Pathology International 2018; **xx:** 1–7 doi:10.1111/pin.12673

Editorial

Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) in thyroid tumor classification

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In 2016, a new morphological thyroid tumor entity, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), was introduced to replace a group of low-risk tumors known as noninvasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC).[1] Since then, there have been more than 60 publications with a keyword of NIFTP according to a PubMed literature survey on October 28, 2017. These publications cover many aspects on this new tumor entity, cytological diagnosis, ultrasound features, molecular genotyping, clinical management and long-term outcome of NIFTP patients. They supported an indolent nature of NIFTP even in large size (>4 cm) tumors.[2–5] Under ultrasound examination, NIFTPs are usually in low-suspicion nodules while invasive EFVPTC in intermediate-suspicious nodules and infiltrative FVPTCs in high-suspicion nodules.[3,6,7] In FNA cytology, the majority of NIFTP are classified in indeterminate (atypia of uncertain significance/follicular lesion of uncertain significance, follicular neoplasm/suspicious for follicular neoplasm or suspicious for malignancy) categories.[7–18] The new 4th edition of the World Health Organization (WHO) Classification of Tumours of Endocrine Organs including thyroid tumors was published in 2017 and it incorporated a new chapter on borderline tumors of follicular cell origin.[19] These included hyalinizing trabecular tumor,[20] uncertain malignant potential (UMP),[21] and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).[1] UMP and NIFTP were incorporated as subchapters in a new chapter of other encapsulated follicular-patterned thyroid tumors[19] (Table 1). Their behavior codes were set as /1 (unspecified, borderline, or uncertain behavior), and not /0 (benign tumors), /2 (carcinoma in situ and grade III intraepithelial neoplasia), or /3 (malignant tumors).[19]

This editorial was written by seven authors, on behalf of all authors of the NIFTP working group,[1] to refine diagnostic criteria for NIFTP in order to improve concordance in the diagnosis and to address several issues with the diagnosis of NIFTP raised in recent publications.

DEFINITION OF NIFTP BY NIKIFOROV *ET AL*. AND ITS PROGNOSIS

Prior to the introduction of the NIFTP nomenclature, all encapsulated follicular pattern tumors with nuclear features of PTC were categorized as malignant tumors even without invasive growth.[22] Several reports questioned the biological behavior of noninvasive encapsulated follicular pattern tumors.[23–32] An international panel of 24 expert thyroid pathologists reviewed 109 patients with noninvasive EFVPTC and confirmed all patients were alive with no evidence of disease after a median of 13 years follow up, and proposed a new tumor name, NIFTP, to replace the term noninvasive EFVPTC.[1] These authors suggested that NIFTP is an oncogene-driven neoplasm that belongs to a category of borderline tumors, with a potential to progress to an invasive EFVPTC.[1,33]

In the original definition of well differentiated tumor-UMP (WDT-UMP) by Williams published in 2000,[21] an overlap between NIFTP and WDT-UMP occurred in cases with incomplete PTC-type nuclear features when capsular and vascular invasion were absent (Figs. 1, 2). The 4th edition WHO classification modified the diagnostic criteria slightly, i.e., no capsular or lymphovascular invasion for NIFTP, questionable capsular or vascular invasion for WDT-UMP, and definite capsular or vascular invasion for invasive

Table 1 Borderline/precursor tumors in the 2017 WHO classification of thyroid tumors.

2	Hyalinizing trabecular tumor
2A	Other encapsulated follicular-patterned thyroid tumors
2A-1	Uncertain malignant potential (UMP)
2A-1-1	Follicular tumor of uncertain malignant potential (FT-UMP)
2A-1-2	Well differentiated tumor of uncertain malignant potential (WDT-UMP)
2A-2	Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

EFVPTC (Fig. 2).[19] The 4th edition WHO classification further provided a diagnostic algorithm (Fig. 3) for NIFTP, UMP, follicular adenoma (FA), and carcinoma (FTC and invasive EFVPTC). Moreover, a nuclear scoring method to quantify nuclear changes (available at http://jamanetwork.com/journals/jamaoncology/fullarticle/2513250) was found useful to identify subtle papillary-like nuclear features characteristic of NIFTP (Fig. 4).[1,19,34,35]

