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Risk of Malignancy According to the Sub-classification of Atypia of Undetermined Significance and Suspicious Follicular Neoplasm Categories in Thyroid Core Needle Biopsies

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Abstract
The objective of this study was to evaluate the risk of malignancy (ROM) associated with atypia of undetermined significance (AUS) and suspicious follicular neoplasm (SFN) core needle biopsy (CNB) categories after further sub-classification. Data from 2267 thyroid nodules evaluated by ultrasound-guided CNB, from January to December 2015, were retrospectively reviewed. AUS nodules ($n = 556$) were sub-classified as follows: (1) architectural atypia (AUS-A; $n = 369$, 66.4%), (2) cytologic atypia (AUS-C; $n = 35$, 6.3%), (3) cytologic/architectural atypia (AUS-C/A; $n = 85$, 15.3%), or (4) oncocytic atypia (AUS-O; $n = 67$, 12.1%). SFN nodules ($n = 172$) were sub-classified as follows: (1) architectural atypia only (SFN-A; $n = 110$, 64%), (2) cytologic/architectural atypia (SFN-C/A; $n = 24$, 14%), or (3) oncocytic atypia (SFN-O; $n = 38$, 22%). Diagnostic surgery was performed in 162 (30.2%) AUS cases and 105 (61%) SFN cases. The ROM of each sub-category was evaluated. The overall ROM was 15.3–52.5% in AUS nodules and 35.5–58.1% in SFN nodules. The ROM was higher in the AUS-C (22.9–88.9%) and AUS-C/A (32.9–90.3%) groups than AUS-A (11.9–40%) and AUS-O (7.5–41.7%). In the SFN category, ROM in the SFN-C/A group was also higher than SFN-A or SFN-O (37.5–75%, 40–57.9%, and 21.1–47.1%, respectively). Our study shows that the ROM was higher in AUS or SFN sub-categories with cytologic atypia than those without cytologic atypia. Because of the heterogeneous nature of AUS and SFN categories, sub-classification may be a more effective approach for risk stratification, allowing optimal management of patients with thyroid nodules.

Keywords Thyroid · Atypia of undetermined significance · Follicular neoplasm · Core needle biopsy · Risk of malignancy · Sub-category

Introduction

Ultrasound (US)-guided fine needle aspiration (FNA) is widely accepted as the gold standard for the diagnosis of thyroid nodules because of its safety and diagnostic accuracy [1, 2]. The Bethesda System of Reporting Thyroid Cytopathology (TBSRTC), introduced in 2009, standardized the reporting of thyroid FNA and introduced a six-tier system, which provides the risk of malignancy and appropriate management for each category [3]. However, there is an indeterminate diagnostic group, the atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) and suspicious for follicular neoplasm/follicular neoplasm (SFN/FN) categories. These encompass a heterogeneous group of lesions that contain follicular cells exhibiting architectural atypia and/or cytologic atypia that exceed expected benign reactive changes but are not sufficient to justify classification into any of the other categories [3–5]. Recent studies have suggested that the risk of malignancy (ROM) differs according to the nature of the atypia and that AUS/FLUS can be further sub-classified into more distinct sub-types

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[6–11]. The 2017 revised TBSRTC also recommends sub-classification of the atypia into (i) cytologic atypia, (ii) architectural atypia, (iii) cytologic and architectural atypia, (iv) Hurthle cell AUS/FLUS, and (v) atypia, not otherwise specified. Sub-classification of AUS/FLUS lesions may improve the risk stratification of individual patients in order to achieve better clinical management. In contrast to the AUS/FLUS category, there are few studies investigating the sub-classification of SFN/FN on FNA [12–14].

US-guided core needle biopsy (CNB) was first introduced as an alternative to thyroid FNA in the 1990s [15] and is now used for the evaluation of thyroid nodules with excellent results [16]. The advantages of CNB include the ability to sample a large amount of tissue, which can improve the diagnostic rate and the ability to identifying malignancy compared with FNA [17]. However, compared with FNA, only limited data are available to describe the ROM of AUS and SFN sub-categories for thyroid CNB. As an understanding of the ROM associated with these sub-types would be useful for patient management, this study aimed to evaluate and compare the ROM of AUS and SFN CNB sub-categories.

Materials and Methods

Thyroid Nodules and Patients

From January to December 2015, 4281 thyroid nodules were evaluated by US-guided CNB ($n = 2267$) or US-guided FNA ($n = 2014$) at the Asan Medical Center (Seoul, Korea). Among the 2267 CNB specimens, AUS (Bethesda category III) and SFN (Bethesda category IV) lesions were retrospectively reviewed. This retrospective study was approved by the institutional review board. Informed consent was obtained from all patients prior to thyroid CNB.

Ultrasound-Guided Core Need Biopsy Procedure

US examination was performed using either an iU22 unit (Philips Healthcare, Bothell, WA, USA) or EUB-7500 unit (Hitachi Medical Systems, Tokyo, Japan) equipped with a linear high-frequency probe (5–14 MHz). All US examinations and US-guided CNBs were performed by radiologists under the supervision of faculty experts.

