

Experience on NIFTP Cytology, with a Mini Meta-Analysis of the Literature

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Abstract

NIFTP or “noninvasive follicular thyroid neoplasm with papillary-like nuclear features” is a recently introduced term that redefines the previously called “encapsulated follicular variant of papillary thyroid carcinoma without capsular and/or vascular invasion”. NIFTP are indolent neoplasms and patients with NIFTP need no further treatment after surgery.

The present review focuses on cytology of this redefined entity: papers published so far revealed that NIFTP share many of the diagnostic features of the follicular variant of papillary thyroid carcinoma and are usually categorized as indeterminate in thyroid cytology. A few papers detected *RAS* mutations and specific miRNA expression profiles in cytological specimens of NIFTP and this will probably add some diagnostic tools in the pre-operative triage of thyroid nodules. Finally, the “newly defined” not malignant nature of NIFTP will have a profound impact on the risk of malignancy assessment of the Bethesda diagnostic categories, by reducing the risk mainly in categories III, IV and V. However, further studies are needed in order to exactly re-establish the risk of malignancy. The aim will eventually be the planning of an appropriate risk-adapted management to reduce overtreatment, complications and costs.

Keywords: Thyroid FNA, cytology, follicular variant papillary carcinoma, encapsulated, NIFTP

Case Report: Starting from the Everyday Practice...

A single 18-mm node in the right thyroid lobe was incidentally discovered in a 50-year-old woman. The ultrasound pattern revealed a hypoechoic nodule, with well-defined margins, intra and perinodal vascularization, and an intermediate elastosonographic pattern. The node was submitted to fine needle aspiration biopsy (FNA) using a 22 Gauge needle. Alcohol-fixed H&E-stained and air-dried Giemsa-stained smears were obtained, together with paraffin-embedded cell-block slides.

A highly cellular microfollicular patterned lesion was observed (Figure 1), with scant or absent colloid. The nuclei were at least twice the size of a red blood cell, and showed focal clearing and some irregularities of nuclear contour (grooves, indentations) without pseudoinclusions. Thus, a diagnosis of follicular neoplasm (FN) (Category IV sec. Bethesda) was formulated.

Three months later the patient underwent total thyroidectomy. Gross sampling confirmed the presence of a single nodule that histologically was almost completely microfollicular, except for the presence of a small area (nearly 5% the entire tumor area) with papillary formations. The capsule was thoroughly sampled: it was thin and complete. The nuclei were large, nearly twice the diameter of the nuclei of the surrounding normal thyroid parenchyma, and were clear in the majority of the lesion. Some nuclear grooves and irregularities were observed, but not in all cells. Colloid was dark and dense. No sign of vascular invasion was present.

The present case posed some diagnostic difficulties and considerations. First of all, we wondered whether this case could represent an example of the novel entity “NIFTP” (noninvasive follicular thyroid neoplasms with papillary-like nuclear features) as recently published (1). In particular, the question was whether the presence of a focal papillary architecture and of focal nuclear clearing and irregularities (with mostly dark nuclei) would prevent a diagnosis of NIFTP. Secondly, we retrieved the slides of this case and looked for any cytological features that could help in recognizing a NIFTP on FNA before surgery, and addressed several questions, including: How do NIFTP look like in FNA? Do they have any distinctive features, so that “NIFTP” can be recognized at FNA cytology? Which cytological category are NIFTP more likely to fall into? Can molecular biology be of help in detecting NIFTP in cytology? And finally: how is the recent downgrading of NIFTP into the “not malignant lesion” category expected to impact on the risk of malignancy of the different cytological diagnostic categories?

Histopathology of NIFTP

The encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) without capsular and/or vascular invasion accounts for 10-20% of all thyroid malignancies and is traditionally known as an indolent carcinoma with excellent prognosis (2-4). Notwithstanding the very low risk of adverse outcome, however, patients receiving a diagnosis of EFVPTC without invasion continue to be treated with therapies similar to those for more aggressive types of thyroid carcinoma (5). Moreover, several authors reported that the diagnosis of EFVPTC without invasion is afflicted by high rate of subjectivity in pathological interpretation, since it can rely solely on the detection of proper papillary-like nuclear irregularities (which can be only partially or focally expressed) and not on other more established criteria, such as capsular invasion or vascular invasion (6-9). As a consequence, in many cases with incomplete evidence of papillary-type nuclei, the differential diagnosis between PTC and follicular adenoma can be challenging and attempts have been made to solve the problem, such as the introduction of the category of “atypical adenoma” or of well-differentiated tumors of uncertain malignant

