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Nodules with nonspecific ultrasound pattern according to the 2015 American Thyroid Association malignancy risk stratification system

A comparison to the Thyroid Imaging Reporting and Data System (TIRADS-Na)

Pingping Xiang, MM[a], Xiaoqiu Chu, MM[a], Guofang Chen, MD[a], Binbin Liu, BS[b], Wenbo Ding, MS[c], Zheng Zeng, MM[b], Xinping Wu, BS[c], Jianhua Wang, MM[d], Shuhang Xu, MD[a,*], Chao Liu, MD[a,*]

Abstract

New sonographic patterns have been recommended by the 2015 American Thyroid Association (ATA) to stratify nodules in terms of malignancy risk and help guide biopsy decision. This study aimed to compare the ultrasound part of the ATA guidelines and the Thyroid Imaging Reporting and Data System (TIRADS-Na).

In 2013 to 2016, 708 thyroid nodules in 505 patients were confirmed by postoperative histopathology. Hypoechogenicity, solidity, microcalcification, irregular margin, and a taller-than-wide shape were considered features suggesting malignancy. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were obtained for the TIRADS and ATA guidelines.

Of the 708 nodules, 341(48.2%) and 367(51.8%) were benign and malignant, respectively. Based on the ultrasound 2015 ATA guidelines, 62 nodules had nonspecific pattern (both malignant and benign features); malignancy rates of nodules with very low, low, intermediate, and high suspicion, and nonspecific pattern were 0, 17.7%, 57.9%, 90.0%, and 69.4%, respectively ($P < .001$). Malignancy rates of categories 2/3/4/5 nodules by TIRADS were 0, 8.1%, 67.0%, and 90.1%, respectively ($P < .001$). Based on pathological results, the AUC, sensitivity, specificity, NPV, and PPV were 0.926, 96.7%, 81.5%, 84.9%, and 95.9% for TIRADS, and 0.920, 93.5%, 82.4%, 85.1%, and 92.1% for ATA patterns, respectively. The TIRADS was generally more efficient than the 2015 ATA guidelines, especially for nodules >2 cm in diameter or those with nonspecific pattern.

The TIRADS show a relative superiority over the ultrasound 2015 ATA guidelines, especially for nodules with >2 cm diameter or nonspecific pattern.

Abbreviations: AACE = American Association of Clinical Endocrinologists, ATA = American Thyroid Association, AUCs = areas under the curves, FT_3 = free triiodothyronine, FT_4 = free thyroxine, NPV = negative predictive value, PPV = positive predictive value, ROC = receiver operating curve, TGAb = anti-thyroglobulin antibody, TIRADS = Thyroid Imaging Reporting and Data System, TPOAb = thyroid peroxidase antibody, TSH = serum thyrotropin, TSH = Thyrotropin, US = ultrasound.

Keywords: American Thyroid Association guidelines, sonographic pattern, Thyroid Imaging Reporting and Data System, thyroid nodule, ultrasound

1. Introduction

Thyroid nodules are very common, and an increasing number of people have been recently diagnosed with thyroid cancer, mainly because of the large-scale use of imaging techniques such as computed tomography, magnetic resonance imaging, positron emission tomography, and high-resolution ultrasound (US).[1] In a cross-sectional, population-based study conducted in 2011 in Nanjing (China), a high-frequency US system equipped with a 12-MHz transducer was introduced to detect thyroid nodules in 10,050 participants aged 40 to 79 years, with a detection rate

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[a] Endocrine and Diabetes Center, [b] Department of Pathology, [c] Department of Ultrasound, [d] Department of General Surgery, Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Traditional Chinese Medicine, Nanjing, China.

[*] Correspondence: Shuhang Xu, and Chao Liu, Endocrine and Diabetes Center, Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Traditional Chinese Medicine, No.100 Shizi Street, Hongshan Road, Nanjing 210028, China (e-mail: shuhangxu@vip.163.com, profliuchao@163.com).

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reaching 28.7%.[2] 50% to 70% of healthy subjects are found to have thyroid nodules by US.[3,4] Moreover, the rate of thyroid nodule malignancy can reach 5% to 7%.[5]

As the most effective tool predicting the risk of thyroid nodule malignancy, US assesses nodule composition (solidity, cystic proportion, or spongiform), echogenicity, margin, calcification status, taller-than-wide shape, and vascularity.[6,7] It is widely accepted that such US features are independent predictors for thyroid nodular malignancy.[8] However, no individual feature is reliable enough to identify the suspected nodules.[9] Besides, lack of clinical experience may lead to diagnostic errors if sonographic data are wrongly interpreted. A combination of suspected US characteristics increases the accuracy of malignancy detection.

