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Original Research

Comparison of Conventional Smear and Liquid-Based Cytology in Adequacy of Thyroid Fine-Needle Aspiration Biopsies without an Accompanying Cytopathologist

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Abstract

Objectives: In this study, we aimed to compare the adequacy of conventional smear (CS) and liquid-based cytology (LBC) methods in thyroid fine-needle aspiration biopsy (FNAB) samples obtained without an accompanying cytopathologist during the procedure. Furthermore, we aimed to investigate the presence of a significant difference between the rates of nodules classified as Bethesda Category III and malignancy in both techniques and the features of the nodules affecting malignancy.

Methods: A total of 625 nodules from 572 patients who were found suitable for biopsy were included in this retrospective study. FNABs were performed by interventional radiologists without an accompanying cytopathologist during the procedures. The specimens were either prepared using CS or LBC preparation methods. Cytopathological diagnostic adequacy and cytopathological results of the specimens were evaluated according to Bethesda category, and the relationship between the morphological findings was evaluated retrospectively.

Results: Of all the biopsy preparations, 338 (54.1%) of them were transferred to pathology in liquid-based solution and 287 (45.9%) were transferred as CS. Malignancy rates of the biopsy samples were found similar in both LBC and CS methods. Considering the nodules classified as Bethesda Category II, III, IV, V, and VI, there was no statistical difference between the results of both methods. Non-diagnostic biopsy rate was higher in the specimens prepared by CS method ($p<0.001$).

Conclusion: In this study, the adequacy rate of FNAB was found significantly higher in LBC method compared to the CS method. LBC was more practical and faster than the CS method. We think that LBC method may be preferred in FNAB of thyroid nodules.

Keywords: Bethesda classification, conventional smear, fine-needle aspiration biopsy, liquid-based cytology, thyroid nodule, ultrasonography

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Thyroid nodules (TNs) are commonly encountered in clinical practice and they can be detected by either palpation during the physical examinations or by radiologic imaging.[1] The American Thyroid Association defined TNs as the lesions that are located in the thyroid gland and are with unique radiological characteristics compared to the

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surrounding thyroid parenchyma.[2] With the increased use of ultrasonography, the number of TNs detected in asymptomatic patients has increased.[3]

TN incidence has been reported more frequently in women than in men, in elderly people, in individuals living in iodine-deficient areas and in people with radiation exposure history.[4] As TNs are more frequent in women, thyroid cancer incidence is also higher in women; however, incidence of cold TN being malignant has been reported more frequently in males.[5]

The major point is to distinguish between benign and malignant nodules while evaluating the TNs and to prevent unnecessary surgical procedures. Thyroid function tests and ultrasonography are routinely performed in the process of diagnosis of TNs, but the exact discrimination between benign and malignant nodules cannot be made using these methods.[1,6] Fine-needle aspiration biopsy (FNAB) is the "gold standard" method in distinguishing malignant nodules from benign nodules with >95% negative predictive value for benign cytology and >99% positive predictive value for malignant cytology.[7] FNAB is routinely performed to exclude malignancy in nodules which have increased risk for malignancy according to different classification systems depending on size and suspicious findings on ultrasound (US) examination.[8]

Success in thyroid FNAB depends on factors such as biopsy technique, adequate sampling, and presence of an experienced cytopathologist. In daily clinical practice, aspiration material is prepared by several conventional smear (CS) methods. Liquid-based cytology (LBC) smear technique has been widely performed for preparations of FNAB smears for three decades.[9] Compared to the CS method, preparation time is shorter and transport is easier in LBC.[10] Furthermore, a previous study reported that LBC has the higher sensitivity compared to CS.[11] LBC is feasible for cytopathologists with some advantages such as elimination of artifacts (in air drying step), undesirable elements that can make evaluation difficult; providing ability to prepare additional smear preparations from the existing sample when necessary; better evaluation of a large number of cells and nuclear details in a small area; and no requiring to learn smearing technique.[10,12,13]

In this study, we aimed to compare the adequacy rates of FNABs of TNs performed with either CS method or LBC methods without an accompanying cytopathologist during the procedure. Furthermore, we aimed to investigate the presence of a significant difference between the rates of nodules classified as Bethesda Category III and malignancy in both techniques and the features of the nodules affecting malignancy.

Methods

Subjects

All procedures followed in this study were in accordance with the ethical standards of the responsible committee on human and animal experimentation (institutional or regional) and with the Helsinki Declaration. This retrospective study was approved by the Local Institutional Clinical Research Ethics Committee (Date: 04/12/2018, number: 2193).

