DOI: 10.4274/jcrpe.galenos.2020.2020.0213

Original article

Evaluation of Children and Adolescents with Thyroid Nodules: A Single Center Experience

Short Running Title: Thyroid Nodules in Children and Adolescents

Selin Elmaogullari[1], Servan Ozalkak[1], Semra Cetinkaya[1], Ibrahim Karaman[2], Cigdem Uner[3], Nilufer Arda[4], Senay Savas Erdeve[1], Zehra Aycan[1,5]
[1]Dr. Sami Ulus Children's Training and Education Hospital, Pediatric Endocrinology
[2]Dr. Sami Ulus Children's Hospital and Education Hospital, Pediatric Surgery
[3]Dr. Sami Ulus Children's Hospital and Education Hospital, Pediatric Radiology
[4]Dr. Sami Ulus Children's Hospital and Education Hospital, Pediatric Pathology
[5]Ankara University Medical School, Pediatric Endocrinology

What is already known on this topic?
Thyroid nodules in children have high potential for malignancy (%22-26). Sonographic findings such as parenchymal heterogeneity hypoechogenicity, irregular margins, increased intranodular blood flow, presence of microcalcifications and abnormal cervical lymph nodes increase the likelihood of malignancy and nodules even < 1cm diameter with risk factors require fine needle aspiration biopsy.

What this study adds?
According to the data limited to small cohort evaluated in this study, malignancy rate was %10 in children and adolescents with thyroid nodules. Patients with atypia of undetermined significance/follicular lesion of undetermined significance as FNA result had 9% potential for malignancy and patients with initially benign FNA result had a 5.3% false negative rate.

Abstract
Objective: We aimed to evaluate the clinical, radiological and pathological findings of children and adolescents with thyroid nodules.
Method: Data of 121 children and adolescent with thyroid nodule and had fine needle aspiration (FNA) were examined retrospectively. Concomitant thyroid disease, ultrasound (US) features of the nodule, FNA and histopathological results were recorded. FNA results were assessed according to The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC).
Results: Median age of the cases was 14 years (range 3-18 years) and 81% were female. FNA results of patients were insufficient in 1 (0.8%), benign in 68 (56.2 %), indeterminate in 44 (36.4%) and malignant in 8 (6.6%) patients. Among 39 patients who were directed to surgery, 10 patients had differentiated thyroid cancer (DTC). The total malignancy rate was 10.0% (10/100). Control FNA results showed progress according to TBSRTC in 18.7% of benign results and 4 of 75 patients had DTC in surgical excision. 2 of 22 patients with atypia of undetermined significance (AUS) who continued follow-up was diagnosed with DTC. Male gender, presence of Hashimoto thyroiditis and US findings of uninodularity; hypoechogenicity; increased blood flow; irregular margins; solid structure; microcalcification and presence of abnormal cervical lymph nodes were associated with malignancy.
Conclusion: Our results revealed that, thyroid nodules are 10% malignant in children and adolescents. Patients with AUS has 9% potential for malignancy and patients with initially benign FNA result may have changes in TBSTRC findings in repeat FNA with a 5.3% false negative rate.
Keywords: Adolescents, Children, Fine-needle aspiration, Thyroid nodule

Selin Elmaogullari, MD, Dr. Sami Ulus Children's Training and Education Hospital, Pediatric Endocrinology, Ankara, Turkey
ekerbicerselin@yahoo.com
+90 (532) 5808862
07.09.2020
20.12.2020
ORCID 0000-0003-4879-7859

Introduction
Thyroid nodule is a lesion characterized by focal abnormal overgrowth of thyroid cells within thyroid tissue. They are clinically appreciable when noted by the patient; by a clinician during routine physical examination; or during radiologic procedures. Prevalence of thyroid nodules depends on many factors including age, sex, iodine deficiency and therapeutic and environmental radiation exposure. Autoimmune thyroiditis which affects 2-15% of the population is also associated with increased risk of

nodule formation and thyroid malignancy(1). However, there isn't an identifiable risk factor in majority of the patients with thyroid nodule(2).

Thyroid nodules are not as common in children (1-1.5%) and adolescents (up to 13%) as in adults (19-68%)(3,4). Although most thyroid nodules are benign, thyroid gland is more susceptible to irradiation and carcinogenesis in children and risk for malignancy in thyroid nodules is higher in childhood (22-26% versus 7-15%)(5,6,7). Therefore, thyroid nodules in children should be handled carefully regardless of whether they are symptomatic or asymptomatic.

Nodules that warrant fine-needle aspiration biopsy (FNA) are identified according to ultrasonography (US) characteristics and clinical context. The American Thyroid Association (ATA) recommends US guided FNA for thyroid nodules over 1 cm or <1 cm with concerning ultrasonographic features (hypoechogenicity, irregular margins, increased intranodular blood flow, microcalcifications and abnormal cervical lymph nodes) with the exception of hyperfunctioning nodules requring surgery directly (8). Cyopathology findings are categorized as nondiagnostic, benign, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), follicular neoplasm/suspicious for follicular neoplasm (FN/SFN), suspicious for malignancy (SFM), and malignant according to The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)(9). Further treatment plan is structured according to TBRSTC category as intermittant controls with US, repeat of FNA or surgery.

