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Title: An institutional experience: a retrospective analysis of the effect of transitioning from follicular lesion of undetermined significance (FLUS) to atypia of undetermined significance (AUS) with subclassified atypia on interobserver concordance, rates of neoplasia, and rates of malignancy.

Running title: Transitioning from FLUS to AUS subcategorization in an institution

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ABSTRACT:

Introduction: The rate of malignancy (ROM) in thyroid fine needle aspirations (FNA) classified under "atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS), including Hürthle cell type (HLUS)" category of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) in literature is highly variable. The 2018 TBSRTC was updated to note a preferred categorization of AUS cases into subcategories. This study evaluates the impact of AUS subclassification on rates of neoplasia (RON), ROM, and cytopathologist (CP) concordance.

Methods: 93 thyroid FNAs previously diagnosed as FLUS or HLUS from 1/1/2013 to 12/31/2014 with subsequent surgical resection were identified. Four CPs reclassified these cases using TBSRTC AUS subcategories of follicular cells with architectural and/or cytologic atypia, predominantly Hürthle cells, and atypical lymphocytes. RON and ROM were calculated for each diagnostic subcategory for each CP.

Results: The original RON and ROM for FLUS cases were 31.4% and 15.1% and were 77.8% and 22.2% for HLUS cases. 10.8% of cases showed diagnostic concordance among the 4 CPs. The most frequently utilized subcategory was architectural atypia. RON range for architectural atypia, cytologic atypia, architectural and cytologic atypia, and predominantly Hürthle cells were 28.1-35.7%, 0-33.3%, 35.3-66.7%, and 57.1-87.5%. The range of ROM was 13.9-16.7%, 0-33%, 0-42.9%, and 0-25%, respectively.

Conclusion: RON for AUS predominantly Hürthle cells subcategory was higher than previously reported, which may indicate use for tailored patient management pathways. AUS subclassification can result in significant interobserver variability. Therefore, institutions may consider consensus/quality control sessions to optimize diagnostic concordance.

INTRODUCTION:

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) utilizes the atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS) category to designate thyroid fine needle aspiration (FNA) specimens that contain lesser degrees of cytologic and/or architectural atypia that is otherwise insufficient for a more definitive diagnosis.

While TBSRTC provided architectural and cytologic descriptors for what were deemed atypical follicular cells, TBSRTC did not provide a strict directive on how to utilize the FLUS/AUS category, leading to a variability on how these diagnoses are applied across institutions. In 2008, TBSRTC noted that the AUS/FLUS diagnostic category had an expected rate of malignancy (ROM) of 5-15%. However, more recent studies have indicated that the ROM for this diagnostic category is more variable across institutions, ranging anywhere from 18 to 81%[1-15]. The wide range of ROM can be attributed to several factors, including disease prevalence amongst different study populations as well as selection of study cohorts (i.e. selecting for patients who underwent surgical resection only rather than including all patients managed by radiologic surveillance, repeat FNA, and surgical resection).

Several studies indicated that subcategorizing atypia in the AUS category (by architectural, cytologic, or combined architectural and cytologic atypia) resulted in differential ROM in subsequent resections. As such, TBSRTC was updated in 2018 to note a preferred categorization of atypical thyroid FNAs into AUS subcategories, which included cytological atypia, architectural atypia, cytologic and architectural atypia, Hürthle cell predominance, atypia not otherwise specified, and atypical lymphoid cells[16].

The University of Michigan had previously labeled all atypical thyroid FNAs under the umbrella term of the FLUS up until July 2018, at which point we began reporting thyroid FNA results as AUS with subclassified atypia. This study evaluates whether the preferred reporting system for atypical thyroid FNAs would substratify rate of neoplasia (RON) and ROM based on AUS subcategory classification, which could potentially impact patient management. Additionally, this study also evaluates the interobserver variability in the use of different subcategories of AUS.

METHODS:

The electronic medical records system database was searched for thyroid FNA specimens diagnosed as FLUS or Hürthle cell lesion of undetermined significance (HLUS) with a subsequent surgical resection from 1/1/2013 to 12/31/2014. Thyroid FNA specimens originally diagnosed as “suspicious for follicular neoplasm” or “suspicious for Hürthle cell neoplasm were excluded from this study cohort. This search yielded a total of 100 cases with available slides for review. Five resections had no correlating sampling from pre-operative FNA sites and were excluded, leaving 95 cases. 1 patient underwent 3 FNA procedures for 3 distinct thyroid nodules (right superior, left inferior, and left superior nodules) initially. On subsequent repeat FNA, 2 (right superior, left inferior) were

called benign and 1 (right superior) was called FLUS, leading to surgical resection. Given the benign interpretation on the repeat thyroid FNA for two of the nodules, these 2 specimens were excluded from the study, for a total of 93 cases.