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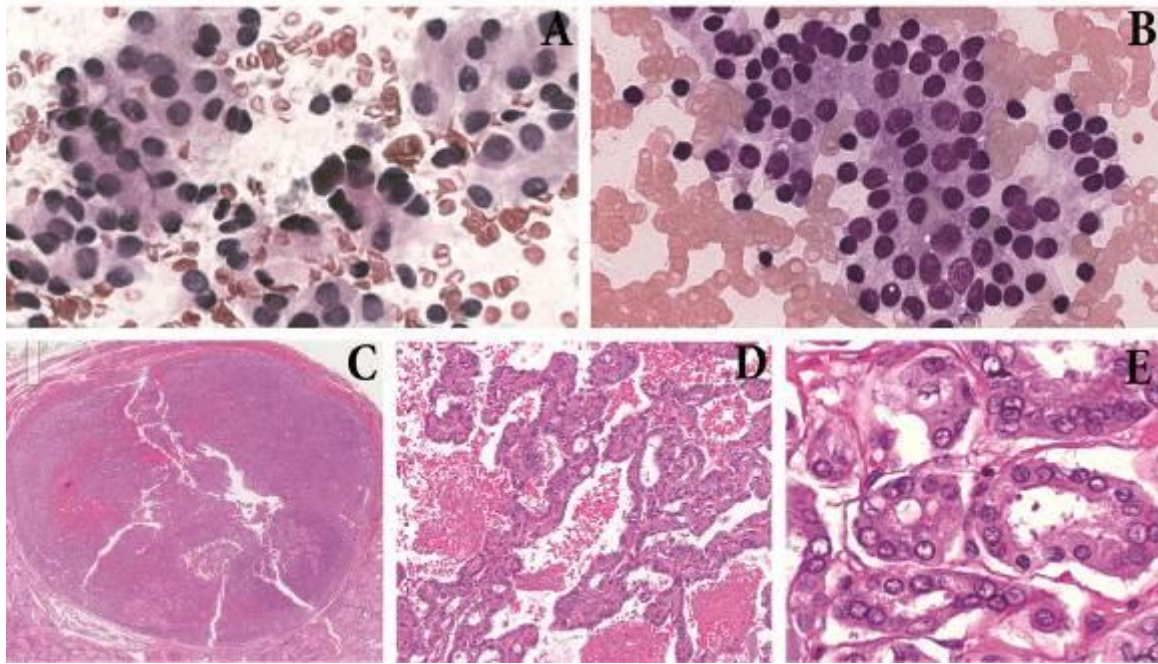


Fig. 1: Cytological (A-B) and histological (C-D-E) appearance of a 18-mm thyroid nodule. In FNA (A, B, smears stained with Papanicolaou and Giemsa, 400x magnification), the node shows microfollicles with nuclear enlargement (defined as nuclei being at least twice the size of a red blood cell), irregularities of contour, while nuclear clearing was uncommon; a diagnosis of Bethesda Category IV was rendered. At histology, the same lesion appears well capsulated and shows a predominant microfollicular architecture (C; H&E stain, 20x magnification) with focal presence of papillae (D; H&E, 100x magnification), accounting for approximately 5% of the entire volume. At high magnification (E; H&E, 400x magnification) the nuclei are clear, large and show irregularities of nuclear contour and grooves (total nuclear score 3). Even if capsulated and with significant nuclear irregularities, the nodule cannot be diagnosed as NIFTP because of the presence of a focal papillary architecture.

potential (WDT-UWP) as proposed by some European authors (10).

In order to face these two major problems (i.e. overtreatment and reproducibility of pathological diagnosis), a working group of thyroid experts joined in 2015 to reevaluate the EFVPTC category and its diagnostic criteria. Nikiforov *et al.* demonstrated that the noninvasive EFVPTC neoplasms have a very low risk of adverse outcome and proposed to rename such tumors as “NIFTP” (1). The term neoplasm instead of carcinoma better reflects its biological behavior and points out its not malignant nature: a NIFTP does not require completion thyroidectomy, nor radioiodine therapy.