US-guided CNBs were performed using disposable 18-gauge double action, spring-activated needles (1.1 or 1.6 cm excursion; TSK Ace-cut; Create Medic, Yokohama, Japan) under local anesthesia with 1% lidocaine [2, 18]. The tip of the core needle was advanced to the edge or within the nodule using a freehand technique, and the stylet and cutting cannula of the needle were then fired sequentially. After CNB, firm, local compression was applied to the biopsy site for 10–20 min [19].

Pathologic Evaluation of Core Needle Biopsy Specimens

All CNB specimens were diagnosed by an experienced pathologist in accordance with the criteria proposed by the Korean endocrine pathology thyroid CNB study group [20]. According to the original published criteria for the assessment of thyroid CNBs [18], category III comprised indeterminate lesions, which were sub-categorized as indeterminate follicular lesions with nuclear atypia and indeterminate follicular lesions with architectural atypia. Category IIIA included follicular proliferative lesions with focal and equivocal nuclear atypia or atypical follicular cells embedded in fibrotic stroma, whereas category IIIB included microfollicular/solid/trabecular proliferative lesions lacking a fibrous capsule or an adjacent non-lesional thyroid tissue. Category IV included nodules diagnosed as "follicular neoplasm or suspicious of a follicular neoplasm," based on the presence of a fibrous capsule and various follicular proliferative lesions that differed from the adjacent thyroid parenchyma.

Cases of category III indeterminate lesion and Category IV SFN/FN specimens were retrospectively reviewed and the terms were modified for better comparison with the corresponding FNA categories of the TBSRTC. For category III, we used AUS instead of indeterminate lesion and sub-classified them into one of following: (1) architectural atypia only (AUS-A), (2) cytologic atypia only (AUS-C), (3) both cytologic and architectural atypia (AUS-C/A), and (4) oncocytic atypia (AUS-O). AUS-A (Fig. 1a) was defined as microfollicular, macrofollicular, mixed micro- and macrofollicular, solid, or trabecular proliferative lesions lacking a tumor capsule or an adjacent non-lesional thyroid tissue and/or showing equivocal fibrotic capsule mimicking a tumor capsule. AUS-C (Fig. 1b) was the same category IIIA. AUS-C/A (Fig. 1c) was defined as the presence of mild cytological atypia [21] in a background of microfollicular, macrofollicular, mixed micro- and macrofollicular, solid, or trabecular proliferative lesions. A tumor capsule or adjacent non-lesional thyroid tissue was lacking, and equivocal fibrotic capsule mimicking a tumor capsule was occasionally observed. AUS-O (Fig. 1d) was defined as the presence of predominant proliferative oncocytic cells without a tumor capsule or adjacent non-lesional thyroid tissue. An equivocal fibrotic capsule mimicking a tumor capsule was occasionally observed and lymphocytic thyroiditis background was absent. For category IV, only the SFN term was used and sub-classified into one of following: (1) architectural atypia only (SFN-A), (2) both cytologic and architectural atypia (SFN-C/A), and (3) oncocytic atypia (SFN-O). SFN-A (Fig. 1e) was defined as microfollicular, macrofollicular, mixed micro- and macrofollicular, solid, and trabecular follicular proliferative lesions with a definite tumor capsule. SFN-C/A (Fig. 1f) was defined as the presence of mild cytological atypia [21] in a background of microfollicular, macrofollicular, mixed micro- and macrofollicular, solid, or trabecular proliferative lesions with a definite tumor capsule. SFN-

