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Preoperative Diagnostic Categories of Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features in Thyroid Core Needle Biopsy and Its Impact on Risk of Malignancy

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Abstract

This study was designed to evaluate the preoperative diagnostic categories of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) using thyroid core needle biopsy (CNB) and to analyze its impact on the risk of malignancy (ROM). A total of 2687 consecutive thyroid CNBs were reviewed retrospectively and classified into six diagnostic categories using a standardized reporting system similar to the Bethesda System for Reporting Thyroid Cytopathology. Diagnostic categories of CNBs were compared with the final surgical diagnoses, and the ROM in each category was calculated both before and after excluding NIFTP from malignancy. Of 946 surgically resected cases, 683 were diagnosed as papillary thyroid carcinoma (PTC), and 32 (4.7% of PTC) were reclassified as NIFTP. The CNB diagnostic categories of NIFTP were as follows: follicular neoplasm in 20 (62.5%; 14, with nuclear atypia), indeterminate lesion in 11 (34.4%), and suspicious for malignancy in one (3.1%). When combined, NIFTP and encapsulated follicular variant of PTC (EFVPTC) were more often categorized as follicular neoplasm compared with other PTC variants including infiltrative FVPTC. Exclusion of NIFTP from malignant diagnosis led to a significant decrease in the ROM in follicular neoplasm with nuclear atypia category. Thus, thyroid CNB enables to differentiate NIFTP/EFVPTC from other PTCs, providing a useful guide for optimal treatment in patients with these tumors.

Keywords Thyroid · Core needle biopsy · Encapsulated follicular variant of papillary thyroid carcinoma · Noninvasive follicular thyroid neoplasm with papillary-like nuclear features · Risk of malignancy

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Introduction

Thyroid fine-needle aspiration cytology (FNAC) is considered as the gold standard for diagnostic and screening tests for thyroid nodules, and the results are most often reported according to the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) [1, 2]. Each of the six categories of TBSRTC possesses a different implied risk of malignancy (ROM) that helps clinicians determine the appropriate treatment strategy [3]. However, the non-diagnostic/unsatisfactory and atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) results comprise up to 23.6% and 20.5% of total FNACs respectively, leading to diagnostic delays [4–6].

Ultrasonography-guided thyroid core needle biopsy (CNB), which was first introduced in the 1990s, can be a useful complementary tool for these nodules with inconclusive FNAC results [7–11]. By including not only the inside of nodule but also nodule boundary and extra-nodular normal

thyroid tissue, CNB has shown advantages over FNAC, especially in diagnosing follicular-patterned tumors [12, 13]. Moreover, there are accumulating evidence that CNB can be used as a first-line diagnostic method, reducing non-diagnostic and indeterminate results [14–16].

Recently, a new diagnostic term, "noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)" was introduced by a panel of endocrine pathologists in place of noninvasive encapsulated follicular variant of papillary thyroid carcinoma (noninvasive EFVPTC) [17]. Owing to the extremely low risk of metastasis or recurrence in NIFTP, more conservative treatment is recommended in order to minimize potential complications from aggressive management, such as total thyroidectomy and radioactive iodine therapy [18–20]. However, the diagnosis of NIFTP can be made only after a thorough pathologic examination of a surgically resected specimen. Nikiforov et al. have recently suggested stricter revised criteria that the presence of even single true papillae should exclude a diagnosis of NIFTP [21].

This paradigm shift has, however, brought forth some controversies in the preoperative diagnostic field, especially concerning changes in ROM in the diagnostic categories of thyroid FNAC and CNB. Previous studies have shown a substantial decrease in ROM for indeterminate categories including AUS/FLUS, follicular neoplasm, and suspicious for malignancy in thyroid FNAC when NIFTP was no longer considered as malignancy [22–24]. As for thyroid CNB, the data is limited, and only a few studies reported that the malignancy rates in nodules categorized as AUS with architectural atypia and follicular neoplasm greatly decreased when noninvasive EFVPTC was reclassified as NIFTP [25, 26].

In a previous study, we analyzed the cytologic diagnoses of NIFTP and its impact on ROM in each diagnostic category of TBSRTC, which showed that the decrease in ROM was not significant, even in the indeterminate categories, when NIFTP was excluded from malignancy [27]. This finding was related to the low incidence of NIFTP and the different distribution of preoperative diagnostic categories of this tumor in FNAC compared with those in Western series. However, as CNB is frequently performed as an alternative diagnostic tool for thyroid nodules with previous inconclusive FNAC results and allows better discrimination of follicular-patterned lesions than FNAC, the distribution of diagnostic categories of NIFTP in thyroid CNB and change in ROM may differ from that of FNAC. Thus, in the current study, we aimed to evaluate the CNB diagnostic categories of NIFTP using a standardized reporting system similar to TBSRTC and compared the results with a final diagnosis from surgical specimens. We also compared the diagnostic categories of NIFTP/EFVPTC with those of other PTC variants, follicular thyroid adenoma (FTA) and follicular thyroid carcinoma (FTC) in thyroid CNB. Finally, we analyzed the changes in ROM for each diagnostic category in order to determine the impact of the NIFTP diagnosis.

Materials and Methods

Case Selection

We reviewed retrospectively a total of 2746 thyroid CNBs from 2499 patients who were diagnosed at the Seoul National University Bundang Hospital from January 2013 to December 2015. Of the 2499 patients, 179 had separate biopsies for multiple nodules, and each CNB was counted as an individual case. In 58 patients, repeated CNBs were performed for the same nodule, and the diagnostic category with the highest ROM was selected. Ultimately, 2687 CNBs were included in this study.

