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Manuscript Title: Both ultrasound features and nuclear atypia are associated with malignancy in thyroid nodules with atypia of undetermined significance

Running title: AUS subtype and ultrasound

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Synopsis

The optimal management of patients with thyroid nodules with atypia of undetermined significance is ill-defined. We found that nodules with nuclear atypia and high-risk ultrasound features are more likely to be a thyroid carcinoma.

ABSTRACT:

Background: The optimal management of thyroid nodules that undergo fine-needle aspiration (FNA) with findings of atypia of undetermined significance (AUS) is unclear. Categorizing nodules by AUS subtype and ultrasound characteristics may improve risk stratification. Therefore, the purpose of this study is to evaluate the association between AUS subtype and ultrasound features on risk of malignancy (ROM).

Methods: We performed a review of all patients with a thyroid nodule who underwent an FNA at our institution between January 2010 and November 2015. Patients with AUS were divided into groups with 1) nuclear atypia, 2) architectural atypia, or 3) Hurthle cell atypia. Their ultrasound features were assessed using the American Thyroid Association (ATA) thyroid nodule sonographic patterns. We conducted a univariate and multivariable analysis to determine the association between AUS subtype and other variables of interest with ROM.

Results: 237 (6.9%) of the 3428 thyroid nodules that underwent FNA had AUS. Of the 97 surgically resected nodules, 67 (69%) were benign and 30 (31%) were malignant. On univariate analysis nuclear atypia ($p<0.01$) was associated with a thyroid malignancy. On multivariable analysis both ATA high-risk ultrasound features (p=0.04, OR=3.68) and nuclear atypia (p<0.01,

OR=11.8) were independently associated with a final diagnosis of thyroid carcinoma.

Conclusions:

Nuclear atypia and ATA high-risk ultrasound features are useful in identifying patients with AUS that are at a higher risk of thyroid malignancy. Surgeons should take these factors into consideration when evaluating patients with AUS.

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Introduction

Thyroid nodules are very common, occurring in up to 70% of women and 40% of men [1]. The majority of thyroid nodules are benign, but approximately 7 to 15% are malignant [2]. The cornerstone to evaluation of many thyroid nodules is a sonographic assessment followed by fine-needle aspiration (FNA) [2]. To standardize cytology reporting, the American Thyroid Association (ATA) and the National Cancer Institute recommend that FNA aspirates be evaluated according to the guidelines set forth by the Bethesda System for Reporting Thyroid Cytopathology (BSRTC), which uses six diagnostic categories to stratify the risk of malignancy (ROM) [3]. BSRTC category III, atypia of undetermined significance (AUS), is a heterogeneous category in which cytology cannot be categorized as benign, suspicious, or malignant [3]. Although the intended ROM for nodules designated as AUS is between 5 and 15%, several studies have suggested that the malignancy rate may be higher [4].

The optimal management of patients with AUS is ill-defined with recommendations including continued observation with ultrasound, molecular studies, repeat FNA, or thyroidectomy [2, 5]. In the 2017 update to the BSRTC, Cibas et al recommend subclassification of thyroid nodules with AUS to better stratify the ROM [6]. Previous studies have found that subclassifying AUS may improve risk stratification by dividing AUS into

categories with 1) nuclear atypia, 2) architectural atypia, and 3) Hurthle cell atypia [7, 8].

Ultrasound characteristics have also been shown to be helpful in stratifying the ROM in nodules with AUS [9]. Some authors have advocated that ultrasound characteristics can be used to select patients with AUS who would benefit from thyroid surgery [10, 11]. The relationship between AUS subtype and ultrasound characteristics has not been well studied. Furthermore, prior reports have not well evaluated the role of AUS subclassification in determining the utility of repeat FNA, which is a common practice following an initial FNA that demonstrates AUS. The purpose of this study is to 1) evaluate the association between AUS subtype and the ROM, 2) assess the relationship between AUS subtype and ultrasound characteristics on the ROM, and 3) determine the association of AUS subtype and the outcomes of repeat FNA.

