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Malignancy rate of Bethesda category III thyroid nodules according to ultrasound risk stratification system and cytological subtype

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Abstract

The risk of malignancy is considered to be 10% to 30% for cases of thyroid nodules with atypia or follicular lesion of undetermined significance (AUS/FLUS). However, only a minority of patients with AUS/FLUS undergo surgery; therefore, the risk of malignancy might be overestimated due to selection bias. To overcome this problem, we categorized cases of thyroid nodules with AUS/FLUS using the ultrasound risk stratification system (US-RSS) to calculate the malignancy rate and identify the patients most suitable for surgical treatment.

In this retrospective observational study, we subcategorized 382 pathologically confirmed thyroid nodules with AUS/FLUS using current US-RSSs (American Thyroid Association, Korean-Thyroid Imaging Report and Data System, American College of Radiology-Thyroid Imaging, Reporting and Data System, European Thyroid Imaging Report and Data System) and calculated the malignancy rate. Additionally, cases of nodules with AUS/FLUS were categorized according to their cytological subtypes, and the malignancy rate was calculated.

Current US-RSSs showed good or moderate agreement among them. The overall malignancy rate for thyroid nodules with AUS/FLUS was 38.7%. On categorization of the nodules with AUS/FLUS, the malignancy rates were found to be 60% to 67.5% for the high suspicion category, 32.2–36.6% for the intermediate suspicion category, and 12.4% to 16.3% for the low suspicion category. The malignancy rate for nodules with cytologic atypia was significantly higher than that for nodules with architectural atypia, especially in the intermediate suspicion category.

Categorization of thyroid nodules with AUS/FLUS using current US-RSSs helps to determine the optimal course of management of patients, especially when combined with cytological subtype characterization.

Abbreviations: ATA = American Thyroid Association, AUS/FLUS = Atypia of undetermined significance/ Follicular lesion of undetermined significance, CNB = core needle biopsy, EU-TIRADS = European Union- Thyroid Imaging Report and Data System, FNA = fine needle aspiration, NIFTP = neoplasm with papillary-like nuclear features, US = ultrasound, US-RSS = ultrasound risk stratification system.

Keywords: atypia of undetermined significance, cytology, follicular lesion of undetermined significance, ultrasonography, ultrasound risk stratification system

1. Introduction

Fine needle aspiration (FNA) biopsy is considered as a modality to confirm the cytological diagnosis in patients identified with thyroid nodules on palpation or ultrasonography. Recently, several committees have suggested the use of ultrasound risk stratification systems (US-RSSs) to decide whether the identified nodules require FNA or sonographic follow-up.[1–4] These US-RSSs are similar in that they categorize nodules according to ultrasound (US) findings, define the estimated risk of malignancy, and recommend follow-up FNA biopsy according to the nodule size.

After FNA biopsy, the cytological results are reported using the 6 categories outlined by the Bethesda system. However, nodules classified as Bethesda III category cannot be easily distinguished as benign or malignant; these nodules are reported as having atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS). The Bethesda system recommends a repeat follow-up FNA biopsy for cases of thyroid nodules with AUS/FLUS. Reports indicate that about 30% of such cases were still diagnosed as being cytologically indeterminate thyroid nodules despite a repeat FNA biopsy.[5]

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According to the 2017 Bethesda system,[6] the risk of malignancy of thyroid nodules with AUS/FLUS depends on whether noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is included in risk assessment. In cases where NIFTP is regarded as cancer, the risk of malignancy is 10% to 30%, and when it is not considered cancerous, the risk of malignancy reduces to 6% to 18%. To assess the risk of malignancy in patients with thyroid nodules, the 2017 Bethesda system additionally recommends the subclassification of atypia (cytologic and architectural atypia);[6] cases of thyroid nodules with AUS/FLUS that demonstrated cytologic atypia showed significantly higher malignancy rate than did those with architectural atypia.[7] However, the precise calculation of malignancy rate in cases of thyroid nodules with AUS/FLUS remains difficult because only a minority of cases eventually undergo surgery. Therefore, limiting pathological confirmation in cases of thyroid nodules with AUS/FLUS in the assessment of malignancy rate can overestimate the risk of malignancy due to selection bias. Surgery is usually performed in patients whose ultrasonographic findings are indicative of malignancy or in those diagnosed with cytologically indeterminate thyroid nodules on repeat FNA biopsy.

