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Evaluation of Fine Needle Aspiration Cytology [Bethesda Classification] Versus Ultrasonography [Thyroid imaging recording and data system [TIRADS] Classification] in Diagnosis of Thyroid Nodule

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ABSTRACT

Background: Thyroid nodules are prevalent worldwide. Accurate diagnostic tools are required to differentiate between benign and malignant types.

The Aim of the work: This study aims to evaluate the diagnostic accuracy of ultrasonography [US] and FNAC [fine needle aspiration cytology] in distinguishing the nature of thyroid nodules, considering histopathology as the gold standard.

Patients and Methods: A total of 100 patients with thyroid nodules were categorized into two groups: Group I [n=50] underwent ultra-sonographic assessment and Thyroid Imaging Reporting and Data System [TIRADS] classification. Group II [n=50] underwent FNAC and Bethesda classification. Clinical parameters, ultrasound features, and histo-pathological findings were compared between the groups.

Results: The study groups were comparable [no significant differences] in terms of demographic characteristics and most clinical parameters. However, a significant difference was noted in the site of nodules. Histopathologically, benign nodules were identified in 72% of Group I and 68% of Group II. However, malignant nodules were found in 28% of Group I and 32% of Group II. FNAC demonstrated 72% accuracy for benign and 94.42% accuracy for malignant nodules, compared to [84% accuracy for benign and 16% for malignant nodules] for ultrasound.

Conclusion: Our findings affirm the diagnostic specificity of both USG and FNAC. USG is effective in identifying thyroid nodules. However, FNAC exhibits higher accuracy, making it a reliable, minimally invasive method to distinguish between benign and malignant tumors.

Keywords: Thyroid nodules; Ultrasonography; Fine needle aspiration cytology; Diagnostic accuracy; Histopathology.

INTRODUCTION

The thyroid gland is one of endocrine glands. It is situated in front of the neck [on the sides of the lower part]. It concerned with the regulation of basal metabolic rate, regulates calcium metabolism, stimulates somatic growth and plays crucial role in psychic growth. Its name is of Greek origin that means the shield [*Thyros* – shield, *eidos* – form] [1].

Among other endocrine glands, the thyroid is unique, as it the first developed fetal endocrine gland, it is the largest [~ 25 g] and it is the only superficial endocrine gland. Its unique position permits direct clinical examination. However, it is a common place for the development of benign and malignant nodules. Thus, it is very important to have an early diagnostic tool to achieve better management of these conditions [2].

Goiter describes any enlargement in the thyroid gland. It may be solitary or multiple. The solitary nodule appears clinically as a single nodule, confined to one lobe of the gland with no palpable abnormality in any other part of the thyroid gland. These nodules are very common and females are 4 times affected more than males [1]. In addition, nodular goiter is common with advancing age especially after exposure to external irradiation [2].

The estimated prevalence of thyroid nodules ranges from 4% [by clinical examination] to 67% by ultrasonography. In addition, about 50% of adults had non-palpable nodules that discovered in autopsy [1]. The multinodular goiter [MNG] is more susceptible to the risk of malignancy when compared to solitary nodules [3].

Clinically, the thyroid nodules may be asymptomatic or presented with systemic thyrotoxic manifestations. The asymptomatic conditions [non-toxic] are associated with normal values of thyroid stimulating hormone [TSH]. However, the clinically manifested conditions are toxic multinodular goiter or Plummer's disease [2].

The solitary nodule is a common presentation and usually benign in nature. The incidence of malignant transformation ranges between 8 and 20%. This is important as the most neoplasms starts in an active focus of replicating cells, that presented clinically as a solitary nodule in the early stages of malignancy [2].

Many investigations are available for diagnosis and differentiation between benign and malignant conditions to prevent un-needed surgery [1]. Of these**,** imaging modalities are more common and include plain x-rays and ultrasonography among others [2].

Fine needle aspiration cytology [FNAC] and ultrasonography [USG] are the two most common tools used with clinical features for diagnosis of thyroid nodules. However, each of them had its own drawbacks and limitations [1].

