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THE ROLE OF THYROID FINE-NEEDLE ASPIRATION CYTOLOGY IN THE TREATMENT AND FOLLOW-UP OF THYROID NODULES IN THE PEDIATRIC POPULATION

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Abstract

Objective. Thyroid fine-needle aspiration (FNA) and cytology is a reliable diagnostic method used in the assessment of malignancy when evaluating thyroid nodules, in conjunction with clinical and ultrasonographic findings. The aim of this study is to compare clinical, ultrasonographic, cytological and histopathological findings in children who underwent thyroid FNA.

Methods. Subjects comprised 80 patients (52 female) aged 13.7±2.8 years at the time of FNA who where evaluated for thyroid nodules. Clinical, ultrasonographic and cytological findings of patients were evaluated retrospectively.

Results. Autoimmune thyroiditis was present in 30% and history of radiotherapy to the head or neck in 10%. The cytological diagnosis of patients included: inadequate or hemorrhagic sample in 10%; benign in 42.5%; atypia or follicular lesion of undetermined significance (AUS/FLUS) in 15%; suspicion of follicular neoplasia (SFN) in 7.5%; suspicion of malignancy (SM) in 8.8%; and malignant in 16.3%. Thirty-seven patients underwent thyroidectomy. Malignancy rates for histopathologic follow-up were 75%, 85.7% and 100% for SFN, SM and malignant categories, respectively. Only one benign and two AUS/FLUS FNAs were found to be malignant on histopathological examination. Among patients who had received radioiodinetherapy, 87.5% had malignancy. In this study, the sensitivity of FNA was 96%, specificity 50%, positive predictive value 90.9%, negative predictive value 75%, and diagnostic value of FNA was 89.2%.

Conclusion. Thyroid FNA results were highly compatible with histopathological examination. Sensitivity, positive predictive value and diagnostic value of FNA were high.

Key words: thyroid, fine needle aspiration, malignancy, nodule.

INTRODUCTION

Although thyroid nodules are rarer in children than in adults, the risk of malignancy is considerably higher. Evaluation starts by determining the differentiated thyroid cancer (DTC) risk. In adults, 7-15% of all thyroid nodules are malignant, while in children this risk is much higher at approximately 22-26%. Family history, radiation exposure, history of thyroid disease and several genetic syndromes are some of the risk factors for thyroid cancer (1). Radiologic imaging of thyroid nodules is important for early diagnosis, follow-up and determining optimal treatment options for the disease. However studies increase to differentiate DTC from benign nodules by using ultrasonography, the results are still unsatisfactory for certain diagnosis and fine needle aspiration requirement continues (2). Ultrasonographic findings suggestive of malignancy include: microcalcification, disrupted peripheral calcification, indistinct margin, solid echotexture, hypoechogenicity, increased intranodular blood flow, and lymph node alterations (3). Fine needle aspiration (FNA) followed by cytological examination is the initial diagnostic test for any identified thyroid nodules and helpful in determining whether these nodules are benign or malignant. In children, it is recommended that all solid thyroid nodules greater than 10 mm in diameter should be biopsied by FNA. Nodules smaller than 10 mm should be biopsied if any other historical, clinical or ultrasonographic risk factors are present (4, 5). An FNA result of a benign thyroid nodule reduces unnecessary surgery. According to studies, both sensitivity and specificity of FNA range from 50%–90%, respectively (6, 7). The Bethesda six-category diagnostic scheme is used to classify the nodules and each diagnostic category is associated with relative risk of malignancy (6). The Bethesda scheme has universal application because of its simplicity, safety

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and cost-effectiveness, leading to a correct diagnosis in >70% of patients (8). However cytology has limitations. Thyroid nodules of Bethesda III and IV are a diagnostic dilemma. Final histopathology of nodules with atypia or follicular lesion of undetermined significance (AUS/FLUS) on thyroid FNAs are malignant in 6%–48% of cases (9,10). Although the malignancy risk for Bethesda class is not well documented in children, the American Thyroid Association (ATA) guidelines suggest the same management for each Bethesda class for children and adults, with some exceptions (5). Other clinical factors should be considered because it is difficult to determine whether the atypia seen on cytology are benign or malignant.

The aim of this study was to compare clinical, ultrasonographic, cytological and histopathological findings in pediatric patients who underwent FNA, to estimate the malignancy potential of the thyroid nodules and to find out the risk factors for malignancy.