To overcome this selection bias, it would be helpful to classify pathologically confirmed cases of thyroid nodules with AUS/FLUS according to the US-RSS and to calculate the malignancy rate in each US-RSS category. In addition, we aimed to identify the difference in malignancy rates, calculated by US-RSS, following the categorization of nodules with AUS/FLUS according to cytological subtypes and identify the patients most suitable for surgical treatment.

2. Materials and methods

2.1. Patient selection

This retrospective observational study, which involved a review of medical records, included patients who underwent FNA for thyroid nodules that were diagnosed as AUS/FLUS. The data were obtained from Seoul National University Bundang Hospital from January 2010 to May 2012, and from Chung-Ang University Hospital from January 2012 to October 2015. The Institutional Review Boards of both hospitals approved this study. We only included nodules that underwent subsequent core needle biopsy (CNB) during the study period, 3 to 6 months after the initial diagnosis of AUS/FLUS by FNA. Due to its high sensitivity and positive predictive value, CNB has been suggested to be more useful than repeat FNA for the definitive diagnosis of nodules with AUS/FLUS.[8] During the study period, 485 nodules were diagnosed with AUS/FLUS by FNA and subsequently underwent CNB 3 to 6 months after the initial FNA. Among these 485 nodules, 103 cases of cytologically indeterminate thyroid nodules were excluded. A total of 382 nodules were eventually included in this study. Final diagnoses of malignancy were confirmed surgically, whereas final diagnoses of benign nodules were determined by

(i) surgery or
(ii) absence of malignancy by CNB and
(iii) decreased or stable nodule size on US follow-up more than 12 months after initial FNA.

2.2. Analysis of sonographic findings

Both transverse and longitudinal sonograms obtained by real-time imaging of the thyroid nodules using Digital Imaging and Communications in Medicine images protocol were examined. The sonographic findings were independently reviewed by two board-certified radiologists (HSA and MS) and one endocrinologist (WSY) with 10 to 12 years of experience. In case of discordance, a mutual agreement was achieved after discussion.

The sonographic findings were analyzed by assigning the examined features to each category of US-RSS of the 2015 American Thyroid Association (ATA) guidelines,[1] Korean-Thyroid Imaging Report and Data System (K-TIRADS),[2] American College of Radiology, Thyroid Imaging, Reporting and Data System (ACR TIRADS),[3] and European Thyroid Association guidelines (EU-TIRADS).[4] The width, depth, and height of thyroid nodules were measured in millimeters (mm). Regarding the consistency of nodules, they were classified as solid (cyst $\leq$ 10%), predominant solid (10% $<$ cystic $\leq$ 50%), predominant cyst (50% $<$ cystic $\leq$ 90%), and cystic (cyst $>$ 90%).[2] Nodular orientation was divided into

1. parallel and
2. nonparallel (taller-than-wide).

Echogenicity of the nodules was classified as being

1. marked hypoechoic,
2. hypoechoic,
3. isoechoic, or
4. hyperechoic.

A marked hypoechoic lesion was defined as a thyroid nodule that showed a relatively hypoechoic pattern compared to the adjacent strap muscles of the neck. Nodular margins were categorized and defined as being

1. ill-defined,
2. spiculated or microlobulated,
3. smooth, or
4. showing extrathyroidal invasion.

Calcification was subdivided into

1. microcalcification (defined as calcifications that were equal to or less than 1 mm in diameter and visualized as tiny punctate hyperechoic foci, either with or without acoustic shadows);
2. macrocalcification (defined as hyperechoic foci larger than 1 mm); or
3. rim calcification (defined as nodules with peripheral curvilinear or eggshell calcifications).

Nodular shapes were divided as

1. ovoid to round or
2. irregular.

After the analysis of sonographic features, the nodules were divided into one of the following categories: US-RSS of ATA, K-TIRADS, ACR TIRADS, and EU-TIRADS.

2.3. US-guided FNA and CNB

US-guided FNA were performed using a 23-gauge needle attached to a 5-mL syringe with numerous multidirectional passes performed through the nodule for successful sampling. The specimens were preserved in 95% ethanol for liquid-based cytological examination. US-guided CNB were performed using a free-hand technique with a disposable 20-gauge, single- or dual-action spring-activated needle (approximately 1 or 2 cm excursion; TSK Acecut or Stericut, Create Medic, Yokohama, Japan).