USG was first introduced in 1967 for diagnosis of thyroid nodules. Its first aim was essentially to differentiate solid from cystic lesions. Currently, USG is the first method used to investigate the thyroid gland. This attributed to its advantages being convenient, relatively cheap, quick, easily perform without exposure to ionizing radiation. It easily differentiates cystic than solid lesions. However, its limitations include difficulties in evaluation of ectopic thyroid lesions, prediction of the thyroid nodule activity and surveying the neck for metastatic lymphadenopathy [2].

There are different systems to stratify thyroid nodules, on the basis of imaging results. The thyroid imaging recording and data system [TIRADS] is one of these systems used to stratify the risk of thyroid nodules. It categorizes thyroid nodules into 5 TIRADS stages based on 5 characters [shape, composition, echogenicity, margin, echogenic foci/calcification]. Each character gives a point, and the sum of all points is calculated and reflected the TIRADS score [1].

The main aim of FNAC is to define nodules requiring surgery and differentiates them from benign lesions that can be treated conservatively and reduce the overall thyroidectomies in patients with benign nodules. FNAC also had some limitations; lower accuracy in suspicious cytology and in follicular types [4].

Bethesda classification is another classification system used to determine patients who should undergo surgery. In addition, the aspiration cytology provides help for clinician to decide on the required additional investigations, patients need surgery, the type of surgery and which patient [with unequivocal malignancy criteria] may benefit from non-surgical than surgical management [2].

FNAC provides preoperative pathologic or cytologic data about the thyroid nodule. However, it had some limitations. For example, the high incidence of false negativity for malignant degenerative nodules and deficient sampling capsules or vessels by a limited core of tissue [1].

The available literature provides results about the value of USG and FNAC in different thyroid lesions. However, results are heterogenous and comparison between both methods still needs more clarification.

This study aimed to assess the accuracy [sensitivity and specificity] of FNAC versus USG for differentiating benign from malignant thyroid nodules. Results are compared against histopathology [as the gold-standard] after thyroidectomy.

PATIENTS AND METHODS

This was a prospective cross-sectional study. It was conducted at the department of general surgery, Al-Hussein Hospital [Al-Azhar University]. It included 100 patients of all age groups attending outpatient clinic of the general surgery department with a thyroid nodule either solitary or multiple. The included patients were allocated in to two equal groups. The first group [n=50] were submitted to USG assessment and TIRADS classification. The second group included patients who were submitted to FNAB followed by Bethesda classification.

We included patients with clinically recognized solitary or multiple thyroid nodules, with normal or abnormal thyroid function tests.

Ethical consideration: Ethical considerations were rigorously adhered to throughout the study. No undue influence was exerted on participants to compel their involvement in the research, and an informed written consent was signed. Participants were informed of the study results, and their right to withdraw at any time without providing a reason was emphasized.

Methods

In the conducted study, a comprehensive evaluation was undertaken for all participating patients, encompassing personal, past, and present medical history. Personal history parameters included essential details such as name, age, occupation, and habits of medical significance, including smoking habits and the duration of follow-up. Past medical history considerations extended to family history of thyroid disorders and autoimmune diseases, residence details for iodine exposure assessment, and information on antithyroid medication, levothyroxine replacement therapy, radioiodine therapy, and thyroid surgery.

The present medical history component involved a detailed exploration of associated symptoms and current diseases or medications. General examinations covered vital signs, body mass index [BMI], and blood pressure, along with chest, heart, limb, and thyroid examinations. The size of the thyroid gland and assessment of thyroid nodules were conducted using the TIRADS, categorizing lesions into six classifications. Abdominal examinations included inspection and superficial palpation [5].

The investigatory phase comprised a range of laboratory and radiological examinations. Complete blood count, kidney and liver function tests, and thyroid function tests were conducted using chemiluminescence technique. The guidelines issued by the American Thyroid Association [ATA] were followed in all stages of thyroid nodules management. All biopsies were done under ultrasound guidance, and additional investigations included lateral neck X-ray, chest X-ray, neck ultrasonography, and FNAC.

