original article

Thyroid fine-needle aspiration cytology: malignancy rate in the category of indeterminate significant atypia/ indeterminate significant follicular lesion

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BACKGROUND: Fine needle aspiration cytology (FNAC) is a standard preoperative diagnostic modality for thyroid nodules. The Bethesda Thyroid Cytopathology Reporting System (TBSRTC) defines the FNAC atypia group as atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS).

OBJECTIVES: Determine the risk of malignancy after surgical resection in patients with AUS/FLUS.

DESIGN: Retrospective

SETTING: Pathology department of a tertiary care center

PATIENTS AND METHODS: All thyroid FNACs between 2015 and 2023 that were diagnosed as AUS/FLUS in Turkey. Patient demographics, preoperative ultrasonographic features, and follow-up data were collected.

MAIN OUTCOME MEASURES: Relationship between AUS/FLUS diagnosis and final histopathological diagnosis.

SAMPLE SIZE: 562

RESULTS: In total, 562 thyroid nodules were diagnosed as AUS/FLUS, and 267 (47.5%) were surgically excised. A malignant histopathological diagnosis was given in 28 cases (10.4%). Malignancy risk sensitivity of AUS/FLUS diagnosis was 75.68% (95% CI=58.80–88.23%), specificity was 55.24% (95% CI=50.91–59.52%), positive predictive value was 10.49% (95% CI=8.71–12.58%), and negative predictive value was 97.04% (95% CI=94.86–98.31%). In the ultrasonographic data, having symptomatic nodules, nodule calcification, and irregular nodule borders were all statistically significant signs of cancer in a one-variable analysis ($P<.01$). The presence of a family history emerged as a statistically significant prognostic marker for malignancy ($P=.012$). Although not statistically significant, the malignancy rate for nodules with nuclear atypia was 11.9%, significantly higher than the rate of 8.3% for nodules with architectural atypia only ($P=0.32$).

CONCLUSIONS: The diagnosis of AUS/FLUS has a high rate of predicting the risk of malignancy and should continue to be offered. In addition to cytopathological features, ultrasound data and family history should be taken into consideration when evaluating the case.

LIMITATIONS: Retrospective design and no molecular studies.

CONFLICT OF INTEREST: None.

The global prevalence of thyroid neoplasms has exhibited a consistent upward trajectory over recent decades, with thyroid nodules constituting a prominent manifestation in clinical contexts. According to the available literature, thyroid nodules are present in between 4% and 7% of adults, but only a small percentage—less than 5%—have malignant characteristics. Fine needle aspiration (FNA) cytology (FNAC) has become the standard way to get an accurate diagnosis of thyroid nodules before surgery in this setting.[1] This technique has progressively garnered eminence due to its expeditious, secure, and uncomplicated nature, effectively demarcating between malignancies and benign entities.[2] Its reliability is robust, boasting an accuracy quotient scaling as high as 97%. As a corollary, it has acquired the distinction of being the quintessential front-line diagnostic modality for the comprehensive appraisal of thyroid nodules.[3]

The year 2017 witnessed a revision of the Bethesda Thyroid Cytopathology Reporting System (TBSRTC), reorganizing it into six distinct diagnostic strata.[4] The underlying reason for the TBSRTC lies in standardizing the communication of findings derived from FNAC, thus engendering the seamless transmission of meticulous and clinically pertinent outcomes between pathologists and attending medical practitioners.[4]

Even though FNAC and the Bethesda system have a lot of good points, it is important to recognize that they also have some problems. One example of this is cases that are labeled as "atypical," which can be written as "atypia of undetermined significance (AUS)" or "follicular lesion of undetermined significance (FLUS)". Within this category, the incidence of malignancy incidence exhibits considerable heterogeneity across different institutions, spanning a wide spectrum ranging from 15.8% to 81.0%.[5] A recent inquiry pertaining to the AUS/FLUS grouping has revealed a malignancy risk between 5% and 15%.[6]

Also, there is a lot of variation among the cytological subcategories in this layer, with each showing a different tendency to become cancerous. This intricate divergence contributes to the sustained diagnostic and therapeutic complexities inherent to this classification, compounded by the absence of a universal agreement among medical practitioners and institutions regarding the most optimal approach to management. This prevailing lack of consensus poses a formidable challenge in clinical practice.[7]

Against this backdrop, our current investigation endeavors to undertake a comparative analysis of outcomes arising from surgical resection procedures conducted on patients diagnosed with atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) within the purview of cytopathological assessment of thyroid nodules. The central objective of this study thus revolves around delineating the extent to which the AUS/FLUS diagnosis informs the assessment of malignancy risk. At the same time, we wanted to figure out how well FNAC worked by looking at its sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV), all in the context of cyto-histopathological correlation.