MATERIALS AND METHODS

We performed a retrospective search of pediatric thyroid nodule biopsies recorded in the Istanbul Faculty of Medicine, Pediatric Endocrinology Department from June 2003 to May 2016. The Institutional Ethics Committee approved the study protocol. All procedures were done in agreement with Helsinki declaration for studies on human subjects. Prior to FNA, patients and their tutors were informed about the procedure and gave their written informed consent, signed by the parent or tutor. Retrospective analysis revealed 120 patients who underwent FNA during this period. Eighty of these patients who had complete clinical, radiological, histopathological and follow-up data were included in this study. Of these 80 patients, 41 had thyroid nodules at presentation and the remaining 39 developed nodules during the follow-up of previously diagnosed thyroid disease: autoimmune thyroiditis (n=24); dyshormogenesis (n=2); other congenital hypothyroidism (n=5); Graves disease (n=1); multinodular goiter (n=2); secondary hypothyroidism (n=2); and subclinical hypothyroidism (n=3). Fourteen patients had additional diseases such as Down syndrome (n=1), extrathyroidal malignancy (n=8), nonclassic congenital adrenal hyperplasia (n=1), primary adrenal insufficiency (n=1), Guillain Barre syndrome (n=1) and type 1 diabetes mellitus (T1DM) (n=2). Eight patients had a history of radiation treatment for: Hodgkin's lymphoma (n=5); medulloblastoma (n=1); pons glioma (n=1); and liposarcoma (n=1).

Assays of thyroid hormone levels were performed in all patients. Antithyroid peroxidase antibodies (TPOAb) and anti-thyroglobulin antibodies (TgAb) were measured in cases with clinical or radiological evidence of autoimmune thyroid disease. The clinical features include goiter, symptoms originating from compression of the thyroid gland like hoarseness, cough and systemic manifestations like constipation, bradycardia, and changes of skin and appendages, etc. (11). From the radiological perspective, focal hypoechogenic areas within the thyroid gland in addition to a perithyroidal increased number of lymph nodes with ovoid shape suggests Hashimato's thyroiditis on ultrasound (12). All patients underwent neck ultrasound (US) at the time of initial presentation. FNA was performed under sonographic guidance by an experienced pediatric radiologist in all patients. FNA criteria for thyroid nodules included; nodules ≥10 mm without suspicious sonographic findings, and nodules <10 mm in patients with a history of radiation treatment, and nodules that showed growth or developed suspicious US findings during follow-up. Suspicious sonographic features of thyroid nodules were as defined earlier: solid hypoechoic nodule; irregular margins; microcalcification; and hypervascularity. During the FNA procedure, an on-site cytopathologist evaluated the FNA specimen for adequacy. All smears were alcohol fixed and/or air-dried and stained with Papanicolaou or May-Grünwald-Giemsa stain. Reporting of the cytological specimens were performed according to the Bethesda System which included six diagnostic categories; Bethesda I nondiagnostic or unsatisfactory, Bethesda II benign, Bethesda III AUS/FLUS, Bethesda IV follicular/Hurthle neoplasm or suspicious for follicular/Hurthle neoplasm (SFN), Bethesda V suggestive of malignancy (SM), Bethesda VI malignant (5, 13).

Surgery was planned in all patients in whom FNA cytology was reported as Bethesda V and VI. In patients with cytologic features reported as Bethesda I-IV, either active sonographic surveillance or repeat FNA was performed according to the initial cytological diagnosis, clinical risk factors or radiological findings during follow-up. Clinicopathologic data including age, gender, medical history (exposure to ionizing radiation, extrathyroidal malignancy, autoimmune thyroiditis), US findings of nodules (nodule size, solid or cystic component, echogenicity, irregular border, calcification, vascularity, halo formation) and cytological diagnosis were documented in all patients. In patients who underwent thyroid surgery,

clinicopathologic data, sonographic features of nodules and FNA results were evaluated in nodules which proved to be benign or malignant on final histopathological examination. FNA cytology results except for benign ones were labeled as positive in determining the true positive (TP), false negative (FN), true negative (TN), and false positive (FP) results. The sensitivity (TP/(TP+FN)), specificity (TN/(TN+FP)), positive predictive value (TP/(TP+FP); PPV), negative predictive value (TN/(TN+FN); NPV) and diagnostic value [(TP+TN)/(TP+TN+FP+FN)] of FNA were determined.

