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The Value of Cytological Examination in the Diagnosis of Noninvasive Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP)

Chiara Saglietti and Massimo Bongiovanni*

Service of Clinical Pathology, Lausanne University Hospital, Institute of Pathology, Lausanne, Switzerland

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Abstract

Since the introduction of the concept that the noninvasive encapsulated follicular variant of papillary thyroid carcinoma does not warrant a diagnosis of carcinoma and shall be renamed noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), many questions have arisen among thyroid cytopathologists concerning the implications of this changing paradigm on the cytological classification of thyroid nodules. Specifically, whether it is possible to diagnose NIFTP by fine-needle aspiration, how will the risk of malignancy of the diagnostic categories of thyroid cytopathology be affected, and which changes will be made to the current cytological workup of thyroid nodules. The aim of our work was to review published literature to analyze how cytopathologists are dealing with this changing paradigm in thyroid pathology and how, in turn, it is affecting their current practice.

Keywords: Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), thyroid, cytology, fine-needle aspiration

Introduction

Thyroid fine-needle aspiration (FNA) is an essential procedure in the initial evaluation and clinical management of thyroid nodules. Currently, most thyroid cytology specimens are classified in the frame of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), which was introduced following the National Cancer Institute (NCI) Thyroid FNA State of the Science Conference held in Bethesda in 2007 (Table 1). Other national systems exist (in Japan, Italy, United Kingdom, and Australia); the common endeavor of all being the effort to address terminology issues related to thyroid FNA and to make reporting of thyroid FNA uniform across different laboratories (1).

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*Correspondence author: Dr. Massimo Bongiovanni, Service of Clinical Pathology, Lausanne University Hospital, Institute of Pathology
25, rue du Bugnon, CH-1011 Lausanne, Switzerland.
Tel: Tel: +41 21 314 72 02
Fax: +41 21 314 72 05
Email: massimo.bongiovanni@chuv.ch

Table 1. The Bethesda System for Reporting Thyroid Cytopathology diagnostic categories with implied risk of malignancy and recommended clinical management.*

Diagnostic Category		Risk of Malignancy	Usual Management
I.	Nondiagnostic or Unsatisfactory	1-4%	Repeat FNA with ultrasound guidance
II.	Benign	0-3%	Clinical follow-up
III.	Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	~5-15%	Repeat FNA
IV.	Follicular Neoplasm or Suspicious for a Follicular Neoplasm	15-30%	Surgical lobectomy
V.	Suspicious for Malignancy	60-75%	Near-total thyroidectomy or surgical lobectomy
VI.	Malignant	97-99%	Near-total thyroidectomy

FNA, fine-needle aspiration; *Adapted from Cibas *et al*. (1).

Independently of the reporting system used, thyroid FNA serves as a diagnostic test in cases of benign proliferations, papillary thyroid carcinomas (PTCs) and other malignancies, but it is best considered as a screening test for follicular-patterned lesions, including hyperplastic nodules, follicular adenomas, follicular carcinomas, and a number of follicular variants of PTC. FNA has a limited accuracy in these lesions because of overlapping cytomorphological features among them and because histopathological examination is required to establish a definitive diagnosis (2).

Noninvasive Thyroid Neoplasm with Papillary-like Nuclear Features: A Paradigm Shift Affecting Thyroid Cytopathology

During the Endocrine Pathology Society's conference held in Boston, Massachusetts, in March 2015, a working group composed of well-known and experienced pathologists re-evaluated the concept of noninvasive encapsulated follicular variant of PTC (EFVPTC). They concluded that these tumors were to be renamed "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP), on the basis of the uneventful clinical course of these patients during follow-up (3, 4). Since then, critical questions have arisen among thyroid cytopathologists concerning

Table 2. Cytological features allowing NIFTP to be distinguished from other thyroid lesions.