REPORTED NIFTPS WITH METASTASIS AND/OR BRAF V600E MUTATION

Although most previous reports confirmed the biologically indolent nature of NIFTP, there have been a few studies that reported metastatic NIFTPs.[3,6,36–40] In a study by Valderrabano, *et al*. two tumors with metastases initially classified as NIFTP, were found to be invasive upon re-review (capsular invasion in one and vascular invasion in the other one) (Valderrabano and Kakudo, 2017, personal communication).[36] Rosario reported lymph node metastasis in his one NIFTP among 10 patients whose histological examination of lymph nodes were available, but the patient had coexisting conventional papillary microcarcinoma associated with NIFTP.[3] Parente *et al*. retrospectively examined 102 (2.1%) tumors reclassified as NIFTP among from 4790 PTCs with strict criteria for NIFTP with no papillae, and found 5 (4.9%) cases with lymph node metastasis and 1 (1%) case with distant metastasis.[37]

Relatively frequent BRAF V600E mutation in NIFTPs has been reported in studies from Korea,[6,38–40] in which lymph node metastases were also reported. According to Kim *et al*., NIFTPs defined by the proposed criteria exhibited lymph node metastasis in 9 (12%) of their 74 NIFTPs, but importantly 5 of their 9 cases had coexisting conventional PTCs.[38] One of the author of this publication (YN) examined 4 out of 5 reported NIFTPs with BRAFV600E mutation reported by Lee *et al*.[39] One case had true papillae, another one show capsular invasion on deeper cut sections. The remaining 2 cases met the NIFTP criteria, but the number of tissue sections was likely to be inadequate. Cho, *et al*. examined 152 EFVPTCs among 62,969 PTCs with their proposed cutoff point for papillae, either at 0% papillae (45 invasive and 95 noninvasive) or less than 1% papillae (47 invasive and 105 noninvasive).[40] They found 3 (3%) cases with central lymph node metastasis, 1 (1%) case with distant metastasis, and 10 (10%) cases with BRAF V600E mutation in their 105 NIFTPs with less than 1% papillae (based on the original definition by Nikiforov, *et al*.). When stricter criteria (no papillae) were applied, all cases with BRAF V600E mutation were eliminated from their 95 cases without invasion, but central lymph node metastasis remained in 2 (3%) cases.[40] One of the authors of this publication (KK) reviewed these two cases with microscopic lymph node metastasis (less than 2 mm) using virtual slide and found these two cases met NIFTP criteria

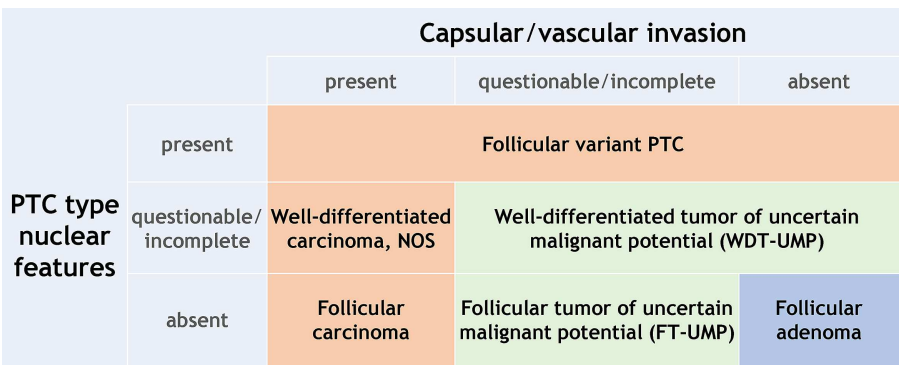

Figure 1 Recommended nomenclature for encapsulated well differentiated follicular-patterned thyroid tumors on the basis of the presence or absence of papillary thyroid carcinoma (PTC)-type nuclear features and capsular invasion proposed by Williams ED in 2000. Light orange indicates malignant tumors, light green for borderline tumors, and light blue for benign follicular adenoma.