PATIENTS AND METHODS

Among the FNAC samples that received AUS/FLUS approval between 1 January 2015, and 1 June 2023, the archive data of the University Hospital Pathology Laboratory was subjected to a public review. The clinical research ethics committee approved the ethical precepts of our investigation in strict accordance with the guidelines stated in the Declaration of Helsinki. This endorsement was formalized on August 16, 2023, under the aegis of Decision Number 2023/11-13.

Preceding surgical interventions, fine needle aspirations were conducted using a 25-gauge needle, with the process involving multiple penetrations in situ. Each specimen was meticulously processed to produce either alcohol-fixed smears or underwent liquid-based cytology (utilizing the Surepath method). After the samples were prepared, Papanicolaou staining was used to make the final cytopathologic interpretation easier.

The inclusion criteria for the AUS category encompassed nodules featuring both architectural and nuclear atypia. Instances characterized by nuclear atypicality, albeit lacking a complete nuclear groove and devoid of concurrent inclusions, were deemed inadequate to definitively ascertain malignancy, consequently affiliating with the AUS classification (**Figure 1**). Nodules manifesting a microfollicular pattern, accompanied by a conspicuous presence of Hurthle cell constituents, were classified within the ambit of architectural atypia and correspondingly categorized as FLUS (**Figure 2**).

Full patient information was recorded, including gender, age, family medical history, the presence of symptomatic nodules, preoperative ultrasound findings, mean nodule dimensions, nodule location, calcification symptoms, nodule morphology and contour, consistency attributes, echogenicity levels, and internal vascularity.

Post-surgical histopathological findings encompassed malignant instances of papillary, follicular, medullary, or anaplastic thyroid carcinoma. The incidence of malignancy for both AUS and FLUS diagnoses was computed distinctly. To determine the comprehensive malignancy rate within the AUS/FLUS category, exclu-

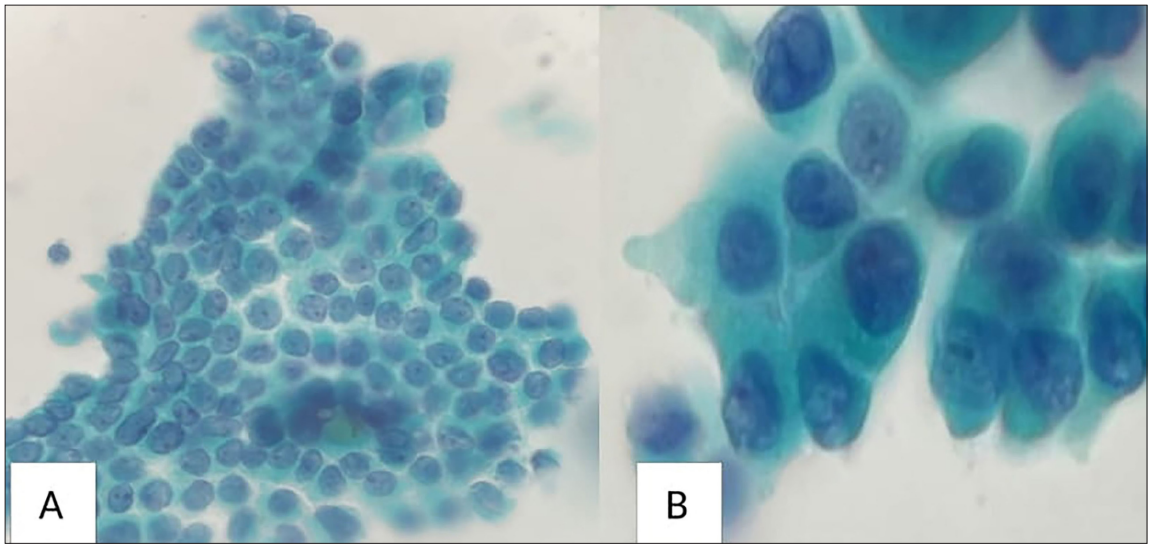

Figure 1. This case was categorized as atypical primarily because of nuclear features on cytology. In the trabecular pattern, groups consisting of crowded (A) or few cells (B) are noticeable. The follicular cells display some degree of nuclear crowding with mild nuclear enlargement, occasional oval nuclei, some cells exhibiting pale chromatin, and an occasional nuclear groove without evidence of nuclear inclusions (A, B: Papanicolaou stain, original magnification ×1000).

