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Prevention of total thyroidectomy in noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) based on combined interpretation of ultrasonographic and cytopathologic results

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Summary

Objective: To explore the potential preoperative ultrasonography (US) and cytopathological features to avoid total thyroidectomy in NIFTP.

Context: Recently, it has been proposed that that noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP) be classified as tumours, rather than cancer.

Patients: A total of 142 surgically proven follicular variant papillary thyroid carcinomas (FVPTCs; 45 NIFTP, 97 non-NIFTP; mean size: 20.4±11.0 mm, range: 10.0-65.0 mm) from 142 patients were included in this study.

Measurements: Three preoperative features of thyroid nodules (each US finding, US and Bethesda category) were compared in NIFTP and non-NIFTP groups. The preoperative decision-making process to avoid total thyroidectomy in NIFTP was evaluated based on combination of those features.

Results: In each US finding, there was only significantly less macrocalcification in the NIFTP group than in the non-NIFTP group (8.8% [4/45] vs 32.0% [31/97], $P = .006$). In US category, all of the NIFTP nodules were a low or intermediate suspicion (100% [45/45]). In Bethesda category, 26.7% [12/45] of the NIFTP was diagnosed as either suspicious malignancy or malignant, which increased the risk of a total thyroidectomy. In our study, a total thyroidectomy might be avoided in all of the NIFTP cases if lobectomy was selected for the nodules classified as a low or intermediate suspicion in US, despite being classified as a suspicious malignancy or malignant by cytopathology.

Conclusions: Combining the US and cytopathological results could sensitively reduce total thyroidectomy in cases of NIFTP.

KEYWORDS

Bethesda, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), thyroid gland, thyroid neoplasm, thyroid nodule, thyroidectomy, ultrasonography

Ji-hoon Kim and Jae-Kyung Won are equally contributed to this study.

1 | INTRODUCTION

The follicular-variant papillary thyroid cancer (FVPTC) is the second most common subtype of papillary thyroid cancer (PTC).[1] There are two main subtypes of FVPTC: encapsulated FVPTC (EFVPTC) and infiltrative FVPTC (IFVPTC). The growth pattern and metastatic potential of EFVPTC has been reported to be similar to that of a follicular neoplasm, while that of IFVPTC resembles that of a classical PTC.[2] EFVPTC is divided into two subgroups according to the presence or absence of capsular/vascular invasion: noninvasive EFVPTC (ni-EFVPTC) and invasive EFVPTC (i-EFVPTC). Among the FVPTCs, ni-EFVPTC is well described in the literature as having a good prognosis.[2,3] Based on several previous studies which have documented the indolent behaviour and genetic differences of ni-EFVPTC when compared to other PTC subtypes,[2-7] Nikiforov et al.[8] recently suggested a new term, noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), to replace ni-EFVPTC. They recommended that this tumour should be classified as a neoplasm instead of a cancer and treated by lobectomy rather than total thyroidectomy.

Preoperative ultrasonography and fine needle aspiration (FNA)/core needle biopsy (CNB) are the two main diagnostic tools used to evaluate a thyroid nodule.[9-13] As for ultrasonographic (US) features, several studies have reported that FVPTC tends to have more benign US features than classical PTC.[14-17] With regard to the cytological results, most recently, Faquin et al[18] documented that Bethesda categories 3 (atypia of undetermined significance/follicular lesion of undetermined significance [AUS/FLUS]) and 4 (follicular neoplasm/suspicious for follicular neoplasm [FN/SFN]) are the most frequent cytological findings of NIFTP. However, despite the several instances that US results have significantly complemented the cytopathological results for clinical decision-making in patients with thyroid nodules,[19,20] the utility of the combined interpretation and a method for the combination of US and cytopathological results has yet to be elucidated in patients with NIFTP.

Therefore, the purpose of our study was to explore the potential preoperative US and cytopathological features that could be used to screen NIFTPs and to reduce the total thyroidectomy in NIFTP by using that.

