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Original Research

Evaluation of Thyroid Fine-Needle Aspiration Biopsies according to Cytological Methods and Comparison with Histopathological Diagnosis

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Abstract

Objectives: In this study, we aim to compare the results of aspiration of thyroid nodules evaluated according to the Bethesda category (BC) with tissue diagnoses in the operation materials and to compare the sensitivity, specificity and accuracy rates according to cytology methods.

Methods: The previous fine-needle aspiration biopsy (FNAB) of thyroid nodules of 879 cases diagnosed histopathologically between 2010 and 2017 was examined. The FNAB results determined according to the Bethesda system were matched with tissue diagnoses, sensitivity, specificity, and accuracy rates were investigated according to cytology methods.

Results: Sensitivity, specificity, Positive predictive value (PPV), Negative predictive value (NPV) and accuracy rates were found in all FNAB results (in units of %; Sensitivity; 84.7, Specificity; 81.1, PPV; 74.1, NPV; 89.2, Accuracy; 82.5). All of the cytological evaluation methods of thyroid FNABs were found to be reliable and effective (Generally, the results are 80% and above). Specificity and accuracy rates were close to the general average (82.5%) in all methods. However, in cases evaluated with liquid base cytology (LBC) method and in addition to LBC or conventional smear (CS), the sensitivity rates in cases where cell block (CB) were evaluated together were higher than cases in which LBC and CS were used alone (92.6% and 91.0%). When examined statistically, there was no significant difference concerning sensitivity, specificity and accuracy rates of cytological methods ($p>0.05$, respectively, $p=0.576$, 0.065, 0.643).

Conclusion: In cytopathology, when evaluating thyroid aspirations, it is seen that the LBC method is used instead of CS. In our study, we recommend the use of the LBC method, which seems to have the highest sensitivity (taking into account its technical advantages), instead of CS. However, we think that both CS and LBC methods should be evaluated by supporting them with cell block sections.

Keywords: Bethesda category; cell block; cytology methods; FNAB; thyroid nodules.

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Fine-needle aspiration biopsy (FNAB) examination of thyroid nodules is performed routinely as a preferred method concerning cytological high sensitivity and specificity, which is easy to apply in practice, without severe complications.[1-4] Cytological diagnosis standardization has advanced with the widespread use of the Bethesda

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system.[1-3] The evaluation of thyroid FNABs according to cytological methods, their advantages-disadvantages and superiority against each other have become the subject of this research. In this study, we compared thyroid FNABs diagnosed according to the Bethesda Category with the results of histopathological diagnosis in resection materials. We also investigated the possible advantages of cytological methods (CS, LBC, CB) against each other concerning sensitivity, specificity and accuracy.

Methods

Conventional smear (CS) method is the traditional method in which cells obtained by FNAB are examined by spreading directly to the slide. The method in which the cells are placed in a solution in a special tube and the preparation is created in the automatic device is the liquid-based cytology (LBC) method. Most of the time, after the preparation of CS or LBC preparations, the method in which the remaining cells are brought together and fixed using a special solution and sectioned by creating a paraffin block is known as the cell block (CB) method. In our department, those who were excised by the operation of thyroid nodules examined with FNAB between 2010 and 2017 were included in this study. Their preparations obtained by CS, LBC, CB, in addition to these methods, were examined and matched with tissue diagnoses. Those with a definite histopathological diagnosis of the nodules examined by FNAB were evaluated. Cases without FNAB examination, cases not operated in our institution, cases with more than one nodule and more than one FNAB examination, cases with unconfirmed and controversial results were not included in the study. In our department, 879 patients who were examined by FNAB between 2010 and 2017 were operated according to surgical indications and histopathologically diagnosed. Papanicolaou (PAP) stain was used in CS and LBC preparations. Hematoxylin-Eosin (HE) stain was used in CB sections. Sample preparations selected from these cases are shown in Figures 1-8. The cases were grouped according to the evaluation results of CS, LBC, CB (addition to CS or LBC) preparations and compared with tissue diagnoses. The cases diagnosed cytologically using the Bethesda category (BC)-2010 system were collected in six main groups.

Thyroid Cytology Categories, Bethesda Terminology, 2010. [1, 2] Nondiagnostic or unsatisfactory.