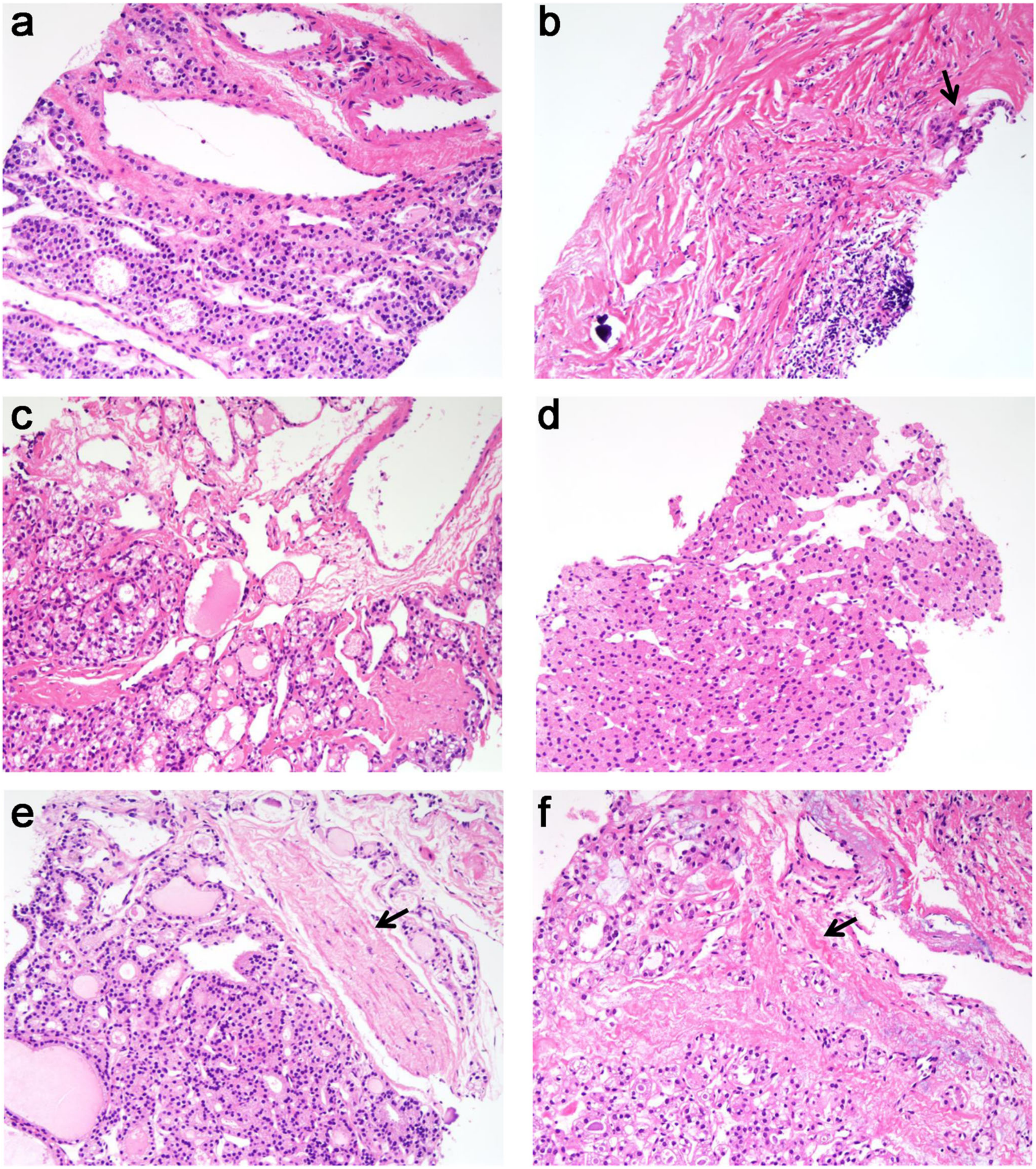

Fig. 1 Histologic features of various sub-categories of atypia of unknown significance (AUS; **a–d**) and suspicious follicular neoplasm (SFN, **e** and **f**) at the border between lesion and non-lesional areas in core needle biopsies of the thyroid (hematoxylin–eosin [H&E], original magnification × 200). **a** The AUS-architectural atypia only specimen shows microfollicular and trabecular proliferative follicular cells without a definite tumor capsule. **b** The AUS-cytologic atypia only specimen shows a few atypical follicular cells (arrow) in a background of dense fibrotic stroma with suspicious psammoma body calcification. **c** The AUS-both cytologic and architectural atypia specimen shows microfollicular proliferative follicular cells with mild nuclear atypia and without a definite tumor capsule. **d** The AUS-oncocytic atypia specimen shows trabecular proliferative oncocytic cells without adjacent non-lesional thyroid tissue. **e** The SFN-architectural atypia only specimen shows microfollicular proliferative follicular cells with a thin definite tumor capsule (arrow). **f** The SFN-both cytologic and architectural atypia specimen shows microfollicular proliferative follicular cells with mild nuclear atypia and a thin fibrous tumor capsule (arrow)

O was defined as the presence of predominant proliferative oncocytic cells with a definite tumor capsule. The lymphocytic thyroiditis background was usually absent.

In addition, surgical specimens were reviewed for the diagnosis of the non-invasive encapsulated follicular variant of papillary thyroid carcinoma (NI-EFVPTC) and diagnosed in accordance with the 2017 WHO criteria [21]. Histological diagnostic criteria of NI-EFVPTC included a follicular growth pattern, encapsulation (completely or partially) with clear demarcation from the adjacent thyroid parenchyma, the presence of mild nuclear atypia, and the absence of capsular or vascular invasion in all tumor capsules, similar to the criteria reported by Nikiforov et al. [22].

Estimation of Malignancy Risk

Considering the inherent bias in the estimation of ROM in thyroid nodules, the ROM was determined as a range. The "lower-bound estimate" was calculated by dividing the number of confirmed malignancies by the total number of each sub-category. The assumption that all non-operated AUS or SFN nodules were benign is subject to verification bias and, therefore, underestimates the prevalence of malignancy. The "upper-bound estimate" was calculated by dividing the number of confirmed malignancies by the number of AUS or SFN nodules selected to undergo surgery.

Statistical Analysis

IBM SPSS Statistics for Windows v19.0 (IBM Corp., Armonk, NY) was used for all statistical analyses. Continuous variables are expressed as mean ± standard deviation, and categorical variables are shown as percentages. To evaluate differences in demographic data and ultrasound features between the AUS and SFN groups, the Student's *t* test was used for continuous variables and the chi-square test or Fisher's exact test was used for binary variables. The comparison of ROM between AUS/SFM category with cytologic atypia and without atypia was performed using chi-square test.

