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# Thyroid Nodules in Children and Adolescents: A Single Institution's Experience

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## What is already known on this topic?

- *Thyroid nodules are less frequent in children, but malignancy potential for pediatric thyroid nodules is as high as 22%-26%.*

## What this study adds on this topic?

- *In the present study, we found a high rate of malignancy (13.4%) in thyroid nodules in children with autoimmune thyroiditis (AT). We find this noteworthy since it indicates the necessity of close ultrasonographic follow-up of patients with AT.*

## ABSTRACT

**Objective:** The risk of malignancy in pediatric thyroid nodules is higher compared to the risk in adults. Our aim was to investigate the clinical, radiological, and histopathological characteristics of pediatric thyroid nodules.

**Materials and Methods:** The data of 132 children and adolescents who had thyroid nodules were collected retrospectively from medical records.

**Results:** The mean age of the patients was 12.07 ± 4.08 years and 67% were female. Fine-needle aspiration biopsy was performed in 86 patients (65%) and the results were as follows: benign in 53.4% (n = 46), atypia or follicular lesion of undetermined significance in 3.5% (n = 3), suspicious for follicular neoplasia in 2.3% (n = 2), and malignancy in 32.5% (n = 28). The overall malignancy rate was 22.7% (n = 30). Malignancy was detected after surgery in 2 thyroid nodules belonging to the atypia or follicular lesion of undetermined significance category. Malignancy was detected in 7 patients who had autoimmune thyroiditis and in 1 patient who had congenital dyshormonogenesis. The malignancy rate of the nodules in the patients, who had autoimmune thyroiditis, was found to be 13.4%. Mixed echogenicity, microcalcifications, nodules larger than 10 mm, abnormal lymph nodes, and irregular borders were more common in the malignant group. The nodule size, abnormal lymph nodes, and irregular borders were found to be significant in terms of predicting malignancy.

**Conclusion:** We found malignancy in 22.7% of the thyroid nodules, and the malignancy rate of nodules in the patients, who had autoimmune thyroiditis, was 13.4%. The nodule size, abnormal lymph nodes, and irregular nodule borders emerged as the most significant risk factors for malignancy.

**Keywords:** Thyroid nodule, malignancy, autoimmune thyroiditis

## INTRODUCTION

Thyroid nodules are rare in children. However, thyroid nodules in children have a malignancy risk of 22% to 26%, which is higher compared to adults. The malignancy rate of thyroid nodules in adults ranges between 7% and 15%.[1] Furthermore, increased incidences of pediatric thyroid nodules and thyroid cancers have been observed in recent studies.[2,3] Until recent years, pediatric thyroid nodules were managed according to the recommendations of adult guidelines. However, a more sophisticated diagnostic approach is necessary in pediatric thyroid nodules, as pediatric thyroid cancers have different clinical outcomes. In 2015, a guideline was published by the American Thyroid Association (ATA) to evaluate thyroid nodules in children and adolescents.[4]

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It is known that pediatric thyroid cancers are more advanced at presentation and have increased risks of recurrence, and lymph node and distant metastasis.[5] Thus, early diagnosis is crucial in the management of pediatric thyroid nodules.

Initially, children with thyroid nodules are evaluated according to the clinical, laboratory, and ultrasonographic (US) findings. Investigating the risk factors of thyroid cancer is crucial in making a decision for when to perform fine needle aspiration biopsy (FNAB). Fine needle aspiration biopsy is performed for nodules larger than 10 mm or nodules with risk factors suggestive of malignancy (SM) even if they are smaller than 10 mm. Presence of hypoechogenicity, irregular borders, microcalcifications, abnormal cervical lymph nodes, and increased central vascularization in nodule is considered suspicious for malignancy.[4,6] The cytopathologic findings of thyroid nodules are categorized according to the Bethesda system and further treatment strategy is planned as intermittent follow-up with US, repeat FNAB, or surgery based on the Bethesda category.[7]

The malignancy risk is defined according to several characteristics suggesting benignity or malignancy, mostly inferred from studies in adults. Data on the risk of malignancy of the thyroid nodule in children are limited due to the rarity of the thyroid nodule. Most studies in children are retrospective and include a limited number of cases.[8-10]

We aimed to compare clinical and US characteristics of patients with benign and malignant thyroid nodules and reported our experience in the management of patients with thyroid nodules who were followed up in the last 13 years.