I. Cyst fluid only/Virtually acellular specimen other (e.g., obscuring blood and clotting artifact)

   Benign

   Consistent with a benign follicular nodule (e.g., includes adenomatoid nodule and colloid nodule),

   Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context Consistent with granulomatous (subacute) thyroiditis

II. Atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS)

IV. Follicular neoplasm/ "suspicious" for follicular neoplasm (FN/SFN) Specify if Hürthle cell type

V. Suspicious for malignancy Suspicious for papillary carcinoma Suspicious for medullary carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma

VI. Malignant

   Papillary thyroid carcinoma Poorly differentiated carcinoma Medullary thyroid carcinoma

   Undifferentiated (anaplastic) carcinoma

   Squamous cell carcinoma Carcinoma with mixed features Metastatic

Cytological diagnosis was compared with histopathological diagnosis of these cases. Histopathological diagnosis were benign (Adenomatous hyperplasia-Adenoma, Lymphocytic thyroiditis and other changes) and malignant (Papillary carcinoma, Follicular carcinoma, Medullary carcinoma and other malignancies).

Statistical Analysis

SPSS 15.0 for Windows program was used for statistical analysis. Descriptive statistics and categorical variables were given as numbers and percentages, mean, standard deviation, minimum and maximum for numerical variables. Comparison of rates in dependent groups was made by Mc Nemar Analysis. The consistency of the results was analyzed with Cohen's Kappa compliance test. As a result of the evaluation, the test's ability to find positive sensitivity, the test's ability to find negative specificity, the ones that are really positive in the test's positive results, Positive Predictive Value, the ones that are really negative in what the test found negative, Negative Predictive Value, all correct results were given as correct awareness. In independent groups, rates were compared with Chi-Square Analysis. Alpha significance level was accepted as $p<0.05$.

The patients' files were retrospectively studied.

Our study was approved by the local medical ethics commission.

Results

Cytologically, 271 (30.8%) patients were examined by CS, 67 (7.6%) patients with LBC and 541 (61.6%) patients with both conventional and LBC techniques. Additional cell blocks were prepared for 371 (43%) of the cases as shown in Figures 1–8. There were 700 females and 179 males with a mean age of 46.7 (18-82 years). The total number of cases

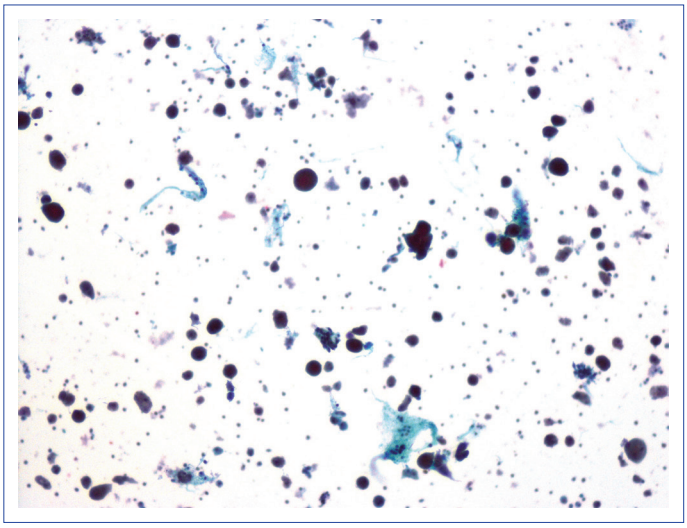

Figure 1. Benign thyrocytes, histiocytes and colloid, BC-2, LBC, PAP, X 40.