PTC type nuclear features	Capsular/vascular invasion: present	Capsular/vascular invasion: questionable/incomplete	Capsular/vascular invasion: absent
present	Follicular variant PTC	Well-differentiated tumor of uncertain malignant potential (WDT-UMP)	Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)
questionable/incomplete	Well-differentiated carcinoma, NOS		
absent	Follicular carcinoma	Follicular tumor of uncertain malignant potential (FT-UMP)	Follicular adenoma

Figure 2 A new definition of follicular variant papillary thyroid carcinoma (PTC), Noninvasive Follicular Thyroid neoplasm with Papillary-like nuclear features (NIFTP), and WDT-UMP (well differentiated tumor of uncertain malignant potential) in the 4th edition WHO classification. Noninvasive parts of follicular variant PTC and WDT-UMP were merged into NIFTP. Questionable/incomplete capsular invasion of follicular variant PTC was merged into WDT-UMP. Light orange indicates malignant tumors, light green for borderline tumors, and light blue for benign follicular adenoma.

and had florid nuclear features of PTC. Molecular test revealed that these two cases had BRAF wild type (Jung and Kakudo, 2017, personal communication).

PROPOSED MODIFICATIONS OF DIAGNOSTIC CRITERIA (EXCLUSION CRITERIA) FOR NIFTP

The authors of this editorial concluded that reported NIFTPs with lymph node metastasis and/or BRAF V600E mutation are likely due to using more relaxed histological criteria for NIFTP or incomplete examination of the tumor capsule or the entire tumor. In the original publication of NIFTP by Nikiforov *et al*., six exclusion criteria were listed: (i) true papillae >1%, (ii) psammoma bodies, (iii) invasion, (iv) tumor necrosis, (v) high mitotic activity, and (vi) >30% solid growth pattern or other morphological characteristics of specific PTC variants.[1] These exclusion criteria were aimed to exclude conventional PTC (true papillae <1% and psammoma bodies), invasive EFVPTC (invasion), poorly differentiated carcinoma (tumor necrosis and high mitotic activity), and other PTC variants (cellular/morphological characteristics of other PTC variants). The presence of <1% papillae in the initial NIFTP definition was allowed to account for few delicate, poorly-formed, hyperplastic-type papillae that should be distinguished from true papillae seen in classical PTC. However, in light of the fact that this criterion has been used to allow for true papillae, leading to misdiagnosis of classical PTC as NIFTP, the NIFTP working

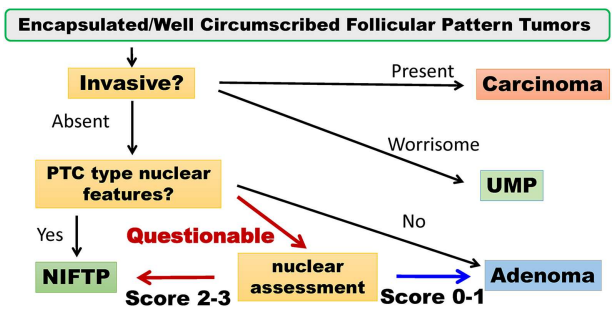

Figure 3 Diagnostic algorithm for carcinoma, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), uncertain malignant potential (UMP), and follicular adenoma, proposed in the 4th edition WHO classification of Endocrine Organs. First, it must be an encapsulated follicular pattern tumor. When capsular and/or vascular invasion is present, it is classified as carcinoma, either follicular carcinoma or invasive encapsulated follicular variant papillary thyroid carcinoma (PTC). When there is worrisome capsular/vascular invasion, it becomes UMP, either WDT-UMP (with PTC-type nuclear features) or FT-UMP (without PTC-type nuclear features). If it is noninvasive, PTC-type nuclear features are assessed. When PTC-type nuclear features are negligible (score 1 or 0), it is classified as follicular adenoma. If present (nuclear score 2 or 3), it is diagnosed as NIFTP . The nuclear assessment guide is available at http://jamanetwork.com/journals/jamaoncology/fullarticle/2513250.