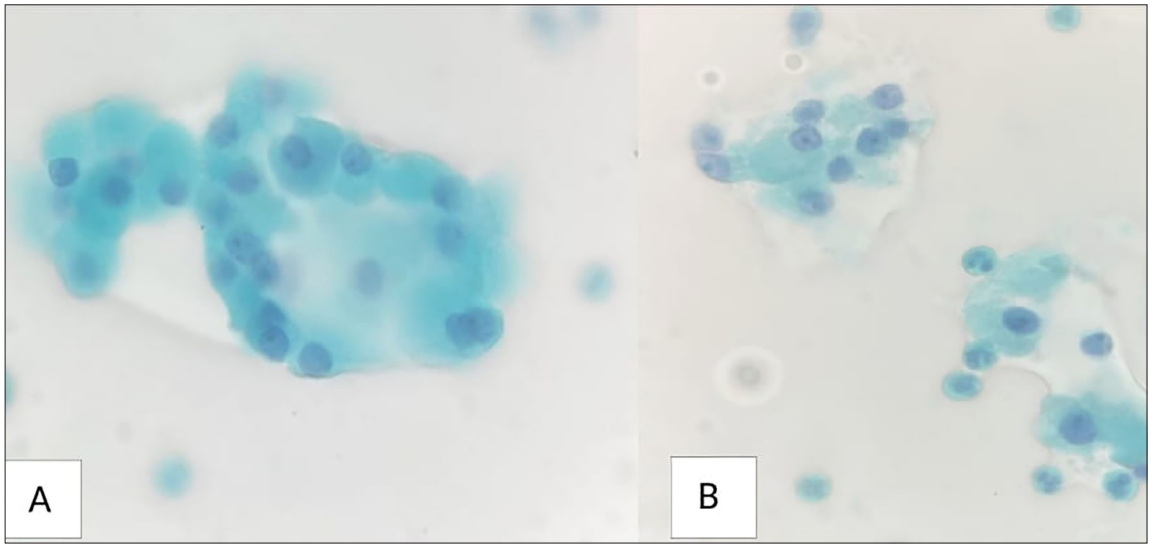

Figure 2. These cases were categorized as atypia primarily because of architectural features on cytology. A smear with a predominant microfollicular pattern of Hurthle cells is seen (A). The smear reveals roughly equal proportions of both flat sheets, microfollicular structures, and small, round, normochromatic nuclei without significant atypia (B). (A,B: Papanicolaou stain, original magnification ×1000).

sive inclusion was accorded to patients who underwent surgical intervention and received a conclusive histopathological diagnosis. Notably, individuals who underwent subsequent repeat FNAC procedures were excluded from the study cohort.

We used IBM SPSS version 21 (IBM Corporation, Armonk, NY) for the statistical analysis. A sequential assessment of demographic and ultrasonographic variables was conducted by chi-square analysis with Yates correction. $P \leq .05$ was deemed indicative of statistical significance. Additionally, a univariate logistic regression model was used to find independent predictors of cancer. The performance metrics of cytological diagnosis, namely sensitivity, specificity, NPV, and PPV, were subject to rigorous calculation within the study parameters.

Table 1. Demographic and ultrasonographic features between benign and malignant nodules (n=267).