In the same paper, the diagnostic criteria for NIFTP are provided: the tumor has to be encapsulated or clearly demarcated from the adjacent normal thyroid; the growth pattern should be almost exclusively follicular, with less than 1% papillae and less than 30% solid/trabecular/insular growth pattern. No psammoma bodies, necrosis, vascular or capsular invasion are admitted and mitotic activity should be low (<3 mitoses per 10 high-power fields). Most importantly, the problem of assessing papillary-like nuclear irregularities is discussed. A nuclear score ranging from 0 to 3 should be assigned to the lesion on the basis of the absence (score 0) or presence (score 1) of each of the following three nuclear parameters yielding a range from 0 to 3: (a) size and shape (nuclear enlargement/overlapping/crowding, elongation), (b) nuclear membrane irregularities (irregular contours, grooves, pseudoinclusions), and (c) chromatin characteristics (clearing with margination/glassy nuclei). These features should be assessed by comparing tumoral nuclei with the nuclei in the surrounding

normal follicular cells: if a total score of 2-3 is obtained and in the presence of all the other parameters, a diagnosis of NIFTP can be formulated.

Final diagnosis of case report

Question:

Does the presence of a 5% papillary architecture and of only focal irregular and prevalently dark nuclei exclude the diagnosis of NIFTP?

Answer:

Yes, it does; in fact, even though nuclear irregularities are sufficiently expressed yielding a total nuclear score of 2, and all the other histopathological criteria for a diagnosis of NIFTP are met, the current case cannot be considered a NIFTP because of its 5% papillary architecture, as the only exclusion criterion, a diagnosis of noninvasive EFVPTC was thus made.

Cytopathology of NIFTP

Morphology and categorization - In the past, several papers dealt with the diagnostic problems posed by the cytological diagnosis of EFVPTC, the main issue being if it was more similar to the classical form of PTC or to follicular tumors, thus belonging to the indeterminate category of thyroid cytology schemes.

Nowadays, the introduction of the term NIFTP poses more or less the same diagnostic problems (Figure 2). In recent papers, several authors demonstrated that the cytological diagnosis of NIFTP is not possible.

