

Thyroid Nodules: Cytopathological Correlations with the Update Bethesda System 2017: Our Experience and a Systematic Review

Taha MM Hassan¹, Ahmed M.S. Hegazy^{2*}, Mohammed M. Mosaed³, Nashwa Alzahrani⁴ and Abdalla Taher El-Enizi⁵

¹Beni Sueif University, Egypt & Histopathology Head; Regional Lab. Northern Border Zone, KSA

²Faculty of Medicine, Northern Border University (NBU), Saudi Arabia., Benha Faculty of Medicine, Benha University, Banha City, Egypt

³Department of Anatomy, Al-azhar Faculty of Medicine, Al-azhar University, Assuit City, Egypt

⁴Teaching assistant, Collage of Medicine, Northern Border University

⁵Regional Lab. Director & Forensic Medicine Organizer; Northern Border Zone; KSA

Abstract

Thyroid nodules (TNs) consider alarming problem among women. Although benign nodules far outnumber cancerous one. The risk of malignancy can be evaluated preoperatively using fine needle aspiration cytology (FNAC) under ultrasonographic guidance is widely used. The Bethesda system for Reporting Thyroid Cytopathology (TBSRTC) was worldwide accepted as standardized approach for cytological interpretation of these nodules. The purposes of this study are to apply and determine the risk of malignancy (ROM) of each standard cytological category of TBSRTC correlating with histopathological examinations and other publications. This study was performed on 1500 patients were complaining of thyroid nodules. All patients underwent for FNAC under ultrasonographic guidance. The obtained materials were diagnosed and categorized according the standard cytological categories of TBSRTC 2017. The cases which were diagnosed C4, C5, and C6 underwent to thyroid surgery, then all the taken specimens were examined and evaluated microscopically. The ROM in FNAC and a correlation with the histopathological findings were done.

Conclusion: Cytological interpretation of thyroid nodules applying the standard categories of the Bethesda system can minimize the risk of over surgical treatment and yielding more accurate approach for patient's management.

Keywords: FNAC • Thyroid Nodules • TBSRTC • Histopathological Correlations

Introduction

The thyroid gland is one of endocrine system and is located between the C5-T1 vertebrae of vertebral column. It consists of right and left lobes connected by a narrow isthmus and surrounded by a sheath derived from the pretracheal layer of deep fascia [1-3]. The thyroid gland consists of two endocrine cell types, the follicular cells that produce the thyroid hormones T3 and T4 and the parafollicular C-cells that synthesize calcitonin [2,4,5].

The recent introduction and usage of high resolution neck ultrasound in the diagnosis of thyroid nodules, their prevalence was rising to exceed 50%. Only 10% of these nodules correspond to thyroid carcinoma, which is 2 to 4 times more frequently in women [6-8].

FNAC particularly ultrasound guided is widely used as one of diagnostic methods in patients with thyroid lesions [9]. The main purpose of FNAC is to distinguish patients with malignant cytology who will require surgery, from those with benign cytology, especially colloid nodules and cysts, which require simple surveillance. Generally, FNAC is a safe procedure, minimally invasive and cost-effective with low risk of complications. It is extremely useful in diagnosis of higher percentage of benign thyroid nodules, avoiding the patient of unwanted surgery and reducing the post-operative complications [10,11].

There are many formatting systems in regard reporting FNAC of thyroid like equivocal, insufficient, indeterminate, atypical, suspicious of malignancy,