In this study, we planned to evaluate the clinical, radiological and pathological findings of children and adolescents with thyroid nodules who were followed-up in our clinic.

Methods

Children and adolescents who were followed up with thyroid nodules and examined with FNA between January 2010 and June 2019 were included in the study and their files were examined retrospectively. Thyroid function tests at the time of diagnosis were grouped as euthyroid, subclinical hypothyroidism, hypothyroidism, subclinical hyperthyroidism and hyperthyroidism. Cases followed with congenital hypothyroidism, Hashimoto's thyroiditis (HT) or Graves' disease were also mentioned. Patients with sonographic changes in thyroid gland (decrease in parenchymal echogenicity, irregularity, heterogeneity or nodular appearance) in addition to the positivity of thyroid peroxidase antibody (anti TPO) or thyroglobulin antibody (anti TG) were considered as HT(10). In patients with subclinical hyperthyroidism or hyperthyroidism, Graves thyroiditis was considered if there was TSH receptor antibody positivity(11). Normal serum levels of laboratory tests were accepted as, TSH: 0.6-5.5 µIU / ml, free thyroxine (FT4): 0.8-1.9 ng /dl, free triiodothyronine (FT3): 2-6.5 pg / ml, anti TPO: 0-60 IU / ml, anti TG: 0-60 IU / ml, calcitonin: 2-11.5 and thyroglobulin: 0-60 ng / ml.

US and FNA of all cases were performed by experienced radiologists. Thyroid gland parenchymal structure (homogeneous, heterogeneous); number of nodules (single, multiple); size (largest of 3-dimensional measurement); structure (solid, semisolid, cystic); echogenicity (hyperechoic, isoechoic, hypoechoic); margin (regular, irregular, lobulated) and the presence of calcification were examined. FNA was performed with a 22-gauge needle on a 10- mL injector. Three or four samples were taken (from the largest nodule with the highest risk for malignancy if there were multiple nodules) in each process. Patients were discharged after bleeding control with US.

FNA and thyroidectomy materials were evaluated by experienced pathologists. FNA specimens were categorized according to TBSRTC(9). In all cases with nondiagnostic results, FNA was repeated. Benign results were continued to be followed every 6 months and FNA was repeated if there was change in the nature and size of the nodule. Decision of surgery for further categories (AUS/FLUS, FN/SFN, SFM and malignant) made by a council consisting of pediatric endocrinologists, a pediatric surgeon, a pediatric oncologist, a radiologist and a pathologist.

Statistical Analysis

SPSS version 22 (Statistical Package for Social Sciences, Chicago, IL, USA) for Windows program was used for statistical analysis. Results were expressed as mean ± standard deviation for parametric data and median + range for nonparametric data. Chi-square test or Fisher Exact test was used for comparing non-numeric data according to minimum expected value. Independent Samples Median Test was used for comparison of nonparametric numerical data medians. Significance level was accepted as $p<0.05$.

Ethics

This study was approved by The Dr. Sami Ulus Children Education and Research Hospital Specialty and Education Review Board with the decision number 2019/12. The need to obtain informed consent from the study participants was waived due to the study's retrospective nature.

Results

One hundred and twenty-one cases with thyroid nodules were included in the study. Mean age of the cases was 13±3 years (3.4-18 years) and 81% of them were female (Figure-1). Thyroid US detecting thyroid nodules were performed because 78 (64.4%) of the patients had enlarged thyroid gland by inspection or palpation; 23 (19.0%) were on Hashimoto thyroiditis, 4 (3.3%) were on congenital hypothyroidism and 2 (1.7%) were on Graves follow up; 11 (9.1%) had defects in thyroid function tests, 2 (1.7%) had a history of thyroid malignancy in family and 1 (0.8%) had a history of radiotherapy. While 93 (76.7%) patients had normal thyroid function tests at the time of diagnosis, it was found compatible with hypothyroidism in 12 (9.9%), subclinical hypothyroidism in 9 (7.4%), hyperthyroidism in 3 (2.5%) and subclinical hyperthyroidism in 4 (3.3%) of them. Median TSH level was 1.8 µIU/ml (0.06-100.0 µIU/ml). At least one of Anti TPO or Anti TG antibodies were positive in 34 (28.1%) patients. Serum calcitonin and thyroglobulin levels were increased in 1 (0.8%) and 43 (35.5%) patients, respectively.

