Three ultrasound phenotypes of non-invasive follicular thyroid neoplasm with papillary-like nuclear features proposed for imaging-pathology analysis: single center experience

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Background: The terminology "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) was introduced to reduce overtreatment of thyroid carcinomas with indolent behavior. However, limited literature discussed the sonographic features of the entity in depth. The objective of this study is to summarize sonographic subtypes of NIFTP for precise diagnosis.

Methods: From January 2017 to June 2020, 13,531 consecutive patients underwent surgery for thyroid nodules were reviewed; 30 patients (0.22%) with 30 NIFTP were eligible for this retrospective observational study. We evaluated ultrasound features of all the lesions and distributed them into 3 major types of ultrasound appearance using pattern recognition. Systemic literature review concerning ultrasonography of NIFTP was also performed.

Results: At sonography, all the NIFTP lesions were classified into three types: 19 (63.3%) were categorized into type A-oval and solid nodule without other high-suspicion features, 7 (23.3%) into type B-partially cystic mass without high-suspicion features, 4 (13.3%) into type C-hypoechoic solid nodule with high-suspicion features including irregular margins, microcalcifications, taller-than-wide shape.

Conclusions: Three ultrasound patterns were proposed by us for ultrasound-cytopathology correlation analysis.

Keywords: Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP); ultrasonography; 2015 American Thyroid Association management guideline; thyroid imaging reporting and data system

Introduction

Nikiforov *et al.* in 2016 firstly termed NIFTP to reduce overtreatment of a group of highly indolent thyroid "cancer", non-invasive encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC) (1). The tumor was previously classified in the follicular variant of PTC, and it harbors a more favored prognosis with scarce recurrence, metastases and death from disease compared with its

counterparts-infiltrative FVPTC and invasive encapsulated FVPTC (2). According to the modified diagnostic criteria, clear demarcation with lack of invasion is the prerequisite of NIFTP, while the follicular growth pattern, nuclear features scoring of 2 or 3, no necrosis and no high mitotic activity jointly determine its nature as a borderline neoplasm (3). In the 2017 World Health Organization (WHO) Classification of Tumors of Endocrine organ book (4), NIFTP was categorized into a section entitled 'Other encapsulated follicular patterned thyroid tumors', suggesting its acceptance among specialists. Although NIFTP gets rid of the suffix of 'carcinoma', it still holds very low malignant potential as the lymph node metastases and lung metastases of NIFTP were identified in previous studies (5,6).

Preoperative ultrasound and subsequent US-guided fine needle aspiration are the mainstay procedures for evaluation of suspected thyroid nodule. We hold the opinion that the accurate recognition of NIFTP preoperatively should not only depend on cytopathological results by biopsy, but also referring to ultrasound findings for comprehensive analysis. As for cytopathological results, Bethesda categories 3 [atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS)], 4 [follicular neoplasm/suspicious for follicular neoplasm (FN/SFN)] and 5 (suspicious for malignancy) are the most frequent findings of NIFTP (7-10). In terms of US presentation, NIFTP always shows less risk features than classical PTC and radiologists may prone to divide NIFTP into benign groups in previous researches (11-13). Thus, it seems either methods have limited power in the assessment of NIFTP. However, few articles drilled the US findings of NIFTP particularly and in depth. As the first-line modality, more understanding of the nodule such as detailed US appearance subtypes would shed light of some confusion from equivocal cytopathological indications and facilitate preoperative diagnosis combined with clinical features. Therefore, we summarized US features of NIFTP on the basis of our data as well as published literature, aiming to unravel the US subtypes of the entity for radiology-histology correlation analysis. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/gs-20-612).

Methods

Patients

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Peking Union Medical College Hospital (No. S-K1304) and individual consent for this retrospective analysis was waived. Between January 2017 to June 2020, 41 patients with 41 NIFTP were identified among 13,531 all histological variants of papillary thyroid carcinoma (41/13,531, 0.30%). Of the 41 cases, 11 patients were excluded from the study for the absence of matched US-surgery-pathology data—8 did not have US records of the lesions, 3 did not receive operation in our center. We finally included 30 patients with 30 NIFTP into the retrospective analysis (*Figure 1*). Their medical records and imaging data were reviewed in a continuously maintained database. The histologic criteria for the diagnosis of NIFTP were as following: (I) well-demarcated tumor without any suspected sign of capsular or vascular invasion; (II) follicular growth pattern and nuclear features of papillary thyroid carcinoma; (III) none papillae or psammoma bodies, necrosis and less than three mitoses per 10 high-power fields (400×) (*Figure 2*). All the patients enrolled must meet the prerequisites below: (I) preoperative US localization and characterization of every thyroid nodule; (II) undergone surgical procedure with operation documents; (III) affirmative pathology results in our center. Patients ill with multiple thyroid lesions should get each nodule exactly screened prior to surgery. Meanwhile, the operation findings of every nodule must in line with the US and pathology discovery.