possibly neoplastic, possibly malignant, and probably malignant. All these formats are ranging from benign to malignant categories [11,12]. For interpretation of these terminologies and other issues related to thyroid FNACs, the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), which includes standardization, definitions, and therapy plan was published and became worldwide accepted. TBSRTC included six-categories scheme of thyroid cytopathology reporting (Table 1). This system was agreed and organized by National Cancer Institute (NCI) under "The NCI Thyroid Fine Needle Aspiration State of the Science Conference" at Bethesda, Maryland [13-17]. Additionally, the last revision in 2017 was inspired by new data and new developments in the field of thyroid cytopathology. In the same them with adding of molecular testing in the cytopathological examination thyroid FNAC, separating the noninvasive follicular variant of papillary thyroid carcinoma as noninvasive follicular thyroid neoplasm with papillary like nuclear features [NIFTP] [13,14]. A variety of tests have been applied to separate benign from malignant thyroid nodules. These tests include isotope scanning and FNAC. Combined use of them, and histopathology of thyroid tissue offers the best diagnostic strategy [18-20]. The objectives of this study that was done in KSA, Northern zone were to classify thyroid FNAC smears by TBSRTC into various diagnostic categories, analyze their cytological findings using TBSRTC standards in the panel of management plan of thyroid nodules.

Materials and Methods

Patient selection

During 4-years duration from January; 2012 to January 2018, 1500 patients were participating in this work, all the patients were seen in the endocrinology and surgery outpatient clinics; Northern zone's Hospitals, KSA. These patients were suffering from thyroid swelling. The patients were evaluated clinically and followed by routine laboratory investigations which were including T3, T4, and TSH. Inclusion criteria included solitary thyroid nodule, hypothyroid and euthyroid patients, whereas the exclusion criteria

***Address for Correspondence:** Ahmed MS Hegaz, Faculty of Medicine, Northern Border University (NBU), Saudi Arabia., Benha Faculty of Medicine, Benha University, Banha City, Egypt, E-mail: ahmed0562301954@yahoo.com

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Table 1. TBSRTC including recommended diagnostic categories, implied risk of malignancy, and recommended management.

Diagnostic category	ROM (%)	Usual management
1. Nondiagnostic or unsatisfactory (ND/UNS): Cyst fluid only Virtually acellular specimen Other (obscuring blood, clotting artifact, etc.)		Repeat FNA with ultrasound guidance.
2. Benign Consistent with a benign follicular nodule (includes adenomatoid nodule, 0-3 colloid nodule etc.) Consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context Consistent with granulomatous (subacute) thyroiditis Other		Clinical follow-up
3. Atypia of undetermined significance or follicular lesion of undetermined significance (AUS/FLUS)	5-15	Repeat FNA
4. Follicular neoplasm or suspicious for follicular neoplasm (FN/SFN). -specify if Hurthle cell (oncocyctic) type	15-30	Surgical lobectomy
5. Suspicious for malignancy (SFM) Suspicious for papillary carcinoma Suspicious for medullary carcinoma Suspicious for metastatic carcinoma Suspicious for lymphoma Other	60-75	Near-total thyroidectomy or surgical lobectomy
6. 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	97-99	Near-total thyroidectomy

included patients with abnormal hyperthyroid function tests, and multiple thyroid nodules.

Pre-FNAC informed consent was taken according to an institutional policy and procedure. All patients were underwent for thyroid ultrasonographic scanning with nodule localization using a high resolution linear array-transducer. A 20-23 gauge needle was used for the procedure and at least 2 passes of FNAC were obtained. All the cases which categorized as non-diagnostic or unsatisfactory (ND/UNS), FANC repeated for more accuracy.

Cytology

All the obtained materials were immediately smeared in labeled slides with numbers according to the laboratory's policy and procedure, then placed in jars with 95% alcohol for fixations (wet preparations), and sent for preparation of stained slides. All the prepared slides were stained with Hematoxylin and Eosin (H&E). The remaining materials used for preparation of paraffin-embedded tissue blocks. Sections with 3 micron thickness were prepared and stained with (H&E). Cytologically, all the cases were reported and categorized into 6-categories according to the TBSRTC by 2 experienced pathologists [21,22] (Table 1). The smears were considered adequate if there are at least five groups of well visualized-follicular cells, each group containing ten or more cells in association with an adequate colloid materials[13-15].

