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Interobserver and intraobserver variation in the morphological evaluation of noninvasive follicular thyroid neoplasm with papillary-like nuclear features in Asian practice

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To evaluate the current diagnostic criteria in reporting nuclear features of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), nine Asian pathologists with expertise in thyroid reviewed virtual slides of 30 noninvasive follicular patterned thyroid lesions according to the nuclear scoring system originally proposed by an international expert and a more detailed scoring system proposed by the Asian Working Group. The interobserver agreement for nuclear grading score was generally moderate (kappa value = 0.452). The best consistency fell on the chromatin features (kappa value = 0.658–1.000). A fair to moderate interobserver agreement was demonstrated in the evaluation of nuclear elongation, nuclear overlapping, membrane irregularities and distribution of papillary thyroid carcinoma (PTC) type nuclear features. A slight agreement was rendered for the evaluation of the nuclear enlargement. Intraobserver agreement was substantial to perfect when comparing results of both scoring systems. However, both scoring systems were not able to reliably separate NIFTP from an encapsulated follicular variant PTC with

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minimal lymph node metastasis or *BRAF*^{V600E} mutation. Although the three-point nuclear scoring system for the diagnosis of NIFTP is widely used in Asian practice, interobserver variation was considerable. Ancillary immunohistochemical or molecular testing might be helpful in differentiating NIFTP from true PTC.

KEYWORDS
digital pathology, noninvasive follicular thyroid neoplasm with papillary-like nuclear features, nuclear scoring system, observer variation, tumors of uncertain malignant potential

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy with an excellent long-term survival. The follicular variant of PTC (FVPTC) was first introduced by Lindsay,[1] who noted that these tumors with a follicular growth pattern shared PTC type nuclear features with conventional PTCs. The diagnostic criteria and definition of FVPTC have been evolving over the last decades owing the better clinicopathological recognition and molecular advances. In 1977, Chen and Rosai reported a small series of six carefully analyzed cases and defined the FVPTC as a tumor that resembled PTC in its biologic behavior and all morphologic features with the exception that true papillae were absent.[2] FVPTC was further divided into three subtypes according to their biological behavior and morphology, which included infiltrative type and encapsulated type with invasion and without invasion.[3,4] Recent studies reported that the noninvasive encapsulated FVPTC had no tumor-related adverse outcomes even after the simple excision, and well-differentiated thyroid tumor with uncertain malignant potential or uncertain clinical behavior were proposed to cover a group of tumor with questionable invasion or without invasion.[3–7]

A category of other encapsulated follicular patterned thyroid tumors with extremely low malignant potential was proposed in the current WHO classification, and the noninvasive encapsulated FVPTC was included.[8] A simple excision is nearly always curative for these kind of lesions.[6,9,10] Those lesions together with the other thyroid malignancy with extremely low malignant potential were proposed to be the borderline category by Kakudo *et al*. in 2002.[9] According to the consensus of an international study, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was proposed as a new thyroid tumor entity to rename noninvasive encapsulated FVPTC. In addition, the NIFTP Working Group established a nuclear scoring system for PTC type nuclear features.[11] Shortly after introduction, NIFTP was included in the newly introduced group of borderline thyroid neoplasms in the new WHO classification.[8] The standardized nuclear scoring system and absence of the capsular/vascular invasion and high-grade histologic features are the key points for a correct diagnosis of NIFTP.

Previous studies indicated that up to 61% of follicular patterned thyroid tumors meet diagnostic discrepancy even among expert pathologists.[12–15]A recent interobserver variation study for the diagnosis of NIFTP showed an excellent interobserver agreement after pre-education of the diagnostic criteria of NIFTP using an education module.[16] However, this study was based on a single high power still image per case, which probably could not reproduce the whole complexity of lesion encountered in practical settings. In addition, several recent institutional reports from the USA and Korea described NIFTP cases with *BRAF*^{V600E} and *TERT* promoter mutations characteristic for conventional PTC.[17,18] These controversial findings prompted ramifications of NIFTP diagnostic criteria released in 2018.[19] It is likely that the existing three-point scoring system for evaluation of PTC type nuclear features is not able to exclude all PTC from NIFTP. Therefore, we modified the three-point scoring system to the more comprehensive eight-point scoring system described below and compared their utility for diagnosing NIFTP. The use of two distinct scoring systems also allowed us to evaluate intraobserver variation, which has not been addressed in the previous concordance studies on follicular patterned thyroid tumors. The present study was performed within the network of the Working Group of Asian Thyroid FNA Cytology with the aim to evaluate the interobserver and intraobserver variability in the morphological evaluation of NIFTP among the international experts.[20]