The ultrasound examination involved a detailed assessment using a portable scanner with a high-frequency linear transducer. Parameters such as internal echogenicity, acoustic halo, microcalcification, and blood supply to the nodules were meticulously examined. Two-dimensional and color Doppler blood flow imaging provided insights into vascularity, with evaluations of peak systolic velocity [PSV], end-diastolic velocity [EDV], pulsatility index [PI] and resistive index [RI].

FNAC procedures were conducted with a 23-gauge needle, applying the FNAC Bethesda grading and diagnostic report system. The surgical phase involved thyroidectomy, and histopathological examination of excised specimens was performed. This exhaustive methodology ensures a nuanced understanding of the clinical and diagnostic aspects of thyroid nodules, contributing valuable insights to the existing body of knowledge in this domain [6].

Statistical Methods: The collected data were coded, processed and analyzed after feeding to personal computer using the SPSS [Statistical Package for Social Sciences] version 26 for Windows® [Armonk, NY: IBM Corp; 2019]. The arithmetic means and standard deviations [SD] were used to represent the normally distributed quantitative data. On the other side, frequency and percentages used to express categorical data. The sensitivity and specificity were calculated by equations after plotting the results of USG or FNAB against the results of histopathology. Data were divided into true positive [TP], true negative [TN], False positive [FP] and false negative [FN] and sensitivity and specificity equations were used [Sensitivity = TP/TP+FN, specificity = TN/ TN + FP]. Groups were compared by independent samples or Chi square tests [Or their equivalent] for quantitative and qualitative data respectively. P value < 0.05 was considered significant.

RESULTS

In the current study, both groups were comparable regarding patient age, sex, weight, height and BMI. In addition, no significant differences were recorded regarding systolic and diastolic blood pressure and laboratory blood indices [Table 1].

In the current work, about two thirds of both groups had solitary nodule [66.0% and 68% of group I and II respectively]. However, multiple nodules were reported for 20% and 16% of groups I and II successively. The largest nodule length and width were comparable between both groups. The left lobe was the commonest affected lobe in both groups [50% and 68.0% of groups I and II respectively]. The bilateral lobes reflected the multiple nodules [20% and 16% of groups I and II respectively] [Table 2].

Our results revealed non-significant difference between the two groups regarding to ultrasound features [calcifications, shape, echogenicity, halo, Doppler central flow] [Table 3].

In the current work, both groups were comparable regarding TIRADs and Bethesda classifications [Table 4].

From table [5] and using equations, the sensitivity of ultrasound and FNAC for diagnosis of malignant thyroid nodules were 57.1% and 87.5% respectively. However, both were 100% specific for detection of malignant nodules.

Table [1]: Patient characteristics of the study population

	Items	Group I [n=50] No [%]	Group II [n=50] No [%]	p-value
Age [years]	Mean± SD	48.77±6.04	49.31±5.39	0.718
Sex [n, %]	Males Females	16 [32] 34 [68]	11[22] 39 [78]	0.111
Weight [kg]	Mean± SD	60.42±17.02	73.52±23.25	0.11
Height [cm]	Mean± SD	168 ±2	162.3±1.07	0.512
Body mass index [kg/m^2]	Mean± SD	25.71±1.32	24.51±2.35	0.624
Blood pressure [mmHg], [mean ± SD]	Systolic	120.67 ± 14.06	126.77 ± 18.88	0.833
	Diastolic	86.50 ± 8.00	84.00 ± 15.26	0.267
Blood picture indices	Hemoglobin [g/dl]	13.24±2.53	11.24±1.55	0.563
	Platelets x 10^3/ml	252.7±47.42	263.2±48.63	0.493
	TLC x 10^3 /ml	7.73±1.46	7.42±1.14	0.715