Authors	Cytological Features Associated with NIFTP	Is NIFTP Differential Diagnosis Possible on Cytology?
Maletta *et al*. (6)	The presence of: - Nuclear enlargement - Nuclear membrane irregularities - Optically clear, ground glass nuclei - Nuclear molding shows statistical significance in distinguishing NIFTP from benign adenomas.	Possible: NIFTP *vs*. FA.
Strickland *et al*. (10)	In cases raising concern for PTC because of characteristic nuclear features, the presence of: - Abundant papillae and intranuclear pseudoinclusions is significantly associated with PTC; - A predominantly microfollicular pattern, is significantly associated with NIFTP and I-FVPTC.	Possible: NIFTP *vs*. PTC.
Ibrahim and Howard (7)	I-FVPTC shows higher cellularity and more obvious nuclear aberrations as compared with NIFTP, which presents lower cellularity and subtle nuclear changes.	Possible: NIFTP *vs*. I-FVPTC.
Bizzarro *et al*. (8)	A higher number of follicular clusters with <10 thyrocytes is associated with NIFTP as compared with I-FVPTC; Cytoplasmic volume is low in NIFTP as compared to FA; Nuclear size <20 µm permits distinction of NIFTP from FA and PTC.	Possible: NIFTP *vs*. I-FVPTC. Possible: NIFTP *vs*. FA and PTC

NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; FA, follicular adenoma; I-FVPTC, invasive follicular variant of papillary thyroid carcinoma; PTC, papillary thyroid carcinoma.

the impact of this changing paradigm on the cytological classification of thyroid nodules, notably:

1) Is it possible to diagnose NIFTP by thyroid FNA cytology?
2) How will the change in terminology affect the current practice of thyroid FNA cytology, and specifically the risk of malignancy (ROM) of the different diagnostic categories?
3) How will the current management algorithm be associated with each diagnostic category change?

Over the months that followed the introduction of NIFTP as a new diagnostic entity, numerous papers were published as thyroid cytopathologists strived to answer these questions. We report a summary of the main findings, which could be useful in daily cytopathology practice.

Diagnosis of NIFTP on Thyroid FNA

Definition of the role of cytopathology in the diagnosis of NIFTP and characterization of the cytomorphological features that could help in correctly identifying these lesions on FNA material have been a main focus of thyroid cytopathologists since the proposal of noninvasive EFVPTC reclassification. Table 2 summarizes the results of studies on the cytological diagnosis of NIFTP.

Maletta *et al*. assessed a series of cytological parameters and found that nuclear enlargement, nuclear membrane irregularities, optically clear, ground glass nuclei, and nuclear molding showed statistical significance in distinguishing NIFTPs from benign adenomas on FNA cytology. Among these parameters, the first three are the same criteria applied by Nikiforov and colleagues in their score for evaluating NIFTP histology (3, 5).

Strickland and colleagues compared FNA of cases histologically diagnosed as noninvasive EFVPTCs and classical PTCs and scored them for a series of features. They found that, in cases where nuclear features already raised significant concerns for a diagnosis of PTC, the presence of abundant papillae and nuclear pseudoinclusions was significantly associated with PTC, whereas a predominantly microfollicular pattern was associated with NIFTP and a follicular variant of PTC (FVPTC). They therefore recommended that such parameters be used by cytopathologists to triage patients with putative NIFTP for consideration of diagnostic lobectomy while recognizing patients with putative classical PTC who need total thyroidectomy (6).

Ibrahim and Wu compared FNA diagnoses of noninvasive EFVPTC/NIFTPs versus invasive EFVPTC and infiltrative FVPTC, and noted a clear difference between the two groups: whereas the invasive EFVPTC and the infiltrative FVPTC subtypes were diagnosed in almost 75% of cases as suspicious for malignancy or malignant, 4% and 0% of noninvasive EFVPTC/NIFTPs were classified as suspicious for malignancy or were malignant, respectively. The authors suggest that a cytomorphological distinction exists between invasive and noninvasive EFVPTC, with invasive EFVPTC showing higher cellularity and more obvious nuclear aberrations as compared to noninvasive EFVPTC/NIFTP, which displays subtle nuclear changes and an overall lower cellularity (7).