2 | MATERIALS AND METHODS

2.1 | Patient population

This retrospective study was approved by the institutional review board, and informed consent was waived. From January 2009 to May 2014, 157 consecutive patients who satisfied the following criteria were included in this retrospective study: (i) patients who underwent a total thyroidectomy or thyroid lobectomy and were diagnosed as FVPTC, (ii) patients whose preoperative US images were available for analysis and (iii) the thyroid nodule diagnosed as FVPTC was >1 cm in the preoperative US. Of these, 15 patients were excluded due to: (i) impairment of pathologic slides for retrospective review (n = 8), or (ii) revision of the final pathologic diagnosis from FVPTC to classic PTC (n = 5), nodular hyperplasia (n = 1) or metastasis (n = 1). Finally, 142 FVPTCs (mean size, 20.4 ± 11.0 mm; range, 10.0-65.0 mm) from 142 patients (35 men, 107 women; mean age, 50.1 ± 14.0; range, 18-74 years) were included in this study. Clinical characteristics of all patients, including age, sex, type of operation (total thyroidectomy or lobectomy), pathologic nodal staging and the existence of a combined classical PTC, were reviewed.

2.2 | Ultrasound examination technique

All US examinations were performed with two high-resolution US machines equipped with a 10-12 MHz linear transducer (IU22, Philips Medical Systems, Bothell, WA; AixPlorer, Supersonic Imagine, Aix en Provence, France). The scanning protocol in all cases included both transverse and longitudinal real-time imaging of the thyroid nodules, and representative images of the thyroid nodules were stored in a picture archiving and communication systems. Any lymph node (LN) that showed suspicious features (cystic change, calcification, hyperechogenicity and abnormal vascularity on color Doppler study) on the scan was marked as metastatic LN. A faculty radiologist (J.-H.K.) with 14 years of experience in performing thyroid US performed or supervised the examination performed by board-certified radiologists and residents who were participating in the thyroid radiology training programme.

2.3 | Retrospective US imaging analysis

Two radiologists (J.-H.K. and S.-H.Y. with 14 and 6 years of experience in performing thyroid US, respectively) reviewed all of the US images. The reviewers were blinded to the clinical history of patients and the final pathologic diagnosis of the nodules. Final decisions were obtained by consensus between two radiologists. According to the consensus statement and recommendations of Korean Society of Thyroid Radiology (KSThR),[11] size, internal contents, echogenicity, shape, margin, presence of calcification (microcalcification, macrocalcification and rim calcification), hypoechoic halo and vascularity of the nodules were analysed. All thyroid nodules were categorized as 5 categories according to the 2015 American Thyroid Association (ATA) Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer (ATA guidelines) and Korean Thyroid Imaging Reporting and Data System (K-TIRADS).[10,11] For US categorization, 5 categories were arbitrarily numbered A1 to A5 if the nodule was analysed according to the ATA guideline (benign = A1, very low suspicion = A2, low suspicion = A3, intermediate suspicion = A4, high suspicion = A5) and numbered K1 to K5 if the nodule was analysed according to the K-TIRADS (no nodule = K1, benign = K2, low suspicion = K3, intermediate suspicion = K4, high suspicion = K5).

2.4 | Pathologic analysis

Preoperative cytopathological results which were derived from preoperative FNA or CNB were retrospectively reviewed in all patients

(FNA only = 115, CNB only = 11, FNA and CNB = 22). The results were recorded according to the Bethesda categorization[21,22] where 6 categories were labelled B1 to B6 (nondiagnostic = B1, benign = B2, AUS/FLUS for FNA/indeterminate for CNB = B3, FN/SFN = B4, suspicious for malignancy = B5, malignant = B6). If the patient underwent both FNA and CNB, the highest categorical result was adopted as the final preoperative cytopathological result.

All of the histological specimens obtained by thyroidectomy were retrospectively reviewed by two pathologists (J.-K.W., K.C.J. with 12 and 22 years of experience in pathology, respectively). Final decisions were obtained by a consensus between two pathologists. All of the thyroid nodules were classified into one of the following three groups: ni-EFVPTC (n = 45), i-EFVPTC (n = 46) and IFVPTC (n = 51). Nodules that were originally classified as ni-EFVPTC were now classified as NIFTP based on newly suggested consensus diagnostic criteria,[8] and i-EFVPTC and IFVPTC were included in non-NIFTP group (n = 97).

