Research Article

What to Do for Atypia of Uncertain Significance in Pediatric Thyroid Nodules?

Ozdemir Uslu Z et al. Management of Pediatric Thyroid Nodules with AUS Cytology

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What is already known on this topic?
Thyroid nodules in children and adolescents are less common but likelihood of malignancy is higher than in adults. The ATA pediatric guidelines recommend surgery while The ETA guidelines recommend fine-needle aspiration biopsy repetition after 6 months for thyroid nodules with atypia of undetermined significance cytology.

What this study adds?
Lobectomy appears to be a more appropriate approach in AUS cases only with nuclear atypia to avoid diagnostic leap and unnecessary surgery.

Abstract
Objective: In the management of the pediatric thyroid nodules with atypia of undetermined significance (AUS) cytology, The American Thyroid Association (ATA) pediatric guidelines recommend surgery while The European Thyroid Association (ETA) guidelines recommend fine-needle aspiration biopsy (FNAB) repetition after 6 months. The aim of this study is to determine the markers of malignancy in AUS cases and to discuss the management of pediatric AUS nodules.
Methods: The specimens of the 20 patients who underwent surgery due to AUS cytology were re-evaluated and subcategorized according to the Bethesda 2023 classification.
Results: On the histological diagnosis of the cases, 11 (55%) were benign; while 9 were malignant (45%). On the subcategorization of AUS, nuclear atypia was present in 14 patients (70%), other atypia in 6 patients (30%). Of the cases with nuclear atypia, 64.3% were malignant (n=9) while no malignancy was detected in the cases with other atypia (p=0.012). Among the cytopathological features, chromatin clearing, nuclear enlargement, and irregular margins were significantly associated with malignancy (p=0.035, p=0.003, p=0.012, respectively). Adhering to ETA recommendations would delay diagnosis by at least 6 months in 45% of our malignant cases. Conversely, performing lobectomy according to ATA recommendations may lead to unnecessary surgery in 55% of our cases.
Conclusion: Based on the data from our study, lobectomy appears to be a more appropriate approach in AUS cases only with nuclear atypia to avoid diagnostic leap and unnecessary surgery. Guidelines should be updated according to the latest Bethesda.
Keywords: Pediatric thyroid nodules, rate of thyroid malignancy, thyroid fine needle aspiration biopsy, The Bethesda System for Reporting Thyroid Cytopathology classification, atypia of undetermined significance, nuclear atypia

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Introduction

Thyroid nodules in children and adolescents are less common than in adults (0.2-5% vs. 19-35%), although likelihood of malignancy is higher in children and adolescents than adults (up to 20-26% vs. 7-15%)(1–6). Key ultrasonographic features of thyroid nodules such as hypoechogenicity, solid composition, microcalcifications, irregular nuclear contour, increased intranodular vascularity, and a taller-than-wide shape are the significant indicators of thyroid malignancy(7–9). The American Thyroid Association (ATA) adult guidelines recommend ultrasound-guided fine-needle aspiration biopsy (FNAB) for solid or partially cystic thyroid nodules ≥1 cm or nodule with suspicious ultrasonographic findings in patient without risk factors for thyroid malignancy, similar to The European Thyroid Association (ETA) guidelines which recommend FNAB for suspicious nodules based on multiple ultrasound characteristics(6,10). FNAB results are reported according to The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) that is 6-category-based reporting system that provides a uniform reporting scheme for thyroid FNAB since the publication of the first edition in 2009(11). TBSRTC has been updated in 2023. The latest edition simplified the terminology of the 6 categories and leave using the title of ''unsatisfactory'', ''follicular lesion of undetermined significance'' and ''suspicious for a follicular neoplasm'' for the TBSRTC category I, III and IV respectively. The new categories are: (I) nondiagnostic; (II) benign; (III) atypia of undetermined significance (AUS); (IV) follicular neoplasm; (V) suspicious for malignancy; and (VI) malignant(12). Additionally, in TBSRTC 2023, AUS subcategories are newly divided into 2 groups: nuclear and others (architectural, oncocytic and lymphocytic atypia) whereas in TBSRTC 2017, they were divided into 5 subcategories: cytologic, architectural, cytologic and architectural atypia, Hürthle cell AUS, and atypia not otherwise specified(12).

