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Should encountering atypia of undetermined significance / follicular lesion of undetermined significance after thyroid biopsy lead to the operation?

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ABSTRACT

Objectives: Nodular goiter is the most common disease of the thyroid gland. Thyroid nodules are malignant in 3-5% cases. To determine the incidence of malignancy in patients defined as atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) as a result of fine needle aspiration biopsy (FNAB) and evaluate the clinical, biochemical and sonographic features as possible predictors of malignancy.

Methods: Patients who had undergone at least one FNAB and diagnosed as AUS/FLUS from January 2011 to December 2015 were included in the study. Age, gender, benign disease, thyroid stimulating hormone (TSH) level, size, localization, number, time of FNAB, ultrasonography (USG) characteristics, follow-up data on repeated FNAB results and, if surgical excision was performed, final pathological results were analyzed.

Results: A total of 5181 thyroid nodules were biopsied in 4089 patients, and the biopsy specimen taken from 611 nodules was diagnosed histopathologically as AUS/FLUS (11.79%). After FNAB, 167 of 611 patients diagnosed with AUS/FLUS were operated. While 65.9% (n = 110) of 167 patients who underwent surgery were made a benign diagnosis; malign diagnosis was made to 34.1% (n = 57).

Conclusions: The rate of malignancy in surgically confirmed nodules was 34.1% in this study, which is higher than the Bethesda classification. Due to the high malignancy rate which determined in cytologically diagnosed AUS/FLUS, we think that the repeat decision of the FNAB should be reconsidered and the surgical plan after the first FNAB should be considered more seriously.

Keywords: Thyroid biopsy, thyroid cancer, thyroidectomy

Nodular goiter is the most common disease of the thyroid gland, especially in areas with iodine deficiency [1]. Thyroid nodules are found in 4-8% by palpation in adults, 41% by ultrasonography (USG), and 50% in autopsy series [2]. Thyroid nodules are malignant in 3-5% cases although thyroid cancers are more rare, constituting less than 1% of all malignant neoplasms [3]. Important information is obtained by thyroid function tests (TFT), scintigraphy and USG in clinical and diagnostic approach in thyroid nodules but

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the distinction of benign and malignant lesions cannot be made with these tests [4].

Today, the most commonly used, fast, simple, least invasive, inexpensive and reliable method for the malignant-benign differentiation of thyroid nodules is cytological examination of fine needle aspiration materials [5]. Diagnostic accuracy of thyroid fine needle aspiration biopsy (FNAB) increases up to 80-95% in experienced clinics [6].

The Bethesda Classification Reporting Thyroid Cytopathology was defined by the National Cancer Institute (NCI) to improve communication between cytopathologists and clinicians and standardize the terminology used for FNAB. This system is divided into six diagnostic categories that provide an assessment of the risk of malignancy and management guidelines for each category [7]. Atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) is a Bethesda system category that includes various nuclear abnormalities that do not fit into another category after FNAB [8]. According to the Bethesda system, the AUS/FLUS category covers approximately 7% or less of all thyroid FNABs and the expected risk of malignancy in the AUS/FLUS category according to NCI is between 5% and 15% [9]. However, several recent studies have reported various malignancy rates ranging from 6% to 76% for surgically confirmed cases [10].

In this study, by analyzing the data of our hospital, we aimed to determine the incidence of malignancy in patients defined as AUS and FLUS as a result of FNAB in our own patient group and evaluate the clinical, biochemical and sonographic features as possible predictors of malignancy. In addition, this study aims to contribute to the follow-up and treatment processes of patients.

METHODS

This study was conducted in an education and research hospital in the Eastern Black Sea Region, which is considered an endemic region for goiter. The patient consent forms required for the FNAB and surgical procedures to be performed within the framework of ethical recommendations were obtained. The study was approved by the hospital ethics committee (No: 2016/44). FNAB cytologic evaluation of the cases was performed according to the widely accepted and applied Bethesda classification.

A retrospective review of institutional electronic medical records was performed and cases diagnosed as AUS/FLUS from January 2011 to December 2015 were identified. Patients who had undergone at least one FNAB and diagnosed as AUS/FLUS were included in the study. Patients with malignant, malignant suspicious, follicular neoplasia or follicular neoplasia suspected as a result of biopsy performed in different thyroid nodules and patients with synchronous malignancy in another organ and contralateral thyroid lobe were excluded from the study. Age, gender, benign disease, thyroid stimulating hormone (TSH) level, size, localization, number, time of FNAB, ultrasonography (USG) characteristics, follow-up data on repeated FNAB results and, if surgical excision was performed, final pathological results were analyzed. Only patients who underwent surgical excision were included in the final analysis after adequate follow-up data and exclusion of cases without a descriptive pathological diagnosis. All FNABs were performed by an experienced endocrinologist or interventional radiologist with USG guidance from a suspected thyroid nodule. USG features of thyroid nodules were recorded using electronic database or by scanning patients' files. Among these features, hypoechogenicity, microcalcification, presence of halo and presence of solid component were defined as suspicious criteria for malignancy [11].