Four cytopathologists (CP) (ML, XJ, RC, JP) reclassified pre-operative FLUS and HLUS cases using TBSRTC AUS subclassification. Subclassification categories included architectural atypia, cytologic atypia, architectural & cytologic atypia, predominantly Hürthle cells, and atypical lymphocytes. In addition, some FNAs were reclassified into other TBSRTC categories, including suspicious for follicular neoplasm, suspicious for Hürthle cell neoplasm, suspicious for papillary thyroid carcinoma (PTC), benign, and non-diagnostic, upon re-review of the specimen by CPs.

The cohort was further stratified into subgroups based on number of pre-operative thyroid FNA specimens obtained prior to definitive surgical resection of the sampled thyroid nodules. Rates of neoplasia (RON) and malignancy (ROM) were calculated for each diagnostic subcategory for each CP. RON and ROM were compared between different diagnostic categories within the entire patient cohort.

RESULTS:

84 (90.3%) and 9 (9.7%) cases were originally classified as FLUS and HLUS, respectively, for a total of 93 cases. Of the 93 cases, 66 were from a single thyroid nodule diagnosed on one pre-operative FNA as either FLUS or HLUS, leading to subsequent surgical resection. The remaining 27 cases were from 15 patients. 12 of these 15 patients had two pre-operative FNAs diagnosed as either FLUS or HLUS before subsequent surgical resection

available for re-review. The remaining 3 patients only had the second pre-operative thyroid FNA available for re-review.

Subsequent surgical resection in the study cohort yielded 34 neoplasms, 15 of which were malignant. Of the 19 benign neoplasms, 16 were follicular adenomas and 3 were Hürthle cell adenomas on surgical resection. Of the 15 malignant neoplasms, 13 were papillary thyroid carcinomas (9 classic type, 4 follicular variant), 1 was a follicular carcinoma, and 1 was an anaplastic thyroid carcinoma. RON and ROM for originally diagnosed FLUS cases were 31.4% and 15.1%. RON and ROM for originally diagnosed HLUS cases were 77.8% and 22.2%.

Diagnostic rates

Results of reclassification into AUS subcategories among the 4 CPs in this cohort are shown in Table 1 and Figures 1-2. Although most of the cases were classified under the AUS diagnostic category by all CPs, the utilization of AUS subcategories was variable amongst the CPs. The most frequently utilized AUS subcategory was architectural atypia, ranging from a diagnostic rate of 25.8% to 77.4%. The diagnostic rate for the combined architectural and cytologic atypia subcategory ranged from and 3.2% to 35.5%. The cytologic atypia subcategory was the least commonly utilized amongst all CPs. Of the originally diagnosed FLUS cases, each CP upgraded 1-4 cases to the diagnostic category of suspicious for papillary thyroid carcinoma, all of which had neoplasms on subsequent surgical resections (one case was a follicular adenoma while all other upgraded cases had histologic diagnoses of papillary thyroid carcinoma).

Interobserver concordance:

There was a low level of concordance, with only 10 cases (10.8%) showing concordant diagnoses between 4 CPs. Of these 10 cases, 3 were classified as benign, 6 were classified as AUS (architectural atypia), and the remaining case was classified as AUS (predominantly Hürthle cells). All 3 concordant benign cases showed nodular hyperplasia on subsequent resection of the thyroid. Of the 6 concordant AUS (architectural atypia) cases, 5 were benign and one was diagnosed as PTC on subsequent resection of the respective nodules. The AUS (predominantly Hürthle cells) concordant case was shown to be a follicular adenoma on subsequent resection.

Rates of neoplasia (RON) and malignancy (ROM) in patients with 1 pre-operative t-FNA:

The RON and ROM in the 66 patients with a single thyroid nodule that underwent a single pre-operative t-FNA procedure are summarized in Table 2.