AUS is the most doubtful category, as it is neither benign nor clearly malignant, and can march to malignant or suspicious for malignancy. The rate of malignancy (ROM) of AUS nodules in adults averages 22% (range 13-30%), while it is 28% (range 11-54%) in pediatric

population(12). The management of adult thyroid nodules with AUS cytology includes some combination of FNAB repetition, molecular testing, and surgery depending on risk factors, patient history, clinical features, sonographic pattern, and patient preference. Guidelines provide different recommendations for the management of thyroid nodules with AUS cytology in children. In the management of the pediatric thyroid nodules with AUS cytology, the ATA pediatric guidelines recommend surgery (mostly lobectomy and isthmusectomy) while the ETA guidelines recommend FNAB repetition after 6 months(5,6). This discrepancy in the guidelines is attributed to the lack of data and limited research on this subject.

The aim of this study is to determine the rate of malignancy and the markers of malignancy in AUS cases among children and to discuss the approach and management of pediatric thyroid nodules with AUS cytology.

Materials and Methods

Records of children and adolescent who were followed up for thyroid nodules with AUS cytology in the Pediatric Endocrinology division of Dr. Sami Ulus Child Health and Diseases Research and Training Hospital were retrospectively evaluated. Since the first edition of TBSRTC was published in 2009, patients were screened from 2009 to 2023. Age at diagnose, gender, TSH levels at diagnosis (μIU/mL), patient history, thyroid ultrasound (US) findings, FNAB cytopathology, and histopathological results were recorded.

Experienced radiologists performed US and FNAB procedures on the patients using high-frequency linear-array transducers (Toshiba Aplio 500, Toshiba Medical Systems, Tokyo, Japan). The US results were evaluated for composition (solid, semisolid, cystic), echogeinicity (isoechoic, hypoechoic), margin characteristics (regular, irregular), and presence of microcalcifications. Sampling was done with 22-gauge needles attached to 10 mL syringes. Five or six samples were spread on slides for each treatment. For patients with multiple nodules, the most suspicious nodule was selected. Surgery decisions for children with AUS cytology were made by experienced multidisciplinary thyroid team, including experts in pediatric endocrinology, radiology, pathology, oncology, and surgery, following ATA guidelines.

Within the scope of this study, FNAB samples were re-evaluated by the same experienced pathologist and subcategorized into two groups - nuclear and other - according to the new TBSRTC criteria. Nuclear atypia was defined as focal nuclear changes such as chromatin clearing, nuclear enlargement, irregular nuclear contour.

In the literature, the terms "malignancy rate" and "risk of malignancy" are used interchangeably to describe the percentage of malignant cases in each TBSRTC category. In most studies, the number of malignant cases is divided by the number of cases with histopathological diagnosis. However, due to variations in surgical selection rates, determining the actual ROM is challenging. In this study, two different methods were used to estimate the most accurate ROM. The first method (ROM-H) was calculated by dividing the number of malignant cases by the number of AUS cases that underwent surgery and had a histopathological diagnosis. The second method (ROM-O) was calculated by dividing the number of malignant cases by the overall number of AUS cases.

Statistical Analysis

Statistical Package for the Social Sciences, version 22 (IBM Inc., Chicago, IL, USA) software was used for statistical analysis. In descriptive statistics, qualitative variables were expressed as frequency (n), and percentage (%); quantitative variables as mean± standard deviation (SD) and median. χ^2 test used in the analysis of categorical variables, and the Mann-Whitney U test was used for nonparametric continuous variables. P values <0.05 were considered significant.

Results

Among 312 children and adolescent who underwent FNAB for thyroid nodule in our outpatient clinic, 28 (9%) patients had AUS cytology. These patients were recommended lobectomy in line with the ATA guidelines. Five patients (17.8%) refused surgery, three patients (10.7%) transferred to adult clinics upon turning 18, and were followed up according to the adult guidelines. Twenty patients who underwent surgical evaluation were included in the study.

The mean age of cases was 14.3±3 (Range: 7.7-18); the female/male ratio was 4. Backgrounds, complaints on admission, and final diagnoses of the patients are presented in Table 1. Six patients (30%) had Hashimoto's thyroiditis, 2 patients (10%) had congenital hypothyroidism, 1 patient each (5%) had thyroglossal duct cyst, Turner syndrome, insulin depended diabetes mellitus, precocious puberty, and epilepsy. On admission, 45% of the patients (n=9) had no symptoms. Among the others 25% (n=5) had swelling in the neck, 25% (n=5) had alterations of thyroid function tests, and 5% (n=1) had breathing difficulty. Three patients (15%) had *DICER1* mutation (Table 1).

Regarding thyroid ultrasound findings, 25% of the patients (n=5) had parenchymal heterogeneity. Sixty-five percent of the nodules (n=13) were solid, 10% (n=2) were semisolid, and 25% (n=5) were cystic. Thirty-five percent of the nodules (n=7) were hypoechoic, 65% of the nodules (n=13) were isoechoic. Microcalcifications were observed in 35% of the nodules (n=7), irregular margins in 15% (n=3), and increased intranodular vascularity in 15% (n=3).