2.5 | Statistical analysis

SPSS version 12.0 (SPSS, Chicago, Ill) was used for statistical analysis. All variables in two groups (NIFTP vs non-NIFTP) and three groups (NIFTP vs i-EFVPTC vs. IFVPTC) were compared. Differences in age and nodule size were analysed using an independent t test for comparison between the NIFTP and non-NIFTP groups. A one-way ANOVA followed by the Bonferroni post hoc test was used to compare the NIFTP, i-EFVPTC and IFVPTC groups. Fisher's exact test was used for categorical variables, and the pairwise comparisons were carried out for the comparison of the three groups. Generally, a $P < .05$ was considered to indicate statistical significance, but a P of 0.017 was considered to indicate statistical significance on post hoc test accounting for a Bonferroni correction. All tests were two-tailed. As there were no nodules with the US categorizations of A1, A2, K1 or K2 in either group, simulation using two candidate cut-off values ($\leqq 3$ and $\leqq 4$) was performed for differentiating NIFTP from non-NIFTP. As for the cytopathological categories (B1-6), receiver operator characteristic (ROC) curve analysis was used. The optimal cut-off values were defined as the value at which the sum of the sensitivity and specificity was maximized. Sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and accuracy for differentiating NIFTP from non-NIFTP were calculated. McNemar's test was used to compare the Sn, Sp and accuracy among the diagnostic criteria obtained.

3 | RESULTS

3.1 | Baseline characteristics and comparison of clinical findings

The comparisons of the clinical findings between the NIFTP and non-NIFTP groups are summarized in Table 1. There was no significant difference in age or sex between the two groups, but lobectomy was more commonly performed in the NIFTP group than in the non-NIFTP group (51.1% [23/45] vs 30.9% [30/97], $P = .033$). Lymph node metastasis was significantly less frequent in the NIFTP group than in the non-NIFTP group (2.2% [1/45] vs 25.8% [25/97], $P = .003$). In NIFTP group, only 1 case (size, 1.9 cm; US category, low suspicion; Bethesda category, suspicious malignancy) showed micrometastasis and was staged as N1a.

3.2 | Comparison of US findings

The comparisons of the US findings between the NIFTP and non-NIFTP groups and among the NIFTP, i-EFVPTC and IFVPTC groups are summarized in Tables 2 and S1, respectively. There was no significant difference in most of the US features between the NIFTP and non-NIFTP groups. There was only significantly less macrocalcification in the NIFTP group than in the non-NIFTP group (8.8% [4/45] vs 32.0% [31/97], $P = .006$). They were rare but when they appeared, macrocalcifications in NIFTP tended to be histologically different from those in IFVPTC. Macrocalcifications in NIFTP were focal and had distinct margins, while those in IFVPTC were extensive, dense and showed an indistinct margin with surrounding fibrosis. Although not statistically significant, there was no case with preoperative LN metastasis in NIFTP, while there were 5 cases of non-NIFTP that showed preoperative LN metastasis revealed by US and FNA.

In the analysis of the 3 groups, there was no significant difference in US features between the NIFTP and i-EFVPTC groups, but there were significant differences in the orientation and macrocalcifications between NIFTP vs IFVPTC and/or i-EFVPTC vs IFVPTC.

3.3 | Comparison of US category

Comparisons of US categories based on the ATA guidelines and K-TIRADS between the NIFTP and non-NIFTP groups and among the NIFTP, i-EFVPTC and IFVPTC groups are summarized in Tables 3 and S2, respectively. The US categorization based on the ATA guidelines and K-TIRADS resulted in almost the same category in the individual nodules except for 1 nodule (K4 and A3). There were no significant differences in most of the US categorization except for ATA category 3 between the two groups.

Low suspicion (A3) was significantly more frequent in the NIFTP group than the non-NIFTP group (75.6% [34/45] vs 55.7% [54/97], $P = .037$). It is noteworthy that category 5 (high suspicion) was classified exclusively in the non-NIFTP (8.2% [8/97]) but not in the NIFTP group (0.0% [0/45]) in both ATA guidelines and K-TIRADS.

In the analysis of the three groups, low suspicion (A3, K3) was significantly more frequent in the NIFTP group than in the IFVPTC group (ATA guidelines, 75.6% [34/45] vs 47.1% [24/54], $P = .008$; K-TIRADS, 73.3% [33/45] vs 47.1 [24/54], $P = .016$, respectively).