Before March 2017, FNABs were performed with CS method in our clinic, and after this, date the LBC method was used. Therefore, both radiologists who performed the biopsies used both methods. The patients aged 18 and over who were referred for thyroid FNAB from various clinics to the interventional radiology unit of our hospital between September 2016 and 2017 were eligible for the study. Demographical data of patients (age and gender) were recorded. A total of 625 nodules of 572 patients who were deemed suitable (aged 18 and over patients, solid or mixed solid-cystic nodules) for biopsy were included in the study. The procedure to be performed was explained to all patients and their informed consents were obtained. Before the biopsy was performed, the patients were asked about the presence of contraindications (i.e., use of anticoagulants and tendency to bleeding). All patients included in the study had an US examination report before the procedure that was performed in our clinic or an external center. In addition, US characteristics of biopsied nodules were recorded and evaluated by the radiologists during the procedure. The procedures were performed by two experienced interventional radiologists without an accompanying cytopathologist.

Nodule Characterization in Ultrasonography

In sonographic examination, the internal texture, echo structure, and presence of calcification in TNs were evaluated. The largest diameter was determined by three dimensional measurements of the nodules. The texture of the nodule was evaluated in three groups as solid, cystic, or mixed solid-cystic. Pure cystic nodules were excluded from the study. Echogenicity of TNs was grouped as hyperechoic, isoechoic, hypoechoic, and anechoic compared with normal thyroid parenchyma.[14] In the presence of more than one nodule in the same patient, FNAB was performed on the largest sized dominant nodule and/or one with suspicious structures. Nodules with microcalcification, hypoechoic structure, irregular contour, and intranodular vascularization were preferred in addition to larger nodules under US to be biopsied (Fig. 1). Attention was paid to take samples from the solid part of the semi-solid nodules.

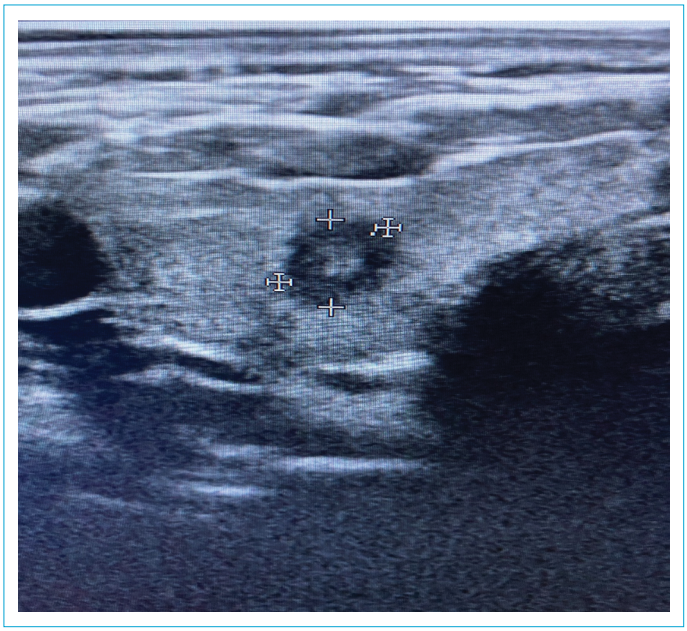

Figure 1. Ultrasonography image of a 28-year-old female patient. Transverse plan gray scale ultrasound image shows a hypoechoic solid nodule with microlobulated contour in the middle part of the thyroid right lobe, with punctate echogenic foci in the center. FNAB revealed a diagnosis of papillary thyroid carcinoma (Bethesda category VI).

FNAB Procedure and Sample Preparation

Biopsy area was sterilized with povidone iodine. Ultrasonography procedure was performed using a superficial probe at 7 MHz. FNAB was performed using a sterile 5 cc injector with a 22-23 G disposable needle tip. Aspiration was performed on different parts of the most suspicious (solid and heterogeneous) regions of the nodule determined in ultrasonography by applying light pressure. One or two needle-passes were performed for each of the nodules and after the procedure was terminated, probable bleeding was evaluated by ultrasonography, and the patient was removed from the stretcher.