When the FNAB slides were re-evaluated by the same pathologist, nuclear atypia findings revealed chromatin clearing in 50% (n=10), nuclear enlargement in 50% (n=10), irregular nuclear contour in 70% (n=14), and histiocytoid cells in 5% (n=1). Among other atypia findings, three-dimensional groups were present in 10% (n=2), microfollicles in 30% (n=6). On the subcategorization of AUS, nuclear atypia was found in 14 patients (70%), and other atypia in 6 patients (30%).

On the histological diagnosis, neoplasia was detected in 18 patients (90%). Of the cases, 11 (55%) were benign [follicular adenoma=1 (9.1%), nodular hyperplasia=8 (72.7%), chronic lymphocytic thyroiditis=2 (18.2%)], while 9 were malignant (45%) [papillary thyroid carcinoma (PTC)=4 (44.5%), follicular variant-PTC=2 (FV-PTC) (22.2%), papillary microcarcinoma=3 (33.3%)]. The ROM of nodules with AUS cytology based on histopathological diagnosis (ROM-H) was 45% (9/20), and when all aspirated AUS nodules were included, the overall ROM (ROM-O) was 32.1% (9/28). In the benign and malignant groups, no significant differences were found in terms of age, gender, pubertal status, genetic predisposition, and serum TSH levels (Table 2). There was no significant difference in the ultrasound findings between malignant and benign nodules (Table 3). Benign nodules appeared to be larger (p=0.036) (Table 3). The mean diameter of the cystic nodules was 25.8±22.2 cm, while the non-cystic nodules had a mean diameter of 13.4±5.5 cm (p=0.003). Eighty percent of the cystic nodules (n=4) were benign, while 20% (n=1) was malignant. The ROM-H was higher in patients with nuclear atypia findings such as chromatin clearing, nuclear enlargement, and irregular nuclear contour (p=0.035, p=0.003, p=0.012, respectively) (Table 4). All nodules with microfollicles were benign (p=0.012) (Table 4). Of the cases with nuclear atypia 64.3% were malignant (9/14) while no malignancy was detected in other atypia (p=0.012) (Table 5).

In our study, we examined patients with *DICER1* mutations separately due to their predisposition to malignancy. We found that only one out of the patients with *DICER1* mutation had malignant histology (PTC), while the other two had nodular hyperplasia. So, the ROM-H of the patients with *DICER1* mutation was found to be 33.3% whereas it was 47% for those without the mutation. The ROM was not different between the two groups (p= 0.57) (Table 2).

Discussion

In the literature, there are varying data on the ROM of pediatric AUS cases. The ROM-H was 45% while ROM-O was 32.1% in our cohort. The true ROM lies between the ROM-H and the ROM-O. Considering resection rates ranging from 52% to 100%, the ROM-H of thyroid nodules with AUS cytology in the literature has been estimated to be between 20% and 75%(13–18). In our clinic, 3 of the 28 AUS cases were transferred to adult clinics due to being over 18 years old, and 5 patients refused surgery. Therefore, since our surgery rate (80%) is relatively high compared to the literature, we believe that the ROM-H found in our study reflects a nearly realistic ROM.

DICER1 syndrome is an autosomal-dominant, pleiotropic tumor-predisposition disorder, increasing the risk of non-toxic multinodular goiter, adenoma, and thyroid cancer, caused by pathogenic variants in the *DICER1*(19–21). In our cohort, only one of the patients with *DICER1* mutation had differentiated thyroid cancer while other two had nodular hyperplasia. In our study, the ROM-H of the patients with *DICER1*

mutation was found to be 33.3% compared to 47% for those without mutation. Contrary to the literature, *DICER1* mutation does not increase the rate of malignancy in our cohort. The low number of patients with *DICER1* mutations, which is one of the limitations of the study, may have led to the conclusion that DICER1 does not increase the malignancy rate.

In studies, ultrasonographic findings such as solid structure, hypoechogenicity, presence of microcalcifications, irregular nuclear contour, increased intranodular vascularity, and abnormal cervical lymph nodes have been found to be associated with malignancy(22,23). Lee *et al.* also found that microcalcifications and irregular margins on US was associated with malignancy in AUS cases(24). However, no significant relationship was found between malignancy and US findings in our study, likely due to the small sample size. In our cohort benign nodules were found to be larger. Most of the cyctic nodules were benign and larger. It is thought that the diameters of benign nodules were larger due to their cystic component.

