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Original Research Article

Thyroid Lesions Classification Using Bethesda System with Histopathological Correlation and Calculating Each Category Malignancy Risk.

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Abstract

Introduction: Fine-needle aspiration is well established and the best test in the primary diagnosis of disorders of Thyroid with a high accuracy. A uniform reporting system for thyroid FNA will facilitate effective communication among all health professionals. *Aims and Objectives*: The aim of the study is to provide consistent diagnostic terminology by using new reporting system – Bethesda system. Cytopathology to histopathology correlation help us to calculate the malignancy risk rates of the different BSRTC categories at each individual institution. *Material and Methods*: The evaluation begins with demographic factors, physical examination, appropriate investigations, cytological, histopathological correlation and calculating malignancy risk for each category. 1,057 patients of all ages and sexes with clinical diagnosis of goitre in teritiary health care centre were studied. *Results:* Out of 1,057 patients, 931 were female and 126 were male patients. Fnac was done in all 1,057 cases and classified the lesions on FNAC using standard system of Bethesda. Out of 1,057 cases, 35 cases were diagnosed as Non Diagnostic/Unsatisfactory, 906 cases as Benign, 57 case as Atypia of undetermined significance/atypical follicular lesion of undetermined significance, 29 as follicular neoplasm/suspicious of follicular neoplasm/ Hurthle cell neoplasm/suspicious of Hurthle cell neoplasm, 11 as suspicious of malignancy and 19 as Malignancy. Out of 1,057 patients, 130 were undergone different modalities of surgical treatment. On histpathology examination out of 130 cases, 43 were Multinodular goitre, 06 were colloid goitre/Colloid cyst, 09 were Hashimotos thyroiditis, 21 were Adenomatoid Goitre, 21 were Follicular Adenoma, 1 was hurthle cell adenoma, 3 were Follicular Carcinoma, 2 were Hurthle cell neoplasm, 17 were Papillary Carcinoma, 3 were Follicular variant of Papillary carcinoma and 4 were Micropapillary carcinoma. *Conclusion:* Standard reporting system will help to reduce different diagnostic schema used by different institutions.

Keywords: Bethesda System; Cytology; Goitre; Histopathology; Malignancy Risk.

Introduction

Fine-needle aspiration (FNA) of the thyroid gland is an important and widely accepted, cost-effective, simple, safe, and accurate method for triaging patients with thyroid nodules [1-11]. FNAC gives an idea for the management of patients with thyroid nodules. It is the first line diagnostic test for evaluation of goitre and single most effective test for the preoperative diagnosis of solitary thyroid nodule [12-15]. Fine-needle

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aspiration is well established and the best test in the primary diagnosis of disorders of Thyroid with an accuracy approaching 95% [16]. The main goal of thyroid FNA is to distinguish nodules that require surgical treatment from those which need a follow-up, consequently reducing the rate of unnecessary thyroid surgeries. At the same time it increases the percentage of resection of malignant thyroid nodules [17-24]. Historically, terminology for thyroid FNA has varied significantly from one institute to another, creating confusion. To address the terminology and other issues related to Thyroid FNA, the national cancer institute (NCI) hosted the NCI thyroid FNA state of science conference at Bethesda, Maryland. There the participants acknowledged the importance of developing a uniform terminology for reporting thyroid FNA results [25]. The conclusions of the above mentioned conference led to the Bethesda thyroid atlas and form the frame work for nomenclature for the interpretation of thyroid FNAs, known as The Bethesda System for Reporting Thyroid Cytopathology. It describes 6 diagnostic categories of thyroid lesions: Nondiagnostic or Unsatisfactory, Benign, Atypia of undetermined significance/Follicular lesion of undetermined significance, Follicular neoplasm/"Suspicious" for follicular neoplasm, Suspicious for malignancy, and Malignant. It also describes implied risk of malignancy and clinical management for each category [20]. A 6-tier reporting system for thyroid FNA is effective for determining which patients needed surgery versus follow-up FNA and also guided the clinician on the extent of surgery. This Bethesda system of reporting similar to that of cervical cytology represents a major step forward for standardization of thyroid FNA reporting [26].