MATERIAL AND METHODS

A total of 30 cases of NIFTP diagnosed as per criteria of Nikiforov *et al.* were collected from three countries (17 from Japan, 6 from Korea, and 6 from Thailand).[11] Detailed diagnostic criteria and a process of cases selection was described previously.[21,22] All the slides of each case were reviewed by three pathologists from the same institution and the final diagnosis of NIFTP was rendered morphologically. No papillae as recently described was found in all the slides of each cases.[19,23] A series from Korea included

three noninvasive follicular patterned thyroid tumors with minimal microscopic lymph node metastasis (<2 mm) and three cases with *BRAF*^{V600E} mutation. These noninvasive tumors contained no papillae and were eligible for NIFTP diagnosis according to the aforementioned original criteria[11] also adopted by the new WHO classification.[8] A single representative whole slide per case was scanned and made into a virtual slide using available on-site slide scanners (Pannoramic MIDI II, 3D Histech, Budapest, Hungary; Aperio CS2, Leica, San Diego, CA, USA). Corresponding commercial web browser-based image viewers were used for remote review. Nine pathologists from six Asian countries were invited to review the cases remotely. No clinicopathological and molecular data were provided before reviewing. An Excel spreadsheet for data collection and instructions for evaluation of the cases were distributed. The data collection included the number of years as a practicing pathologist and an approximate number of thyroid surgical cases per year diagnosed and the score of the judgment.

Two different scoring systems were applied to evaluate the agreement of each diagnostic parameter of PTC nuclear features, including the three-point scoring system proposed by the international expert group[11] and the more detailed eight-point scoring system proposed by our group. Nuclear size and shape of the three-point scoring system were classified into three subtypes (nuclear enlargement, nuclear elongation, and nuclear overlapping or crowding), each providing one point in the eight-point scoring system. Membrane irregularities of the three-point scoring system was further divided into three histologic features (irregular contours, pseudoinclusions and nuclear grooves), each providing one point in the eight-point scoring system. The chromatin features classified in the three-point scoring system was accepted in the eight-point scoring system as it is. Individual histologic features were scored as either present (1) or absent (0). The distribution of PTC nuclear features in each whole slide was added as the additional scoring point with added value of 0 (focal) or 1 (diffuse). Adjacent benign thyroid follicular cells used as a reference for nuclear scoring were available in all cases. In the three-point scoring system, a total score of 0 or 1 was considered inadequate for the diagnosis of NIFTP and a total score of 2 or 3 was considered sufficient for the diagnosis of NIFTP. In the eight-point scoring system, a total score of 0–4 was considered inadequate for the diagnosis of NIFTP and a total score of 5–8 was considered sufficient for the diagnosis of NIFTP. Finally, participants were asked whether the particular tumor fulfilled the NIFTP criteria would be instead sign out as PTC in their institutions.

The degree of the interobserver agreement for each criterion and intraobserver agreement for each pathologist was assessed by Cohen's kappa statistics.[24] The Cohen's kappa statistic (kappa coefficient) uses 1 to indicate perfect agreement and 0 indicating agreement by pure chance alone, and there is consistency when $P < 0.01$. The degree of kappa agreement is shown in Table 1.[25] Statistical analysis was performed by an expert statistician (Sui S.) using STATA software 15.1(Version 11; StataCorp, College Station, TX, USA).

RESULTS

The years as a practicing pathologist were between 9 and 43 at an average of 22.9 years. The average number of surgical thyroid cases diagnosed by each pathologist was 750 per year.

