Cytopathology In Focus: The significance of NIFTP for thyroid cytology

Cytopathology infocus
FROM THE CAP CYTOPATHOLOGY COMMITTEE; KRISTEN E. NATALE, DO, EDITOR

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January 2017—A recent landmark study performed under the auspices of the Endocrine Pathology Society has proposed a new diagnostic entity in the thyroid: noninvasive follicular thyroid neoplasm with papillary-like nuclear features, or NIFTP.[1] While the study focused on histologic features and clinical outcomes, any significant change in surgical pathology classification will raise important questions for the practice of thyroid cytology as well, since nearly all thyroid nodules are initially evaluated by fine needle aspiration. While much remains to be settled about this new entity and its effect on cytology, we attempt to answer some of these questions.

What is NIFTP?

NIFTP is the proposed terminology for neoplasms previously classified as noninvasive encapsulated follicular variant of papillary thyroid carcinoma (PTC), which account for 10 to 20 percent of all diagnoses of PTC.

Why create a new name?

Over the past several decades the rate of diagnosis of thyroid cancer has markedly increased, with essentially all of the increase attributable to PTC.[2,3] This has been due mostly to increasing radiological detection of thyroid nodules. However, it is also due in part to pathologists increasingly recognizing that the nuclei within some follicular-patterned neoplasms have features that resemble those seen in classic PTC, resulting in higher rates of diagnoses of the follicular variant of PTC (FVPTC). Despite a marked increase in the diagnosis of PTC, the mortality associated with PTC has remained entirely unchanged, raising concerns that these diagnoses largely represent indolent lesions and that the diagnosis of PTC may result in unnecessary and harmful overtreatment. In particular, the available literature shows extremely indolent behavior for the encapsulated, noninvasive form of FVPTC. The Endocrine Pathology Society gathered 109 such cases with 10 to 25 years of clinical follow-up and identified no recurrences or evidence of lymph node involvement. Similarly, unpublished data from the University of Utah on a retrospective review of cases that would meet the criteria for NIFTP found that none of the 47 NIFTP patients had nodal disease either at the time of surgery or on clinical follow-up.

Moreover, they and others have found an absence of the *BRAF* V600E mutation common to classic PTC in NIFTP. Instead of *BRAF* V600E mutations, they found mutations commonly seen in follicular adenomas and carcinomas, most commonly *RAS* mutations, further supporting a distinction from PTC.

Based on the literature and the data the Endocrine Pathology Society collected, revised terminology was believed to be needed to remove the term carcinoma from the name of these lesions; hence the recommendation of NIFTP. They did not claim that the lesion was necessarily benign but that it was better classified as an indolent neoplasm than as carcinoma. Moreover, they proposed that hemithyroidectomy should be sufficient treatment for this lesion, with no role for completion thyroidectomy or radioactive iodine therapy.

What are the diagnostic criteria for NIFTP?

The formal criteria for diagnosis are as follows:

- Encapsulation or clear demarcation.
- Follicular growth pattern with
- Nuclear score 2–3 (as defined here).
- No vascular or capsular invasion.
- No high mitotic activity (

The nuclear score is based on:

- Nuclear size and shape (enlargement, overlapping, elongation).
- Nuclear membrane irregularities (irregular contours, grooves, pseudoinclusions).
- Chromatin characteristics (clearing with margination/glassy nuclei).

Each nuclear feature is scored as present (1) or absent (0), so if two or three are present, the tumor has nuclear features of NIFTP; if zero or one, it is a follicular neoplasm.

Can I make the diagnosis on cytology?

Cytologists will quickly recognize that several of the preceding diagnostic criteria can be assessed only on surgical specimens. It is therefore not possible to make a definitive diagnosis of NIFTP cytologically. Already, several studies have evaluated the cytologic interpretations that precede a surgical diagnosis of NIFTP, and they have shown that NIFTP can be found in every category of the Bethesda System for Reporting Thyroid Cytopathology. The vast majority, however, are classified in the indeterminate categories: atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), and suspicious for malignancy (SFM).[4,5]

This fits with the limited available literature on cytologic features of NIFTP, which typically finds overlapping follicular groups of cells rather than features associated with papillary architecture (for example, true papillae, branching groups, caps, or psammoma bodies) and nuclei that have some but not all of the nuclear features of PTC. In particular, intranuclear pseudoinclusions are absent or rare in the vast majority of cases of NIFTP. So while a diagnosis of NIFTP cannot be made cytologically, there does appear to be a constellation of cytologic features that raise its consideration.[6-9]

There is no consensus at present as to what Bethesda category to assign to a lesion in which NIFTP is suspected. Depending on the degree of nuclear and architectural changes, AUS/FLUS, FN/SFN, or SFM may be appropriate, perhaps with a comment noting the pathologist's consideration of the NIFTP diagnosis. As total thyroidectomy is considered unnecessary for NIFTP, an attempt should be made to avoid using the malignant category for cases with these features. A commentary by Krane, et al., published last year provides a more in-depth discussion of the cytologic interpretation of a possible NIFTP.[10]

Can I still make a diagnosis of papillary carcinoma on cytology?