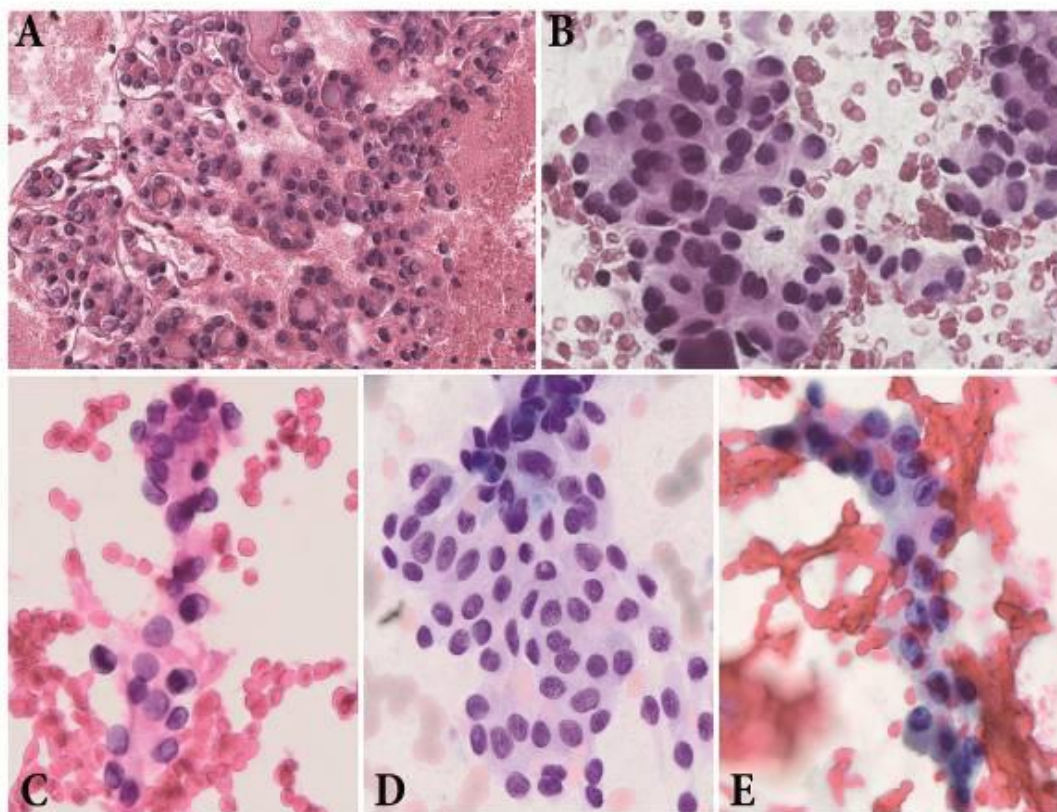


Fig. 2: Cytological features of NIFTP. In sections obtained from cell-block samples (A, H&E stain, 200x magnification), NIFTP shows a microfollicular architecture, with dense colloid; nuclei are variably large, clear and irregular. In smears (B, C, D, E, stained respectively with Papanicolaou, H&E, Giemsa and Papanicolaou, 400x magnification), small and discohesive microfollicular groups of thyrocytes are admixed with scant and dense colloid. Nuclei tend to be at least twice the size of a red blood cell, clear and show diffuse irregularities of nuclear contour (grooves, indentations).

First of all, since this diagnosis requires the absence of capsular and/or vascular invasion, histology is necessary to differentiate between FVPTC, EFVPTC and NIFTP. Moreover, it is well known that in all FVPTC variants (encapsulated, not encapsulated, with or without invasion) a major problem is the heterogeneous expression of papillary carcinoma-type nuclei in terms of both qualitative and quantitative changes (11-12). In FNA samples, these changes, if focally expressed, can be easily overlooked or missed, and the tumor is at risk of being under- or mis-diagnosed as a follicular neoplasm or a benign lesion, respectively. Thus, the cytological diagnosis of FVPTC is challenging due to overlapping features with both benign and malignant follicular-derived lesions, including a hyperplastic goiter, follicular adenoma, and follicular carcinoma.

At present, most thyroid FNA specimens are classified according to the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), which includes six diagnostic categories: category I or nondiagnostic (ND), II or benign (B), III or atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), IV or follicular lesion/suspicious for follicular neoplasm (FN/SFN), V or suspicious for malignancy (SFM), and VI or malignant (FM) (13). Several papers pointed out that FVPTC variants tend to be diagnosed in indeterminate categories (category III or IV), while classic PTC is properly recognized and is usually diagnosed in higher risk categories (category V and VI) (14).

In 2016, soon after the introduction of the new terminology of NIFTP (1), a series of papers dealing with the cytological diagnosis of NIFTP appeared as summarized in Table 1 (15-22).

Our group reported the cytological features on FNA of 96 histologically proven NIFTP in comparison with control groups of benign (goiter, adenoma) or malignant lesions (infiltrative FVPTC) (21). A significant correlation of nuclear characteristics between histological and cytological samples was demonstrated, despite the heterogeneous expression of papillary carcinoma nuclear features in individual cases. After the blind revision, cytological samples generally belonged to nuclear score 2 or 3. However a fraction of cases was labeled "score 1" in the FNA material only. This was related to incomplete evidence of large/clear/irregular nuclei in the scant material available in smears and/or cell blocks (21). Regarding FNA cytology categorization, NIFTP tend to be diagnosed in the intermediate categories of FN/SFN and SFM: in our series, more than half of cases (56%, 54/96) were diagnosed as FN/SFN and a quarter of cases (27%, 26/96) as SFM. The remaining 15% of cases (14/96) and 2% (2/96) were respectively diagnosed in the category AUS/FLUS and FM. Overall, the most common cytological diagnosis rendered in FNA of histologically-proven NIFTP nodules is "follicular neoplasm" (Bethesda category IV) and only a minority of cases had sufficiently evident nuclear features to suggest a diagnosis of suspected malignancy (category V), or papillary carcinoma (category VI).

