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The Bethesda system of reporting cytopathology of thyroid nodules in correlation with radiological and clinicopathological findings

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***Abstract*---**Background: Thyroid nodules are common, affecting up to 76% of the population. One in every two patients with ultrasonography has a thyroid nodule. Aim of the study: To reporting cytopathological study of thyroid FNA nodules and to correlate it with radiological findings and to compare patient characteristics in low and high-risk groups. Materials and Methods: A retrospective study included FNA cytology of 100 patients with a total of 103 thyroid nodules. Slides were retrieved and reviewed, and Bethesda categories were recorded. Ultrasound reports with TIRADS classification and patients' demographics were retrieved from archived patient notes. The data were tabulated and analyzed. Results: Most nodules were classified as low or moderately suspicious (TIRADS 2 and 3), with only 4 (3.8%) classified as very suspicious (TIRADS 5). Benign (Bethesda II) was reported in 52 (50.5%), follicular neoplasm (Bethesda IV) in 7 (6.8%), and papillary carcinoma (Bethesda V) in 3 (2.9%) of FNA assessed nodules. TIRADS 5 and cytological impressions agreed perfectly. TIRADS 1&2 and cytological impressions also agreed well. Conclusion: TIRADS improves thyroid carcinoma diagnosis and avoids needless interventions. The strong concordance of TIRADS II with Bethesda II demonstrates its reliability in detecting nodules that do not require FNA or further study.

***Keywords*---**Bethesda system, cytopathology, thyroid nodules, radiological, clinicopathological findings.

Introduction

Thyroid nodules are a frequent condition that affects up to 50% of the adult population, particularly women. The most prevalent cause of benign thyroid nodules is nodular hyperplasia, however, a steady increase in the incidence of thyroid carcinoma was observed worldwide over a period of several decades [1]. Population-based studies have revealed a large increase in thyroid cancers of all sizes and stages, as well as an increase in papillary thyroid cancer mortality [2]. Epidemiological studies reported variation in the incidence rate according to geographic area, age, and sex [1]. In Iraq, thyroid cancer incidence grew from 1.22 to 2.96 per 100,000 during the period between 2000- 2016, with a sharp spike in 2007 [3]. This is consistent with the global trend of low- and middle-income nations and regional countries such as Iran (2.2/100 000) [4] and Jordan (2.6/100 000) [5]. Although the precise reasons for the increase are not fully known, it is possible that they are related, at least in part, to the advent of new diagnostic methods (e.g., ultrasonography, thyroid scans, and fine-needle aspiration biopsy) and improvements in cancer registration practices [1]. Generally, palpable thyroid nodules were detected in 4% to 7% of individuals based on physical examination, but ultrasonography is more sensitive and allows for a higher identification rate [2]. Thyroid nodules are detected incidentally in up to 67% of neck ultrasounds, the advancement of medical imaging resolution and its growing use have resulted in an increase in the detection of thyroid nodules and, consequently, thyroid cancer [2]. Thyroid lesions detected during ultrasound scanning exhibit a highly variable pattern and several classification systems have been developed previously [6]. Unlike other system, the American College of Radiology's-Thyroid Imaging Reporting & Data System (ACR-TIRADS) classification system was released in 2017 and has gained widespread popularity because it uses easy to apply pattern-oriented system for risk stratification that can identify most clinically significant malignancies while reducing the number of biopsies performed on benign nodules [7, 8]. When it comes to diagnosing thyroid nodules, fine-needle aspiration cytology (FNAC) is the most sensitive and accurate. Using this technology, thyroid nodules may be classified as either benign or cancerous, avoiding the need for unneeded surgery [9]. Standard language for thyroid cytology reporting was adopted in 2007 with the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). Six categories of thyroid cytology reporting were employed by the Bethesda system, and each category was complemented with a set of criteria for reporting purposes [10].

Aim of the study

To apply the Bethesda system in reporting cytopathological study of thyroid FNA nodules and to correlate it with radiological findings and to compare patient characteristics in low and high-risk groups represented by age, sex, site, nodularity, and history of the previous thyroidectomy.