Cytologically, the aspirates were categorized as positive or negative for malignancy. According to TBSRTC, benign results are considered as a negative test results and results included C3 through C6 were considered as a positive test results. A cytological negative FNAC and on subsequent histological examination diagnosed as malignant or suspicious of malignancy were considered as false-negative cases. Patients with positive cytological examination and diagnosed as nodular goiter or thyroiditis on histopathological examination were considered as false positive [16]. All the categorized cases as C4, C5, & C6 underwent for surgical intervention, either excision of nodules/lobectomy or subtotal/near total thyroidectomy, whereas the C3 cases were informed to repeat the FNAC procedure. All the received tissue specimens were grossly examined and processed according to standard guidelines and reported by consultant histopathologist.

The sensitivity, specificity, positive and negative predictive values, and

diagnostic accuracy of FNAC, relative to the final histopathological findings were statistically analyzed using standardized formulas [23] and through SPSS software. All the cases of inadequate FNAC findings were excluded from the calculation.

Results

A total of 1500 cases, comprised of 300 (20%) men and 1200 (80%) women, were included in this study. The female/male (F/M) ratio was 4:1. The patients' age ranged from 14-70 year, with an average age of 40. Majority of patients were in the age group 24-34 years. Symptoms like dysphagia, hoarseness of voice, and compression troubles were rare. The categorization of the FNAC findings according to the Bethesda system was as follows, there were 75 (5%) cases were C1, 550 (36.7%) cases C2, 400 (26.7%) cases C3, 300 (20.0%) cases C4, 125 (8.3%) cases C5, and the remaining 50 (3.3%) cases were C6 (Table 2). Out of the 1500 cases, FNAC adequacy was found in 1475 cases (95%). Surgery was done in 700 cases that were including 150 cases of C2, 200 cases of C3, 200 cases of C4, 100 cases of C5, and all the 50 cases of C6 (Figures 1-9). The histopathological findings of all the surgical received thyroid materials including the relative incidence of malignancy in each of Bethesda category were summarized in Table 3 (Figures 11-15). The incidence of malignancy in all Bethesda categories from C2 through C6 were as follow: 15%, 40%, 50%, 85%, and 98%. The overall malignant cases in the received surgical specimens were 200 out of the 1500 cases (13.3%), majority of them was follicular variant papillary thyroid carcinoma (FVPTC) that was observed in 12 cases, well differentiated tumor of undetermined malignant potential (WDTUMP) found in 8 cases, whereas conventional papillary thyroid carcinoma detected in 3 cases, medullary thyroid carcinoma seen in 2 cases, and each of follicular carcinoma and anaplastic carcinoma observed in one case. In concern to the remaining surgical specimen 48 cases were benign, majority of them were related to C2 that were comprising 25 cases. Follicular adenoma was the commonest histopathological diagnosis among all benign cases which seen in 13 out of the 48 benign cases, nodular goiter and adenomatoid hyperplasia each of them was forming of 10 cases, Hashimoto thyroiditis found in 7 cases whereas, Hurthle cell adenoma was found in one case (Table 3).

Table 2. Distribution of studied cases according to the clinical variables and BTSRTC.

Age groups	# of cases	Gender		Bethesda Category	Frequency	% of categories
		Men	Women			
14-24	100	20	80	C1	75	5
24-34	700	115	585	C2	550	36.7
34-44	450	75	375	C3	400	26.7
44-54	150	50	100	C4	300	20
54-64	75	30	45	C5	125	8.8
64-74	25	10	15	C6	50	3.3
Total	1500	300	1200		1500	100

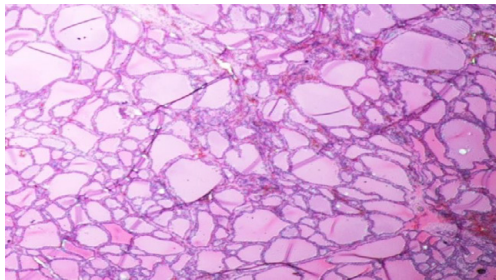


Figure 1: A case of normal thyroid tissue formed of variable sized acini filled with colloid and lined by follicular epithelia (H&E x40).