Ultrasound examination

Most of the patients prior to surgery for thyroid nodule in our center had undergone ultrasound examination and the US data were stored in an imaging archiving system. After retrospectively screening, all the patients diagnosed as NIFTP by histopathology and equipped with US imaging were selected. Philips iU22 5–12 MHz or GE Logiq 9 6–15 MHz linear probe were used for examination for patients in supine position. A resident collected information from the original ultrasound reports on pre-defined US characteristics and retrieved images for analysis. Two radiologists specialized in thyroid field with 8 and 20 years of experience reappraised these nodules to identify variable features not described in the original report. All the NIFTP lesions were sorted into two groups by size measured at sonography, with lesion size ≥1 and <1 cm in macro-group and micro-group, respectively. US features included localization, size, echogenicity, composition, shape, margin,
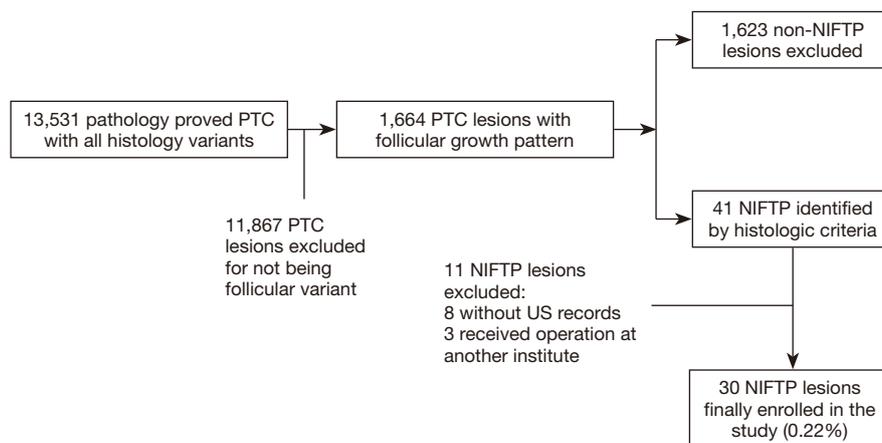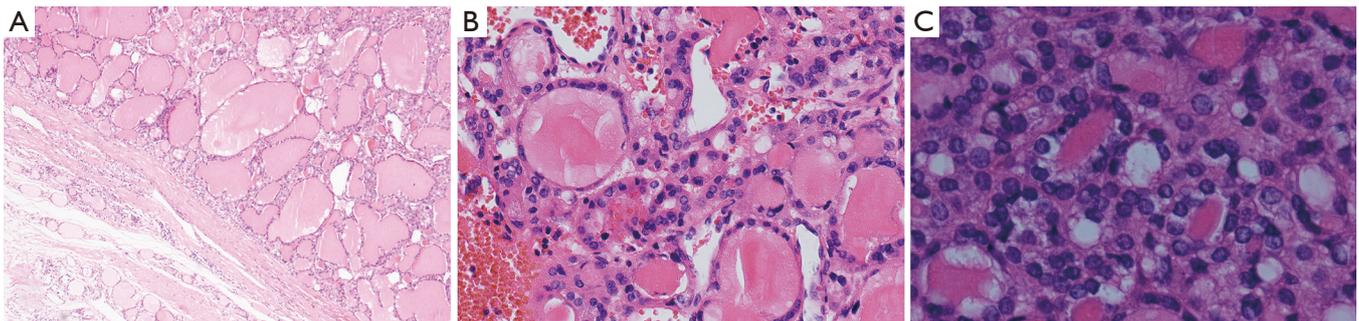
Figure 1 Flow scheme of patients' selection.

Figure 2 The histopathologic evaluation showed (A) a thyroid neoplasm with follicular growth pattern and without invasive signs (HE, ×40); (B,C) cells lining the follicles demonstrated nuclear features of papillary thyroid carcinoma, while none papillae or psammoma bodies, necrosis and less than three mitoses per 10 high-power fields were observed (HE, B: ×200, C: ×400).

calcification, halo rim, extra-thyroidal-extension and color Doppler flow were documented during review. Size was defined as the maximum diameter of a NIFTP lesion, which was measured on longitudinal or transverse plane using internal calipers. The three US patterns of NIFTP were derived from these features: All solid lesions without suspicious features as calcifications, taller-than-wide shape and irregular margin were classified into type A. All partially cystic lesions were classified into type B, regardless of other US features. In contrast, all hypoechoic solid lesions with suspected features mentioned above were classified into type C. All the NIFTP lesions were classified into the 3 major subtypes using pattern recognition. Moreover, the radiologists distributed all the NIFTP lesions to different categories based upon TIRADS (proposed by Kwak and ACR) and American Thyroid Association (ATA) guideline (14-16), and the disagreement would be solved by discussion

and verdict of a specialists with over 20 years' experience. Kappa values for the inter-observer agreements of each US feature were calculated.