The latest edition of TBSRTC divided AUS into 2 subcategories: AUS-nuclear and AUS-other. In our cohort, the ROM-H of cases with nuclear atypia was found to be 64.3% while ROM-H of the cases with other atypia was found to be 0%. In the literature, both in adult and pediatric studies, the ROM in nuclear atypia is 2 to 4 times higher than in other atypia(25–30). Similar to our study, Smith *et al.* found that, in a study including 43 pediatric AUS cases, the ROM-H of nuclear atypia (formerly known as cytological atypia) was 50%(25). Another recent pediatric study by Jin *et al.* found ROM-H to be 52%(14). According to the study of Cherella *et al.* including 68 pediatric thyroid nodules with AUS cytology, ROM-O in the presence of nuclear atypia increases to 59%, which is 10 times higher than in the absence of nuclear atypia(17).

Guidelines recommend different managements for thyroid nodules with AUS cytology in children. The ATA pediatric guidelines recommend surgery while the ETA guidelines recommend FNAB repetition after 6 months(5,6). When lobectomy is performed based on ATA recommendations for AUS cases, the likelihood of missed diagnosis is minimized, yet some patients undergo unnecessary surgery. Following ETA recommendations with repeat FNAB in 6 months reduces the risk of unnecessary surgery but may delay diagnosis in malignant cases. Our data suggests that adhering to ETA recommendations would delay malignancy diagnosis by at least 6 months in 45% of our cases, which is a considerable risk. However, when we perform lobectomy according to the ATA recommendations for our cases, 55% of cases undergo unnecessary surgery. Due to the significantly higher ROM-H in cases with nuclear atypia in our study, performing lobectomy for these cases reduces the risk of unnecessary surgery from 55% to 35.7%, while the risk of misdiagnosis remains at 0%. Based on clinical and cytological evaluations, we agree that surgical decisions should be individualized for each patient, even in the absence of nuclear atypia. AUS cases without nuclear atypia may carry a lower risk, but surgical decisions should also take other clinical factors into consideration. According to our findings, performing surgery only on cases with nuclear atypia, FNAB repetition after 6 months for cases with other atypia is more appropriate than the recommendations of both ATA and ETA guidelines.

One of the limitations of our study, which reached significant results regarding the management of malignancy in pediatric AUS cases, is the small sample size. Additionally, since not all AUS cases were operated on, we cannot calculate the true ROM. We only know that the true ROM falls between ROM-H and ROM-O. However, given our high operation rates, the ROM-H we found closely reflects the true ROM.

Conclusion

The literature indicates that the rate of malignancy in AUS in children is higher than in adults. Recommending FNAB six months later for AUS cases can lead to a significant number of missed malignancy diagnoses. However, performing surgery on every AUS case often results in unnecessary surgery. Based on our findings, it is essential to consider the subgroups in the latest TBSRTC classification for the management of AUS cases. The association between nuclear atypia and malignancy has been clearly demonstrated, and lobectomy appears to be a more appropriate approach in AUS cases with nuclear atypia to avoid diagnostic delay and unnecessary surgery. Therefore, management decisions for AUS cases should be based on the presence of nuclear atypia, and guidelines should be updated according to the latest Bethesda classification to avoid diagnostic leaps and unnecessary surgeries.

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Table 1 The characteristics of AUS cases

Abbreviations: AUS: Atypia of undetermined significance; PTC: Papillary thyroid cancer; FV-PTC: Follicular variant- papillary thyroid cancer

Patient no	Background	Complaint	Nuclear atypia	Histological diagnosis
1	N/A	Alterations in thyroid function tests	+	PTC
2	N/A	Swelling in the neck	-	Follicular adenoma
3	Hashimoto's thyroiditis	Alterations in thyroid function tests	+	PTC
4	N/A	Swelling in the neck	-	Nodular hyperplasia
5	DICER1 mutation	Swelling in the neck	-	Nodular hyperplasia
6	Hashimoto's thyroiditis	N/A	+	FV-PTC
7	Thyroglossal duct cyst	Swelling in the neck	+	FV-PTC
8	Hashimoto's thyroiditis	Alterations in thyroid function tests	+	Papillary microcarcinoma
9	Hashimoto's thyroiditis	Difficulty breathing	+	Papillary microcarcinoma
10	Hashimoto's thyroiditis	Alterations in thyroid function tests	+	Chronic lymphocytic thyroiditis
11	Insulin depended diabetes mellitus	N/A	+	PTC
12	Turner syndrome	N/A	+	Chronic lymphocytic thyroiditis
13	Congenital hypothyroidism	N/A	-	Nodular hyperplasia
14	N/A	Swelling in the neck	+	Nodular hyperplasia
15	DICER1 mutation	N/A	+	PTC
16	Epilepsy	N/A	+	Papillary microcarcinoma
17	Hashimoto's thyroiditis	N/A	+	Nodular hyperplasia
18	Precocious puberty	Alterations in thyroid function tests	-	Nodular hyperplasia
19	DICER1 mutation	N/A	+	Nodular hyperplasia
20	Congenital hypothyroidism	N/A	-	Nodular hyperplasia