All tissue cores were immediately immersed into 10% buffered formalin solution for fixation.

2.4. Specimen interpretation

Results of FNA (cytological) and CNB (histological) were evaluated by 2 pathologists (SYP and HSK, with 20 years of experience) in both hospitals. The cytological results were evaluated as per the Bethesda classification system. We also classified the nodules with AUS/FLUS into subcategories according to their predominant morphological features as cytologic atypia or architectural atypia.

Given that no standard diagnostic criteria for CNB of thyroid were defined during our study period, we used routine diagnostic criteria for interpretation of the CNB results as previously cited.[9]

2.5. Data and statistical analyses

Continuous variables are presented as mean ± standard deviation and were evaluated using Student's *t* test or Mann-Whitney *U* test. Categorical variables were analyzed using Pearson Chi-square test. The agreement between each US-RSS was evaluated by Cohen kappa test. The kappa coefficient was interpreted as follows: 0.00–0.20, poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; and 0.81–1.00, excellent agreement. The results were considered statistically significant if *P* value was less than .05. Statistical analyses were performed using SPSS (SPSS, Windows version 25.0, IBM Corporation, Armonk, NY).

3. Results

3.1. Demographic and sonographic characteristics of thyroid nodules initially diagnosed as Bethesda category III

Of the 382 thyroid nodules examined, 234 (61.3%) were benign and 148 (38.7%) were malignant according to surgical or subsequent CNB results. As shown in Table 1, patients with malignant nodules were younger than those with benign nodules (47.4 ± 12.6 vs 52.5 ± 12.2 years, $P < .001$). The malignant nodules were smaller than benign nodules (1.14 ± 0.82 vs 1.56 ± 0.88 cm, $P < .001$). In sonographic findings, the malignant thyroid nodules had a greater degree of solid consistency, nonparallel orientation, marked hypoechogenicity, spiculated or microlobulated margins, and microcalcification, compared with benign nodules ($P < .001$).

Table 1

Demographic and sonographic features of thyroid nodules initially diagnosed with Bethesda category III.

	Benign (n = 234, 61.3%)	Malignant (n = 148, 38.7%)	*P* value
Age	52.5 ± 12.2	47.4 ± 12.6	< .001
M/F (female %)	56/178 (76.1)	29/119 (80.4)	.337
Nodule size (cm)	1.56 ± 0.88	1.14 ± 0.82	< .001
Content – no (%)			.005
Solid (cystic ≤ 10%)	178 (76.1)	134 (90.5)	
Predominant solid (10% < cystic ≤ 50%)	41 (17.5)	11 (7.4)	
Predominant cystic (50% < cystic ≤ 90%)	14 (6.0)	3 (2.0)	
Cystic (> 90%)	1 (0.4)	0 (0.0)	
Orientation – no (%)			< .001
Parallel	218 (93.2)	106 (71.6)	
Nonparallel (taller than wide)	16 (6.8)	42 (28.4)	
Echogenicity – no (%)			< .001
Marked hypoechoic	19 (8.1)	54 (36.5)	
Hypoechoic	102 (43.6)	74 (50.0)	
Isoechoic	110 (47.0)	20 (13.5)	
Hyperechoic	3 (1.3)	0 (0.0)	
Margin – no (%)			< .001
Ill-defined	52 (24.2)	41 (27.7)	
Spiculated/microlobulated	23 (10.4)	55 (37.2)	
Smooth	158 (65.4)	43 (29.1)	
Extrathyroidal extension	1 (0.4)	9 (6.1)	
Calcification – no (%)			< .001
None	174 (74.4)	71 (48.0)	
Microcalcification	29 (12.4)	48 (32.4)	
Macrocalcification	26 (11.1)	24 (16.2)	
Rim calcification	5 (2.1)	5 (3.4)	
Halo – no (%)	34 (14.5)	13 (8.8)	.111
Shape – no (%)			.069
Ovoid to round	213 (91.0)	125 (84.5)	
Irregular	21 (9.0)	23 (15.5)	

3.2. Agreement between ultrasound risk stratification systems

To evaluate the agreement between the results of US-RSSs of 2015 ATA guidelines,[1] K-TIRADS,[2] ACR TIRADS,[3] and EU-TIRADS[4] in the thyroid nodules with AUS/FLUS, we measured Cohen's kappa coefficient between the four systems using two US-RSSs at a time. Each US-RSS demonstrated good or moderate agreement with each other (Table 2). US-RSS of ATA and K-TIRADS showed the best agreement ($\kappa = .979$, $P < .001$).

