Noninvasive follicular thyroid neoplasm with papillary-like nuclear features: its updated diagnostic criteria, preoperative cytologic diagnoses and impact on the risk of malignancy

Hee Young Na\textsuperscript{1,2}, So Yeon Park\textsuperscript{1,2}

\textsuperscript{1}Department of Pathology, Seoul National University Bundang Hospital, Seongnam; \textsuperscript{2}Department of Pathology, Seoul National University College of Medicine, Seoul, Korea

As nuclear features of papillary thyroid carcinoma (PTC) have been increasingly recognized, the incidence of follicular variant PTC (FVPTC), especially encapsulated subtype, rose 2- to 3-fold over the past decade in Europe and North America \cite{1}. Because of the indolent behavior reported in a subset of noninvasive encapsulated FVPTCs (noninvasive EFVPTCs), the terminology “noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)” was proposed in 2016 by the Endocrine Pathology Society working group \cite{2} to avoid overdiagnosis and unnecessary psychological and financial burden on both clinicians and patients. The advent of this new terminology has brought up certain issues including the proper diagnostic criteria, actual incidence, preoperative fine-needle aspiration cytology (FNAC) diagnosis, and clinical impact of this neoplasm. This review highlights on the changes in diagnostic criteria of NIFTP, actual incidence in different regions, cytologic features, preoperative FNAC diagnostic categories, and its impact on the risk of malignancy in the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC).

**Key Words:** Thyroid; Noninvasive follicular thyroid neoplasm with papillary-like nuclear features; Fine-needle aspiration cytology; Risk of malignancy

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**Corresponding Author:** So Yeon Park, MD, PhD, Department of Pathology, Seoul National University Bundang Hospital, 82 Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam 13620, Korea

Tel: +82-31-787-7712, Fax: +82-31-787-4012, E-mail: sypmd@snu.ac.kr

The initial diagnostic criteria proposed by Nikiforov et al. in 2016 \cite{2}, the revised criteria suggested in 2018 \cite{3}, and the most recent criteria in the 2022 World Health Organization (WHO) classification \cite{4} are summarized in Table 1. In initial criteria, noninvasive EFVPTCs with < 1% papillae, no psammoma bodies and < 30% solid/trabecular/insular growth pattern were renamed as NIFTP in the absence of necrosis and high mitotic activity \cite{2}.

**UPDATES ON DIAGNOSTIC CRITERIA OF NONINVASIVE FOLLICULAR THYROID NEOPLASM WITH PAPILLARY-LIKE NUCLEAR FEATURES**

As nuclear features of papillary thyroid carcinoma (PTC) have been increasingly recognized, the incidence of follicular variant PTC (FVPTC), especially encapsulated subtype, rose 2- to 3-fold over the past decade in Europe and North America \cite{1}. Because of the indolent behavior reported in a subset of noninvasive encapsulated FVPTCs (noninvasive EFVPTCs), the terminology “noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)” was proposed in 2016 by the Endocrine Pathology Society working group \cite{2} to avoid overdiagnosis and unnecessary psychological and financial burden on both clinicians and patients. The advent of this new terminology has brought up certain issues including the proper diagnostic criteria, actual incidence, preoperative fine-needle aspiration cytology (FNAC) diagnosis, and clinical impact of this neoplasm. This review highlights on the changes in diagnostic criteria of NIFTP, actual incidence in different regions, cytologic features, preoperative FNAC diagnostic categories, and its impact on the risk of malignancy in the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC).
Table 1. Diagnostic criteria for noninvasive follicular thyroid neoplasm with papillary-like nuclear features

| Initial criteria [2]                                      | Revised criteria [3]                                      | The 2022 WHO classification [4]                           |
|----------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|
| 1. Encapsulation or clear demarcation                     | 1. Encapsulation or clear demarcation                     | Essential                                                |
| 2. Follicular growth pattern with <1% papillae            | 2. Follicular growth pattern with <1% papillae            | 1. Encapsulation or clear demarcation                     |
| No psammoma bodies                                        | No psammoma bodies                                        | 2. Follicular growth pattern with                       |
| <30% solid/trabecular/insular growth pattern              | <30% solid/trabecular/insular growth pattern              | <1% true papillae                                        |
| 3. Nuclear score 2–3                                     | Nuclear score of 2–3                                     | No psammoma bodies                                       |
| 4. No vascular or capsular invasion                       | No vascular or capsular invasion                          | <30% solid/trabecular/insular growth pattern              |
| 5. No tumor necrosis                                      | No tumor necrosis                                         | Nuclear score of 2–3                                     |
| 6. No high mitotic activity                               | 2. Secondary                                             | 3. Nuclear score of 2–3                                 |
|                                                          | Lack of BRAF V600E mutation detected by molecular         | 4. No vascular or capsular invasion                      |
|                                                          | assays or immunohistochemistry                           |                                                          |
|                                                          | Lack of BRAF V600E-like mutations or other high-risk     |                                                          |
|                                                          | mutations (TERT, TP53)                                    |                                                          |
|                                                          | 7. Lack of cytoarchitectural features of papillary        |                                                          |
|                                                          | carcinoma variants other than follicular variant          |                                                          |
|                                                          | Desirable                                                |                                                          |
|                                                          | Immunohistochemistry or molecular testing                 |                                                          |
|                                                          | for BRAF and NRAS mutation                               |                                                          |