The Statistical Package for Social Sciences (SPSS) for Windows 21.0 (IBM Inc., Chicago, Ill. USA) was used for statistical analysis. Data for quantitative variables were reported as mean ±standard deviation (SD) or median (ranges) while for qualitative ones as absolute and relative (%) frequencies. Nonparametric tests (Mann-Whitney U or Kruskal Wallis) and Pearson chi-square test were used to test for significant differences between quantitative and qualitative data, respectively. In a 2x2 table, if n<20 or 20<n<40 and one of the expected values were <5 Fisher exact test was applied, however if n>40 chi-square test with Yates continuity correction was applied; p value <0.05 was accepted as significant.

RESULTS

Clinicopathological and radiological features and FNA results

Eighty patients were included in the study consisting of 52 females (65%) and 28 males (35%). The mean±SD age of the study population at the time of initial FNA was 13.7±2.8 years, ranging from 6 to 17.5 years old.

Thirty percent of the patients had clinical or radiological evidence of autoimmune thyroid disease. One or both of the thyroid antibodies were positive, and there were sonographic findings indicative of autoimmune thyroid disease in all of these 24 patients.

In the whole cohort, the initial cytological diagnoses following FNA were reported as inadequate or hemorrhagic in eight (10%), benign in 34 (42.5%), AUS/FLUS in 12 (15%), SFN in six (7.5%), SM in seven (8.8%) and malignant in 13 (16.3%) patients. Clinical characteristics of the patients who underwent FNA and sonographic features of the biopsied nodules are listed in Table 1. Twenty-three patients underwent a second FNA, seven patients due to an initial inadequate, AUS / FLUS or SFN cytology and 16 patients due to the growth of the nodule during follow-up, after a median (range) interval of 0.8 (0.2-6.0) years from the first FNA. Second FNA results were as follows: Benign (n=17),

Table 1. Patient characteristics: clinical, ultrasonographic and FNA results Data for quantitative variables were reported as mean ± SD while for qualitative ones as absolute and relative (%) frequencies

	Inadequate (n=8)	Benign (n=34)	AUS/FLUS (n=12)	SFN (n=6)	SM (n=7)	Malignant (n=13)	*p*
TSH (mIU/L)*	3.0±2.1	3.2±3.1	10.0±21.3	3.8±1.9	15.3±22.2	3.0±1.9	0.5
fT4 (pmol/L)*	17.0±3.5	15.7±2.8	14.6±2.8	16.7±2.8	16.0±4.3	16.3±3.5	0.84
Nodule diameter (mm)*	14.4±5.8	13.1±6.9	14.1±9.1	17.7±6.3	8.6±2.5	15.2±10.0	0.33
Diameter groups(%)**							
≥10 mm(n=54)	13.0	38.6	14.8	11.1	5.6	16.7	0.2
<10 mm (n=26)	3.8	50	15.4	0	15.4	15.4	
Nodule component **(%)							
Cystic (n=14)	6.3	62.5	18.8	6.3	0	6.3	
Solid (n=46)	4.3	39.1	13.0	8.7	13.0	21.7	
Mixed (n=12)	25.0	41.7	16.7	0	8.3	8.3	0.26
Echogenicity (%)**							
Iso/hyper (n=18)	16.7	38.9	5.5	16.7	5.5	16.7	
Hypo (n=45)	6.7	44.4	20.0	6.7	6.7	15.6	
Mixed (n=8)	0	50.0	0	0	25.0	25.0	0.46
Irregular (%) border (n=13)**	0	15.4	23.1	0	15.5	46.3	0.09
Vascularization(%) (n=6)**	0	66.6	16.6	16.6	0	0	0.28
Halo (%)(n=12) **	8.3	41.7	25	16.7	8.3	0	0.26
Microcalcification (%)(n=12) **	0	25	16.7	0	16.7	41.7	0.07

* Kruskal Wallis, ** Pearson Chi-square test.