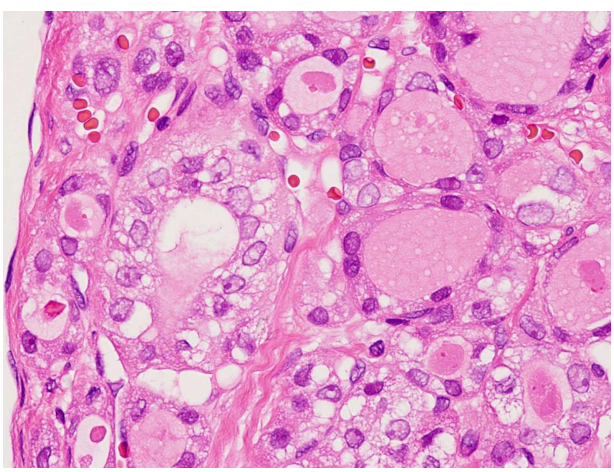

Figure 4 Papillary-like nuclear features, nuclear score 3 (positive for nuclear enlargement, nuclear membrane irregularity, and chromatin clearing) seen in a 40-year-old female patient with NIFTP. These nuclear features are very minor compared with the florid nuclear changes shown in Fig. 5.

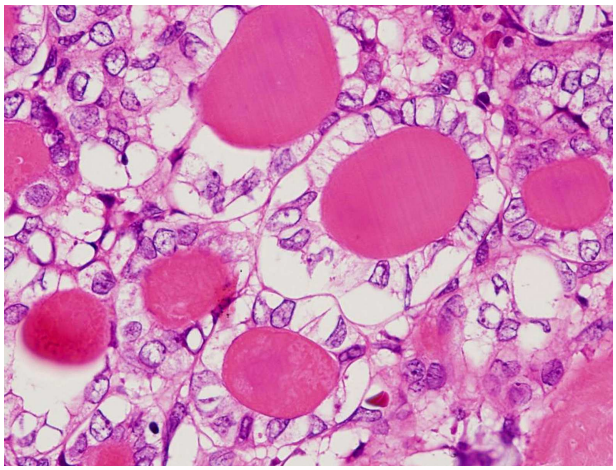

Figure 5 Fully developed papillary thyroid carcinoma-type nuclear features seen in a 65-year-old female patient with invasive encapsulated follicular variant of papillary thyroid carcinoma. Note the florid nuclear features of the papillary carcinoma-type with nuclear score 3 (positive for nuclear enlargement, pronounced nuclear membrane irregularity, and positive chromatin clearing).

group proposes the following modification to the original NIFTP diagnostic criteria as follows:

1) No any true papillae are allowed for the diagnosis of NIFTP, so that the previous exclusion criteria "true papillae $<$ 1%" should be replaced with "no true papillae".

2) Florid nuclear features of PTC (reflected in cases that would have a nuclear score equal to "3") is not an exclusion criterion, but is rarely seen without true papillae. If such nuclear features are seen (Fig. 5), examination of the entire tumor, not just the capsule, with optional, but recommended analyses for BRAF V600E using either immunohistochemical methods or molecular techniques may be necessary. As NIFTP is associated with RAS and other RAS-like mutations,[1,16,26,28,31,32,37–45] misclassification of invasive EFVPTC (Fig. 5) and infiltrative FVPTC with BRAFV600E mutation as NIFTP should be avoided. With detailed histological examination of the entire tumor, most NIFTPs with suggested metastasis and/or BRAF V600E mutation can be eliminated. If genotyping is available, BRAF V600E mutation, RET/PTC rearrangements, and TERT mutations should be used to exclude NIFTP. Needless to say, any tumors with histologically confirmed metastasis should not be classified in the borderline tumor category.

PREOPERATIVE DIAGNOSIS OF BORDERLINE TUMORS

In the 4th edition WHO classification, it was stated that a reliable distinction between NIFTP and PTC cannot be made cytologically,[19,46,47] although the majority of NIFTPs are placed in indeterminate cytological categories and approximately half of them are in the high-risk indeterminate (Bethesda category IV) FN/SFN cytological category.[7–18,44] Similarly, a reliable distinction between NIFTP and FTC or invasive FVPTC cannot be made using molecular testing, although the finding of RAS-like mutations in the FNA sample provides strong evidence for NIFTP or other low-risk cancer in the tested nodule.[45] The authors of this editorial believe that cytologial, molecular, and sonographic findings should be integrated to improve preoperative diagnostic accuracy to facilitate the most optimal management of patients.