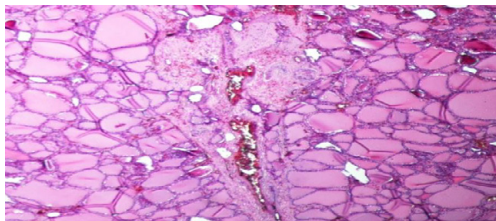


Figure 2: Normal thyroid tissue formed of variable sized acini filled with colloid and lined by follicular epithelia with foci of fibrosis and hemorrhages (H&E x40).

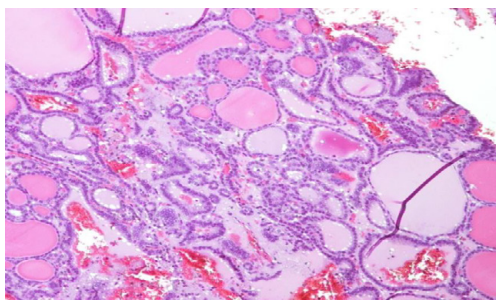


Figure 3: A case of adenomatoid hyperplasia with variable sized acini filled with colloid and lined by variable hyperplastic follicular epithelia (H&E x40).

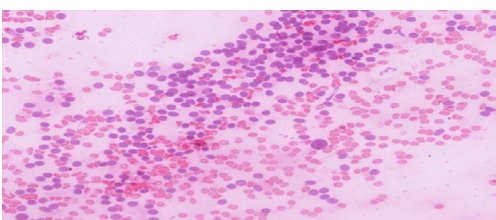


Figure 4: A case of FNAC of thyroid nodule with Bethesda category C3 showing sheets of AUS / FUS (H&E x100).

Discussion

In spite of several classification schemes for thyroid FNAC have been

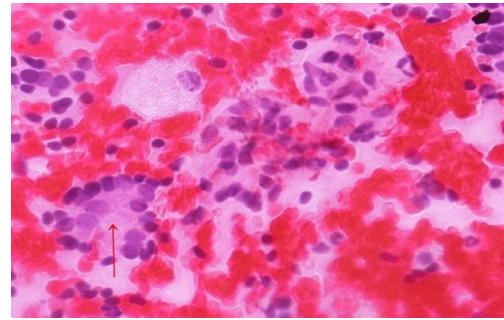


Figure 5: A case of FNAC of thyroid nodule with Bethesda category C4 showing groups of atypical cells and microfollicles (H&E x400).

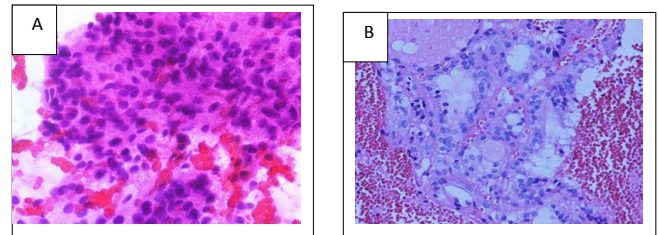


Figure 6 A: A case of FNAC thyroid nodule with Bethesda category C4 showing sheets of atypical cells of FN/SFN (H&E x400). **B:** Cell block of the previous FNAC showing numerous mixed microfollicles with overlapping cells (H&E x200).

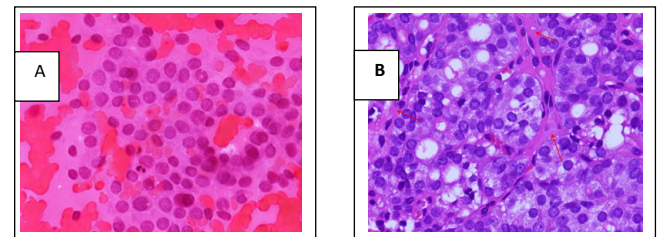


Figure 7. A: A case of FNAC of thyroid nodule with Bethesda category C5 showing increased cellularity with nuclear clearing and vague pseudoinclusions of follicular cells (H&E x400). **B:** A case of cell block of the previous FNAC showing numerous dispersed atypical cells with microfollicles and nuclear clearing with fibrohyaline bands (arrows) (H&E x400).