Ultrasonography and USG-Guided CNB Procedures

All thyroid USG (iU22, Philips Medical Systems, Bothell, WA) and USG-guided thyroid CNBs were performed by one of three in-house, board-certified radiologists. At our institution, FNAC is a first-line diagnostic tool for thyroid nodules. However, due to high non-diagnostic rate, primary CNB has been performed when the performing radiologists expect a high possibility of non-diagnostic FNAC results [28, 29]. CNBs were executed using 18-gauge automatic biopsy needles with a 1.1-cm excursion (TSK Ace-cut; Create Medic, Yokohama, Japan). One to two cores of specimen was obtained for each thyroid nodule. As previously described [30], CNBs were performed after considering the size and imaging features of the thyroid nodules including (1) any suspicious malignant nodule (with any one of the following features: taller than wide shape, spiculated margin, marked hypoechoicism, microcalcification, or macrocalcification), over 5 mm; (2) an indeterminate nodule (without probably benign features or suspicious malignant features), over 10 mm; and (3) a probably benign nodule (isoechoic spongiform nodule, comet-tail artifact, predominantly cystic) over 20 mm, according to the 2009 ATA management guidelines [31] and the consensus statement of the Korean Society of Thyroid Radiology [32].

Pathologic Review of CNBs and Surgical Resection Specimens

All thyroid CNB slides were reviewed by two experienced pathologists (SYP and HYN) in a blind manner, after which discordant cases were discussed for consensus. The diagnosis in each case was based on the histomorphologic features of the biopsied thyroid nodule subsequently classified into one of six categories according to the standardized reporting system proposed by the Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group. This framework is similar to that of

TBSRTC: I. non-diagnostic, II. benign lesion, III. indeterminate lesion, IV. follicular neoplasm, V. suspicious for malignancy, and VI. Malignant [33]. This reporting system was validated in a previous study and demonstrated accurate diagnostic performance in the evaluation of thyroid nodules [30].

Of the 2687 CNBs, surgical resection was performed on a total of 946 thyroid nodules. The pathology reports for these cases were extracted from electronic medical records. Histologic diagnoses in surgical specimens were matched with the CNB diagnostic categories. For cases with a final diagnosis of PTC, we re-evaluated histologic variants, including conventional, encapsulated follicular, infiltrative follicular, tall cell, and other rare variants. We reviewed all slides from the EFVPTCs and selected NIFTPs according to the following criteria, which included recent updates [17, 21]: (i) encapsulation or clear demarcation, (ii) follicular growth pattern, (iii) nuclear features of PTC (nuclear score 2–3), (iv) no capsular or lymphovascular invasion, and (v) no tumor necrosis or high mitotic activity. Regarding the follicular growth pattern, specific conditions were set as follows: (a) no well-formed papillae, (b) no psammoma bodies, and (c) a < 30% solid/trabecular/insular pattern.

Statistical Analyses

Statistical analyses were performed using SPSS version 22.0 (IBM, NY, USA). The Pearson chi-square test and Fisher's exact test were used to compare frequencies of categorical variables between two groups. A p value of less than 0.05 was considered statistically significant. All p values reported were two-sided.

Results

Diagnostic Categories of Thyroid CNB

The diagnostic categories of the 2687 thyroid CNBs and their frequencies are summarized in Table 1. There were 164 (6.1%) cases of category I (non-diagnostic), 1023 (38.1%) cases of category II (benign lesion), 472 (17.6%) cases of category III (indeterminate lesion), 275 (10.2%) cases of category IV (follicular neoplasm), 100 (3.7%) cases of category V (suspicious for malignancy), and 653 (24.3%) cases of category VI (malignant). A sub-classification of category III (indeterminate lesion) was made to distinguish indeterminate lesion with nuclear atypia (62 cases, 2.3%) from indeterminate lesion with architectural atypia (408 cases, 15.2%). Category IV (follicular neoplasm) was divided into follicular neoplasm without nuclear atypia (184 cases, 6.8%) and follicular neoplasm with nuclear atypia (91 cases, 3.4%).

Table 1 Distribution of thyroid core needle biopsy results according to the pathologic reporting system proposed by the Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group