3.3. Assessment of the composition and malignancy rate of Bethesda category III nodules by US-RSSs

After the nodules were classified according to the four US-RSSs, 31.2% to 40.6% of the thyroid nodules with AUS/FLUS belonged to the high suspicion category, 28.0% to 39.7% to the intermediate (or moderate) suspicion category, and the remaining 24.1–34.0% to the low (or mild) suspicion category (Table 3). The calculated malignancy rates were 60.0% to 67.5% for nodules in the high suspicion category, 32.2% to 36.6% for nodules in the intermediate suspicion category, and 12.4% to 16.3% for nodules in the low suspicion category.

However, 20 (5.2%) nodules did not belong in any of the categories of the 2015 ATA US-RSS, and thus, as previously described, were classified as "not specified nodules."[10] Malignancy rates of the "not specified nodules" were 30%.

Table 2

Agreement of ultrasound risk stratification systems of each guidelines.

	Kappa	95% CI	*P* value
ATA vs. ACR TI-RADS	0.806	0.757–0.855	< .001
ATA vs. K-TIRADS	0.979	0.961–0.997	< .001
ATA vs. EU-TIRADS	0.847	0.800–0.894	< .001
ACR TI-RADS vs. K-TIRADS	0.792	0.741–0.843	< .001
ACR TI-RADS vs. EU-TIRADS	0.753	0.698–0.808	< .001
K-TIRADS vs. EU-TIRADS	0.778	0.725–0.831	< .001

ACR TI-RADS = American College of Radiology, Thyroid Imaging Reporting and Data System, ATA = American Thyroid Association, EU-TIRADS = European Union Thyroid Imaging Reporting and Data System, K-TIRADS = Korean Thyroid Imaging Reporting and Data System.

Table 3

Rates of malignancy in ultrasound risk stratification system categories in Bethesda category III nodules.

	Total (n = 382) n (% of total)	Benign (n = 234) n (% in category)	Malignant (n = 148) n (% in category)
ATA (2015)			
Very low suspicion	2 (0.5)	2 (100.0)	0 (0.0)
Low suspicion	129 (33.8)	108 (83.7)	21 (16.3)
Intermediate suspicion	107 (28.0)	68 (63.6)	39 (36.4)
High suspicion	124 (32.5)	42 (33.9)	82 (66.1)
Not specified	20 (5.2)	14 (70.0)	6 (30.0)
K-TIRADS (2016)			
Benign	2 (0.5)	2 (100.0)	0 (0.0)
Low suspicion	130 (34.0)	109 (83.8)	21 (16.2)
Intermediate suspicion	131 (34.3)	83 (63.4)	48 (36.6)
High suspicion	119 (31.2)	40 (33.6)	79 (66.4)
ACR TI-RADS (2017)			
Not suspicious	12 (3.1)	11 (91.7)	1 (8.3)
Mildly suspicious	92 (24.1)	79 (85.9)	13 (14.1)
Moderately suspicious	152 (39.7)	103 (67.8)	49 (32.2)
Highly suspicious	126 (33.0)	41 (32.5)	85 (67.5)
EU-TIRADS (2017)			
Benign	1 (0.3)	1 (100.0)	0 (0.0)
Low-risk	113 (29.6)	99 (87.6)	14 (12.4)
Intermediate-risk	113 (29.6)	72 (63.7)	41 (36.3)
High-risk	155 (40.6)	62 (40.0)	93 (60.0)

ACR TI-RADS = American College of Radiology, Thyroid Imaging Reporting and Data System, ATA = American Thyroid Association, EU-TIRADS = European Union Thyroid Imaging Reporting and Data System, K-TIRADS = Korean Thyroid Imaging Reporting and Data System.

Sonographic findings of these nodules were isoechoic with the presentation of one of the suspicious sonographic features, such as microcalcification, nonparallel orientation, and spiculated margins (Table 4).

