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ORIGINAL ARTICLE

Utility of subcategorization of atypia of undetermined significance/follicular lesion of undetermined significance category in ultrasound-guided thyroid fine-needle aspiration in a large referral cancer center

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Introduction Subclassification of atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) is encouraged in the Bethesda System. In our practice, we subclassified AUS/FLUS into 3 subcategories: atypical follicular cells of undetermined significance (ACUS) for cases with cytologic atypia; follicular lesion (FL) for cellular cases with follicular cells with-minimal or no atypia, arranged in a macro- and micro-follicular pattern with scant colloid; and indeterminate follicular lesion, favor benign (IFL-FB) for cases with few clusters of follicular cells without atypia associated with minimal or no colloid.

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The objective of our study was to evaluate the prevalence, clinical management, and risk of malignancy for each subcategory.

Materials and methods We retrospectively identified ultrasound-guided fine-needle aspiration (US-FNA) of thyroid cases that were subcategorized as ACUS, IFL-FB, and FL at our-institution during 2014-2016. The results of US-FNA were correlated with clinical outcome in the subsequent 2 years including repeat US-FNA, thyroid surgery, and clinical/imaging follow-up.

Results Of 3207 thyroid US-FNA cases, 718 (22.4%) cases were included in the study. Of these 718 cases, 104 (14.5%) were subcategorized as ACUS, 166 (23.1%) as FL, and 448 (62.4%) as IFL-FB. The surgery rate was 39.4% (41 of 104) for ACUS, 13.6% (61 of 448) for IFL-FB, and 27.1% (45 of 166) for FL. The risk of malignancy (ROM) was 25% (26 of 104) for ACUS, and 2.9% (13 of 448) for IFL-FB, 6.0% (10 of 166) for FL. The surgery rate and ROM was significantly higher for ACUS in comparison to IFL-FB ($P < 0.05$) and FL ($P < 0.05$).

Conclusions Subclassification of AUS/FLUS into 3 groups based on cytopathologic findings alone not only improved the triage of patients for subsequent clinical management but also effectively stratified the risk of malignancy.

Introduction

In the initial evaluation of patients with thyroid nodules, fine-needle aspiration (FNA) is commonly used to guide clinical management.[1,2] In a large proportion of patients, the cytomorphologic features of the thyroid aspirates allow classification of the findings into either benign or malignant, which aids in the selection of appropriate treatment strategy. In some patients, however, definitive categorization is not possible, and this results in an indeterminate cytologic diagnosis, creating a dilemma for the clinical management team.[3-5] The subjectivity of interpreting thyroid FNAs can influence the categorization of the findings and can be a challenge.[6] The variability in reporting thyroid FNA specimens has been largely overcome by the introduction of the Bethesda System of Reporting Thyroid Cytology (TBSRTC).[4,5] This system was introduced to standardize the terminology of reporting thyroid cytology so as to facilitate communication between pathologists, endocrinologists, and surgeons. The goal was to enable pathologists to communicate the interpretations to the referring physicians in terms that are succinct, unambiguous, and clinically useful. The initial TBSRTC was recently revised in 2017 with the availability of new data and developments in the field of thyroid malignancies. These included revised guidelines for the management of patients with thyroid nodules, molecular testing as adjunct to cytomorphologic examination and the reclassification of the noninvasive follicular variant of papillary thyroid carcinoma (PTC) as noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP).[4,7-10] Thyroid FNAs are categorized in TBSRTC into 6 diagnostic categories. These categories include nondiagnostic, benign, atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS), follicular neoplasm or suspicious for a follicular neoplasm, suspicious for malignancy, and malignant.[4,5]

The AUS/FLUS category in the TBSRTC remains the most challenging one in clinical practice with significant implications regarding clinical management.[6,11-14] The revised 2017 TBSRTC recommends subclassification of the AUS/FLUS using descriptive language including "cytologic atypia" and "architectural atypia".[4] AUS and FLUS are regarded as synonymous in the TBSRTC and using 2 terms independently to denote 2 distinct interpretations is discouraged. Nevertheless, a few recent reports indicate the value of separating AUS and FLUS categories, as cytologic atypia is associated with a higher risk of malignancy in comparison with architectural atypia, with a lower risk of malignancy.[11,13-16]