Diagnostic categories of thyroid CNB	No. (%)
I. Non-diagnostic	164 (6.1)
Normal thyroid tissue only	38 (1.4)
Extrathyroid tissue only	18 (0.7)
Virtually acellular specimen	8 (0.3)
Acellular/paucicellular fibrotic nodule	97 (3.6)
Blood clot only	3 (0.1)
II. Benign lesion	1023 (38.1)
Benign follicular nodule	816 (30.4)
Hashimoto's thyroiditis	148 (5.5)
Granulomatous thyroiditis	51 (1.9)
Other benign or nonthyroidal lesion	8 (0.3)
III. Indeterminate lesion	472 (17.6)
III A. Indeterminate lesion with nuclear atypia	62 (2.3)
Follicular proliferative lesions with focal nuclear atypia	8 (0.3)
Follicular proliferative lesions with equivocal or questionable nuclear atypia	25 (0.9)
Atypical follicular cells embedded in a fibrotic stroma	29 (1.1)
III B. Indeterminate lesion with architectural atypia	408 (15.2)
Microfollicular proliferative lesion lacking a fibrous capsule	260 (9.7)
Solid or trabecular follicular lesion lacking a fibrous capsule	0 (0)
Macrofollicular proliferative lesion with a fibrous capsule	43 (1.6)
Hurthle cell proliferative lesion lacking a fibrous capsule	105 (3.9)
III C. Other indeterminate lesion	2 (0.1)
IV. Follicular neoplasm	275 (10.2)
IV A. Follicular neoplasm without nuclear atypia	184 (6.8)
Microfollicular proliferative lesion with a fibrous capsule	110 (4.1)
Mixed microfollicular and normofollicular proliferative lesion with a fibrous capsule	15 (0.6)
Solid/trabecular follicular proliferative lesion with a fibrous capsule	2 (0.1)
Hurthle cell proliferative lesion with a fibrous capsule	57 (2.1)
IV B. Follicular neoplasm with nuclear atypia	91 (3.4)
V. Suspicious for malignancy	100 (3.7)
VI. Malignant	653 (24.3)
Total	2687

CNB core needle biopsy, *No.* number

Comparison of Diagnostic Categories of Thyroid CNB with Final Surgical Diagnoses

Of the 946 cases that underwent surgical resection, 731 (77.3%) were finally diagnosed as malignancies, including 683 (72.2%) PTCs, 35 (3.7%) FTCs, 10 (1.1%) medullary carcinomas, one poorly differentiated carcinoma, one anaplastic carcinoma, and one malignant lymphoma (Table 2). Of the

Table 2 Diagnostic categories of thyroid CNBs compared with the final diagnoses of surgical specimens

CNB diagnostic category	No. of surgical specimen	No. of malignancy (%)	Final diagnosis				
			Nodular hyperplasia	Follicular adenoma	Follicular carcinoma	Papillary carcinoma	Other[a]
I. Non-diagnostic	10	7 (70.0)	2 (20%)	1 (10%)	0 (0%)	7 (70%)	0 (0%)
II. Benign lesion	52	2 (3.8)	47 (90.4%)	2 (3.8%)	2 (3.8%)	0 (0%)	1 (1.9%)
III. Indeterminate lesion	143	50 (35.0)	41 (28.7%)	52 (36.4%)	11 (7.7%)	39 (27.3%)	0 (0%)
III A. Indeterminate lesion with nuclear atypia	22	17 (77.3)	5 (22.7%)	0 (0%)	1 (4.5%)	16 (72.7%)	0 (0%)
IIII B. Indeterminate lesion with architectural atypia	120	32 (26.7)	36 (30%)	52 (43.3%)	10 (8.3%)	22 (18.3%)	0 (0%)
III C. Other indeterminate lesion	1	1 (100)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)
IV. Follicular neoplasm	161	92 (57.1)	4 (2.5%)	65 (40.4%)	22 (13.7%)	69 (42.9%)	1 (0.6%)
IV A. Follicular neoplasm without nuclear atypia	99	36 (36.4)	3 (3%)	60 (60.6%)	19 (19.2%)	16 (16.2%)	1 (1%)
IV B. Follicular neoplasm with nuclear atypia	62	56 (90.3)	1 (1.6%)	5 (8.1%)	3 (4.8%)	53 (85.5%)	0 (0%)
V. Suspicious for malignancy	69	69 (100)	0 (0%)	0 (0%)	0 (0%)	61 (88.4%)	8 (11.6%)
VI. Malignant	511	511 (100)	0 (0%)	0 (0%)	0 (0%)	507 (99.2%)	4 (0.8%)
Total no.	946	731 (77.3)	94 (9.9%)	120 (12.7%)	35 (3.7%)	683 (72.2%)	14 (1.5%)

CNB core needle biopsy, *No* number

[a] Others include parathyroid adenoma in benign lesion; one poorly differentiated carcinoma in follicular neoplasm; seven medullary carcinomas and one lymphoma in suspicious malignancy; three medullary carcinomas, one anaplastic carcinoma in malignant category

683 cases of PTC, 7 (1.0%) were categorized as non-diagnostic in CNB due to targeting error. Detailed information about these 7 cases was summarized in Table 3. Most of them were less than 1-cm-sized nodules, and the 1.1-cm sized-nodule (case no. 2172) was associated with dense calcification. Three cases showed heterogeneous echogenicity due to background lymphocytic thyroiditis. In thyroid CNBs, only normal thyroid tissue was sampled in 6 cases, and only acellular fibrotic nodule was found in the remaining 1 case. However, surgery was performed due to suspicious USG finding, histologically proven PTC in the contralateral lobe or lymph node metastasis.

We re-evaluated the 683 cases of PTC and classified them into histologic variants as follows: 500 conventional PTCs, 32 NIFTPs, 32 EFVPTCs, 45 infiltrative FVPTCs, 34 tall cell variant of PTCs, and 40 other rare variants of PTCs. The distribution of CNB categories was compared in the variants of PTC (Table 4). Conventional PTCs were mainly diagnosed as malignant (86.0%) and rarely diagnosed as indeterminate lesion (2.8%) or follicular neoplasm (0.8%) category in thyroid CNB. All of the tall cell variants were categorized as malignant. On the other hand, a CNB diagnosis of NIFTP was indeterminate lesion in 11 cases (34.4%; 2 cases, with nuclear atypia; 9 cases, with architectural atypia), follicular neoplasm in 20 cases (62.5%; 6 cases, without nuclear atypia; 14 cases, with nuclear atypia), and suspicious for malignancy in one case (3.1%). Diagnostic categories of EFVPTC were as follows: indeterminate in 4 (12.5%; 1 case, with nuclear atypia; 3 cases, with architectural atypia), follicular neoplasm in 27 (84.4%; 6 cases, without nuclear atypia; 21 cases, with nuclear atypia), and malignant in one (3.1%).