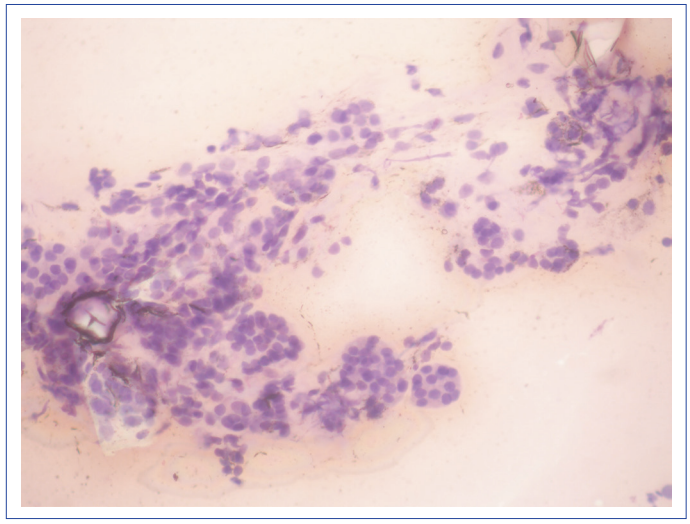

Figure 3. Follicle structures that are poor in colloid, suggesting mild nuclear and structural atypia, BC-3, CS, PAP, X100.

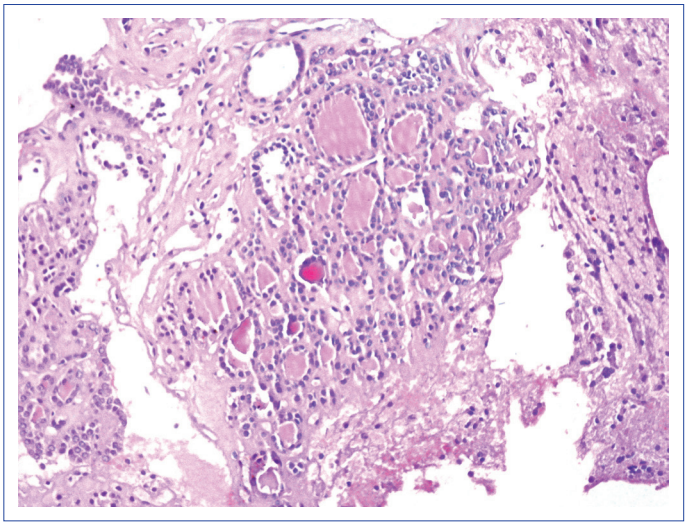

Figure 2. Follicle structures lined with benign thyrocytes and rich in colloid, BC-2, CB, HE, X40.

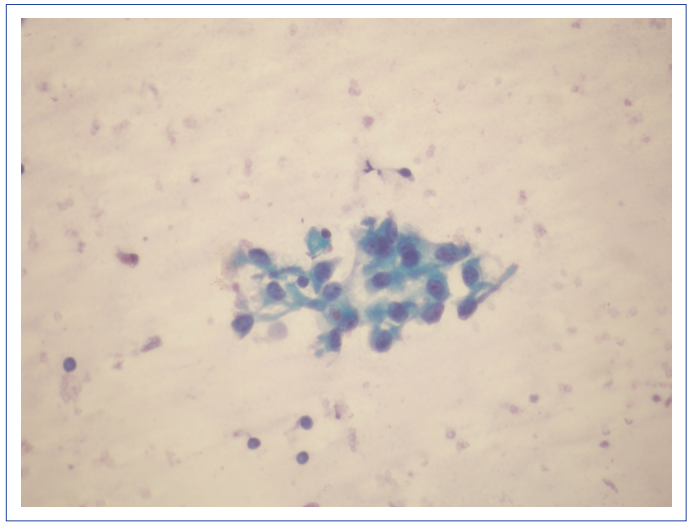

Figure 4. Follicle structures that are poor in colloid, suggesting nuclear and structural atypia, BC-3, LBC, PAP, X200.

was 879, 534 (60.8%) of them were benign, and 345 (39.2%) of them were diagnosed as malignant tissue (lobectomy or thyroidectomy). The cases and general data included in the study are summarized (Table 1).