Methods

The institutional review board at the University of California, Davis (Sacramento, CA) approved a retrospective review of all patients who had an FNA between January 2010 and November 2015. Patients were identified from our Pathology Laboratory Information System. Each patient's electronic medical record was reviewed, and information on preoperative symptoms, physical exam, radiologic imaging, intraoperative findings, final cytology,

and surgical diagnoses were recorded. Our inclusion criteria were all patients > 18 years of age with thyroid cytology interpreted by our cytopathologists during our study period. We excluded vulnerable patient populations such as employees, prisoners, and cognitively impaired adults.

Preoperative cytology was categorized according to the BSRTC [3]. At our institution it is common practice for the cytopathologist reviewing the slides to document the reason for classifying a nodule as AUS. The cytology reports were reviewed and categorized into three subcategories: 1) AUS with nuclear atypia, 2) AUS with architectural atypia, and 3) AUS with Hurthle cell atypia. Nuclear atypia was defined as cytology with focal nuclear features of papillary thyroid carcinoma (PTC) in an otherwise benign appearing sample or aspirates with extensive, mild nuclear features of PTC. Architectural atypia was defined as those aspirates that showed a microfollicular pattern, not sufficient to be diagnosed as a follicular neoplasm. Hurthle cell atypia was defined as those aspirates with a predominance of Hurthle cells in a sparsely cellular aspirate or those with Hurthle cell atypia in a background of lymphocytes to suggest underlying thyroiditis. If the cytologic description did not fit into these three categories or if the cytology report did not contain adequate information to characterize the type of cytology the patient was excluded.

To determine the role of subclassification on the utility of repeat FNA the initial subclassification category was compared to the FNA results of the same nodule. To evaluate the influence of AUS subclassification on ROM, the location and size of the nodule described in the initial FNA procedure note was correlated and matched with the thyroidectomy specimen. Multifocal papillary thyroid carcinomas on surgical pathology were treated as independent tumors for the statistical analysis.

Ultrasound images were retrospectively reviewed by two authors (GF and MJC), and the nodule that underwent FNA was classified according to the risk categories put forth in the 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer [2]. The ultrasound features of the nodules of interest were divided into two groups: 1) those meeting the criteria for an ATA high suspicion for malignancy nodule and 2) those not meeting the criteria for an ATA high suspicion for malignancy (i.e. all other nodules). Nodules meeting the criteria for “high suspicion for malignancy” (ATA high-risk) were included in the univariate and multivariable analysis. Our hypothesis was that nuclear atypia on FNA cytology and ATA high-risk ultrasound features would be independently associated with malignancy on surgical pathology.

Statistical Analysis

All statistical analysis was conducted using IBM SPSS Statistics 25 (Ithaca, NY). Continuous data were reported as mean and were analyzed using the ANOVA or students t-test. The Fisher Exact test was used for categorical data. A multivariable logistic regression model was developed for the finding of ROM on final pathology including variables of interest. Odds ratios (ORs) with 95% confidence intervals (CIs) are presented.

Results

Of the 3428 nodules that underwent FNA during our study period, 237 (6.9%) nodules had AUS. We identified 188 patients with 195 thyroid nodules that met our inclusion criteria. The mean patient age was 56.2 years and 83% were women. The mean nodule size was 2.4 cm. There was no difference in the baseline patient characteristics among the AUS subtypes (Table 1).

Sixty-nine patients with 69 nodules underwent a repeat FNA. Nine patients (13%) had nuclear atypia, 38 (55%) patients had architectural atypia, and 22 (32%) patients had Hurthle cell atypia on their initial FNA. On repeat FNA, twenty-seven (39%) nodules were benign, 37 (54%) had indeterminate cytology and 5 (7%) had insufficient cytology to make a diagnosis. There was no association among the AUS subtypes and the results of the second FNA (p=0.67 – Table 2).

Ninety-four patients with 97 nodules underwent a thyroidectomy. Nineteen patients (20%) had nuclear atypia, 41 (42%) patients had architectural atypia, and 37 (38%) patients had Hurthle cell atypia. Sixty-seven (69%) nodules were benign on surgical pathology and 30 (31%) were malignant. There was a statistical association between AUS subtype and ROM ($p<0.01$ – Table 3).