When comparing EFVPTC with NIFTP, EFVPTC was more frequently diagnosed as follicular neoplasm ($p = 0.048$) and less frequently diagnosed as indeterminate lesion ($p = 0.039$) than NIFTP. However, there were no statistical differences found between CNB diagnoses of NIFTP and EFVPTC in the subcategories of indeterminate lesion and follicular neoplasm. Malignant CNB diagnosis was found in only one EFVPTC case, of which the difference was not statistically significant.

Comparison of CNB Diagnostic Categories Between Follicular-Patterned Tumors: NIFTP/EFVPTC, Infiltrative FVPTC, and FTA/FTC

To find out whether NIFTP/EFVPTC is differentiated from other follicular-patterned tumors in thyroid CNB, we compared CNB diagnostic categories between NIFTP/EFVPTC, infiltrative FVPTC, and FTA/FTC (Table 5; Figs. 1 and 2).

NIFTP/EFVPTC were more frequently categorized as follicular neoplasm than infiltrative FVPTC (73.4% vs. 26.7%, $p < 0.001$) and rarely categorized as suspicious for malignancy (1.6% vs. 26.7%, $p < 0.001$) or malignant (1.6% vs. 28.9%, $p < 0.001$).

As there was no difference in CNB diagnoses between FTA and FTC, we combined them in a group and analyzed the differences between the NIFTP/EFVPTC group and the FTA/

Table 3 Characteristics of malignant nodules with non-diagnostic CNB results

Case no.	Cause of non-diagnostic CNB results	Size of tumor (cm)	Gross findings	USG category	Final surgical diagnosis
1	Normal thyroid tissue only	0.8	Well-demarcated solid mass	Indeterminate	Conventional PTC
123	Normal thyroid tissue only	0.8	Irregular solid mass	Suspicious malignancy	Conventional PTC
627	Normal thyroid tissue only	0.3	Well-demarcated solid mass	Indeterminate	Conventional PTC
628	Normal thyroid tissue only	0.2	Irregular solid mass	Suspicious malignancy	Conventional PTC
820	Normal thyroid tissue only	0.5	Irregular solid mass	Suspicious malignancy	Conventional PTC
1974	Acellular fibrotic nodule	0.7	Irregular solid mass with dense fibrosis	Suspicious malignancy	Conventional PTC
2172	Normal thyroid tissue only	1.1	Irregular solid mass with calcification	Suspicious malignancy	Conventional PTC

CNB core needle biopsy, *USG* ultrasonography, *PTC* papillary thyroid carcinoma

FTC group. NIFTP/EFVPTC were more frequently diagnosed as follicular neoplasm ($p = 0.022$) and less frequently categorized as indeterminate lesion ($p = 0.020$), compared with FTA/FTC. In the follicular neoplasm subcategory, NIFTP/EFVPTC were more frequently classified as follicular neoplasm with nuclear atypia ($p < 0.001$), compared with FTA/FTC.

The Impact of NIFTP on ROM in Each Diagnostic Category of Thyroid CNB

In 946 cases with final surgical diagnoses, the ROM in each category was as follows, when NIFTPs were regarded as malignant tumors (Table 6): non-diagnostic, 70.0%; benign, 3.8%; indeterminate lesion, 35.0%; follicular neoplasm, 57.1%; suspicious for malignancy, 100.0%; and malignant, 100.0%. In indeterminate lesion category, ROM was significantly higher in the nuclear atypia subcategory than that of architectural atypia subcategory (77.3% vs. 26.2%; $p < 0.001$). Regarding the follicular neoplasm category, ROM was significantly higher in cases of follicular neoplasm with nuclear atypia than in those without nuclear atypia (90.3% vs. 36.4%; $p < 0.001$). When NIFTPs were excluded from malignancy, the absolute decrease in ROM ranged from 0 to 22.6% with a relative decrease in ROM ranging from 0 to 28.1%. A significant decrease in ROM was found in the follicular neoplasm

Table 4 Distribution of thyroid CNB categories in variants of PTC

CNB diagnostic category	Variants of PTC in final diagnosis					
	Conventional	NIFTP	EFVPTC	Infiltrative FVPTC	Tall cell variant	Other rare variants
I. Non-diagnostic	7 (1.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
II. Benign lesion	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
III. Indeterminate lesion	14 (2.8%)	11 (34.4%)[a]	4 (12.5%)[a]	8 (17.8%)	0 (0%)	2 (5.0%)
III A. Indeterminate lesion with nuclear atypia	10 (2.0%)	2 (6.3%)	1 (3.1%)	3 (6.7%)	0 (0%)	0 (0%)
III B. Indeterminate lesion with architectural atypia	3 (0.6%)	9 (28.1%)	3 (9.4%)	5 (11.1%)	0 (0%)	2 (5.0%)
III C. Other indeterminate lesion	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
IV. Follicular neoplasm	4 (0.8%)	20 (62.5%)[b]	27 (84.4%)[b]	12 (26.7%)	0 (0%)	6 (15.0%)
IV A. Follicular neoplasm without nuclear atypia	0 (0%)	6 (18.8%)	6 (18.8%)	1 (2.2%)	0 (0%)	3 (7.5%)
IV B. Follicular neoplasm with nuclear atypia	4 (0.8%)	14 (43.8%)	21 (65.6%)	11 (24.4%)	0 (0%)	3 (7.5%)
V. Suspicious for malignancy	45 (9.0%)	1 (3.1%)	0 (0%)	12 (26.7%)	0 (0%)	3 (7.5%)
VI. Malignant	430 (86.0%)	0 (0%)	1 (3.1%)	13 (28.9%)	34 (100%)	29 (72.5%)
Total no.	500	32	32	45	34	40