In our study, 109 cases (12.4%); BC-1 (non-diagnostic- unsatisfactory), 324 cases (36.9%); BC-2 (Benign), 103 cases (11.7%), BC-3 (AUS/FLUS), 116 cases (13.2%), BC-4 (FN/SFN), 131 cases (BC-5 (Suspicious for malignancy), 96 cases (10.9%); He was diagnosed with BC-6 (Malignant). Histopathologically, 534 (60.8%) of these cases were benign and 345 (39.2%) were malignant. Bethesda category and postoperative tissue diagnoses were compared; Of the 109 unsatisfactory/non-diagnostic (BC-1) cases, 64 had benign and 45 had malignant histopathology. While the histopathological diagnosis was benign in 299 of 324 cases in the BC-2 group, malignancy was detected in 25 cases. Of 103 patients with AUS/FLUS (BC-3) category, 82 were diagnosed as benign and 21 as malignant histopathology. Histopathologically, 66 cases were benign and 50 cases were malignant in 116 cases in the FN /SFN (BC-4) category. Of the 131 cases in the category of suspicious malignancy (BC-5), 108 had malignant and 23 had benign histopathology. Histopathologically, malignancy was detected in all 96 cases in the malign category (BC-6) group (Table 2). When the results were evaluated in general, sensitivity-specificity-accuracy rates were high. There was no significant superiority between the methods ($p>0.05$, CS, LBC, LBC/CS+CB, respectively, $p=0.576$, 0.065, 0.643). However, in cases examined with LBC and LBC/CS+CB, sensitivity was superior (Table 3).

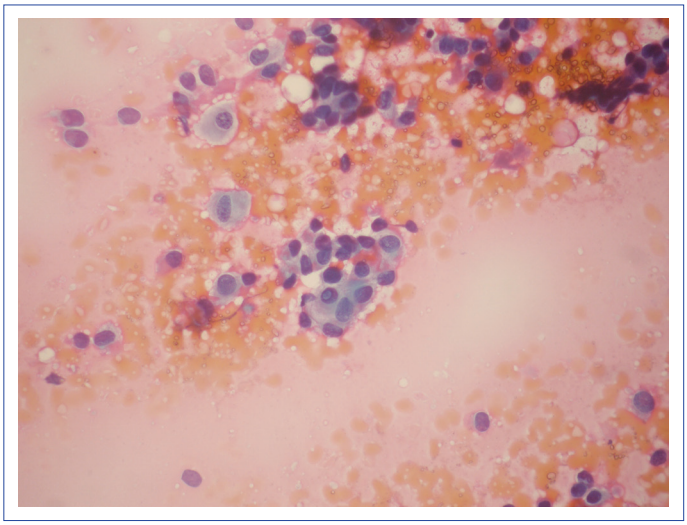

Figure 5. Cytology suggestive of papillary carcinoma follicular variant, atypical thyrocytes with intranuclear inclusions in one, absence of colloid, BC-5, CS, PAP, X200.

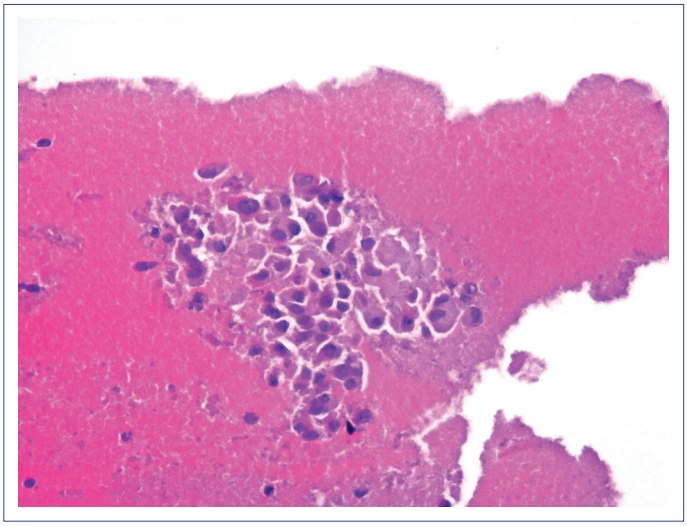

Figure 6. Colloid-free, pure oncocytic thyrocyte group, BC-4, CB, PAP, X200.