In our practice, we perform rapid onsite evaluation of ultrasound-guided FNA (US-FNA) specimens and request additional passes when needed in cases of suboptimal quality of the specimens. Unlike the recommendation of TBSRTC to regard AUS and FLUS as synonymous entities, we have divided the AUS/FLUS category into 3 subcategories that have proven to be useful in our practice to facilitate clinical management of patients. These subcategories include atypical follicular cells of undetermined significance (ACUS); indeterminate follicular lesion, favor benign (IFL-FB); and follicular lesion (FL). The ACUS subcategory included specimens exhibiting cytologic atypia including some but not all of the features that were worrisome for PTC. The IFL-FB subcategory included specimens that demonstrated sparse thyroid follicular cells including 6 clusters with 10 cells each without atypia and associated with scant or no colloid, and with sonographic findings that could be consistent with a colloid nodule. The FL subcategory included cellular specimens with greater cellularity than IFL-FB, comprising thyroid follicular cells with minimal or no nuclear atypia arranged in a macro- and micro-follicular pattern with scant or no colloid. Therefore, these cases cannot be accurately and definitely placed in either the benign or neoplastic category. The subclassification of AUS/FLUS category therefore differed from TBCRTC. We relied on cytomorphologic features alone for the management of AUS/FLUS category without utilizing ancillary molecular testing in our practice. The primary objective of the study was to estimate the prevalence and risk of malignancy in the 3 subcategories of AUS/FLUS—namely ACUS, IFL-FB, and FL—and to elucidate the utility of this modification of the TBSTRC for clinical management.

Methods

This study was approved by the institutional review board of The University of Texas MD Anderson Cancer Center in Houston, Texas. We retrospectively reviewed our pathology electronic medical record system to identify all cases of US-FNA of the thyroid performed by radiologists specialized in head and neck sonography at The University of Texas MD Anderson Cancer Center from January 1, 2014 through December 31, 2016. In accordance with American Thyroid Association guidelines, US-FNA was performed on thyroid nodules that were equal to or greater than 1 cm in size with suspicious sonographic findings.

The thyroid FNA procedure was performed using a 20- to 25-gauge needle attached to a 20-mL syringe. The needle was inserted under ultrasound guidance and sonographically confirmed within the targeted nodule while aspiration was performed. The aspirated material was smeared on glass slides, which were air-dried for Diff-Quik staining and fixed in carnoys solution for Papanicolaou staining. The needle was rinsed in Roswell Park Memorial Institute medium that was then centrifuged. Depending on the size of the cell pellet, either a cytospin smear or a cell block preparation was made to generate formalin-fixed and paraffin-embedded tissue blocks. The adequacy of thyroid US-FNA was evaluated immediately by cytopathologists and the preliminary findings were communicated to the radiologist on site. Final results of thyroid cytology were reported according to the modified TBSRTC including our 3 AUS/FLUS subcategories, namely, ACUS, IFL-FB, and FL. The ACUS subcategory included cases exhibiting cytologic atypia with some but not all the features such as nuclear enlargement with fine nuclear chromatin/nuclear grooves/intranuclear pseudoinclusion that were worrisome for PTC; IFL-FB included cases with sparse cellularity barely sufficient for diagnosis including 6 groups with 10 cells each associated with scant or no colloid; the FL group included cellular specimens that had greater cellularity than IFL-FB, comprising thyroid follicular cells with minimal or no nuclear atypia arranged in a macro- and micro-follicular pattern with scant or no colloid in the background, and that could not be accurately and definitely placed in either the benign or neoplastic category.