Data are presented as number of cases and column percentage

CNB core needle biopsy, *PTC* papillary thyroid carcinoma, *NIFTP* noninvasive follicular thyroid neoplasm with papillary-like nuclear features, *EFVPTC* encapsulated follicular variant of PTC, *FVPTC* follicular variant of PTC

[a] $p = 0.039$

[b] $p = 0.048$

Table 5 Comparison of CNB diagnostic categories between follicular-patterned tumors

CNB diagnostic category	NIFTP/EFVPTC	Infiltrative FVPTC	FTA/FTC	*p* value[a]	*p* value[b]	*p* value[c]
I. Non-diagnostic	0 (0%)	0 (0%)	1 (0.6%)	1.000	1.000	1.000
II. Benign lesion	0 (0%)	0 (0%)	4 (2.6%)	1.000	0.324	0.577
III. Indeterminate lesion	15 (23.4%)	8 (17.8%)	63 (40.6%)	0.476	0.020*	0.005*
III A. Indeterminate lesion with nuclear atypia	3 (4.7%)	3 (6.7%)	1 (0.6%)	0.689	0.076	0.036*
III B. Indeterminate lesion with architectural atypia	12 (18.8%)	5 (11.1%)	62 (40%)	0.279	0.003*	< 0.001*
III C. Other indeterminate lesion	0 (0%)	0 (0%)	0 (0%)	1.000	1.000	1.000
IV. Follicular neoplasm	47 (73.4%)	12 (26.7%)	87 (56.1%)	< 0.001*	0.022*	0.001*
IV A. Follicular neoplasm without nuclear atypia	12 (18.8%)	1 (2.2%)	79 (51%)	0.014*	< 0.001*	< 0.001*
IV B. Follicular neoplasm with nuclear atypia	35 (54.7%)	11 (24.4%)	8 (5.2%)	0.002*	< 0.001*	< 0.001*
V. Suspicious for malignancy	1 (1.6%)	12 (26.7%)	0 (0%)	< 0.001*	0.292	< 0.001*
VI. Malignant	1 (1.6%)	13 (28.9%)	0 (0%)	< 0.001*	0.292	< 0.001*

Data are presented as number of cases and column percentage

CNB core needle biopsy, *PTC* papillary thyroid carcinoma, *NIFTP* noninvasive follicular thyroid neoplasm with papillary-like nuclear features, *EFVPTC* encapsulated follicular variant of PTC, *FVPTC* follicular variant of PTC, *FTA*, follicular thyroid adenoma, *FTC* Follicular thyroid carcinoma

[a] NIFTP/EFVPTC vs. infiltrative FVPTC

[b] NIFTP/EFVPTC vs. FTA/FTC

[c] Infiltrative FVPTC vs. FTA/FTC

*Statistically significant *p* value, two-tailed

category (57.1 to 44.7%, $p = 0.026$) and its subcategory, follicular neoplasm with nuclear atypia (90.3 to 67.7%, $p = 0.002$).

When calculated in all 2687 CNBs, the ROM in each category (when NIFTP was included in malignant tumor) was as follows (Table 7): non-diagnostic, 4.3%; benign, 0.2%; indeterminate lesion with nuclear atypia, 27.4%; indeterminate lesion with architectural atypia, 7.8%; follicular neoplasm without nuclear atypia, 19.6%; follicular neoplasm with nuclear atypia, 61.5%; suspicious for malignancy, 69.0%; malignant, 78.3%. When NIFTP was excluded from malignancy, the absolute decrease in ROM ranged from 0 to 15.3%, and the relative decrease in ROM ranged from 0 to 28.2%. The ROM decrease was prominent only in the follicular neoplasm with nuclear atypia category (61.5 to 46.2%, $p = 0.037$).

Discussion

The advent of the new diagnostic terminology "NIFTP," and its exclusion from malignancy, caused a significant change in the management of patients with these tumors [17]. The intent of the reclassification of these tumors was prevention of overtreatment and reduction of economic and psychological burden on patients. Considering that NIFTP rarely recurs or presents with metastasis, lobectomy without post-operative radioactive iodine therapy is generally recommended. Moreover, introduction of NIFTP impacts on ROM in the diagnostic categories of thyroid FNAC and CNB. Because ROM in each diagnostic category is the basis for clinical decision-making, changes in ROM are critical and should be noted in daily practice to make proper adjustment.