Table 1. FNA cytology categorization according to the Bethesda system of NIFTP (or similar entities)

| Authors | Definition | Type of Sample | Bethesda Category |
|-------------------------------|-------------------|----------------|--|
| Baser H <i>et al.</i> (15) | TT-UMP | FNA | I 13%, II 30.4%, III 30.4%, IV 13%, V 13% |
| Bizzarro T <i>et al.</i> (16) | NIFTP | LBC | III 13.5%, IV 40.6%, V 35.1%, VI 10.8% |
| Canberk S <i>et al.</i> (17) | EFVPTC | FNA | I 14%, II 16%, III 15%, IV 25%, V 17%, VI 13% |
| Faquin WC <i>et al.</i> (18) | NI-FVPTC | FNA | I 0.6%, II 8.7%, III 31.2%, IV 26.5%, V 24.3%, VI 8.7% |
| Hahn SY <i>et al.</i> (19) | NIFTP | FNA | I 5.7%, II 14.3%, III 25.7%, IV 5.7%, V 28.6%, VI 20% |
| Hahn SY <i>et al.</i> (19) | NIFTP | CNB | IV 45.5%, V 36.4%, VI 18.2% |
| Ibrahim AA and Wu HH (20) | Noninvasive FVPTC | FNA | II 17%, III 61%, IV 17%, V 5% |
| Maletta F <i>et al.</i> (21) | NIFTP | FNA | III 15%, IV 56%, V 27%, VI 2% |
| Rosario PW <i>et al.</i> (22) | NIFTP | FNA | Indeterminate 62%, malignant 4% |

Abbreviations: FNA: fine needle aspiration; NIFTP: noninvasive follicular thyroid neoplasm with papillary-like nuclear features; TT-UMP: thyroid tumors of uncertain malignant potential LBC: liquid-based cytology; EFVPTC: encapsulated follicular variant of papillary thyroid carcinoma; NI-FVPTC: noninvasive; CNB: core needle biopsy.

Moreover, we tried to apply the nuclear score proposed by Nikiforov (1) to cytology specimens and found that either all of the three features or at least chromatin clearing and irregular borders can be recognized in FNA cytology samples, if a sufficient cellularity is obtained. In FNA cytology specimens, nuclear enlargement was the most difficult feature to recognize, perhaps due to the difficulty of reliably scoring nuclear size in cytology.

Similar though not identical results were obtained by Canberk *et al.*; in a series of 1,886 FNA, EFVPTC FNA accounted for 94 cases (nearly 5%) that were categorized: 14% (13/94) category I, 16% (15/94) in category II, 15% (14/94) in category III, 25% in category IV (23/94), 17% (17/94) in category V, and 13% (12/94) in category VI (17). As reported in our study, EFVPTC cases are mostly diagnosed in categories IV and V, though more homogeneously distributed also among the other categories (21). A further paper by Rosario *et al.* confirmed that NIFTP frequently exhibited indeterminate cytology (62%), while malignant cytology is uncommon (4%) (22).

In our series, we demonstrated that NIFTP nuclear score was significantly different from score observed in benign lesions, while no significant differences were found between NIFTP and infiltrative (both capsulated or not) FVPTC (21). Ibrahim and WU *et al.*, however, found that cytological features of NIFTP were significantly different from those of invasive FVPTC: the invasive subtype was diagnosed by FNA as suspicious for PTC or PTC in nearly 75% of cases, while only 4% of cases in the noninvasive subtype were diagnosed as suspicious for PTC (20).

Baser *et al.* adopted the term thyroid tumors of uncertain malignant potential (TT-UMP) to define a group of borderline, encapsulated, follicular-patterned neoplasms with suspicious architectural and/or cytological features which do not fulfill the criteria for malignancy: even if TT-UMP is not a synonym of NIFTP, the concept of TT-UMP at least in part overlaps with NIFTP (15). In his paper, the authors found that none of the TT-UMP patients were evaluated as malignant in preoperative cytology, but were mainly diagnosed in the benign or AUS/FLUS Bethesda categories.

A recent paper by Bizzarro *et al.* dealt with the NIFTP appearance on liquid-based cytology samples (16). In particular, they collected 37 NIFTP cases and 24 infiltrative FVPTC cases at histology. They found that both NIFTP and infiltrative FVPTC have a predominant microfollicular pattern; however, if compared to infiltrative FVPTC, NIFTP nuclei tend to be smaller and less irregular, thus favoring a diagnosis of category IV rather than VI.

NIFTP features were also evaluated in core needle biopsy (CNB) of the thyroid (19). In a series of 34 cases, NIFTP diagnosis was more reliable in the CNB group than in the corresponding FNA specimens. In particular, all CNB cases were properly recognized and sent to surgery (category IV or higher), while FNA samples were nondiagnostic (category I) in 6% of cases, and benign (category II) or AUS-FLUS (category III) in 14% and 26% of cases, respectively (thus limiting the indication for surgery to 54% of cases only).