The interobserver agreement for the diagnosis of NIFTP was moderate (kappa value = 0.452) in the three-point scoring system (Table 2). Of 30 cases, 10 were diagnosed as NIFTP by all nine pathologists. The interobserver agreement for chromatin features and membrane irregularities was fair (kappa value = 0.375 and 0.208, respectively) (Fig. 1) whereas only slight agreement (kappa value = 0.188) was achieved for nuclear size and shape.

The interobserver variation for each detailed nuclear feature was investigated using the eight-point scoring system (Table 2). A moderate agreement fell on the judgment of chromatin features (kappa value = 0.417, Fig. 1). Fair agreement was demonstrated for the evaluation of nuclear elongation, nuclear overlapping, irregular contours, nuclear grooves, and pseudoinclusions (Table 1, Fig. 2). Perfect agreement was found in 13 cases with score of 0 for the evaluation of pseudoinclusions, nuclear grooves, and irregular contours, and three cases with a score of 0 for the nuclear overlapping. The worst agreement was for the evaluation of nuclear enlargement (kappa value = 0.065, Fig. 3).

The intraobserver variation was investigated by comparing the results of two different scoring systems (Table 3). Substantial to perfect agreement for the evaluation of chromatin features was demonstrated for all the pathologists

Table 1 The degree of kappa agreement between pathologists, adapted from Landis and Koch[22]

Kappa value	Strength of agreement*
<0	Poor agreement
0.00–0.20	Slight agreement
0.21–0.40	Fair agreement
0.41–0.60	Moderate agreement
0.61–0.80	Substantial agreement
0.81–1.00	Almost perfect agreement

*There is consistency when $P < 0.01$

Table 2 The diagnostic criteria of the nuclear features of two different score systems and the interobserver agreement of the evaluation of papillary thyroid carcinoma type nuclear features using the three-point scoring system and the eight-point scoring system.

Three-point scoring system					**Eight-point scoring system**				
Nuclear features	**Score**	**Kappa**	**Z**	**Prob**	**Nuclear features**	**Score**	**Kappa**	**Z**	**Prob**
Nuclear size and shape	0 or 1	0.188	6.18	0.0000	Nuclear enlargement	0 or 1	0.065	2.14	0.0163*
					Nuclear elongation	0 or 1	0.271	8.92	0.0000
					Nuclear overlapping	0 or 1	0.317	10.41	0.0000
Membrane irregularities	0 or 1	0.228	7.47	0.0000	Irregular contours	0 or 1	0.326	10.70	0.0000
					Pseudoinclusions	0 or 1	0.234	7.69	0.0000
					Nuclear grooves	0 or 1	0.227	7.46	0.0000
Chromatin features	0 or 1	0.375	12.32	0.0000	Chromatin features	0 or 1	0.417	13.70	0.0000
					Distribution	0 or 1	0.240	7.90	0.0000
Total score	0∼3	0.232	12.44	0.0000	Total score	0∼8	0.072	6.07	0.0000
NIFTP or not	0, 1: benign 2, 3: NIFTP	0.452	14.81	0.0000	NIFTP or not	0∼4: benign 5∼8: NIFTP	0.389	12.77	0.0000

*There was no kappa agreement.

(kappa value = 0.658–1.000). Moderate to substantial agreement for the evaluation of membrane irregularities was demonstrated for eight pathologists (kappa value = 0.444–1.000), and no intraobserver agreement was found for one pathologist. As to the evaluation of nuclear size and shape, substantial agreement was confirmed only for one pathologist (kappa value = 0.603) and less agreement for five pathologists and no statistical agreement for the other three pathologists. Perfect agreement was found in two pathologists for evaluation of nuclear size and shape, and another two pathologists for membrane irregularities.

As per the diagnosis of "PTC or not", moderate agreement was rendered for all the 30 cases (kappa value = 0.410) and the 24 cases without lymph node metastasis (kappa value = 0.452) (Table 4). Only fair concordance (kappa value = 0.240) was confirmed for those six cases with microscopic lymph node metastasis or BRAF mutation, and none of those cases was diagnosed as conventional PTC by all the endocrine pathologists according to the morphology of the primary tumor. At the same time six cases of NIFTP with fully developed PTC type nuclear features were favored to be signed out as a FVPTC by all the pathologists.