Incidence of NIFTP is known to be quite low in Asian countries, reportedly from 0 to 4.7% of PTCs [34, 35], whereas it comprises 7 to 28% of PTCs in Western countries [22, 23, 36]. As change in ROM after the introduction of NIFTP largely depends on the incidence of NIFTP, the impact of NIFTP diagnoses on ROM in the diagnostic categories of thyroid FNAC or CNB is expected to be low in Asian countries, including Korea. In the previous study, our group did not find significant changes in ROM [27], while reports from Western countries showed a prominent decrease in ROM in the indeterminate categories-AUS/FLUS, follicular neoplasm/suspicious for a follicular neoplasm, and suspicious for malignancy of thyroid FNAC [22–24]. In contrast, in the present study evaluating thyroid CNB specimens, a significant decrease of ROM in the follicular neoplasm category was found. This may be associated with a significantly higher incidence of NIFTP in this study dealing with CNB specimens (4.7% of all PTCs) than that (1.5%) in our previous study using FNAC specimens, although the number is still lower than what has been reported in Western countries [27]. Another explanation for this discrepancy between the two diagnostic modalities is the difference in the distribution of diagnostic categories for NIFTP. For instance, NIFTPs were most commonly categorized as follicular neoplasm in thyroid CNB. On the other hand, the most common FNAC diagnosis of NIFTP was AUS (56%) followed by benign (20%), which suggests that

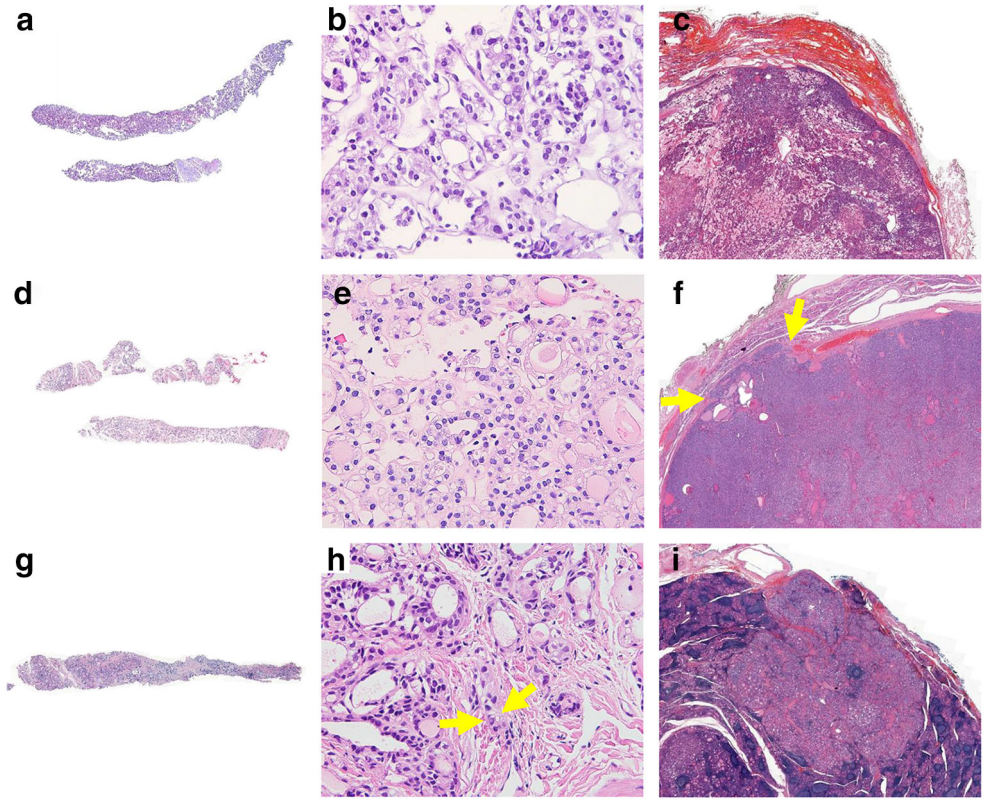

Fig. 1 Representative examples of noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP), invasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC), and infiltrative FVPTC in core needle biopsies and resection specimens. **a**–**c** NIFTP. **a** A low-power view of core needle biopsy (CNB) shows microfollicular proliferative lesion with fibrous capsule. **b** In the high-power view of CNB, tumor cell nuclei show slight nuclear enlargement, chromatin clearing, and a few nuclear grooves, leading to a diagnosis of follicular neoplasm with nuclear atypia. **c** The tumor shows no capsular or vascular invasion with final diagnosis of NIFTP in the resected specimen. **d**–**f** Invasive EFVPTC. **d** A low-power view of CNB shows an encapsulated microfollicular-patterned lesion. **e** A high-power view reveals nuclear atypia similar to (**b**), resulting in a CNB diagnosis of follicular neoplasm with nuclear atypia. **f** A surgical resection specimen reveals EFVPTC with minimal capsular invasion (arrows). **g**–**i** Infiltrative FVPTC. **g** A low-magnified view of CNB reveals a follicular-patterned tumor showing desmoplastic stroma and infiltrative growth into the surrounding normal thyroid tissue, categorized as suspicious for PTC. **h** A high-magnification view shows PTC-like nuclear changes in a majority of the tumor cells. A nuclear pseudoinclusion (arrows) is also identified. **i** A resected specimen shows infiltrative FVPTC

not all cases of NIFTP might have undergone surgical resection after FNAC [27]. In addition, the fact that CNB is usually performed for thyroid nodules with indeterminate USG features might also have caused a selection bias.