Median nodule size was 13 (5-55) mm and 54 (44.6%) patients had a single nodule. Other US findings were as follows: nodule structure was solid in 63 (52.1%), cystic in 8 (6.6%), solidcystic in 47 (38.8%) and there was a calcificated area without an evident nodul formation in 3 (2.5%) patients; hypoechoic in 67 (55.4%), isoechoic in 34 (28.1%) and hyperechoic in 20 (16.5%)

patients; blood flow was increased in 30 (24.8%) patients; nodule margins were irregular in 31 (25.6%) patients; microcalcification and parenchymal heterogeneity were present in 35 (28.9%) and 68 (56.2%) patients, respectively.
Fifty-three patients (43.8%) had multiple FNA and 192 FNA results were evaluated with a 30.2% nondiagnostic rate in total. Initial FNA results of patients (including the first biopsy results of the patients with multiple FNA) were as follows; nondiagnostic in 18 (14.9%), benign in 62 (51.2%), AUS/FLUS in 19 (15.7%), FN/SFN in 9 (7.4%), SFM in 7 (5.8%) and malignant in 6 (5.0%) patients. Final FNA results of patients (considering the most recent FNA results in patients with multiple FNA) were insufficient material in 1 (0.8%), benign in 68 (56.2%), AUS/FLUS in 22 (18.2%), FN/SFN in 12 (9.9%), SFM in 10 (8.3%) and malignant in 8 (6.6%) patients.
The thyroid council decided that nodules of 55 patients required surgery and follow up of 39 of them was continued in our center [nodulectomy n=2 (they were performed only in the early period of the study), lobectomy n=10, subtotal thyroidectomy n=5, total thyroidectomy n= 22]. Among 39 patients, one of 12 patients with AUS, 4 of 8 patients with FN/SFN, 2 of 4 patients with SFM and 3 of 3 patients with malignancy as cytological diagnosis with FNA had differentiated thyroid cancer (DTC) [papillary carcinoma (PTC) n=7, follicular carcinoma (FTC) n=3] as histopathological diagnosis. The total malignancy rate was 10% (10/100) among all the cases (excluding the ones whose thyroidectomies weren't performed in our center and whose histopathologic diagnosis were not known). None of them had a history of radiotherapy or history of thyroid malignancy in family. The median thyroid nodule length of these cases with DTC was 12 mm (5-48 mm), there were two cases with a nodule size below 10 mm (both 5 mm) and FNA was planned due to the presence of microcalcification in these two patients. Individual clinical and ultrasonographic properties of patients with DTC is given in Table-1.
There were 35 patients with at least one nondiagnostic FNA result [either as an initial FNA result (n=18) or in repeat FNA's of initially benign or indeterminate results] and their subsequent FNA results were as follows, nondiagnostic in 1 (2.9%) patient, benign in 22 (62.8%), AUS in 7 (20%), SFN in 4 (11.4%) and malign in 1(2.9%) patient.
When follow-up of 80 patients with at least one benign FNA result [either as an initial FNA result (n=62) or repeat FNA of initially nondiagnostic (n=14), AUB (n=4) or FN/SFN (n=2)results] was evaluated, 15 (18.7%) patients' control biopsies showed progress according to TBSRTC stage (AUS n= 9, FN/SFN n=3, SFM n=2, malignant n=1), 22 (27.5%) patients' control biopsies were benign and 43 (53.8%) patients' follow-up US did not required repeat FNA. 5 patients with indeterminate (AUS, FN/SFN or SFM) repeat FNA results quitted follow up or refused surgery. Consequently, 4 patients with an initial benign FNA among 75 patients with at least one benign result (excluding 5 patients quitting follow up) had DTC in surgical excision with a 5.3% false negative rate.
In the follow-up of 31 patients with AUS as a result of FNA, FNA was repeated in 13 patients (benign n = 4, AUS n = 3, FN/SFN n = 5, SFM n = 1), 9 patients had thyroidectomy and 5 patients were directed to adult endocrinology/quit follow-up. Two of the 15 patients operated in our hospital were diagnosed with PTC (Figure-2).
Risk factors for malignancy were evaluated among 100 patients who were not directed to adult group, did not quit follow up or did not refuse surgery (DTC n=10 vs benign n= 90). TSH levels and nodule size were similar in both groups. Male gender, presence of Hashimoto thyroiditis, uninodularity, hypoechogenicity, increased blood flow, irregular margins, solid structure, microcalcification of the nodule, parenchymal and presence of abnormal cervical lymph nodes were found to be associated with malignancy. Parenchimal heterogeneity was found to be associated with benign nodules (Table 2).