Table 2. Pathologic results and nodule size of patients who underwent thyroidectomy

Patient	Age	Diagnosis at presentation	Nodule Size (mm)	First FNA (age-years)	First FNA Result	2nd FNA age	Second FNA result	Surgery age	Pathology
1	14.9	AT	21	14.9	papillary ca			15.3	papillary ca
2	12.4	Nodular goiter	21	15.5	Benign	17.2	papillary ca	17.3	papillary ca
3	16.7	AT	5.3	16.8	Chronic lymphocytic thyroiditis	17.6	papillary ca	17.6	papillary ca
4	8	Hypothyroidism	9	12.5	AUS/FLUS			12.4	papillary ca
5	14.3	Thyroid nodule	18	14.5	papillary ca			17.3	papillary ca
6	7.3	Thyroid nodule	26	7.4	papillary ca			7.5	papillary ca
7	16.9	Secondary hypothyroidism	10	17.4	papillary ca			17.4	papillary ca
8	11.4	AT	8	12.8	SM			13	papillary ca
9	9	Thyroid nodule	33	9.1	AUS/FLUS	10.8	papillary ca	10	papillary ca
10	10	Thyroid nodule	4.4	10	papillary ca			10.3	papillary ca
11	10.3	Osteomalacia, HL	31	17.5	SM			17.7	papillary ca
12	13.2	AT	9	13.5	SFN			15.1	papillary ca
13	4.7	Hodgkin Lymphoma	5	14	hyperplastic nodule	15	SFN	16	papillary ca
14	14.2	Thyroid nodule	10	14.2	AUS/FLUS			14.2	papillary ca
15	12.6	Thyroid nodule	19	12.6	SFN			12.9	papillary ca
16	14.3	Thyroid nodule	19	14.3	papillary ca			14.3	papillary ca
17	9.1	AT	16	9.1	Inadequate	15.8	Hyperplastic nodule	16.3	papillary ca
18	16.1	Thyroid nodule	6.2	16.1	papillary ca			16.3	papillary ca
19	14.1	Thyroid nodule	37	14.3	papillary ca			14.3	papillary ca
20	8.6	AT	11	14.5	papillary ca			14.5	papillary ca
21	16.7	AT	5.3	17.4	SM			17.7	papillary ca
22	10.2	AT	9	10.7	SM			11.1	papillary ca
23	13.1	AT, T1DM	5	17.9	SM			17.9	papillary ca
24	16.9	AT, Obesity	10.6	17	SM			17.3	papillary ca
25	14.6	Pons glioma, thyroid nodule	5	14.7	papillary ca			14.8	papillary ca
26	14.1	Liposarcoma, thyroid nodule	5.8	19.5	papillary ca			19.5	papillary ca
27	18.3	HL	10	18.3	SFN			18.3	papillary ca
28	13.4	Thyroid nodule	18	13.4	papillary ca			13.4	papillary ca
29	12.8	AT, T1DM	8	15	papillary ca			15.2	papillary ca
30	10	AT	13	16.9	hyperplastic nodule	17.3	SFN	17.3	papillary ca
31	6	Thyroid nodule	27	6	SFN			6.3	papillary ca
32	12.5	Thyroid nodule	9.6	12.5	Benign	18	Benign	18	Benign
33	9.1	Thyroid nodule	24	10.2	Benign			11	Benign
34	11.7	Thyroid nodule	12	11.8	SM			12	Benign
35	1.7	CH	22	12.2	SFN			12.5	Benign
36	1.7	CH	16	13.1	SFN			13.1	Benign
37	0.1	CH	21	16.1	Benign			18.3	Benign

AT: autoimmune thyroiditis, CH: Congenital hypothyroidism, SFN: Suspicious of follicular neoplasia, T1DM: type 1 diabetes mellitus, HL: Hodgkin lymphoma, SM: Suspicious of malignancy.

inadequate (n=1), SFN (n=2), papillary ca (n=3). The results of first and second FNA of thyroidectomized patients are listed in Table 2. Of 80 patients 37 underwent thyroid surgery. Total thyroidectomy was performed in 34 patients. The remaining three patients underwent thyroid lobectomy, as two of these patients had unifocal papillary microcarcinoma and the other patient had benign histopathologic results. Five of 34 patients with total thyroidectomy had benign histopathological results. Total thyroidectomy was judged to be appropriate in these patients because of suspicious findings (dyshormogenesis and previous history of malignancy).