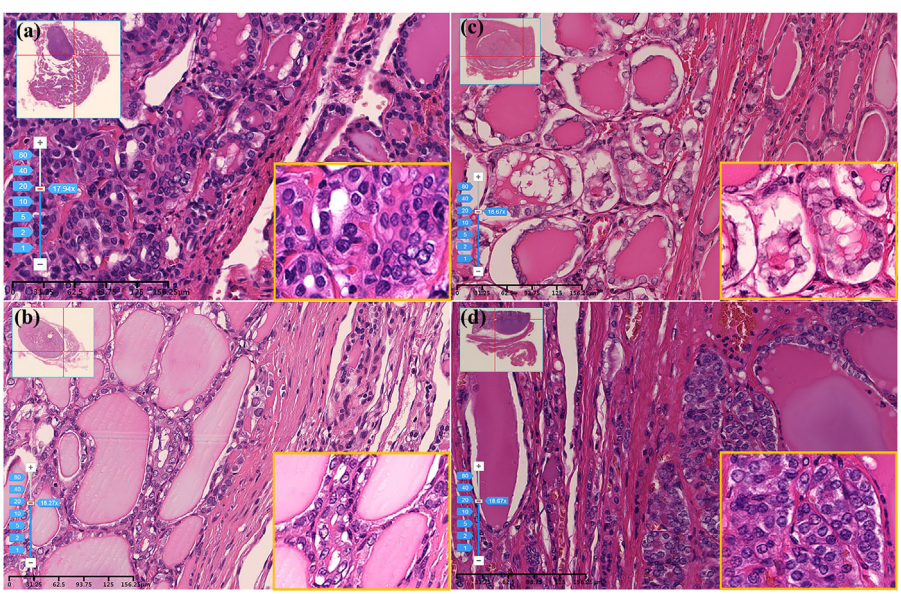

Figure 1 Scoring of chromatin features. (**a**) All pathologists scored as 0 (case 11). (**b**) All pathologists scored as 1 (Case 8). (**c**) Seven pathologists scored as 1 and two pathologists scored 0 (case 10). (**d**) Six pathologists scored as 0, while three pathologists scored 1 (case 12). Hematoxylin and eosin, ×20.