## MATERIALS AND METHODS

The study population consisted of children and adolescents with thyroid nodules who were followed up in our clinic between June 2006 and July 2019. Medical records of the patients were retrospectively reviewed.

Assays of serum thyroid-stimulating hormone (TSH) and free T4 were performed in all patients. Antithyroid peroxidase antibodies and anti-thyroglobulin antibodies were measured in patients with clinical or radiological evidence of autoimmune thyroiditis (AT).

### Ultrasonographic Evaluation

Ultrasonographic evaluation of thyroid nodules was performed by experienced pediatric radiologists. Thyroid gland parenchyma, number of nodules, size and structure (solid, cystic, mixed) of nodules; echogenicity (hyperechoic, isoechoic, hypoechoic, anechoic) of nodules; characteristics of the nodule border (regular, irregular); vascularization pattern and the presence of microcalcifications and abnormal cervical lymph nodes were evaluated. Fine needle aspiration biopsy was performed under US guidance in all patients. Biopsy was performed in all nodules larger than 10 mm, and nodules that showed growth or developed suspicious US findings during follow-up. Suspicious US features for thyroid nodules were as follows: solid hypoechoic nodule, irregular nodule borders, microcalcifications, central hypervascularization, and presence of abnormal cervical lymph nodes. In addition, biopsy was performed in all patients who had previously treated with RT, even if the thyroid nodule size was <10 mm.

### Cytological Examinations

The cytological examinations of the nodules were reported according to the Bethesda system which included 6 categories: Bethesda I as nondiagnostic or inadequate, Bethesda II as benign, Bethesda III as atypia or follicular lesion of undetermined significance (AUS/FLUS), Bethesda IV as follicular neoplasm or suspicious for follicular neoplasm (SFN), Bethesda V as suggestive of malignancy (SM), and Bethesda VI as malignant.[4] Surgery was performed in all patients in whom cytologic results were reported as Bethesda III–VI. In the patients with Bethesda I–II categories, either intermittent follow-up with US or repeat FNAB or surgery was performed according to the clinical and radiological findings at follow-up. The patients who did not undergo surgery or FNAB, based on clinical and radiological findings suggestive of benign nodules, were evaluated closely every 6-12 months with clinical and US examinations.

### Statistical Analysis

The Statistical Package for Social Sciences for Windows version 22.0 (IBM Inc., Armonk, NY, USA) was used for statistical analysis. The data for quantitative variables were reported as mean ± standard deviation or median (ranges), while the data for qualitative variables were reported as absolute and relative (%) frequencies. The normality of the distribution of continuous parameters was evaluated by Shapiro–Wilk test. Mann–Whitney *U*-test was used to test for significant differences between quantitative data. Chi-square test or Fisher exact test was used for comparing qualitative data according to minimum expected value. Variables as sex, nodule size, nodule echogenicity, nodule component, abnormal cervical lymph node, microcalcification, irregular nodule borders, and AT were analyzed with logistic regression analysis to determine the predictive factors of thyroid cancer. The variables with a *P* value of <.25 in univariate logistic regression analysis were analyzed with a multivariate logistic regression analysis. A 2-tailed *P*-value of <.05 was defined as significant.

### Ethics Statement

The study was conducted according to the principles of Declaration of Helsinki and approved by the ethic committee of Cerrahpaşa Faculty of Medicine (Approval Number: 218613).