Question:

How do NIFTP look like in FNA? Do they have any distinctive features, so that "NIFTP" can be recognized at FNA cytology? Which cytological category are NIFTP more likely to fall into?

Answer:

In FNA cytology, NIFTP appear as microfollicular lesions with variable degree of nuclear atypia and irregularities. Their features are at least in part comparable to cytological features of FVPTC, but recently published papers do not fully agree on the differences between these two entities. This is likely to reflect the well-known diagnostic overlap and variability existing in the spectrum of follicular-patterned thyroid lesions. In FNA, NIFTP cannot be diagnosed with certainty and tend to be diagnosed in the indeterminate categories of thyroid cytology (mainly IV and, in varying percentages according to different papers, III and V). Thus a FNA diagnosis of NIFTP is not possible with certainty, and histology is needed for a definitive diagnosis.

Molecular data - It is well known that the molecular profile of EFVPTC is similar to that of follicular adenoma or carcinoma, with a high prevalence of *RAS* mutations and *PAX8/PPAR γ* fusions, whereas the non-encapsulated FVPTC is more commonly associated to *BRAF* mutations (1). In cytology, the role of preoperative molecular testing has been valued by several papers, concluding that molecular results must be carefully interpreted in individual contexts, since they do not replace clinical judgment: however, molecular testing is thought to bear a high diagnostic potential, mainly in the study of thyroid nodules with indeterminate cytology.

As EFVPTC, NIFTP are not expected to show molecular alterations associated with classical PTC, such as *BRAF* V600E mutations. In a series of NIFTP, in fact, Nikiforov demonstrated the presence of *RAS* and other mutations associated with follicular-

Table 2. Risk of malignancy (expressed as %) changes within the different cytological categories (according to Bethesda system) after downgrading NIFTP to a “not malignant” neoplasm

| | I | II | III | IV | V | VI |
|----------------------------------|-------|--------|-------------|---------------|--------|--------|
| Canberk S <i>et al.</i> (17) | - 50 | - 14 | - 33 | - 66 | - 33 | - 11.2 |
| Faquin WC <i>et al.</i> (18) | - 5.5 | - 37.6 | - 43.6 | - 45.5 | - 28.3 | - 3.3 |
| Jeon MJ <i>et al.</i> (26) | | | 7-35 → 5-24 | 28-49 → 23-39 | | |
| Strickland KC <i>et al.</i> (27) | - 10 | - 59 | - 45% | - 18 | - 48 | - 5 |

Abbreviations: NIFTP: noninvasive follicular thyroid neoplasm with papillary-like nuclear features.

patterned thyroid tumors, while *BRAF* mutations or *RET/PTC* rearrangements were absent (1). A few recently published papers dealt with molecular testing of NIFTP in FNA cytology materials.

Bizzarro *et al.* confirmed the findings of resected specimens: *BRAF* gene mutation was found in 38.4% of infiltrative FVPTC, while all NIFTP were *BRAF* gene wild-type (16). Paulson *et al.* collected a series of thyroid tumors with *RAS* mutations, demonstrating that over half (59%) of them would now be diagnosed as NIFTP and that they are typically associated with an indeterminate diagnosis on FNA: in the appropriate clinical context (that is, where clinical and sonographic data support a low-risk profile), these results may suggest lobectomy as the initial surgical approach for a *RAS* mutated nodule with an indeterminate FNA cytology (23). Borelli *et al.* investigated the use of miRNA expression profiles in distinguishing between NIFTP versus follicular adenomas and infiltrative FVPTC: specific panels of miRNA could be of help in the triage of indeterminate thyroid nodules at FNA (for example, miR-10a-5p and miR-320e can discriminate between NIFTP and infiltrative FVPTC) (24). Finally, Jiang *et al.* tested the performance of the Afirma gene expression classifier (GEC) and the University of Pittsburgh Medical Center (UPMC) targeted mutation panel tests in NIFTP nodules (25). In particular, all four NIFTP tested with GEC were identified as “suspicious”, while all the other four cases tested with UPMC ThyroSeq V2 showed *RAS* mutations (and one of them a double *RAS* and *TERT* mutation), thus implying that both the GEC and UPMC methods indicate abnormalities in NIFTP.