The Thyroid Imaging Reporting and Data System (TIRADS), a malignancy-risk-stratification tool for thyroid nodule classification initially introduced by Horvath,[10] quantifies malignancy risks using main sonographic features. Although an updated TIRADS based on the solidity and echogenicity of thyroid nodules has been proposed recently,[11] no standardized TIRADS risk-stratification system is currently available.[10,12,13] Therefore, no TIRADS classifications have been widely adopted, particularly in the United States.[14]

According to the updated management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer, the American Thyroid Association (ATA) has put forward a new US system for malignancy risk stratification based on sonographic features, but its effectiveness has not been validated.[15] Therefore, the aim of the present study was to compare the US 2015 ATA guidelines and the newly proposed TIRADS-Na for malignancy risk stratification of thyroid tumors.

2. Material and methods

2.1. Study population

In this retrospective study, a total of 946 thyroid nodules from 813 patients were examined from January 2013 to December 2016. Malignant or benign thyroid nodules were diagnosed by surgical pathology at the Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine (a tertiary referral center). The inclusion criteria were:

1. US examination;
2. surgery;
3. thyroid function test; and
4. diagnosis of benign or malignant tumors by postoperative histopathology.

The exclusion criteria were:

1. lack of demographic information;
2. <18 years of age; or
3. lack of US data, including nodule size, composition, echogenicity, margin, shape, and calcification status.

All procedures involving human participants were approved by the ethics committee of the Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Traditional Chinese Medicine, in line with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was waived by the committee because of the retrospective nature of the study.

2.2. Image analysis and scoring

Color ultrasound was performed routinely in all patients for thyroid before being included into this study and the images were routinely examined by 5 radiologists. For this study, 2 chief radiologists (5 years of experience in thyroid US) who were not among the 5 radiologists analyzed the ultrasound features. This was to be able to ensure the accuracy of the retrospective analysis of ultrasound features and avoid bias. The 2 radiologists were blind to the final histopathological diagnosis. The images were reviewed independently by the 2 radiologists. Any discordant opinions were solved by discussion.

2.3. US examination and image analysis

The 2 radiologists performed all the classification process. High-resolution US scanning was performed with a 7.5-13-MHz linear-array transducer (HI VISION Preirus, Japan) by radiologists with >5 years of clinical experience in thyroid US. All US features of thyroid nodules, recorded in our online system, were retrospectively reviewed. The reviewer assessed the following US features of thyroid nodules: composition, echogenicity, calcification status, margin, shape, and comet-tail artefact.[11,16,17] The comet-tail artifact is characterized by revereberation artifacts within the cystic component.[11] "Partially cystic nodules" with "comet-tail artefact" were considered to be benign. For the solid portion of the partially cystic nodules, the configuration was categorized as concentric, eccentric with an acute angle, eccentric with a blunt angle, and unspecified patterns; eccentric with an acute angle is risk of malignancy. Tumor composition was categorized as solid (no obvious cystic content), predominantly solid (≤50% of solid proportion), predominantly cystic (>50% of cystic proportion), and cystic (no obvious solid content). Compared to normal thyroid tissues and the adjacent thyroid parenchyma, nodule echogenicity was classified as marked hypoechogenicity, mild hypoechogenicity, hyperechogenicity, and isoechogenicity. Spongiform nodules were classified as isoechoic. Calcification was categorized into microcalcification and macrocalcification (including eggshell calcification [18]). Calcification large enough to result in posterior acoustic shadowing was considered as macrocalcification.[14] Combination of macrocalcification with microcalcification was considered to be a malignant microcalcification because the malignancy risk has been shown to be equivalent between the 2 entities.[17] Therefore, a nodule showing both types of calcification (macrocalcification, including rim calcifications, intermingled with microcalcification) was grouped with those showing microcalcification.[13] Tumor margins were described as regular or irregular (infiltrative, micro-lobulated, or spiculated). Shape was classified as taller-than-wide or wider-than-taller (measured on a transverse view). Comet-tail artifact was defined as intracystic echogenic foci accompanied by reverberation artifacts.[11] Malignancy was suspected with the following US features: solidity, hypoechogenicity, irregular margin, microcalcification, a taller-than-wide shape, and vascularity.[17,19–22]

2.4. TIRADS classification

Based on the criteria proposed by Na et al,[11] all nodules were classified into 5 categories: TIRADS1, no nodules; TIRADS2, spongiform, purely cystic, or partially cystic nodules with comet-tail artifact (only 1%–3% at the risk of malignancy); TIRADS 3, partially cystic or iso- and hyperechoic nodules without any of the

3 suspicious US features (microcalcification, taller-than-wide shape, and irregular margin) (low suspicion with 3%–15% at risk of malignancy); TIRADS 4, partially cystic or iso- and hyperechoic nodules with any of the 3 suspicious US features, or solid hypoechoic nodules without any of the 3 suspicious US features (intermediate suspicion with 15%–50% at risk of malignancy); TIRADS 5, solid hypoechoic nodules with any of the 3 suspicious US features (high suspicion with >60% at risk of malignancy).

