

## Evaluation of Thyroid Nodules by the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC)

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### ABSTRACT:

#### BACKGROUND:

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was introduced to standardize terminology used in reporting thyroid cytology. The Bethesda system used six categories for thyroid cytology reporting. Each diagnostic category is linked to a certain risk of malignancy and recommended clinical management.

#### AIMS:

To evaluate FNAC in thyroid nodules based on the Bethesda system for thyroid cytopathology.

#### SETTINGS AND DESIGN:

A cross-sectional study.

#### METHODS AND MATERIAL:

Study conducted in Al-Imamain Al-Kadhimian (AS) Medical City in period from 1<sup>st</sup> Jan 2019 – 1<sup>st</sup> August 2019. We performed FNAC either directly or under U/S guide, and all slides were examined by one cytopathologist and residents of histo- cytopathology.

#### RESULTS:

There were 357 patients who enrolled in this study. Their mean age was  $44.25 \pm 13.49$  years. Female patients represent 88.8% of total patients with male to female ratio is 1:6. The non-diagnostic sample (Bethesda I) was found in 66 (18.5%) patients, the benign thyroid lesion (Bethesda II) was found in 217 (60.8%), atypia of undetermined significance (Bethesda III) was found in 34 (9.5%), follicular neoplasm or suspicious for follicular neoplasm (Bethesda IV) was found in 38 (10.6%), and suspicious for malignancy (Bethesda V) was found in 2 (0.6%), while no case was diagnosed with malignancy (Bethesda VI). The higher value of TSH is associated with lower Bethesda score; also, the higher value of T4 is associated with lower Bethesda score too. There were 16 (4.5%), 74 (20.7%), 10 (2.8%), and 11 (3.1%) of patients that presented with nodular surface of thyroid gland that were diagnosed with I, II, III, and IV Bethesda system respectively.

#### CONCLUSION:

Bethesda system gave us a uniform terminology in reporting thyroid cytopathology. The most frequent category was category II. Thyroid nodules presented in older age group compared to other studies. Most of thyroid nodules are benign rather than malignant.

**KEYWORDS:** Bethesda system, Thyroid Nodules, TBSRTC

### INTRODUCTION:

Thyroid nodules are lumps that develop in or around the thyroid gland. A person may have one or more nodules. They are common, affecting an estimated 20 to 76 percent of adults in the United States. Some nodules are easy to feel, but others may be deep in the thyroid tissue or low in the gland, making them hard to find or detect. In fact, only 4 to 7 percent of thyroid nodules are palpable. The majority of nodules do not cause any symptoms and are non-cancerous. Nodules are more likely in females, those who are exposed to radiation, and in those who are iodine deficient.<sup>(1,2)</sup>

There are different types and forms of nodule, including:<sup>(3)</sup>

- Thyroid cyst or nodule that is filled with fluid or blood.
- Benign nodule, as is usually the case, although some are cancerous.
- Nodule that secretes thyroid hormone. (Toxic nodules).

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) was introduced in 2007 to standardize terminology used in reporting thyroid cytology. The Bethesda system used six categories for thyroid cytology reporting, and each category is supplemented by a list of criteria. These categories are nondiagnostic, benign, atypia of undetermined

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significance (AUS)/follicular lesion of undetermined significance (FLUS), follicular neoplasm/suspicious for follicular neoplasm (SFN), suspicious for malignancy, and malignant. Each diagnostic category is linked to a certain risk of malignancy and recommends clinical management. Hence, our aim is to evaluate FNAC in thyroid nodules based on the Bethesda system for thyroid cytopathology in Iraq.

### SUBJECTS AND METHODS:

A cross-sectional study conducted in AL Imamain Khadimian (AS) Medical city on patients referred to Teaching Lab Department for Thyroid FNA. The collection period is from 1<sup>st</sup> January 2019 till 1<sup>st</sup> August 2019. There were 357 patients referred at that period and for each patient, a questionnaire was done. The ethical committee of the Iraqi Board for Medical Specializations approved this study. Informed consents were taken from all participants.

### Inclusion Criteria

Every patient with thyroid nodules referred for thyroid FNA had been included in this study.