Among the malignant nodules, 12 were classic PTC, 2 were follicular carcinoma (FTC) and 16 were follicular variant of PTC (FVPTC). Among the nodules with nuclear atypia, 8 were classic PTC and 6 were FVPTC. In the nodules with architectural atypia, 1 was classic PTC, 2 were FTC and 6 were FVPTC. Among the patients with Hurthle cell atypia, 3 were classic PTC and 4 were FVPTC. AUS subtype on the initial FNA was not associated with type of carcinoma found on surgical pathology ($p=0.10$).

Among the patients that underwent a thyroidectomy, 20 nodules had an ATA high suspicion sonographic pattern, 35 had an intermediate suspicion sonographic pattern, 33 had a low suspicion sonographic pattern, two had a very low suspicion sonographic pattern, and 7 nodules did not have ultrasound images that could be reviewed. The malignancy rate for the ATA high suspicion sonographic pattern nodules was 10/20 (50%). The malignancy rate for the nodules with an intermediate suspicion sonographic

pattern was 15/35 (43%). The malignancy rate for nodules with a low suspicion sonographic pattern was 5/33 (15%).

On univariate analysis, only nuclear atypia ($p<0.01$) was associated with a thyroid malignancy (Table 4). Age ($p=0.48$), gender ($p=1.0$), nodule size ($p=0.76$), family history of thyroid malignancy ($p=1.0$), ATA high-risk ultrasound features ($p=0.11$), architectural atypia ($p=0.12$), and Hurthle cell atypia ($p=0.07$) were not associated with thyroid malignancy on surgical pathology. On multivariable analysis both ATA high-risk ultrasound features ($p=0.04$, OR=3.68) and nuclear atypia ($p<0.01$, OR=11.8) were independently associated with a final diagnosis of thyroid carcinoma. Conversely, age ($p=0.98$, OR = 0.93 – 1.02), gender ($p=0.68$, OR= 0.15 – 2.9, nodule size ($p= 0.99$, OR = 0.71 – 1.4), and family history of thyroid cancer ($p= 0.42$, OR = 0.081 – 2.9) were not associated with a final diagnosis of thyroid carcinoma (Table 5).

Discussion

The BSRTC is the cornerstone of interpreting thyroid cytopathology. BSRTC category III, AUS, is a heterogeneous category with differing rates of malignancy across different institutions [4]. The optimal management of these patients is ill-defined with options including observation with ultrasound, molecular studies, repeat FNA, or thyroidectomy [2, 5]. In this study we found a high overall ROM in patients with AUS and that patients

with nuclear atypia and ATA high-risk ultrasound features are at increased risk of having a thyroid malignancy. AUS subtype was not associated with the outcomes of repeat FNA.

In our study group, 6.9% of thyroid nodules undergoing FNA over the 5-year study period had AUS, which is consistent with the recommendations of <7% set by the BSRTC [3]. Our overall ROM was 31%, which is higher than the 5 – 15% recommended by the BSRTC, but is within the range of 6 - 48% described in previous studies [4]. Our higher than expected ROM is likely because it was calculated from patients that underwent a thyroidectomy. This leads to a selection bias of higher-risk patients. Our calculated ROM, if we assume that all patients who did not undergo a thyroidectomy had benign nodules, is 15%. This is similar to the ROM suggested by the BRSTC, but likely underestimates the true ROM as a number of patients in our study were lost to follow-up after a short period of observation. The true ROM for our patients with AUS likely is between 15% and 31%.

We found that among patients with nuclear atypia the ROM was 74%, which was significantly greater than patients with other AUS subtypes. On multivariable analysis, nuclear atypia was independently associated with a final diagnosis of thyroid carcinoma. Our findings support those previously reported by other groups that have found that nuclear atypia (sometimes referred to as cytologic atypia or AUS cannot rule out PTC) has an increased

ROM ranging from 28% to 66% [7, 8, 12-17]. This is likely because of the similarities between AUS with nuclear atypia and BSRTC category V "suspicious for malignancy" which has a ROM of 45 – 75% [6]. The distinction between these categories can be challenging [18]. Conversely, in specimens with AUS with architectural atypia or Hurthle cell atypia subtypes the cytopathologist is often trying to make a distinction between a benign sample, i.e. hyperplastic changes, and a follicular neoplasm or Hurthle cell neoplasm, which have a lower ROM [6].