National Cancer Institute recommendations are followed in our hospital; for all patients diagnosed with AUS / FLUS in the first FNAB, a repeated FNAB is recommended [12]. After repeated FNAB, surgical excision is recommended for patients having AUS/FLUS, follicular neoplasia suspicious, follicular neoplasia, malignant suspicion and malignancy. If the diagnosis cannot be made after repeated FNAB, it is recommended to repeat the FNAB or perform surgery. If the results of repeated FNAB are benign, follow-up is recommended. Despite these recommendations, several factors (eg, clinical features, USG features, cosmetic problems, or patient preferences) may influence treatment decision.

The electronic medical records were reviewed using the database of our hospital and in case of insufficient data in the medical records, the current status of the patients was asked by telephone interview.

Table 1. Distribution of patients by gender

Gender	n	%
Female	504	82.5
Male	107	17.5

When the follow-up data were insufficient to confirm the prognosis of the nodule, the patient refused FNAB recurrence and / or surgical excision, or the patient died for other reasons, the patient was considered a missing case (Data Loss = DL).

Statistical Analysis

Continuous variables were presented as mean ± standard deviation in the parametric distribution and median in the nonparametric distribution. For statistical analysis, Chi-square test, Fisher's exact test, Mann-Whitney U test and Student's t-test were used for intergroup comparisons based on categorical or continuous properties of variables. Univariate analysis of the variables was performed using a logistic regression test to identify possible markers for malignancy. For logistic regression testing, categorical variables were converted to binomial data using known risk factors for a more appropriate assessment. In order to determine the lower and upper threshold values of malignancy rates, all nodules followed without surgery were assumed to be benign or malignant. The low threshold value was calculated by dividing the number of patients with malignancy detected after surgery by the total number of AUS/FLUS nodules after assuming benign patients. The upper threshold value was calculated by dividing the total number of patients who had malignancy with surgery and the patients under follow-up after the assumption of malignant patients, by the total number of AUS/FLUS nodules. Statistical analysis package (SPSS 20.0, IBM Corp, Armonk, NY, USA) was used for all statistical analysis. All reported p values are bilateral and $p < 0.05$ is considered significant. Also, confidence intervals (CI) were calculated at the level of 95%.

RESULTS

Clinical Findings in Nodules Diagnosed as AUS/FLUS with FNAB

A total of 5181 thyroid nodules were biopsied in 4089 patients, and the biopsy specimen taken from 611 nodules was diagnosed histopathologically as AUS/FLUS (11.79%). Patients whose histopathological diagnoses were reported as AUS/FLUS were included in the study group. Five hundred and four (82.5%) of these patients are females; 107 (17.5%) of them were males (Table 1). The female / male ratio was determined as 4.72. The mean age of the patients included in the study group was 52.97 ± 13.2 years, the average TSH level was 1.88 ± 5.8 mIU/L, and the average diameter of the biopsied nodules was 20.8 ± 9.86 mm (Table 2). Twenty-six of the patients had undergone a surgical operation due to benign disease. Diagnosis was made by performing biopsy from 495 (81%) patients from a single nodule, 113 (18.5%) patients from two nodules, three (3.5%) patients from three or more nodules (Table 3).

Histopathological Results in Operated Cases

After FNAB, 167 of 611 patients diagnosed with AUS/FLUS were operated and clear information about histopathological diagnosis was reached. While 65.9% (n = 110) of 167 patients who underwent surgery were made a benign diagnosis; malign diagnosis was made to 34.1% (n = 57) (Table 4).