### METHODS:

- After patient reassurance
- Wearing the gloves and examine the patient in sitting position

- If it was palpable nodule then sterilize of the site of aspiration by iodine
- Fixation of the nodule by left hand and holding syringe with attached needle (Needle gauge (21-22) by right hand
- Insert it and do negative pressure with 10 to 20 excursions (back and forth cutting motions of the needle and in rotatory way)
- Then release the negative pressure slowly while the needle still inside
- Pull the needle out, Material obtained directly spread over the slides (number of slides will vary from case to case) and put in the fixative material (95% ethanol) for 20 to 30 minutes.
- If it was impalpable thyroid nodule, then the patient is advised for U/S-guided aspiration, U/S performed by radiologist, patient is asked to lie in supine position and the aspiration done by the pathologist in the same manner that was done for direct aspiration.

### Interpretation of results:

All slides were examined by one cytopathologist and residents of histocytology. Each case assessed was based on Bethesda system for 2017.<sup>(4)</sup>

**Table 1: The 2017 Bethesda System for Reporting Thyroid Cytopathology: Recommended Diagnostic Categories**

I. Nondiagnostic or unsatisfactory	Cyst fluid only, Virtually acellular specimen, Other (obscuring blood, clotting artifact, etc.).
II. Benign	
III. Atypia of undetermined significance or follicular lesion of undetermined significance	Consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.), Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context, Consistent with granulomatous (subacute) thyroiditis, Other.
IV. Follicular neoplasm or suspicious for a follicular neoplasm.	Specify if Hürthle cell (oncocyctic) type.
V. Suspicious for malignancy	Suspicious for papillary carcinoma, Suspicious for medullary carcinoma, Suspicious for metastatic carcinoma, Suspicious for lymphoma, Other.
VI. Malignant	Papillary thyroid carcinoma, Poorly differentiated carcinoma, Medullary thyroid carcinoma, Undifferentiated (anaplastic) carcinoma, Squamous-cell carcinoma, Carcinoma with mixed features (specify), Metastatic carcinoma, Non-Hodgkin lymphoma, Other.

### RESULTS:

There were 357 patients who enrolled in this study. Their mean age was  $44.25 \pm 13.49$  years. The female patients represent 88.8% and male patients represent 11.2% of total patients with male to female ratio is 1:6. Out of 357 patients, 349 patients presented with lump that moves with swallowing (97.8%) and only 6 patients (1.7%) have local tenderness. None of patients had Lymphadenopathy

clinically. There were 36 (10.1%) of patients have previous thyroid surgery. There were 291 (81.5%), 19 (5.3%), and 47 (13.2%) of patients presented with euthyroid, hypothyroid and hyperthyroid status respectively. The thyroid function test (T3, T4, and TSH) are done for all patients, the mean of T3, T4, and TSH was 2.09, 94.1 and 1.6 respectively (Table 2).

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**Table 2: Descriptive statistic of thyroid function test.**

	Range	Minimum	Maximum	Mean	SD	Variance
T3	8.20	0.00	8.20	2.09	1.12	1.25
T4	189.40	10.60	200.00	94.17	28.77	828.0
TSH	16.00	0.00	16.00	1.65	2.08	4.36

There were 152, 141, and 18 patients have only right, left or isthmus lump only at presentation respectively. Four patients did not have any lump at presentation, and it was only detected by ultrasound. There were 32 patients have both right and left lump at presentation, 8, 2 patients have isthmus and right side lump, isthmus and left side respectively. The surface of the gland was nodular in 111 (31.1%) patients, and smooth surface found in 246 (68.9%) patients.

With ultrasound examination, 53 (14.8%), and 84 (23.5%) patients have either left side involvement or right side respectively. The rest of patients 220 (61.6%), had bilateral involvements of thyroid gland (Table 3.3). Regarding the number of nodules by U/S, the nodules of left side, there were 43 (12%) of patients with single nodule and 10 (2.8%) with multiple nodules. For the right side, there were 47 (13.1%) of patients with single nodule, while 37 (10.3%) of patients have multiple nodules. Total of 90 (25.2%) of patients have only single nodules by U/S.

Increase in vascularity noted in 52 patients, and the rest of patients (305) showed normal vascularity. The cervical LN was observed in 119 patients (all with preserved hilum), while 238 patients did not have any LN involvements.