Clinical features	Benign	Malign	*P* value
Gender			NS
Female	126	18	
Male	113	10	
Age	53.0 (16-87)	50.5 (22-74)	NS
Family history			
Positive (n=5)	1 (20)	4 (80)	.012
Negative (n=78)	57 (73)	21 (26.9)	
Symptomatic nodules			
Yes (n=47)	28 (59.5)	19 (40.4)	<.01
No (n=106)	97 (91.5)	9 (8.4)	
Ultrasonographic features			
Nodule average size (cm)	2.3	2.7	NS
Side			
Left lobe	41 (74.5)	14 (25.4)	NS
Right	56 (82.3)	12 (17.6)	
Isthmus	40 (97.5)	1 (2.4)	
Bilateral	102 (99)	1 (0.9)	
Calcifications			
Yes (n=77)	51 (66.2)	26 (33.7)	<.01
No (n=190)	188 (98.9)	2 (1)	
Concistency			
Solid (n=64)	46 (71.8)	18 (28.1)	NS
Cystic (n=159)	153 (96.2)	6 (3.7)	
Mixed (n=44)	40 (90.9)	4 (9)	
Echogenicity			
Hyperechoic	55%	45%	NS
Isoechoic	46%	54%	
Hypoechoic	60%	40%	
Heterogenous	58%	42%	
Presence of internal vascularity	31.8	68.2	NS
Margins			
Well defined	98.5	1.4	<.01
Irregular	60.3	39.6	

Data are median (minimum-maximum) for age and number (percentage) for remaining categorical data.

RESULTS

During the period spanning from 2015 to 2023, a total of 2676 cases undergoing thyroid cytopathological examination were documented, among which 562 were diagnosed as AUS/FLUS. Within this subset, 408 cases (72.5%) were female, while 154 cases (27.4%) were males.

The assessment of various demographic and ultrasonographic attributes unveiled noteworthy trends (**Table 1**). Notably, in the univariate analysis, having symptomatic nodules, calcification of nodules, and irregular nodule borders were all statistically significant predictors of malignancy (*P*<.01). The mean nodule dimensions were determined to be 2.3 cm for benign nodules and 2.7 cm for malignant nodules.

In the context of familial predisposition, among the five patients with a history of thyroid carcinoma within their families, one (20%) exhibited benign nodules, while four (80%) displayed malignancy. Contrarily, among patients lacking such familial antecedents, 57 (73%) manifested benign thyroid nodules, whereas 38 (58%) exhibited malignant nodules. Consequently, the presence of a family history emerged as a statistically significant prognostic marker for malignancy (*P*=.012). Regarding clinical characteristics within the cohort of selected cases, no statistically significant disparity was discerned between benign and malignant nodules with respect to age and gender distributions.

Figure 3 delineates the clinical trajectory and outcomes for the patients under consideration; 267 of 562 cases (47.5%) were surgically excised. Notably, 258 patients (45.9%) opted for surgical resection, 56 out of 304 (18.4%) underwent repeat FNAC procedures, and the remaining 248 (81.5%) were managed through clinical follow-up without further intervention. Of the 258 cases diagnosed as AUS/FLUS with the first biopsy, 27 (10.4%) were diagnosed as malignant, while 1 of the 9 cases (11.1%) diagnosed with the second biopsy and surgical resection were diagnosed as malignant. Subsequent histological evaluation of resected specimens indicated malignancy in 28 out of 267 cases exhibiting atypical features (10.4%). The diagnostic performance metrics for cytological diagnosis were established as follows: sensitivity at 75.68% (95% CI=58.80-88.23%), specificity at 55.24% (95% CI=50.91-59.52%), positive predictive value at 10.49% (95% CI=8.71-12.58%), and negative predictive value at 97.04% (95% CI=94.86-98.31%).

The spectrum of benign histopathologic diagnoses obtained after surgical resection was 68 cases (28.4%) of follicular adenoma, 56 cases (23.4%) of Hurthle cell adenoma, 42 cases (17.5%) of adenomatoid nodules, 31 cases (12.9%) of Hashimoto's thyroiditis, 23 cases

(9.6%) of cystic degenerated thyroid nodules, and 19 cases (7.9%) of colloidal nodules.

Of the cohort comprising 56 individuals who underwent one or more repeat FNAC, a notable proportion of 47 patients (83.9%) were subjected to a regimen of three successive repeat FNAC procedures, ultimately culminating in benign diagnoses. Consequently, neither surgical resection nor clinical surveillance were advocated for this subgroup. On the other hand, nine patients had two repeat FNAC sessions. In these nine patients, five (55.5%) had cancerous findings, three (33.3%) had suspected cancerous findings, and one (11.1%) had a benign outcome. Consequently, surgical resection was deemed requisite for the cases yielding malignancy or suspected malignancy.