3.4. Malignancy rate and composition of thyroid nodules according to subtype of Bethesda category III

Subsequently, we investigated the difference in malignancy rates among the subtypes (cytologic atypia or architectural atypia) of thyroid nodules with AUS/FLUS in each category of US-RSS. For this analysis, 53 cytologically indeterminate nodules were excluded from subtype categorization. As shown in Table 5, the malignancy rate of the cytologic atypia subtype was 44.9% (119 of 265 nodules), which was significantly higher than that of architectural atypia subtype (12.5%; 8 of 64 nodules; $P < .001$). In addition, the malignancy rate of nodules in the cytologic atypia subtype was significantly higher when they belonged to the low or indeterminate suspicion category. In contrast, the malignancy rate, according to subtype, was not different in the high suspicion category.

4. Discussion

After the categorization of thyroid nodules with AUS/FLUS as Bethesda category III following initial FNA, the Bethesda system recommends a repeat FNA, molecular testing, or lobectomy.[6] However, about 30% to 40% of those nodules are still diagnosed as AUS/FLUS despite repeat FNA,[11,12] which makes treatment decisions difficult for clinicians concerned with the optimal management of thyroid nodules. To overcome this problem, several modalities other than repeat FNA have been proposed, such as CNB,[13] gene expression classifier test,[14] and multi-gene next-generation sequencing assay.[15] However, these modalities have not demonstrated complete diagnostic accuracy, and to date, are unavailable or expensive in many countries. Recent studies have attempted to predict the risk of malignancy by combining various suspicious sonographic findings.[16–18] Furthermore, combined evaluation of cytological results and

Table 4

Summary of ultrasound features and malignancy in 20 not specified nodules by ultrasound risk stratification system of American Thyroid Association (ATA) guideline.

No	Echogenicity	Calcification	Orientation	Margin	Malignancy*	Korean TIRADS category	ACR TIRADS category
1	Isoechoic	Microcalcification	Parallel	Smooth	No	4	4
2	Isoechoic	Rim calcification	Parallel	Smooth	No	4	4
3	Isoechoic	Microcalcification	Nonparallel	Ill-defined	Yes	4	5
4	Isoechoic	Microcalcification	Parallel	Smooth	No	4	4
5	Isoechoic	Microcalcification	Parallel	Smooth	No	4	4
6	Isoechoic	Microcalcification	Parallel	Ill-defined	No	4	4
7	Isoechoic	None	Nonparallel	Ill-defined	Yes	4	4
8	Isoechoic	None	Nonparallel	Ill-defined	No	4	4
9	Isoechoic	Microcalcification	Parallel	Ill-defined	Yes	4	4
10	Isoechoic	Microcalcification	Parallel	Spiculated	No	4	5
11	Isoechoic	Macrocalcification	Nonparallel	Smooth	Yes	4	5
12	Isoechoic	Microcalcification	Parallel	Ill-defined	Yes	4	4
13	Isoechoic	Microcalcification	Parallel	Smooth	No	4	4
14	Isoechoic	None	Parallel	Spiculated	No	4	4
15	Isoechoic	Microcalcification	Parallel	Ill-defined	Yes	4	4
16	Isoechoic	Microcalcification	Parallel	Spiculated	No	4	5
17	Isoechoic	Microcalcification	Parallel	Spiculated	No	4	5
18	Isoechoic	Macrocalcification	Parallel	Spiculated	No	4	4
19	Isoechoic	Microcalcification	Parallel	Smooth	No	4	4
20	Isoechoic	Microcalcification	Parallel	Spiculated	No	4	5
	Isoechoic	Microcalcification	Nonparallel	Spiculated	Malignancy	Intermediate suspicion	Moderate suspicious
No (%)	20 (100%)	14 (70%)	4 (20%)	6 (30%)	6 (30%)	20 (100%)	14 (70%)

ACR = American College of Radiology, TIRADS = Thyroid Imaging Reporting and Data System.
* Confirmed by surgery or core needle biopsy.

Table 5

Malignancy rate according to subclassification of atypia and ultrasound risk stratification.