3.4 | Comparison of preoperative cytopathological category

There was no significant difference between the two groups in most of the Bethesda classification, except that the frequency of FN/SFN

TABLE 1 Comparisons of clinical findings of NIFTP and non-NIFTP

	NIFTP (n=45)	Non-NIFTP (n=97)	Total (N=142)	*P*
Age (years)	49.2 ± 13.5	50.6 ± 14.3	50.1 ± 14.0	.578
Sex				.556
Male	13 (28.9)	22 (22.7)	35 (24.6)	
Female	32 (71.1)	75 (77.3)	107 (75.4)	
Operation type				.033
Total thyroidectomy	22 (48.9)	67 (69.1)	89 (62.7)	
Lobectomy	23 (51.1)	30 (30.9)	53 (37.3)	
Gross ETE				.060
Positive	0 (0.0)	10 (10.3)	10 (7.0)	
Negative	45 (100.0)	87 (89.7)	132 (93.0)	
N staging				.003
N0	44 (97.8)	72 (74.2)	116 (81.7)	
N1a	1 (2.2)	18 (18.6)	19 (13.4)	
N1b	0 (0.0)	7 (7.2)	7 (4.9)	
Distant metastasis				.838
Positive	0 (0.0)	2 (2.1)	2 (1.4)	
Negative	45 (100.0)	95 (97.9)	140 (98.6)	
Coincidental classical PTC				.571
Positive	3 (6.7)	11 (11.3)	14 (9.9)	
Negative	42 (93.3)	86 (88.7)	128 (90.1)	

Data are mean ± standard deviation (SD) for continuous variables and number of patients (%) for nominal variables.

n, number of patients; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; ETE, extrathyroidal extension; N staging, lymph node staging; PTC, papillary thyroid cancer.

(B4) was significantly higher in the NIFTP group than in the non-NIFTP group (42.2% [19/45] vs 23.7% [23/97], *P* = .040) (Table 3). The frequency of the malignant category (B6) was higher in the non-NIFTP group than in the NIFTP group (8.9% [4/45] vs 21.6% [21/97], *P* = .105), but there was no statistical significance.

3.5 | Diagnostic accuracies of a significant US feature (absence of macrocalcification), US and cytopathological categories

In differentiating the NIFTP from the non-NIFTP, ROC curve analysis suggested that a category 4 or less as the optimal cut-off value for both US and Bethesda categories. In the Bethesda categorization, a category 4 or less was significantly more frequent in NIFTP (68.9% [31/45] vs 48.5% [47/97], *P* = .036). In the US categorization, a category 4 or less was more frequent in NIFTP (100.0% [45/45] vs 91.8% [89/97], *P* = .111), but there was no statistical significance.

All 3 criteria for a positive NIFTP screen (absence of macrocalcification, US category 4 or less, Bethesda category 4 or less) was the least diagnostically accurate overall (50.70%, 37.32%, 57.04%, respectively). However, the US category demonstrated a very high sensitivity and negative predictive value (100%, 100%; Table 4 and Figure 1).

Based on this result, a total thyroidectomy might be avoided in all of the NIFTP cases if lobectomy was selected for nodules of US category 4 or less, even though the cytopathological result was a category 5 or 6.

Representative images for NIFTP and non-NIFTP including US and cytopathologic features are shown in Figures 2 and S1-S2.

4 | DISCUSSION

This study showed that no single clinical, US or cytopathological feature alone could give enough diagnostic accuracy to differentiate NIFTP from non-NIFTP in the preoperative stage, which might be because NIFTP and i-EFVPTC had very similar findings on US and cytopathological results. Therefore, reducing overtreatment for NIFTP seems to be the best practical goal prior to the operation. Based on the ATA guidelines,[10] a total thyroidectomy is recommended for patients with thyroid cancer that meets any of the following conditions: (i) >4 cm, (ii) gross extrathyroidal extension (ETE), (iii) nodal metastasis or (iv) distant metastasis. Both lobectomy and total thyroidectomy are surgical options for patients with thyroid cancer 1-4 cm in size. Although the rate of lobectomy performance has recently increased, the risk of total thyroidectomy for cases of NIFTP exists. According