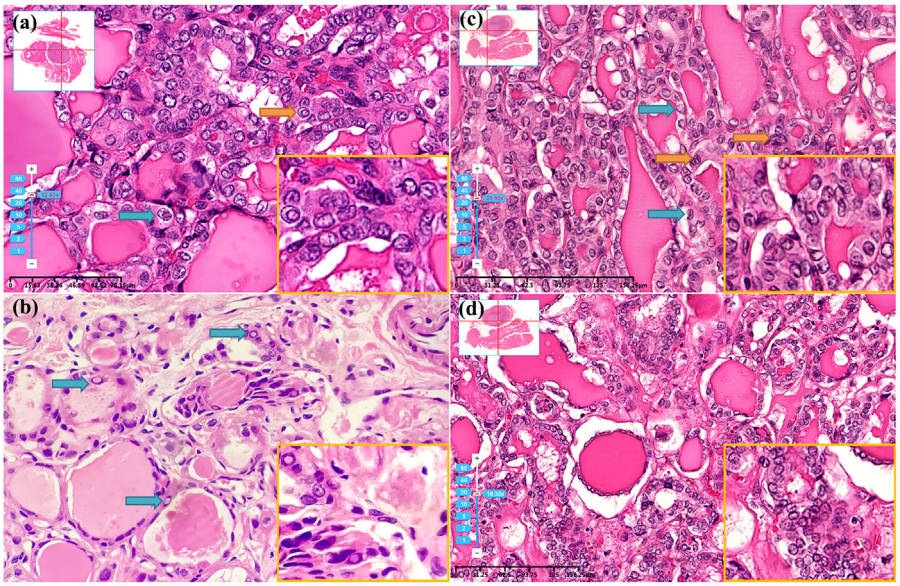

Figure 2 Evaluation of nuclear pseudoinclusions, irregular contours, and nuclear overlapping. (**a**) All pathologists scored as 1 (case 17). The diameter of the typical nuclear pseudoinclusion is more than one-third of the nucleus (yellow arrow). Small intranuclear cytoplasmic inclusion could not be regarded as pseudoinclusion (blue arrow). (**b**) Pseudoinclusion could be found in normal thyroid tissue (blue arrow). (**c**) Coffee-bean like nuclear grooves (yellow arrow) and irregular contours (blue arrow). (**d**) Nuclear overlapping. The only case (case 10) that was scored 1 by all the pathologists. Hematoxylin and eosin, ×20.

DISCUSSION

A moderate agreement among Asian observers was rendered in reaching an interpretation of the presence or absence of nuclear features to diagnose NIFTP, which is different from excellent agreement reported in the international study by Thompson *et al*. recently.[16] Interobserver and intraobserver variation may be caused by education influence, working experience, individual interpretation of the diagnostic criteria, geographic differences and even some uncertain reasons.[8,12] The present study used virtual slides which made it possible to evaluate the whole

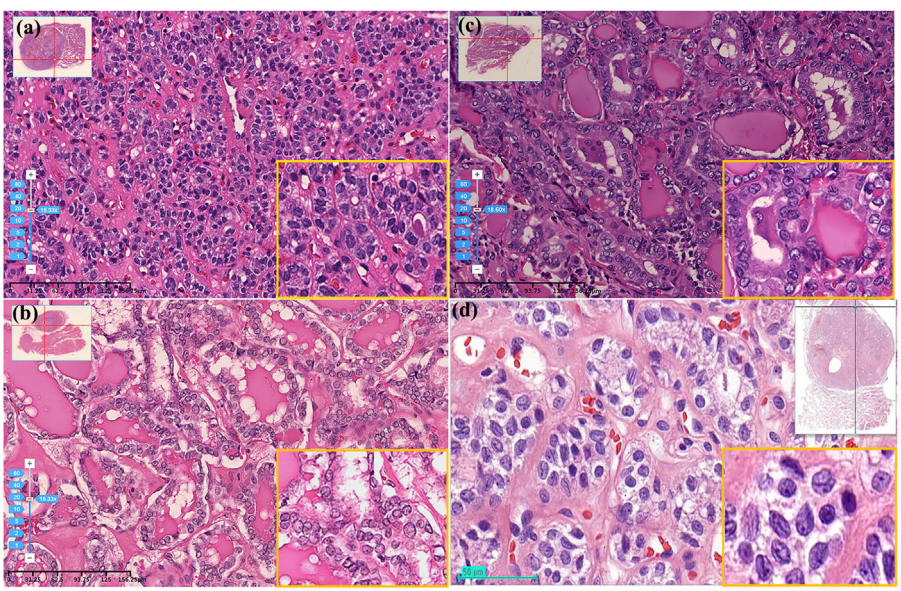

Figure 3 Scoring of nuclear enlargement. (**a**) Four pathologists scored as 0 and five pathologists scored as 1 (case 6). (**b**) All pathologists scored as 1 (case 3). (**c**) Eights pathologists scored 1 and one pathologist scored as 0 (case 5). (**d**) Six pathologists scored as 0, while three pathologists scored as 1 (case 12). Hematoxylin and eosin, ×20.