Table [2]: Distribution of all studied cases number of nodules

		Group I [n=50] No [%]	Group II [n=50] No [%]	p-value
Number of nodules	**One**	33 [66%]	34[68%]	**0.738**
	Two	7 [14%]	8 [16%]	
	Multiple	10[20%]	8[16%]	
Nodule	**Length**	3.36±1.23	3.63±1.45	0.436
	Width	2.84±1.57	2.85±1.48	0.785
Site [side] [n, %]	**Right lobe**	15[30]	8[16]	0.024*
	Left lobe	25[50]	34[68]	
	Bilateral	10[20]	8[16]	

Table [3]: Comparison between the two groups regarding to ultrasound features

		Group I [n=50] No [%]		Group II [n=50] No [%]		p
		No.	**%**	**No.**	**%**	
Calcification	Absent	20	40	27	54	0.297
	Macro	12	24	10	20	
	Coarse	3	6	1	2	
	Micro	3	6	2	4	
	Eggshell	12	24	10	20	
Echogenicity	Hyper	24	48	25	50	0.460
	hypo	13	26	10	20	
	Isoechoic	13	26	15	30	
Shape	Ovoid to round	14	28	12	24	0.679
	Taller than wider	11	22	15	25	
	Wider than taller	25	50	23	46	
Halo	Thin	15	30	13	26	
	Incompletely thin	25	50	27	54	
	Absent	10	20	10	20	
Doppler central flow	Negative	32	64	31	62	0.422
	Positive	18	36	19	38	

Table [4]: Distribution of the studied cases according to TIRADs and Bethesda classification

Variable		Group I [n=50] No [%]	Group II [n=50] No [%]	P value
TIRADs classification	**1**	10[20%]	13[26%]	0.727
	2	12[24%]	13[26%]	
	3	12[24%]	12[24%]	
	4	8[16%]	7[14%]	
	5	8[16%]	5[10%]	
Bethesda classification	I	10[20%]	9[18%]	0.721
	II	13[26%]	9[18%]	
	III	6[12%]	8[16%]	
	IV	10[20%]	10[20%]	
	V	7[14%]	9[18%]	
	VI	4[7%]	5[10%]	

Table [5]: Relation between histopathology and each of FNAC and ultrasound among study populations

		histopathology		Total
		Benign	**Malignant**	
Ultrasound	**Benign**	36	6	42 [84%]
	Malignant	0	8	8 [16%]
FNAC	**Benign**	34	2	36 [72%]
	Malignant	0	14	14 [28%]
Ultrasound	**Sensitivity**	57.1%		
	Specificity	100.0%		
FNAC	**Sensitivity**	87.5%		
	Specificity	100.0%		

DISCUSSION

Thyroid ultrasonography can provide information about different nodule parameters [e.g., diameter, structure [cystic or solid], presence of calcification, its margin regularity and absence of halo sign]. However, other reliable criteria for differentiating malignant from benign nodules are still present. In addition, multinodular and large size nodules are difficult to be diagnosed [7]. Thus, radiological system was developed to establish the diagnosis of malignant thyroid nodules. In addition, the TIRADs as a classification system based on the ultrasound features was introduced to permit better selection of nodules liable for further FNAC to avoid unnecessary procedures. It is a worldwide system used by radiologists and endocrinologists. Thus, prevents any misunderstanding [8].

FNAC is a vital tool to provide a basis for the clinical treatment decision of thyroid nodules and determines the right surgical method when surgery is required. Similar to other medical tests, it is expected that FNAC of the thyroid gland should yield high sensitivity and specificity [4].

The current study aimed to find out the accuracy of FNAC versus USG for differentiating nature of thyroid nodules [malignant or benign] against histopathology after thyroidectomy. To elucidate this aim 100 patients of all age groups attending outpatient clinic of general surgery with a thyroid nodule either solitary or multiple and divided into two groups were included. The first group of 50 patients who were submitted to US assessment and further TIRADS classification. Group two of 50 patients who were underwent FNAB and further Bethesda classification.