Method

This retrospective study was done on 100 patients collected from archived materials of cytology lab of Oncology Teaching Hospital, Medical City Complex, Baghdad during the period from January 2021 to July 2021. Slides for a total of

103 thyroid nodules belongs to 100 conspirative patients were collected. Slides were retrieved and reviewed with a specialist and Bethesda categories were recorded. Ultrasound report with TIRADS classification and patients' demographics were retrieved form archived patients notes. Inclusion criteria: any thyroid nodules aspirated under ultrasound guide with available TIRADS classification with no age or gender limitations. Exclusion criteria: patients with incomplete radiological or demographical data and nodules that were aspirated without an ultrasound guide. Tap water, 100% alcohol, 70% alcohols, Hematoxylin stain and Eosin stain, Xylol, Dibutylphalate polystyrene xylene (DPX). All included nodules were sampled under ultrasound guide even palpable ones [11]. All statistical analyses were carried out using Statistical Package for Social Sciences (IBM SPSS) software version 25. Observational data were presented as frequency and percentages. Continuous variables were expressed as mean± standard deviation (SD) or range according to data distribution. Statistical comparisons were performed using Chi-square test or Fisher's exact tests as appropriate to assess proportions of nominal/ ordinal variables in different groups. A P value of less than 0.05 was considered statistically significant.

Results

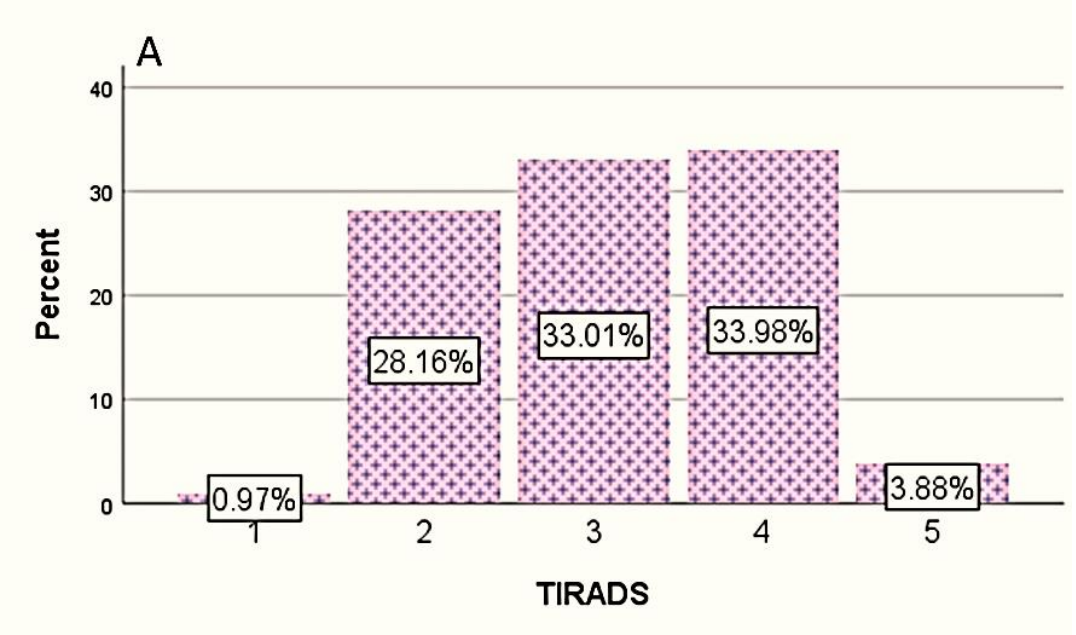
The study group consisted of 100 patients 3 of them have left and right nodules so the study group with a total of 103 thyroid nodules. The mean age of the patients was 40.8 ±13.9 years, ranged between 10-84 years, most of them were females. Half of the patients were 40 years and older, and 3 were younger than 19 years. Thyroid nodules were similarly distributed between the left and right lobes and only 8 (7.8%) were from the isthmus. Multinodular thyroid constituted two-thirds of the cases and the rest were solitary as shown in Table 1.