TABLE 2 Comparisons of sonographic findings of NIFTP and non-NIFTP

	NIFTP (n = 45)	Non-NIFTP (n = 97)	Total (N = 142)	*P*
Size (range), mm	22.9 ± 12.2 (11.0-43.0)	19.2 ± 10.3 (10.0-65.0)	20.4 ± 11.0 (10.0-65.0)	.065
Internal contents				
Solid	29 (64.4)	71 (73.2)	100 (70.4)	.387
Predominantly solid	16 (35.6)	23 (23.7)	39 (27.5)	.204
Predominantly cystic	0 (0.0)	3 (3.1)	3 (2.1)	.572
Echogenicity				
Marked hypoechoic	3 (6.7)	17 (17.5)	20 (14.1)	.141
Mild hypoechoic	11 (24.4)	28 (28.9)	39 (27.5)	.728
Isoechoic	31 (68.9)	52 (53.6)	83 (58.5)	.125
Shape				.239
Round to oval	44 (97.8)	88 (90.7)	132 (93.0)	
Irregular	1 (2.2)	9 (9.3)	10 (7.0)	
Orientation				.317
Parallel	44 (97.8)	89 (91.8)	133 (93.7)	
Nonparallel	1 (2.2)	8 (8.2)	9 (6.3)	
Margin				
Smooth	45 (100.0)	90 (92.8)	135 (95.1)	.152
Ill-defined	0 (0.0)	2 (2.1)	2 (1.4)	.838
Spiculated, microlobulated	0 (0.0)	5 (5.2)	5 (3.5)	.289
Calcification				
None	37 (82.2)	53 (54.6)	90 (63.4)	.003
Rim calcification	4 (8.9)	7 (7.2)	11 (7.7)	.992
Macrocalcification	4 (8.9)	31 (32.0)	35 (24.6)	.006
Microcalcification	0 (0.0)	6 (6.2)	6 (4.2)	.209
Halo				.167
Positive	19 (42.2)	28 (28.9)	47 (33.1)	
Negative	26 (57.8)	69 (71.1)	95 (66.9)	
Vascularity				
No Doppler study	29 (64.4)	72 (74.2)	101 (71.1)	.318
Perinodular vascularity	1 (2.2)	1 (1.0)	2 (1.4)	1.000
Mild intranodular vascularity	13 (28.9)	17 (17.5)	30 (21.1)	.186
Marked intranodular vascularity	2 (4.4)	7 (7.2)	9 (6.3)	.794
Preoperative lymph node metastasis				.289
Positive	0 (0.0)	5 (5.2)	5 (3.5)	
Negative	45 (100.0)	92 (94.8)	137 (96.5)	

Data are mean ± standard deviation (SD) for continuous variables and number of patients (%) for nominal variables.

n, number of patients; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC, papillary thyroid cancer.

to the results of our study, total thyroidectomy could be reduced in cases of NIFTP if the interpretation of the cytopathological category is combined with the US category.

Approximately 50% of the NIFTPs (48.9%) underwent total thyroidectomies in our study. Preoperative cytopathological results may be the leading cause of total thyroidectomy. A significant proportion

TABLE 3 Comparisons of ultrasonographic categorization based on both ATA guideline and K-TIRADS and Bethesda categorization between NIFTP and non-NIFTP

	NIFTP (n = 45)	Non-NIFTP (n = 97)	Total (N = 142)	*P*
ATA category				
Low suspicion (A3)	34 (75.6)	54 (55.7)	88 (62.0)	.037
Intermediate suspicion (A4)	11 (24.4)	35 (36.1)	46 (32.4)	.236
High suspicion (A5)	0 (0.0)	8 (8.2)	8 (5.6)	.111
K-TIRADS category				
Low suspicion (K3)	33 (73.3)	54 (55.7)	87 (61.3)	.068
Intermediate suspicion (K4)	12 (26.7)	35 (36.1)	47 (33.1)	.359
High suspicion (K5)	0 (0.0)	8 (8.2)	8 (5.6)	.111
Bethesda category				
Nondiagnostic (B1)	0 (0.0)	0 (0.0)	0 (0.0)	
Benign (B2)	3 (6.7)	4 (4.1)	7 (4.9)	.814
AUS/FLUS (B3)	9 (20.0)	20 (20.6)	29 (20.4)	1.000
FN/SFN (B4)	19 (42.2)	23 (23.7)	42 (29.6)	.040
Suspicious malignancy (B5)	10 (22.2)	29 (29.9)	39 (27.5)	.452
Malignant (B6)	4 (8.9)	21 (21.6)	25 (17.6)	.105

Data are number of patients (%) for nominal variables.
ATA, American Thyroid Association; K-TIRADS, Korean Thyroid Imaging Reporting and Data System; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; n, number of patients; A, ATA category; K, K-TIRADS category; B, Bethesda category; AUS/FLUS, atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN, follicular neoplasm/suspicious for follicular neoplasm.