2.5. US pattern by the 2015 ATA

According to the US part of the 2015 ATA guidelines,[7] thyroid nodules were categorized as high, intermediate, low, and very low suspicion of malignancy and benignancy. Benign nodules were purely cystic, without any solid component. Nodules with very low-suspicion were spongiform or partially cystic, without any sonographic feature of nodules with low, intermediate, or high suspicion. Nodules with low suspicion were isoechoic or hyperechoic, solid or partially cystic, with eccentric solid areas, without microcalcification, irregular margin, extrathyroidal extension, or a taller-than-wide shape. Nodules with intermediate-suspicion were hypoechoic, solid and marginally smooth, without microcalcification, extrathyroidal extension or a taller-than-wide shape. Highly-suspicious nodules were solid hypoechoic or solid hypoechoic component of a partially cystic nodule, with at least 1 of the following features: irregular margin, microcalcification, taller-than-wide shape, rim calcification with small extrusive soft tissue component, and extrathyroidal extension. Surprisingly, a few solid or partially cystic nodules with hyperechogenicity/isoechogenicity, irregular margins, microcalcification, or a taller-than-wide shape could not be assigned to any of the above categories because they showed both malignant and benign features. These nonspecific nodules were considered to be positive because they nevertheless showed US suspicion features, including solidity, microcalcification, a taller-than-wide shape,[17,20–22] and irregular margins, or were even partially cystic with hyper- or iso-echogenicity.

2.6. Statistical analyses

Statistical analysis was performed with the SPSS 23.0 software (IBM, Armonk, NY, USA). Quantitative values were expressed as mean ± standard deviation or median (interquartile range) for abnormal distribution. Differences in categorical variables were determined by the 2-tailed Chi-Squared (χ^2) test or Fisher exact test. The independent 2-sample *t* test or Chi-Squared test was used to compare demographic data between benign and malignant thyroid nodules. Receiver operating curve (ROC) analysis was used to compare 2015 ATA patterns with TIRADS, and to determine the optimal cut-off value between benign and suspicion nodules. MedCalc 15.0 (MedCalc Software bvba, Ostend, Belgium) was used for the comparison of ROC curves. Considering category 3 to be benign and 4 to 5 to be malignant in the TIRADS, very low to low suspicion of malignancy to be negative, and intermediate to high suspicion of malignancy to be positive, sensitivities, specificities, positive predictive values (PPVs), negative predictive values (NPVs), and areas under the curves (AUCs) were obtained to compare these methods for diagnostic efficiency. $P < .05$ was considered statistically significant.

3. Results

3.1. Patients

A total of 4 nodules lacking demographic information, 166 with inadequate US information, 5 being <18 years of age, and 63 without thyroid function information were excluded. Finally, 708 thyroid nodules from 515 patients were included in this study. Mean patient age was 48.9 ± 2.2 years, ranging from 18 to 82 years. Nodule size was 1.78 ± 1.42 cm, ranging from 0.16 to 7.1 cm. Demographic, clinical, and US features of patients and nodules are summarized in Tables 1 and 2. The patients with benign nodules were aged between 18 and 82 years (54.0 ± 14.0 years), significantly older than those with malignant nodules (ranging from 18 to 81 years; 46.0 ± 16.0 years) ($P < .01$).

Table 1

Demographic and clinical features.

Parameter	Postoperative histopathology		Total	*P* value
	Benign	Malignant		
Number of nodules	341	367	708	
Number of patients	213	302	515	
Age (year)				
Mean ± SD	54.0 ± 14.0	46.0 ± 16.0	/	<.001
Range	18–82	18–81	/	
Sex				
Male	38	76	114	.053
Female	175	226	401	
Diameter (cm)				
Mean ± SD	2.30 ± 2.55	0.88 ± 0.70	/	<.001
Range	0.23–7.1	0.16-6.1	/	
Thyroid function				
FT_3 (pmol/L)	4.65 ± 1.03	4.78 ± 0.88	/	.087
FT_4 (pmol/L)	16.31 ± 3.48	16.25 ± 4.18	/	.591
TSH (μIU/ml)	1.78 ± 2.04	2.09 ± 2.30	/	.003
TGAb (nmol/L)	15.20 ± 24.65	17.80. ± 65.30	/	.004
TPOAb (nmol/L)	36.00 ± 28.05	40.6 ± 116.0	/	.008

FT3 = free triiodothyronine, FT4 = free thyroxine, TGAb = anti-thyroglobulin antibody, TPOAb = thyroid peroxidase antibody, TSH = thyrotropin.

Table 2

Ultrasound features.

Parameter	Postoperative histopathology		Total	Malignancy rate (%)	*P* value
	Benign	Malignant			
Composition					<.001
Solid	125	361	486	74.3	
Predominantly solid	48	5	53	9.4	
Predominantly cystic	168	1	169	0.6	
Echogenicity					<.001
Marked hypoechoic	6	67	73	91.8	
Mild hypoechoic	47	227	274	82.9	
Isoechoic	279	71	350	20.3	
Hyperechoic	9	2	11	18.2	
Margin					<.001
Regular margin	270	67	337	19.9	
Irregular margin	71	300	371	80.7	
Calcification					<.001
None	224	106	330	32.1	
Microcalcification	82	243	325	74.8	
Macrocalcification	35	18	53	34.0	
Shape					<.001
Taller-than-wide	14	101	115	87.7	
Wider-than-tall	327	266	593	44.9	

P value, Comparison between categories.