In CS method, the biopsied samples were smeared on a slide and then fixed with 95% ethanol. Slides fixed with ethanol were stained with Papanicolaou (Pap) stain in the pathology laboratory. In LBC method, the biopsied samples were placed in a liquid-based smear solution (SurePathTM, BD Biosciences) and sent to the pathology clinic. The cell block was prepared from the biopsy material placed in the special liquid-based solution by centrifugation and the sections obtained were stained with hematoxylin-eosin (H and E) staining. Slides prepared with Pap and H and E staining were evaluated under a light microscope. In the cytological evaluations of the biopsy samples, the presence of colloid in the ground, cell density, cell size, pleomorphism, nucleus features, cohesion, chromatin features, nucleus/cytoplasm ratio, cytoplasmic staining features, necrosis, and presence of inflammatory cells was taken into consideration (Figs. 2, 3).

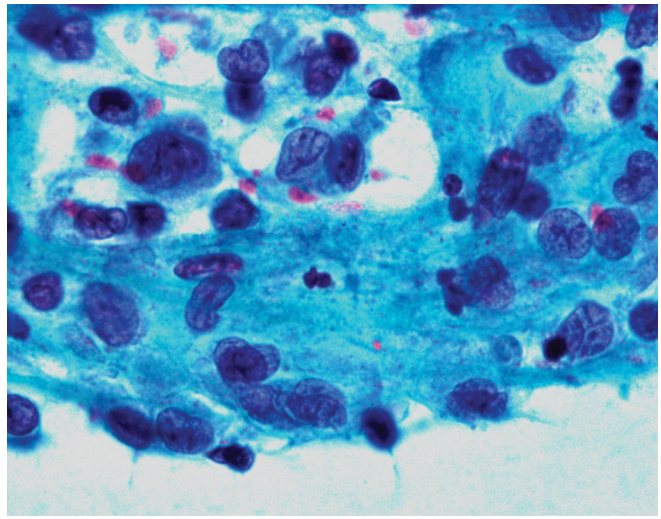

Figure 2. Syncytial group of cells with nuclear pleomorphism and nuclear membrane irregularity in papillary carcinoma (Liquid-based smear [SurePath], Pap staining [Magnification: 1000× using immersion oil]).

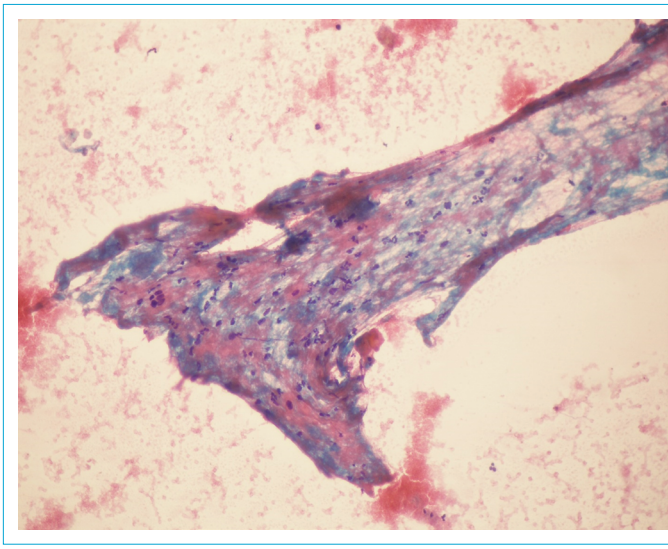

Figure 3. Inefficient smear sample, blood elements are observed in degenerated tissue fragments (Conventional smear, Pap staining [Magnification: 200×]).

In the biopsy report, the location of the nodule on which FNAB was performed, ultrasonographic features of the nodule, and the way the materials were transferred to pathology (CS or in liquid-based solution), were defined. Nodule classifications were made according to Bethesda Classification System.[15] Bethesda category 5 and 6 nodules were considered as malignant. The relationship between the preparation techniques (CS or in liquid-based solution) of the samples for cytopathological evaluation, diagnostic adequacy (out of Bethesda I nodules), malignancy, and Bethesda Category III rates in both techniques and the relationship between the morphological findings

Table 1. Characteristics of the nodules with non-diagnostic and diagnostic cytopathological results

Results according to Bethesda category	Non-diagnostic (1)		Diagnostic (>1)		p
	n	%	n	%	
Nodule Size (mean±SD (Min-max/median)	27.1±10.0 (12-70/27)		22.4±9.7 (12-72/20)		**<0.001**
Gender					
Female	80	69.6	406	79.8	**0.017**
Male	35	30.4	103	20.2	
Nodule structure					
Solid	85	73.9	345	67.6	0.190
Mixed solid-cystic	30	26.1	165	32.4	
Echogenicity					
Hypoechoic	53	46.1	250	49.0	0.187
Isoechoic	55	47.8	206	40.4	
Hyperechoic	7	6.1	54	10.6	
Punctate echogenic foci	4	3.5	54	10.6	**0.018**
Macrocalcification	14	12.2	52	10.2	
Peripheral calcification	3	2.6	6	1.2	
Smear preparation method					
Conventional	68	59.1	219	42.9	**0.002**
Liquid-based	47	40.9	291	57.1	

(texture, echogenicity, size, and calcification) and cytopathological adequacy were evaluated.