Materials and Methods

The present study was conducted in a teritiary health care centre for a period of 2 years. 1,057 patients of all ages and sexes with clinical diagnosis of goitre came to teritiary health care centre were considered as sample size.

The patients of both the sexes and all age groups presenting with thyroid swelling clinically were included in the study. Patients unwilling or apprehensive about being in the study were excluded.

Demographic data like age, gender, address and occupation were recorded in predesigned and pretested proforma. At OPD detailed history was collected in every patient with attention to the symptoms of thyroid swelling in relation to duration of swelling and any recent increase in size or associated with pain, pressure symptoms and symptoms of primary or secondary thyrotoxicosis or hypothyroidism.

All base line investigations as per the predesigned and pretest proforma like Hb%, total and differential counts, blood urea, serum creatinine, serum electrolytes, were done at admission.

Special investigations like Thyroid profile, FNAC, X-ray neck, ultrasound of the thyroid swelling, Indirect laryngoscopy, ECG, Echocardiography were done preoperatively. Finally histopathology was done for admitted patients.

Results

The present study was conducted in a teritiary health care centre on 1,057clinically thyroid swelling patients. Of the 1,057 patients, 931 were female and 126 were male patients (Table 1). A total number of 1,057 thyroid FNACs were performed and were classified into six categories and malignancy risk was calculated for each category according to Bethesda system of reporting. Out of 1,057 cases, 35 cases were diagnosed as Non Diagnostic/ Unsatisfactory, 906 cases as Benign, 57 case as Atypia of undetermined significance/atypical follicular lesion of undetermined significance, 29 as follicular neoplasm/suspicious of follicular neoplasm/ Hurthle cell neoplasm/suspicious of Hurthle cell neoplasm, 11 as suspicious of malignancy and 19 as Malignancy (Table 2). Out of 1,057 patients, 130 were undergone different modalities of surgical treatment. On histpathology examination out of 130 cases, 43 were Multinodular goitre, 06 were colloid goitre/Colloid cyst, 09 were Hashimotos thyroiditis, 21 were Adenomatoid Goitre, 21 were Follicular Adenoma, 1was hurthle cell adenoma, 3 were Follicular Carcinoma, 2 were Hurthle cell neoplasm, 17 were Papillary Carcinoma, 3 were Follicular variant of Papillary carcinoma and 4 were Micropapillary carcinoma (Table 3). Correlation of cytology and Histopathology was possible in 130 cases (Table 4). Malignancy risk was calculated for each category (Table 5).

Table 1: Incidence of Thyroid lesions according to sex

Sex	Total no. of cases	ND/US	Benign	AFLUS/AUS	SFN/F or SHN/HN	SM	M
F	931	29(2.94)	854(86.6)	7(0.71)	25(2.54)	8(0.81)	8(0.81)
M	126	6(7.41)	52(64.2)	50(61.7)	4(4.94)	3(3.70)	11(13.6)

Table 2: Classification of the lesions on FNAC using standard system of Bethesda

Category	No. of cases	Percentage (%)
ND/US	35	3.31
Benign	906	85.71
AUS/AFLUS	57	5.39
SFN/FN or SHN/HN	29	2.74
Suspicious for malignancy	11	1.04
Malignancy	19	1.80
Total	1,057	100

Table 3: Distribution of histopathological reports

Histopathological diagnosis	No. of cases
MNG	43
CG/CC	6
HT	9
AG	21
FA	21
HA	1
FC	3
HN	2
PC	17
FVPC	3
MICRO PC	4
TOTAL	130

Calculating Malignancy Risk for Each Category:

We categorised all the 1,057 Thyroid cases into 6 categories and calculated malignancy risk for each category.