Histopathological results were based on the final and standard diagnosis from the surgical specimen, not from biopsies or cytology. After surgery in 515 patients with 708 thyroid nodules, histopathological examination showed 341 benign and 367 malignant cases, including 193 follicular adenomas, 134 goiters, 8 atypical adenomas, 6 oncocytic (Hürthle cell) adenomas, 188 classical papillary carcinomas, 159 papillary thyroid microcarcinomas, 9 follicular variants of papillary carcinomas, 9 follicular carcinomas, 1 medullary carcinoma, and 1 poorly differentiated carcinoma. The diameter of benign nodules was 2.30 ± 2.55 cm (0.26–7.1 cm), significantly larger than that of malignant nodules (0.88 ± 0.70 cm; range, 0.16–6.1 cm) ($P < .01$). Serum thyrotropin (TSH), anti-thyroid globulin antibody (TGAb), and TPOAb levels in patients with benign nodules were lower compared with those with malignant nodules [(1.78 ± 2.04 vs 2.09 ± 2.30 μIU/ml), (15.20 ± 24.65 vs 17.8 ± 65.3 U/ml), and (36.0 ± 28.05 vs 40.6 ± 116.0 U/ml), respectively] ($P < .05$). There were no significant differences in sex, free triiodothyronine (FT_3), and free thyroxine (FT_4) between the benign and malignant groups. Compared with benign nodules, malignant ones had significantly higher rates of solid mass, hypoechoic area, irregular margins, microcalcification, and a taller-than-wide shape ($P < .01$).

3.2. Malignancy risk stratification

Based on postoperative histopathology, the malignancy rates of nodules in TIRADS categories 2, 3, 4, and 5 were 0% (0 of 142 nodules), 8.1% (12 of 148 nodules), 67.0% (63 of 94 nodules), and 90.1% (292 of 324 nodules), respectively, with significant differences among categories ($P < .01$) (Table 3). For nodules <1 cm, the malignancy rates in TIRADS categories 2, 3, 4, and 5 nodules were 0, 23.3%, 69.2%, and 91.6%, with significant differences among categories ($P < .01$). For nodules of 1 to 2 cm, the malignancy rates were 0, 5.3%, 84.2%, and 86.7%, in TIRADS categories 2, 3, 4, and 5, respectively, with significant differences among categories ($P < .01$). For nodules >2 cm, the malignancy rates were 0, 6.0%, 56.3%, and 92.6% in TIRADS categories 2, 3, 4, and 5, respectively, with significant differences among categories ($P < .01$) (Table 3). Those groups are based on the definition of microcarcinoma (<1 cm), while 2 cm is the cutoff used by the K-TIRADS and ATA for fine needle aspiration.[11,23]

For nodules with very low, low, intermediate, high suspicion of malignancy, and nonspecific pattern by US ATA guidelines, malignancy rates were 0 (0 of 174 nodules), 17.7% (24 of 136 nodules), 57.9% (11 of 19 nodules), 90.0% (289 of 321 nodules), and 69.4% (43 of 62 nodules), respectively. For nodules <1 cm, the malignancy rates were 0, 29.4%, 79.0%, 92.5%, and 64.3%, respectively, in the very low, low, intermediate, and high suspicion, and nonspecific pattern groups. For nodules 1 to 2 cm, malignancy rates were 0, 13.3%, 50.0%, 87.1%, and 81.3%, respectively. Nodules >2 cm showed malignancy rates of 0, 13.5%, 33.3%, 92.5%, and 61.1%, respectively, with significant differences among patterns ($P < .01$) (Table 3).

3.3. Diagnostic values of TIRADS and ATA guidelines

Of the 708 thyroid nodules, 62 failing to meet the US 2015 ATA guidelines were classified as "nonspecific pattern" (Fig. 1). They were solid or partially solid, isoechoic or hyperechoic, with some suspicious features like irregular margins, taller-than-wide shape or microcalcification. Among them, 19 benign and 43 malignant nodules were confirmed by postoperative histopathology. The diagnostic value of the 2 systems (including the nonspecific pattern nodules or not) is shown in Table 4.