Statistical analysis

All statistical analyses were conducted using SPSS software (version 25.0, SPSS Chicago, IL, USA). The meta-analysis was performed using STATA 15.0 (Stata Corporation, College Station, TX, USA). The Forest Plots was plotted using package ggplot2 of R 3.6.3 (R foundation for Statistical Computing, www.R-project.org). The normality of variables was verified using a Shapiro-Wilk test. Biochemical variables were expressed as median and interquartile range, with Mann-Whitney test using for comparison. Other continuous variables were exhibited as mean ± SD and compared using independent samples

Student's *t*-test. Categorical variables were shown as counts and percentages and compared using chi-square statistics or the Fisher's exact test. Inter-observer agreements were assessed employing Cohen's Kappa statistics. Based on guidelines, kappa values were interpreted as follows: 0.00–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, strong agreement; and 0.81–1.0, almost perfect agreement. A 2-tailed P<0.05 was viewed as threshold for statistically significant difference between two groups.

Literature review and meta-analysis

The PubMed and MEDLINE databases were searched for studies on sonographic features of NIFTP. We used search terms 'non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)' and 'ultra*', setting the search period between August 2016 and June 2020. Fifty-one studies were yielded and potentially eligible studies were selected by briefly reviewing of the titles and abstracts. The tables and outcomes in these studies were evaluated and those having requested data were included for analysis. Random effects meta-analysis was performed and the pooled estimates of proportions of each US feature were calculated.

Results

Baseline characteristics

Thirty patients with NIFTP lesions were eligible for inclusion in this study. Overall, 24 (80.0%) patients were female, 6 (20.0%) patients were male, and the mean age was 44.6±13.5 years. Of these cases, 17 (56.7%) cases were accompanied by papillary thyroid carcinoma, with 3 of follicular variant and 14 of classical variant. No significant difference in gender was observed between the macro-group and micro-group (P=0.660). Six of thirty NIFTP specimens had gone through immunohistochemical analysis. The tumor cells were positive for CK19 in two cases, SDHB, CD56 and Cyclin D1 in one case. Ten patients (35.7%) were found with comorbid Hashimoto's thyroiditis (*Table 1*). Twenty patients (66.7%) had received total thyroidectomy, 4 (13.3%) patients treated with subtotal thyroidectomy and 6 (20%) patients treated with lobectomy. Type A (n=19, 63.3%) and type C (n=4, 13.3%) US patterns were mostly presented in NIFTP nodules less than 1 cm, while type B (n=7, 23.3%) US pattern was more frequent

among NIFTP nodules larger than 1 cm.

Ultrasonography features

Three patterns of US appearance were presented in our series (*Figures 3–5*). Type A: oval hypoechogenic, iso-or hyperechoic solid nodule with (n=7) or without halo (n=12); type B: partially cystic mass with halo (n=5) or without halo (n=2); type C: hypoechogenic solid mass with suspected features like irregular margin (n=1) or microcalcifications (n=4). Amid all the NIFTP lesions, Hypoechogenic texture was found in 16 nodules, while Iso-or hyperechogenic texture was found in 12 nodules. The location of the tumor showed no preference between right or left lobes (P=0.264). Composition changed significantly between micro-group and macro-group, with partially cystic content appears more in macro-group and solid content distributes more in micro-group (P=0.024). Halo rim were highly prevalent in the macro-group (P=0.007). With regard to shape, no nodule exhibited nonparallel orientation or taller-than-wide shape in all the cases. Extrathyroidal extension (ETE) were negative for all the NIFTP nodules, either (*Table 1*). Of all nodules, none were beyond the classification system of the ATA, Kwak-TIRADS and ACR TIRADS guidelines. The detailed data were shown in the *Figure 6*, and notably, the classifications of all the 30 NIFTP lesions were consistent between ACR-TIRADS and Kwak-TIRADS. The inter-rater and original reports read agreement kappa value was showed in *Table 2*.