## RESULTS

### Participant Demographics

We evaluated 132 patients followed up in our clinic with the diagnosis of thyroid nodule. The mean age of the patients was 12.07 ± 4.08 years (2.5-17.6 years) and 67.4% (n = 89) of them were female. The flowchart of the study population is shown in Figure 1. Swelling in the neck was the most common symptom at presentation and was present in 53.7% (n = 71) of the patients. Thyroid nodule was detected during the etiological evaluation of hypothyroidism/subclinic hypothyroidism and hyperthyroidism in 19.6% (n = 26) and 5.3% (n = 7) of the patients, respectively. Thyroid nodule was detected incidentally in 21.9% (n = 29) of the patients. Nodule was palpable in 14.3% (n = 19) of the patients. The clinical characteristics of the patients are shown in Table 1. The mean size of the nodules was 15.5 ± 12.6 mm (median; 10.2 mm, range; 3-60 mm) and the nodules were greater than 10 mm in 55.3% (n = 73) of the patients. A single nodule was observed in 72.7% (n = 96) of

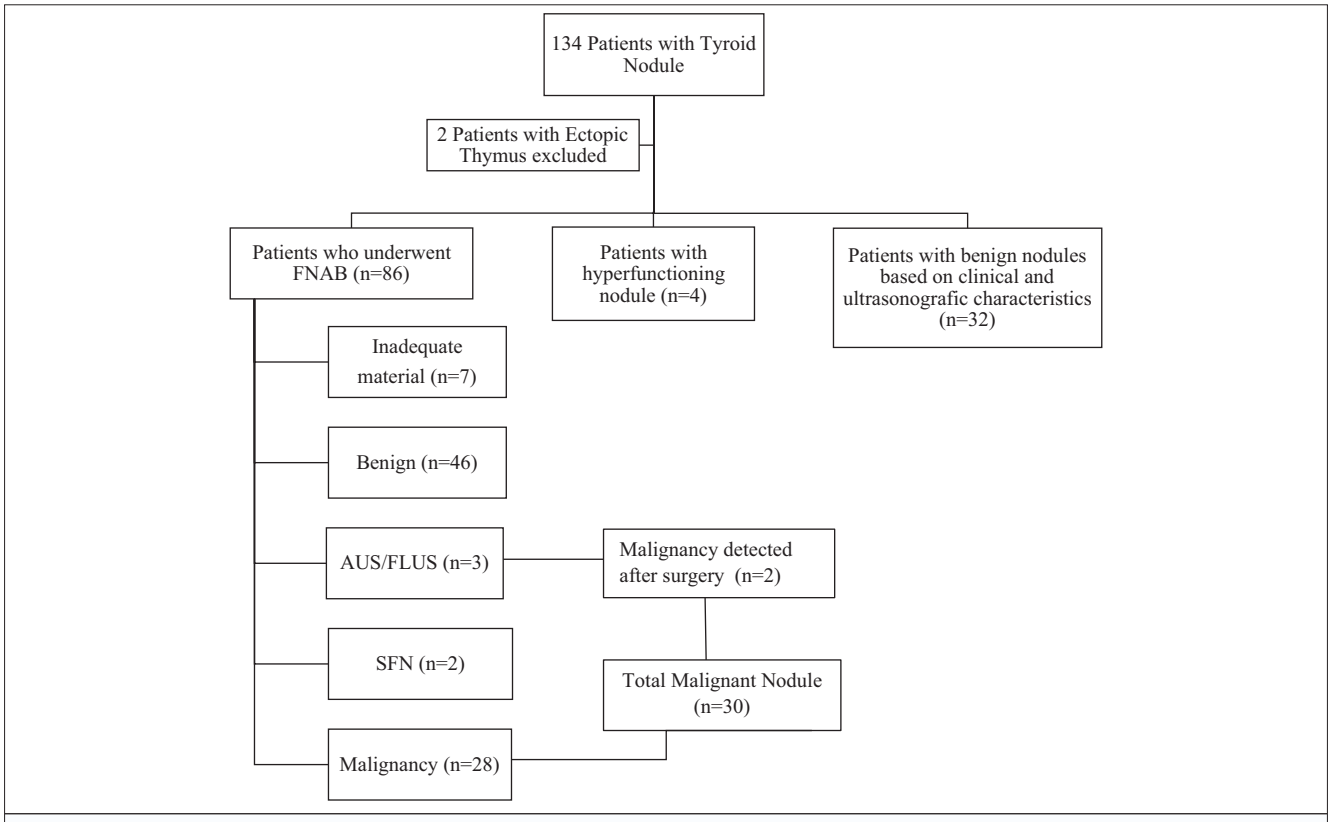


**Figure 1.** Flowchart of the study population.

the patients. Thyroid nodule was detected during the follow-up of AT in 39.3% (n = 52) and during the follow-up of congenital hypothyroidism due to dyshormonogenesis in 5.3% (n = 7). In 2 patients, who were referred with a diagnosis of thyroid nodule, the nodular structure was found to be ectopic thymus. These 2 patients were not included in the further evaluations. In 4 patients with thyroid nodule, the diagnosis was toxic adenoma. Since these nodules were going to be surgically removed, FNAB was not performed in these patients. Operation was curative in all 4 patients and none of them had malignancy.

**Table 1.** Clinical Characteristics of the Patients with Thyroid Nodule

| **Age, years** | **12 ± 4.2** |
|---|---|
| Sex, female, n (%) | 89 (67.4) |
| Pubertal status, pubertal, n (%) | 89 (67.4) |
| Nodule diameter, mm | 10.2 (6.7-19.5) |
| Largest nodule diameter, n (%) | |
| ≥10 mm | 73 (55.3) |
| Risk factors, n (%) | |
| Autoimmune thyroiditis | 52 (39.3) |