Upon the initial cytological scrutiny of all cases, nuclear cytologic atypia was apparent in 317 instances (56.4%), while architectural atypia was identified in 245 cases (43.5%). Among the 267 cases that subsequently underwent surgical resection, nuclear cytologic atypia was documented in 159 cases (59.5%), whereas architectural cytologic atypia was identified in 108 cases (40.4%). Although the malignancy rate was comparatively higher in cases characterized by nuclear atypia (11.9% among the nuclear atypia group, as opposed to 8.3% among the architectural atypia group), this difference failed to yield statistically significant results (*P*=.32) (**Figure 4**).

The malignancy rates of nuclear atypia were established following a univariate analysis: sensitivity at 67.86% (95% CI=47.65% to 84.12%), specificity at 51.56% (95% CI=45.63% to 57.45%), positive predictive value of 96.38% (95% CI=95.26% to 97.24%), and negative predictive value of 7.78% (95% CI=4.65% to 12.76%). Furthermore, the malignancy rates of architectural atypia atypia were established as follows: sensitivity of 32.14 % (95% CI= 15.88% to 52.35%), specificity of 69.54% (95% CI=64.22% to 74.50%) positive predictive value of 95.25 % (95% CI=91.95% to 97.24%) and negative predictive value of 5.12 % (95% CI=3.97% to 6.57%) risk of neoplasia was 32% with nuclear atypia and 75% with structural atypia.

Within the subset of 56 cases subjected to repeat FNAC, nuclear cytologic atypia was apparent in 31 cases (55.3%), while architectural atypia was observed in 25 cases (44.6%). Notably, 9 out of 31 cases evincing nuclear atypia were subsequently ascertained to exhibit malignancy following surgical resection, amounting to a malignancy detection rate of 29%. Conversely, the cases characterized by architectural atypia were adjudged benign in the course of repeat FNAC, thereby obviating the need for surgical intervention.

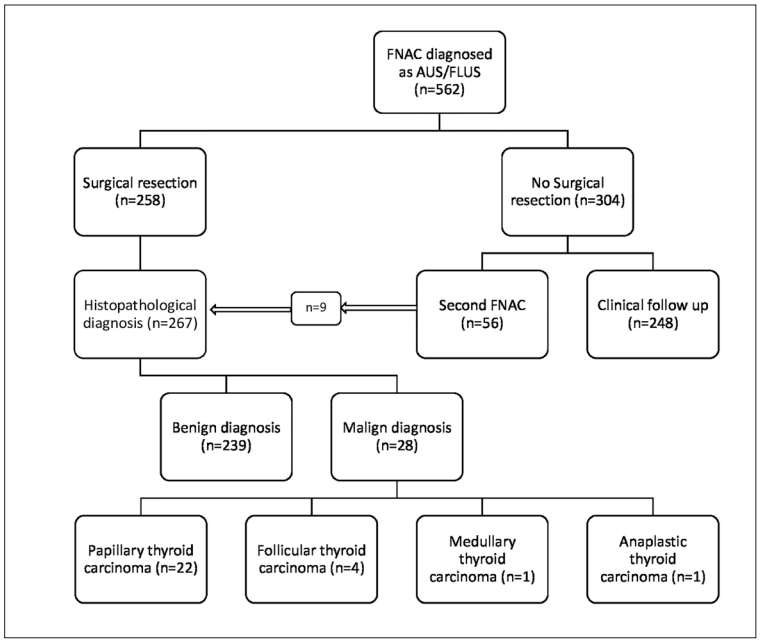

Figure 3. Final histopathological diagnoses of the cases in the study after surgical resection and clinical follow-up.

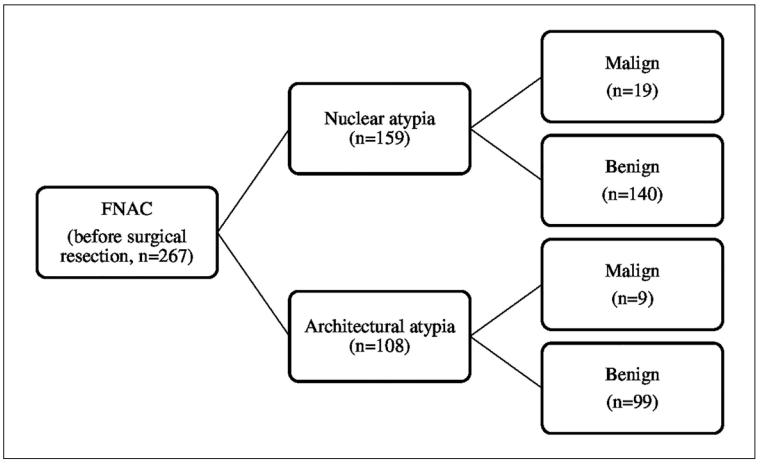

Figure 4. Malignant outcomes according to subclassification.