Table 1: Characteristics of the study group

Parameter	Frequency	Percentage (%)
Age (Y)		
<19	3	3
20-29	13	13
30-39	34	34
≥40	50	50
Sex		
Female	87	87
Male	13	13
Site		
Left	49	47.6
Right	46	44.7
Isthmus	8	7.8
Number of nodules		
Solitary	38	38
Multiple	62	62
History of a previous thyroidectomy		

No	96	96
Yes	4	4

As Figure 1A shows, more than two-thirds of the nodules were distributed between the low and moderately suspicious categories and only 4 (3.8%) were highly suspicious. FNA cytology impression was benign in 52 (50%) of the nodules, suspicious of follicular neoplasm in 7 (6.8%) (Figure 3-4A and B), suspicious for papillary carcinoma in 3 (2.9%) (Figure 3-5). Recurrence was confirmed in 2 (1.9%) of the nodules as shown in Figure 1B.



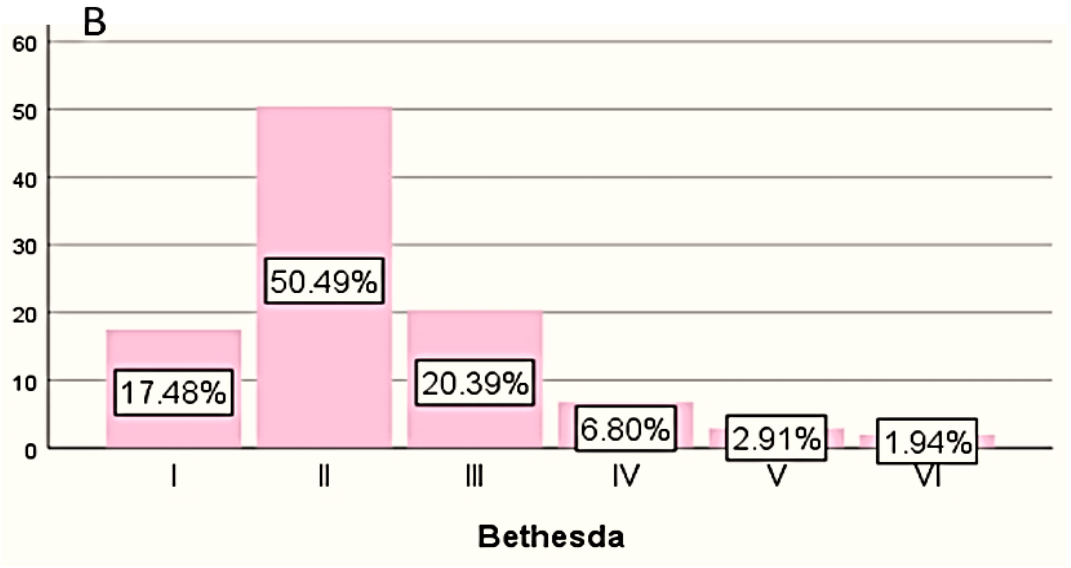


Figure 1 The distribution of thyroid nodules A) according to ultrasound TIRADS system B) according to cytology Bethesda system.

There were 18 (17.48%) nodules reported as inadequate for diagnosis according to the Bethesda system. 5 (27.7%) of them were actually cystic with colloid cyst (Figure 3-3 B) which is inherently scanty cellular and collapsed completely after aspiration or nodules with cystic degeneration (Figure 3-2A). 4 (22.2%) of the cases did not meet adequacy criteria, however, the abundant colloid (Figure 3-3A) with or without the presence of granuloma features was assuring, and repeat aspirate was deferred for 3 months. All other nodules in Bethesda I category were scheduled for re-aspiration. On the other hand, 16 (32.6 %) of the nodules with a benign impression (Bethesda II) were hyperplastic with relatively high cellularity and mixed micro and macro follicular pattern (Figure 3 C-E). Lymphocytic thyroiditis was reported in 6.1%. Bethesda III category included 20% of the cases because of the focal nuclear enlargement and incomplete cytological papillary thyroid carcinoma criteria and follow up was scheduled after 3 months to re-evaluate the nodule. The cytological impression of seven out of 103 nodules (6.8%) was suspicious for follicular neoplasm because of the high cellularity and the dominance of the micro follicular pattern.