Literature review and data synthesis

Since the formally proposal of NIFTP in 2016, 12 publications on the ultrasonography of NIFTP were identified till June 2020 (11-13,17-25), one of which merely described the vascularity of NIFTP (19), and three of which generally reported the US features of NIFTP without requested details (22,23,25). After evaluation, 6 studies consisted of required US features of NIFTP (12,13,17,18,20,21). The pooled data of our cases combined with previous works were demonstrated in *Table 3* and *Figure* 7. Overall, NIFTP nodules mainly presented solid composition, being either hypoechoic or iso-or hyperechoic, showing shape of wider-than-tall and circumscribed margin, less exhibiting calcifications, and with a significant fraction (50%) sharing halo rim on US.

Discussion

Table 1 Sonographic, clinical and demographic details of NIFTP cases (n=30)

Characteristics	Size <1 cm (n=12)	Size ≥1 cm (n=18)	P
Mean age, years	47.2±13.7	42.9±13.4	0.404
Gender			0.660
Female	9	15	
Male	3	3	
Size, cm	0.6±0.2	2.6±1.7	
Location			0.264
Right	4	11	
Left	8	7	
Echogenicity			0.284
Iso- or hyper-echogenicity	4	10	
Hypoechogenicity	8	8	
Shape			1
Wider-than-tall	12	18	
Taller-than-wider	0	0	
Margin			1
Smooth	12	17	
Irregular	0	1	
Composition			0.024
Partially cystic	0	7	
Solid	12	11	
Microcalcification	2	2	1
Halo rim	1	11	0.007
Vascularity			0.074
Absent	2	1	
Mild	7	5	
Moderate to marked	3	12	
Sonographic pattern			0.045
Type A	10	9	
Type B	0	7	
Type C	2	2	
Hashimoto comorbidity	3	7	0.694
PTC comorbidity	9	8	0.141
Operation			0.083
Lobectomy	1	5	
Subtotal thyroidectomy	0	4	
Total thyroidectomy	11	9	

Immunohistochemical analysis: CK19 (2/6), SDHB (1/6), CD56 (1/6), Cyclin D1 (1/6). PTC, Papillary thyroid carcinoma; NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; n, number of cases.
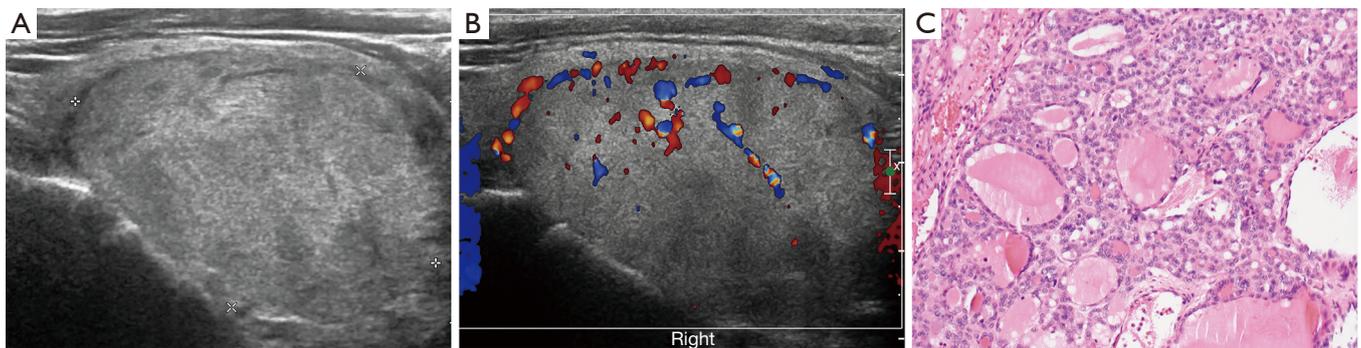
Figure 3 Longitudinal oriented B-mode imaging (A) and Color Doppler imaging (B) of type A NIFTP showing a solid isoechoic nodule surrounded by halo rim, without other suspicious features, accompanying with moderate vascularity. (C) HE stain, ×100.
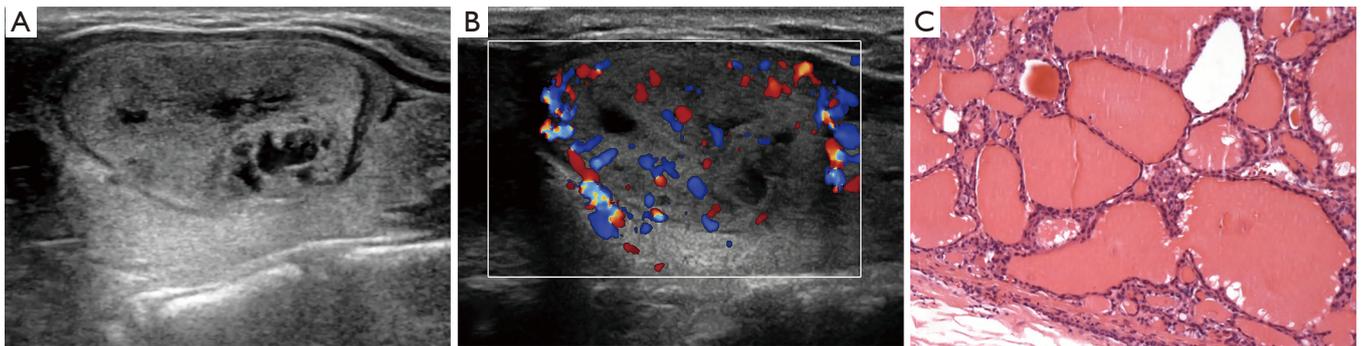