Receiver operating characteristic (ROC) curves revealed the best cutoff of 3 for the TIRADS and low suspicion of malignancy for the US 2015 ATA guidelines. For nodules without nonspecific US ATA patterns, AUCs, sensitivities, specificities, PPVs and NPVs were 0.934 (95%CI 0.907–0.948), 96.3% (95%CI 93.6–98.1), 85.4% (95%CI 81.1–89.1), 86.9% (95%CI 83.0–90.2), and 95.8% (95%CI 92.8–97.8), respectively, for the TIRADS, and 0.930 (95%CI 0.912–0.952), 92.6% (95%CI 89.2–95.2), 87.3% (95%CI 83.1–90.7), 88.0% (95%CI 84.0–91.2), and 92.1% (95%CI 88.5–94.9), respectively, for the US ATA system

Table 3

Comparison between the TI-RADS and ATA patterns.

Scoring system and category			Final diagnosis			*P* value
			Benign	Malignant	Malignancy rate (%)	
Overall	TIRADS					<.001
		2	142	0	0	
		3	136	12	8.1%	
		4	31	63	67.0%	
		5	32	292	90.1%	
	ATA					<.001
		Very low suspicion	170	0	0	
		Low suspicion	112	24	17.7%	
		Intermediate suspicion	8	11	57.9%	
		High suspicion	32	289	90.0%	
		Unspecific	19	43	69.4%	
<1 cm	TIRADS					<.001
		2	18	0	0	
		3	25	11	23.3%	
		4	17	30	69.2%	
		5	16	200	91.6%	
	ATA					<.001
		Very low suspicion	22	0	0	
		Low suspicion	24	10	29.4%	
		Intermediate suspicion	4	15	79.0%	
		High suspicion	16	198	92.5%	
		Unspecific	10	18	64.3%	
1–2 cm	TIRADS					<.001
		2	31	0	0	
		3	18	1	5.3%	
		4	3	16	84.2%	
		5	9	60	86.7%	
	ATA					<.001
		Very low suspicion	35	0	0	
		Low suspicion	13	2	13.3%	
		Intermediate suspicion	1	1	50.0%	
		High suspicion	9	61	87.1%	
		Unspecific	3	13	81.3%	
>2 cm	TIRADS					<.001
		2	83	0	0	
		3	94	6	6.0%	
		4	14	18	56.3%	
		5	2	25	92.6%	
	ATA					<.001
		Very low suspicion	105	0	0	
		Low suspicion	77	12	13.5%	
		Intermediate suspicion	2	1	33.3%	
		High suspicion	2	25	92.6%	
		Unspecific	7	11	61.1%	

P value, Comparison between categories.

(Table 4). For all nodules, AUCs, sensitivities, specificities, PPVs and NPVs were 0.926 (95%CI 0.904–0.944), 96.7% (95%CI 94.4–98.3), 81.5% (95%CI 77.0–85.5), 84.9% (95%CI 81.1–88.2), and 95.9% (95%CI 92.9–97.8) for the TIRADS, and 0.920 (95%CI 0.898–0.939), 93.5% (95%CI 90.4–95.8), 82.4% (95%CI 77.9–86.3), 85.1% (95%CI 81.3–88.4), and 92.1% (95%CI 88.5–94.9) for the US ATA system, respectively. The TIRADS had higher AUC, sensitivity, and NPV ($P < .05$, respectively) (Table 4).

3.4. Subgroup analysis

For nodules <1 cm, the AUC, sensitivity, specificity, NPV, and PPV were 0.853, 83.0%, 80.3%, 93.0%, and 59.8% for the TIRADS, respectively, and 0.859, 88.4%, 75.0%, 91.8%, and 67.1% for US ATA patterns, respectively. The US ATA patterns had a higher NPV compared with the TIRADS ($P < .05$). There were no differences in AUC, sensitivity, and specificity between the 2 systems. For nodules of 1 to 2 cm, the AUC, sensitivity, specificity, NPV, and PPV were 0.902, 98.7%, 80.3%, 86.4%, and 98.0% for the TIRADS, respectively, and 0.899, 97.4%, 78.7%, 85.2%, and 96.0% for US ATA patterns, indicating a higher NPV in the TIRADS ($P < .05$). For nodules >2 cm, the AUC, sensitivity, specificity, NPV, and PPV were 0.941, 87.8%, 91.8%, 72.9%, and 96.7% for the TIRADS, and 0.926, 75.5%, 94.3%, 77.1%, and 93.8% for US ATA patterns. These data indicated that the TIRADS had higher AUC, sensitivity, and NPV (Table 5).