	Cytologic atypia (n = 265)*			Architectural atypia (n = 64)*			*P* value†
	Total N (%)	Benign 146 (55.1) N (%)	Malignant 119 (44.9) N (%)	Total N (%)	Benign 56 (87.5) N (%)	Malignant 8 (12.5) N (%)	< .001
ATA							
Very low suspicion	2 (0.8)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
Low suspicion	78 (29.4)	59 (75.6)	19 (24.4)	33 (51.6)	31 (93.9)	2 (6.1)	.032
Intermediate suspicion	79 (29.8)	45 (57.0)	34 (43.0)	22 (34.3)	19 (86.4)	3 (13.6)	.012
High suspicion	92 (34.7)	31 (33.7)	61 (66.3)	6 (9.4)	3 (50.0)	3 (50.0)	.415
Not specified	14 (5.3)	9 (64.3)	5 (35.7)	3 (4.7)	3 (100)	0 (0)	
K-TIRADS							
Benign	2 (0.6)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
Low suspicion	78 (29.4)	59 (75.6)	19 (24.4)	33 (51.6)	31 (93.9)	2 (6.1)	.032
Intermediate suspicion	96 (36.2)	55 (57.3)	41 (42.7)	25 (39.0)	22 (88.0)	3 (12.0)	.005
High suspicion	89 (33.6)	30 (33.7)	59 (66.3)	6 (9.4)	3 (50.0)	3 (50.0)	.415
ACR TI-RADS							
Not suspicious	8 (3.0)	7 (87.5)	1 (12.5)	1 (1.6)	1 (100)	0 (0)	
Mildly suspicious	54 (20.4)	43 (79.6)	11 (20.4)	28 (43.8)	26 (92.9)	2 (7.1)	.201
Moderately suspicious	110 (41.5)	68 (61.8)	42 (38.2)	27 (42.2)	24 (88.9)	3 (11.1)	.006
Highly suspicious	93 (35.1)	28 (30.1)	65 (69.9)	8 (12.5)	5 (62.5)	3 (37.5)	.109
EU-TIRADS							
Benign	1 (0.4)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
Low-risk	65 (24.5)	53 (81.5)	12 (18.5)	32 (50.0)	30 (93.8)	2 (6.3)	.092
Intermediate-risk	85 (32.1)	48 (56.5)	37 (43.5)	22 (34.4)	19 (86.4)	3 (13.6)	.007
High-risk	114 (43.0)	44 (38.6)	70 (61.4)	10 (15.6)	7 (70.0)	3 (30.0)	.056

ACR TI-RADS = American College of Radiology, Thyroid Imaging Reporting and Data System, ATA = American Thyroid Association, EU-TIRADS = European Union Thyroid Imaging Reporting and Data System, K-TIRADS = Korean Thyroid Imaging Reporting and Data System.

* 53 ambiguous nodules in subclassification of atypia were excluded in this analysis.

† P value for malignancy rate between cytologic atypia vs architectural atypia.

sonographic findings might provide more accurate predictions of risk of malignancy.

The results of our study might aid clinical decision-making related to the surgical management of nodules that were still indeterminate after a repeat FNA or CNB. For example, if a thyroid nodule with AUS/FLUS belongs to the high suspicion category by US-RSS, the malignancy rate for such a nodule is more than 60%, and surgical intervention can be considered. In addition, for a nodule with AUS/FLUS classified with cytologic atypia, the risk of malignancy is higher compared with a nodule with architectural atypia, and for such a nodule belonging to the low or indeterminate suspicion category, surgery can be recommended. On the contrary, when the subtype of a nodule with AUS/FLUS is architectural atypia, the overall risk of malignancy is relatively low (12.5%) but presents a 50% malignancy rate for nodules belonging to the high suspicion category. Therefore, for nodules with AUS/FLUS presenting with architectural atypia, regular sonographic follow-up will indicate if they belong to low or intermediate suspicion categories, but surgery should be recommended if the nodules belong to the high suspicion category. Figure 1 summarizes our recommendations for the management of thyroid nodules with AUS/FLUS according to the US-RSS and cytological subtypes.

In this study, the malignancy rates for high, intermediate, and low suspicion categories of several US-RSSs for thyroid nodules with AUS/FLUS were 60.0–67.5%, 32.2–36.6%, and 12.4–6.3%, respectively. In a previous study, the malignancy rates for 181 nodules with AUS/FLUS were 62.5%, 34%, and 20.2% in the high, intermediate, and low suspicion categories, respectively, by K-TIRADS US-RSS, which was similar to our results.

While US-RSS is particularly useful for predicting malignancy, it is still not an absolute tool. In our study, about 30% of the AUS/FLUS nodules of the high suspicion category were eventually diagnosed as benign nodules by subsequent CNB. Unnecessary surgery was thus avoided in about 30% of cases with highly suspicious thyroid nodules. Therefore, clinical decisions on the need for surgery can be made by considering the results of subsequent CNB, US-RSS, other clinical factors, and patients' preference. In summary, the use of US-RSS in combination with cytological results is expected to enable personalized treatment (US surveillance, repeat biopsy, diagnostic surgery, and molecular study) for cases of thyroid nodules with AUS/FLUS.