DISCUSSION

In our study, 267 (47.5%) of 562 cases with AUS/FLUS were diagnosed histopathologically. In total, 239 cases (89.5%) were diagnosed as benign and 28 cases (10.5%) were diagnosed as malignant. The rate of malignant diagnosis was consistent with other studies in the literature.[8,9]

This study revealed a malignancy rate of 10.4% after surgical resection in lesions identified as AUS/FLUS after FNAC and showed that papillary thyroid carcinoma was the predominant malignant diagnosis. This rate is

within the spectrum of malignancy rates encountered after surgical resection of cases with atypical diagnoses, and there are studies with similar rates of malignancy.[3,8] In the Huhtamella et al study, the malignancy risk rate was 14.7%, similar to our study.[9]

In histologically confirmed cases, the risk of malignancy was 10.4% after the first FNAC and 11.1% after the second FNAC, and there was a slight significance in determining the risk of malignancy with repeated FNAC. In the study by Huhtamella et al,[9] malignancy was detected in 38.2% after the first FNAC and 21.7% after the second FNAC, which was significantly higher than in our study.

Within the AUS/FLUS classification, the TBSRTC approximates the risk of malignancy to range from 6% to 18% in instances where the diagnosis of "noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)" is not classified as cancer. However, when NIFTP is encompassed within the malignant diagnosis, this range widens to 10% to 30%. Nevertheless, the malignancy rates reported across different institutions exhibit substantial variability, spanning from 15.7% to 81%. The empirical observations diverge from the TBSRTC predictions, indicating a notable departure from the anticipated malignancy risk within this category.[3,10,11]

Numerous independent investigations have consistently shown that the actual risk of malignancy within this category far exceeds the range that the TBSRTC has set forth. Specifically, the mean risk of malignancy across studies involving cases progressing to surgical resection stands at 34%, which substantially exceeds the risk reported within the present study. This incongruity in malignancy risk estimations can be attributed to several factors, including variations in the pathologist's level of expertise in interpreting cases, nuances associated with the needle employed during procedures, variability in physician proficiency conducting the procedure, and discrepancies in cytological processing techniques, such as the continued use of conventional smear in lieu of liquid-based cytology within certain centers.[1,12,13]

In certain institutional contexts, a substantial number of cases do not undergo postoperative follow-up, thereby exacerbating the challenge of procuring precise statistical data regarding actual malignancy rates. This limitation contributes to the complexity of accurately assessing the true malignancy landscape.[13,14]

In our study, malignancy was detected in 55.5% of the cases in which bacteria were repeated, which is much higher than the 21.7% rate in the literature.[9]

In the investigation conducted by Partyka et al, the diagnostic classification of AUS/FLUS exhibited noteworthy sensitivity (ranging from 80% to 100%) and NPV (ranging from 90% to 100%) in relation to malignancy, although specificity (ranging from 10% to 64%) and PPV (ranging from 21% to 44%) demonstrated relatively diminished performance.[15] Similar observations were recorded by Rossi et al, who documented elevated sensitivity (ranging from 74% to 94%) and NPV (ranging from 91% to 97%), but encountered substantial variability in specificity (ranging from 25% to 91%) and PPV (ranging from 37% to 82%).[16] Our own findings were consistent with this sensitivity-NPV pattern, although slight decrements were noted in specificity and PPV.