To date, there have been only a few studies that analyzed changes in ROM of CNB diagnostic categories after the introduction of NIFTP. Jeon et al. reported that ROM was estimated to change from 7–35% to 5–24% in the AUS with architectural atypia category (which corresponds to the indeterminate lesion with architectural atypia category in the present study), and from 28–49% to 23–39% in the follicular neoplasm category, after excluding NIFTP from malignancy [26]. Recently, Chung et al. have shown that decrease of ROM in indeterminate and follicular neoplasm categories was 4.5–15.4% and 8.1–13.3%, respectively. Especially, ROM change was greatest in indeterminate category with both cytologic and architectural atypia (11.8–32.3%) and follicular neoplasm category with nuclear atypia (16.7–33.3%) [25]. These results are similar to the present study, although we found that the decrease of ROM was less prominent in the indeterminate category. However, those studies focused their evaluation to thyroid nodules diagnosed as indeterminate and follicular neoplasm category, and thus could not give information about the change in ROM in other diagnostic categories [25, 26].

In our series, NIFTP was most often classified as follicular neoplasm (62.5%), followed by indeterminate lesion (34.4%). In previous studies using thyroid CNB, NIFPT was categorized as follicular neoplasm in 45.5 to 51% and as indeterminate in 0 to 49% [26, 37]. The majority of NIFTPs was diagnosed as follicular neoplasms, implying a need for lobectomy, although a substantial proportion was recognized as indeterminate lesion. Additional immunohistochemical analysis and correlation of the USG findings of the lesions may help to better triage patients with these nodules. In our previous study using thyroid FNAC, only 8% of NIFTPs were diagnosed as follicular neoplasm [27]. This could have resulted from intrinsic differences in FNAC and CNB. By incorporating the histologic information of nodule with its relationship with the

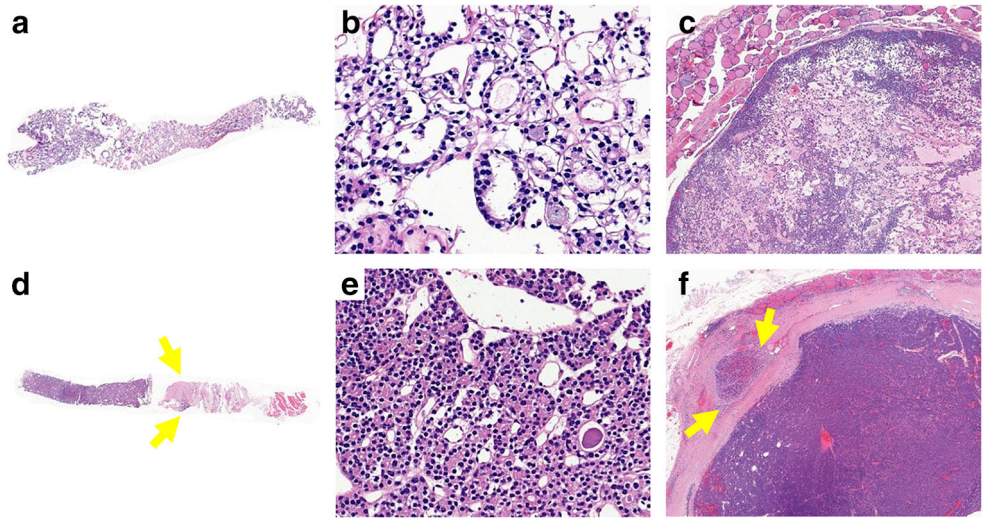

Fig. 2 Representative examples of follicular thyroid adenoma (FTA) and follicular thyroid carcinoma (FTC) in thyroid core needle biopsies and resection specimens. **a**–**c** FTA. **a** A low-power view of thyroid core needle biopsy (CNB) shows a microfollicular proliferative lesion lacking capsule or adjacent thyroid tissue, diagnosed as indeterminate follicular lesion with architectural atypia. **b** A high-magnification view reveals hyperchromatic round tumor cell nuclei lacking PTC-like nuclear features. **c** A surgical resection specimen revealed FTA. **d**–**f** FTC. **d** A low-magnification view of thyroid CNB shows an encapsulated microfollicular-patterned lesion with suspicious capsular invasion (arrow). **e** A high-power view reveals hyperchromatic round tumor cell nuclei, resulting in a diagnosis of follicular neoplasm without nuclear atypia. **f** A surgically resected specimen reveals FTC with minimal capsular invasion (arrows)

capsule and adjacent thyroid follicles, NIFTP might have been more often categorized as follicular neoplasm in CNB specimens than in FNAC. This finding has clinical implications because CNB has the possibility to reduce the incidence of repeated examinations in the preoperative diagnosis of NIFTP.

In this study, the most clinically relevant finding was that NIFTP/EFVPTC was more frequently diagnosed as follicular neoplasm than other PTC variants including infiltrative FVPTC. They were rarely categorized as suspicious for malignancy or malignant. Hahn et al. also found that NIFTPs were most often categorized as follicular neoplasm (45.5%) while other FVPTCs were most frequently diagnosed as malignant [37]. In NIFTPs, less profound nuclear features of PTC along with the lack of invasive growth pattern and desmoplastic stroma, which are usually found in other PTC variants, may have contributed to these results [17, 23, 38].