Results

Diagnostic Rates According to the Bethesda Categories

Table 1 shows a comparison of the diagnostic rates according to the Bethesda categories of both FNAs and CNBs among the 4281 patients included in the analysis. For Bethesda category III (AUS), the diagnostic rate was similar between FNA (24.1%) and CNB (24.5%). However, for Bethesda category IV (SFN), the CNB diagnostic rate was significantly higher than FNA (7.6% vs. 0.9%, respectively; $p < 0.001$). The rate of non-diagnostic Bethesda category I was significantly lower in the CNB than the FNA group (5.9% vs. 10.3%, respectively; $p < 0.001$).

Risk of Malignancy in CNB Specimens

Overall, 24.5% (556/2267) and 7.6% (172/2267) of all thyroid CNB specimens were classified as AUS and SFN, respectively. Patient demographic information showed that the AUS group had a significantly higher proportion of female patients and a higher median age (Table 2). Comparative analysis of ultrasound features also showed some significant differences between the two groups. In addition, FNA prior to CNB was performed in 222 patients of AUS group and 67 patients of SFN group, and its previous FNA results were followed: Bethesda I ($n = 33$), Bethesda II ($n = 76$), Bethesda III ($n = 104$), Bethesda IV ($n = 6$), and Bethesda V ($n = 3$) in AUS group and Bethesda I ($n = 4$), Bethesda II ($n = 22$), Bethesda III ($n = 37$), Bethesda IV ($n = 2$), and Bethesda V ($n = 2$) in SFN group.

The final pathologic diagnosis was obtained by diagnostic surgery in 162 cases (30.2%) of AUS and 105 cases (61%) of SFN. For nodules categorized as AUS, 38 cases were seen to be non-neoplastic hyperplasia and 124 cases were neoplasms (Table 3). Malignancy was diagnosed in 85 cases, which included follicular thyroid carcinoma (FTC, $n = 26$), NI-EFVPTC ($n = 25$), invasive encapsulated FVPTC ($n = 22$), classical type PTC ($n = 9$), infiltrative FVPTC ($n = 5$), and other variants of PTC ($n = 3$). For nodules categorized as SFN, eight cases (7.6%, 8/105) were non-neoplastic hyperplasias and 97 cases were neoplasms (Table 4). Malignancy was diagnosed in 61 cases, which included infiltrative FVPTC ($n = 24$), FTC ($n = 18$), NI-EFVPTC ($n = 14$), solid variants of PTC ($n = 2$), poorly differentiated thyroid carcinomas ($n = 2$), and metastasis from renal cell carcinoma ($n = 1$).

The ROM of AUS and SFN nodules was 15.3–52.5% and 35.5–58.1%, respectively. When the ROM was recalculated by removing NI-EFVPTC from the evaluation of malignancies, the ROM diminished to 10.8–37% and 27.3–44.8%, respectively (Table 5).

Risk of Malignancy According to Sub-classification of AUS and SFN

The final pathologic diagnosis for each sub-category of AUS and SFN is shown in Table 3. The ROM in the AUS category differed according to the nature of the atypia. The ROM was higher in AUS-C (22.9–88.9%) and AUS-C/A (32.9–90.3%) sub-categories than the AUS-A (11.9–40%) and AUS-O (7.5–41.7%) sub-categories. The ROM in the AUS category with cytologic atypia was significantly higher than in the AUS category without cytologic atypia (p value < 0.01). This trend was similarly in the SFN category, as the ROM in the SFN-C/A (37.5–75%) sub-category was higher than in SFN-A (40–

Table 1 Comparison of diagnostic rate of FNA and CNB according to the Bethesda categories

Bethesda categories	FNA	CNB	Total	*p* value
Bethesda I	208 (10.3%)	133 (5.9%)	341 (8.0%)	< 0.001*
Bethesda II	1019 (50.6%)	869 (38.3%)	1888 (44.1%)	< 0.001*
Bethesda III	485 (24.1%)	556 (24.5%)	1041 (24.3%)	0.735*
Bethesda IV	18 (0.9%)	172 (7.6%)	190 (4.4%)	< 0.001*
Bethesda V	97 (4.8%)	58 (2.6%)	155 (3.6%)	< 0.001*
Bethesda VI	187 (9.3%)	479 (21.1%)	666 (15.6%)	< 0.001*
Total	2014	2267	4281	

FNA fine needle aspiration, *CNB* core needle biopsy

*Based on the Bonferroni correction, $p < 0.004$ (= 0.5/12) refers to significant difference in distribution between FNAs and CNBs in each Bethesda category

57.9%) and SFN-O (21.1–47.1%). NI-EFVPTCs accounted for 4.5–15.4% of the AUS category and 8.1–13.3% of the SFN category and were primarily found in the AUS-C/A and SFN-C/A sub-categories. The ROM in the SFN category with cytologic atypia was significantly higher than in the SFN category without cytologic atypia (*p* value = 0.04).