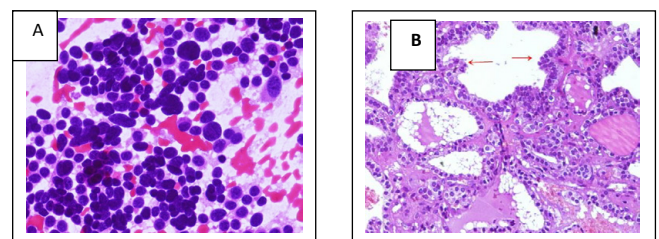


Figure 8. A: A case of FNAC of thyroid nodule with Bethesda category C6 showing increased cellularity with dispersed pleomorphic cells (H&E x400). **B:** A case of cell block with Bethesda category C6 showing follicles with abortive papillae formations (arrows) (H&E x200).

proposed by various professional organizations, TBSRTC undoubtedly represents a major step toward standardization, reproducibility, and ultimately improved clinical significance, usefulness, and

predictive value of thyroid FNAC [21-27]. The main difficulty among all these scheme is represented by “borderline” lesions characterized by atypia of undetermined significance and/or a microfollicular pattern [28-29].

The six original general categories of Bethesda 2010 have been retained in the 2017 revision without changed, yet risk of malignancy (ROM), changes in the plan of surgical and ROMs calculated in two ways after the introduction of NIFTP as its consideration as it is not considered a malignancy, and when

Table 3. Correlation of Cytologic diagnosis with final histopathological with incidence of malignancy in each Bethesda category.

Cytological diagnosis	# of surgery	%	Histological Diagnosis		Frequency		% of benign	% of malignant
			Benign	Malignant	Benign	Malignant		
Bethesda C2	150/550	27.2	NG	FVPTC	155	5	96.7%	3.3%
			AH	WDTUMP	15	2		
			HT		15			
			FA		8			
Bethesda C3	200/400	50	NG	FVPTC	65	20	85%	15%
			AH	WDTUMP	35	10		
			HT		10			
			FA		10			
Bethesda C4	200/300	66.7	AH	FVPTC	12	40	64.3%	36.7%
			FA	WDTUMP	30	30		
			HCA	PTC	3	2		
Bethesda C5	100/125	86	FA	FVPTC	35	40	40%	60%
				WDTUMP		20		
				PTC		3		
				MTC		2		
Bethesda C6	50	5.3	FA	PTC	1	25	2%	98%
				FTC		12		
				MTC		8		
				AC		5		
Total	700	100						

NG: Nodular goiter; AH: Adenomatoid hyperplasia; FA: Follicular adenoma; HT: Hashimoto thyroiditis; HCA: Hurthle cell adenoma; FVPTC: Follicular variant papillary thyroid carcinoma; WDTUMP: Well differentiated tumor of undetermined malignant potential, PTC: Papillary thyroid carcinoma, MTC: Medullary thyroid carcinoma; FTC: Follicular thyroid carcinoma; AC: Anaplastic carcinoma.

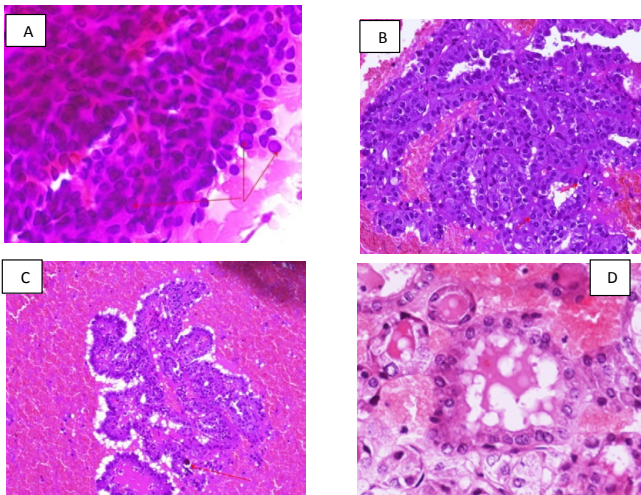


Figure 9. A: A case of FNAC of thyroid nodule with Bethesda category C6 showing hypercellular smear with dispersed atypical cells had nuclear inclusion (arrows) (H&E x400). B: A case of cell block with Bethesda category C6 showing fibrovascular papillae with nuclear inclusion (arrows) (H&E x200). C: A case of cell block with C6 showing fibrovascular papillae with psammoma body (arrow) (H&E x100). D: A case of cell block with C6 showing mixed follicles with nuclear inclusions (H&E x400).