Discussion

Clinical, radiological and pathological findings of 121 children and adolescents with thyroid nodules were evaluated in this study. The frequency of nodules increased and female dominance became evident with increasing age, especially after onset of puberty. Thyroid nodules are more common in women and their frequency increases with age. Female dominance can be explained by increased incidence of autoimmune thyroiditis together with the influence of estrogen and progesterone on thyroid cells(12,13). Dyshormonogenes, Hashimoto thyroiditis, Graves, iodine deficiency, history of radiotherapy and some genetic disorders, are conditions known to increase nodule development (6,8). In this study, the vast majority of patients did not have any known thyroid disease or thyroid dysfunction, and only one patient had a history of radiotherapy. The fact that diagnostic ultrasonography was requested according to the inspection and palpation findings in most of cases emphasize the importance of holistic examination in pediatric practice.
A wide range of malignancy rate (6.6- 56%) has been reported for childhood thyroid nodules(14,15,16). There may be overestimation in series of tertiary centres where patients with indeterminate and malignant FNA results are referred(16). Discordant results also can be explained by small sample sizes and the variation in inclusion criteria of the studies. Malignancy risk is underestimated in pediatric series which include cases up to the age of 21 and overestimated in series which limit inclusion to operated nodules(15,17,18). The overall incidence of thyroid carcinoma among operated children with nodules was given as 26.2% in a review summarizing 16 studies including 1164 patients since 1960(6). When we evaluated the malignancy rate among the operated cases only, the malignancy rate in our study (10/36, 25.6%) was compatible with the literature.
FNA is a reliable method to assess possibility of malignancy of a thyroid nodule and necessity for surgery. Its accuracy is 95% with 83% sensitivity, 92% specificity, 5% false negativity and 3% false positivity(19). Although FNA is a safe method and complications are very rare, it is an interventional process and patient selection should be done carefully. Which nodules should undergo FNA is decided according to US findings. Adult guidelines, which consider the size of the nodule primarily as FNA indication and not recommend FNA for a <1 cm nodule unless the patient is considered high risk with a history of ionizing radiation exposure or pathologic regional lymph nodes, had been applied to children and adolescents for a long time(20). But children and adolescent demonstrate differences in pathophysiology and clinical presentation and 2015 ATA guideline for children with thyroid nodules and differentiated thyroid cancer recommends using US features and clinical context rather than size alone to identify nodules that require FNA(7). However, extended indications for FNA, considering US features and clinical

context primarily, had already been in use in most pediatric endocrinology clinics including ours. Thus, two patients with nodule size of 5 mm, who were directed to FNA because of microcalcifications within the nodule, were diagnosed with PTC.
Categorizing FNA results according to TBSRTC in children has equal accuracy, sensitivity and specificity as in adults(5,21). Risk of malignancy in nondiagnostic samples in adults is very low, however it is not known in children(22). Repeat of FNA at least three months after, is given as an option in ATA guideline(8). In this study, FNA was repeated in all cases with nondiagnostic results and malign result was present in 1 (2.9%) patient. However, this can not be given as malignancy rate of nondiagnostic results because nearly one third of the repeated FNA were compatible with AUS or SFN which have potential for malignancy.
Patients with benign FNA are controlled with US after 6-12 month. Repeat FNA and/or lobectomy plus isthmusectomy is required if the nodule is growing or there are suspicious US findings(8). The probability of having a benign nodule on surgical excision is 90% in patients with one benign FNA and 98% in patients with at least two benign FNA. Patients can be safely monitored without going to surgery with repetitive biopsies unless clinical changes develop(23). There is a small but significant false negative rate of FNA(20). False negativity is increased in larger nodules and lobectomy is an option in patients with nodules over >4 cm(8,24). In this study, 17.5% of the 80 patients with initial benign FNA, had indeterminate cytology and one patient with a 12 mm nodule had malignant cytology in repeat FNA. The mean nodule size was 17±8 mm in patients with indeterminate cytology. False negativity in FNA is not specific to very large nodules. FNA should be repeated if there is increase in nodule size or there are specific US features like microcalcification.
Repeat FNA in indeterminate results is recommended as an option in adult guidelines that had been in use for children for a long time(20). Risk of malignancy in indeterminate nodules is higher in children (28% in AUS/FLUS and 58% in FN/SFN) than in adults (5-15% in AUS/FLUS and 15-30% in FN/SFN)(25,26). Hence, 2015 ATA Guideline for children recommends definitive surgery for indeterminate results (8). All follow up decisions for indeterminate nodules were made by thyroid council directing FN/SFN and SFM results to surgery. AUS/FLUS results were tended to be directed to surgery after 2015 and total malignancy rate was 9% (2 among 22 patients who didn't quit follow up or refuse surgery). Recently, Cheralla et al. reported that 28% of nodules with AUS on initial FNA were benign on repeat FNA, which is 31% in this study (27). Based on this data, repeat FNA may be still considerable for AUS/FLUS cytology, however small number of cases in these studies suggest further investigation (2).
TSH has a major role on proliferation and functioning of thyroid cell and persistently elevated TSH levels increase the risk of DTC formation(28). Even patients with a nodule and TSH levels in upper tertiles of reference range may have increased risk for malignancy(29). Mussa et al. had shown that TSH levels of children with DTC were higher than children with benign nodules excluding the ones already on levothyroxine treatment or the ones with hypo/hyperthyroidism(30). However, its hard to documentate how long the patients' TSH levels had been over or within the upper tertile of the normal range. So that, in this study, none of the 10 patients with DTC had subclinical or overt hypothyroidism (six of them were on already levothyroxine) and TSH levels were similar in both groups even after excluding the patients with abnormal TSH levels from benign group.
HT is the most common inflammatory thyroid disease characterized by a wide range of morphological changes in the gland. Coexistence of DTC and HT has been stated in many publications so far. However, it is not clear whether lymphocytic infiltration due to HT facilitates DTC formation or the immune response against the tumour initiates lymphocytic infiltration(28). Most adult studies are focused on prevalence of HT among patients with DTC with a wide range of 5% and 85% (31). Our findings were compatible with Hacıhamdioglu et al.'s study reporting HT prevalence as 45% (all with PTC) among 20 children with DTC. Older ages at diagnosis and smaller tumour sizes were also reported by them supporting our findings(32). In a study focusing on malignancy risk among children with HT, risk of malignancy among nodules that required FNA was 25% which was 17.9% (5/28) in our study, both showing higher malignancy prevalences than nodules without HT(33).
US findings such as hypoechogenicity, increased blood flow, irregular margins, solid structure, microcalcification of the nodule and presence of abnormal cervical lymph nodes, which which we identified as risk factors, are already known to be more common in malignant nodules. (34,35,36,37). Although hypoechogenicity and increased blood flow have high negative predictive value and high sensitivity, microcalcifications and presence of abnormal cervical lymph nodes have the highest specificity and positive predictive value and because of this, FNA is recommended for nodules with microcalcifications and abnormal lymph nodes independent of nodule size(21). The two subcentimeter malignant nodules both with microcalcifications and one with abnormal lymph nodes but without hypoechogenicity or increased blood flow in this study supports the importance of this recommendation.