Clinical Features

Twenty-seven (16.2%) of 167 patients who had undergone surgery were male and 83.8% (n = 140) were female. In the examination among female patients, 67.1% (n = 94) and 32.9% (n = 46) were diag-

Table 2. Age-TSH value-nodule diameter values of the patients

	n	Minimum	Maximum	Mean	Standart deviation
Age (years)	611	18	93	52.97	13.296
TSH (mIU/L)	547	0.01	127.5	1.887	5.82794
Nodule diameter (mm)	581	4	61	20.82	9.86

Table 3. Number of nodules taken by biopsy according to the number of patients

Number of biopsied nodules	n	%
From one nodule	495	81
From two nodules	113	18.5
From three or more nodules	3	0.5
Total	611	100

nosed as malignant. The average age of 110 patients in the benign disease group was 48.22 ± 11.39 years, and the average age of the patients in the malignant group was 52.3 ± 12.30 years (p = 0.034). Among male patients, this rate was 59.3% (n = 16) benign and 40.7% (n = 11) malignant (p = 0.429). Only 1.2% (n = 2) of 167 patients had undergone a previous surgical operation for thyroid due to a benign disease (p = 0.306) (Table 5). Sixty-four (38.3%) of the patients were operated after the first diagnosis of AUS/FLUS, and 47.9% (n = 80) were second and 13.8% (n = 23) were third. Of these, 31.3% (n = 20) of those who were operated after the first biopsy, 38.8% (n = 31) of those operated after the second biopsy, and 26.1% of those who were operated after the third biopsy (n = 6) a malignant diagnosis was made ($p = 0.437$) (see Table 5). Data related to TSH were reached in 159 of 167 patients whose histopathological diagnosis was confirmed surgically, while 8 patients could not. The average TSH value of 104 patients in the benign group was measured as 1.205 (0.01-127.49) mIU/L; the average TSH value of 55 patients in the malignant group. was measured as 1.08 (0.01-18.09) mIU/L ($p = 0.621$) There was no significant difference between malignant and benign groups in terms of gender, thyroid surgery, median TSH level, number of FNAB. It was observed that the average age was higher only in the malignant group than in the benign group. ($p = 0.034$) (Table 5).

Table 4. Histopathological distribution of the AUS/FLUS diagnosed nodules after surgical confirmation (n = 167)

Pathological diagnoses	n	%
Benign pathological diagnoses		
Adenomatous nodule	8	7.3
Follicular adenoma	4	3.6
Hashimoto's thyroiditis	9	8.2
Nodular goiter	10	9.1
Multinodular goiter	79	71.8
Total	110	100
Malign pathological diagnoses		
Papillary carcinoma (Classic variant)	28	49.1
Papillary carcinoma (Follicular variant)	23	40.4
Papillary carcinoma (Oncocytic variant	4	7
Follicular carcinoma	2	3.5
Total	57	100
General total	167	100

USG Features

Echogenicity, wall irregularity, halo presence, nodule component, calcification and nodule size were evaluated, and the data availability was 86.82%, 86.22%, 88.62%, 89.82%, 88.62% and 98%, respectively. Data on echogenicity could not be obtained in 22 of 167 patients whose histopathological diagnosis was clarified after surgery. 28.3% (n = 41) of the patients whose data were available had hypoechogenicity, 66.2% (n = 96) isoechogenicity and 5.5% (n = 8) hyperechogenicity. 36% (n = 15) of patients with nodules with hypoechogenicity, 34.4% (n = 33) of patients with nodules with isoechogenicity and 37.5% (n = 3) of patients with nodules with hyperechogenicity were diagnosed as malignant ($p = 0.96$) (Table 6). While 144 patients' USG information was obtained about wall irregularity, 23 patients did not have any data. While 3.5% (n = 5) of 144 patients had wall irregularities; no wall irregularity was found in 96.5% (n = 139). To 20% (n = 1) of patients with wall irregularities in thyroid nodules taken biopsy; 35.3% (n = 49) of patients without wall irregularities were given a malignant diagnosis. One hundred forty-eigth patients had information about the presence of halo, while 19 patients could not. While halo was found in 19% (n = 29) of the patients whose data were reached, 80.4% (n = 119) did not. While 37.1% (n = 11) of patients with halo in the nodule undergoing biopsy had a malignant diagnosis after surgery; This rate was 34.5% in patients with nodules without halos (n = 41) ($p = 0.725$) after surgery ($p = 0.482$). In the data analysis made for the components of the nodules, the data could be accessed in 150 patients. Data were not available in 17 patients. The patients whose data were available had 54.7% (n