A wide range for RON was displayed in the AUS subcategories of cytologic atypia (0 – 33%) and combined architectural and cytologic atypia (0-66.7%). The AUS subcategory of architectural atypia had a tighter range for the RON amongst the CPs, from 21.4% to 32.3%. Among the AUS categories, the highest rates of neoplasia were seen in the AUS predominantly Hürthle cells subcategory, with a range of 50% to 75%. However, there was a limited number of cases subclassified in this category, as the diagnostic rate amongst the CPs was between 4.5 and 7.6%. 1 CP upgraded 3 FLUS cases to the diagnostic category of suspicious for follicular neoplasm, but these 3 cases were benign on surgical resection. All other cases that any of the CPs in this cohort reclassified to the diagnostic categories of suspicious for Hürthle cell neoplasm or suspicious for papillary thyroid carcinoma were neoplastic on subsequent surgical resection.

There was also wide ranges for ROM displayed in the AUS subcategories of cytologic atypia (0-33.3%) and combined architectural and cytologic atypia (0-12.5%). The ROM for the AUS subcategory of architectural atypia had a narrower range than that observed for RON, from 7.1% to 12%. While the AUS subcategory of predominantly Hürthle cells had displayed a high RON amongst all CPs, the ROM was expectedly lower, as all of these cases on surgical resection were diagnosed as follicular or Hürthle cell adenomas. Of all the cases upgraded to the diagnostic category of suspicious for papillary thyroid carcinoma by all CPs, all but one were diagnosed as papillary thyroid carcinoma on surgical resection.

Rates of neoplasia (RON) and malignancy (ROM) in patients with 2 pre-operative t-FNAs:

The RON and ROM in the 15 patients with a single thyroid nodule that underwent two pre-operative t-FNA procedures are summarized in Table 3. Similar to the cohort of patients with 1 pre-operative t-FNA procedure, the AUS subcategory of artchitectural atypia was the most frequently utilized. However, the RON and ROM for this subcategory were higher in the cohort of patients with 2 pre-operative thyroid FNAs (38.1-50% RON, 14.8-36.3% ROM) than in patients with 1 pre-operative thyroid FNA (21.4-32.3% RON, 7.1-11.8% ROM) for each CP. Also similar to the cohort of patients with 1 pre-operative t-FNA procedure, among the AUS categories, the highest RON was seen in the AUS predominantly Hürthle cells subcategory, with a range of 66.7 to 100%.

DISCUSSION:

Since TBSRTC's inception, many studies have found that ROMs vary depending on subclassification of AUS/FLUS. Specifically, the AUS subcategory of cytologic/nuclear atypia has frequently shown a higher ROM than other AUS subcategories in several studies, which has ranged from 34.4 – 97% compared to range of ROM for the

architectural atypia (5-26.9%) and predominantly Hürthle cells (5-22.2%) subcategories[1-15]. However, in our study, the AUS subcategory of cytologic atypia alone was only rarely used, with the highest rate of use by one CP of 3.2% and a ROM ranging from 0-33% amongst all CPs. The low rate of utilization of this specific subcategory may be related to several factors. For one, different thresholds for utilization of more or less severe diagnostic categories could impact the utilization of the AUS cytologic atypia subcategory. For example, a small subset of cases originally classified as FLUS were upgraded by the study CPs to the "suspicious for papillary thyroid carcinoma," suggesting that this may be partially attributed to a lower diagnostic threshold of the study CPs to use a more severe diagnostic category in some cases. In all but one of these upgraded cases, subsequent surgical resections showed papillary thyroid carcinoma, with the remaining case showing a follicular adenoma. Conversely, in some cases, some cytopathologists can display an increased threshold for the diagnosis of cytologic atypia, and therefore utilize the benign category more readily. In our study, our CPs reclassified 4.3 – 37.6% of cases originally diagnosed as FLUS into the benign category. An additional factor that could contribute to the low diagnostic rate of the AUS cytologic atypia subcategory is the concurrent availability of a subcategory that includes both architectural and cytologic atypia. If combined, the diagnostic rate among CPs for any cases with cytologic atypia increases to 6.4 to 36.6%. In contrast to many previous studies that evaluated the effect of substratifying AUS thyroid FNAs, our study included a category that combined both architectural and cytologic atypia, which had a range of ROM amongst the CPs of 0-42.9%. In comparison, a study by Guleria et al.[14], 62.9% of AUS thyroid FNAs were subcategorized into a combined cytologic and architectural atypia subcategory with a RON of 68.6% and a ROM of either 58.8% (if the entity of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is considered malignant) or 37.3% (if NIFTP is considered not malignant). However, the limited data available of RON and ROM for an AUS subcategorization of both architectural and cytologic

atypia precludes a meaningful conclusion on its clinical significance[17]. Further evaluation of a combined subcategory across institutions may further elucidate utility of this combination of atypia.

