Thyroid Cytopathology

	Faquin 2016[21a]				Strickland 2015[20]			
FNA Diagnosis	Total No. of Cases	% ROM	% ROM Excluding NIFTP	% Decrease in ROM	Total No. of Cases	% ROM	% ROM Excluding NIFTP	% Decrease in ROM
ND	70	25.3	23.9	1.4	53	18.9	17	1.9
Benign	426	9.3	5.8	3.5	167	13.2	5.4	7.8
AUS/FLUS	397	31.2	17.6	13.6	97	39.2	21.6	17.6
FN/SFN	304	33.2	18	15.1	88	45.5	37.5	8
SM	179	82.6	59.2	23.4	94	87.2	45.7	41.5
Malignant	450	99.1	95.7	3.3	156	98.7	93.6	5.1

Abbreviations: AUS/FLUS, atypical/follicular lesion of undetermined significance; FN/SFN, follicular neoplasm/suspicious for follicular neoplasm; FNA, fine-needle aspiration; ND, nondiagnostic; NIFTP, noninvasive follicular tumor with papillary-like nuclei; ROM, risk of malignancy; SM, suspicious for malignancy.
[a] This was a multi-institutional study.

that noninvasive EFVPTC comprises a significant proportion of malignant diagnoses associated with the indeterminate TBSRTC categories.

Unlike classic PTC, FVPTC may not demonstrate sufficient cytomorphologic features to be definitely classified as malignant on FNA.[11,15] A recent study by Howitt et al indicated that no noninvasive FVPTCs were classified as malignant on FNA,[22] whereas others observed that only a minor percentage was classified as malignant.[21,23] Based on these limited data, the magnitude of impact that a diagnosis of NIFTP will have on the ROM for TBSRTC categories cannot be predicted. The effects are likely to differ based on case demographics and the institutional frequency of rendering a surgical pathology diagnosis of noninvasive EFVPTC. What can be predicted is that the decrease in the ROM for the SM and malignant TBSRTC categories because of NIFTP may lead to a change in the management paradigm, specifically, the type of surgery (ie, lobectomy instead of total thyroidectomy), and may prevent further treatment, such as RAI ablation, as recommended by the American Thyroid Association for low-risk thyroid neoplasms.[24] In addition, the conservative approach to this low-risk tumor may prove to be cost effective in an era of shrinking health care spending.

Clearly one of the most important issues for our cytopathology colleagues is the inevitable increase in the "false-positive" rates and the possible medicolegal implications because of NIFTP diagnoses that are rendered for cases diagnosed as suspicious or compatible with PTC. This may be even more concerning, in that, currently, most clinicians will advise total thyroidectomy because of the high ROM associated with these cytologic diagnoses. The cytologic determination of these nuclear features mandates surgery to make a definitive histologic diagnosis of malignancy or NIFTP. The surgical decision making for unilateral versus bilateral thyroidectomy must be made by the clinician by weighing all existing preoperative clinical and known prognostic factors. It is important to stress that, in this regard, NIFTP is a surgical disease, and its diagnosis can only be rendered upon excision and depends totally on adequate or entire sampling of the interface between the tumor and its capsule/periphery to exclude invasive characteristics.[9] In the era of personalized medicine, adjunct molecular testing will be of value in tailoring management, whether it entails clinical and radiologic observation or surgery. Patients who have thyroid nodules with indeterminate or low-risk ultrasonographic features,[25–27] with an FNA diagnosis of suspicious for malignancy, and only *RAS*-mutations and/or *PPARG* and *THADA* gene fusions (and lacking *BRAF* and *TERT* promoter mutations) can undergo limited surgical resection and no further treatment if a diagnosis of NIFTP is rendered on histopathologic evaluation. Therefore, the cytopathologist may consider including NIFTP in their differential diagnosis in cases diagnosed as indeterminate, ie, AUS/FLUS, FN/SFN, and suspicious for PTC.

CONCLUSION

We conclude that the change in the diagnosis of noninvasive EFVPTC to NIFTP, ie, not carcinoma, will have significant an impact on the ROM for TBSRTC categories, especially the indeterminate categories. On the basis of future studies, this may lead to the modification of

cytomorphologic criteria and the diagnostic threshold for classifying a thyroid FNA specimen as "suspicious for malignancy," the implementation of molecular studies, and dynamic rather static thinking on the part of clinicians to conservatively manage low-risk thyroid neoplasms.

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AUTHOR CONTRIBUTIONS

Zubar W. Baloch: Conceptualization, writing–original draft, writing– review and editing, and supervision. **Raja R. Seethala**: Conceptualization, methodology, resources, writing–original draft, and writing–review and editing. **William C. Faquin**: Conceptualization, writing–original draft, and writing–review and editing. **Mauro G. Papotti**: Methodology and writing–review and editing. **Fulvio Basolo**: Conceptualization and methodology. **Guido Fadda**: Methodology, validation, investigation, and writing–review and editing. **Gregory W. Randolph**: Conceptualization, writing–original draft, and writing–review and editing. **Steven P. Hodak**: Conceptualization, writing–original draft, and writing–review and editing. **Yuri E. Nikiforov**: Conceptualization and writing–review and editing. **Susan J. Mandel**: Writing–review and editing.

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