Figure 4 Longitudinal oriented B-mode imaging (A) and Color Doppler imaging (B) of type B NIFTP showing a partially cystic mass with halo rim and absence of other suspicious features, accompanying with marked vascularity. (C) HE stain, ×40.
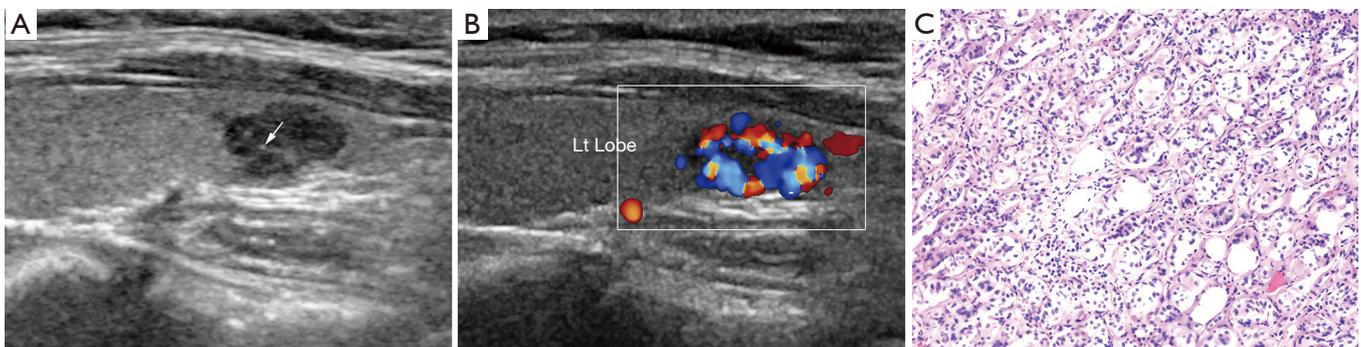

Figure 5 Longitudinal oriented B-mode imaging (A) and Color Doppler imaging (B) of type C NIFTP showing a solid hypoechoic nodule with microcalcifications (arrow), accompanying with marked vascularity. (C) HE stain, ×40.

NIFTP was suggested to prevent overtreatment of thyroid carcinoma, but its current paradigm for treatment could not be overlooked in the heated debate. Lobectomy without adjuvant therapy is still the preferred choice of treatment for the entity. Ultrasound plays an essential role in the management of thyroid lesions. The ultrasound findings, to a great extent, determine the fate of a thyroid nodule—follow up, FNA or surgery. In this study, we found that NIFTP were mainly composed of three sonographic phenotypes. The solid composition and hypoechogenicity
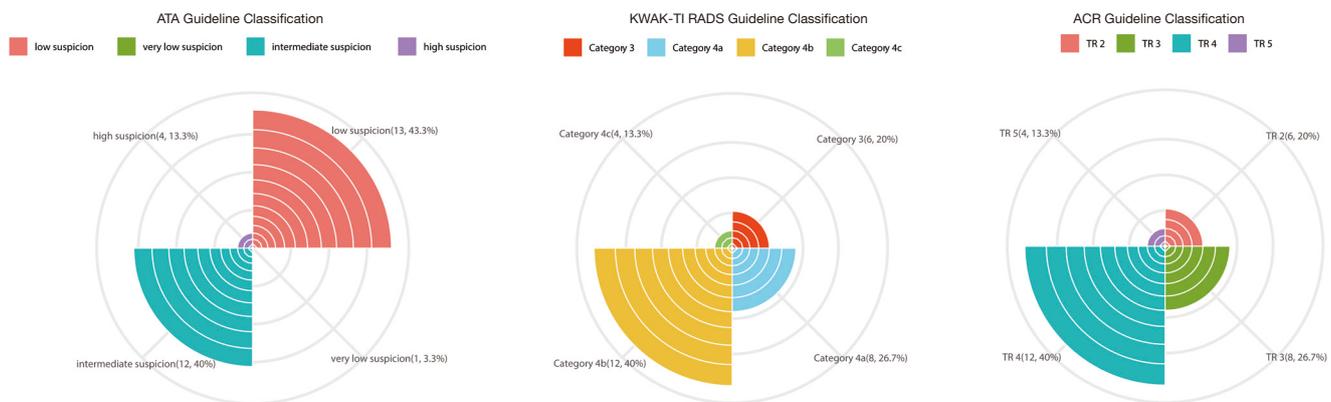
Figure 6 Classification results of each NIFTP lesion in this study using 2015 ATA guideline, Kwak-TIRADS and ACR TIRADS. NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; ATA, American Thyroid Association; Kwak-TIRADS, thyroid imaging, reporting and data system proposed by Kwak; ACR TIRADS, thyroid imaging, reporting and data system proposed by American College of Radiology.