Table 3 Intraobserver agreement of evaluation on the papillary thyroid carcinoma type nuclear judged by the three- and eight-point scoring systems

	Nuclear size and shape			Membrane irregularities			Chromatin features		
Pathologist	**kappa**	**Z**	***P* > Z**	**kappa**	***Z***	***P* > Z**	**kappa**	**Z**	***P* > Z**
P1	0.129	1.438	0.150*	−**			0.730	4.034	0.000
P2	0.603	3.599	0.000	1.000	5.477	0.000	0.932	5.114	0.000
P3	0.250	2.070	0.038*	0.706	3.885	0.000	0.889	4.899	0.000
P4	0.225	1.952	0.051*	0.059	0.951	0.341*	1.000	5.477	0.000
P5	0.595	3.563	0.000	0.636	3.742	0.000	0.889	4.899	0.000
P6	0.444	2.928	0.003	0.791	4.429	0.000	0.933	5.123	0.000
P7	0.545	3.354	0.001	−**			0.816	4.716	0.000
P8	−**			0.444	2.928	0.003	0.658	3.610	0.000
P9	−**			1.000	5.477	0.000	1.000	5.477	0.000

*There was no kappa agreement. There is kappa agreement when $P < 0.01$.

**No statistics was computed because the values of eight-point classification are a constant.

specimen, whereas still high power images were used in Thompson's study.[16] We believe that virtual slides are superior to still images in representing a real life diagnostic situation. Another possible reason may also be the different diagnostic threshold of the PTC type nuclear features between Asian and the international working groups. In our study, the pathologists were selected from Asian countries and an education module was not applied before the evaluation.

In order to evaluate the intraobserver reproducibility of the PTC type nuclear features, the three-point nuclear scoring system was compared to the eight-point scoring system. The best agreement in the evaluation of nuclear features fell on chromatin features. However, no intraobserver agreement was found in the evaluation of nuclear shape and size by three pathologists, and the evaluation of membrane irregularities by one pathologist. The results of the intraobserver variation suggest that the current diagnostic criteria for nuclear shape and size, and membrane irregularities are not perfect especially in cases with subtle nuclear changes. There has been no detailed consensus for nuclear enlargement by far, which should be one important reason for both intraobserver and interobserver variations. Liu *et al*. previously developed an intimate description of the nuclear enlargement, which proposed that the nuclei size of the tumor cells should be two to four times of that of normal thyroid follicular cells adjacent to the tumor.[6] Major/minor axis ratio of the neoplastic cells was once proposed to evaluate the elongation by Nishigami *et al*., it will be regarded as nuclear elongation only when the ratio is more than one.[26] These calculation-based methods may be useful to improve intraobserver reproducibility and interobserver reliability for the diagnosis of PTC nuclear features and NIFTP.

Pseudoinclusion is a relatively specific characteristic of PTC type nuclear features but can also be observed in a hyalinizing trabecular tumor, medullary thyroid carcinoma and even benign thyroid lesions.[27,28] As definite nuclear pseudoinclusions are rarely found in NIFTPs, stricter criteria were recommended for the diagnosis of definitive malignancy in cytologic specimens.[29–32] A fair agreement for this relatively easily recognized microscopic feature found in our study was likely caused by the various depth of browsing through the whole virtual slide on the high magnification by different reviewers. For example, a simple continuous panning of 25×15 mm digital slide on $40\times$ magnification requires at least 20 min. A similar fair agreement was found for another type of membrane irregularity known as nuclear groove, which was described as a line running across the long axis of the nucleus. Nishigami *et al*. demonstrated that the nuclear groove of well-differentiated tumor of uncertain malignant potential was thin and faintly visible, while that of PTC was dense.[26] We believe that considerable variability in appreciation of various diagnostically relevant microscopic

Table 4 Interobserver agreement on rendering diagnosis of "Papillary thyroid carcinoma or not"

Number of cases	Kappa	Z	*P*
24 (without lymph node metastasis)	0.452	13.53	0.0000
6 (with lymph node micro-metastasis or $BRAF^{V600E}$ mutation)	0.240	13.27	0.0002
Total	0.410	13.46	0.0000

features found in our study is partially due to absence of clear definitions for nuclear enlargement, elongation, grooves, etc.

