

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

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What is already known on this topic?

Thyroid nodules in children and adolescents are less common than in adults but the likelihood of malignancy is higher. The American Thyroid Association pediatric guidelines recommend surgery while the European Thyroid Association guidelines recommend fine-needle aspiration biopsy repetition after six months for thyroid nodules with a cytological finding of atypia of undetermined significance.

What this study adds?

Lobectomy appears to be a more appropriate approach in cases of atypia of undetermined significance, but only when nuclear atypia is present, to avoid diagnostic leap and unnecessary surgery.

Abstract

Objective: International guidelines recommend different approaches for the management of the pediatric thyroid nodules with a finding of atypia of undetermined significance (AUS) on cytology. The American Thyroid Association (ATA) pediatric guidelines recommend surgery while The European Thyroid Association (ETA) guidelines recommend repeat fine-needle aspiration biopsy after six months. Our objective was to determine markers of malignancy in AUS cases and to discuss the management of pediatric AUS nodules.

Methods: The specimens of pediatric patients who underwent surgery due to AUS cytology were re-evaluated and subcategorized according to the Bethesda 2023 classification.

Results: Of the 20 cases included, 11 (55 %) were histologically benign, while 9 (45 %) were malignant. On the subcategorization of AUS, nuclear atypia was present in 14 patients (70 %) and 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, and 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 but only when

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nuclear atypia is present, to avoid diagnostic leap and unnecessary surgery. Guidelines should be updated according to the latest Bethesda classification.

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

Introduction

Thyroid nodules in children and adolescents are less common than in adults (0.2-5% vs. 19-35%), although the likelihood of malignancy is higher in children and adolescents than adults (up to 20-26% vs. 7-15%) (1,2,3,4,5,6). 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 significant indicators of thyroid malignancy (7,8,9). The American Thyroid Association (ATA) adult guidelines recommend ultrasound (US)-guided fine-needle aspiration biopsy (FNAB) for solid or partially cystic thyroid nodules ≥ 1 cm or nodule with suspicious ultrasonographic findings in a patient without risk factors for thyroid malignancy, which is similar to The European Thyroid Association (ETA) guidelines that recommend FNAB for suspicious nodules based on multiple ultrasound characteristics (5,6). FNAB results are reported according to The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). The TBSRTC is a category-based reporting system, comprising six categories, that has provided a uniform reporting scheme for thyroid FNAB since the publication of the first edition in 2009 (10). TBSRTC was updated in 2023. The latest edition simplified the terminology of the six categories and recommends dropping the terms “unsatisfactory”, “follicular lesion of undetermined significance” and “suspicious for a follicular neoplasm” for TBSRTC categories 1, 3 and 4 respectively. The new categories are: (1) non-diagnostic; (2) benign; (3) atypia of undetermined significance (AUS); (4) follicular neoplasm; (5) suspicious for malignancy; and (6) malignant (11). Furthermore, in TBSRTC 2023 the AUS subcategories are newly divided into two groups: nuclear and others (including architectural, oncocytic and lymphocytic atypia), whereas in TBSRTC 2017, they were divided into five subcategories: cytologic, architectural, cytologic and architectural atypia, Hürthle cell AUS, and atypia not otherwise specified (11).

AUS is the most doubtful category, as it is neither benign nor clearly malignant, and can progress to malignant or suspicious for malignancy. The rate of malignancy (ROM) of AUS nodules in adults is around 22% (range 13-30%), while it is 28% (range 11-54%) in the pediatric population (11). 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 repeat FNAB after six 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, therefore, was to determine the ROM and the markers of malignancy in AUS cases among children and to discuss the approach and management of pediatric thyroid nodules with AUS cytology.