For calculating malignancy risk, papillary microcarcinomas (<1cm) on resection are excluded, except when prior cytologic interpretation was a 'suspicious of malignancy' or malignant. In calculating the malignancy follow up rate for benign category, the total number of original FNA diagnoses is used as the denominator, as similarly performed in other studies. For remaining diagnostic categories, malignancy follow- up rates is calculated by using the number of cases with follow-up histology results.

Of the 1,057 FNA samples, 35 are Nondiagnostic. There are 11 follow-up FNAs for these cases. On repeat aspiration, the distribution of diagnoses is as follows: 8 benign (72.7%), 2 AUS (18.2%) and 1 Malignant (9.09%). Among these 35 cases, 8 had subsequent surgical resection yielding the following diagnosis: Nodular goitre (3), Adenomatoid goitre (1), Hashimotos thyroiditis (1), colloid cyst (1), Follicular Adenoma (1), papillary carcinoma (1). Overall a single case is diagnosed as malignant yielding a malignancy risk of (12.5%).

Table 5: Malignancy risk of various categories

Diagnostic Category	Malignancy Rate, % (No. of cases)
Nondiagnostic (8)	12.5(1)
Benign(906)	0.9(8)
Atypical follicular lesion of undetermined significance(29)	6.9(2)
Suspicious for follicular lesion(18)	27.8(5)
Suspicious for malignancy(2)	50(1)
Malignant(8)	100(8)

Of the total FNA samples, 906 are categorized as benign. There are 9 follow-up FNAs for these cases. On repeat aspiration, the distribution of diagnoses is as follows: 3 SFN/FN (33.3%), 1 SPC (11.1%), 1 PC (11.1), 1SHN (11.1), 3 AUS (33.3%). Follow-up histopathology is available for 65 cases, yielding the following diagnoses: Follicular adenoma (5), Adenomatoid goitre (8), MNG (26), CG/CC (5), Follicular carcinoma (1), FVPC (1), Papillary carcinoma (5), Hashimotos thyroiditis (8), Hurthle cell Adenoma (1), Hurthle cell neoplasm (1), micro papillary carcinomas (4). These micropapillary carcinomas are excluded because none among them was diagnosed in FNAC as Suspicious of malignancy or malignant. Overall 8 malignant diagnoses are made on resection yielding a malignancy risk of (0.9%).

We categorised 57 cases as AFLUS. In 24 cases, there is repeat FNA, and the following diagnoses are found: 3 remained as AUS (12.5%), 13 as nodular goitre (54.2%), 6 as SFN/FN (25%), 1 as Adenomatoid nodule (4.2%), 1as Papillary carcinoma (4.2%). Follow-up histology is available for 29 cases, yielding the following diagnoses: Nodular goitre (12), Follicular Adenoma (8), Adenomatoid goitre (7), Papillary carcinoma (1) and FVPC (1). Overall 2 malignant diagnoses are made on resection yielding a malignancy risk of (6.9%).

Table 4: Correlation of cytology with histopathology

Cytology diagnosis	No. of cases	MNG	CG/CC	HT	AG	FA	HA	FC	HN	PC	Micro PC	FVPC
UN/ND	8	3	1	1	1	1				1		
Benign	65	26	5	8	8	5	1	1	1	5	4	1
AUS	29	12			7	8				1		1
SFN/FN	16				5	7		2		1		1
SHN/HN	2	1							1			
SM	2	1								1		
Malignant	8									8		

We categorised 29 cases as SFN/FN. Follow-up histology is available for 18 cases, yielding the following diagnoses: Follicular adenoma (7), Adenomatoid goitre (5), MNG (1), Follicular carcinoma (2), FVPC (1), Papillary carcinoma (1), Hurthle cell neoplasm (1). Overall 5 malignant diagnoses are made on resection yielding a malignancy risk of (27.8%).

We categorised 11 cases as suspicious of malignancy (suspicious of papillary carcinoma). Follow-up histology is available for 2 cases only, yielding the following diagnoses: MNG (1), papillary carcinoma (1). Overall 1 malignant diagnosis is made on resection yielding a malignancy risk of (50%).