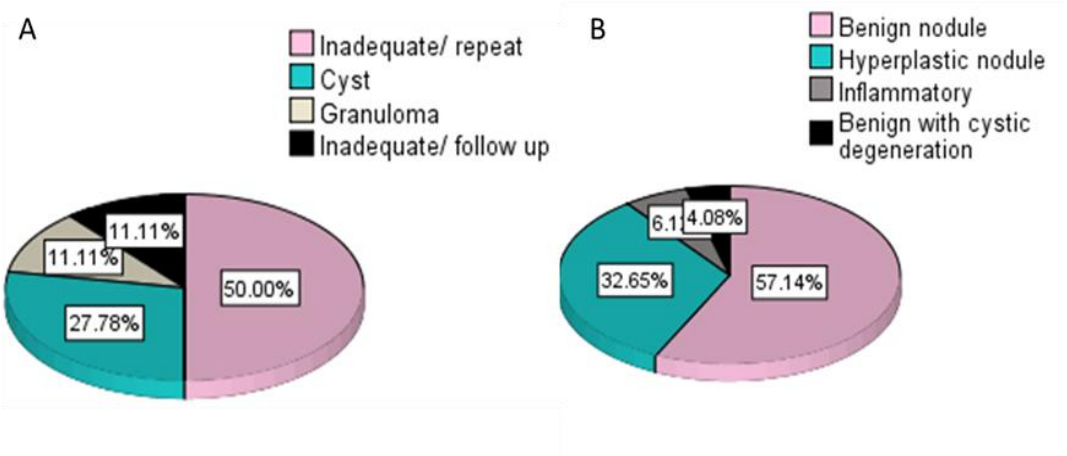


Figure 2 The cytological diagnosis in A) Bethesda I category; B) Bethesda II category

There was a perfect agreement between TIRADS 5 and cytological impression. As Table 2 shows, 3 (75%) of the nodules in TIRADs 5 categories were suspicious for papillary thyroid carcinoma and one (25%) was malignant with LN metastasis. Similarly, good concordance was seen between TIRADS 1& 2 and cytological impression. The cyst in TIRADS 1 was confirmed by cytology. In TIRADS 2, more than half of the cases were adequate within the benign Bethesda II category, and 4/11 nodules that did not meet Bethesda adequacy criteria but had an overall benign impression. There were 2 (6.9%) of the cases in TIRADS 2 that showed focal atypia and were assigned as Bethesda 3 but none of the nodules in this category showed neoplastic features. Benign cytology was observed in 73.5% of TIRADS 3, and 31.4% of TIRADS 4 categories. Follicular neoplasm was suspected in 1 (2.9%) of TIRADS 3 and 6 (17.1%) of TIRADS 4. Papillary thyroid carcinoma was confirmed in 1 (2.9%) of TIRADS 4.

Table 2: The distribution of TIRADS categories according to Bethesda system

	Bethesda						
	I No (%)	II No (%)	III No (%)	IV No (%)	V No (%)	VI No (%)	Total
TIRADS 1	1 (100)	0	0	0	0	0	1
TIRADS 2	11 (37.9)	16 (55.2)	2 (6.9)	0	0	0	29
TIRADS 3	4 (11.8)	25 (73.5)	4 (11.8)	1 (2.9)	0	0	34
TIRADS 4	2 (5.7)	11 (31.4)	15 (42.9)	6 (17.1)	0	1 (2.9)	35

TIRADS 5	0	0	0	0	3 (75)	1 (25)	4
Total	18	52	21	7	3	2	103

To compare the characteristics of patients with high and low risk lesion Bethesda I, II and III were grouped as low risk while Bethsaida IV, V and VI as high risk. High risk lesions were more prevalent in younger age group and only 2 (16.7%) were 40 years or older, this was significant different compared to low-risk nodules which 48(54.5%) were older than 40 years (P=0.007). Additionally, most of the high-risk lesions that were sent for surgical resection were solitary 10 (83.3%). This was significantly different compared to the low-risk lesion which was part of multinodular goiter in 61 (68.5%) of the cases (P=0.001). There was no significant different in terms of gender and site, Table 3 shows.

Table 3: Comparison of patient characteristics between low and high-risk groups.