The results of thyroid US-FNA were correlated with outcome in the 2 years following the initial diagnosis. For patients with ACUS, IFL-FB, and FL, we noted whether follow-up consisted of repeat US-FNA, surgical excision (thyroid lobectomy or total thyroidectomy), or clinical and imaging work-up alone. The findings on repeat US-FNA or surgical excision were grouped for the purpose of correlation as 1) benign, including follicular adenoma, hyperplastic nodule, colloid/nodular goiter, and thyroiditis; 2) indeterminate, including ACUS, follicular neoplasm for FNA as well as follicular tumor of uncertain malignant potential after surgical resection because these lesions are encapsulated or well-circumscribed tumor with no nuclear features of papillary thyroid carcinoma and with questionable capsular or vascular invasion[17]; 3) malignant, including PTC, follicular carcinoma, medullary carcinoma, and anaplastic carcinoma. Tumors that would qualify to be designated as NIFTP were included in the malignant category because this entity was described subsequent to the time period of patient accrual in our study.

Statistics

We determined the total number of US-FNA cases that were categorized as AUS/FLUS in the time period of the study and also the number of patients in each of the 3 subcategories of this group including ACUS, IFL-FB, and FL to establish the prevalence of AUS/FLUS group as a whole as well as the individual subcategories in the study. The risk of malignancy was calculated for AUS/FLUS as a whole group and for the individual subcategories in 2 ways: by dividing the number of patients proven to have thyroid malignancy after thyroid surgery by 1) the total number of patients in each subcategory irrespective of follow-up, and 2) the number of patients selected for thyroid surgery. We used χ^2 test- for comparison of risk of malignancy and rate of thyroid surgery between the 3 different subcategories of AUS/FLUS. A value of $P < 0.05$ was considered statistically significant.

Results

Our search of pathology files revealed 3207 thyroid US-FNA cases performed at our institution during 2014-2016. Of these 3207 cases, 737 (22.9%) had FNA findings categorized as AUS/FLUS, including 110 patients (3.4%) patients with findings subcategorized as ACUS, 452 (14%) with findings subcategorized as IFL-FB, and 175 (5.5%) with findings subcategorized as FL. In order to accurately evaluate the follow-up procedures for each subcategory, cases with a concurrent FNA diagnosis of malignancy in another nodule were excluded for further analysis. Thus, there were a total of 718 cases of AUS/FLUS including 104 (14.5%) cases of ACUS, 448 (62.4%) cases of IFL-FB, and 166 (23.1%) cases of FL that were included in the final analysis. Representative cases of these 3 subcategories are illustrated in Figs. 1 and 2 (Fig. 1A, C for ACUS, Fig. 1B, D for IFL-FB, and Fig. 2 for FL).

The proportion of patients selected for repeat US-FNA or thyroid surgery and the final diagnosis after surgery differed by the subcategories of AUS/FLUS. Of the 104 patients in the ACUS subcategory, 10 (9.6%) patients underwent repeat US-FNA and 41 (39.5%) patients underwent surgery (lobectomy in 19 [46.3%, 19 of 41] and total thyroidectomy in 22 [53.6%, 22 of 41]). Therefore a total of 51 (49.0%) patients underwent repeat US-FNA or thyroid surgery in our institution. The final diagnoses of the thyroid nodules after repeat US-FNA or surgery were benign in 22 (21.1%)