Table 2: Clinical and Laboratory Characteristics of Benign and Malignant Cases with AUS Cytology

	Total (n=20)	Benign (n=11)	Malignant (n=9)	p
Age, y, mean ±SD	14.3±3	13.9±3.2	14.6±2.8	0.5
Gender, n (%)				0.62
Female	16 (80)	9 (56.3)	7 (43.8)	
Male	4 (20)	2 (50)	2 (50)	
Puberty, n (%)				0.65
Prepubertal	9 (45)	5 (55.6)	4 (44.4)	
Pubertal	11 (55)	6 (54.5)	5 (45.5)	
TSH(μIU/mL),median (min-max)	1.73 (0.02-6.98)	1.59 (1-3.59)	1.77 (1.09-3.80)	0.11
Genetic predisposition (*DICER1*), n (%)				0.57
Absent	17 (85)	9 (52.9)	8 (47.1)	
Present	3 (15)	2 (66.7)	1 (33.3)	

Table 3 Ultrasonographic Features of Benign and Malignant Cases with AUS Cytology

	Total (n=20)	Benign (n=11)	Malignant (n=9)	p
Echotexture, n (%)				0.98
Homogeneous	15 (75)	10 (66.7)	5 (33.3)	
Heterogeneous	5 (25)	1 (20)	4 (80)	
Composition, n (%)				0.47
Solid	13 (65)	6 (46.2)	7 (53.8)	
Semisolid	2 (10)	1 (50)	1 (50)	
Cystic	5 (25)	4 (80)	1 (20)	
Echogenicity, n (%)				0.63
Isoechoic	13 (65)	7 (53.8)	6 (46.2)	
Hypoechoic	7 (35)	4 (57.1)	3 (42.9)	
Microcalcification, n (%)				0.63
Absent	13 (65)	7 (53.8)	6 (46.2)	
Present	7 (35)	4 (57.1)	3 (42.9)	
Margin, n (%)				0.42
Regular	17 (85)	10 (58.8)	7 (41.2)	
Irregular	3 (15)	1 (33.3)	2 (66.7)	
Intranodular vascularization, n (%)				0.57
Absent	17 (85)	9 (52.9)	8 (47.1)	
Present	3 (15)	2 (66.7)	1 (33.3)	
Thyroid volume SDS, median (min-max)	1.29[(-2)-(9.21)]	1.17[(-2)-(9.21)]	1.39[(-0.93)-(8.61)]	0.73
Diameter of the thyroid nodules (mm),mean ±SD	16.51±12.54	20.84±15.71	11.22±2.82	0.036

Table 4 Cytopathological Features of Benign and Malignant Cases with AUS Cytology

	Total n (%)	Benign n (%)	Malignant n (%)	P
Findings of nuclear atypia				
Chromatin clearing				**0.035**
Absent	10 (50)	8 (80)	2 (20)	
Present	10 (50)	3 (30)	7 (70)	
Nuclear enlargement				**0.003**
Absent	10 (50)	9 (90)	1 (10)	
Present	10 (50)	2 (20)	8 (80)	
Irregular nuclear contour				**0.012**
Absent	6 (30)	6 (100)	0 (0)	
Present	14 (70)	5 (35.7)	9 (64.3)	
Histiocytoid cells				0.45
Absent	19 (95)	13 (59.1)	8 (36.4)	
Present	1 (5)	0 (0)	1 (4.5)	
Findings of other atypia				
Three-dimensional groups				0.71
Absent	18 (90)	10 (55.6)	8 (44.4)	
Present	2 (10)	1 (50)	1 (50)	
Microfollicles				**0.012**
Absent	14 (70)	5 (35.7)	9 (64.3)	
Present	6 (30)	6 (100)	0 (0)	

Table 5 Rate of Malignancy of Pediatric Thyroid Nodules with AUS Cytology

Atypia subcategory	Total n (%)	Benign, n (%)	Malignant, n (%)	p
Total	20 (100)	11 (55)	9 (45)	**0.012**
Nuclear atypia	14 (70)	5 (35.7)	9 (64.3)	
Other atypia	6 (30)	6 (100)	0 (0)	