Question:

Can molecular tests be of help in NIFTP FNA cytology characterization?

Answer:

Invasive PTC are more likely to contain *BRAF* mutations, while pure follicular patterned neoplasms with papillary-type nuclei, including invasive EFVPTC and NIFTP, frequently carry *RAS* mutations or *PAX8-PPARγ* fusions. Since NIFTP lesions tend to be diagnosed in the indeterminate categories of thyroid cytology, molecular tests are expected to have a role in its diagnosis and recognition. A few papers detected *RAS* mutations and specific miRNA expression profiles in FNA specimens of NIFTP, thus adding some diagnostic tools in the pre-operative triage of thyroid lesions. However, experiences and cases series are limited and further studies needed.

NIFTP Induced Shift in the Risk of Malignancy Assessment of the Bethesda Categories

The redefinition of NIFTP as a neoplasm rather than a carcinoma is expected to alter the intrinsic risk of malignancy for the diagnostic categories of TBSRTC. Four papers dealt with this

topic and their findings are summarized in Table 2 (17, 18, 26, 27). The downgrading of NIFTP in the “not malignant” category will have an impact mainly in the indeterminate categories of Bethesda System (category III-IV-V), where the risk is expected to be reduced, while the benign (II) and the malignant categories (VI) will probably be less affected. Of course, changes in FNA reporting and predicting the risk of malignancy in Bethesda cytological categories are needed, but further studies are required. At present, the change on the risk of malignancy for each diagnostic categories cannot be assessed with certainty since it depends on several factors (reproducibility of diagnostic criteria, in both cytological and histological specimens, prevalence of thyroid lesions and mainly of NIFTP in different populations and availability of ancillary technique such as molecular testing, which may impact on the risk of malignancy and need to be integrated with morphology).

Question:

How is the recent downgrading of NIFTP into the “not malignant lesion” category expected to impact on the risk of malignancy of the different cytological diagnostic categories?

Answer:

The use of the NIFTP terminology and the shift of a part of EFVPTC from the malignant into the “not malignant” category will have repercussions on the risk of malignancy assessment of the different categories of thyroid cytology: in particular indeterminate categories (III, IV and VI sec. Bethesda System) will be most affected with a significant reduction in the risk of malignancy. Further studies, however, are needed, in order to accurately define the new risks of malignancy for each diagnostic category.

Conclusions

“NIFTP” is a recently introduced acronym that renamed the previously called “encapsulated follicular variant of papillary thyroid carcinoma without capsular and/or vascular invasion”. The downgrading of this entity from a malignant lesion potentially needing radioiodine treatment after radical surgery to an indolent neoplasm with no need of further treatment is expected to have a profound impact on clinical management of patients affected by follicular thyroid nodules. The American Thyroid Association Thyroid Nodules and Differentiated Thyroid Cancer Guidelines Task Force recently joined to review and make recommendations related to this newly proposed entity. Given the excellent prognosis of this variant, the Task Force recommended the adoption of this new terminology, but also expressed the need of further retrospective studies to validate the study by Nikiforov *et al.* (28). Waiting for validation studies, the forthcoming edition of the WHO fascicle on Tumor of Endocrine Organs (expected May

2017), will include NIFTP together with Well Differentiated Tumors of Uncertain Malignant Behavior (or WDT-UMP) in a separate paragraph on “Other encapsulated follicular-patterned thyroid tumors”.

In FNA cytology, NIFTP share many of the diagnostic features of FVPTC, but are usually categorized as indeterminate, due to somewhat incomplete evidence of papillary carcinoma nuclei and the prevalent follicular growth pattern. Their “newly defined” not malignant nature will have a profound impact on the risk of malignancy assessment of the Bethesda diagnostic categories (III, IV and V). All this will eventually affect the extent of surgery since patients with NIFTP are at very low risk of unfavorable outcome after lobectomy. By combining ultrasound features, cytological and molecular information and after careful stratification, clinicians may be prompted to offer hemithyroidectomy instead of total thyroidectomy in selected “indeterminate” category patients. Reclassification of the FVPTC to NIFTP will favor a risk-adapted management, much more appropriate in terms of overtreatment, iatrogenic complications, emotional burden on patients and cost implications.

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