Parameter	Bethesda		P value
	Low risk	High risk	
Age (years)			0.007
< 20	1 (1.1)	2 (16.7)	
20-29	11 (12.5)	2 (16.7)	
30-39	28 (31.8)	6 (50)	
>40	48 (54.5)	2 (16.7)	
Gender			0.705
Women	77 (86.5)	11 (91.7)	
Men	12 (13.5)	1 (8.3)	
Site			0.805
Left	42 (46.2)	7 (58.3)	
Right	42 (46.2)	4 (33.3)	
Isthmus	7 (7.7)	1 (8.3)	
Number of Nodules			0.001
Single	28 (31.5)	10 (83.3)	
Multiple	61 (68.5)	2 (16.7)	

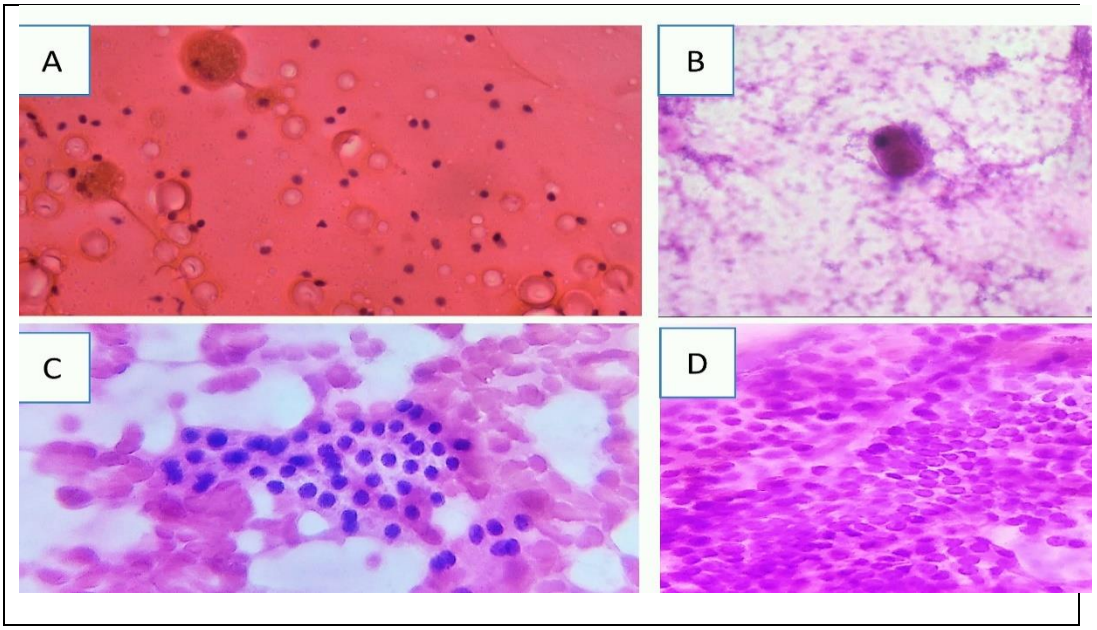


Figure **Error! No text of specified style in document.**-3 Micrographs showing cytological features of Bethesda I and II. A) Inadequate scanty cellular smear with few scattered of follicular in a background of abundant a relatively colloid mixed with inflammatory cells Bethesda I, (200×, H and E stain), B) colloid cyst showing thin abundant colloid with histiocyte, Bethesda I, (200×, H and E stain) c) adequate smears with monolayered clusters of follicular cells Bethesda II, 200X, H&E stain) D) A monolayered sheet of follicular cells with macrofollicular pattern, (200×, H and E stain).

Discussion

Thyroid nodules are a frequent finding in ultrasonography. When patients are examined with ultrasonography, one in every two will have a thyroid nodule; however, clinically perceptible nodules account for just 4-7 percent of instances [12,13]. While the majority of nodules are benign, there has been a worldwide rise in the frequency of thyroid cancer over the previous several decades. FNA cytology is a minimally invasive procedure that efficiently distinguishes malignant from benign thyroid nodules, hence avoiding needless surgery [14]. Euthyroid nodular goiter is generally more prevalent in women [15]. Similar prevalence was reported by several other local studies from northern and middle parts of Iraq ranging between 83-86.5% [8,16]. Although this might reflect women's willingness to undertake diagnostic procedures, some studies suggested sex hormone and metabolic syndrome as contributing factors for sex disparity [17]. In a community-based study conducted in China, Ding and colleagues found that among men and women aged over 45 years, the prevalence of thyroid nodules was one-third higher in women than in men (38.5% versus 26%, resp.). This frequency was higher with advancing age. The mean age of patients in our study was 40.8 ±13.9 years, half of them were older than 40 years old which was consistent with other Iraqi studies [18]. Malignancy is connected with both solitary and multinodular