Study limitations

The main limitations of this study were the small sample size and retrospective design of the study. Additionally, about 1/6 of the patients' progress was unknown due to quitting following up, refusing surgery, or having surgery at elsewhere mostly because they turn 16-18 years old and apply to adult clinics.

Conclusion

There is a considerable malignancy risk of %10 in childhood thyroid nodules. Nodules ≥1 cm or <1 cm with additional high-risk US findings such as microcalcification or abnormal lymph nodes should be directed to FNA. Because of 5.3% false negative rate in FNA, patients with benign FNA result should continue to be followed regularly and FNA should be repeated if their findings progress. Although malignancy rate was not different in AUS/ FLUS cases compared to the general sample of this study, due to the low number of cases, routinely repeating FNA before surgery decision can not be recommended in patients with AUS.

References

1. Silva de Morais N, Stuart J, Guan H, Wang Z, Cibas ES, Frates MC, Benson CB, Cho NL, Nehs MA, Alexander CA, Marqusee E, Kim MI, Lorch JH, Barletta JA, Angell TE, Alexander EK. The Impact of Hashimoto Thyroiditis on Thyroid Nodule Cytology and Risk of Thyroid Cancer. J Endocr Soc 2019;3:791-800. Epub 2019/04/10
2. Bauer AJ. Thyroid nodules in children and adolescents. Curr Opin Endocrinol Diabetes Obes 2019;26:266-274. Epub 2019/07/31
3. Niedziela M, Korman E, Breborowicz D, Trejster E, Harasymczuk J, Warzywoda M, Rolski M, Breborowicz J. A prospective study of thyroid nodular disease in children and adolescents in western Poland from 1996 to 2000 and the incidence of thyroid carcinoma relative to iodine deficiency and the Chernobyl disaster. Pediatr Blood Cancer 2004;42:84-92. Epub 2004/01/31
4. Guth S, Theune U, Aberle J, Galach A, Bamberger CM. Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. Eur J Clin Invest 2009;39:699-706. Epub 2009/07/16
5. Gupta A, Ly S, Castroneves LA, Frates MC, Benson CB, Feldman HA, Wassner AJ, Smith JR, Marqusee E, Alexander EK, Barletta J, Doubilet PM, Peters HE, Webb S, Modi BP, Paltiel HJ, Kozakewich H, Cibas ES, Moore FD, Jr., Shamberger RC, Larsen PR, Huang SA. A standardized assessment of thyroid nodules in children confirms higher cancer prevalence than in adults. J Clin Endocrinol Metab 2013;98:3238-3245. Epub 2013/06/06
6. Niedziela M. Pathogenesis, diagnosis and management of thyroid nodules in children. Endocr Relat Cancer 2006;13:427-453. Epub 2006/05/27
7. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26:1-133. Epub 2015/10/16
8. Francis GL, Waguespack SG, Bauer AJ, Angelos P, Benvenga S, Cerutti JM, Dinauer CA, Hamilton J, Hay ID, Luster M, Parisi MT, Rachmiel M, Thompson GB, Yamashita S. Management Guidelines for Children with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2015;25:716-759. Epub 2015/04/23
9. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid 2017;27:1341-1346. Epub 2017/11/02
10. Caturegli P, De Remigis A, Rose NR. Hashimoto thyroiditis: clinical and diagnostic criteria. Autoimmun Rev 2014;13:391-397. Epub 2014/01/18
11. Scappaticcio L, Trimboli P, Keller F, Imperiali M, Piccardo A, Giovanella L. Diagnostic testing for Graves' or non-Graves' hyperthyroidism: A comparison of two thyrotropin receptor antibody immunoassays with thyroid scintigraphy and ultrasonography. Clin Endocrinol (Oxf) 2020;92:169-178. Epub 2019/11/20
12. Manole D, Schildknecht B, Gosnell B, Adams E, Derwahl M. Estrogen promotes growth of human thyroid tumor cells by different molecular mechanisms. J Clin Endocrinol Metab 2001;86:1072-1077. Epub 2001/03/10
13. Wang K, Yang Y, Wu Y, Chen J, Zhang D, Liu C. The association of menstrual and reproductive factors with thyroid nodules in Chinese women older than 40 years of age. Endocrine 2015;48:603-614. Epub 2014/07/12
14. Altıncık A, Demir K, Abacı A, Böber E, Büyükgebiz A. Fine-needle aspiration biopsy in the diagnosis and follow-up of thyroid nodules in childhood. J Clin Res Pediatr Endocrinol 2010;2:78-80. Epub 2011/01/29
15. Roy R, Kouniavsky G, Schneider E, Allendorf JD, Chabot JA, Logerfo P, Dackiw AP, Colombani P, Zeiger MA, Lee JA. Predictive factors of malignancy in pediatric thyroid nodules. Surgery 2011;150:1228-1233. Epub 2011/12/06
16. Gupta A, Ly S, Castroneves LA, Frates MC, Benson CB, Feldman HA, Wassner AJ, Smith JR, Marqusee E, Alexander EK. A standardized assessment of thyroid nodules in children confirms higher cancer prevalence than in adults. The Journal of Clinical Endocrinology & Metabolism 2013;98:3238-3245.
17. Group CPTNS. The Canadian Pediatric Thyroid Nodule Study: an evaluation of current management practices. J Pediatr Surg 2008;43:826-830.
18. Kapila K, Pathan SK, George SS, Haji BE, Das DK, Qadan LR. Fine needle aspiration cytology of the thyroid in children and adolescents: experience with 792 aspirates. Acta Cytol 2010;54:569-574.
19. Sakorafas GH. Thyroid nodules; interpretation and importance of fine-needle aspiration (FNA) for the clinician - practical considerations. Surg Oncol 2010;19:e130-139. Epub 2010/07/14
20. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-1214. Epub 2009/10/29
21. Mussa A, De Andrea M, Motta M, Mormile A, Palestini N, Corrias A. Predictors of Malignancy in Children with Thyroid Nodules. J Pediatr 2015;167:886-892.e881. Epub 2015/07/15
22. Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid Cytopathology. Thyroid 2009;19:1159-1165. Epub 2009/11/06
23. Oertel YC, Miyahara-Felipe L, Mendoza MG, Yu K. Value of repeated fine needle aspirations of the thyroid: an analysis of over ten thousand FNAs. Thyroid 2007;17:1061-1066. Epub 2007/10/04
24. McCoy KL, Jabbour N, Ogilvie JB, Ohori NP, Carty SE, Yim JH. The incidence of cancer and rate of false-negative cytology in thyroid nodules greater than or equal to 4 cm in size. Surgery 2007;142:837-844; discussion 844.e831-833. Epub 2007/12/08