Statistical Analysis

Statistical analysis was carried out using SPSS for Windows software (v. 15.0; IBM, USA). In descriptive statistics, number and percentage for categorical variables were used, while for numerical variables mean, standard deviation, minimum, and maximum values were used. In case, the numerical variables were not distributed normally, two independent groups were compared using the Mann-Whitney U-test. The relationship between factors was analyzed using Chi-square test, while logistic regression analysis was implemented to investigate the relationship between explanatory binary variables. P-value lower than 0.05 was accepted as statistically significant.

Results

Of all the patients who underwent biopsy, 446 (77.9%) were female and 126 (22.1%) were male. The mean age of the patients were 54.3±10.16 years (min-max=19-80 years). Of all the biopsy preparations, 338 (54.1%) of them were transferred to pathology in liquid-based solution and 287 (45.9%) were transferred as CS.

Non-diagnostic biopsy rate was higher in the specimens prepared by CS method (Conventional=68 (23.7%) vs. liquid-based=47 (13.9%) (Tables 1, 2). Malignancy rates of the biopsy samples were found similar in both the liquid-based and the CS methods. Considering the nodules classified as Bethesda Category II, III, IV, V, and VI, there was no statistical difference between the results of two methods (Table 2).

Table 2. Distribution rates of nodules by Bethesda categories

Type of the procedure	Conventional smear		Liquid-based cytology		p
	n	%	n	%	
Bethesda category					
I	68	23.7	47	13.9	**<0.05**
II	181	63.1	241	71.3	
III	11	3.8	7	2.1	0.189
IV	2	0.7	9	2.7	
V	16	5.6	20	5.9	
VI	9	3.1	14	4.1	

Bethesda V and VI nodules are malignant nodules

The mean size of the nodules with non-diagnostic cytopathological results was significantly higher than the ones with the diagnostic results (p<0.001; Table 1). Four hundred and thirty (68.8%) of the nodules had solid and 195 (31.2%) had mixed solid-cystic texture. Fifty-three (46.1%) of the nodules were hypoechoic, 55 (47.8%) were isoechoic, and 7 (6.1%) were hyperechoic in the non-diagnostic group. There was no significant relationship between neither diagnostic adequacy and nodule texture (solid or semi-solid) nor nodule echogenicity (p>0.05; Table 1). A total of 58 (9.3%) of the nodules had microcalcification as punctate

echogenic foci, 66 (10.6%) had macrocalcification which causes acoustic shadowing, and 9 (1.4%) had peripheral type calcification which completes or incomplete along margin. Diagnostic adequacy rate of the nodules that had punctate microcalcification was significantly higher (p=0.018; Table 1). On the other hand, independent from the specimen preparation technique, hypoechogenicity, and presence of microcalcification were associated with malignancy according to Bethesda classification (p<0.001). Moreover, the malignancy rate was higher in hypoechoic nodules compared to isoechoic and hyperechoic nodules (15.8%, p<0.001). Moreover, in the present study, the malignancy rate in nodules containing microcalcification was significantly higher than those without microcalcification (p<0.001) and 44.8% of the nodules reported as papillary carcinoma had microcalcifications.

Discussion

FNAB is important in definitive diagnosis of TNs as it is microinvasive, easy to apply and has a high true positivity rate.[16] Although it is known that the diagnostic adequacy of FNAB is higher when it is performed with the guidance of US and with an accompanying onsite cytopathologist,[17] the rates of non-diagnostic biopsies vary significantly between 0.6% and 47%.[18,19] Some researchers have reported higher diagnostic adequacy rates in LBC method compared to CS in the previous studies.[11] LBC is suggested to be an advantageous and effective method especially with experienced cytopathologists to analyze the morphological details and detect malignancy.[20-22] In the present study, our main aim was to assess and compare the diagnostic adequacy rates of CS method and LBC in patients who underwent thyroid FNAB.