Methods

Records of children and adolescent who were followed up for thyroid nodules with AUS cytology in the Pediatric Endocrinology division of University of Health Sciences Türkiye, Ankara Dr. Sami Ulus Child Health and Diseases Training and Research Hospital were retrospectively evaluated. Since the first edition of TBSRTC was published in 2009, patients were screened from 2009 to 2023. Age at diagnosis, gender, thyroid stimulating hormone (TSH) levels at diagnosis (in $\mu\text{IU/mL}$), patient history, thyroid 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), echogenicity (isoechoic, hypoechoic), margin characteristics (regular, irregular), and presence of microcalcifications. Sampling was performed with 22-gauge needles attached to 10 mL syringes. Five or six samples were spread on slides for each patient. For patients with multiple nodules, the most suspicious nodule was selected. Surgery decisions for children with AUS cytology were made by an 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 by type of atypia, nuclear and other, as described in the new TBSRTC criteria. Nuclear atypia was defined as focal nuclear changes such as chromatin clearing, nuclear enlargement, and 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 the present study, two different methods were used to estimate the most accurate ROM. The first method (ROM-H: ROM of nodules with AUS cytology based on histopathologically diagnosed) 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: Overall ROM) was calculated by dividing the number of malignant cases by the overall number of AUS cases.

Approval was obtained from the Ankara Atatürk Sanatorium Training and Research Hospital Clinical Research Ethics Committee (decision no: 2012-KAEK-15/2767, date: 23.08.2023).

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 are expressed as frequency (n), and percentage (%); quantitative variables as mean $\pm$ standard deviation for normally distributed data and as median (minimum-maximum) for non-normally distributed data. Normality was assessed using the Shapiro-Wilk test. The χ^2 test was used in the analysis of categorical variables. The Student's t-test was used for comparisons of normally distributed continuous variables, and Mann-Whitney U test for non-normally distributed variables. A $p < 0.05$ was considered statistically significant.

Results

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

The mean age of cases was 14.3 ± 3 years (range: 7.7-18 years); the female/male ratio was 4:1. Backgrounds, complaints on admission, and final diagnoses of the patients are presented in Table 1. Six patients (30%) had Hashimoto thyroiditis, two patients (10%) had congenital hypothyroidism, one patient each (5%) had thyroglossal duct cyst, Turner syndrome, insulin dependent 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).

In terms of thyroid US 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 making the newly recommended subcategorization of AUS, nuclear atypia was found in 14 (70%), and other atypia in 6 (30%).

Histological diagnosis included neoplasia in 18 patients (90%). Of these, 11 (55%) were benign [follicular adenoma 9.1% (n=1), nodular hyperplasia in 72.7% (n=8), and chronic lymphocytic thyroiditis in 18.2% (n=2)], while nine were malignant (45%) [papillary thyroid carcinoma (PTC) in 44.5% (n=4), follicular variant-PTC in 22.2% (n=2), and papillary microcarcinoma in 33.3% (n=3)]. The ROM-H of nodules with AUS cytology was 45% (9/20), and when all aspirated AUS nodules were included, the 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, or serum TSH levels (Table 2). There was no significant difference in the US findings between malignant and benign nodules (Table 3) with the exception of the benign nodules being significantly larger in diameter ($p = 0.036$) (Table 3). The mean diameter of cystic nodules was 25.8 ± 22.2 mm, while the non-cystic nodules had a mean diameter of 13.4 ± 5.5 mm ($p = 0.003$). Eighty percent (n=4) of the cystic nodules were benign, while 20% (n=1) were malignant. The ROM-H was higher

Table 1. The characteristics of AUS cases

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	<i>DICER1</i> 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	<i>DICER1</i> 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	<i>DICER1</i> mutation	N/A	+	Nodular hyperplasia
20	Congenital hypothyroidism	N/A	-	Nodular hyperplasia

AUS: atypia of undetermined significance, PTC: papillary thyroid cancer, FV-PTC: follicular variant-papillary thyroid cancer, N/A: not applicable

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 $\pm$ SD	14.3 $\pm$ 3	13.9 $\pm$ 3.2	14.6 $\pm$ 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 (μ U/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 (<i>DICER1</i>), n (%)				0.57
Absent	17 (85)	9 (52.9)	8 (47.1)	
Present	3 (15)	2 (66.7)	1 (33.3)	

min-max: minimum-maximum, TSH: thyroid stimulating hormone, AUS: atypia of undetermined significance, SD: standard deviation

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 the "other atypia" group ($p = 0.012$) (Table 5).

In the present study, patients with *DICER1* mutations were examined 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 ($p = 0.57$) (Table 2).