25. Monaco SE, Pantanowitz L, Khalbuss WE, Benkovich VA, Ozolek J, Nikiforova MN, Simons JP, Nikiforov YE. Cytomorphological and molecular genetic findings in pediatric thyroid fine-needle aspiration. Cancer Cytopathol 2012;120:342-350. Epub 2012/05/19
26. Baloch ZW, LiVolsi VA, Asa SL, Rosai J, Merino MJ, Randolph G, Vielh P, DeMay RM, Sidawy MK, Frable WJ. Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. Diagn Cytopathol 2008;36:425-437. Epub 2008/05/15
27. Cherella CE, Angell TE, Richman DM, Frates MC, Benson CB, Moore FD, Barletta JA, Hollowell M, Smith JR, Alexander EK, Cibas ES, Wassner AJ. Differences in Thyroid Nodule Cytology and Malignancy Risk Between Children and Adults. Thyroid 2019;29:1097-1104. Epub 2019/07/13
28. Zirilli G, Salzano G, Corica D, Pajno GB, Mignosa C, Pepe G, De Luca F, Crisafulli G. Thyrotropin serum levels and coexistence with Hashimoto's thyroiditis as predictors of malignancy in children with thyroid nodules. Ital J Pediatr 2019;45:96. Epub 2019/08/08
29. McLeod DS, Watters KF, Carpenter AD, Ladenson PW, Cooper DS, Ding EL. Thyrotropin and thyroid cancer diagnosis: a systematic review and dose-response meta-analysis. J Clin Endocrinol Metab 2012;97:2682-2692. Epub 2012/05/25
30. Mussa A, Salerno MC, Bona G, Wasniewska M, Segni M, Cassio A, Vigone MC, Gastaldi R, Iughetti L, Santanera A, Capalbo D, Matarazzo P, De Luca F, Weber G, Corrias A. Serum thyrotropin concentration in children with isolated thyroid nodules. J Pediatr 2013;163:1465-1470. Epub 2013/08/27
31. Lee JH, Kim Y, Choi JW, Kim YS. The association between papillary thyroid carcinoma and histologically proven Hashimoto's thyroiditis: a meta-analysis. Eur J Endocrinol 2013;168:343-349. Epub 2012/12/06
32. Hacıhamdioğlu B, Oçal G, Berberoğlu M, Savaş Erdeve S, Camtosun E, Kocaay P, Fitoz S, Ceyhan K, Dindar H, Yağmurlu A, Kır M, Unal E, Sıklar Z. The evaluation of thyroid carcinoma in childhood and concomitance of autoimmune thyroid disorders. J Pediatr Endocrinol Metab 2014;27:901-908. Epub 2014/05/24
33. Corrias A, Cassio A, Weber G, Mussa A, Wasniewska M, Rapa A, Gastaldi R, Einaudi S, Baronio F, Vigone MC, Messina MF, Bal M, Bona G, de Sanctis C. Thyroid nodules and cancer in children and adolescents affected by autoimmune thyroiditis. Arch Pediatr Adolesc Med 2008;162:526-531. Epub 2008/06/06
34. Joseph-Auguste J, Lin L, Demar M, Duffas O, Molinie V, Sulpicy C, Dorival MJ, Luxembourger O, Sabbah N. Epidemiologic, Clinical, Ultrasonographic, and Cytological Features of Thyroid Nodules in Predicting Malignancy Risk: A Retrospective Study of 442 French Afro-Caribbean Patients. Int J Endocrinol 2020;2020:4039290. Epub 2020/04/23
35. Lyshchik A, Drozd V, Demidchik Y, Reiners C. Diagnosis of thyroid cancer in children: value of gray-scale and power doppler US. Radiology 2005;235:604-613. Epub 2005/03/17
36. Leboulleux S, Girard E, Rose M, Travagli JP, Sabban N, Caillou B, Hartl DM, Lassau N, Baudin E, Schlumberger M. Ultrasound criteria of malignancy for cervical lymph nodes in patients followed up for differentiated thyroid cancer. J Clin Endocrinol Metab 2007;92:3590-3594. Epub 2007/07/05
37. Grani G, D'Alessandri M, Carbotta G, Nesca A, Del Sordo M, Alessandrini S, Coccaro C, Rendina R, Bianchini M, Prinzi N, Fumarola A. Grey-Scale Analysis Improves the Ultrasonographic Evaluation of Thyroid Nodules. Medicine (Baltimore) 2015;94:e1129. Epub 2015/07/15