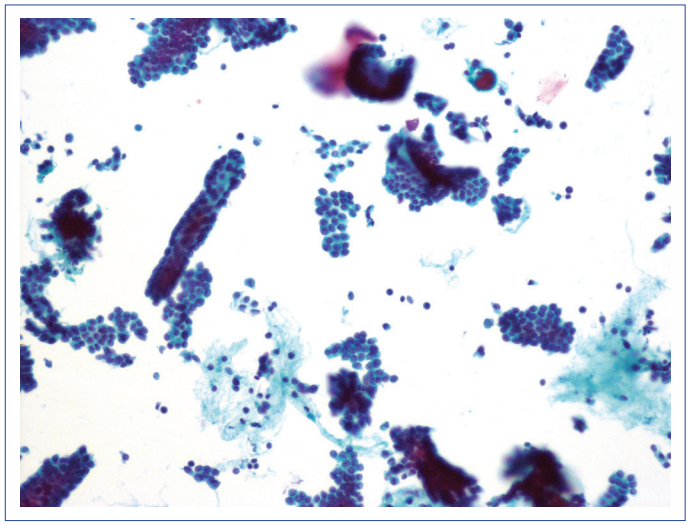

Figure 7. Malignant cytology, colloid-poor papillary structures, BC-6, LBC, HE, X40.

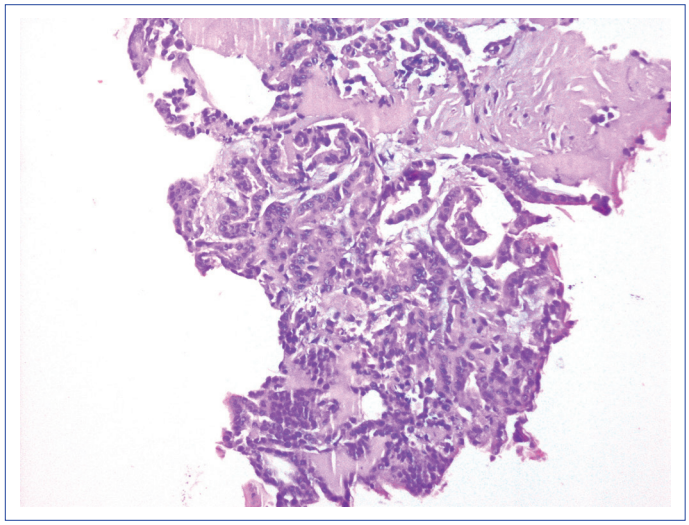

Figure 8. The cell block section obtained from the aspiration of the case in which LBC preparation was shown in Figure 7 is compatible with papillary carcinoma. BC-6, CB, HE, X40.

Discussion

Thyroid diseases are a common group of diseases that affect a large number of people worldwide. For this reason, it is the common goal of many clinicians and pathologists that the diagnostic and therapeutic studies reach maximum effectiveness.[1-5] In our study, we investigated the efficacy of cytological diagnosis in a large number of cases with a histopathological diagnosis. Moreover, we compared it with the results of other studies. When the distribution of our cases and literature data were compared, it was seen that our BC-1 ratio (12.4%) was slightly above the Bethesda system limit (<10%).[1, 2] In a meta-analysis study, the range of 1.8-23.6% was reported.[3] There are different rates in previous studies.[6-11] However, the incidence of malignancy in the diagnosis of tissue is significantly higher in our patients (41.3%). In this category, the risk of malignancy in the Bethesda system is in the range of 1-4%.[1, 2] In previous studies, one of the highest rates was 33.3%.[12] In the studies, there are rates between 0-22%.[3, 6-8] The reasons for this are the lack of second FNAB in the majority of our nondiagnostic/inadequate cases, the immediate use of the surgical option due to suspicion of malignancy clinically and radiologically, as well as difficulty in sampling due to calcification and other degenerations. In addition, it is also important that FNAB is not performed with ultrasonographic imaging in some of the cases and problems are related to the aspiration technique.

Table 1. General data

	Avg±SD	Min-Max
Age	46.7±13.1	18-82
	n	%
Gender		
Male	179	20.4
Female	700	79.6
Location		
Right lobe	432	49.2
Left lobe	409	46.5
Istmus	38	4.3
Method		
CS	271	30.8
LBC	67	7.6
CS+LBC	541	61.6
CB (addition to LBC or CS)	378	43.0
Cytological diagnosis		
BC-1	109	12.4
BC-2	324	36.9
BC-3	103	11.7
BC-4	116	13.2
BC-5	131	14.9
BC-6	96	10.9
Pathological diagnosis		
Benign	534	60.8
Malignant	345	39.2
Papillary carcinoma	313	35.6
Non-papilary carcinoma	32	3.6

CS: Conventional smear; LBC: Liquid-based cytology; CB: Cell block.