Table 2 The concordance test between different raters and between original reports and final records

Variability	Echogenicity	Shape	Margin	Composition	Calcification	Halo
Interobserver variability	0.664	1	0.651	0.556	0.609	0.733
Records variability*	0.664	0.651	0.366	0.627	0.672	0.585

*, the variability between original records and the records re-evaluated and determined by two radiologists.

are the most common suspected features suggesting its potential malignancy.

The baseline characteristics of our NIFTP patients were consistent with previous reports of a preponderance of female and mean age of 40–50 years old. Immunohistochemical profiles of 6 NIFTP demonstrated positive staining in CK19 (2/6), SDHB (1/6), CD56 (1/6) and Cyclin D1 (1/6), which may add evidence to the differentiation between NIFTP and non-NIFTP lesions, as Cho *et al.* detected different expression in four markers of HBME-1, CK19, CD56, Galectin-3 between NIFTP and IFVPTC (26).

On the basis of size measured on ultrasonography, two groups of NIFTP were divided at the cutoff value of 1 cm. We render such grouping meaningful and meeting the real-world demand because the less discussed <1 cm NIFTP nodules may influence the incidence of NIFTP and management of some anxious patients who claim for FNA. Our analysis showed that NIFTP in micro-group mostly manifested as circumscribed solid oval nodule, which accorded with common perception of ultrasound appearance of NIFTP. However, we found that large

NIFTP lesions in macro-group exhibited more cystic change and halo rim compared with the micro-group counterparts. Thus, three US patterns were summarized from our data of NIFTP. Type-A, the most distinguished US pattern of NIFTP in previous reports, accounted for the largest proportion in our series as well. In line with our pooling data of a series of literature, this type of NIFTP consists of US feature appearing mostly frequent of its kind-solid composition (185/241, 76.7%), parallel shape (235/241, 97.5%) and circumscribed margin (226/241, 93.7%). Type-B was identified more frequently in macro-group of our cases, which means that it may be associated with NIFTP in larger size. The pooling data showed that partially cystic change occupies 20% among all types of component, therefore, this US subset of NIFTP should not be ignored (12,13,17,18,20,21). As for type-C, it contains NIFTP showing other suspected features, including irregular margin, nonparallel shape, and calcifications. Type-C US appearance often mimics that of papillary thyroid carcinoma at sonography for it had at least three suspected traits, but luckily, except for solid composition and hypoechogenicity, other suspected features are relatively

Table 3 Pool estimates of ultrasound features of NIFTP in the literature from 2016 to 2020

Ultrasound features	Soo Yeon Hahn (n=34)	Sung-Hye You (n=45)	Hye Seung Lee (n=20)	Chanchal Rana (n=20)	Vincent Larouche (n=44)	Kwon (n=48)	Present study (n=30)	Number (pooled proportions)*
Size (cm)	1.7±1.0	2.3±1.2	2.5 (0.5–6.0)	NR	2.3±1.2	1.9±1.2	1.9 (0.3–6.1)	
Composition								
Solid	29	29	18	10	41	35	23	185 (78%)
Predominantly solid or partially cystic	3	16	2	10	3	11	7	52 (20%)
Cystic or predominantly cystic	2	0	0	0	0	2	0	4 (2%)
Echogenicity								
Hypoechoic or marked hypoechoic	17	14	8	3	24	23	16	105 (42%)
Hyper-or isoechoic	17	31	12	17	20	25	14	136 (58%)
Shape (orientation)								
Taller-than-wide (non-parallel)	3	1	0	0	1	1	0	6 (3%)
Wider-than-tall (parallel)	31	44	20	20	43	47	30	235 (97%)
Margin								
Spiculated/microlobulated	5	0	0	0	4	3	1	13 (8%)
Circumscribed	29	45	20	20	40	43	29	226 (92%)
Calcification								
Absent	25	37	14	20	38	35	26	195 (80%)
Macrocalcification	3	4	2	0	5	4	0	18[#]
Peripheral (rim) calcification	2	4	3	0	0	5	0	14[#]
Microcalcification	4	0	1	0	1	4	4	14[#]
Halo rim	NR	19	NR	12	NR	27	12	70 (49%)