Bizzarro *et al*. analyzed a number of architectural, cytoplasmic and nuclear features, and compared them in a series of noninvasive EFVPTCs/NIFTPs, invasive EFVPTCs, follicular adenomas (FAs) and PTCs. From an architectural point of view, they found that NIFTPs as well as invasive EFVPTCs lacked papillary structures on cytology and were characterized instead by follicular clusters. When they considered the number of thyrocytes in such clusters, a slightly higher number of clusters with <10 cells were associated with NIFTP compared to invasive EFVPTC. Among the analyzed cytoplasmic parameters, low cytoplasmic volume of NIFTP as compared to FA was the only one that reached statistical significance. A nuclear size cutoff of <20 µm was statistically significant in distinguishing NIFTPs from FAs and PTCs, but not from invasive EFVPTCs. The authors also proposed a diagnostic algorithm to detect NIFTP by combining cytomorphological features with the results of an immunocytochemical panel (8).

A provisional approach for cytopathologists in dealing with NIFTP has been suggested by Krane and colleagues in a

commentary published in Cancer Cytopathology (9). According to them, when the evaluation of NIFTP is performed within the framework of TBSRTC, features that suggest NIFTP by FNA (i.e., lesions presenting microfollicular architecture with enlarged nuclei, pale chromatin, irregular membranes with nuclear grooves but lacking intranuclear pseudoinclusions, psammoma bodies or papillae) should be used to minimize the classification of potential NIFTP cases as malignant. The diagnosis of Bethesda VI (malignant, PTC) should be limited to cases with frequent intranuclear pseudoinclusions, papillae or psammoma bodies (9).

Impact of the NIFTP Proposal on the Practice of Thyroid FNA Cytology and ROM of Diagnostic Categories of TBSRTC

The ROM for each diagnostic category of TBSRTC has been defined with noninvasive EFVPTC being considered as a malignancy; the reclassification of this lesion as NIFTP is therefore expected to modify the ROM of the diagnostic categories to which noninvasive EFVPTC/NIFTP is currently allocated.

This issue has been addressed by Strickland *et al*. and Faquin and colleagues, who evaluated the impact of noninvasive EFVPTC reclassification as a benign lesion on the ROM for each of the 6 current diagnostic categories of TBSRTC. The former group analyzed a cohort of 655 FNAs with subsequent resection specimens and found the following decrease in the rate of malignancy: 1.9% for non-diagnostic; 7.8% for benign; 17.6% for atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS); 8% for follicular neoplasm/suspicious for a follicular neoplasm (FN/SFN); 41.5% for suspicious for malignancy (SM); and 5.1% for the malignant category (10). In a large multi-institutional cohort of thyroid FNA cases, Faquin *et al*. investigated a study cohort of 6943 nodules, 26.3% of which (n = 1827) with corresponding surgical resection specimen; exclusion of noninvasive EFVPTC from the calculation of the ROM led to the following decrease in the ROM: 1.4% for non-diagnostic cases; 3.5% for cases diagnosed as benign; 13.6% for AUS/FLUS cases; 15.1% for FN/SFN cases; 23.4% for cases SM; and 3.3% for malignant cases. The majority of noninvasive EFVPTC FNA cases were diagnosed in one of the indeterminate categories (AUS/FLUS, FN/SFN and SM), for which the greatest decrease in ROM was observed (11).

Before the introduction of NIFTP as a diagnostic entity, non-invasive encapsulated follicular tumors with equivocal PTC type nuclear changes were classified by some authors as "well-differentiated tumors of uncertain malignant potential" (WDT-UMP), a possible borderline thyroid lesion. In reason of its questionable nuclear features, including faint nuclear grooves and uncompelling nuclear vacuoles, WDT-UMP was most often found in the indeterminate cytological categories, as shown by Nishigami and colleagues (12).

The magnitude of the impact that reclassification of noninvasive EFVPTC into NIFTP will have is difficult to predict; overall, for each institution, the decrease in ROM implied by each of the diagnostic categories of TBSRTC is expected to be affected by patient demographics and by the institutional frequency of rendering a noninvasive EFVPTC diagnosis (13).

Impact of NIFTP Proposal on Cytologic Workup of Thyroid FNA

A significant decrease in the ROM for the indeterminate categories may lead to a change in the management paradigm of thyroid nodules that can affect the workup of cytological specimens.