Discussion

In the current analysis of thyroid nodule CNB specimens, we found that the ROM of AUS and SFN nodules was 15.3–52.5% and 35.5–58.1%, respectively. The ROM differed when specimens were further sub-classified according to the

Table 2 Patients demographics, US, and histologic characteristics of the thyroid nodules

Characteristics	Total	AUS	SFN	*p* value
Number	728	556	172	
Age[a] (years)	52.2 (30–79)	52.7 (30–74)	50.5 (36–79)	0.046
Gender (male/female)	151/577	105/451	46/126	0.026
Size of nodule[a] (cm)	23.0 (4–100)	21.9 (4–100)	26.7 (7–90)	< 0.001
Composition of nodule				0.905
Solid	519	397 (71.4%)	122 (70.9%)	
Solid and cystic	209	159 (28.6%)	50 (29.1%)	
Sonographic echogenicity				0.289
Hyper/isoechoic	462	347 (62.4%)	115 (66.9%)	
Hypoechoic	266	209 (37.6%)	57 (33.1%)	
Shape of nodule				0.159
Ovoid to round	709	538 (96.8%)	171 (99.4%)	
Taller than wide	17	16 (2.9%)	1 (0.6%)	
Irregular	2	2 (0.4%)	0	
Margin of nodule				< 0.001
Smooth	568	415 (74.6%)	153 (89.0%)	
Ill-defined	125	109 (19.6%)	16 (9.3%)	
Spiculated	35	32 (5.8%)	3 (1.7%)	
Calcification				0.001
None	585	430 (77.34%)	155 (90.1%)	
Microcalcification	48	43 (7.73%)	5 (2.9%)	
Macrocalcification/rim calcification	95	83 (14.93%)	12 (7.0%)	
Biopsy needle size				0.001
1.1 cm	466	375 (67.4%)	91 (52.9%)	
1.6 cm	262	181 (32.6%)	81 (47.1%)	
Number of biopsy	1.2 (1–3)	1.2 (1–3)	1.2 (1–3)	0.509

[a] Data are expressed as the median with a range in the parenthesis

AUS atypia of unknown significance, *SFN* suspicious follicular neoplasm

Table 3 Comparison of the risk of malignancy according to sub-classification of atypia of undetermined significance, category III for reporting thyroid CNBs

Sub-classification categories (*n* = total, surgery)	Nodular hyperplasia	Neoplasm	Malignancy (ROM)	NI-EFVPTC
AUS-A	31	79	44	13
(*n* = 369, 110)	(8.4–28.2%)	(21.4–71.8%)	(11.9–40%)	(3.5–11.8%)
AUS-C	1	8	8	1
(*n* = 35, 9)	(2.9–11.1%)	(22.9–88.9%)	(22.9–88.9%)	(2.9–11.1%)
AUS-C/A	2	29	28	10
(*n* = 85, 31)	(2.4–6.5%)	(34.1–93.5%)	(32.9–90.3%)	(11.8–32.3%)
AUS-O	4	8	5	1
(*n* = 67, 12)	(6.0–33.3%)	(11.9–66.7%)	(7.5–41.7%)	(1.5–8.3%)
Total AUS	38	124	85	25
(*n* = 556, 162)	(6.8–23.5%)	(22.3–76.5%)	(15.3–52.5%)	(4.5–15.4%)

ROM risk of malignancy, *AUS-A* atypia of undetermined significance-architectural atypia only, *AUS-C* atypia of undetermined significance-cytologic atypia only, *AUS-C/A* atypia of undetermined significance-both cytologic and architectural atypia, *AUS-O* atypia of undetermined significance-oncocytic atypia, *NI-EFVPTC* non-invasive follicular variant of papillary thyroid carcinoma

nature of the atypia. The ROM was higher in AUS or SFN with cytologic atypia than those without cytologic atypia. Therefore, sub-classification of the AUS and SFN category in CNB specimens can provide valuable information, allowing risk stratification of individual patients and supporting the diagnostic or therapeutic management of indeterminate thyroid nodules.

Due to a high degree of heterogeneity, many studies of FNA have proposed the use of sub-classifications of the AUS/FLUS category to identify higher-risk sub-group and to refine management protocols. Several studies have shown an increased ROM in nuclear atypia sub-categories [6–8, 12, 23–26]. In our study, sub-classification of AUS on CNB, as recommended by TBSRTC, showed similar results. The ROM differed according to the nature of the atypia, with the ROM of AUS with cytologic atypia being higher than that of AUS without cytologic atypia (AUS-A and AUS-O).