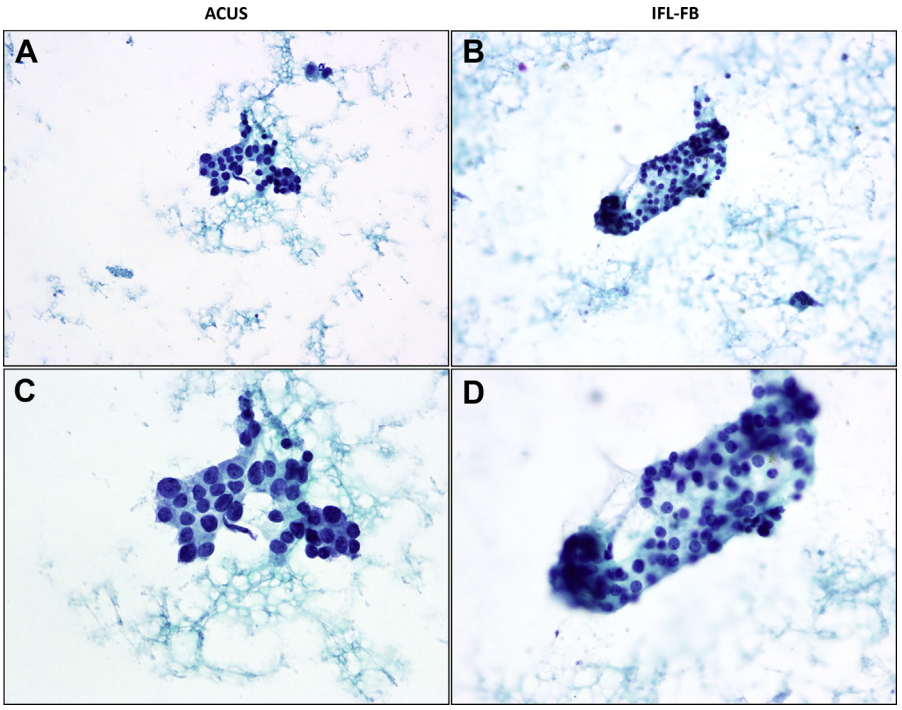

Figure 1 Fine-needle aspiration cytology of atypical follicular cells of undetermined significance (ACUS) (A and C) and indeterminate follicular lesion, favor benign (IFL-FB) (B and D). A and C, One cluster of follicular cells (A, Papanicolaou, ×200) showing cytologic atypia including nuclear enlargement, mild nuclear irregularity, slight chromatin pallor, rare nuclear grooves, and without nuclear pseudoinclusions (C, Papanicolaou, ×400). The nodule on surgical resection was diagnosed as conventional papillary thyroid carcinoma. B and D, Rare clusters of follicular cells with a macro-follicular pattern (B, Papanicolaou, ×200) and without cytologic atypia (D, Papanicolaou, ×400). The thyroid on surgical resection was diagnosed as multinodular goiter.

patients, malignant in 25 (24.0%) patients, and indeterminate which was ACUS in 3 (2.9%) patients (Table 1 and Fig. 3). The risk of malignancy for the subcategory of ACUS patients who were selected for surgery was 58.5% (24 of 41) and for the entire ACUS subcategory irrespective of follow-up was 24.0% (25 of 104).

Of the 448 patients with a diagnosis of IFL-FB, 3 (<1%) underwent repeat FNA and 61 (13.6%) underwent surgery (lobectomy in 49 [80.3%, 49 of 61] and total thyroidectomy in 12 [19.7%, 12 of 61]), for a total of 64 patients (14.3%) who underwent repeat FNA or thyroid surgery. Most of the patients in the IFL-FB group (384; 85.7%) did not undergo repeat US-FNA or surgery (Table 1 and Fig. 3). The final diagnosis of the IFL-FL thyroid nodule after repeat FNA or surgery was benign in 46 (10.3%) patients, malignant in 13 (2.9%), and indeterminate in 5 (1.1%) (Fig. 4). The risk of malignancy was 21.3% (13 of 61) for the patients selected for surgery and 2.9% (13 of 448) for all patients in the IFL-FB subcategory (Fig. 5).

Of the 166 patients in the FL category, 1 (<1%) underwent repeat FNA and 45 (27.1%) underwent thyroid surgery (lobectomy in 43 [95.5%, 43 of 45] and total thyroidectomy in 2 [4.5%, 2 of 45]), for a total of 46 patients (27.7%) who underwent repeat US-FNA or thyroid surgery (Table 1 and Fig. 3). The final diagnosis of the FL thyroid nodule after repeat US-FNA or surgery was benign in 31 patients (18.7%), malignant in 10 (6.0%), and indeterminate in 5 patients (3.0%). The risk of malignancy was 22.2% (10 of 45) for the patients selected for surgery and 6.0% (10 of 166) for all patients in the FL subcategory.