TABLE 4 Diagnostic accuracies of the significant US feature (macrocalcification), US and Bethesda category

	NIFTP (n = 45)	Non-NIFTP (n = 97)	Total (N = 142)	*P*	Sn	Sp	PPV	NPV	Accuracy
Macrocalcification				.006	91.11%	31.96%[ab]	38.32%	88.57%	50.70%[ab]
Negative, n (%)	41 (91.1)	66 (68.0)	107 (75.4)						
Positive, n (%)	4 (8.9)	31 (32.0)	35 (24.6)						
US category				.111	100.00%[c]	8.25%[ac]	33.58%	100.00%	37.32%[ac]
Low grade (A 3-4, K3-4), n (%)	45 (100.0)	89 (91.8)	134 (94.4)						
High grade (A5, K5), n (%)	0 (0.0)	8 (8.2)	8 (5.6)						
Bethesda category				.036	68.89%[c]	51.55%[bc]	38.74%	78.13%	57.04%[bc]
Low grade (B1-4), n (%)	31 (68.9)	47 (48.5)	78 (54.9)						
High grade (B5-6), n (%)	14 (31.1)	50 (51.5)	64 (45.1)						

[a]$P < .05$ absence of macrocalcification versus US category.
[b]$P < .05$ absence of macrocalcification versus Bethesda category.
[c]$P < .05$ US category versus Bethesda category.
NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; Sn, sensitivity; n, number of patients; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; US, ultrasonographic; A, American Thyroid Association category; K, Korean Thyroid Imaging Reporting and Data System category; B, Bethesda category.

of the NIFTPs was diagnosed as B5 or B6 in our and previous studies (31.1% and 38.7%, respectively).[18] According to the ATA guidelines, NIFTP categorized as B5 or B6 has the risk of undergoing total thyroidectomy.[10] Fortunately, all of the NIFTPs that were Bethesda category 5 or 6 were classified as US category 4 or less in our study. Therefore, if the surgeon selected lobectomy for the thyroid nodule with US category 3 or 4 even though the result of FNA was suspicious for malignancy (B5) or malignant (B6), overtreatment for NIFTP might be avoided. However, careful evaluation for the presence of preoperative lymph node metastasis should be performed, because a few recent studies reported lymph node metastasis in NIFTP, as in our study.[23,24]

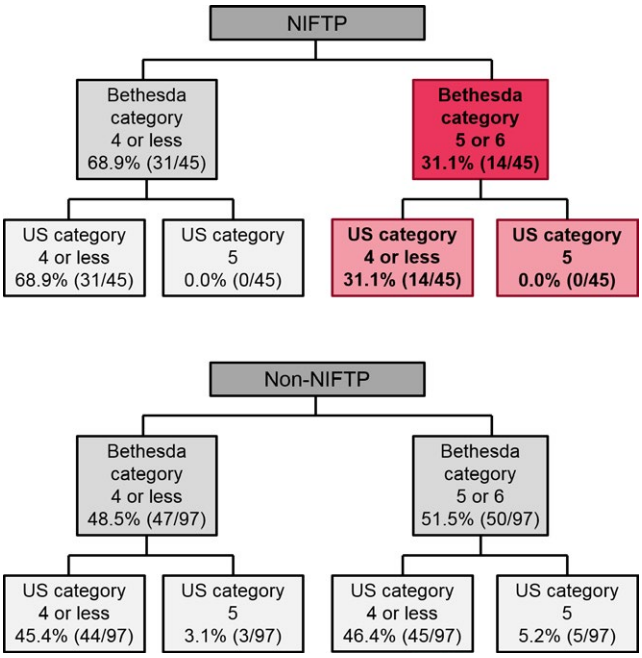

FIGURE 1 Flow chart for the US and Bethesda categorization of NIFTP (top) and non-NIFTP (bottom). NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear feature; US, ultrasonography [Colour figure can be viewed at wileyonlinelibrary.com]