| Dyshormonogenesis and hypothyroidism | 7 (5.3) |
| Thyroid functions, n (%) | |
| Euthyroidism | 71 (53.8) |
| Hypothyroidism/subclinic hypothyroidism | 54 (41) |
| Hyperthyroidism | 7 (5.3) |

Data presented as number (%), mean ± standard deviation or median (interquantile range).

## Fine Needle Aspiration Biopsy Results

Fine needle aspiration biopsy was performed in 65% (n = 86) of the patients. Initial FNAB results of the patients were as follows: inadequate or hemorrhagic in 8% (n = 7), benign in 53.4% (n = 46), AUS/FLUS in 3.5% (n = 3), SFN in 2.3% (n = 2), and malignant in 32% (n = 28). Lobectomy was performed in 3 patients whose FNAB results were reported as AUS/FLUS. The final diagnosis was papillary thyroid cancer (PTC) in 2 patients and diffuse thyroid hyperplasia in 1 patient. Complementary thyroidectomy was performed in these 2 patients who were diagnosed with PTC. Lobectomy was also performed in 2 patients whose FNAB results suggested SFN, and the final diagnosis was follicular adenoma in 1 patient and diffuse adenomatosis hyperplasia in the other one. Additionally, we wanted to present the follow-up data of 7 patients who had inadequate or hemorrhagic FNAB results. One patient was lost during the follow-up. Lobectomy was performed in 2 patients because the nodule size was larger than 3 cm, and the definitive diagnosis was follicular adenoma in both. The nodules disappeared in 2 patients after FNAB. A second FNAB was performed in 2 patients and both had benign results (Figure 1).

## Patients with Thyroid Cancer

In total, malignancy was diagnosed in 22.7% (n = 30) of the patients with thyroid nodules. The definitive diagnosis after thyroidectomy was PTC in 60% (n = 18), follicular variant PTC in 33.3% (n = 10), and follicular thyroid cancer in 6.6% (n = 2). The median size of the malignant nodules was 22 (10-60) mm. Most of the patients with malignancy had a single nodule (n = 22; 73.3%). The frequencies of lymph node metastasis and distal metastasis were 53.3% (n = 16) and 20% (n = 6), respectively.