WHO, World Health Organization.

(Fig. 1). Among these histologic criteria, the proportion of papillae has become the center of controversy. Above all, it is important to acknowledge that the authors intended to count the proportion of “true papillae”, not rudimentary or hyperplastic type papillae. Although Nikiforov et al. [2] have reported no adverse events in cases with NIFTPs in the initial study, lymph node metastases and even distant metastases of NIFTPs were reported by other researchers [5]. Moreover, some of these cases harbored BRAF V600E mutation, which is rather a hallmark of conventional PTC [5]. These findings led to the revised criteria which restricted the diagnosis of NIFTP to cases without any well-formed papillae (true papillae) [3]. Also, absence of BRAF V600E or other high-risk mutations involving TP53 or TERT promoter, were additionally described as helpful but not required features of NIFTP [3]. However, larger number of studies demonstrated lack of metastasis and disease recurrence in cases harboring <1% papillae [6-9]. In the study by Xu et al. [8], lymph node metastasis was only observed in cases with >10% papillae. The 2022 WHO classification endorses the original criteria allowing <1% papillae based on these studies [4]. However, lymph node metastases [5,10], and even distant metastases [10] were found in NIFTPs with 0% papillae, despite thorough microscopic examination. Authors of these studies underscored the low-risk malignant nature of NIFTP and the necessity of including NIFTP in cancer registry [5,10]. Although cases less than 1cm or showing oncocytic features that are otherwise consistent with NIFTP were not included in the initial study [2], the new WHO classification will also include these scenarios because previous studies have confirmed similar behavior as NIFTPs without these features [9,11].

**ACTUAL INCIDENCE OF NONINVASIVE FOLLICULAR THYROID NEOPLASM WITH PAPILLARY-LIKE NUCLEAR FEATURES**

Although it was initially suspected that a substantial proportion of EFVPTCs would be regrouped as NIFTPs, the actual incidence varies greatly according to geographic regions as depicted in recent meta-analyses [12]. The reported incidences of NIFTP range from 1.3% to 23.4% in North America [13-15], from 0.7% to 34.9% in Europe [16-18], and from 0.4% to 29.4% in Asia [19-21]. The pooled incidence of NIFTP was 9.3% and 9.6% in North American and Europe, which was far higher than in Asia with 2.1%, indicating the geographical or ethnic differences [12]. In Korea, the incidence of NIFTP investigated by a multi-institutional study was 0.8%, even lower than Asian average [22]. Of note, the worldwide incidence of NIFTP was 6.0% in the same meta-analysis, suggesting that the impact of NIFTP would not be as considerable as initially estimated [12]. Interestingly, different institutes in the same region also reported widely varying incidences of NIFTP [10,13,15,23], suggesting that interpreting nuclear atypia still lays in subjective area despite the effort to objectifying the nuclear features into three-tiered score.

**PREOPERATIVE CYTOLOGIC DIAGNOSES OF NONINVASIVE FOLLICULAR THYROID NEOPLASM WITH PAPILLARY-LIKE NUCLEAR FEATURES**

More conservative management is considered for NIFTPs
compared with conventional PTCs (cPTCs) which require lymph node dissection and radioactive iodine treatment if indicated. Therefore, it has become a major interest whether NIFTP can be diagnosed preoperatively or not.