The reason why an NIFTP was not US category 5 could be explained by the histopathologic definition of NIFTP. In the US categorization based on both ATA guidelines and K-TIRADS, suspicious US features, including microcalcification, nonparallel orientation (taller-than-wide) and a speculated/microlobulated margin, are essential for the grading of high suspicion being apart from solidity and hypoechogenicity.[11,25] However, in the US, these suspicious features are hardly seen in NIFTP based on the pathologic definition of NIFTP. According to the pathologic definition, it should have encapsulation or clear demarcation, so it is difficult to have a spiculated or microlobulated margin.[8] In addition, because microcalcification represents the histological pattern of psammoma bodies, which pathologically excludes a NIFTP, microcalcification is difficult to be demonstrated in NIFTP on US.[26] NIFTP rarely has a nonparallel orientation, because dense fibrosis is rare in NIFTP.[27-29] To summarize, it is essentially difficult to classify NIFTP into a high suspicion group based on US due to its pathologic characteristics.

Although our data had been collected before the definition of NIFTP was introduced, total thyroidectomy was less commonly performed for NIFTP when compared to non-NIFTP (48.9% vs 69.1%). There were two reasons for this difference. First, on cytopathological analysis, FN/SFN (B4) and AUS/FLUS (B3) were common preoperative cytopathological results in NIFTP. Our results are consistent with that from a previous study.[18] According to the pathological definition of NIFTP, it should have nuclear features of PTC,[8] but it has been reported that the nuclear features of PTC are less evident in NIFTP than those in non-NIFPT or classical PTC.[30] For this reason, the results of

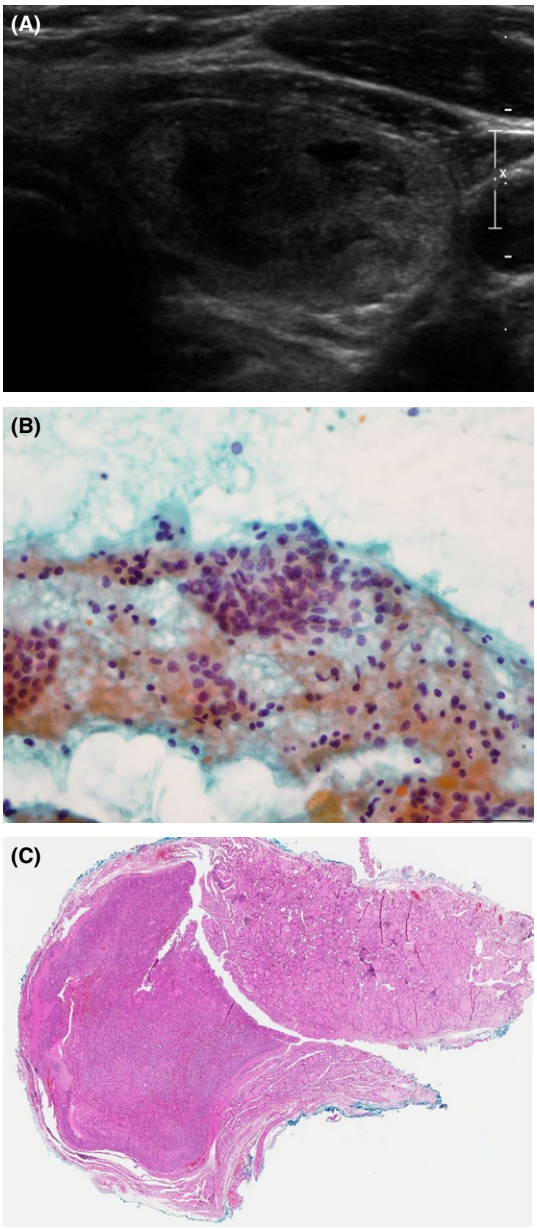

FIGURE 2 An example of a NIFTP with a low US category and high Bethesda category. (A) An approximately 3.2 cm category 3 nodule based on both ATA guidelines and K-TIRADS shows a smooth margin, isoechoic solid portion and parallel orientation with a small cystic portion. (B) The cytological result of the fine needle aspiration (FNA) for this nodule was malignant. The cytological image from the FNA (×400) shows the typical features of papillary thyroid carcinoma such as nuclear pseudoinclusions (C) The patient with this nodule underwent total thyroidectomy, and the final pathologic result was NIFTP. A low magnification image of the resected tumour (×10) shows a well demarcated margin suggesting NIFTP. If lobectomy was considered for the nodule with an US category of 4 or less, even though the cytopathological result was category 5 or 6, this patient could have avoided total thyroidectomy. ATA, American Thyroid Association; K-TIRADS, Korean Thyroid Imaging Reporting and Data System; NIFTP, noninvasive follicular thyroid neoplasm with papillary-like nuclear features; US, ultrasonography [Colour figure can be viewed at wileyonlinelibrary.com]

FNA were frequently B3 or B4 in the NIFTP group, which guided the surgeons towards a lobectomy. Second, the absence of the preoperative LN metastasis in the NIFTP group also influenced them to perform a lobectomy.

