



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

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Due to the extremely indolent behavior, a subset of noninvasive encapsulated follicular variant papillary thyroid carcinomas has been classified as “noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)” since 2016 and is no longer considered carcinoma. Since the introduction of this new terminology, changes and refinements have been made in diagnostic criteria. Initially, the incidence of NIFTP was estimated substantial. However, the reported incidence of NIFTP varies greatly among studies and regions, with higher incidence in North American and European countries than in Asian countries. Thus, the changes in the risk of malignancy (ROM) in the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) differ inevitably among regions. Because more conservative surgery is recommended for NIFTPs, distinguishing NIFTPs from papillary thyroid carcinomas in preoperative fine-needle aspiration cytology became one of the major concerns. This review will provide comprehensive overview of updates on diagnostic criteria, actual incidence and preoperative cytologic diagnoses of NIFTP, and its impact on the ROM in TBSRTC.

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

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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 [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 [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).

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

The initial diagnostic criteria proposed by Nikiforov et al. in 2016 [2], the revised criteria suggested in 2018 [3], and the most recent criteria in the 2022 World Health Organization (WHO) classification [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 [2]

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. Primary Encapsulation or clear demarcation | Essential 1. Encapsulation or clear demarcation |
| 2. Follicular growth pattern with < 1% papillae No psammoma bodies < 30% solid/trabecular/insular growth pattern | Follicular growth pattern with no papillae No psammoma bodies <30% solid/trabecular/insular growth pattern | 2. Follicular growth pattern with < 1% true papillae No psammoma bodies <30% solid/trabecular/insular growth |
| 3. Nuclear score 2–3 | Nuclear score of 2–3 | 3. Nuclear score of 2–3 |
| 4. No vascular or capsular invasion | No vascular or capsular invasion | 4. No vascular or capsular invasion |
| 5. No tumor necrosis | No tumor necrosis or high mitotic activity (3 or more mitoses per 10 high power fields) | 5. No tumor necrosis |
| 6. No high mitotic activity | 2. Secondary Lack of <i>BRAF</i> V600E mutation detected by molecular assays or immunohistochemistry Lack of <i>BRAF</i> V600E-like mutations or other high-risk mutations (<i>TERT</i> , <i>TP53</i>) | 6. Low mitotic count (<3 mitoses/2 mm ²) 7. Lack of cytoarchitectural features of papillary carcinoma variants other than follicular variant |
| | | Desirable Immunohistochemistry or molecular testing for <i>BRAF</i> and <i>NRAS</i> 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