it is still included among the carcinomas [13,14].

The reports of FNAC aspirates were issued in accordance with the update Bethesda System 2017. This system bridges an accurate communication between clinicians and pathologists helping them to take appropriate therapeutic interventions. It makes the cytology report unambiguous, clear, succinct and clinically relevant [13,14]. Each category of the TBSRTC has an implied risk of malignancy (ROM) which ranges from 0 to 3% for the “benign” category to virtually 100% for the “malignant” category [13,14].

Non diagnostic or unsatisfactory FANC (ND/UNS)

One of the advantages of the update 2017 Bethesda system is considering

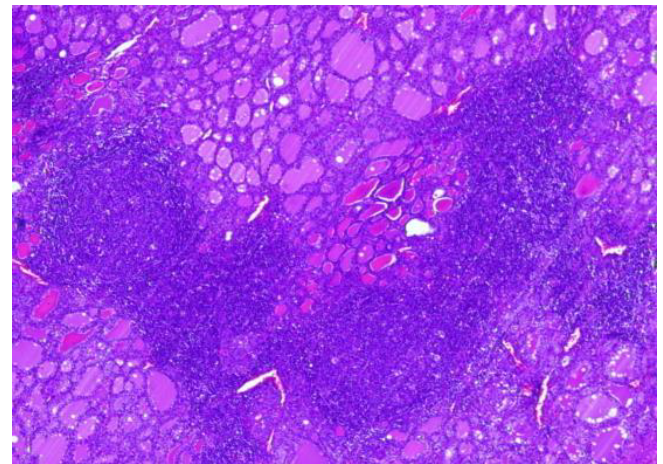


Figure 10: A case of thyroidectomy showing well-formed lymphoid follicles of Hashimoto thyroiditis (H&E x100).

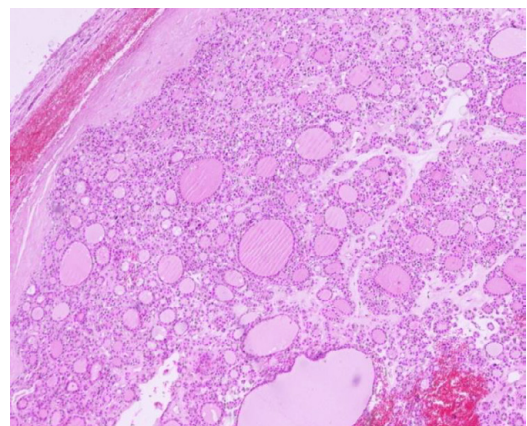


Figure 11: A case of lobectomy showing well differentiated tumor with undetermined malignant potential had a site of capsular permeation and variable sized follicles (H&E x40).

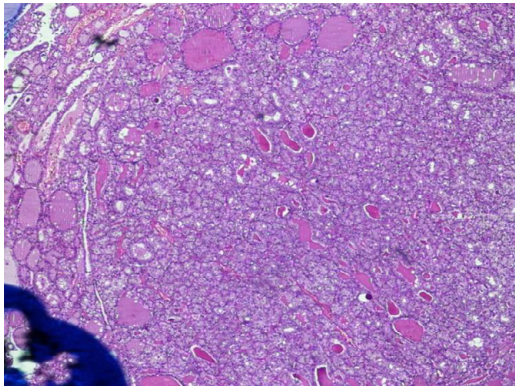


Figure 12: A case of lobectomy with of FVPTC showing solid sheets and follicles filled with thick eosinophilic colloid (H&E x40).