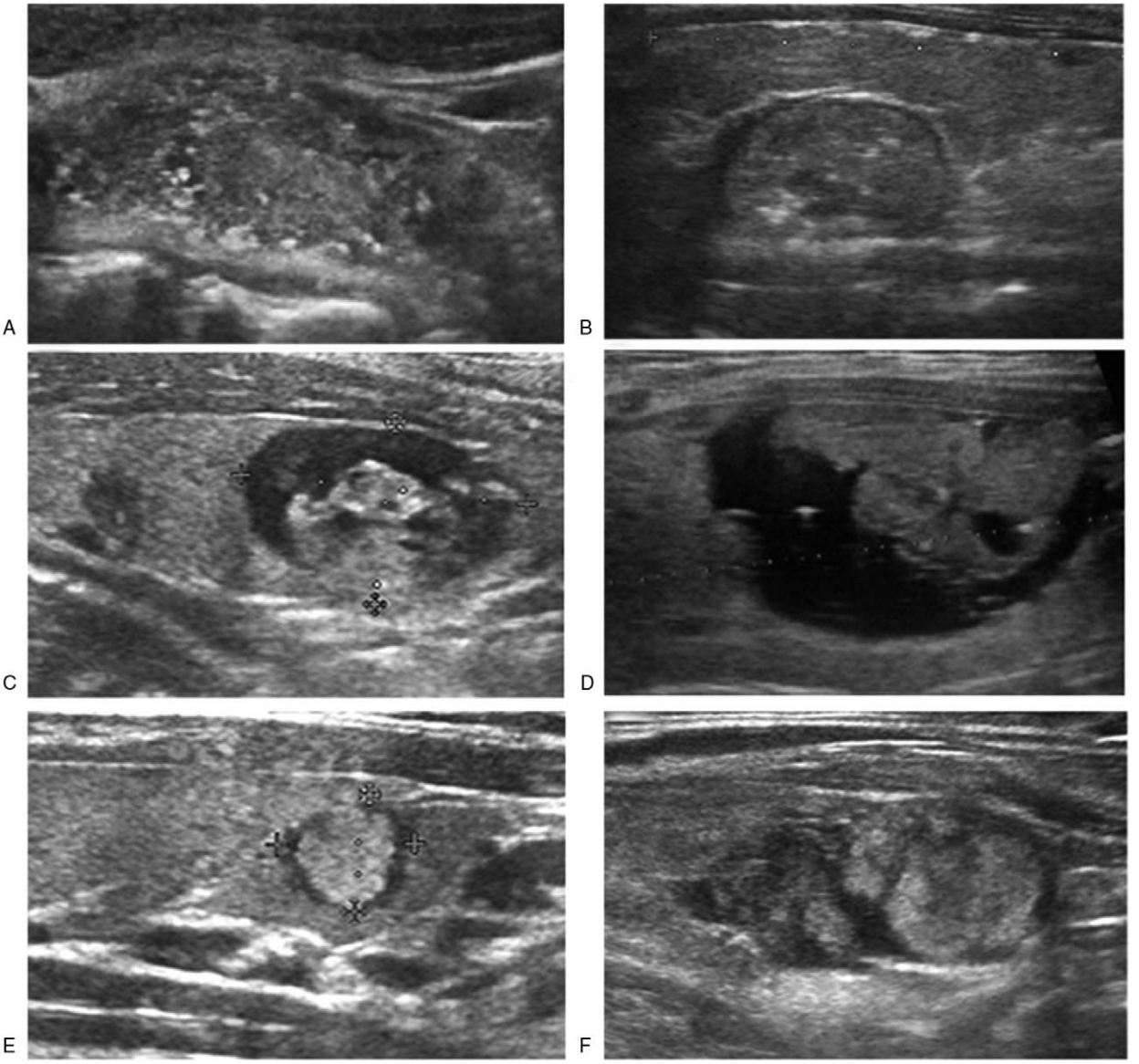

Figure 1. Ultrasound scans of thyroid nodules with nonspecific sonographic patterns. (A and B) A solid isoechoic nodule with multiple microcalcification areas. (C and D) A partially cystic isoechoic nodule with multiple microcalcification areas within the solid portion or an irregular margin. (E and F) A hyperechoic nodule with an irregular margin or multiple microcalcification areas.

Table 4

Diagnostic values of the TI-RADS and ATA 2015 guidelines.

Scoring system	Cutoff	Accuracy	AUC (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
Overall, without unspecific nodules							
TIRADS	4	0.909	0.934 (0.907–0.948)	96.3 (93.6–98.1) *	85.4 (81.1–89.1) *	86.9 (83.0–90.2)	95.8 (92.8–97.8) *
ATA	Intermediate Suspicion	0.899	0.930 (0.912–0.952)	92.6 (89.2–95.2)	87.3 (83.1–90.7)	88.0 (84.0–91.2)	92.1 (88.5–94.9)
Overall							
TIRADS	4	0.894	0.926 (0.904–0.944) *	96.7 (94.4–98.3) *	81.5 (77.0–85.5)	84.9 (81.1–88.2)	95.9 (92.9–97.8) *
ATA	Intermediate Suspicion	0.847	0.920 (0.898– 0.939)	93.5 (90.4–95.8)	82.4 (77.9–86.3)	85.1 (81.3–88.4)	92.1 (88.5–94.9)

Compared to ATA patterns.
* $P < .05$.

Table 5

Subgroup analysis of the TI-RADS and ATA patterns.