Overall, a total of 147 out of 718 (20.5%) patients in this AUS/FLUS group underwent thyroid surgeries and the risk of malignancy including all patients irrespective of follow-up was 6.7% and including only those that went for surgery was 32% (Fig. 5). The selection of patients for thyroid surgery varied between the 3 subcategories. Patients subcategorized as ACUS were more often selected for surgery than those subcategorized as IFL-FB ($P < 0.05$) or FL ($P < 0.05$). Moreover, patients from the FL subgroup were selected for surgery more than those in IFL-FB subgroup ($P < 0.05$). The type of thyroid surgery that was performed was also different for the subcategories. Patients in the ACUS subcategory underwent lobectomy in 46.3% (19 of 41) and total thyroidectomy in 53.6% (22 of 41) patients. On the other hand, in subcategories of IFL-FB and FL, 80.3% (49 of 61) and 95.5% (43 of 45) were selected for lobectomy, compared with 19.7% (12 of 61) and 4.5% (2 of 45) who were selected for total thyroidectomy, respectively. The risk of malignancy was also different for the 3 subcategories. The risk of malignancy was highest for the ACUS subcategory, which was significantly higher than either IFL-FB ($P < 0.05$) or FL ($P < 0.05$) subcategories

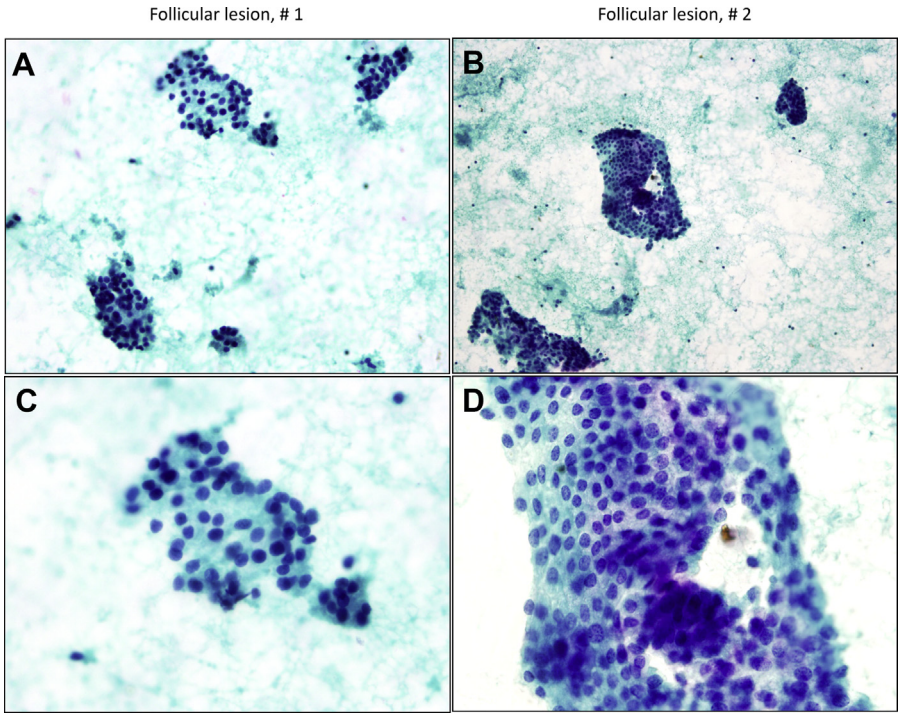

Figure 2 Fine-needle aspiration cytology of 2 examples of follicular lesion. A and C, Cluster of follicular cells arranged in predominantly in a macrofollicular pattern (A, Papanicolaou, ×200) without cytologic atypia (C, Papanicolaou, ×400). The nodule was diagnosed as follicular adenoma on surgical resection. B and D, Cluster of follicular cells arranged in predominantly in a macrofollicular pattern (B, Papanicolaou, ×200) and with no to minimal cytologic atypia (D, Papanicolaou, ×400). The nodule on surgical resection was diagnosed as papillary thyroid carcinoma, follicular variant.

either calculated taking all the patients in each group irrespective of follow-up or only those patients who underwent thyroid surgery (Fig. 5). The risk of malignancy between IFL-FB and FL was not statistically different ($P = 0.07$ for calculation based on all patients in the group, and $P = 0.92$ for calculation based on patients underwent surgery). The details of the type of follow-up and outcome following surgery are depicted in Table 1.