Upon the introduction of NIFTP terminology, researchers have investigated the differences in cytologic features of NIFTP and other related lesions such as benign follicular lesion, follicular thyroid adenoma, FVPTC, and cPTCs. The results of studies comparing cytologic features of NIFTP and other lesions are summarized in Table 2. In FNAC, NIFTPs generally show crowded syncytial-like fragments containing microfollicles (Fig. 1) [24,25]. Compared with cPTCs, NIFTPs are more commonly associated

Fig. 1. Histologic and cytologic features of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). (A) A well-demarcated mass composed of variable-sized neoplastic follicles is observed in scan view. (B) In high power view, mild nuclear atypia including chromatin clearing, and occasional nuclear grooves which corresponds to “nuclear score 2” is seen (B). (C, D) Fine-needle aspiration cytology of NIFTP generally shows syncytial cell clusters containing microfollicles. Thick colloid can be observed in the microfollicles (arrows). (E, F) Pale chromatin, occasional nuclear grooves, marginal nucleoli are seen. The nuclear atypia is typically mild and patchy. Intranuclear pseudoinclusions, psammomatous calcifications are absent in the presented cases.
with predominant microfollicular pattern in bidimensional clusters and show absent or rare papillary structure [26-30]. Monolayered sheet pattern and tridimensional clusters are more frequent in cPTCs [29,30]. Papillary-like nuclear features, including nuclear enlargement, nuclear elongation, chromatin clearing, intranuclear pseudoinclusion are usually mild and patchy (Fig. 1) [14,26,27,29-32]. Diffuse nuclear change and presence of nuclear score 3 can be observed but are reported to be less frequent than in cPTCs [32]. Regarding the nature of colloid, NIFTPs are associated with thick, dense colloid found both in and out of the microfollicles, while cPTCs tend to show ropy colloid [30]. Psammoma bodies and multinucleated giant cells are also absent or infrequent in NIFTPs compared with cPTCs [14,30]. Indeed, Strickland et al. [33] have demonstrated that NIFTPs and invasive FVPTCs can be efficiently separated from cPTCs in preoperative FNAC when diagnosed according to the criteria as following: (1) cPTC: presence of papillae, pseudoinclusions, or psammomatous calcifications; (2) NIFTP and invasive FVPTC:

Table 2. Comparison of cytologic features of NIFTP with other lesions

| Reference            | NIFTP vs. benign/FTA | NIFTP vs. FVPTC | NIFTP vs. cPTC | NIFTP/FVPTC vs. cPTC |
|----------------------|----------------------|-----------------|----------------|----------------------|
| Legesse et al. [14]  | -                    | Less frequent PIs, marginal micronucleoli, irregular branching sheets, and linear arrangement in NIFTP | Absence of PIs/Less frequent MNGs in NIFTP | - |
| Bizzarro et al. [26] | More frequent scant cytoplasm, NE, nuclear elongation, chromatin clearing, grooves, and membrane irregularities in NIFTP | Less frequent grooves in NIFTP | Less frequent papillae, NE, PIs, grooves, and membrane irregularities in NIFTP | - |
| Brandler et al. [27] | More frequent chromatin clearing, crowding, and NE in NIFTP | - | Less frequent PIs, papillae, crowding, NE, membrane irregularities, chromatin clearing, calcifications, and MNGs in NIFTP | - |
| Chandler et al. [28] | -                    | More frequent MF predominance/ Less frequent nuclear elongation, grooves, and PIs in NIFTP | - | - |
| Diaz Del Arco et al. [29] | - | Less frequent nuclear folds in NIFTP | More frequent bidimensional groups and MFs/Less frequent papillary or pseudopapillary architecture, tridimensionality, MNGs, and nuclear folds in NIFTP | - |
| Koshkikawa et al. [30] | - | No differences | - | More frequent MFs, and dense globules of colloids/less frequent PIs, true papillary cell clusters, monolayered cell sheets, ropy colloids, MNGs, psammoma bodies, and cystic background in NIFTP and FVPTC |
| Howitt et al. [31]  | -                    | - | More frequent MFs/Less frequent sheet pattern in NIFTP | - |
| Mahajan et al. [32] | -                    | No differences in nuclear features/ Less frequent 3-dimensional fragments in NIFTP | Less frequent PIs, nuclear score of 3, and diffuse nuclear change in NIFTP | - |
| Salvaggi et al. [34] | -                    | Less frequent MNGs in NIFTP | - | - |
| Malefta et al. [35]  | -                    | No differences | - | - |
| Strickland et al. [33] | - | - | MF predominance without papillae, PIs or psammoma bodies in NIFTP and FVPTC | - |

NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; FTA, follicular thyroid adenoma; FVPTC, follicular variant papillary thyroid carcinoma; cPTC, conventional papillary thyroid carcinoma; PI, pseudoinclusion; MNG, multinucleated giant cell; NE, nuclear enlargement; MF, microfollicle.
microfollicle predominance without papillae, pseudoinclusions, or psammomatous calcifications. These criteria surely are not perfect because papillae or pseudoinclusions, by definition, can also be observed in NIFTPs albeit low frequency. Nevertheless, the criteria itself with some additional cytologic features mentioned above appear to be helpful in distinguishing NIFTPs from cPTCs. In addition, some researchers reported that marginal micronucleoli, nuclear grooves, pseudoinclusions, irregular branching sheet and multinucleated giant cells were more common in invasive FVPTCs than in NIFTPs [14,26,28,29,34]. However, these findings are inconsistent among different studies, and others have failed to reveal significant differences between NIFTPs and invasive FVPTCs [32,35]. Pathologists should be aware of the fact that the diagnosis of NIFTP is determined only after the histopathologic examination of surgical specimen, although certain cytologic features are more or less often associated with NIFTP than other lesions.