In our study, sensitivity and specificity between nuclear atypia and malignancy risk were 67.9% and 51.6%, respectively, and a malignant diagnosis was given in 11.9% of cases with nuclear atypia. While the incidence of malignancy within our institution remains relatively modest, our prevalence of AUS/FLUS diagnoses through FNAC (21%) mirrors observations documented in other investigations.[17,18] Contrary to the Bethesda system's stipulation that this category should represent a last-resort classification, accounting for 7% or less of all thyroid FNA, achieving this specific benchmark proves challenging for many laboratories. Consequently, an ideal threshold of 10% may be more pragmatic.[4] Nonetheless, disparate investigations proffer divergent rates, spanning from 3% to 27.2%.[3,19]

The frequency of AUS/FLUS diagnoses varies across institutions, largely attributed to the heterogeneity of fluid preparation techniques.[20,21] Remarkably, within our study, the diagnosis of AUS/FLUS was rendered through both conventional smear and liquid-based cytology preparations, and no statistically significant distinction emerged between these methodologies ($P>.05$).

There exists a body of research suggesting the subdivision of the AUS/FLUS diagnosis into distinct subcategories, aiming either to curtail the prevalence of the AUS/FLUS classification or to mitigate the elevated malignancy rate associated with it. These efforts are envisioned as strategies to enhance diagnostic precision and clinical management effectiveness.[22,23]

In our study, similar to other studies, we re-evaluated the cases diagnosed with AUS/FLUS microscopically and divided them into two groups as nuclear atypia and architectural. This process led to the classification of cases into two distinct groups based on nuclear atypia and architectural atypia. In instances featuring nuclear atypia, the observed malignancy rate stood at 11.9%, marginally surpassing the 8.3% rate discerned within cases characterized by architectural atypia. However, statistical analysis did not yield a significant difference

(*P*=.32). From this vantage point, our findings suggest the potential utility of forming a subgroup in which nuclear features assume greater prominence, potentially contributing to a refined diagnostic framework.[3,4] The relationship between the neoplasia risk rate and nuclear and structural atypia in our study was similar to the data in the literature, with rates of 32% and 75%.[9]

The management of patients afflicted with AUS/FLUS warrants repeat FNAC, molecular analysis as mRNA gene expression or DNA mutations (BRAF, KRAS, HRAS, NRAS, PIK3CA, RET/PTC1, RET/PTC3, PAX8/PPARγ), or surgical resection within a three-month window, in accordance with the Bethesda system recommendations.[4,15] In our study, 16% of cases that underwent repeat FNAC and were subsequently subjected to surgical resection were ultimately diagnosed as malignant. This outcome is consistent with the anticipated malignancy rate range of 10%–30%.[3,4] For a substantial proportion of cases (83.9%) subjected to repeat FNAC, benign results were ascertained. This observation is consistent with similar findings documented in the literature.[24-26]

Clinical and radiological correlations play a pivotal role in guiding decision-making for patients harboring AUS/FLUS nodules. Our study confirmed what other research has found: the presence of symptomatic nodules, internal nodule calcification, and irregular nodule margins significantly contribute to predicting malignancy.[27] As such, ultrasonographic features offer a pragmatic avenue for informed decision-making pertaining to the management strategy for individuals exhibiting AUS/FLUS-associated nodules.

In the context of our study, the process of data interpretation was rigorously standardized to ensure consistency. Competent radiologists were entrusted with the task of interpreting ultrasound findings, while experienced senior pathologists from the same department undertook the interpretation of FNAC and repeat FNAC results in accordance with the established standardized TBSRTC. Furthermore, a solitary senior pathologist assumed the responsibility of the final subcategorization of FNAC outcomes and the comprehensive review of histology results. Consequently, this meticulous approach served to minimize inter-observer discrepancies. Notwithstanding these measures, it is pertinent to acknowledge the inherent limitations of the current case pool. A broader scope encompassing a larger dataset would undoubtedly facilitate the attainment of statistically significant outcomes, thereby enhancing the robustness of the study's conclusions.

In conclusion, our investigation affirms a malignancy rate of 10.4% within thyroid nodules categorized as AUS/FLUS upon resection. Among cases subjected to repeat FNACs, 16% received a malignant diagnosis, while 83.9% were characterized as benign upon subsequent resection. This accentuates the crucial role of repeated FNAC in achieving accurate diagnostic outcomes within this category. Although our study did not reveal a statistically significant distinction between the nuclear atypia and architectural atypia subgroups within the AUS/FLUS diagnosis, it is noteworthy that the former exhibited a slightly elevated malignancy rate. This finding underscores the importance of pathologists interpreting FNAC results to be attuned to nuclear atypia patterns. Given the complexities inherent to this classification, the potential for its reconfiguration within the Bethesda system should be explored through extensive investigations encompassing larger case cohorts.

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