In contrast to the AUS/FLUS category, there is a paucity of literature investigating the sub-classification of SFN/FN on FNA [12–14, 27]. Goldstein et al. found that follicular neoplasms with nuclear atypia had a significantly higher ROM of 44.4% compared with 6.8% in those without nuclear atypia [13]. Ustun et al. sub-classified follicular neoplasms into three categories: (i) microfollicular patterned neoplasm, (ii) Hűrthle cell neoplasm, and (iii) follicular lesions with some features suggestive of, but not diagnostic of, the FVPTC [14]. The ROM was seen to be 29%, 26%, and 73%, respectively, indicating that follicular neoplasms with even subtle nuclear atypia had a high positive predictive value for malignancy. Recently, Lim et al. sub-classified SFN/FN into follicular neoplasms with nuclear atypia and without nuclear atypia, and the ROM was significantly higher in follicular neoplasms with nuclear atypia (57.6% vs. 21.8%) [12]. Recent meta-analysis reported that there is no significant difference in the prevalence of malignancy between nodules of SFN/FN with and without nuclear atypia [25], although this study had some limitation by its small sample sizes of the sub-groups. To our knowledge, sub-classifications of SFN/FN on CNB have

Table 4 Comparison of the risk of malignancy according to sub-classification of suspicious follicular neoplasm, category IV for reporting thyroid CNBs

Sub-classification categories (*n* = total, surgery)	Nodular hyperplasia	Neoplasm	Malignancy (ROM)	NI-EFVPTC
SFN-A	6	70	44	8
(*n* = 110, 76)	(5.5–7.9%)	(63.6–92.1%)	(40–57.9%)	(7.3–10.5%)
SFN-C/A	1	11	9	4
(*n* = 24, 12)	(4.2–8.3%)	(45.8–91.7%)	(37.5–75%)	(16.7–33.3%)
SFN-O	1	16	8	2
(*n* = 38, 17)	(2.6–5.9%)	(42.1–94.1%)	(21.1–47.1%)	(5.3–11.8%)
Total SFN	8	97	61	14
(*n* = 172,105)	(4.7–7.6%)	(56.4–92.4%)	(35.5–58.1%)	(8.1–13.3%)

ROM risk of malignancy, *SFN-A* suspicious follicular neoplasm-architectural atypia only, *SFN-C/A* suspicious follicular neoplasm-both cytologic and architectural atypia, *SFN-O* suspicious follicular neoplasm-oncocytic atypia, *NI-EFVPTC* non-invasive encapsulated follicular variant of papillary thyroid carcinoma

Table 5 Impact of reclassifying non-invasive encapsulated follicular variant of papillary thyroid carcinoma on the risk of malignancy in the atypia of undetermined significance and suspicious follicular neoplasm categories for reporting thyroid CNBs

Diagnostic category	NI-EFVPTC = cancer (ROM)	NI-EFVPTC ≠ cancer (ROM)
AUS	85 (15.3–52.5%)	60 (10.8–37%)
SFN	61 (35.5–58.1%)	47 (27.3–44.8%)

NI-EFVPTC non-invasive encapsulated follicular variant of papillary thyroid carcinoma

not been investigated. The current study showed similar results to those performed in the thyroid FNA specimens, with the ROM of SFN with cytologic atypia being higher than that of SFN without cytologic atypia.

In the present study, the ROM of AUS with cytologic atypia and AUS with both cytologic and architectural atypia on CNB (22.9–88.9% and 32.9–90.3%, respectively) far exceeded the implied ROM of 15–30% of the AUS/FLUS category by TBSRTC [28]. Because the second edition of TBSRTC [28] includes diagnostic lobectomy as an option for standard management in the AUS/FLUS category, a diagnostic lobectomy can be an appropriate management approach for AUS with cytologic atypia on CNB, after considering other suspicious clinical features of indeterminate thyroid nodules.

US-guided CNB is a safe and well-tolerated procedure with distinct diagnostic advantages due to the ability to readily assess histological architecture and growth patterns by obtaining larger tissue sample than FNA. However, current guidelines contain limited recommendations for thyroid CNB. The National Cancer Institute, American Association of Clinical Endocrinologists/American College of Endocrinology/Associazione Medici Endocrinologi (AACE/ACE/AME), and the Korean Society of Thyroid Radiology (KSThR) have proposed CNB for thyroid nodules with previous non-diagnostic FNA results [28–30]. The KSThR also recommends the use of CNB as an alternative method for a repeated investigation of nodules with AUS/FLUS on previous FNA evaluation [30]. However, data on the use of CNB for nodules with previous AUS/FLUS FNA results are limited by the lack of a widely accepted reporting system [28].

Recently, a CNB pathology reporting system based on the six TBSRTC categories has been produced by the Korean Endocrine Pathology Thyroid CNB Study Group [20]. While each diagnostic category in the TBSRTC has an implied ROM and clearly recommended clinical management steps, only limited data are available on the ROM in each diagnostic category [16, 20]. Among the six categories of CNB pathology, assessment of the ROM associated with category III-indeterminate lesions and category IV-FN/SFN is particularly important as these are highly heterogeneous groups comprising lesions that could not be confidently labeled as benign or malignant [12]. Therefore, we evaluated the ROM for nodules diagnosed as category III or IV on CNB specimens. We used the term of "AUS" instead of "indeterminate lesions" on CNB, which is considered to allow better comparison with the same TBSRTC category. Indeterminate lesions include TBSRTC categories III, IV, and V in the thyroid FNA; therefore, the use of "indeterminate lesions" on CNB can lead to some confusion among endocrine clinicians. Here, we used the term "SFN" rather than "FN" because the tumor capsule can be observed at the tumor interface of the CNB specimen; however, it is not possible to be certain whether the observed tumor capsule is complete or not. The ROM of AUS and SFN nodules was 15.3–52.5% and 35.5–58.1%, respectively, which is somewhat higher than that with FNA (10–30% and 25–40%, respectively). In the current study, the upper bound of ROM for AUS and SFN was similar (58.1% and 52.5%, respectively) despite the difference in surgery rates between two categories (30.2% and 61%, respectively). One of the possible reasons for the higher ROM observed in the AUS group could be associated with the fact that most patients in this category were recommended for regular follow-up and repeated CNB, rather than a diagnostic lobectomy. Therefore, patients who underwent surgery for nodules with AUS are more likely to have other clinically suspicious features that may increase the final malignancy risk. The NI-EFVPTCs constituted a substantial proportion of malignancies in the categories of AUS and SFN. When NI-EFVPTCs were omitted from the analysis, the ROM diminished to 10–37% and 27.3–44.8%, respectively, which is still somewhat higher than that of FNA, which is estimated to be 6–18% and 10–40%, respectively.