IMPACTS OF BORDERLINE TUMORS IN ASIAN COUNTRIES' THYROID PRACTICE

The prevalence of NIFTP was reported to be high (15–25% of thyroid carcinomas or PTCs) in most Western countries' practices,[1–3,7–18,43,45] but was low (0–5% of PTCs) in most Asian countries' practices[6,27,37–39,48–53] and in some Western practices.[27,37,54,55] Therefore, the impact of NIFTP on risk of malignancy on thyroid fine-needle aspiration diagnosis was estimated to be small in Asian countries[48–50] compared with having a significant impact in Western countries, where more than one third of thyroid carcinomas with indeterminate nodules were NIFTP.[7–18,44,49,50,54,55]

In Western practices, the proposal of NIFTP was intended to downgrade noninvasive EFVPTC from the malignant category to a biologically indolent, borderline category to prevent patient's overtreatment.[1] However, this may be less important in Asian practices because most tumors meting the NIFTP criteria are likely to be classified as benign follicular adenomas in most cases.[28,48,51–60] The introduction of borderline tumors in Asian countries may upgrade FAs to borderline tumors more often than downgrading EFVPTC from carcinoma to borderline tumors.[28,30,48–51,56–60] Therefore it is advisable in Asian practices to follow a more conservative approach when upgrading the diagnosis of FA to NIFTP is considered. In fact, it is important to stress that in minor nuclear changes (nuclear score 0 or 1) is not sufficient to classify a given tumor as NIFTP (Fig. 3).[1,19,61–64]

CLINICAL MANAGEMENT OF BORDERLINE TUMORS IS BEING EVALUATED AND DISCUSSED BY SEVERAL CLINICAL SOCIETIES

Regarding the NIFTP reclassification, the American Thyroid Association (ATA) task force recommended to adopt the NIFTP terminology, noticing that it replaces a group of noninvasive follicular variant PTCs which were considered as low-risk cancers by the ATA cancer risk stratification discussed in the 2015 ATA guidelines.[65] It further added that the proposed reclassification from carcinoma to borderline/precursor tumor should not be interpreted as supporting a

non-surgical approach to NIFTPs, as the diagnosis of NIFTP cannot be made without surgery followed by careful microscopic examination of the tumor.[65] As in most Western practice, it is important that if the diagnosis of NIFTP is suspected pre-operatively, a limited surgery (lobectomy) may be considered for many of these patients to avoid missing malignancy. However, diagnostic surgery is harmful to the patient and should be minimized, even if the surgery is restricted to a lobectomy. It should be noted that significant numbers of patients later develop hypothyroidism and a few exhibit hypoparathyroidism and/or laryngeal nerve dysfunction. Conzo *et al*. reported that 15.1% of 1379 patients treated with thyroidectomy for FN/SFN nodules in 26 Italian hospitals had surgery-related complications.[66] As a conservative approach (active surveillance without invasive test) to patients with AUS/FLUS and FN/SFN thyroid nodules is favored in Asian practice, risk stratification of the patient and close follow up of patients with benign clinical findings has been proposed by the Japan Thyroid Association clinical guidelines.[53,57–60,63–65] With this conservative clinical management of the patient, significant numbers of patients with benign nodules, borderline tumors and low-risk thyroid carcinomas are saved from immediate surgery for diagnostic purposes in Asian practice.[50,61–64,67–69] This is one of the reasons why rates of NIFTP are low in surgically treated patients in Asian countries.[48–50,53,61,64]

As clinical management of these tumors is being evaluated by various professional societies, further recommendations for managing patients with NIFTP and other borderline tumors are expected to be issued incorporated into clinical practice.

ACKNOWLEDGMENTS

The authors of this editorial thank all members of the NIFTP working group (Seethala RR, Tallini G, Baloch ZW, Basolo F, Wenig BM, Al Ghuzlan A, Giordano TJ, Alves VA, Asa SL, Gooding WE, Lloyd RV, Maytal G, Mete O, Nikiforova MN, Papotti M, Poller DN, Sadow PM, Tischler AS, Tuttle RM, Wall KB, LiVolsi VA, Randolph GW, Ghossein RA.).

DISCLOSURE STATEMENT

Dr Nikiforov holds intellectual property related to Thyroseq test. Nothing to disclose by the other authors.

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