Of note, the RON for the AUS predominantly Hürthle cells subcategory was significantly higher amongst the CPs in our study (57.1-87.5%) than RON previously reported, which range from 20.5-31.4%[9-11]. The majority of resultant neoplasms on subsequent resections in our cohort of AUS predominantly Hürthle cells subcategory were follicular adenomas. However, the ROM of the predominantly Hürthle cell subcategory within this cohort (0-25%) was similar to those in previous studies, which range from 0-20%[1,8,10-12,18]. Currently, 2018 TBSRTC guidelines suggest that AUS subcategories are managed similarly. However, our findings suggest that the AUS predominantly Hürthle cells category may have a higher specificity for neoplastic processes, which could suggest a possible differential clinical management pathway for patients with this diagnosis compared to other AUS subcategories. Another finding of note in our study was that the RON and ROM for virtually all AUS subcategories were higher in the cohort of patients with 2 pre-operative thyroid FNAs than in patients with 1 pre-operative thyroid FNA for each CP. This finding suggests that differential management may also be considered in patients who have two sequential AUS diagnoses in comparison to one.

The potential for further substratification of the AUS category into more prognostically meaningful subgroups has been suggested in several studies[7,12,15] to enhance guidance in clinical management of patients with AUS diagnoses. As such, additional studies to further investigate the utility of subcategorization of the TBRSTC AUS category will be beneficial. It is important to note, however, that evaluation of RON in such studies may be

variable in light of the subjective classification of diagnostic entities such as adenomatoid nodules, follicular/Hürthle cell adenomas, and non-invasive follicular thyroid neoplasms with papillary-like features (NIFTP) on surgical resections. Additionally, in many practices, ROM has traditionally been the driving factor in guiding surgical management and prognostication. However, some studies have suggested, especially in light of the categorization of NIFTP as a low-risk tumor rather than a malignancy, that a three-pronged approach in the assessment of cytologic-histologic correlation (that includes benign, neoplastic, and malignant outcomes) may be beneficial in the future [19,20].

Additionally, our study shows that despite the provided diagnostic criteria for AUS subcategories in TBSRTC, there is a significant amount of interobserver variability. As such, other institutions that are considering switching from FLUS to AUS may wish to initially hold consensus/quality control sessions to evaluate the possibility of providing diagnostic guidelines in utilizing AUS subcategory diagnoses. The aim of such sessions would be to increase diagnostic consistency between the cytopathologists within an institution. While this could potentially allow for greater degrees of concordance amongst cytopathologists in indeterminate cases, it may also facilitate adherence to the suggested institutional/laboratory diagnostic rate of AUS of <10%. Studies, such as those by Jing et al, have highlighted the utility of group consensus review in optimizing interobserver agreement and reducing the diagnostic rate of indeterminate diagnoses on thyroid FNA specimens [21]. Promoting more exacting criteria for AUS amongst institution CPs may also have the downstream effect of decreasing the frequency of repeat FNAs, patient anxiety, and cost associated with repeat procedures. Similar sessions could also be considered in institutions in which use of AUS subcategories are utilized for the same

purposes. Using subsequent data on the effect of diagnostic rates and subsequent RON and ROM may be helpful in constructing interinstitutional data and potentially can be utilized to further modify diagnostic criteria in indeterminate thyroid nodules.