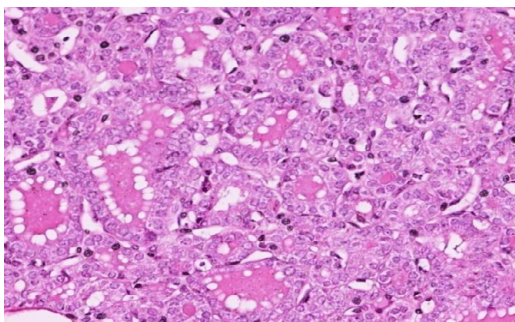


Figure 13: A case of subtotal thyroidectomy showing follicular variant papillary thyroid carcinoma (FVPTC) with follicles lined by atypical overlapped cells with nuclear clearing and inclusions (H&E x400).

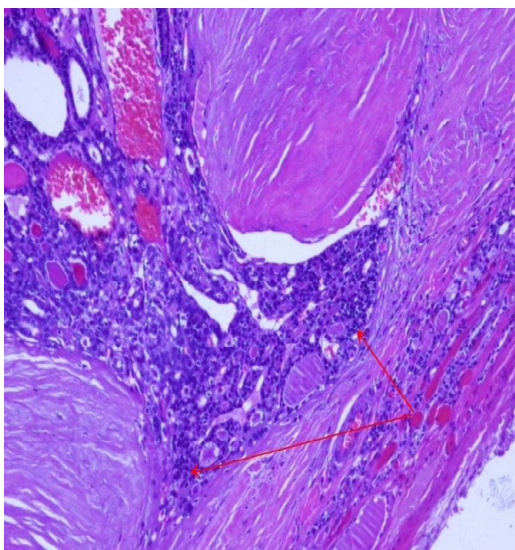


Figure 14: A case of thyroidectomy showing minimally invasive follicular thyroid carcinoma (MTC) with atypical cells permeated through fibrous capsule (arrows) (H&E x100).

an abundant colloid in the FNAC aspirate is an adequate for cytological interpretation and is benign, even if six groups of follicular cells are not detected. A sparsely cellular specimen with abundant colloid and distended follicles is by this definition macrofollicular benign nodule. If there is a specific diagnosis (e.g., lymphocytic thyroiditis) can be rendered, and if there is any significant atypia, the specimen is by definition is an adequate for evaluation [13,14]. In regarding to ROM of ND/UNS, it is difficult to be calculated as majority of nodules are not resected, however a study by Haugen et al., 2016 [30] reported the overall ROM in this category was 5-10% of surgically resected nodule. Bethesda 2017 recommended to repeat FNAC for cases of ND/UNS and excision is considered for persistently ND/UNS yet, American Thyroid association guidelines recommend repeating FNAC for this category

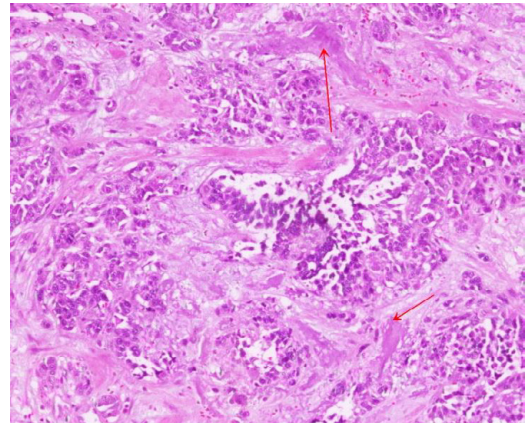


Figure 15: A case of thyroidectomy showing medullary thyroid carcinoma (MTC) with sheets of atypical cells separated by fibrous bands and pinkish amyloid material (arrows) (H&E x100).

at any time after unsatisfactory aspiration [30]. The presence of abundant colloid in the aspirate is reliably identifies most benign processes despite scant follicular cells [31]. The diagnosis of ND / UNS is limited to the conditions where a definite diagnosis cannot be rendered due to increase in blood in smear , improper cell preservation and decrease in thyroid follicular cells [32].