### Evolution of thyroid nodules by the Bethesda system for reporting thyroid cytopathology

The non-diagnostic sample (Bethesda I) was found in 66 (18.5%) patients, the benign thyroid lesion (Bethesda II) was found in 217 (60.8%), atypia of undetermined significance (Bethesda III) was found in 34 (9.5%), follicular neoplasm or suspicious for follicular neoplasm (Bethesda IV) was found in 38 (10.6%), and suspicious for malignancy (Bethesda V) was found in 2 (0.6%). While no case was diagnosed with malignancy (Bethesda VI)

The distribution of age across Bethesda significant association with lower age in association with Bethesda IV. Other Bethesda categories did not show any significant association with age (Table 3).

**Table 3: The association between age and Bethesda.**

		Age				P value
		Mean	Minimum	Maximum	SD	
Bethesda	I	42	14	67	13	0.4
	II	46	21	85	13	0.39
	III	43	12	69	18	0.81
	IV	39	19	67	12	0.027
	V	44	44	44	0	0.91

The distribution of Bethesda scoring was associated with significantly difference across T4 and TSH (i.e. the higher value of TSH is associated with lower Bethesda score, also, the

higher value of T4 is associated with lower Bethesda score too), while there was no significant statistical difference between Bethesda and T3 (Table 4).

**Table 4: The distribution of Bethesda with mean and SD of T3, T4, and TSH.**

		Bethesda					P value
		I	II	III	IV	V	
T3	Mean	2.26	2.03	2.19	2.09	1.90	0.423
	SD	1.45	.94	1.56	1.02	.00	
T4	Mean	88.93	98.91	84.67	86.24	67.00	0.004
	SD	27.43	28.49	29.26	27.82	.00	
TSH	Mean	2.66	1.35	1.13	2.10	1.80	0.0001
	SD	3.07	1.53	1.10	2.82	.00	

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There were 16 (4.5%), 74 (20.7%), 10 (2.8%), and 11 (3.1%) of patients that presented with nodular surface of thyroid nodules that were diagnosed with I, II, III, and IV Bethesda system. There were no significant difference between nodular and smooth surface of thyroid nodules (P value= 0.49).

### DISCUSSION:

In this study, the cross-sectional analysis of 357 patients referred for FNA cytology to evaluate the thyroid nodules based on Bethesda system, the mean age of patients in this study was higher in comparison with other local study by Hassan<sup>5</sup>, and this could be explained by difference in sample size between the two studies. Also, the mean age in our study was much higher than other regional and global studies,<sup>(6,7)</sup> and the explanation to this might be related to early awareness in western countries and the neglecting of Iraqi patients to symptoms, and no proper thyroid clinic in Iraqi hospitals.

The distribution of gender in this study was in agreement with other studies and it is confirming that the thyroid nodules presented in female more than male patients.<sup>(8)</sup> This disparity is still not fully understood, in some researches, authors related this to tumour biology or other factors that may influence it.<sup>(9)</sup>

The recurrence of thyroid nodules that required FNA in patients with previous thyroid surgery was observed in 10.1% patients. This low percent is also observed in other studies,<sup>(10)</sup> and this may be due to incomplete surgical thyroid resection that leave some remnant behind, multinodular goiter, and hemorrhage on the nodule.

Almost all patients presented with a lump with more than 97.8% of them their lump is moving with swallowing. Local tenderness and other constitutional symptoms were nearly zero, and this is comparable with other regional and global researches.<sup>(11)</sup> Usually, the patients seeking medical consultation due to lump that is the first and the earliest symptoms to be observed by patients before pressure effects of nodules.

There was no statistical significance difference between the localization of lump in the right or left side of the thyroid at presentation. Some authors proposed that there might be an association between the side of lump and diagnosis, and this could not be approved.<sup>(12)</sup>

The surface of the thyroid gland was either nodular (31.1%) or smooth (68.9%) in our study. There is no specific correlation with surface of gland in association with diagnosis according to

Bethesda system, and there was no studies investigating this correlation.