In our clinic, thyroid FNAB is performed without an accompanying pathologist. Studies revealed that 17-47% non-diagnostic biopsy samples have been obtained even after repeated FNABs.[23-25] The rate of non-diagnostic biopsy materials obtained was found significantly lower in LBC compared to CS method (23.7% vs. 13.9%, respectively, p<0.001), in accordance with the studies in the literature (Table 1). Moreover, as specimen preparation with a liquid-based solution is more practical and faster than the CS method and has a high diagnostic rate, LBC can be suggested as a preferable method for the evaluation of FNAB specimens.

Some of the studies stated that as the nodule size increases, the rate of non-diagnostic biopsies increases,[26,27] while some other studies indicated that nodule size does not interfere with the adequacy of the biopsies.[23,28] In the present study, we observed that the rate of the non-diagnostic biopsies increased as the size of the nodule increased (Tables 1, 2). As the nodule size increases, the cystic component in mixed solid-cystic nodules and the presence of hemorrhagic-necrotic regions in large nodules also increases and this may explain the cytological inadequacy.[26,27]

The presence of the intra-nodular calcification in TNs may affect the adequacy of the biopsy samples and increase inadequacy.[29] However, some researchers have reported no association between the adequacy rate of the biopsy samples and calcification.[28,30] In our study, we observed that the diagnostic adequacy rate of the nodules that had microcalcification was significantly higher (p=0.018; Table 1). Considering the relationship between punctate calcification and malignancy, one can say that malignancy was easily detected by both techniques.

Although US characteristics are not the main indicator in differential diagnosis of malignant and benign TNs, they are important to presume in the diagnosis. In the literature, hypoechogenicity and presence of microcalcification were reported to be highly predictive features for malignancy of a nodule.[31,32] The most specific US finding for thyroid malignancies is the presence of microcalcification and is seen in 29-59% of the primary thyroid carcinomas, especially in papillary thyroid carcinomas.[33] Similar to the findings reported in the literature, most of the malignant nodules (81.3%) were hypoechoic in our study. The malignancy rate was higher in hypoechoic nodules compared to other nodules (15.8% vs. 3.8% and 1.6%, respectively, p<0.001). Moreover, in the present study, the malignancy rate in nodules containing microcalcification was significantly higher than those without microcalcification (p<0.001) and 44.8% of the nodules reported as papillary carcinoma had microcalcifications.

Our study had several limitations. First, as the study was designed retrospectively, all the US images and nodule characteristics were evaluated from the reports. Moreover, FNABs were performed by two different interventional radiologists with different levels of experience. In addition, the size and texture of the biopsied nodules (solid, semi-solid (solid-cystic), calcified, etc.) were different in these two groups. On the other hand, all the specimens were not evaluated by the same cytopathologist. In addition, the number of needle passes for biopsy of each nodule was not the same (some had one and some had two needle passes).

As it was previously reported, the presence of an accompanying onsite cytopathologist increases the diagnostic rate with an increase in the number of needle passes, and the adequacy rate may decrease to 59.7% if two or less needle passes were performed.[34] Although the number of the needle passes for each nodule in our study was one or two and there was no accompanying onsite cytopathologist

during the procedure, the inadequacy rates of both the LBC and CS methods were not higher than the reported rates.

There was no statistical difference between the results of the two methods when considering Bethesda Category III. This is in parallel with the previous studies,[35,36] suggesting that one is not superior against the other when considering the Bethesda Categorization of the FNAB samples of TNs.

Conclusion

Adequacy rate of FNAB was found significantly higher in LBC method compared to CS method. LBC was more practical and faster than the CS method. We think that LBC method may be preferred in FNAB of TNs. Malignancy rates of the biopsy samples were found similar (p>0.05) in both the liquid-based and CS methods. Considering the nodules classified as Bethesda Category III, there was no statistical difference between the results of the two methods. However, further studies including larger patient groups are required to assess its use as the main technique in cytopathological diagnosis of TNs.

Disclosures

Ethics Committee Approval: The study was approved by the University of Health Sciences, Sisli Hamidiye Etfal Training and Research Hospital Clinical Research Ethics Committee (Date: 04/12/2018, No: 2193).

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Conflict of Interest: None declared.

Authorship Contributions: Concept – A.O.S., D.T.M., B.V.B., B.Y.O., C.S.; Design – A.O.S., D.T.M., B.V.B., B.Y.O., C.S.; Supervision – A.O.S., D.T.M., B.V.B., B.Y.O., C.S.; Materials – B.Y.O., D.T.M.; Data collection &/or processing – A.O.S., B.V.B.; Analysis and/or interpretation – A.O.S., C.S.; Literature search – A.O.S., C.S.; Writing – A.O.S., C.S.; Critical review – C.S.

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