Change in diagnostic criteria of NIFTP has been initiated recently by Nikiforov *et al*. and different diagnostic workup was proposed for NIFTP with different nuclear score.[19] For instance, in cases of NIFTP with pronounced nuclear features of PTC (nuclear score 3), examination of the entire tumor to exclude the presence of papillary structures was suggested. These changes support our proposal that slight differences should exist between the nuclear features of NIFTP and PTC. The present authors believe that NIFTP (*RAS*-like mutated thyroid tumor) has subtle nuclear changes, such as delicate nuclear grooves and no/rare nuclear pseudoinclusions, and is different from those of *BRAF*^{V600E} mutated PTCs, which usually demonstrate fully developed nuclear features (abundant nuclear grooves and pseudoinclusions).[32–35]

The present study was initially intended to enroll cases that met with the definition of NIFTP according to the new WHO classification.[8] However, three cases were found to have lymph node micro-metastasis (in the absence of identifiable papillary microcarcinoma) and another three cases with *BRAF*^{V600E} mutation, which are currently believed to be excluded from the diagnostic entity of NIFTP although diagnosis of NIFTP was rendered morphologically.[8,36] It is a challenge for pathologists to distinguish encapsulated FVPTC with lymph node metastasis and/or *BRAF*^{V600E} mutation from NIFTP (*RAS*-like tumor) morphologically. NIFTP is a morphological phenotype consistent with *RAS*-like tumor, and cases with *BRAF* and/or *TERT* promoter mutation must be excluded, as per the current concept.[8,37,38] *BRAF*^{V600E} mutation was reported in "NIFTP" that fulfilled the morphological criteria by several research groups.[18,39,40] These results show that the current nuclear score systems (either three-point or eight-point) are not able to differentiate noninvasive follicular patterned thyroid tumors with *BRAF*^{V600E} mutation and/or lymph node metastasis from NIFTP. Although morphological overlap between NIFTP and FVPTC is evident, many pathologists were already aware that slight differences exist between nuclear features of NIFTP and conventional PTC (delicate nuclear grooves and rare nuclear cytoplasmic inclusions in NIFTPs and florid nuclear changes in conventional PTC with *BRAF*^{V600E} mutation). Interestingly, all the experts in this study preferred a diagnosis of FV-PTC in 6 cases of NIFTP with fully developed PTC type nuclear features. However, no molecular data to confirm *BRAF*/*RAS* lineage were available for these cases.

For the purpose of excluding true malignant tumors from biologically benign or borderline thyroid tumors, we would like to point out that molecular or immunohistochemical detection of *BRAF*^{V600E} mutation should be the first step to rule out FVPTC when coming across these thyroid lesions with worrisome PTC type nuclear features and follicular architecture. Those fulfill the morphological features of NIFTP but showing *BRAF*^{V600E} mutation or other high-risk genetic abnormalities such as *TERT* promoter and *TP53* mutations should be excluded from NIFTP as suggested by several recent studies, which supports our current proposal.[19,41,42]

Meta-analysis and retrospective study by the Asian Working Group suggested that the incidence of NIFTP and FVPTC in the Asian population is lower than those in non-Asian series, and such difference is probably contributed by various interpretation of diagnostic thresholds for PTC nuclear features.[21,43] In order to reveal the real practice of the diagnosis of NIFTP in Asia, the endocrine pathologists that participated in this study were from various medical centers in Asia. This naturally biased the group toward pathologists who are more experienced with NIFTP in each country.

In conclusion, this study found considerable observer variation in evaluation of nuclear features of PTC and rendering a diagnosis of NIFTP among Asian pathologists. This was contributed by the variable appreciation of nuclear features by the experts and by use of whole-slide images instead still images as a model. The three-point and eight-point nuclear scoring systems were not able to reliably separate NIFTP from noninvasive encapsulated FVPTC with histologically identified lymph node micro-metastasis and/or *BRAF*^{V600E} mutation. Molecular or immunohistochemical testing may be a possible solution when diagnosis of NIFTP vs. PTC is challenged.

DISCLOSURE STATEMENT

None Declared.

AUTHOR CONTRIBUTIONS

Conception and design of the study: ZL, KK. Acquisition of data: ZL, AB, CKJ, MH, SH, CRL, DJ, SC, KK. Analysis of data: SS. Drafting the manuscript or figures: ZL. Modifying the manuscript: AB, CKJ, KK.

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