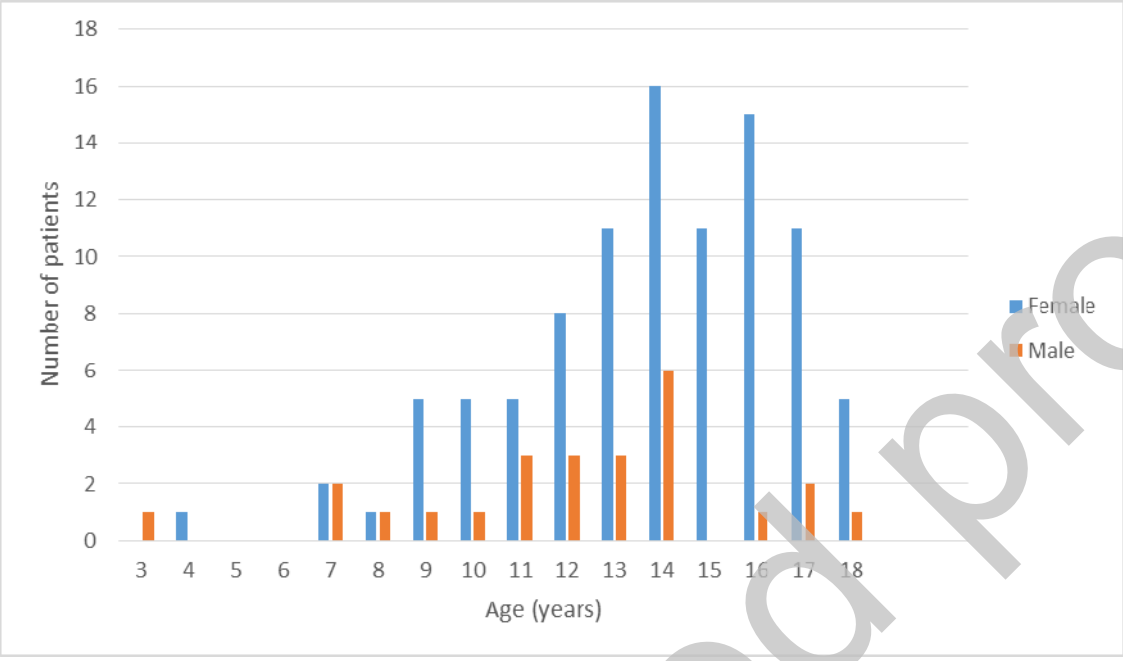

Figure-1 Age and sex distrubition of the patients

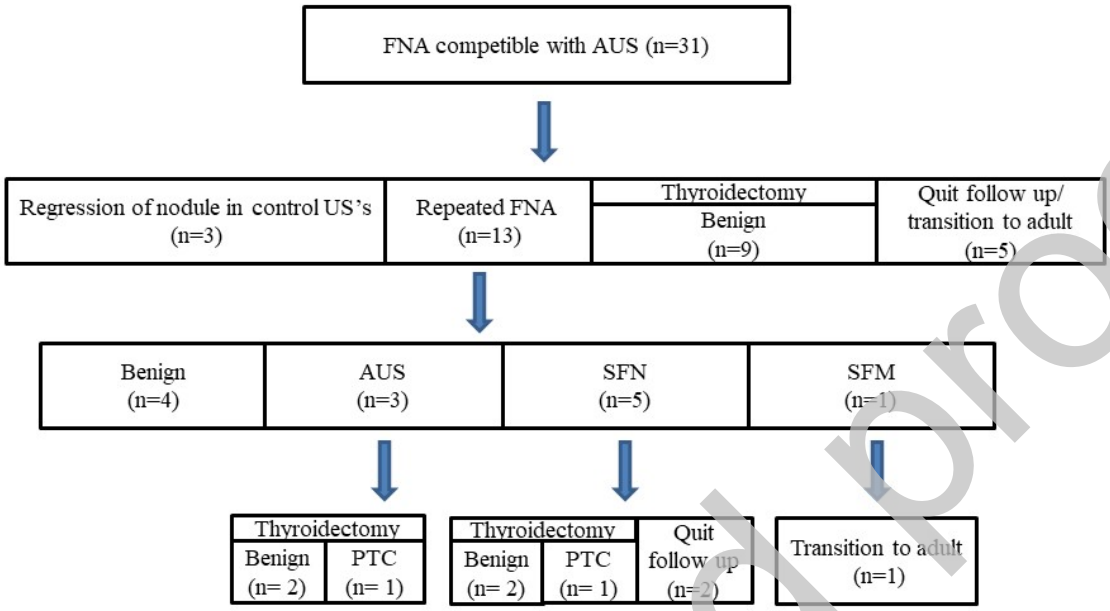

Figure 2

Table-1. Clinical and ultrasonographic findings of patients with differentiated thyroid cancer

Case	Age	G	TD	US Findings of the Nodule			FNA	Histopathological Diagnosis
				L (mm)	Echogenicity	MC		
1	7	F	CH	13	hypo	+	SFM	PTC, CS
2	8	M	-	21	hypo	-	Malignant	PTC, CS
3	10	M	-	48	iso	+	FN/SFN	FTC, invasive
4	13	M	HT	12	hypo	+	FN/SFN	PTC, DSS
5	13	F	HT	12	hypo	-	FN/SFN	FTC, WD
6	13	F	-	35	hypo	+	Malignant	PTC, CS
7	14	F	HT	5	iso	+	FN/SFN	PTC, FS
8	14	F	-	10	hypo	-	AUS	PTC, FS
9	15	F	HT	5	hyper	+	SFM	PTC, CS
10	16	M	HT	39	iso	-	Malignant	FTC, MI

G: gender, F: female, M: male, TD: Thyroid disease, HT: Hashimoto's thyroiditis, CH: congenital hypothyroidism, US: ultrasonography, L:length, MC: microcalcification, FNA: fine needle aspiration biopsy, FN/SFN: follicular neoplasm/suspicious for follicular neoplasm, SFM: suspicious for malignancy, AUS: atypia of undetermined significance, PTC: papillary thyroid carcinoma, FS: follicular subtype, DSS: diffuse sclerosing subtype, CS: classic subtype, FTC: follicular thyroid carcinoma, MI: minimal invasive, WD: well differentiated