Results showed female predominance in both groups [68.0% and 78.0%] of groups I and II respectively. This result is comparable to **Fawzy *et al.*** [8] who found that there was female predominance [83.2%]. In addition, this agreed with almost all the reviewed studies [9, 10]. **De *et al.*** [4] found that thyroid nodules were commonly seen in females, suggestive of female predominance [86.86% of the total study population [N = 137]]. This also in line with earlier studies, in which a prevalence of thyroid nodule in females was 86% [N = 50] [11].

Our results regarding patient age coincide with **Fawzy *et al.*** [8] who found that the mean age of their studied cases was 45.67±12.73. This agrees with the results of other reports [12,13]. However, other researchers found younger age [37.6 years] [9], and others found older age [51.8 years] [14], than the current work. These differences may be explained by the different sample sizes, selection criteria and patient characteristics.

In the current study, there was a non-significant difference in between the two groups regarding calcification, echogenicity, Doppler central flow and that was partially agree with **Al-Ghanimi *et al.*** [15] who found that FNAC and USG were significantly associated for calcifications, nodular echogenicity and margins, while its association for vascularity was insignificant, indicating the role of US aiding identification of malignant nodules.

In the current study, there was a non-significant difference in between the two groups regarding TIRADs classification with p=0.78. Recently, different trials have attempted to assess the diagnostic performance and reliability of TI-RADS, and reported high sensitivity, specificity and overall accuracy for TI-RADS [16-19].

In the present study, by FNAC there were 36 [72%] of the cases were benign while by ultrasound there were 42 [84%] of the cases were benign while in the study done by **Al-Ghanimi *et al.*** [15], in FNAC, 59 of 68 nodules were reported as benign; 56 were also categorized as benign with USG.

In our presentation, there were 72% in group I and 68% in group II were benign and there were 28% in group I and 32% in group II were malignant. In the study done by **Fawzy *et al.*** [8], 73.2% were benign and 26.8% were malignant by surgical biopsy. These results were like **Jabar *et al.*** [10]'s results. They found that after surgery, 81.8% were benign and 18.1% were malignant [11]. Comparable data was reported by **Dy *et al.*** [12] who found benign lesions among 66.4% of cases. These difference in the incidence of malignant cases could be attributed to the different sample size and racial issues that control neoplastic behavior of the cell [13].

In our study, US had 100.0% specificity in detecting malignant thyroid nodules which is near to that mentioned by **Al-Ghanimi *et al.*** [15], who found that USG had a 94.9% specificity in diagnosis of the thyroid nodules.

The British Thyroid Association [BTA] guidelines recommend a multidisciplinary approach when the clinical, cytological, and USG findings are inconsistent [20]. Different USG parameters were recognized as useful indicators for classification of thyroid nodules. These include, the shape, size, orientation, margins, echogenicity, vascularity, calcification and acoustic transmission [16, 21, 22].

Another work aimed to evaluate the diagnostic value of different radiological methods for thyroid nodules reported high accuracy of ultrasound elastography and system classification in the prediction of the risk of malignancy in thyroid nodules. The elastography produced a sensitivity and a specificity of 88.9% and 91.8% respectively, that was confirmed by histological study and that actually agreed with our results [23].

In another work, **Mhuircheartaigh *et al.*** assessed the use of ultrasound thyroid nodule size as a standard indicator and screening test for thyroid nodules. They correlated the size with data of other imaging modalities [e.g., computed tomography [CT], magnetic resonance imaging [MRI], and positron emission tomography [PET]]. The results indicated that the cross-sectional imaging underestimates the size of thyroid nodules and lacks valuable clinical significance [24].

In the current study, the Society of Radiologists in Ultrasound [SRU] diagnostic criteria were used to categorize thyroid nodules on the basis of echogenicity, vascularity, calcification, and margins. They found that these characters have the strongest association with malignancy [25]. This represented one of the strengths of the current work, in that the analysis was not limited to only a single criterion, such as the size of the nodule.