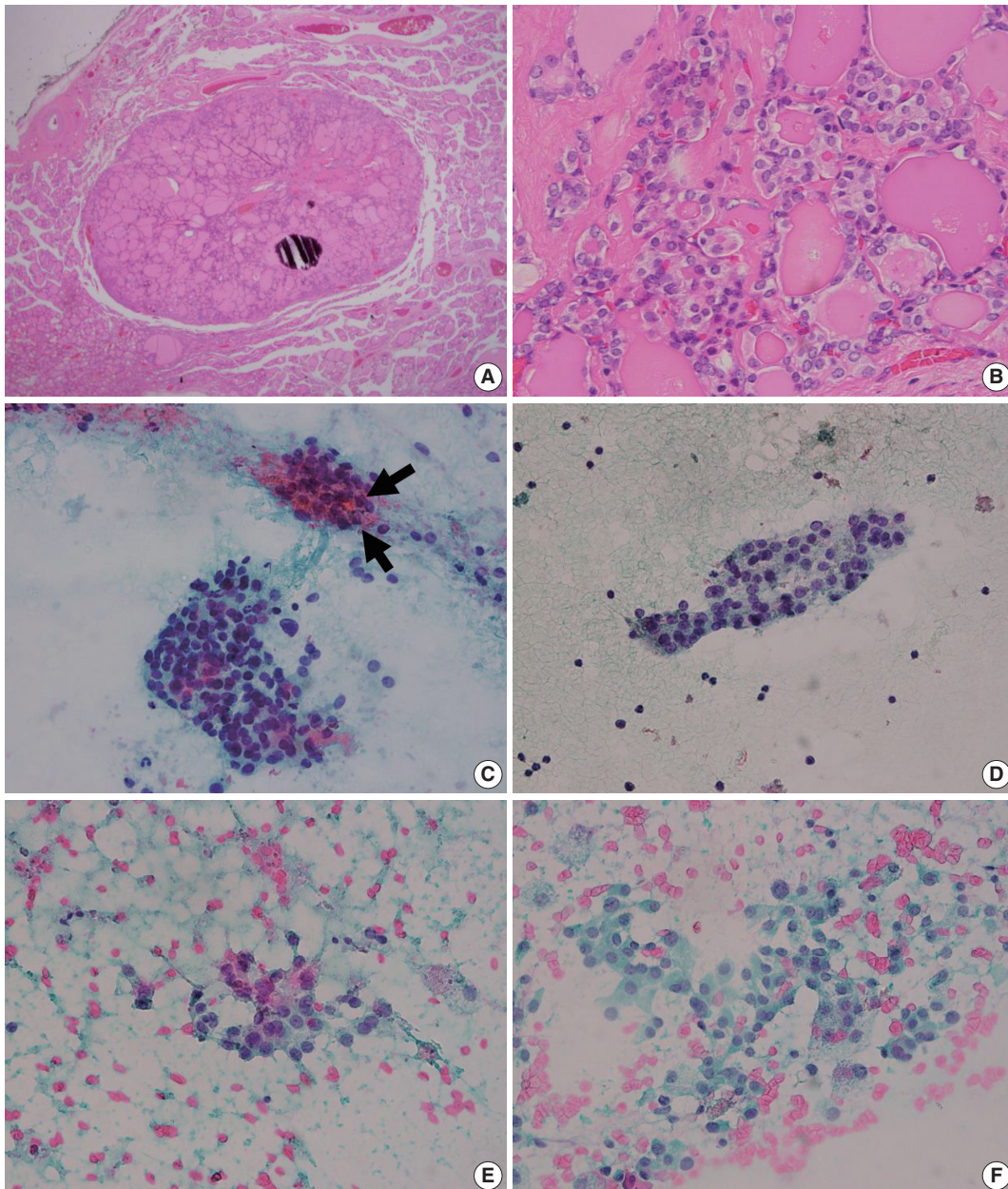


Fig. 1. Histologic and cytologic features of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). (A) A well-demarcated mass composed of variable-sized neoplastic follicles is observed in scan view. (B) In high power view, mild nuclear atypia including chromatin clearing, 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.

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

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 | - |
| Koshikawa 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 | - |
| Selvaggi et al. [34] | - | Less frequent MNGs in NIFTP | - | - |
| Maletta et al. [35] | More frequent NE, membrane irregularities, chromatin clearing, and nuclear molding in NIFTP | 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, pseudo-inclusion; MNG, multinucleated giant cell; NE, nuclear enlargement; MF, microfollicle.

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 pseudo-inclusion 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 asso-

ciated 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, pseudo-inclusions, or psammomatous calcifications; (2) NIFTP and invasive FVPTC:

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].

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 suspi-

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.

cious for malignancy categories compared with other categories. Reported changes in ROM in literature range from 0% to 20.0% in nondiagnostic [12,36,42,43], 0% to 27.6% in benign [19,36, 43,44], 0% to 20.0% in AUS/FLUS [20,36,42,44], 0.2% to 30.8% in FN/SFN [19,36,42,44], 0% to 41.5% in suspicious for malignancy [20,36,42,43], and 0% to 12.8% in malignant diagnostic categories [20,36,44,45]. A recent meta-analysis revealed that the decrease of ROM was 2.4%, 2.7%, 8.2%, 8.2%, 7.3%, and 1.1% in nondiagnostic, benign, AUS/FLUS, FN/SFN, suspicious for malignancy, and malignant diagnostic categories, respectively (Table 3) [41]. While the impact of NIFTP was suspected considerable in European and North American countries due to the high incidence of NIFTP, it does not seem to be the same in Asian counterparts. Compared with European and North American countries, Asian countries generally have reported lower incidence of NIFTPs [22,46,47]. Indeed, results from studies including Asian multi-institutional study performed by Bychkov et al. [48] indicate that magnitude of ROM decrease was slight and not significant [47]. A meta-analysis performed by Vuong et al. [49] compared the ROM decrease in Asian regions to Western counterparts and found that the decrease in ROM in each category is generally lower in Asian countries, with the greatest difference in SM category (5% vs. 18%), followed by AUS/FLUS category (8% vs. 10%).