Table-2. Risk factors for malignancy

	Total[1] (n=100)		p
	Benign[2] (n=90)	Malignant[3] (n=10)	
TSH level (μIU/ml)	1.82 (0.2-100)	1.55 (0.7-5.3)	0.82
Nodule size (mm)	12 (5-55)	12 (5-48)	0.74
Gender (Male/Female)	18/72	4/6	<0.001
Solid Structure n(%)	42 (46.6)	9 (90.0)	0.016
Hypoechogenicity n(%)	48 (53.3)	6 (60.0)	<0.001
Increased blood flow n (%)	15 (16.6)	5 (50.0)	0.025
Irregular margin n (%)	19 (21.1)	3 (30.0)	<0.001
Microcalcification n (%)	20 (22.2)	6 (60.0)	0.02
Parenchymal heterogeneity n (%)	49 (54.4)	4 (40.0)	<0.001
Abnormalcervical lymph nodes n(%)	4 (4.4)	3 (70.0)	0.02
Hashimoto Thyroiditis n(%)	23 (25.6)	5 (50.0)	<0.001
Increased Thyroglobulin n(%)	32 (35.9)[4]	4 (40.0)	>0.99

[1] Patients who quit follow up or refuse surgery were excluded

[2] Patients with cytopathologic or histopathologic benign results

[3] Patients with histopathologic malignant results

[4] Thyroglobulin result was missing in one patient