Yes. Retrospective studies have suggested that even with no changes to diagnostic criteria for PTC, the risk of malignancy for the PTC category would shift only slightly, from 99 percent to 96 percent in the largest such study.[4] With only minor common-sense adjustments to one's diagnostic thresholds (such as requiring evidence of papillary architecture, or more than rare pseudoinclusions, before making a definitive diagnosis of PTC), the changes in

performance characteristics of the malignant category and frequency of its use should be minimal.

What happens to the Bethesda System?

While revisions to the Bethesda System for Reporting Thyroid Cytopathology are underway, they are unlikely to incorporate major categorical changes in response to NIFTP, based on the limited literature to date. However, the risk of malignancy associated with the various categories is likely to shift significantly. The impact will be greatest for the indeterminate categories. In the largest study of this effect, among cases that underwent surgery, the risk of malignancy for AUS/FLUS decreased from 31 percent to 18 percent, FN/SFN decreased from 33 percent to 18 percent, and SFM decreased from 83 percent to 59 percent.4 The change had a much smaller effect on the other Bethesda categories: The risk of malignancy for non-diagnostic decreased from 25 percent to 24 percent, that for benign decreased from nine percent to six percent, and that for malignant decreased from 99 percent to 96 percent.

The appropriate management for some categories may need to be re-evaluated in light of these shifts. In particular, the practice among some surgeons of conducting total thyroidectomy for the SFM category may be excessively aggressive for a category with only a 59 percent risk of malignancy. Because of this it may be worth notifying pertinent clinical teams of the reduced risk of malignancy for the SFM category given the new diagnostic landscape with NIFTP.

What happens with molecular testing?

Many clinicians have begun to request molecular testing in an attempt to better define appropriate management of indefinite thyroid FNAs. The change in terminology will affect the reported performance characteristics of most commercially available tests. The risk of malignancy associated with the *BRAF* V600E mutation should be unaffected, as this mutation appears to be specific to classic and tall cell variants of PTC and is absent in NIFTP. The commercially available gene expression classifier (GEC) type tests included NIFTP in their training sets as malignant and so would be expected to yield an abnormal result for NIFTP. The reclassification of NIFTP can therefore be expected to reduce the specificity and positive predictive value of the test for malignancy, without affecting sensitivity or negative predictive value. The overall effect on the mutation-based panels will be similar; however, the effect on performance of the individual genes reported will be more complicated, with significant reduction in the risk of malignancy associated with some genes, such as *RAS*, but no change in others, such as *BRAF* V600E. Since the current recommendation for NIFTP is hemithyroidectomy, the usefulness of molecular testing for indicating who requires surgery versus clinical follow-up may not be affected substantially.

Should I go back and reclassify all my old thyroid *surgical* pathology diagnoses?

Probably not. As most patients will have already received definitive treatment of their NIFTP, reclassification is unlikely to have an impact on their management going forward. For patients very recently diagnosed as noninvasive follicular variant PTC, discussion with the treating physicians about reclassification and management options for the patient may be appropriate. Our opinion is that patients were accurately diagnosed within the constructs of the time and that applying new or novel principles to prior diagnoses is not a worthwhile endeavor.

My clinicians have questions. What should I discuss with them?

Many aspects of the reclassification are important to clinicians, and they are likely to be receiving guidance from their professional societies and publications. Some of the most important points to share with your clinicians include the following:

- Most noninvasive FVPTCs have been reclassified as NIFTP. Recommended management for NIFTP is hemithyroidectomy alone.
- NIFTP cannot be diagnosed on cytology but can be suggested in some cases. The lesion will usually be classified as AUS/FLUS, FN/SFN, or

SFM.

- The risk of malignancy for a malignant category diagnosis remains very high. The risk of malignancy for indefinite diagnoses will be substantially lower. Thought should be given to management alterations for these categories.
- The performance characteristics of molecular testing will also be altered substantially.

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