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.

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Author Contributions

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Conflicts of Interest

SYP, the editor-in-chief of the *Journal of Pathology and Translational Medicine*, was not involved in the editorial evaluation or decision to publish this article. Remaining author has declared no conflicts of interest.

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References

- Jung CK, Little MP, Lubin JH, et al. The increase in thyroid cancer incidence during the last four decades is accompanied by a high frequency of *BRAF* mutations and a sharp increase in RAS mutations. *J Clin Endocrinol Metab* 2014; 99: E276-85.
- Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. *JAMA Oncol* 2016; 2: 1023-9.
- Nikiforov YE, Baloch ZW, Hodak SP, et al. Change in diagnostic criteria for noninvasive follicular thyroid neoplasm with papillary-like nuclear features. *JAMA Oncol* 2018; 4: 1125-6.
- Baloch ZW, Asa SL, Barletta JA, et al. Overview of the 2022 WHO classification of thyroid neoplasms. *Endocr Pathol* 2022; 33: 27-63.
- Cho U, Mete O, Kim MH, Bae JS, Jung CK. Molecular correlates and rate of lymph node metastasis of non-invasive follicular thyroid neoplasm with papillary-like nuclear features and invasive follicular variant papillary thyroid carcinoma: the impact of rigid criteria to distinguish non-invasive follicular thyroid neoplasm with papillary-like nuclear features. *Mod Pathol* 2017; 30: 810-25.
- Rosario PW, Mourao GF, Nunes MB, Nunes MS, Calsolari MR. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features. *Endocr Relat Cancer* 2016; 23: 893-7.
- Thompson LD. Ninety-four cases of encapsulated follicular variant of papillary thyroid carcinoma: a name change to noninvasive follicular thyroid neoplasm with papillary-like nuclear features would help prevent overtreatment. *Mod Pathol* 2016; 29: 698-707.
- Xu B, Serrette R, Tuttle RM, et al. How many papillae in conventional papillary carcinoma? A clinical evidence-based pathology study of 235 unifocal encapsulated papillary thyroid carcinomas, with emphasis on the diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features. *Thyroid* 2019; 29: 1792-803.
- Xu B, Tallini G, Scognamiglio T, Roman BR, Tuttle RM, Ghossein RA. Outcome of large noninvasive follicular thyroid neoplasm with papillary-like nuclear features. *Thyroid* 2017; 27: 512-7.
- Parente DN, Kluijfhout WP, Bongers PJ, et al. Clinical safety of renaming encapsulated follicular variant of papillary thyroid carcinoma: is NIFTP truly benign? *World J Surg* 2018; 42: 321-6.
- Xu B, Farhat N, Barletta JA, et al. Should subcentimeter non-invasive encapsulated, follicular variant of papillary thyroid carcinoma be included in the noninvasive follicular thyroid neoplasm with papillary-like nuclear features category? *Endocrine* 2018; 59: 143-50.
- Rana C, Vuong HG, Nguyen TQ, et al. The incidence of noninvasive follicular thyroid neoplasm with papillary-like nuclear features: a meta-analysis assessing worldwide impact of the reclassification. *Thyroid* 2021; 31: 1502-13.
- Cubero Rego D, Lee H, Boguniewicz A, Jennings TA. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is rare, benign lesion using modified stringent diagnostic criteria: reclassification and outcome study. *Ann Diagn Pathol* 2020; 44: 151439.
- Legesse T, Parker L, Heath J, Staats PN. Distinguishing non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) from classic and invasive follicular-variant papillary thyroid carcinomas based on cytologic features. *J Am Soc Cytopathol* 2019; 8: 11-7.
- Sung S, Margolskee E, Chen D, Tiscornia-Wasserman P. Incidence of noninvasive follicular thyroid neoplasm with papillary-like nuclear features and change in risk of malignancy for “The Bethesda System for Reporting Thyroid Cytology”. *J Am Soc Cytopathol* 2019; 8: 133-40.
- Borda A, Zahan AE, Piciu D, Barbus E, Berger N, Nechifor-Boila A. A 15 year institutional experience of well-differentiated follicular cell-derived thyroid carcinomas; impact of the new 2017 TNM and WHO Classifications of Tumors of Endocrine Organs on the epidemiological trends and pathological characteristics. *Endocrine* 2020; 67: 630-42.
- Boursier L, Clerc Urmes I, Garon J, Klein M, Demarquet L. Ultrasound and cytological characteristics of non-invasive follicular thyroid neoplasm with papillary-like nuclear features compared to papillary carcinomas. *Ann Endocrinol (Paris)* 2020; 81: 28-33.
- Reinke RH, Larsen SR, Mathiesen JS, Godballe C, Londero SC. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features is rare: a population based study of incidence. *Head Neck Pathol* 2020; 14: 144-9.
- Ke J, Jianyong L, Ying L, et al. The use of The Bethesda System for Reporting Thyroid Cytopathology in a Chinese population: an analysis of 13 351 specimens. *Diagn Cytopathol* 2019; 47: 876-80.
- Rana C, Manjunath S, Ramakant P, Singh K, Babu S, Mishra A. Noninvasive follicular neoplasm with papillary like nuclear features: a comprehensive analysis with a diagnostic algorithm. *Diagn Cytopathol* 2020; 48: 330-41.
- Zhu Y, Song Y, Xu G, Fan Z, Ren W. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC): a report of 2,781 cases in