In this study, we subcategorized thyroid nodules with AUS/FLUS according to US-RSSs of 2015 ATA guidelines, K-TIRADS, ACR TIRADS, and EU-TIRADS. Although subcategorization by these US-RSSs showed excellent agreement in each category, 4.3% of the isoechoic nodules with one or more suspicious malignant findings did not belong to any category of the ATA US-RSS. However, the probability for malignancy in these "not specified" nodules was about 30%; therefore, an US-RSS that includes such "not specified" nodules is preferable for clinical use. Fortunately, the other three US-RSSs did not have this drawback. Since various US-RSSs are currently being used, the development of a unified US-RSS would be more helpful in clinical practice.

The limitations of our study are the retrospective design and the possibility of selection bias because the patients' data were only collected from two tertiary hospitals. Therefore, the malignancy rate of nodules with AUS/FLUS in our study is 38.7%, which is marginally higher compared with the Bethesda system (10 to 30%) when NIFTP is included in the calculations.

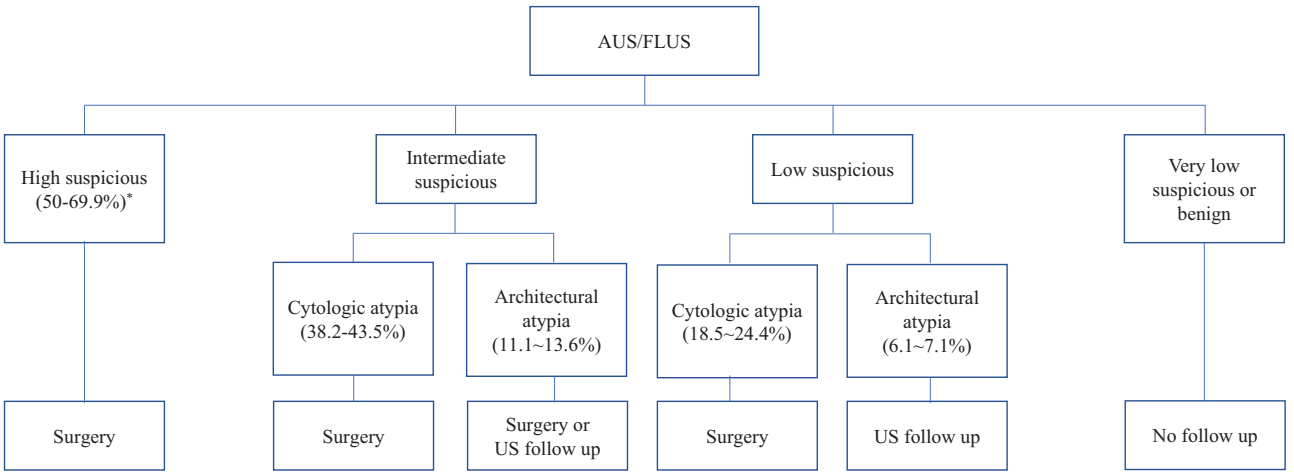

Figure 1. Management guidelines of thyroid nodules with AUS/FLUS according to ultrasound risk stratification system and cytological subtypes. AUS = atypia of undetermined significance, FLUS = follicular lesion of undermined significance.

In our study, the malignant nodules were diagnosed at a young age, and small nodules had more malignant sonographic findings. FNA was performed in patients who preferred further examination for suspicious nodules on US that were less than 1 cm. Therefore, inadvertently, small malignant nodules may have been included in our study. Another limitation is that the malignancy rate of NIFTP among patients diagnosed with risk of malignancy was not examined. Additionally, diagnoses were not confirmed surgically in all patients. However, CNB was performed in all patients after they underwent initial FNA biopsy, which addresses the problem. Since the positive predictive value of CNB for the diagnosis of malignancy was almost 100% in several published studies,[19,20] using the CNB results, instead of surgical results, to diagnose malignancy should not present a major problem.

In conclusion, the categorization of thyroid nodules with AUS/FLUS using current US-RSSs is useful for deciding the optimal course of treatment and management of patients, especially when combined with the results of cytological subcategorization.

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