In FNACs, NIFTPs are usually diagnosed as indeterminate categories including atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm/suspicious for a follicular neoplasm (FN/SFN), and suspicious for malignancy categories due to microfollicular-predominant architectural pattern and subtle nuclear changes. According to previous studies, distribution of TBSRTC diagnostic categories among NIFTPs range from 0% to 25% in nondiagnostic [12,21,26,36], 0% to 35% in benign [12,26,36,37], 0% to 66.7% in AUS/FLUS [27,29,36,38], 0% to 61.9% in FN/SFN [26,29,36,39], 0% to 83.3% in suspicious for malignancy [12,27,29,36], 0% to 65.9% in malignant category [29,36,39,40]. A recent meta-analysis showed the pooled distribution of NIFTP cases in FNAC diagnostic categories as follows; 1.3% (95% confidence interval [CI], 0.8 to 1.7) in nondiagnostic, 8.9% (95% CI, 6.9 to 10.8) in benign, 29.2% (95% CI, 25.0 to 33.4) in AUS/FLUS, 24.2% (95% CI, 19.6 to 28.9) in FN/SFN, 19.5% (95% CI, 16.1 to 22.9) in suspicious for malignancy, and 6.9% (95% CI, 5.2 to 8.7) in malignant diagnostic category, respectively (Table 3) [41].

### Table 3. Distribution of diagnostic categories of noninvasive follicular thyroid neoplasm with papillary-like nuclear features and its impact on the risk of malignancy from recent meta-analysis [40]

| Diagnostic category | Proportion (%) (95% CI) | Change in ROM (%) (95% CI) |
|---------------------|-------------------------|---------------------------|
| I. Nondiagnostic    | 1.3 (0.8 to 1.7)        | -2.4 (-7.5 to 2.7)        |
| II. Benign           | 8.9 (6.9 to 10.8)       | -2.7 (-4.1 to -1.3)       |
| III. AUS/FLUS        | 29.2 (25.0 to 33.4)     | -8.2 (-11.2 to -5.1)      |
| IV. FN/SFN           | 24.2 (19.6 to 28.9)     | -8.2 (-12.3 to -4.1)      |
| V. Suspicious for malignancy | 19.5 (16.1 to 22.9) | -7.3 (-9.6 to -5.1)     |
| VI. Malignant         | 6.9 (5.2 to 8.7)        | -1.1 (-1.6 to -0.5)       |

CI, confidence interval; ROM, risk of malignancy; AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN, follicular neoplasm/suspicious for a follicular neoplasm.

NIFTPs are a group of neoplasm that have been renamed due to the indolent behavior. Although there was a change regarding the amount of papillae in the revised criteria, the initial < 1% cutoff is maintained in the 2022 WHO classification based on the recent studies. Diagnosis of NIFTP can only be made according to the strict criteria after thorough pathological examination in surgical specimen. Still, it is important to be aware that some

### IMPACT OF NIFTP ON THE RISK OF MALIGNANCY IN THE BETHESDA SYSTEM FOR REPORTING THYROID CYTOPATHOLOGY

The impact of NIFTP on the risk of malignancy (ROM) in each TBSRTC diagnostic categories largely depend on distribution of diagnostic categories of NIFTP cases. Therefore, decrease in ROM are more prominent in AUS/FLUS, FN/SFN, and suspiciou

### CONCLUSION

NIFTPs are a group of neoplasm that have been renamed due to the indolent behavior. Although there was a change regarding the amount of papillae in the revised criteria, the initial < 1% cutoff is maintained in the 2022 WHO classification based on the recent studies. Diagnosis of NIFTP can only be made according to the strict criteria after thorough pathological examination in surgical specimen. Still, it is important to be aware that some
cytological features can be helpful in distinguishing NIFTPs from cPTCs. The impact of NIFTP in cytologic diagnostic categories varies among studies, and regions which hold different incidences.

**Ethics Statement**

Not applicable.

**Availability of Data and Material**

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

**Code Availability**

Not applicable.

**ORCID**

Hee Young Na https://orcid.org/0000-0002-2464-0665  
So Yeon Park https://orcid.org/0000-0002-0299-7268

**Author Contributions**

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**Conflicts of Interest**

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