Table 5. Clinical findings in surgically diagnosed nodules

		Cases		
		Benign (n = 110)	**Malign (n = 57)**	***p* value**
Age (years)		48.22 ± 11.39	52.3 ± 12.30)	**0.034**
Gender				
	Female	94 (85.5%)	46 (80.7%)	0.429
	Male	16 (14.5%)	11 (19.3%)	
Previous surgery				
	Yes	2 (1.8%)	0 (0%)	0.306
	No	108 (98.2%)	57 (100%)	
Time of surgery				
	After first FNAB	44 (40%)	20 (35.1%)	0.437
	After second FNAB	49 (44.5%)	31 (54.4%)	
	After third FNAB	17 (15.5%)	6 (10.5%)	
TSH value (mIU/L)		1.205 (0.01-127.49)	1.08 (0.01-18.09)	0.621

= 82) pure solid, 0.7% (n = 1) pure cystic and 44.7% (n = 82) mixed nodules. Of these, 35.4% (n = 29) of patients with pure solid nodules, 100% of pure cystic (n = 1) and 3.8% of mixed type (n = 22) were diagnosed as malignant after surgery ($p = 0.368$) (see Table 6). USG information about the calcification properties of 148 nodules with FNAB was reached. While 18.2% (n = 27) of them have micro, 7.4% (n = 11) macro and 6.1% (n = 9) mix type calcification; there was no calcification in 68.2% (n = 101). 33.3% of patients with nodules with microcalcification (n = 9), 54.5% of patients with nodules with macrocalcification (n = 6) and 33.3% of patients with nodules with mixed type calcification (n = 3) a malignant diagnosis was made. This rate was 32.7% (n = 33) in patients without calcification (p = 0.546). Data on the size of 165 nodules were available. While the average size of nodules in the benign group is 20 ± 11.00 mm; In the malignant group, this ratio was 21 ± 11.70 mm ($p = 0.937$) (Table 6).

In the univariate analysis of clinical and USG data, only age (> 55 years) was found as a sign of malignancy. (odds ratio 0.321; 95% CI: 0.161-0.633; p : 0.001). Univariate analyzes for malignancy are shown in Table 7.

DISCUSSION

In this study, FNAB was performed on 5181 thyroid nodules, and 611 nodes (11.79%) were diagnosed with AUS/FLUS. This rate is slightly higher than the Bethesda forecast, but within acceptable limits. The reason why the rate is higher than the Bethesda classification may be that the hospital where we conduct the study is in an endemic region for goiter and the differences in interpretation among pathologists. According to the prediction of the Bethesda classification, the expected malignancy rate in the AUS/FLUS category is between 5-15% (9). However, the frequency of true malignancy in this group is not fully known, since not all nodules are evaluated histopathologically. In studies involving only cytological follow-up, the rate of malignancy was low, whereas in a large-series study, the rate was reported to be 27.5% [13]. In cases where patients are selected for the operation, this rate varies between 6-48% [14, 15].

In this study, 167 of 611 thyroid nodules diagnosed with AUS/FLUS were surgically diagnosed and 57 (34.1%) of these 167 patients received a malignant diagnosis. This rate is higher than Bethesda's estimate. Possible reasons for the high may include the nodules

Table 6. **USG findings in surgically diagnosed nodules**

		Cases		
		Benign (n = 110)	**Malign (n = 57)**	***p* value**
Echogenity				
	DL	16	6	
	hypoechoic	26 (27.7%)	15 (29.4%)	0.96
	Isoechoic	63 (67%)	33 (64.7%)	
	Hyperechoic	5 (5.3%)	5 (5.9%)	
Calcification				
	DL	13	6	
	Micro	18 (18.6%)	9 (17.6%)	0.546
	Macro	5 (5.2%)	6 (11.8%)	
	Mix	6 (6.2%)	3 (5.9%)	
	Absent	68 (70.1%)	33 (64.7%)	
Halo				
	DL	14	5	
	Yes	18 (18.8%)	11 (21.2%)	0.725
	No	78 (81.3%)	41 (78.8%)	
Component				
	DL	12	5	
	Pure solid	53 (54.1%)	29 (55.8%)	0.368
	Pure cystic	0 (0%)	1 (1.9%)	
	Mix	45 (45.9%)	22 (42.3%)	
Size (mm)		20 (7-53)	21 (9-52)	0.937