In this context, the application of targeted molecular tests to FNA material can help in providing management tailored to the individual patient. In fact, Nikiforov and colleagues have shown that noninvasive EFVPTC/NIFTP demonstrates a high prevalence of RAS mutations, which are generally associated with follicular-patterned thyroid tumors, including FA, follicular thyroid carcinoma and encapsulated FVPTC (13); this is unlike classical PTC and infiltrative FVPTC, whose most frequent genetic alteration is a BRAF mutation (14).

In case of nodules with indeterminate cytology that harbor a RAS mutation, a simple lobectomy can be proposed. If, on the contrary, a lesion of indeterminate cytology shows the presence of a BRAF mutation, then a total thyroidectomy can be advised. The main problem of this approach is the low frequency of mutations in thyroid nodules.

A different approach can involve the application of commercially available tests to FNA material: Jiang *et al*. have evaluated the performance of the Afirma gene expression classifier (GEC) and the ThyroSeq panel in a series of 8 NIFTPs, all of which had been classified as Bethesda III or IV preoperatively. The four nodules investigated by Afirma GEC were all identified as "suspicious", whereas the four nodules evaluated by ThyroSeq harbored RAS mutations. Both the GEC and the ThyroSeq methods indicated abnormalities in NIFTP. Therefore, according to the authors, further study is needed to better classify the molecular characteristics of NIFTP (15).

Our Experience

We were surprised by the high prevalence of NIFTP reported by Nikiforov and colleagues: 13.6% in the Bellaria Hospital, Bologna, Italy (2000-2015); 25% in San Luigi Hospital, Turin, Italy (2005-2014); 18.7% in Hospital of Pisa, Pisa, Italy (2000-2004); and 18.8% in MSKCC, New York, USA (2000-2003), for a mean value of 18.6% (3). We therefore decided to review our cases of surgically resected thyroid cancer to see how frequent NIFTP was in the mountain region of the Swiss Canton of Vaud and, therefore, how often we should expect to encounter NIFTP in our cytological samples. In the 6-year period comprised between January 1st 2011 and December 31st 2016, for a total number of 216 thyroid cancers, we diagnosed only 9 noninvasive EFVPTCs/NIFTPs, accounting for 4.2% of thyroid carcinomas diagnosed at our Institution. Pre-operative cytology was available for 5 of these 9 cases: one was diagnosed as a benign cyst; two as FN/SFN; one as suspicious for PTC; and one as PTC.

A similar prevalence of EFVPTC had been described by Piana and coworkers in 2010, years before the NIFTP proposal, in the Department of Pathology of the Arcispedale Santa Maria Nuova, Reggio Emilia, Italy: EFVPTC represented 4.5% of thyroid carcinomas diagnosed over a period of 25 years comprised between 1979 and 2004 (16).

Similarly, Liu *et al*. reported an even lower diagnostic rate in the Department of Pathology of the Wakayama Medical University, Wakayama, Japan: there, EFVPTC accounted for 0.4% of thyroid cancers diagnosed between 1990 and 2009 (17).

Conclusions

For the time being, NIFTP remains a surgical disease that, in our opinion, cannot be diagnosed on cytological grounds. NIFTP diagnosis can only be provided upon surgical excision. One of the

main concerns for cytopathologists, regarding the reclassification of noninvasive EFVPTC into NIFTP, is the increase in the "false positive" rates and the possible medicolegal implications. Most clinicians would advise total thyroidectomy for cases diagnosed cytologically as suspicious or compatible with PTC because of the high ROM associated with these cytological diagnoses. From the histology, some of these cases will turn out to be NIFTP (and benign) (12).

This is why the decrease of ROM deriving from the reclassification of noninvasive EFVPTC into NIFTP, especially affecting the indeterminate categories, will lead to a modification in the pre-surgical management algorithm associated with TBSRTC, with the potential implementation of molecular testing to distinguish indeterminate nodules at high risk of being malignant from those at low risk. A different approach could consist in the discussion of individual cases in the multidisciplinary setting of a tumor board: by combining cytological, clinical, ultra-sound and molecular features, the risk of malignancy for each patient can be better evaluated.

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