Scoring system	Cutoff	Accuracy	AUC (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)
<1 cm							
TIRADS	4	0.864	0.853 (0.809–0.890)	83.0 (77.6–87.5)	80.3 (69.5–88.5)	93.0 (88.8–96.0)	59.8 (49.6–69.4) *
ATA	Intermediate Suspicion	0.852	0.859 (0.816–0.895)	88.4 (83.6–92.1)	75.0 (63.7–84.2)	91.8 (87.5–95.0)	67.1 (56.0–76.9)
1–2 cm							
TIRADS	4	0.905	0.902 (0.840–0.946)	98.7 (93.0–100.0)	80.3 (68.2–89.4)	86.4 (77.4–92.8)	98.0 (89.4–99.9) *
ATA	Intermediate Suspicion	0.819	0.899 (0.37–0.944)	97.4 (90.9–99.7)	78.7 (66.3–88.1)	85.2 (76.1–91.9)	96.0 (86.3–99.5)
>2 cm							
TIRADS	4	0.909	0.941 (0.903–0.967)*	87.8 (75.2–95.4)*	91.8 (87.0–95.2)	72.9 (59.7–83.6)	96.7 (93.0–98.8)*
ATA	Intermediate Suspicion	0.889	0.926 (0.885–0.955)	75.5 (61.1–86.7)	94.3 (90.1–97.1)	77.1 (62.7–88.0)	93.8 (89.5–96.3)

Compared to ATA patterns.

* $P < .05$.

AUC = area under curve, CI = confidence interval, NPV = negative predictive value, PPV = positive predictive value.

4. Discussion

US is used to evaluate the malignancy potential of thyroid nodules and help in biopsy decision. The TIRADS has been clinically used for a few years. A recent meta-analysis reported pooled sensitivity and specificity of the TIRADS in differentiated diagnosis of thyroid nodules to be 0.79 and 0.71, respectively.[24] However, it has not yet been adopted by the ATA guidelines,[7,23] the American Association of Clinical Endocrinologists (AACE),[3] and the British Thyroid Association.[25] In 2016, an US-assisted risk stratification system was proposed by the ATA guidelines; however, more clinical data are required to determine its sensitivity and specificity.

In this study, the US part of the 2015 ATA guidelines patterns were used to assess 515 patients with 708 thyroid nodules. The results showed a malignancy risk of 90.0% for high suspicion, 57.9% for intermediate suspicion, 17.7% for low suspicion, and 69.4% for nonspecific nodules. According to the US 2015 ATA guidelines, the malignancy rate of nodules with high suspicion can reach 70% to 90%,[7] corroborating our findings. Meanwhile, the malignancy rates for intermediate and low suspicion nodules are 10% to 20% and 5% to 10%, respectively, according to the US ATA guidelines,[7] which are much lower compared with those of the current study. This discrepancy might be explained by the fact that nodules obtained postoperatively may lead to selection bias. Indeed, patients with malignancy-suspected US features, including hypoechoic solid composition, microcalcification, and irregular margins, were more likely to undergo surgery, even though their final diagnoses might be benign tumors. Hypoechogenicity is an effective index in predicting the malignancy rate. A recent study reported that about 55% of benign nodules are hypoechoic, with sub-centimeter benign nodules more likely to be hypoechoic.[17] In addition, no malignancy was found in this study for very low suspicion nodules, while 3% was proposed by the US 2015 ATA guidelines.[7]

The malignancy rates were 90.1%, 67.0%, 8.1%, and 0 for TIRADS 5, 4, 3, and 2 nodules, respectively. Malignancy rates were expected to be >60%, 15% to 50%, 3% to 15%, and <3% for TIRADS 5, 4, 3, and 2 tumors, respectively.[11] In the present study, the malignancy rate obtained for TIRADS 4 nodules was overtly higher. This elevated malignancy risk in category 4 nodules can be attributed to a selection bias, as for the US part of the 2015 ATA classification.

As shown by ROC curves, for nodules without nonspecific ones, the TIRADS system had a relatively higher sensitivity, specificity and NPV compared with the US ATA system for malignancy risk stratification. For nodules with nonspecific ones, the TIRADS system also had a relatively higher AUC, sensitivity and NPV compared with the US ATA system. These findings suggested that the TIRADS system could be used for nodules with nonspecific patterns according to the US ATA guidelines. Meanwhile, the TIRADS had a higher diagnostic value compared with US ATA guidelines for all nodules, including those with nonspecific US ATA patterns. In the sub-centimeter group, US ATA patterns had a better NPV ($P < .05$). For nodules of 1 to 2 cm, the TIRADS had a higher NPV, and slightly but non-significantly higher AUC, sensitivity, specificity, and PPV. For those >2 cm in diameter, the TIRADS had higher AUC, sensitivity, and NPV. Taken together, these findings suggested that the TIRADS is more efficient than the US part of the ATA guidelines in determining the malignancy of larger nodules.