*, pooled proportions: pooled proportions of each US feature in NIFTP using random effects meta-analysis; [#], these three together account for 20%. NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; n, number of cases; NR, no report.

rare with percentage ranging from 2.5% to 7.5% according to our data aggregation (12,13,17,18,20,21). The aggregated data also showed the echogenicity of NIFTP was unspecific with similar distribution between hypoecho/marked hypoecho and isoechoic/hyperecho (105/241, 43.5% *vs.* 136/241, 56.4%). Yang *et al.* once explored the pathologic basis of ultrasound features of NIFTP and indicated that hypoechoic nodules may correlate to microfollicular/solid components, while isoechoic/hyperechoic thyroid nodules may correlate to normofollicular/macrofollicular components. Therefore, it should bear in mind that the internal echogenicity varies in NIFTP and it should not disturb the recognition of the type-A and type-B US patterns in these lesions (27).

The prevalence of NIFTP varies in different regions and the underlying reasons remains unclear. Bychkov *et al.* demonstrated a very low proportion of NIFTP in nine series of Asian institutions: the mean rates of NIFTP was 1.5% (range 0–4.7%) (28). In line with another four institutions in China (28-30), we observed the similar low rates of NIFTP (0.30%) in our center and considered that rigid histopathological criteria of NIFTP could not account for the whole issue. Therefore, we assumed the confusions can be partly resolved from the perspective of sonography. To our knowledge of most Chinese institutes, patients with nodules showing in the macro-group usually
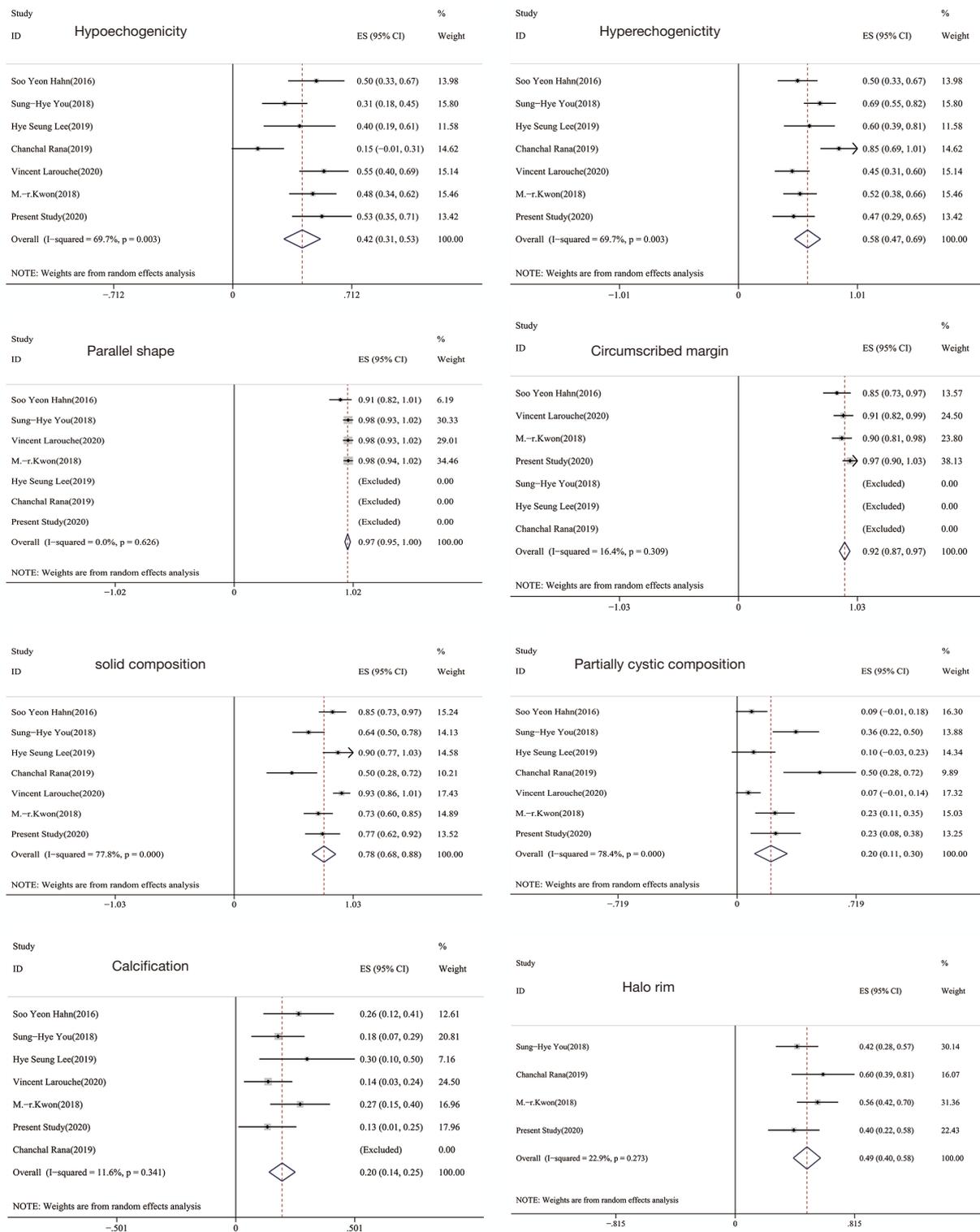
Figure 7 Forest plots of eight major ultrasound features related with NIFTP based on proportion meta-analysis. NIFTP, non-invasive follicular thyroid neoplasm with papillary-like nuclear features; ATA, American thyroid association; Kwak-TIRADS, Thyroid Imaging, Reporting and Data System proposed by Kwak; ACR TIRADS, Thyroid Imaging, Reporting and Data System proposed by American College of Radiology.