Table 2. Cytological/histopathological diagnosis, comparative results

	Histopathological diagnosis			
	Total	Bening n (%)	Papillary carcinoma n (%)	Non-papillary carcinoma n (%)
Cytologic diagnosis				
BC-1	109	64 (58.7)	42 (38.5)	3 (2.8)
BC-2	324	299 (92.2)	13 (4.0)	12 (3.8)
BC-3	103	82 (79.7)	17 (16.5)	4 (3.8)
BC-4	116	66 (56.9)	45 (38.8)	5 (4.3)
BC-5	131	23 (17.6)	104 (79.4)	4 (3.0)
BC-6	96	0 (0)	92 (95.8)	4 (4.2)

In our study, the number of cases in the benign category (BC-2) was 324 (36.9%), which was "<60%"[1, 2] below the Bethesda system. In a meta-analysis study in which Bongiovanni et al.[3] evaluated eight separate series, the rate of the benign lesion was in the range of 39-73.8%. In addition, rates of 30.5-68.3% have been reported in some studies.[6-9, 11, 12] In our series, the tissue equivalent of 324 cases in this group was determined as 299 benign (92.2%) and 25 malignant (7.8%). Of the 25 malignant cases, 13 cases had papillary carcinoma, and 12 had follicular carcinoma and other malignancies (medullary carcinoma, non-Hodgkin's lymphoma, undifferentiated carcinoma). The risk of malignancy in this group in the Bethesda system is 0-3%.[1] This rate ranges from 0% to 17%, according to researches.[3, 6-8, 10-12] The reason for this rate to be higher than the expected risk of malignancy in the Bethesda system can be explained by a large number of non-papillary carcinomas (our cases in this group were follicular carcinoma, undifferentiated carcinoma, medullary carcinoma, non-Hodgkin lymphoma) and more difficult to cytologically recognize.

Table 3. General distribution of all results and evaluation according to methods

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Total results	84.7	81.1	74.1	89.2	82.5
CS	80.6	75.0	83.5	71.1	78.4
LBC	92.6	73.5	73.5	92.6	82.0
CS+LBC	86.8	83.3	67.1	94.2	84.3
CB (addition to CS or LBC)	91.0	81.9	64.3	96.2	84.3

PPV: Positive predictive value; NPV: Negative predictive value; CS: Conventional smear; LBC: Liquid-based cytology; CB: Cell block.

There were 103 cases (11.7%) in the AUS/FLUS group. Although it is suggested that this rate should not exceed 7% in the Bethesda system,[1] recently, it has been reported that it may be increased to 10%.[13] This rate ranges from 3.4% to 39.2% in studies.[3, 6-9, 12, 14, 15] In this group of patients, 21 (17 papillary, four non-papillary malignancies) and 20.3% of the patients were diagnosed as malignant. This rate (20.3%) was higher than the risk of malignancy in the Bethesda system (5-15% [1]), but was consistent with the rate of recurrent aspirations (20-25% [2]). In this group, 21 of 103 cases (20.3%) had malignancy. This malignancy rate (20.3%) is higher than the risk of malignancy in the Bethesda system (5-15% [1]). However, it shows consistency with the rate of malignancy (20- 25%, [2]) that can be determined in cases where aspiration is repeated. In other studies, the risk of malignancy in the AUS / FLUS category has been reported at rates ranging from 12.7-44%.[3, 6-10, 14, 15] When the tissue equivalents of the majority of our malignant cases in this group are examined, it is seen that there are lesions smaller than 1 cm. In addition, insufficient sampling with the aspiration technique and the inability to clarify the cytologi-

cal atypia and its association with benign cellular features were evaluated as the reasons for this.

There were 116 cases (13.2%) in the SFN/FN group (BC-4). Approximately half of these cases (43.1%) were diagnosed with a malignancy in resection materials (45 cases, papillary-especially follicular and oncocytic variants, five cases of follicular carcinoma and minimally invasive follicular carcinomas). While the incidence of this lesion group is 15% in the Bethesda system, the incidence of malignancy can be up to 35%.[1] The rate of lesions reported in this group in the series varies between 3.7-45.4%. The incidence of malignancy is reported between 5.6-39%.[3, 6, 7, 10-12] In most of our cases in this group, structural atypia, oncocytic changes and lymphocytic thyroiditis are more common than nuclear atypia. In cytology practice, evaluation of FNAB with lesions (nodular goiter, follicular adenoma and follicular carcinoma) in this group has overlapping cyto-morphological features.