Recent ATA guidelines (5) advise surgery if the results of the initial FNA suggest AUS/FLUS. Therefore we wanted to present the results of patients who had AUS/FLUS FNA result at first biopsy, although the follow-up of some patients was continued after the end of the research period. Twelve patients' first FNA result was compatible with AUS/FLUS. Three patients were diagnosed with papillary thyroid carcinoma (PTC) during the research period. Two more patients in this group have subsequently been diagnosed with papillary carcinoma after the end of the study who were not included in the overall results. One patient was lost to follow-up and the remaining patients with AUS/FLUS had second FNA which was reported as benign FNA. Thus the current diagnostic proportions in this AUS/FLUS group are: 5/12 papillary carcinoma (41.7%); 6/12 benign FNA (50%) and 1/12 unknown (8.3%).

Additionally, we wanted to present the results of eight patients who had inadequate or hemorrhagic FNA result. Three patients did not continue to their follow-up. Two patients' nodules were dissappeared after FNA. A second FNA was performed to two patients (one of them after the end of the study) and both of them had benign results. One patient had benign FNA result in second biopsy however histopathologic result was compatible with malignancy.

Postoperative results

Of 37 patients who underwent surgery, papillary thyroid carcinoma was found in 31 (83.7%). The remaining 43 patients who have not undergone thyroidectomy were followed-up for a median (range) period of 4.5 (0.8-18) years from their presentation at the endocrinology clinic. None of the 43 patients have had any ultrasonographic or cytological findings that cause malignancy suspicion during the research period.

The clinicopathological features, cytology of initial and repeat FNA, sonographic features and final histopathological results of the patients with PTC and the patients with benign and malignant nodules are summarized in Tables 2 and 3. The mean age of the thyroidectomized patients showed no significant difference between the patients with benign and malignant nodules. The rate of malignancy was higher in female patients compared to male patients although it was not statistically different. Of 31 patients with PTC, the tumor size was ≥1cm in 74.2% and <1cm in 25.8% patients. The frequency of malignancy in patients with autoimmune thyroid disease (n=11) was 91.7%, however the frequency of malignancy in the nonautoimmune patients (n=20) was 80%.

Of the eight patients with a history of radiation exposure, seven underwent thyroidectomy and PTC was found in all of the seven patients. The mean±SD period between the diagnosis of malignancy and earlier radiotherapy was 9.9±3.9 years. In the remaining one patient with a history of radiation treatment, first FNA was reported as AUS/FLUS. However, repeat FNA cytology was found to be benign and the patient was scheduled for active survelliance with neck US.

Although most of the malignant nodules had a solid component, microcalcifications and irregular borders, there was no statistically significant association between these parameters and malignant nodules. Neither were there significant differences between malign and benign nodules in terms of nodule size or echogenicity.

Histopathologic examination confirmed malignancy in 75% of patients with SFN. One patients' first FNA was benign. A second FNA was performed to the other lobe and the result was SFN and the final histological examination of this patient was compatible with papillary microcarcinoma (Patient 13, Table 2). All SFN patients with thyroid carcinoma had PTC with follicular variant.

Histopathologic examination was indicated as malignant in 85.7% of SM and in 100% of malignant FNA results. Two of the AUS/FLUS patients had malignancy on histological follow-up. Only one patient had a false negative result. The first FNA of this patient was inadequate. During follow-up, a second FNA biopsy was performed because of increasing size of the original nodule which yielded benign cytology. The patient had multinodular goiter and because of the increase in nodule size, thyroidectomy was performed. Histopathology examination confirmed malignancy. The overall sensitivity of thyroid FNA in this population was 96%, specificity was 50%, PPV was 90.9%, NPV was 75%, and diagnostic value of FNA was 89.2%.

Table 3. Histopathologic examination and characteristics of the thyroidectomized patients. Data for quantitative variables were reported as mean ± SD and while for qualitative ones as absolute and relative (%) frequencies

	Benign (n=6)	Malignant (n=31)	*P*
Clinical and hormonal findings			
Thyroidectomy age*	14.0±3.9	14.7±3.3	0.938
**Gender % ** **			
Girl (n=24)	8.3	91.7	
Boy (n=13)	30.8	69.2	0.157
Radiotherapy (n=7) (%)**	0	100	0.571
Autoimmunity yes (n=12) (%)**	8.3	91.7	0.641
TSH (mIU/mL)*	11.9 ± 17.7	4.4±8.5	**0.037**
fT4 (pmol/L)*	15.2±4.3	16.1±3.1	0.66
Results of FNA n (%)***			
Benign (n=4)	75	25	
AUS/FLUS (n=2)	0	100	
SFN (n=8)	25	75	
SM (n=7)	14.3	85.7	
Malignant (n=16)	0	100	**0.007**
Nodule characteristics (US)			
Diameter(%)**			
≥10 mm(n=25)	20	80	
<10 mm(n=12)	8.3	91.7	0.389
Component (%)***			
Cystic(n=3)	33.3	66.7	
Solid(n=28)	10.7	89.3	
Mixed(n=3)	33.3	66.7	0.365
Echogenicity (%)***			
Iso/hyper(n=10)	10	90	
Hypo(n=18)	22.2	77.8	
Mixed (n=6)	16.7	83.3	0.716
Border regular/irregular (n=5/11)** (%)	20/9.1	80/90.9	1.0
Vasculature yes/no (n=2/11)(%)**	50/9.1	50/90.9	0.295
Halo yes (n=6) (%)**	33.3	66.7	0.515
Microcalcification yes (n=8)%**	12.5	87.5	0.613