Discussion

The introduction of the TBSRTC not only has standardized the reporting of thyroid cytology but also has provided the opportunity for comparison of prevalence and risk of malignancy for the different categories across different practices. The prevalence of 22.9% for the AUS/FLUS category in our study is much higher than the recommended prevalence of

Table 1 Follow-up methods and final diagnoses in patients with AUS/FLUS findings on thyroid US-FNA by subcategory.

Follow-up method or diagnosis	ACUS (n = 104)	IFL-FB (n = 448)	FL (n = 166)
Follow-up method, n (%)			
Repeat FNA	10 (9.6)	3 (<1)	1 (<1)
Thyroid surgery	41 (39.4)	61 (13.6)	45 (27.1)
Lobectomy	19 (46.3)	49 (80.3)	43 (95.5)
Total thyroidectomy	22 (53.6)	12 (19.7)	2 (4.5)
Clinical/radiological only	53 (51.0)	384 (85.7)	120 (72.3)
Final diagnosis after repeat FNA, n (%)			
Benign	6 (5.7)	1 (<1)	0 (0)
Indeterminate	3 (2.9)	2 (<1)	1 (<1)
Malignant	1 (<1)	0 (0)	0 (0)
Final diagnosis after thyroid surgery, n (%)			
Benign	16 (15.4)	45 (10.0)	31 (18.7)
Indeterminate	0 (0)	3 (<1)	4 (2.4)
Malignant	25 (24.0)	13 (2.9)	10 (6.0)

Abbreviations: ACUS, atypical cells of undetermined significance; AUS/FLUS, atypia of undetermined significance or follicular lesion of undetermined significance; FL, follicular lesion; IFL-FB, indeterminate follicular lesion, favor benign; US-FNA, ultrasound-guided fine-needle aspiration.

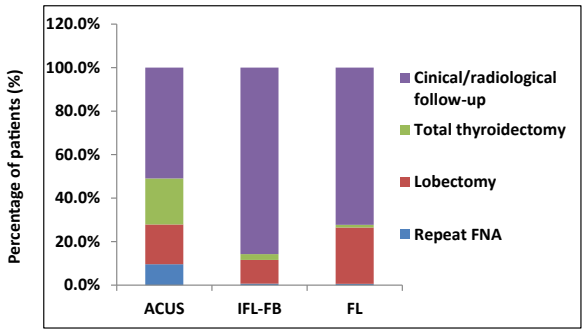

Figure 3 Methods of follow-up by subcategory of AUS/FLUS. ACUS, atypical cells of undetermined significance; IFL-FB, indeterminate follicular lesion, favor benign; FL, follicular lesion; FNA, fine-needle aspiration.

less than 7% in TBSRTC.[4] The referral nature of our practice was most likely the cause of the significantly higher prevalence of AUS/FLUS category in our study. The subjectivity of recognizing atypia in thyroid FNAs together with the availability of less-than-desired cellularity of the aspirated material in many of these cases can be major impediments to render a definite diagnosis in any practice. Therefore, although the TBSRTC recommends that the AUS/FLUS category be used as the last resort and recommends that less than 7% be categorized in this group, there has been significant variability in the rates of AUS/FLUS among institutions.[6,11-16,18]