There were 131 cases (14.9%) in the BC-5 group. Malignancy was detected in 108 (82.4%) of these cases. Expected lesion rate of this group is between 2-8%, and the malignancy rate is 60-77% according to the Bethesda system.[1] In our series, the incidence of lesions in this category and the expected incidence of malignancy are slightly higher than the Bethesda system. The rate of lesions in this category is 2.3-66%. The frequency of malignancy is between 61.3-93%.[3, 6-12]

The findings showed that all of our 96 (10.9%) cases in the category of malignancy (BC-6) had malignancy in their tissue responses (100%). There were no false negative or false positive cases. In the Bethesda system, the rate of lesions in this group varies between 3-7%, while the expected risk of malignancy is reported to be 97-99%.[1] In studies, the incidence ranges from 2.4-23%. Malignancy rate has been reported between 96.5-100%.[3, 6-12] The frequency of lesions determined in this group is higher than the Bethesda system. However, the expected malignancy rate correlates with the Bethesda system.

In many evaluations, advantageous aspects of the LBC method compared to CS (low soil contamination, better evaluation of a large number of cells and nuclear details in a small area) have been reported, but it is stated that there is no clear advantage and its use in combination would be more beneficial.[16-20] In some evaluations, it has been suggested that the LBC method is more useful, especially in the AUS/FLUS and FN group.[17, 20]

In one evaluation, the non-diagnostic category rate was high and the benign category rate was low in the LBC method. The authors suggested that the LBC method had disadvantages and that it was too early to replace the CS method.[21] However, opinions where the LBC method is preferred are also stated.[22, 23] In the meta-analysis study where 37 of 372 studies were selected, a decrease in the LBC method in the category of the insufficient sample (BC-1) was reported. However, it has been reported that sensitivity and specificity are similar or slightly superior to the CS method.[24] It was seen in our study that although there was no significant superiority among the methods, the diagnostic sensitivity and accuracy of LBC was slightly higher than the CS method. In addition, it was observed that it contributed positively to the diagnostic evaluation in cases in which CB was added. In addition, higher sensitivity and accuracy rates were observed in cases where LBC and CS were used together. In our study, high sensitivity, specificity and accuracy rates were observed with the use of LBC and CS methods alone and in combination. In addition to these methods, there has been some improvement in CB utilization at these rates. In one study, the use of CB in addition to the cytology method has been shown to reduce the non-diagnostic category rate by 7.1% compared to cytological examination without a CB.[25] In another study, consistent with the findings obtained in this study, CB examination has been shown to reduce

the non-diagnostic category rate.[26] The increase of sensitivity and specificity of the additional CB that we emphasize has also been reported in a study.[27]

The strengths of this study are a large number of cases in our study and given that their definite confirmed tissue diagnoses were made by an experienced endocrine pathologist. However, retrospective evaluation and not including only the cases operated in our institution and the cases that were considered benign but not operated are its weaknesses. In addition, that not all FNAB samples were taken under USG (some of them were manual FNAB samples) can be considered as the disadvantage of this study.

Conclusion

FNAB is a safe method for the diagnosis of thyroid nodules. The use of the Bethesda category is established in pathology reporting. As data are collected, the reliability of the system increases. Case management is idealized using this system together with the clinician and pathologist. FNAB cytological examination is an effective method in reaching the diagnosis in thyroid nodules. FNAB is preferred as it is a non-invasive, practical and rarely complicated method.

According to the methods, there was no significant difference between sensitivity, specificity and accuracy rates in our data. We think that the LBC method can be used instead of CS, but whatever method is used, it would be ideal to evaluate it with the CB. In FNAB materials, it would be

appropriate to obtain CB as much as possible in addition to CS or LBC methods. Also, it is clear that clinical and radiological experience will increase the accuracy of cytological examination of thyroid nodules.

Disclosures

Ethics Committee Approval: Sisli Etfal Health Application and Research Center Ethics Committee approved. (Date: 20.08.2019 - Number: 2482)

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