In the ATA guidelines, a nonspecific group was identified with a high malignancy risk (69.4%) according to US. In the latter group, most nodules were >1 cm in diameter (1.68 ± 1.20 cm), with partially cystic composition, or iso- or hyper-echogenicity. Indeed, only 5-26% of partially cystic nodules are malignant, and iso- and hyperechogenicity are more likely to reflect benignity compared with hypoechogenicity.[26–28] Recently, Yoon et al [15] also reported that nodules not meeting the criteria for any specific pattern in the US ATA guidelines have a relatively high risk of malignancy (18.2%) as they compared malignancy risk stratification of thyroid nodules by the US ATA guidelines and the TIRADS. In the present study, the proportion of nodules assigned to the "unspecified" category by the US ATA guidelines was higher (8.7% vs 3.4%), with a dramatically higher malignancy rate in those nodules (69.4% vs 18.2%). All these nonspecific nodules could be classified as TIRADS 4 with a similar malignancy rate (69.4% vs 67.4%).

US features are very helpful in determining the follow-up procedure for thyroid nodules with benign cytology diagnoses.[7] The TIRADS adopted in this study was proposed by Na et al,[11] combining specific suspicious US features and less specific ones (solidity and echogenicity) in thyroid nodules. It was shown to be useful for risk stratification of thyroid nodules and management decision.[11] Particularly, for cytologically indeterminate thyroid nodules, both the TIRADS and US ATA guidelines allow high-confidence exclusion of malignancy with stringent negativity cut-offs,[29] and high sensitivity may be obtained using the US part of the ATA guidelines.[30]

The limitations of the present study should be addressed. First, the study is retrospective including only patients who had a surgical resection and thus influenced by many other factors to include selection bias and changes in clinical practice over time during data collection. In our study, 51.8% of the nodules was carcinoma which was higher than that of some retrospective studies [31,32] but comparable to those reported studies with similar design.[33] The malignancy rate of our study was higher than that of some retrospective study, such as 37.2% from Han et al [31] and 39% of Xu et al.[32] An important reason is that in the above 2 studies, 25.9% and 90.1% of the nodules were regarded as benign lesions based on cytology and follow-up US, which may cause false negative results. While in another retrospective study with a similar design,[33] 2544 thyroid nodules in 1758 patients who underwent thyroidectomy were included. Of all the nodules, 863 (33.9%) were benign, whereas 1681 (66.1%) were malignant. The malignancy rate was relatively higher than our study. Secondly, only 2 radiologists retrospectively reviewed the US images and classified the nodules according to the US 2015 ATA guidelines and TIRADS, with possible deviations among investigators. Thirdly, The TIRADS-Na used in this study is a relatively new tool.[11] Therefore the universality of the present study was limit for the small application range. Finally, some patients had multiple nodules, which included nodules <1 cm. Nodules >1 cm may be punctured and, when confirmed as PTC, they undergo surgery. The 2 lobes of the thyroid were removed during surgery and contained the nodules <1 cm. Because the study period was 2013 to 2016 and the ATA guidelines were released in 2015, the understanding of the follow-up observation for thyroid microcarcinoma was not mature at that time, the pathologists suggested that all patients with PTC had to undergo surgery.

In conclusion, both the TIRADS and the US part of the 2015 ATA guidelines have appreciable diagnostic values for thyroid nodules. This study identified thyroid nodules with nonspecific US ATA patterns. The newly proposed TIRADS may be more efficient than the US 2015 ATA guidelines, especially for nodules >2 cm in diameter or those with nonspecific patterns. The identification of nodules with nonspecific US patterns indicates the need for improving the ATA guidelines for risk stratification. The ATA US guideline is used not only for FNA determination, but also for providing a follow-up recommendation for nodules with benign or indeterminate cytology and nodules without FNA. These evaluation and follow-up recommendations remain instructive in the management of nodules with specific patterns. TIRADS is much more used in determining the need of FNA instead of further management. Therefore, a wiser improvement of TIRADS into clinical management of thyroid nodules is required. The best approach is to tailor TIRADS as ATA US guidelines in the aspect of nodules management. The use of US based on these results could be invaluable when combined with clinical features and biopsy results.

Author contributions

Conceptualization: Pingping Xiang, Shuhang Xu, Chao Liu.
Data curation: Pingping Xiang, Xiaoqiu Chu, Guofang Chen, Binbin Liu, Wenbo Ding, Zheng Zeng, Xinping Wu, Jianhua Wang.
Formal analysis: Pingping Xiang, Xiaoqiu Chu, Guofang Chen, Binbin Liu, Wenbo Ding, Zheng Zeng, Xinping Wu, Jianhua Wang, Shuhang Xu, Chao Liu.
Funding acquisition: Shuhang Xu, Chao Liu.
Project administration: Shuhang Xu, Chao Liu.
Writing – original draft: Pingping Xiang.
Writing – review & editing: Xiaoqiu Chu, Guofang Chen, Binbin Liu, Wenbo Ding, Zheng Zeng, Xinping Wu, Jianhua Wang, Shuhang Xu, Chao Liu.

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