There are several limitations to the current study. First, it is a retrospective analysis. Secondly, referral bias for patients in a tertiary center should be considered and may have led to a high malignancy rate for thyroid nodules in this study. Thirdly, not all patients with AUS nodules underwent surgery and therefore the true malignancy rate may differ from the estimated rate seen in our study. Therefore, lower- and upper-bound estimates of ROM were used, as the upper-bound estimate is subject to selection bias and a possible overestimation of the prevalence of malignancy. The true prevalence is likely to lie between the lower- and upper-bound approximations.

In conclusion, both AUS and SFN categories for CNB showed higher ROM than those of the same categories in the second edition of TBSRTC. The ROM was higher in sub-categories with cytologic atypia than without cytologic atypia. Because of the heterogeneous nature of AUS and SFN, sub-classification may help to achieve appropriate risk stratification and therefore allow optimal clinical management of patients undergoing CNB for various thyroid nodules.

Compliance with Ethical Standards

This retrospective study was approved by the institutional review board. Informed consent was obtained from all patients prior to thyroid CNB.

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

References

1. Haugen BR (2017) 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: what is new and what has changed? Cancer 123:372–381
2. Shin JH, Baek JH, Chung J, Ha EJ, Kim JH, Lee YH, Lim HK, Moon WJ, Na DG, Park JS, Choi YJ, Hahn SY, Jeon SJ, Jung SL, Kim DW, Kim EK, Kwak JY, Lee CY, Lee HJ, Lee JH, Lee JH, Lee KH, Park SW, Sung JY, Korean Society of Thyroid Radiology (KSThR) and Korean Society of Radiology (2016) Ultrasonography diagnosis and imaging-based management of thyroid nodules: revised Korean society of thyroid radiology consensus statement and recommendations. Korean J Radiol 17:370–395
3. Cibas ES, Ali SZ (2009) The bethesda system for reporting thyroid cytopathology. Am J Clin Pathol 132:658–665
4. Baloch ZW, LiVolsi VA, Asa SL, et al. (2008) Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the national cancer institute thyroid fine-needle aspiration state of the science conference. Diagn Cytopathol 36:425–437
5. Stanley MW (2009) Thyroid cytology comes to Bethesda. Am J Clin Pathol 132:655–657
6. Renshaw AA (2011) Subclassification of atypical cells of undetermined significance in direct smears of fine-needle aspirations of the thyroid: distinct patterns and associated risk of malignancy. Cancer Cytopathol 119:322–327
7. Renshaw AA (2010) Should "atypical follicular cells" in thyroid fine-needle aspirates be subclassified? Cancer Cytopathol 118:186–189
8. Nayar R, Ivanovic M (2009) The indeterminate thyroid fine-needle aspiration: experience from an academic center using terminology similar to that proposed in the 2007 national cancer institute thyroid fine needle aspiration state of the science conference. Cancer 117:195–202
9. VanderLaan PA, Marqusee E, Krane JF (2011) Usefulness of diagnostic qualifiers for thyroid fine-needle aspirations with atypia of undetermined significance. Am J Clin Pathol 136:572–577
10. Bongiovanni M, Krane JF, Cibas ES, Faquin WC (2012) The atypical thyroid fine-needle aspiration: past, present, and future. Cancer Cytopathol 120:73–86
11. Singh RS, Wang HH (2011) Eliminating the "Atypia of undetermined significance/follicular lesion of undetermined significance" category from the Bethesda system for reporting thyroid cytopathology. Am J Clin Pathol 136:896–902
12. Lim JXY, Nga ME, Chan DKH, Tan WB, Parameswaran R, Ngiam KY (2018) Subclassification of Bethesda atypical and follicular neoplasm categories according to nuclear and architectural atypia improves discrimination of thyroid malignancy risk. Thyroid 28:511–521
13. Williams MD, Suliburk JW, Staerkel GA, Busaidy NL, Clayman GL, Evans DB, Perrier ND (2009) Clinical significance of distinguishing between follicular lesion and follicular neoplasm in thyroid fine-needle aspiration biopsy. Ann Surg Oncol 16:3146–3153