All patients with PTC underwent total thyroidectomy, except for 2 patients whose initial FNAB results were AUS/FLUS. These 2 patients primarily underwent lobectomy and later complementary thyroidectomy was performed. According to the ATA guideline, 13 patients were in the low risk category, 6 patients were in the intermediate risk category, and 11 patients were in the high risk category. According to the tumor node metastasis classification system, 80% (n = 24) of the patients were in stage 1 and 20% (n = 6 ) were in stage 2. As postoperative complication, hypoparathyroidism developed in 16.6% (n = 5) of the patients, recurrent nerve paralysis developed in 6.6% (n = 2), and seroma developed in 1 patient. All patients but 4 received radioactive iodine (RAI). Three patients with PTC had a tumor of <10 mm limited to the thyroid gland and 1 had minimally invasive follicular cancer, so these patients were not given RAI.

Family history was unremarkable for syndromes related with thyroid cancer in all these patients. Also, none had a history of radiotherapy. One of the patients with PTC had congenital hypothyroidism due to thyroglobulin synthesis defect. She was a 12-year-old adolescent girl with grade 3 goiter due to noncompliance with treatment. The malignancy rate of thyroid nodules in the patients, who had congenital dyshormonogenesis, was 14.2% (n = 1/7). In 7 patients, PTC was diagnosed during the follow-up of AT. The malignancy rate of thyroid nodules in the patients who had AT was 13.4% (n = 7/52). Nodule size was larger than 10 mm in all of them, and all but one had abnormal cervical lymph nodes. Nodules were hypoechoic in 4 patients and mixed echogenic in 3 patients, and microcalcifications were present in 4 patients. Five of the patients with AT were euthyroid. The other 2 patients had either subclinic hypothyroidism or overt hypothyroidism at presentation.

### Comparison of Clinical and Ultrasonographic Characteristics of the Patients with Benign and Malignant Thyroid Nodules

Clinical and US characteristics of the patients with benign and malignant thyroid nodules are compared in Table 2. The benign and malignant groups were comparable in terms of sex, age, and pubertal status. The sizes of the malignant nodules were significantly larger than the benign nodules. Microcalcifications, abnormal lymph nodes, and irregular nodule borders were significantly more common in the malignant nodules, and all malignant nodules were solid. The vascularization patterns of the nodules were not different between the benign and malignant groups. In our cohort, hypoechogenicity was more frequently seen in the benign nodules. However, hypoechoic thyroid nodules were present in 73% of the patients with AT and the prevalence of AT in the benign group was as high as 44.1%.

**Table 2.** Comparison of Clinical and Ultrasonographic Characteristics of the Patients with Benign and Malignant Thyroid Nodules

| | Benign (n = 102) | Malignant (n = 30) | *P* |
|---|---|---|---|
| Age, years | 12.1 ± 4.3 | 11.4 ± 3.7 | .25[a] |
| Sex, female, n (%) | 63 (61.7) | 26 (86.6) | .01[b] |
| Pubertal status, pubertal, n (%) | 69 (67.6) | 20 (66.7) | .92[b] |
| Nodule diameter* | 8.7 (5.9-16) | 22.0 (16.3-35.0) | <.001[a] |
| Diameter, n (%) | | | |
| ≥10 mm | 43 (42.1) | 30 (100) | <.001[b] |
| Uninodularity, n (%) | 74 (72.5) | 22 (73.3) | .932[b] |
| Nodule component, n (%) | | | |
| Cystic | 14 (13.7) | 0 (0) | .004[b] |
| Solid | 63 (61.7) | 28 (93.3) | |
| Mixed | 25 (24.5) | 2 (6.7) | |
| Echogenicity, n (%) | | | |
| Hypo | 63 (61.7) | 11 (36.7) | .002[b] |
| Iso | 19 (18.6) | 3 (10) | |
| Hyper | 6 (5.8) | 3 (10) | |
| Mixed | 7 (6.8) | 13 (43.3) | |
| Anechoic | 7 (6.8) | 0 (0) | |
| Irregular nodule border, n (%) | 2 (1.9) | 17 (56.7) | <.001[b] |
| Increased intranodular blood flow, n (%) | 10 (9.8) | 7 (23.3) | .052[b] |
| Microcalcification, n (%) | 10 (9.8) | 15 (50) | <.001[b] |
| Abnormal cervical lymph nodes, n (%) | 2 (1.9) | 17 (56.7) | <.001[b] |

Data presented as number (%), mean ± standard deviation or median (interquartile range).
[a]Mann–Whitney *U*-test.
[b]Chi-square test/Fisher's exact test.