The heterogeneity of the findings in the category of AUS/FLUS including cases with either cytologic atypia or architectural atypia with different outcomes formed the basis of subcategorization of the group into ACUS including cases with cytologic atypia, IFL-FB with features falling short of categorization into clearly benign category, and FL with increased cellularity showing thyroid follicular cells with minimal or no nuclear atypia arranged in a macro- and microfollicular pattern with scant or no colloid. The selection of the patients for thyroid surgery varied significantly between the ACUS, IFL-FB, and FL subgroups. The former patients were more often selected for surgery in comparison to the other 2 groups: 39.4% of patients with ACUS were selected for surgery, compared with only 13.6% of those with IFL-FB and 27.1% of those with FL. The diagnosis of IFL-FB was useful to the clinical management team to most often follow the patient without surgery. It is to be noted that only 13.6% of patients with a diagnosis of IFL-FB were selected for surgery based on clinical, sonographic finding, and multidisciplinary consensus decisions. In addition, the subcategorization of AUS/FLUS into 3 subgroups also influenced the extent of surgery. Whereas patients in the ACUS subgroup underwent thyroid lobectomy and total thyroidectomy in nearly equal numbers, those in IFL-FB and FL subgroups had thyroid lobectomies performed more often than total thyroidectomies.

The subcategorization of AUS/FLUS into the 3 subcategories was also useful in highlighting the variable risks of malignancy of the subgroups. The risk of malignancy of the ACUS subgroup was significantly higher than the IFL-FB and FL subgroups; 61% versus 22.2% and 21.3%, respectively. The overall risk of malignancy for the entire group of AUS/FLUS in our series including the entire group irrespective of follow-up as well as including only those patients who underwent thyroid surgery was 6.7% and 32%, which is at the higher end of the implied risk of malignancy in TBSRTC. A higher risk of malignancy in patients presenting to a comprehensive cancer center has been reported previously by Ho et al.[12] They showed that the malignancy rate in thyroid nodules with AUS/FLUS cytology in their practice in a large referral cancer center was 26.6% to 37.8%, which is very similar to our findings. Given that the AUS/FLUS

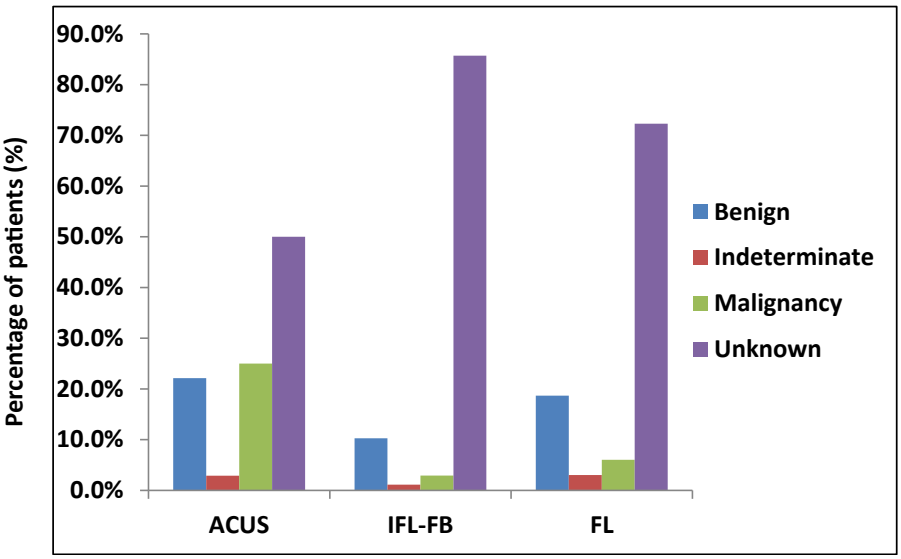

Figure 4 Final diagnoses in each subcategory after repeat US-FNA or thyroid surgery for patients with AUS/FLUS. ACUS, atypical cells of undetermined significance; IFL-FB, indeterminate follicular lesion, favor benign; FL, follicular lesion; FNA, fine-needle aspiration.