Benign FNAC

This category continue from The 2010 BSRT without any changes introduced by The 2017 BSRTC.

FNAC of Follicular Lesion of Undetermined Significance/ Atypia of Undetermined Significance (FLUS/AUS)

The 2017 BSRTC FUS/AUS category with auditing and adding the new NIFTP, the ROM is higher than originally estimated one and become closer to 10–30% in consideration that NIFTP is a malignant one, in contrast to the risk of 6–18% if NIFTP is not considered as malignant [33,34].

Follicular Neoplasm or Suspicious for a Follicular Neoplasm FNAC

The 2017 BSRTC includes a modification to the definition and diagnostic criteria for this category as if there is increased nuclear size, nuclear contour irregularity, and/or chromatin clearing without true papillae and intranuclear pseudo inclusions, the lesion can be classified as FN/SFN [35]. According to the update TBRST 2017, in this category if there is any cytologic features raise the possibility of FVPTC or NIFTP as predominance of microfollicles and focal or mild nuclear changes an optional note describing the above diagnosis can be adding yet the final diagnosis is not possible on cytologic material [13,14].

Suspicious for Malignancy FNAC

As with AUS/FLUS and FN/SFN, Some but not all of the cases in this category raise the possibility of FVPTC or NIFTP. For this possibility a note can be explaining, the cytomorphologic features are suspicious for the above lesion so, lobectomy rather than thyroidectomy is advised [36].

Malignant FNAC

Revised 2017 Bethesda system modifies the definition and criteria for papillary thyroid carcinoma in the malignant category trying to avoid false-positives of the new introduced NIFTP and limits the use of the malignant category to cases with “classical” features of papillary thyroid carcinoma (true papillae, psammoma bodies, and nuclear pseudo inclusions [35,36]

Acell block preparation sections was prepared from FNAC cases aspirates after smears. This technique helps in meeting the architectural details especially to differentiate papillary carcinoma from papillary hyperplasia. Additionally, marker studies, special stains can be done on cell block preparations for better diagnostic accuracy of thyroid nodules. Confirmation

Table 4: Comparisons of findings of present study with previous studies.

Study	Year	No. of patients	Sensitivity	Specificity	Accuracy
Al-sayer et al.	1985	70	76	93	92
Cusick et al.	1990	283	86	58	69
Bouvet et al.	1992	78	9305	75	79.5
Afroze et al.	2002	170	61.3	99.3	94.5
Kohm et al.	2003	207	78.4	98.2	84
Kessler et.al	2005	170	79	98.5	87
Ninama,Nanvati	2014	137	75	98.3	94.5
Present study	2020	700 / 1500	72%	85%	75%

of malignant thyroid conditions, can be done by IHC studies on cell block [37].

Among 1500 cases of thyroid nodules included in this study, 75 (5%) cases were ND / UNS, 550 (36.7%) were true benign nodules whereas, the true malignant cases were 50 (3.3%) yet, if C5 & C6 were considered as malignant, the positive cases will be raised to 150 (10%). This finding goes with agreement with reports of both C 5 and C 6 were considered cytological positive cases (both need surgical excision) and according to the American Thyroid Association guidelines [30,38] reported that C5 is not highly reliable for the diagnosis of malignancy, and excluding this category from counting the malignant diagnostic cases. In addition to the above, in this study the ROM through Bethesda categories was 15% (C2), 40% (C3), 50% (C4), 85 (C5) and 98% (C6). These were in concordance with many previous publications [13,14,30,39,40].

In this study the majority of patients were females (44%) as well as in their third decade of life. These findings are in agreement with a study by Dorairajan and Jayashree [41]. Solitary thyroid nodules were 4–9 times more common in females as compared to males [42]. In regard to gender, this study showed that solitary thyroid nodules were commonest in females than males. Majority of these cases were underwent surgical management and subjected for histopathological study and correlate with other worldwide publications (Tables 2 & 4).

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