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 $\pm$ SD	16.51 $\pm$ 12.54	20.84 $\pm$ 15.71	11.22 $\pm$ 2.82	0.036

min-max: minimum-maximum, AUS: atypia of undetermined significance, SD: standard deviation, SDS: SD score

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)	

AUS: atypia of undetermined significance

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)	

AUS: atypia of undetermined significance

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 % (12,13,14,15,16,17). In our clinic, three of the 28 AUS cases were transferred to adult clinics due to being over 18 years old, and five patients refused surgery. It was noted that the three patients transferred to adult clinics were not operated on but were followed up clinically according to adult guidelines. 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 *DICER1* (18,19,20). In our cohort, only one of the patients with *DICER1* mutation had differentiated thyroid cancer while the other two had nodular hyperplasia. In our study, the ROM-H of the patients with *DICER1* mutation was 33.3% compared to 47% for those without mutation. Contrary to the literature, *DICER1* mutation did not increase the ROM in our cohort but the low number of patients with *DICER1* mutations, which is one of the limitations of the study, may have led to this unusual finding.

In earlier studies, US 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 (21,22). Lee et al. (23) also found that microcalcifications and irregular margins on US was associated with malignancy in AUS cases. However, no significant relationship was found between malignancy and US findings in our study, again likely due to the small sample size. In our cohort benign nodules were, however, found to be significantly larger. Most of the cystic nodules were benign and larger, probably due to the cystic component.

The latest edition of TBSRTC divided AUS into two 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 has been reported to be 2-4 times higher than in other atypia (24,25,26,27,28,29). Similar to our study, Smith et al. (24) in a study including 43 pediatric AUS cases, reported that the ROM-H of nuclear atypia (formerly known as cytological atypia) was 50 % . Another recent pediatric study by Jin et al. (13) found ROM-H to be 52 % . According to the study of Cherella et al. (16) that included 68 pediatric thyroid nodules with AUS cytology, ROM-O in the presence of nuclear atypia increased to 59 %, which was 10 times higher than in the absence of nuclear atypia.

Guidelines recommend different managements for thyroid nodules with AUS cytology in children. The ATA pediatric guidelines recommend surgery while the ETA guidelines recommend repeat FNAB after six 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 after six 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 six months in 45 % of our cases, which is a considerable risk. However, when we performed lobectomy according to the ATA recommendations for our cases, 55 % of children underwent unnecessary surgery. Due to the significantly higher ROM-H in cases with nuclear atypia in our study, performing lobectomy for these cases would reduce 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 suggest 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. Based on our findings, performing surgery only in cases with nuclear atypia and carrying out repeat FNAB after six months for

cases with other atypia would be more appropriate than the recommendations of both ATA and ETA guidelines.

Study Limitations

One of the limitations of our study is the small sample size. Furthermore, 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 report most likely closely reflects the true ROM.

Conclusion

The literature indicates that the ROM in AUS in children is higher than in adults. Recommending FNAB six months later for AUS cases may lead to a significant number of delayed 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 delays or leaps and subsequent unnecessary surgery.

Ethics

Ethics Committee Approval: Approval was obtained from the Ankara Atatürk Sanatorium Training and Research Hospital Clinical Research Ethics Committee (decision no: 2012-KAEK-15/2767, date: 23.08.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Zülal Özdemir Uslu, Nebiyye Genel, Elif Tuğçe Tunca Küçükali, Agah Akın, İbrahim Karaman, Gürses Şahin, Hasan Bulut, Semra Çetinkaya, Nursel Muratoğlu Şahin, Concept: Zülal Özdemir Uslu, Nursel Muratoğlu Şahin, Design: Zülal Özdemir Uslu, Nursel Muratoğlu Şahin, Data Collection or Processing: Zülal Özdemir Uslu, Nebiyye Genel, Elif Tuğçe Tunca Küçükali, Agah Akın, İbrahim Karaman, Gürses Şahin, Hasan Bulut, Semra Çetinkaya, Nursel Muratoğlu Şahin, Analysis or Interpretation: Zülal Özdemir Uslu, Nebiyye Genel, Elif Tuğçe Tunca Küçükali, Nursel Muratoğlu Şahin, Literature Search:

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References

1. Niedziela M. Pathogenesis, diagnosis and management of thyroid nodules in children. *Endocr Relat Cancer*. 2006;13:427-453.
2. Degnan BM, McClellan DR, Francis GL. An analysis of fine-needle aspiration biopsy of the thyroid in children and adolescents. *J Pediatr Surg*. 1996;31:903-907.
3. Rallison ML, Dobyns BM, Meikle AW, Bishop M, Lyon JL, Stevens W. Natural history of thyroid abnormalities: prevalence, incidence, and regression of thyroid diseases in adolescents and young adults. *Am J Med*. 1991;91:363-370.
4. Dean DS, Gharib H. Epidemiology of thyroid nodules. *Best Pract Res Clin Endocrinol Metab*. 2008;22:901-911.
5. Lebbink CA, Links TP, Czarniecka A, Dias RP, Elisei R, Izatt L, Krude H, Lorenz K, Luster M, Newbold K, Piccardo A, Sobrinho-Simões M, Takano T, Paul van Trotsenburg AS, Verburg FA, van Santen HM. 2022 European Thyroid Association Guidelines for the management of pediatric thyroid nodules and differentiated thyroid carcinoma. *Eur Thyroid J*. 2022;11:e220146.
6. Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenega S, Cerutti JM, Dinanuer CA, Hamilton J, Hay ID, Luster M, Parisi MT, Rachmiel M, Thompson GB, Yamashita S; American Thyroid Association Guidelines Task Force. Management guidelines for children with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2015;25:716-759.
7. Russ G, Bonnema SJ, Erdogan MF, Durante C, Ngu R, Leenhardt L. European Thyroid Association Guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: the EU-TIRADS. *Eur Thyroid J*. 2017;6:225-237. Epub 2017 Aug 8
8. Tessler FN, Middleton WD, Grant EG, Hoang JK, Berland LL, Teefey SA, Cronan JJ, Beland MD, Desser TS, Frates MC, Hammers LW, Hamper UM, Langer JE, Reading CC, Scoutt LM, Stavros AT. ACR Thyroid Imaging, Reporting and Data System (TI-RADS): white paper of the ACR TI-RADS Committee. *J Am Coll Radiol*. 2017;14:587-595. Epub 2017 Apr 2
9. Orlando G, Graceffa G, Mazzola S, Vassallo F, Proclamà MP, Richiusa P, Radellini S, Paladino NC, Melfa G, Scerrino G. The role of "critical" ultrasound reassessment in the decision-making of Bethesda III thyroid nodules. *Medicina (Kaunas)*. 2023;59:1484.
10. Cibas ES, Ali SZ. The Bethesda system for reporting thyroid cytopathology. 2009;19:1159-1165.
11. Ali SZ, Baloch ZW, Cochand-Priollet B, Schmitt FC, Vielh P, VanderLaan PA. The 2023 Bethesda system for reporting thyroid cytopathology. *Thyroid*. 2023;33:1039-1044. Epub 2023 Jul 8
12. Baran JA, Halada S, Bauer AJ, Ricarte-Filho JC, Isaza A, Surrey LF, McGrath C, Bhatti T, Jalaly J, Mostoufi-Moab S, Franco AT, Adzick NS, Kazahaya K, Cahill AM, Baloch Z. Indeterminate thyroid fine-needle aspirations in pediatrics: exploring clinicopathologic features and utility of molecular profiling. *Horm Res Paediatr*. 2022;95:430-441. Epub 2022 Jul 22
13. Jin X, Jing X, Smola B, Heider A. Malignant risk of pediatric Bethesda category III thyroid nodules subcategorized by nuclear atypia and other: A single institution experience. *Cancer Cytopathol*. 2024;132:564-568. Epub 2024 May 21