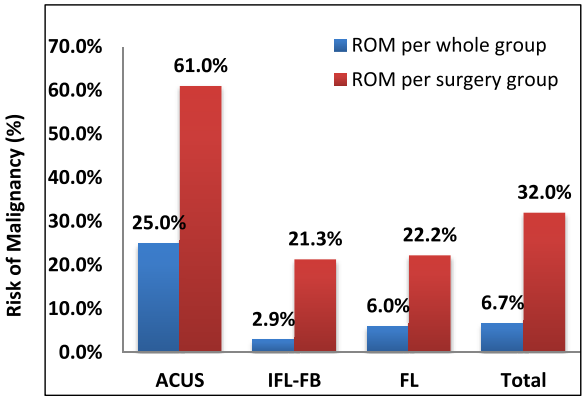

Figure 5 Risk of malignancy (ROM) by subcategory calculated by dividing the number of patients with thyroid malignancy proven following thyroid surgery by (1) the total number of patients in each subcategory (ROM per whole group) and (2) the number of patients selected for surgery (ROM per surgery group). The ROM of ACUS was significantly higher than IFL-FB ($P < 0.05$) and FL ($P < 0.05$). ACUS, atypical cells of undetermined significance; IFL-FB, indeterminate follicular lesion, favor benign; FL, follicular lesion.

category in the TBSRTC is heterogeneous, it is not surprising that the reported rates of malignancy among patients with AUS/FLUS selected for surgery have varied from 6% to 48% in different reports.[4]

Several investigators have previously reported that subcategorizing AUS/FLUS cases has value given that AUS/FLUS with evidence of nuclear atypia is associated with a higher risk of malignancy than AUS/FLUS without nuclear atypia.[11,13-15,18] A recent prospective study showed that among thyroid nodules in the AUS/FLUS category, those exhibiting nuclear atypia had a significantly greater risk of malignancy than those exhibiting architectural atypia; the study also suggested that a second FNA is more likely to result in a final diagnosis of benign lesion in the architectural atypia group than in the nuclear atypia group.[16] Rosario reported that the presence of nuclear atypia and suspicious ultrasound findings could have an 87% prevalence of cancer in thyroid nodules with an AUS diagnosis.[18] Our finding of the higher risk of malignancy in the ACUS subgroup with nuclear atypia is similar to previous reports providing further evidence in support of subcategorization of AUS/FLUS cases. It is to be noted that our strategy of stratifying indeterminate follicular lesions with increased probability of the nodule to be a colloid nodule in the subgroup of IFL-FB has not been reported before. The risk of malignancy in our study for the entire IFL-FB group of 448 patients was only 2.9%. In contrast, the risk of malignancy in the subset of IFL-FB patients selected for surgery was 21.3%, which was similar to the risk of malignancy in the subset of FL and significantly lower than the ACUS subgroup.

In essence, our study provides evidence in support of subcategorization of the AUS/FLUS category in TBSRTC. The ACUS subgroup was selected significantly more often for surgery and also demonstrated significantly higher risk of malignancy in comparison with the other 2 subgroups. The IFL-FB subgroup was more often followed without surgery than any of the other subgroups. The risk of malignancy of IFL-FB and FL was similar and significantly lower than the ACUS subgroup. The subcategorization of AUS/FLUS cases based on cytomorphologic features alone was extremely useful for the clinical management -in our practice in a large referral cancer center with the availability of specialized head and neck sonographers and immediate evaluation of thyroid aspirates.[19-24]

In conclusion, our results provide evidence that subcategorizing AUS/FLUS in TBSRTC can have significant implications for clinical practice. It is possible that the risk of malignancy in the subgroups could be improved further by selecting these patients for additional molecular testing using currently available molecular testing platforms. Nevertheless, our results based on cytomorphologic examination alone clearly demonstrate that our 3 subcategories of AUS/FLUS have significant clinical implications with respect to selection for surgery and determining the ultimate probability of malignancy after surgery.

Disclosure/Conflict of interest

All authors declare no conflicts of interest.

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Author contributions

Qiong Gan: Conceptualization, data analysis, original draft and writing, reviewing and editing. Beth S Edeiken, Melissa M Chen, Elizabeth G Grubbs, Naifa L Busaidy, Mark Zafereo, Nancy D Perrier, Maria D Gule-Monroe: reviewing and editing. Savitri Krishnamurthy: Project administration, conceptualization, supervision, reviewing, editing, and writing.

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