- a Chinese population. *Chin J Cancer Res* 2020; 32: 140-8.
22. Seo JY, Park JH, Pyo JY, et al. A multi-institutional study of prevalence and clinicopathologic features of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) in Korea. *J Pathol Transl Med* 2019; 53: 378-85.
 23. Eskander A, Hall SE, Manduch M, Griffiths R, Irish JC. A population-based study on NIFTP incidence and survival: is NIFTP really a “benign” disease? *Ann Surg Oncol* 2019; 26: 1376-84.
 24. Ali SZ, Cibas ES. *The Bethesda System for Reporting Thyroid Cytopathology*. 2nd ed. New York: Springer, 2018.
 25. Yan L, Sethi S, Park JW. Cytologic and clinical features of NIFTP: can we diagnose based on preoperative fine-needle aspiration. *Diagn Cytopathol* 2019; 47: 1259-66.
 26. Bizzarro T, Martini M, Capodimonti S, et al. Young investigator challenge: the morphologic analysis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features on liquid-based cytology: Some insights into their identification. *Cancer Cytopathol* 2016; 124: 699-710.
 27. Brandler TC, Zhou F, Liu CZ, et al. Can noninvasive follicular thyroid neoplasm with papillary-like nuclear features be distinguished from classic papillary thyroid carcinoma and follicular adenomas by fine-needle aspiration? *Cancer Cytopathol* 2017; 125: 378-88.
 28. Chandler JB, Colunga M, Prasad ML, et al. Identification of distinct cytomorphic features in the diagnosis of NIFTP at the time of preoperative FNA: Implications for patient management. *Cancer Cytopathol* 2017; 125: 865-75.
 29. Diaz Del Arco C, Fernandez Acenero MJ. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features: can cytology face the challenge of diagnosis in the light of the new classification? *Acta Cytol* 2018; 62: 265-72.
 30. Koshikawa T, Fujita N, Ueda N, et al. Important cytological findings for distinction between follicular variant and conventional papillary thyroid carcinoma, including noninvasive follicular thyroid tumors with papillary-like nuclear features. *Endocr J* 2019; 66: 475-83.
 31. Howitt BE, Chang S, Eszlinger M, et al. Fine-needle aspiration diagnoses of noninvasive follicular variant of papillary thyroid carcinoma. *Am J Clin Pathol* 2015; 144: 850-7.
 32. Mahajan S, Agarwal S, Kocheri N, Jain D, Mathur SR, Iyer VK. Cytopathology of non-invasive follicular thyroid neoplasm with papillary-like nuclear features: a comparative study with similar patterned papillary thyroid carcinoma variants. *Cytopathology* 2018; 29: 233-40.
 33. Strickland KC, Vivero M, Jo VY, et al. Preoperative cytologic diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features: a prospective analysis. *Thyroid* 2016; 26: 1466-71.
 34. Selvaggi SM. The presence of multinucleated giant cells: noninvasive follicular thyroid neoplasm with papillary-like nuclear features vs the follicular variant of papillary thyroid carcinoma. *Diagn Cytopathol* 2019; 47: 1007-10.
 35. Maletta F, Massa F, Torregrossa L, et al. Cytological features of “noninvasive follicular thyroid neoplasm with papillary-like nuclear features” and their correlation with tumor histology. *Hum Pathol* 2016; 54: 134-42.
 36. Kim M, Kim JE, Kim HJ, et al. Cytologic diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features and its impact on the risk of malignancy in the Bethesda system for reporting thyroid cytopathology: an institutional experience. *J Pathol Transl Med* 2018; 52: 171-8.