We found that thyroid nodules with ATA high-risk ultrasound characteristics were not associated with malignancy on univarate, but were associated with malignancy on multivariable analysis. Although it is uncommon for a variable to be not significant on univariant analysis and become significant on multivariable analysis, we feel this is likely because on the multivariable analysis we were able to control for other potentially confounding factors. This can happen when the additional variables explain some of the variability in the data enough for the relationship with the primary predictor to be clearer**.** It has been previously established that ultrasound is a powerful tool for evaluating indeterminate thyroid nodules [19-23], but we hypothesized that ultrasound characteristics may not be independently associated with ROM when considering AUS subtype. We suspected that the findings integrated into the ATA high-suspicion category, such as taller-than-wide shape, spiculated margin, marked hypoechogenicity, and microcalcification,

would be sonographic markers of the features seen with nuclear atypia [24]. To the contrary, our findings suggest that clinicians can use both AUS subtype and ultrasound features to help them decide whether a patient should be considered for a thyroidectomy.

Our overall ROM for nodules with ATA high-risk characteristics was lower than expected [2]. This is likely because of variability in interpreting the ATA high-risk sonographic patterns. It has been previously shown that sonographic features such as echogenicity, microcalcification, margin and capsular invasion have a moderate amount of intra-observer variability [25]. We tried to mitigate this weakness by having two experienced clinicians review the ultrasound images, including a board-certified radiologist with five years of experience, and reach consensus. Our ROM may also be influenced by the wide variety of sonographic patterns we see as part of our thyroid practice and the retrospective nature in which they were reviewed.

Our findings support those previously reported by Rosario who found that both high-suspicion ultrasound characteristics and nuclear atypia where independently associated with an increased risk of malignancy [21]. Lee et al found that nodules with nuclear atypia and ATA high-risk ultrasound features were more likely to be malignant. However, they did not find the same risk for patients with architectural atypia. This may be due to their small number of patients with architectural atypia [10].

Some authors have recommended repeat FNA for nodules with AUS [2, 5, 6]. Patients with a second benign FNA can be observed while those with repeat indeterminate or malignant results are usually offered a thyroidectomy. Similar to previous studies we found that 54% of our patients who underwent a repeat FNA had a second indeterminate result [17, 26]. There was no association between AUS subtype and the results of the second FNA. We hypothesized that patients with architectural atypia would be more likely to have a second indeterminate FNA, because cytology with a microfollicular pattern is usually associated with a thyroid neoplasm [15]. Our findings support those by Gan et al who reported patients with nuclear atypia and architectural atypia had similar rates of benign results on a repeat FNA [27].

Our study is comprised of a large group of patients with cytology evaluated at a tertiary referral center, but it does suffer from the expected weaknesses of other retrospective studies. As a single institution study our results are subject to the bias of our cytopathologists and may not be applicable to a broader population. We did not attempt to integrate molecular testing into our study. Molecular testing is a powerful tool to determine the ROM in indeterminate thyroid nodules; however, at our institution over the study period, molecular testing was used infrequently. Therefore, integrating molecular testing into the results likely would have little effect on the overall conclusions. In 2016, Nikiforov et al proposed the renaming of the

encapsulated follicular variant of papillary thyroid carcinoma to noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) to better describe the very low risk potential of the tumor [28]. We did not attempt to reclassify patients with FVPTC into those with NIFTP and those with other forms of FVTPC. This may overestimate the number of patients with thyroid cancer in our results, but because there is still debate over whether NIFTP represents and benign entity or very low risk malignancy it is a reasonable assumption for this study.

We used the cytology report to assign a subtype of AUS and chose not to re-review the original cytology specimen. We did this because it is common practice for our cytopathologists to describe the atypia type in the body of the report and allow clinicians to interpret the risk based upon that description. Only 12 nodules over the study period did not have an adequate description in the cytology report to characterize the type of atypia. An additional 19 nodules were excluded because they had various forms of mixed atypia that were difficult to characterize into a single atypia group. It is possible that the study would have benefited from a review of these slides, but the heterogeneity of the atypia seen in this group would make it difficult to obtain enough patients to derive meaningful conclusions. It has been previously reported that discordance among pathologists regarding the diagnosis of AUS is common [29]; therefore a second blinded review of the pathology may also improve the homogeneity of our atypia subgroups. Because of this we have used this study as a foundation to launch a future

investigation to identify the features of nuclear or architectural atypia that may identify patients at risk for malignancy.