14. Ustun B, Chhieng D, Van Dyke A, et al. (2014) Risk stratification in follicular neoplasm: a cytological assessment using the modified Bethesda classification. Cancer Cytopathol 122:536–545
15. Baek JH (2017) Current status of core needle biopsy of the thyroid. Ultrasonography 36:83–85
16. Jung CK, Baek JH (2017) Recent advances in core needle biopsy for thyroid nodules. Endocrinol Metab (Seoul) 32:407–412
17. Chung SR, Suh CH, Baek JH, Choi YJ, Lee JH (2018) The role of core needle biopsy in the diagnosis of initially detected thyroid nodules: a systematic review and meta-analysis. Eur Radiol 28:4909–4918
18. Lee YH, Baek JH, Jung SL, Kwak JY, Kim JH, Shin JH, Korean Society of Thyroid Radiology (KSThR), Korean Society of Radiology (2015) Ultrasound-guided fine needle aspiration of thyroid nodules: a consensus statement by the korean society of thyroid radiology. Korean J Radiol 16:391–401
19. Na DG, Kim JH, Sung JY, Baek JH, Jung KC, Lee H, Yoo H (2012) Core-needle biopsy is more useful than repeat fine-needle aspiration in thyroid nodules read as nondiagnostic or atypia of undetermined significance by the Bethesda system for reporting thyroid cytopathology. Thyroid 22:468–475
20. Jung CK, Min HS, Park HJ, Song DE, Kim JH, Park SY, Yoo H, Shin MK, Korean Endocrine Pathology Thyroid Core Needle Biopsy Study Group (2015) Pathology reporting of thyroid core needle biopsy: a proposal of the Korean endocrine pathology thyroid core needle biopsy study group. J Pathol Transl Med 49:288–299
21. Lloyd R, Osamura R, Klöppel G, Rosai J (2017) WHO classification of tumours of endocrine organs. 4th edn. Lyon: IARC
22. Nikiforov YE, Seethala RR, Tallini G, Baloch ZW, Basolo F, Thompson LDR, Barletta JA, Wenig BM, al Ghuzlan A, Kakudo K, Giordano TJ, Alves VA, Khanafshar E, Asa SL, el-Naggar AK, Gooding WE, Hodak SP, Lloyd RV, Maytal G, Mete O, Nikiforova MN, Nosé V, Papotti M, Poller DN, Sadow PM, Tischler AS, Tuttle RM, Wall KB, LiVolsi VA, Randolph GW, Ghossein RA (2016) Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. JAMA Oncol 2:1023–1029
23. Ho AS, Sarti EE, Jain KS, Wang H, Nixon IJ, Shaha AR, Shah JP, Kraus DH, Ghossein R, Fish SA, Wong RJ, Lin O, Morris LGT (2014) Malignancy rate in thyroid nodules classified as Bethesda category III (AUS/FLUS). Thyroid 24:832–839
24. Wu HH, Inman A, Cramer HM (2014) Subclassification of "atypia of undetermined significance" in thyroid fine-needle aspirates. Diagn Cytopathol 42:23–29
25. Valderrabano P, Khazai L, Thompson ZJ, Sharpe SC, Tarasova VD, Otto KJ, Hallanger-Johnson JE, Wadsworth JT, Wenig BM, Chung CH, Centeno BA, McIver B (2018) Cancer Risk Associated with Nuclear Atypia in Cytologically Indeterminate Thyroid Nodules: A Systematic Review and Meta-Analysis. Thyroid 28:210–219
26. Ahn SH, Kim SD, Jeong WJ (2017) Comparison of risk of malignancy in a subgroup with atypia of undetermined significance/follicular lesion of undetermined significance: A meta-analysis. Head Neck 39:1699–1710
27. Valderrabano P, Khazai L, Thompson ZJ, Leon ME, Otto KJ, Hallanger-Johnson JE, Wadsworth JT, Wenig BM, Chung CH, Centeno BA, McIver B (2017) Cancer Risk Stratification of Indeterminate Thyroid Nodules: A Cytological Approach. Thyroid 27:1277–1284
28. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, Paschke R, Valcavi R, Vitti P, AACE/ACE/AME Task Force on Thyroid Nodules (2016) American association of clinical endocrinologists, American college of endocrinology, and associazione medici endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid Nodules 2016 Update. Endocr Pract 22:622–639

29. Baloch ZW, Cibas ES, Clark DP, Layfield LJ, Ljung BM, Pitman MB, Abati A (2008) The national cancer institute thyroid fine needle aspiration state of the science conference: a summation. Cytojournal 5:6
30. Na DG, Baek JH, Jung SL, Kim JH, Sung JY, Kim KS, Lee JH, Shin JH, Choi YJ, Ha EJ, Lim HK, Kim SJ, Hahn SY, Lee KH, Choi YJ, Youn I, Kim YJ, Ahn HS, Ryu JH, Baek SM, Sim JS, Jung CK, Lee JH, Korean Society of Thyroid Radiology (KSThR) and Korean Society of Radiology (2017) Core needle biopsy of the thyroid: 2016 consensus statement and recommendations from Korean society of thyroid radiology. Korean J Radiol 18:217–237