After excluding the patients with AT, there was no difference in hypoechogenicity between the groups. The frequency of mixed echogenicity was higher in the malignant nodules ($P < .001$).

### Risk Factors for Malignancy

In the univariate model, sex, nodule size, nodule echogenicity, abnormal cervical lymph nodes, microcalcifications, irregular nodule borders, and presence of AT were found to be significant in the differentiation of malignant and benign nodules. However, multivariate analysis revealed that nodule size, presence of abnormal cervical lymph nodes, and irregular nodule borders were variables that differed between the 2 groups (Table 3).

**Table 3.** Logistic Regression Analysis of the Factors Associated with Malignancy

| | Univariate Model | | | Multivariate Model | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* | OR | 95% CI | *P* |
| Sex | 0.25 | 0.08-0.77 | .015 | | | |
| Nodule size | 1.1 | 1.06-1.14 | <.001 | 1.1 | 1.05-1.16 | <.001 |
| Nodule echogenicity | 1.67 | 1.16-2.39 | .005 | | | |
| Nodule component | 0.87 | 0.41-1.83 | .718 | | | |
| Abnormal cervical lymph node | 65.3 | 13.54-315.85 | <.001 | 54.2 | 8.98-327.55 | <.001 |
| Microcalcification | 9.2 | 3.49-24.23 | <.001 | | | |
| Irregular nodule border | 2.66 | 1.55-4.55 | <.001 | 3.01 | 1.39-6.53 | .005 |
| Autoimmune thyroiditis | 0.39 | 0.15-0.98 | .045 | | | |

## DISCUSSION

In this study, we reported our clinical experience in the management of pediatric thyroid nodules by presenting the clinical and US features of our patients with thyroid nodules. The rate of malignancy was 22.7% and consistent with the literature.[4] Also, 86.6% of the patients with malignancy were female and this was compatible with previous studies reporting that thyroid cancer is more common in females.[2,8,11] Papillary thyroid cancer was the most common malignancy in our series, consistent with the published literature.[4]

One of the remarkable findings of our study was the high frequency (13.4%) of malignancy in the thyroid nodules of the patients who had AT. This is noteworthy in terms of showing the necessity of close US follow-up in patients with AT. In another study from our country, the rates of thyroid nodule and thyroid cancer in children with AT were found to be 13% and 0.67%, respectively.[12] The high rate of thyroid cancer in our study may be due to the fact that our institution is a reference center for thyroid cancer. Chronic inflammation in AT could play a role in the development of malignancy. The association between AT and malignancy has been observed in other studies, but further investigations are needed to demonstrate a causal relationship between AT and malignancy.[13,14] Corrias et al[15] reported that the rate of malignancy was 9.6% in children with AT who had thyroid nodules. In another study, the malignancy rate in children with AT was reported to be 7.9%.[16]

It is a known fact that children with congenital dyshormonogenesis are at risk of developing thyroid nodules and thyroid cancer, and periodic US follow-up is recommended every 2 to 3 years in children with congenital dyshormonogenesis.[17] In our cohort, 5% of the patients with thyroid nodules had congenital hypothyroidism due to dyshormonogenesis and the malignancy rate was 14.2% (n = 1/7) in this group. Our patient who developed thyroid cancer had congenital hypothyroidism due to thyroglobulin synthesis defect. Long-standing goiter and high TSH have been reported in all patients with dyshormonogenesis who developed thyroid cancer.[18-20] The pathophysiological changes underlying the development of thyroid cancer in the dyshormonogenetic thyroid gland are unknown. It has been proposed that prolonged stimulation by TSH may cause malignant transformation of thyroid follicular cells.[21] Poor compliance to treatment causing TSH elevation and goiter was also present in our patient.