In this study, most of the US features did not show significant differences between the NIFTP and non-NIFTP groups. This corresponded well with a previous study that compared the US features between NIFTP and non-NIFTP.[17,31] Only macrocalcification was significantly more frequent in the non-NIFTP group in our study. This finding is concordant with the previous study by Hahn et al[17] and may be in line with the result by Song et al,[32] who found that macrocalcification was more frequent in malignant follicular proliferative lesions than follicular adenomas. The exact mechanism of why macrocalcification is more frequent in non-NIFTP group is not clear, but histologic findings provide a clue for this phenomenon. IFVPTC more frequently shows dense desmoplastic reactions due to the infiltrative growth pattern of tumour nests. It leads to dystrophic calcifications on the fibrotic stroma. Therefore, macrocalcificaiton may help to differentiate non-NIFTP from NIFTP apart from US categorization, because the presence of macrocalcification does not influence the US categorization based on both ATA guidelines and K-TIRADS.[10,11]

There are several limitations to this study. First, it is a retrospective study with a limited number of patients. Although all the sections of the available pathological specimen were retrospectively reviewed again, the unsaved slice could not be examined. Thus, some nodules classified as NIFTP might be i-EFVPTC, and further prospective study is needed. Second, because this study population was limited to FVPTC, the PPV and NPV derived from this study could not be easily applied for all types of thyroid nodules. Third, there is an undertreatment issue. When a lobectomy was chosen for nodules of US category 4 or less, even though cytopathologically they were a category 5 or 6, approximately 12.0% (17/142; nodule size >4 cm, n = 2; gross ETE, n = 5; lymph node metastasis, n = 14; distant metastasis, n = 1, lung) of the patients in our study population with non-NIFTP might require an additional completion thyroidectomy based on the current ATA guidelines. Although a less aggressive surgical approach is consistent with the current treatment philosophy for thyroid cancer,[33] and PTC with benign US features tends to have a better prognosis,[34] the risk of completion thyroidectomy following undertreatment must be considered, especially in patients with a comorbid condition that makes the second operation difficult. This decision-making process should not be applied to patients with a preoperatively proven lymph node or distant metastasis. In cases of other thyroid cancer, a recent prospective study by Strickland et al. suggested that in Bethesda category 5 or 6 nodules, most of the NIFTP/FVPTC could be distinguished from classical PTC by cytological features.[35] The results of a more sophisticated cytopathological analysis taken together with the results from our study might reduce the nudertreatment of non-NIFTP and other thyroid cancer. Fourth, the proportion of cases in the high suspicion category (A5, K5) in US evaluation was lower (NIFTP, 0% [0/45]; non-NIFTP, 8.2% [8/97]) in our study compared to a study by Hahn et al[23] (NIFTP, 0% [0/26]; non-NIFTP, 16.9% [13/77]). US categorization for FVPTC needs to be validated with additional large-scale studies. Finally, we could not re-evaluate the cytological specimens for this study, and instead used cytological results reported before the operation. Recently, several studies have tried to differentiate NIFTP from non-NIFTP or other thyroid cancer cases via cytological specimens obtained by FNA.[30,36-38] Some studies suggested possible cytological features for discrimination of NIFTP.[36-38] Thus, we believe that a prospective study that combines those cytological features and US findings could suggest a better decision-making process in the future.

In conclusion, current clinical, US and cytopathologic findings could not provide sufficient diagnostic accuracy for differentiating an NIFTP from a non-NIFTP. However, combining the US and cytopathologic results could reduce the number of total thyroidectomies in cases of NIFTP, although it would also increase the risk of completion thyroidectomy in cases of non-NIFTP.

CONFLICT OF INTEREST

Nothing to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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