Table 6 Impact of NIFTP on the risk of malignancy in CNB diagnostic categories in cases with final diagnosis

CNB diagnostic category	No.	No. of malignancy including NIFTP (%)	No. malignancy excluding NIFTP (%)	Absolute decrease in ROM (%)	Relative decrease in ROM (%)
I. Non-diagnostic	10	7 (70.0)	7 (70)	0	0
II. Benign lesion	52	2 (3.8)	2 (3.8)	0	0
III. Indeterminate lesion	143	50 (35.0)	39 (27.3)	7.7	22
III A. Indeterminate lesion with nuclear atypia	22	17 (77.3)	15 (68.2)	8.9	11.5
III B. Indeterminate lesion with architectural atypia	120	32 (26.7)	23 (19.2)	7.5	28.1
III C. Other indeterminate lesion	1	1 (100)	1 (100)	0	0
IV. Follicular neoplasm	161	92 (57.1)	72 (44.7)	12.4[a]	21.7
IV A. Follicular neoplasm without nuclear atypia	99	36 (36.4)	30 (30.3)	6.1	16.8
IV B. Follicular neoplasm with nuclear atypia	62	56 (90.3)	42 (67.7)	22.6[b]	25
V. Suspicious for malignancy	69	69 (100)	68 (98.6)	1.4	1.4
VI. Malignant	511	511 (100)	511 (100)	0	0
Total no.	946	731 (77.3)	699 (73.9)	3.4	4.6

CNB core needle biopsy, *No.* number, *NIFTP* noninvasive follicular thyroid neoplasm with papillary-like nuclear features, *ROM* risk of malignancy

[a] $p = 0.026$

[b] $p = 0.002$ by chi-square test

Table 7 Impact of NIFTP on the risk of malignancy in CNB diagnostic categories in total cases

CNB diagnostic category	No.	No. of malignancy including NIFTP (%)	No. malignancy excluding NIFTP (%)	Absolute decrease in ROM (%)	Relative decrease in ROM (%)
I. Non-diagnostic	164	7 (4.3)	7 (4.3)	0	0
II. Benign lesion	1023	2 (0.2)	2 (0.2)	0	0
III. Indeterminate lesion	472	50 (10.6)	39 (8.3)	2.3	21.7
III A. Indeterminate lesion with nuclear atypia	62	17 (27.4)	15 (24.2)	3.2	11.7
III B. Indeterminate lesion with architectural atypia	408	32 (7.8)	23 (5.6)	2.2	28.2
III C. Other indeterminate lesion	2	1 (50)	1 (50)	0	0
IV. Follicular neoplasm	275	92 (33.5)	72 (26.2)	7.3	21.8
IV A. Follicular neoplasm without nuclear atypia	184	36 (19.6)	30 (16.3)	3.3	16.8
IV B. Follicular neoplasm with nuclear atypia	91	56 (61.5)	42 (46.2)	15.3[a]	24.9
V. Suspicious for malignancy	100	69 (69)	68 (68)	1.0	1.4
VI. Malignant	653	511 (78.3)	511 (78.3)	0	0
Total no.	2687	731 (27.2)	699 (26)	1.2	4.4

CNB core needle biopsy, *No.* number, *NIFTP* noninvasive follicular thyroid neoplasm with papillary-like nuclear features, *ROM* risk of malignancy

[a] $p = 0.037$ by chi-square test

Thus, it seems possible to differentiate NIFTP/EFVPTC from other PTC variants including infiltrative FVPTC by using CNB, which can lead to more conservative management in patients with NIFTP/EFVPTC.

When compared with FTA/FTC, NIFTP/EFVPTC was more frequently diagnosed as follicular neoplasm category, especially follicular neoplasm with nuclear atypia. Although preoperative differential diagnosis between NIFTP/EFVPTC and FTA/FTC does not have an effect on surgical management planning, we think that subcategorization of follicular neoplasm category based on presence or absence of nuclear atypia could provide more information to clinicians about the nature of the biopsied tumor by demonstrating the delicate nuance.

There are some limitations to this study. First, it was a retrospective study and subject to selection bias. Because it was conducted in a tertiary medical center, the malignant category comprised 24.3% of all CNB diagnoses, which is much higher than would be found in the overall population of Korea. Therefore, the incidence of NIFTP in our center may not reflect the actual nationwide distribution. Second, the assessment of nuclear changes in NIFTP can show substantial inter-observer variability, making the incidence of NIFTP and its CNB diagnostic categories divergent from other studies. Nevertheless, it is important to evaluate the institution-based incidence of NIFTP and ROM in each category to provide proper information for clinical decision-making.

In conclusion, this is the first study that evaluated the preoperative diagnostic categories of NIFTP in thyroid CNB and systematically calculated the changes in ROM in all CNB diagnostic categories, based on a standardized pathology reporting system. The decrease in ROM was significant in the follicular neoplasm category, especially in the follicular neoplasm with nuclear atypia category, when NIFTP was no longer considered carcinoma. NIFTP/EFVPTC were frequently diagnosed as follicular neoplasm and hardly ever diagnosed as suspicious for malignancy or malignant categories. Thus, it might be feasible to separate NIFTP/EFVPTC from other PTC variants using CNB, reducing repeat FNACs and providing clinicians a useful guide to the optimal management of patients with these tumors.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This study was approved by the Institutional Review Board (IRB) of the Seoul National University Bundang Hospital (IRB No. B-1812-510-108). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Institutional review board waived the requirement for obtaining informed consent for this study.

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