goiters. Some studies show that solitary nodules carry a higher risk of malignancy than multinodular goiters, however this is not universally accepted [19]. recurrence rates following thyroid partial resection range from 2.2% to 49% [20]. Several factors can promote recurrence including insufficient surgery, lack of replacement treatment [20]. The last updated guidelines for diagnosis and management of thyroid nodule issued recommended using clinical, U/S evaluation and FNA when indicated for clinical management of thyroid nodules [12]. Triple assessment is initially proposed in the diagnosis of breast lesions. Piling studies confirmed that this approach increased the accuracy of breast cancer diagnosis to 95%, however, FNA cytology of the breast is widely replaced by core needle biopsy to reduce borderline diagnosis and provide cancer immunoprofile [21]. Unlike breast, high quality evidence confirmed that ultrasound guided thyroid FNA cytological diagnoses is highly reliable with a low rate of equivocal diagnosis compared to palpation-guided FNA [12]. TIRADS 3 nodules constituted 34% of our cohort. FNA filtered 73% of this category as benign, hence no further surgical intervention was needed. There was, however, one case (2.9%) who was diagnosed as suspicious for follicular neoplasm. The risk of malignancy could not be calculated for this group because histopathological diagnosis was not available, however, according to the literature the risk of malignancy in TIRADS 3 category is 5% [22]. 33.9% of our cohort were TIRADS 4 nodules which were moderately suspicious by the U/S. Cytology identified 20% high risk nodules in this category, one (2.9%) papillary thyroid carcinoma with classical nuclear and architectural cytological criteria (Bethesda VI) and 17% suspicious for follicular neoplasm (Bethesda IV). Cancer risk in TIRADS 4 was previously reported as 20% - 40% [22]. The concordance between TIRADS 5 and Bethesda in our study was excellent. All four cases carried TIRADS 5 criteria were papillary thyroid carcinoma some with cervical lymph node involvement. One out of the four nodules was part of a multinodular goiter. These results were relatively higher than Xu et al. findings who reported 81.4% malignancy rate in a total of 741 TIRADS5 nodules. Inadequate for diagnosis, Bethesda I, was reported in 17.5% of our cases. 50% were non diagnostic and repeated particularly for TIRADS 4 nodules, however, about one third of these cases were given a diagnosis of a cyst or inflammation. This is one of the limitations of Bethesda system which disregards the inherent hypocelluar characteristic of thyroid cyst. Other systems, such as the Royal collage (thy) system subdivided category 1 (thy 1 and thy 1c) to avoid confusing the physician who might consider unnecessary repeat. The argument put forward that papillary thyroid carcinoma can be cystic, therefore, in the proper clinical setting (e.g., ultrasound evidence of a simple, unilocular cyst), these specimens may be considered clinically adequate, even though they are reported as inadequate [23]. There was also 11.1% of the cases in this category which did not meet the adequacy criteria but show abundant thin colloid and radiologically were benign (TIRADS 2). These patients were deferred to be re-evaluated after a short follow interval. The rate of Bethesda III (AUS) in our cohort was 20.3%, 15/ 21 (42.9%) of them were moderately suspicious by U/S. Estimating the risk of malignancy in this category is challenging firstly because only a minority of AUS/FLUS cases undergo excision, secondly because resected nodules which were histopathologically confirmed as malignant cases were subjected to selection bias as most of them are TIRADS 4 or 5. This is further complicated by the introduction of NIFTP terminology in 2016 which is frequently fits in this category [23].

Conclusion

The TIRADS-Bethesda system concordance was outstanding in low- and high-risk thyroid nodules. TIRADS improves thyroid carcinoma diagnosis and avoids needless interventions. The strong concordance of TIRADS II with Bethesda II demonstrates its reliability in detecting nodules that do not require FNA or further study.

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