*Mann Whitney U ** Fisher Exact *** Pearson chi-square.

DISCUSSION

Thyroid nodules are rare in the pediatric population. Recent ATA guideline (5) reported that nodules diagnosed in children have a greater risk of malignancy compared to those in adults (22-26% *versus* 5-10%) and a strong female preponderance is evident (5:1), as in the present study. Recently, another study found a malignancy rate of 25% in children (14). These authors also report a two-fold higher risk in children younger than 12 years old when compared to older children. Our data support this finding with a rate of 38.8% of differentiated thyroid carcinoma on histopathologic examination. Our other key finding was that the accuracy rate of malignant cytology was found to be 89.2%, which supports the safety and reliability of FNA in the management of thyroid nodules.

FNA is an essential method for diagnosing thyroid nodules and in children FNA should be performed on all thyroid nodules of more than 10 mm. However if the patient is at high risk because of a history of radiation or the nodule is associated with pathological regional lymph node, or there are any suspicious ultrasonographic features, FNA should be done even when the nodule is smaller than 10 mm (4, 5). The purpose of FNA is to assess the malignancy risk of the nodule and to prevent unnecessary surgery. FNA has a sensitivity of 61.8-98.4% and a specificity of between 71.4 and 100% (7,15,16). Gharib *et al.* published an FNA series in 10,971 adults, which included 1,750 surgical specimens. Analysis of data suggested a false negative rate of 1% to 11%, a false positive rate of 1% to 8%, a sensitivity of 65% to 98%, and a specificity of 72% to 100% (7). Lopez *et al.* reported the specificity of FNA to be 99.8% (17). In another study specificity was found to be 98.8%, although when these authors included the SM patients,

the specificity decreased to 64.7% (18). Some studies have included malignant cases only in determining this ratio, while others have also included cases with SM. In the present study, 85.7% of cytologically "suspicious of malignancy" cases were confirmed as malignant following histological examination of surgical specimens. Sensitivity was found to be 96% in our series.

False negative patients are important because they show malignant lesions not detected by FNA. Lesions predominantly resulting in false negative results in the literature tend to be small neoplasms hidden by a dominant nodule, microcarcinomas and cystic lesions (19, 20). In a recent study, one out of 30 (3.3%) patients was found to have a false negative FNA result and these authors concluded that FNA is a safe, reliable method in the evaluation of pediatric nodules (21). The false negative rate of benign nodules is low (0-3%) and patients should be followed with ultrasound. If the nodule size increases significantly or there are suspicious findings, repeat FNA should be considered (5,13). In our series there was only one case with false negativity in the first and second FNA results. During follow-up and because of enlargement in the nodule, thyroidectomy was performed and malignancy was detected. We recommend that thyroid nodules should be followed closely and, if necessary, surgery should be recommended in suspicious cases, even if the FNA result is benign. We found that FNA is indispensable, has application in histopathologic diagnosis and that the results of FNA of the nodules are in harmony with the results of histopathology.

Indeterminate thyroid nodules are a heterogeneous group that does not fit into benign or malignant categories and they have a variable incidence of malignancy on follow-up. Three categories fall into the indeterminate spectrum in the Bethesda system: AUS/FLUS, SFN and SM. Jiang *et al.* reported a 60% malignancy rate with indeterminate FNA, while Trahan *et al.* reported a much lower 11% malignancy rate with indeterminate FNA in their study (22,23). However, the ATA guideline has helped to identify the risk in each category and to manage suspicious nodules, changing the findings in some studies. Whereas Norlen *et al.* reported 100% of AUS/FLUS, SFN and SM nodules were malignant (24) a further study of 68 cases reported 28% of AUS/FLUS patients, 58% of SFN and 100% of SM patients had malignancy on follow-up (25). In our series SFN had a malignancy rate of 75% and in SM this was 85.7%.