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Figure Legends

Figure 1: Distribution of RON among AUS subcategories

Legend:
AUS = atypia of undetermined significance
AL = atypical lymphocytes
HC = predominantly Hürthle cells
AA = architectural atypia
CA = cytologic atypia

Figure 2: Distribution of ROM among AUS subcategories

Legend:
AUS = atypia of undetermined significance
AL = atypical lymphocytes (not featured; 0% ROM for 1 case)
HC = predominantly Hürthle cells
AA = architectural atypia
CA = cytologic atypia

Table 1: Reclassified pre-operative FLUS/HLUS cases

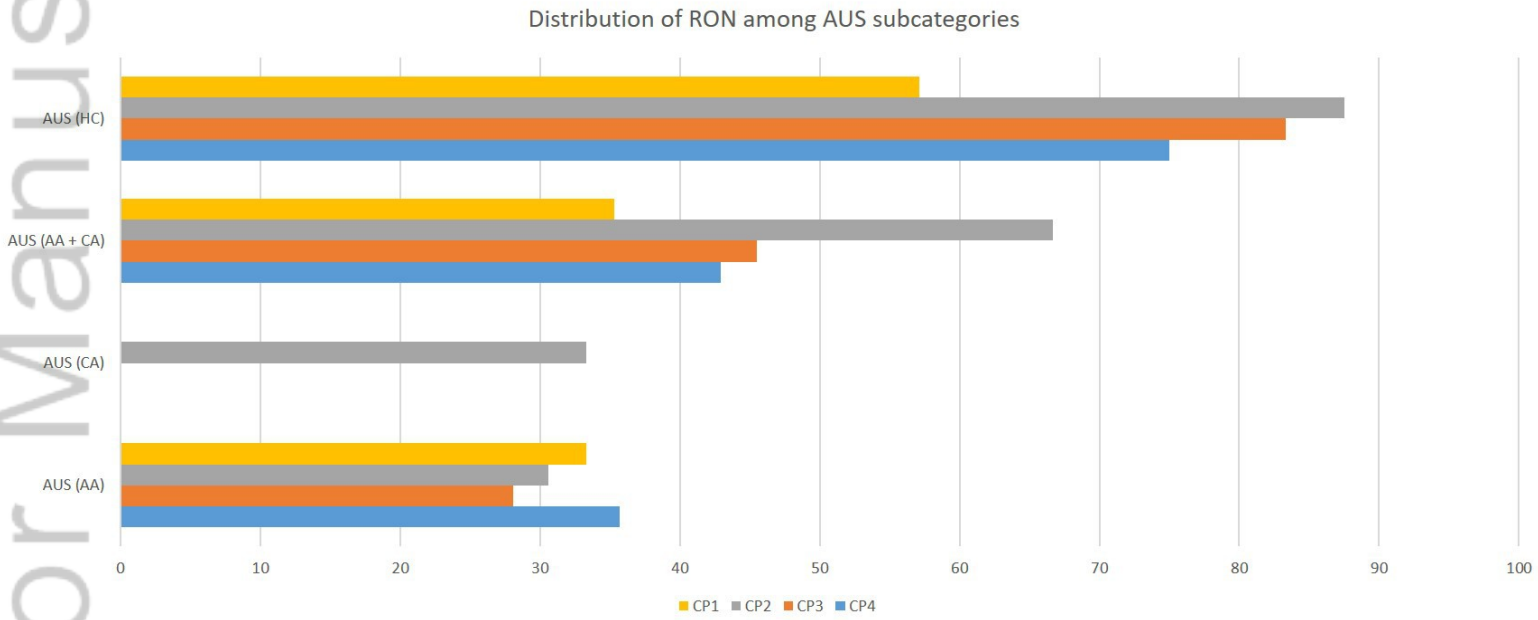
Diagnostic Category	CP 1	CP 2	CP3	CP4
Non-diagnostic	**3 (3.2%)**	**1 (1.1%)**	**1 (1.1%)**	**1 (1.1%)**
Rate of neoplasia	66.7%	0%	100%	100%
Rate of malignancy	66.7%	0%	100%	100%
Benign	**35 (37.6%)**	**4 (4.3%)**	**15 (16.1%)**	**32 (34.4%)**
Rate of neoplasia	28.6%	0%	0%	25%
Rate of malignancy	11.4%	0%	0%	9.4%
AUS (architectural atypia)	**24 (25.8%)**	**72 (77.4%)**	**32 (34.4%)**	**42 (45.2%)**
Rate of neoplasia	33.3%	30.6%	28.1%	35.7%
Rate of malignancy	16.7%	13.9%	15.6%	16.7%
AUS (cytologic atypia)	**0**	**3 (3.2%)**	**1 (1.1%)**	**2 (2.2%)**
Rate of neoplasia	-	33.3%	0%	0%
Rate of malignancy	-	33.3%	0%	0%
AUS (architectural & cytologic atypia)	**17 (18.3%)**	**3 (3.2%)**	**33 (35.5%)**	**7 (7.5%)**
Rate of neoplasia	35.3%	66.7%	45.5%	42.9%
Rate of malignancy	5.9%	0%	18.2%	42.9%
AUS (predominantly Hürthle cells)	**7 (7.5%)**	**8 (8.6%)**	**6 (6.5%)**	**8 (8.6%)**
Rate of neoplasia	57.1%	87.5%	83.3%	75%
Rate of malignancy	14.3%	25%	16.7%	0%
AUS (atypical lymphocytes)	**0**	**0**	**1(1.1%)**	**0**
Rate of neoplasia	-	-	0%	-
Rate of malignancy	-	-	0%	-
Suspicious for follicular neoplasm	**3 (3.2%)**	**0**	**2 (2.2%)**	**0**
Rate of neoplasia	0%	-	100%	-
Rate of malignancy	0%	-	50%	-
Suspicious for Hürthle cell neoplasm	**0**	**0**	**1 (1.1%)**	**0**
Rate of neoplasia	-	-	100%	-
Rate of malignancy	-	-	0%	-
Suspicious for papillary thyroid carcinoma	**4 (4.3%)**	**2 (2.2%)**	**1 (1.1%)**	**1 (1.1%)**
Rate of neoplasia	100%	100%	100%	100%
Rate of malignancy	75%	100%	100%	100%