get conclusion of probably benign lesions or possibly follicular lesions. Maybe out of the traditional conservative concepts of intervention in China, many patients opt for follow-up rather than FNA or surgery after consultation with specialists, let alone those with nodules <1 cm (31). Meanwhile, widely used sonographic classification systems in China including those of the American Thyroid Association, the American College of Radiology and Kwak hold different attitudes toward FNA of thyroid nodules and make the management of NIFTP deferred (32). Another observation worth mentioning is that more than half of the NIFTP in our series were accidentally identified during the total thyroidectomy of a thyroid carcinoma. That is, 50.0% (15/30) of NIFTP were not considered for operation initially, just resected as a whole in the wake of a papillary thyroid carcinoma. Canini *et al.* also found that 7.4% (5/68) cases with NIFTP were associated with classic PTC and 17.6% (12/68) cases were diagnosed with NIFTP incidentally (33). These facts accounted for the rarity of NIFTP in our centre from another aspect. In this regard, we deemed that this newly defined entity may not exert as much influence as western countries in China. Zhu *et al.* also found NIFTP would not decrease risk of malignancy (ROM) when "NIFTP ≠ Ca" was in the analysis of 2,781 Chinese cases using The Bethesda System for Reporting Thyroid Cytology II (TBSRTC II) and supported our hypothesis (29,34).

Our study has some limitations. Firstly, this study investigated NIFTP based on retrospective real-world observation. We could not fully control the diagnostic procedures with respect to ultrasound examination and pathology, which means the inter-observer variance may influence the final analysis. Secondly, the sample size in this study was small. Only a trend of difference in FNA rates was found among three guidelines. Further investigation of larger cohort is necessary to testify whether the difference is statistically significant or not. Thirdly, although literature review with data pooling was carried out to summarize US features of NIFTP, the three US subtypes of NIFTP need to be verified by every single case in different studies to avoid population bias. Lastly, we did not set internal non-NIFTP samples for comparison because the study mainly focused on summarizing ultrasound subtypes of NIFTP and guideline classifications of the entity rather than distinguishing NIFTP from other types of PTC. In the future, a large cohort study, drawing on new technologies like elastography and computer-aided diagnostic system, is expected to better evaluate the NIFTP and make it

acknowledged in a didactic field (35,36).

In conclusion, three US subtypes of NIFTP are summarized for imaging-pathology correlation analysis. Despite the widely accepted type-A US appearance of NIFTP, we also proposed the existence of type-B US presentation that accounts for not a little proportion of NIFTP, and the relatively rare series of type-C for reference. Ultrasonography evaluation also implies the underlying reason for low incidence of NIFTP in China: a large number of patients with thyroid lesions showing US features of NIFTP are probably under follow-up.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/gs-20-612

Data Sharing Statement: Available at http://dx.doi.org/10.21037/gs-20-612

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/gs-20-612). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of Peking Union Medical College Hospital (No. S-K1304). Informed consent from enrolled patients was exempted by the IRB because of the retrospective nature of this study. The study was performed in accordance with the Declaration of Helsinki (as revised in 2013).

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