AUS/FLUS is a heterogeneous category in which the degree of cellular or architectural atypia is not sufficient for an interpretation of SFN or SM (6). Specimen adequacy is important for evaluation of biopsy material. A satisfactory smear contains five or six groups of well-preserved cells and each group consists of at least 10-15 cells. Aspirates with very few cells are assigned as nondiagnostic and they are not negative for malignancy. Inadequate or nondiagnostic smears often occur in the setting of cystic lesions. When there is a suspicion of malignancy, repeat aspiration may provide the diagnosis in up to 50% of cases (7). However this category is a diagnostic dilemma. Although the ATA guideline reported 5%-15% of malignancy risk for AUS/FLUS category (5) other studies have reported much higher malignancy rate (24, 25). In an adult study, the risk of malignancy was found to be approximately 35%. However, if the ultrasonographic findings did not suggest malignancy, the risk of malignancy decreases to 5.3%. As a result, it is recommended to consider ultrasonographic criteria and clinicopathological findings when assessing the risk for malignancy in thyroid AUS nodules (15). The recent ATA guideline recommends surgery (lobectomy) in the case of indeterminate or suspicious FNA cytopathology (5). In the present study 86.7% of indeterminate cytopathology was proven to be malignancy after histopathologic examination, which supports the ATA guideline in this regard. Of our 12 patients with AUS/FLUS FNA, three of them had a malignancy diagnosis during the study period and at follow-up two of them had malignancy subsequently on histopathological examination.

All FNA in children should be performed with US guidance. Nevertheless US is essential for initial evaluation and long term follow-up of all nodules. The US describes thyroid nodule composition (solid, cystic, echogenicity, margins, calcifications, shape, vascularity and presence of suspicious cervical lymphadenopathy). Some studies showed that malignancy risk increased with nodule size (26), while the others found no significant difference between nodule size and malignancy (27). We grouped the thyroid nodules into size categories using a cut-off of 10 mm. Although it was not statistically significant, malignancy was more frequently found in patients with a nodule diameter larger than 10 mm. Despite being used in adults, nodule size in children should not be considered in prediction of malignancy because the thyroid volume changes with age (5). Shape and echogenicity were not found to be significant predictors of malignancy in pediatric age

group. Although there are increasing data to suggest that patients with a nodule and thyrotropin levels in the upper tertiles of the reference range may be at increased risk for malignancy (28), in the present study the relationship was found to be the opposite. Our data revealed that radiation has an association with a higher rate of thyroid cancer. History of head and neck radiotherapy is a significantly important risk factor for DTC. Recently, in a study conducted in Turkey, papillary carcinoma was identified in all of the nodules which were smaller than 10 mm in patients with a history of previous radiotherapy (14).

Overall, FNA had the most pronounced effect of any of the other predictors of malignancy examined in this study. FNA is found to be a reliable method when evaluating thyroid nodules. This result is concordant with the literature. It seems that thyroid FNA is a good diagnostic test and has a high sensitivity (96%), PPV (90.9%) and accuracy (89.2%) in pediatric patients. Furthermore, the findings of this study demonstrate that the Bethesda System for Reporting Thyroid Cytopathology can be applicable. However, it should be borne in mind that as pediatric patients have a higher rate of malignancy, the risk of malignancy may differ from those suggested in the Bethesda System for Reporting Thyroid Cytopathology.

Limitations of this study include the small sample size although it is still one of the largest pediatric cohorts thus far reported. Furthermore, there is a need to mention here that the study was conducted before the definition of the new clinical entity noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) (29). NIFTP was previously known as "encapsulated follicular variant of papillary thyroid carcinoma" and has been shown to affect the malignancy rates for FNA results when included (30-33).

In conclusion, FNA is a valuable diagnostic tool for thyroid lesions and can be used as a first step with ultrasonographic, clinical and biochemical evaluation of thyroid nodules. In most cases, FNA clarifies the clinical pathway to be followed later. Our findings indicate that it is important to undertake close and careful follow-up of risky nodules. Bethesda cytologic examination seems to be helpful in predicting the risk of malignancy in pediatric patients.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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