Table 2: Reclassified cases in cohort of patients with 1 pre-operative FLUS/HLUS diagnosis

Diagnostic Category	CP 1	CP 2	CP3	CP4
Non-diagnostic	**3 (4.5%)**	**1 (1.5%)**	**1 (1.5%)**	**1 (1.5%)**
Rate of neoplasia	66.7%	0%	100%	100%
Rate of malignancy	66.7%	0%	100%	100%
Benign	**28 (42.4%)**	**4 (6%)**	**10 (15.2%)**	**22 (33.3%)**
Rate of neoplasia	25%	0%	0%	27.3%
Rate of malignancy	10.7%	0%	0%	13.7%
AUS (architectural atypia)	**14 (21.2%)**	**51 (77.3%)**	**25 (37.9%)**	**31 (47%)**
Rate of neoplasia	21.4%	27.4%	24%	32.3%
Rate of malignancy	7.1%	11.8%	12%	9.7%
AUS (cytologic atypia)	**0**	**3 (4.5%)**	**1 (1.5%)**	**2 (3%)**
Rate of neoplasia	-	33.3%	0%	0%
Rate of malignancy	-	33.3%	0%	0%
AUS (architectural & cytologic atypia)	**12 (18.2%)**	**3 (4.5%)**	**24 (36.3%)**	**4 (6%)**
Rate of neoplasia	33.3%	66.7%	41.7%	0%
Rate of malignancy	0%	0%	12.5%	0%
AUS (predominantly Hürthle cells)	**4 (6%)**	**4 (6%)**	**3 (4.5%)**	**5 (7.6%)**
Rate of neoplasia	50%	75%	66.7%	60%
Rate of malignancy	0%	0%	0%	0%
AUS (atypical lymphocytes)	**0**	**0**	**1 (1.5%)**	**0**
Rate of neoplasia	-	-	0%	-
Rate of malignancy	-	-	0%	-
Suspicious for follicular neoplasm	**3 (4.5%)**	**0**	**0**	**0**
Rate of neoplasia	0%	-	-	-
Rate of malignancy	0%	-	-	-
Suspicious for Hürthle cell neoplasm	**0**	**0**	**1 (1.5%)**	**0**
Rate of neoplasia	-	-	100%	-
Rate of malignancy	-	-	0%	-
Suspicious for papillary thyroid carcinoma	**2 (3%)**	**0**	**0**	**1 (1.5%)**
Rate of neoplasia	100%	-	-	100%
Rate of malignancy	50%	-	-	100%

Table 3: Reclassified cases in cohort of patients with 2 pre-operative FLUS/HLUS diagnoses