 37. Ibrahim AA, Wu HH. Fine-needle aspiration cytology of noninvasive follicular variant of papillary thyroid carcinoma is cytomorphologically distinct from the invasive counterpart. *Am J Clin Pathol* 2016; 146: 373-7.
 38. Ventura M, Melo M, Fernandes G, Carrilho F. Risk of malignancy in thyroid cytology: the impact of the reclassification of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (Niftp). *Endocr Pract* 2019; 25: 642-7.
 39. Celik M, Bulbul BY, Can N, et al. Comparison of clinicopathological features in patients with noninvasive follicular thyroid neoplasm with papillary-like nuclear features and follicular variant papillary thyroid cancer. *Pol Arch Intern Med* 2020; 130: 100-5.
 40. Hirokawa M, Higuchi M, Suzuki A, Hayashi T, Kuma S, Miyauchi A. Noninvasive follicular thyroid neoplasm with papillary-like nuclear features: a single-institutional experience in Japan. *Endocr J* 2017; 64: 1149-55.
 41. Haaga E, Kalfert D, Ludvikova M, Kholova I. Non-invasive follicular thyroid neoplasm with papillary-like nuclear features is not a cytological diagnosis, but it influences cytological diagnosis outcomes: a systematic review and meta-analysis. *Acta Cytol* 2022; 66: 85-105.
 42. Lau RP, Paulsen JD, Brandler TC, Liu CZ, Simsir A, Zhou F. Impact of the reclassification of “noninvasive encapsulated follicular variant of papillary thyroid carcinoma” to “noninvasive follicular thyroid neoplasm with papillary-like nuclear features” on the Bethesda System for Reporting Thyroid Cytopathology: a large academic institution’s experience. *Am J Clin Pathol* 2017; 149: 50-4.
 43. Strickland KC, Howitt BE, Marqusee E, et al. The impact of noninvasive follicular variant of papillary thyroid carcinoma on rates of malignancy for fine-needle aspiration diagnostic categories. *Thyroid* 2015; 25: 987-92.
 44. Mito JK, Alexander EK, Angell TE, et al. A modified reporting approach for thyroid FNA in the NIFTP era: a 1-year institutional experience. *Cancer Cytopathol* 2017; 125: 854-64.
 45. Layfield LJ, Baloch ZW, Esebua M, Kannuswamy R, Schmidt RL. Impact of the reclassification of the non-invasive follicular variant of papillary carcinoma as benign on the malignancy risk of the Bethesda System for Reporting Thyroid Cytopathology: a meta-analysis study. *Acta Cytol* 2017; 61: 187-93.
 46. Bychkov A, Hirokawa M, Jung CK, et al. Low rate of noninvasive follicular thyroid neoplasm with papillary-like nuclear features in Asian practice. *Thyroid* 2017; 27: 983-4.
 47. Chen CC, Hang JE, Liu CY, Wang YH, Lai CR. Thyroid fine-needle aspiration cytology in Taiwan: a nationwide survey and literature update. *J Pathol Transl Med* 2020; 54: 361-6.
 48. Bychkov A, Keelawat S, Agarwal S, et al. Impact of non-invasive follicular thyroid neoplasm with papillary-like nuclear features on the Bethesda System for Reporting Thyroid Cytopathology: a multi-institutional study in five Asian countries. *Pathology* 2018; 50: 411-7.
 49. Vuong HG, Tran TTK, Bychkov A, et al. Clinical impact of non-invasive follicular thyroid neoplasm with papillary-like nuclear features on the risk of malignancy in the Bethesda System for Reporting Thyroid Cytopathology: a meta-analysis of 14,153 resected thyroid nodules. *Endocr Pract* 2019; 25: 491-502.