In the current research, the inclusion of USG features to differentia benign from suspicious malignant lesions was useful. These results indicated that the existence of features like regular margins, normal homogeneity and vascularity as well as the absence of calcifications on USG were strongly associated with benign thyroid nodules, which was similar to the data from various studies [16, 22, 26, 27].

Our findings agree with previous studies reporting that USG used with FNAC can aid in the precise diagnosis [28-31]. In addition, the specificity of FNAC [89.72%] in our study reflects the FNA validity as an advanced tool for the surgical and pathological examination of thyroid nodules.

In the study of **Durante *et al.*** [32], preoperative recognition of thyroid cancer using FNAC showed a sensitivity of 83% [range, 65%– 98%], specificity of 92% [range, 72%–100%], positive predictive value of 75%, false-negative rate of 5% and false-positive rate of 5%, and that was near to the current results as FNAC had a sensitivity of 87.50%, specificity of 89.72%, and accuracy was 94.42%. Currently, USG-FNAC has been used to improve the success rate of puncture and the accuracy of the puncture results. Some studies reported that the false-negative rate of USG-FNAC was <3% [33, 34].

The methods and terminology for FNAC widely differ between hospitals. However, uniform terminology and criteria are required for diagnosis. The introduction of Bethesda reporting system led to the standardized reporting of the results of FNAC of the thyroid. Actually, the Bethesda system is widely used all over the world. Pathologists use this system to have efficient communication with clinicians. Thus, it offers a uniform reporting system for thyroid fine-needle puncture, as recommended by the American Thyroid Association [ATA] [35]. However, USG-FNAC is susceptible to puncture bleeding, errors in pathological cytological diagnosis, and it is relatively difficult maneuver, that could affect the specimen quality in qualitative diagnosis. Additionally, a considerable percentage of pathological cytological results remain unclear irrespective of the use of repeated punctures [36].

The available literatures showed high false-negative rate for the results of cytological examination of thyroid nodules with highly suspicious USG criteria. Analysis of 1343 cytological specimen results of benign thyroid nodules indicated malignancy among 29% if the USG was suspicious, but only 0.6% if the USG results were normal [33]. Thus, the combination of USG-FNAC and high-resolution USG could decrease the missed diagnosis rate. However, if the thyroid nodule nature remains unclear, certain molecular markers [such as mutations in RAS, RET/PTC, PAX8/PPARgamma, mouse sarcoma filter viral oncogene homolog B1 [BRAF]] can be recognized in the specimens. The detection of these mutations has been found to improve the diagnosis rate [37]. However, such genetic tests need specialized institutions and special methods, and usually expensive and difficult to implement, chiefly for primary institutions. Thus, the use of molecular markers is not a cost-effective solution [38].

Due to the variety of USG-FNAC performance of the thyroid nodules and possibility of false-negative results, the current America Thyroid Association [ATA] guidelines recommended USG follow-up instead of direct surgery in patients with suspected benign nodules [20].

According to the Association Guidelines for the Management of Thyroid Cancer, the multidisciplinary approach is recommended when the clinical, cytological, and USG findings are inconsistent. Moreover, the follow-up of thyroid nodules should depend on the integration between the initial USG appearances and associated cytology [38].

In summary, our study underscores the diagnostic reliability of both USG and FNAC in discriminating thyroid nodule malignancy. While ultrasonography effectively identifies nodules, FNAC exhibits superior accuracy [87.50%], proving to be a minimally invasive technique with a remarkable 94.42% accuracy in distinguishing malignant from benign tumors. A noteworthy finding is the potential for misdiagnosis and missed diagnoses when relying solely on qualitative diagnoses like Bethesda classification. Consequently, we propose a combined diagnostic system incorporating ultrasound TI-RADS grading, offering an enhanced approach for accurately diagnosing malignant thyroid nodules. This study contributes critical insights for clinicians, advocating for a nuanced diagnostic strategy to optimize patient care and intervention.

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