Thyroid US, which is widely used to evaluate thyroid nodules, should be performed by experienced radiologists. Intrathyroidal ectopic thymus may be misdiagnosed as thyroid nodule. In our series, ectopic thymus was found in 2 patients who were referred with a diagnosis of thyroid nodule.

The main aim of evaluation of thyroid nodules is to determine the malignancy risk of the nodules based on clinical and US findings. Although there is ongoing debate about the specific US findings of nodules that indicate malignancy, the findings such as hypoechogenicity, presence of abnormal cervical lymph nodes, increased central vascularization of nodule, irregular nodule borders, and microcalcifications are more frequent in malignant thyroid nodules.[4,6,22] The nodule size, the presence abnormal lymph nodes, and irregular nodule borders emerged as significant risk factors for malignancy in our study. The malignant nodules were more likely to be solid and larger in size in our series. Conversely, all cystic nodules were benign. However, in our series, hypoechogenicity was not found as a risk factor for malignancy. Hypoechoic thyroid nodules were also common in the patients with AT. After exclusion of the patients with AT, the frequency of hypoechoic thyroid nodules was comparable in both benign and malignant groups. Consistent with our results, many histologically benign nodules were also reported to be hypoechoic.[23] In our series, mixed echogenicity rather than hypoechogenicity was significantly more common in malignant nodules. Microcalcifications were more common in malignant nodules, but some benign nodules also had microcalcifications. It is recommended to use US and clinical features rather than nodule size in the determination of nodules for FNAB in children. Nodule size alone should not be considered as a determining factor for malignancy.[18] Nevertheless, all malignant nodules in our series were larger than 10 mm. Although large nodule size was reported as a predictive factor for malignancy in some studies, others did not support this.[23] As a result, no single feature is enough to distinguish malignant nodules.[24]

Hyperfunctioning thyroid nodules are rarely considered as malignant. However, recent studies argue against the assumed low-risk of malignancy in these nodules, suggesting that the rate of malignancy is underestimated.[25-27] In our series, the diagnosis was toxic adenoma in 3% of the patients and all of these adenomas were surgically removed as recommended in the ATA guideline. Malignancy was not detected in any of these. In the recent ATA guideline, preoperative FNAB is not recommended in children, since all hyperfunctioning nodules will be surgically removed.[4]

The results of FNAB are categorized into 6 groups according to the Bethesda system.[7] The AUS/FLUS, SFN, and SM categories are classified in the indeterminate spectrum in the Bethesda system and they have a variable risk of malignancy. The limited data available suggest that 28% of AUS/FLUS lesions and 58% of SFN lesions in children are malignant.[28,29] The recent ATA guideline recommends surgery (lobectomy) in cases of indeterminate or suspicious FNAB results.[4] In the present study, 66.6% of AUS/FLUS lesions were proven to be malignant as a result of histopathologic examination, which supports the ATA guideline in this regard. Conversely, none of the SFN nodules were malignant. However, the number of the patients is insufficient to draw definite conclusions. In the present study, 100% of cytologically "malignant" cases were confirmed as malignant after histological examination of surgical specimens. The diagnostic accuracy of FNAB in this category was 100%.

### Study Limitations

The first limitation of the present study was its retrospective design. Moreover, referral and selection bias was unavoidable since the study population consisted of patients followed up in a single tertiary hospital. Finally, there was a risk of inter-rater variability, as the data of the study were collected from the medical records of the patients followed up for the last 13 years.

## CONCLUSION

In conclusion, the malignancy rate is high in children with thyroid nodules. Comprehensive evaluation of clinical and US features of thyroid nodules is necessary. Our study revealed

that the risk of malignancy increased as the size of the nodule increased. Abnormal cervical lymph nodes and irregular nodule borders emerged as significant risk factors for malignancy. Patients with AT and patients with congenital hypothyroidism due to dyshormonogenesis should be followed up closely for the development of nodule.

**Ethics Committee Approval:** This study was approved by Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, (Approval No: 218613, Date: 09.07.2015).

**Informed Consent:** Written informed consent was obtained from the patients who agreed to take part in the study.

**Peer-review:** Externally peer-reviewed.

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