14. Kılınç Uğurlu A, Bitkay A, Gürbüz F, Karakuş E, Bayram İlkan G, Damar Ç, Şahin S, Kıran MM, Güldalı N, Azılı MN, Şenel E, Ergürhan İlhan İ, Boyraz M. Evaluating postoperative outcomes and investigating the usefulness of EU-TIRADS scoring in managing pediatric thyroid nodules Bethesda 3 and 4. *J Clin Res Pediatr Endocrinol*. 2024;16:160-167. Epub 2024 Jan 18
15. Suh J, Choi HS, Kwon A, Chae HW, Kim HS. Adolescents with thyroid nodules: retrospective analysis of factors predicting malignancy. *Eur J Pediatr*. 2019;179:317-325. Epub 2019 Nov 18
16. Cherella CE, Hollowell ML, Smith JR, Zendejas B, Modi BP, Cibas ES, Wassner AJ. Subtype of atypia on cytology and risk of malignancy in pediatric thyroid nodules. *Cancer Cytopathol*. 2022;130:330-335. Epub 2022 Feb 4
17. Wang H, Mehrad M, Ely KA, Liang J, Solórzano CC, Neblett WW, Coogan AC, Weiss VL. Incidence and malignancy rates of indeterminate pediatric thyroid nodules. *Cancer Cytopathol*. 2019;127:231-239. Epub 2019 Feb 15
18. Rutter MM, Jha P, Schultz KA, Sheil A, Harris AK, Bauer AJ, Field AL, Geller J, Hill DA. DICER1 mutations and differentiated thyroid carcinoma: evidence of a direct association. *J Clin Endocrinol Metab*. 2016;101:1-5. Epub 2015 Nov 10
19. van der Tuin K, de Kock L, Kamping EJ, Hannema SE, Pouwels MM, Niedziela M, van Wezel T, Hes FJ, Jongmans MC, Foulkes WD, Morreau H. Clinical and molecular characteristics may alter treatment strategies of thyroid malignancies in DICER1 syndrome. *J Clin Endocrinol Metab*. 2018;104:277-284.
20. Stewart DR, Best AF, Williams GM, Harney LA, Carr AG, Harris AK, Kratz CP, Dehner LP, Messinger YH, Rosenberg PS, Hill DA, Schultz KAP. Neoplasm risk among individuals with a pathogenic germline variant in DICER1. *J Clin Oncol*. 2019;37:668-676. Epub 2019 Feb 4
21. Han M, Fan F. Bethesda system for reporting thyroid cytopathology—an updated review. *J Clin Transl Pathol*. 2023;3:84-98.
22. Frates MC, Benson CB, Charboneau JW, Cibas ES, Clark OH, Coleman BG, Cronan JJ, Doubilet PM, Evans DB, Goellner JR, Hay ID, Hertzberg BS, Intenzo CM, Jeffrey RB, Langer JE, Larsen PR, Mandel SJ, Middleton WD, Reading CC, Sherman SI, Tessler FN. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. *Ultrasound Q*. 2006;22:239-240.
23. Lee JH, Han K, Kim EK, Moon HJ, Yoon JH, Park VY, Kwak JY. Risk stratification of thyroid nodules with atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) cytology using ultrasonography patterns defined by the 2015 ATA Guidelines. *Ann Otol Rhinol Laryngol*. 2017;126:625-633. Epub 2017 Jul 18
24. Smith M, Pantanowitz L, Khalbuss WE, Benkovich VA, Monaco SE. Indeterminate pediatric thyroid fine needle aspirations: a study of 68 cases. *Acta Cytol*. 2013;57:341-348. Epub 2013 Jul 12
25. Zhao H, Guo H, Zhao L, Cao J, Sun Y, Wang C, Zhang Z. Subclassification of the Bethesda Category III (AUS/FLUS): a study of thyroid FNA cytology based on ThinPrep slides from the National Cancer Center in China. *Cancer Cytopathol*. 2021;129:642-648. Epub 2021 Jun 17
26. Glass RE, Levy JJ, Motanagh SA, Vaickus LJ, Liu X. Atypia of undetermined significance in thyroid cytology: nuclear atypia and architectural atypia are associated with different molecular alterations and risks of malignancy. *Cancer Cytopathol*. 2021;129:966-972. Epub 2021 Aug 16
27. VanderLaan PA, Marqusee E, Krane JF. Usefulness of diagnostic qualifiers for thyroid fine-needle aspirations with atypia of undetermined significance. *Am J Clin Pathol*. 2011;136:572-577.
28. Olson MT, Clark DP, Erozan YS, Ali SZ. Spectrum of risk of malignancy in subcategories of 'atypia of undetermined significance'. *Acta Cytol*. 2011;55:518-525. Epub 2011 Dec 9
29. Guzmán-Arocho YD, VanderLaan PA, Nishino M. Binary subclassification scheme (AUS-nuclear versus AUS-other) adequately risk-stratifies thyroid fine needle aspiration specimens classified as atypia of undetermined significance. *J Am Soc Cytopathol*. 2024;13:23-32. Epub 2023 Oct 13