DL = Data loss

that are considered to be at risk of high malignancy radiologically and clinically, and heterogeneity in the content of the AUS/FLUS. Assuming that all patients who were under follow-up and not surgically diagnosed with pathology were malignant or benign, the lower limit was 16.3% for malignancy and the upper limit was 68.3%. According to this wide range, the rate of malignancy in our study was higher than the predictions of Bethesda. However, some recent studies have indicated the malignancy rate in a range of 6% to 76% for cases confirmed surgically [10, 16]. This high range suggests that the malignancy rate predicted by Bethesda possibly for AUS/FLUS must be reconsidered. Although the actual incidence is currently unknown, this is likely due to the fact that only a small proportion of patients diagnosed with AUS/FLUS have been surgically confirmed and while determining these rates in the researches, the patients who underwent surgery should not be included in this rate and the patients who are under clinical follow-up should not be included. Recent studies have focused on increasing the validity and reliability of FNAB [17, 18]. In this study, 55 (97%) of 57 patients in the malignant group were detected as papillary carcinoma. In various studies, it was observed that the most common subtype among thyroid cancers diagnosed in patients diagnosed with AUS/FLUS was papillary carcinoma [19-22].

Table 7. Univariate data analysis according to clinical and USG data

		Odds ratio	95% CI	*p* value
Age	< 55y	reference	0.161-0.633	**0.001**
	≥ 55y	0.321		
Gender	Female	reference	0.604-3.27	0.43
	No	1.405		
Previous surgery	Yes	reference	0.542-2.063	0.871
	No	1.057		
TSH value	Less / Normal	reference	0.754-3.078	0.241
	High	1.523		
Size of nodule	≤ 20mm	reference	0.632-2.284	0.576
	> 20mm	1.201		
Time of surgery	After first FNAB	reference	0.635-2.392	0.536
	After second FNAB	1.233		
Hypoechogenity	No	reference	0.432-1.949	0.823
	Yes	0.918		
Microcalcification presence	No	reference	0.483-2.365	0.87
	Yes	1.068		
Halo presence	No	reference	0.502-2.693	0.725
	Yes	1.163		
Pure solid	No	reference	0.544-2.105	0.843
	Yes	1.071		

USG features of patients who were diagnosed with AUS/FLUS and who underwent surgical confirmation were evaluated with univariate analysis method for each feature and no significant relationship was found between USG features and malignancy. The accuracy of these results, which were obtained due to the retrospective nature of the study, the loss of data and this evaluation only in patients undergoing surgery, is uncertain and open to discussion. In addition to the fact that the data are different in various studies after the literature review, some researchers have suggested that the diameter of the nodule may be helpful in assessing the risk of malignancy, while some researchers have suggested that the diameter of the nodule is not associated with malignancy [23].

The relationship between the TSH values of the patients and the gender difference with malignancy were also evaluated statistically, but no statistical difference was found similar to previous studies [24].

There are differences between studies for the relationship between age and malignancy rate. In one of these studies, the rate of malignancy was analyzed higher in patients under 40 years of age [25], while in a similar study [26] patients with thyroid malignancy were younger than patients in the benign group. In current study, after the evaluation for malignant and benign groups without determining a reference value, the mean age was higher in the malignant group (p = 0.034).

According to the Bethesda classification, the biopsy should be repeated 3-6 months after the initial diagnosis of AUS/FLUS, and surgery should be performed in the case of a suspected malignant or malignant diagnosis [14].

In this study, no significant difference was found between the nodules repeating biopsy and the nodules not performed in terms of malignancy frequency. Considering the whole study, we think that surgical decision can be made earlier rather than repeat biopsy due to our higher rate of malignancy than expected.

CONCLUSION

Since the Bethesda classification predicts malignancy rate low, it recommends repeat biopsy for patients diagnosed with AUS/FLUS [27]. In this study, the rate of malignancy in surgically confirmed nodules was 34.1%, which is higher than the Bethesda classification. When the USG features of the malignant nodules were examined, it was seen that none of the features supported malignancy. As for clinical features, data were obtained that only over 55 years of age increased the risk of malignancy. According to our study, the risk of malignancy was three times higher in patients over 55 years old compared to those less than 55 years old. Due to the high malignancy rate which determined in cytologically diagnosed AUS/FLUS, we think that the repeat decision of the FNAB should be reconsidered and the surgical plan after the first FNAB should be considered more seriously. Based on data, it was not possible to create a successful algorithm using USG features or clinical features. Alternatively, new imaging techniques and molecular analyzes are promising methods to increase predictive validity of AUS/FLUS [28]. However, valuable analyzes are needed for all these newly defined methods.

Authors' Contribution

Study Conception: BÇ; Study Design: HAT; Supervision: HAT; Funding: EK, HAT; Materials: EK, HAT; Data Collection and/or Processing: BÇ, HAT; Statistical Analysis and/or Data Interpretation: EK; Literature Review: BÇ; Manuscript Preparation: BÇ, HAT and Critical Review: EK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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