Conclusion:

Nuclear atypia and ATA high-risk ultrasound features are useful in identifying patients with AUS that are at an increased risk of thyroid malignancy. AUS subtype does not appear to influence the results of repeat FNA. Surgeons should take these factors into consideration when evaluating patients with AUS.

Table 1: Baseline characteristics of patients with atypia of undetermined significance					
	All n = 188 patients with 195 thyroid nodules	Nuclear atypia n=34 patients, 34 nodules	Architectural atypia n=88 patients, 90 nodules	Hurthle cell atypia n=66 patients, 71 nodules	p-value
Mean age – years	56.2	58.4	55.0	56.6	0.43
Female gender (%)	156 (83)	27 (79)	69 (78)	60 (91)	0.09
Mean nodule size – cm	2.4	2.6	2.6	2.2	0.11
Family history of thyroid malignancy (%)	15 (8.5)	3 (10)	5 (6.0)	7 (11)	0.48
Compressive symptoms (%)	73 (40)	14 (44)	34 (41)	25 (40)	0.96
Levothyroxine therapy (%)	31 (17)	7 (22)	13 (16)	11 (17)	0.73
Nodules that underwent repeat fine-needle aspiration (%)	69 (35)	9 (27)	38 (42)	22 (31)	0.18
Patients who underwent thyroidectomy (%)	95 (49)	19 (56)	39 (44)	37 (52)	0.43

Table 2: Results of repeat fine-needle aspiration by atypia of undetermined significance subtype				
	Repeat FNA benign	Repeat FNA indeterminate	Repeat FNA insufficient	p-value
Nuclear atypia, n= 9 (%)	4 (44)	5 (56)	0	0.66
Architectural atypia, n = 38 (%)	17 (45)	18 (47)	3 (8)	
Hurthle cell atypia, n = 22 (%)	6 (27)	14 (64)	2 (9)	
Total, n = 69(%)	27 (39)	37 (54)	5 (7)	
FNA = Fine-needle aspiration				

Table 3: Results of thyroidectomy by atypia of undetermined significance subtype			
	Benign	Malignant	p-value
Nuclear atypia, n= 19 (%)	5 (26)	14 (74)	<0.01
Architectural atypia, n = 41 (%)	32 (78)	9 (22)	
Hurthle cell atypia, n = 37 (%)	30 (81)	7 (19)	
Total, n = 97 (%)	67 (69)	30 (31)	

Table 4: Univariate analysis of the variables associated with a thyroid carcinoma			
	Benign, n=67	Cancer, n=30	p-value
Mean Age – years	54.8	53.0	0.48
Female Gender (%)	57 (85)	26 (87)	1.0
Mean nodule size – cm	2.6	2.5	0.76
Family history of thyroid malignancy (%)	8 (12)	3 (10)	1.0
ATA High-risk (%)	10 (15)	10 (33)	0.11
Nuclear atypia (%)	**5 (7.5)**	**14 (47)**	**<0.01**
Architectural atypia (%)	32 (48)	9 (30)	0.12
Hurthle cell atypia (%)	30 (45)	7 (23)	0.07
Bold = significant result, p<0.05	ATA High-risk = American Thyroid Association high suspicion sonographic pattern		

Table 5: Multivariable analysis of the variables independently associated with a thyroid carcinoma			
	Odds Ratio	95% Confidence Interval	p-value
Mean Age	0.98	0.93 – 1.02	0.26
Female Gender	0.68	0.15 – 2.9	0.60
Tumor Size	0.99	0.71 – 1.4	0.96
Family History of Thyroid cancer	0.42	0.081 – 2.9	0.43
ATA High-risk	**3.68**	**1.06 – 12.7**	**0.04**
Nuclear atypia	**11.8**	**3.34– 42.0**	**<0.01**
ATA High-risk = American Thyroid Association high suspicion sonographic pattern		**Bold = significant result, p<0.05**	

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