The radiology report of U/S of thyroid showed that the majority of patients have bilateral involvement of both lobes of thyroid glands. The increase vascularity was reported in 52 patients only and LN involvement was in 119 patients. These U/S reports are considered weak compared to recommended U/S report of TIRAD, which showed high reproducibility of description and give clear guide for diagnosis.<sup>(13, 14, 15)</sup>

In the recommendation of diagnosis and management of thyroid nodules by Shrikant,<sup>(16)</sup> they recommended that, in normal or high TSH, the patients need U/S if nodules diameter is more than 1 cm then FNA accordingly. This was in conflict with our study that the physicians sent all thyroid nodules for FNA irrespective to TSH (its level in our study was  $1.65 \pm 2$ ), below normal level of TSH, patients should be sent for thyroid scan according to previous recommendation.<sup>(17)</sup>

The non-diagnostic sample (Bethesda I) was found in 66 (18.5%) patients, the benign thyroid lesion (Bethesda II) was found in 217 (60.8%), atypia of undetermined significance (Bethesda III) was found in 34 (9.5%), follicular neoplasm or suspicious for follicular neoplasm (Bethesda IV) was found in 38 (10.6%), and suspicious for malignancy (Bethesda V) was found in 2 (0.6%), while no case was diagnosed with malignancy (Bethesda VI). This interpretation was in agreement with regional and global research regarding the categorization based on Bethesda system.<sup>(17, 18)</sup>

For the non-diagnostic sample (Bethesda I) which was found in 66 of patients, which is slightly higher than other researches mentioned above, this could be explained by the fact that our clinicians sent every patients with thyroid nodules for FNA cytology regardless thyroid function test levels.<sup>(17)</sup>

On the other hand, due to deficient U/S report (did not follow TIRAD system).<sup>(14)</sup> Also, most of thyroid nodules are colloid nodules and might underwent hemorrhage, so it will be less cellular, or may be due to faulty technique.

Also, no case was diagnosed as malignant (Bethesda VI) in our study, while in other studies, the percentages of cases that diagnosed with Bethesda VI are ranging from 1.6 – 5.1 %, <sup>(13,19)</sup> and multiple factors have been implicated with this finding.

The distribution of age across Bethesda significant association with lower age in association with Bethesda IV in our study, this

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was also observed in other studies that the Bethesda IV associated with lower age; however, no research showed statistical significance.<sup>(20)</sup> This could be explained by the fact that the younger age group tends to have earlier consultation than other groups for cosmetic reasons. Other Bethesda categories did not show any significant association with age.

The distribution of Bethesda system in gender group was associated with higher score in female compared to male (P value = 0.0001) Also, the high number of female cases could have some bias with this interpretation. The association of Bethesda system with previous thyroid surgery have showed that, out of 36 cases, 24 patients the recurrences was benign Bethesda II.

The distribution of Bethesda scoring was associated with significant difference across T4 and TSH (i.e. the cases with higher value of TSH are associated with lower Bethesda scores, also the cases with higher value of T4 are associated with lower Bethesda scores too), and this was in reverse of other global studies that showed that higher TSH level is associated with malignancy.<sup>(21,22,23)</sup>

The recommendation mentioned that, the patients with high TSH should be sent for thyroid U/S to determine the diameter of nodule, rather than to FNAC, while the practice in our institute, they sent all patients with thyroid nodules for FNAC irrespective to their diameter by U/S even in cases where nodules less than 1 cm in diameter, which it needs only follow up, so sending all patients for FNAC is responsible for the lower Bethesda score.<sup>(17)</sup>

After categorization of patients to Euthyroid, hyper, and hypo thyroidism, according to the thyroid function test, there was no significant association between Bethesda system and the distribution of disease status. The observation here is numerically higher percentage of patients that are Euthyroid have been diagnosed with Bethesda I and II. Also, this observation applied to hypo and hyper thyroidism.

There were 16 (4.5%), 74 (20.7%), 10 (2.8%), and 11 (3.1%) of patients that presented with nodular surface of thyroid that were diagnosed with I, II, III, and IV Bethesda system. There was no significant difference between nodular and smooth surface of thyroid (P value= 0.49). And this was in agreement with other regional and global researches.<sup>(24)</sup>

### CONCLUSION:

1. Bethesda system gave us a uniform terminology in reporting thyroid cytopathology and it is applicable in our institutes and privet labs.

2. The most frequent category was Bethesda II (Benign) according to the Bethesda system of reporting thyroid cytopathology.
3. Thyroid nodules presented in older age group compared to other studies.
4. Thyroid nodules are more common in female than in male gender.
5. Most of thyroid nodules are benign rather than malignant.

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