Diagnostic Category	CP 1	CP 2	CP3	CP4
Benign	**7 (25.9%)**	**0**	**5 (18.5%)**	**10 (35.7%)**
Rate of neoplasia	42.9%	-	0%	30%
Rate of malignancy	14.3%	-	0%	10%
AUS (architectural atypia)	**10 (37%)**	**21 (77.8%)**	**7 (25.9%)**	**11 (40.7%)**
Rate of neoplasia	50%	38.1%	42.9%	45.5%
Rate of malignancy	30%	14.8%	28.6%	36.3%
AUS (architectural & cytologic atypia)	**5 (18.5%)**	**0**	**9 (33.3%)**	**3 (11.1%)**
Rate of neoplasia	40%	-	55.6%	100%
Rate of malignancy	20%	-	33.3%	100%
AUS (predominantly Hürthle cells)	**3 (11.1%)**	**4 (14.8%)**	**3 (11.1%)**	**3 (11.1%)**
Rate of neoplasia	66.7%	100%	100%	100%
Rate of malignancy	33.3%	50%	33.3%	0%
Suspicious for follicular neoplasm	**0**	**0**	**2 (7.4%)**	**0**
Rate of neoplasia	-	-	100%	-
Rate of malignancy	-	-	50%	-
Suspicious for papillary thyroid carcinoma	**2 (7.4%)**	**2 (7.4%)**	**1 (3.7%)**	**0**
Rate of neoplasia	100%	100%	100%	-
Rate of malignancy	100%	100%	100%	-



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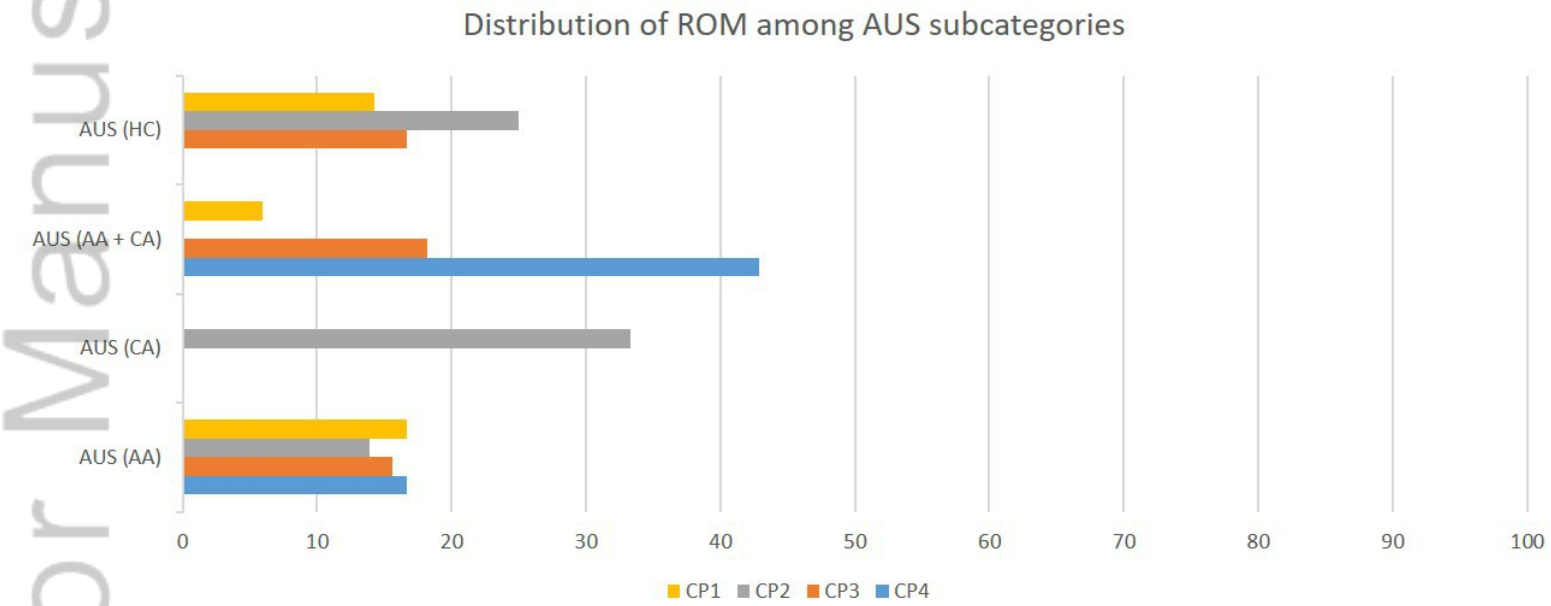

DC_24611_Figure 2.jpg