We categorised 19 cases as malignant. Among them 17 are papillary carcinoma, 1 is Anaplastic carcinoma, 1 is Medullary carcinoma. Follow-up histology is available for 8 papillary carcinoma cases, yielding the following diagnoses: papillary carcinoma (8). Overall 8 malignant diagnoses are made on resection yielding a malignancy risk of (100 %).

Discussion

By using "The Bethesda system for reporting Thyroid Cytopathology" criterion, we divided the 1,057 thyroid cases into 6 categories and the results are compared with the other studies as shown in the Table 6

According to the Bethesda System, a non-diagnostic/unsatisfactory thyroid FNA aspirate is a sparsely cellular smear, where there are less than 6 groups of thyroid follicular cells, each composed of 10 or more cells. 3.4% of the present study cases are classified as ND taking the above criteria into consideration and the value is correlated with other studies as shown in the Table 6.

Table 6: Comparison of percentages of Distribution of Fine-Needle Aspiration Diagnoses – various studies [1]

Diagnostic category	Present study	Vickie. Y. Jo et al	Yassa et al	Yang et al	Nayar and Ivanovic
ND/US	3.4%	18.6%	7%	10.4%	5%
Benign	85.71%	59.0%	66%	64.6%	64%
AFLUS/AUS	5.39%	3.4%	4%	3.2%	18%
SFN/FN	2.74%	9.7%	9%	11.6%	6%
SM	2.74%	2.3%	9%	2.6%	2%
Malignant	1.7%	7%	5%	7.6%	5%

These categories of cases are followed and reaspirated. 1/35 non diagnostic cases, on reaspiration is diagnosed as papillary carcinoma. This case on initial aspiration yielded cyst fluid and the smears showed only cyst macrophages (Fig. 1). Repeat aspiration is done under ultrasound guidance which showed an intracystic solid focus. The smears showed typical features of papillary carcinoma (Fig. 2) and is confirmed by histopathology. In present study, repeated nondiagnostic aspirates had a malignancy risk of (0%), which is less than the risk of single aspirate (12.5%). Similarly in the study by Andrew A Renshaw [27], mentioned that repeated nondiagnostic aspirates had a risk of malignancy of 4%, which is less than the risk of a single aspirate (8.5%). This study has shown that patients with repeat thyroid aspirates have a significantly lower risk of malignancy than do patients with a single nondiagnostic aspirate.

This study confirms the importance of reaspiration in ND cases [27,28].

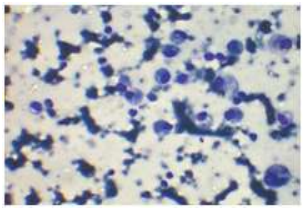

Fig. 1: Non-Diagnostic: only cyst macrophages

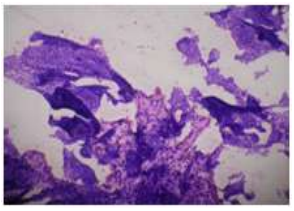

Fig. 2: Repeat FNA: Papillary structures with fibrovascular cores

Table 7: Malignancy risk in AUS diagnosed Using the Bethesda System for Reporting Thyroid Fine-Needle Aspirations [38]:

Study	Total/AUS	AUS Rate (%)	Malignancy rate (%)
Nayar and Ivanovic	5,194/924	17.8	6 in resected case
Layfield et al	6,872/664	9.7	5 in all cases; 28 in resected cases
Theoharis et al	3,037/95	3.1	12 in all cases; 48 in resected cases
Shi et al	8,150/174	2.1	35 in resected cases
Faquin and Baloch	?/509	9-12	15 without repeated FNA; 27 with repeated FNA
Renshaw	7,089/548	7.7	25 in resected cases
Jo et al	3,080/104	3.4	17 in resected cases
Somma et al	1,737/275	15.8	26 in resected cases
Marchevsky et al	879/86	9.8	12.8 in all cases; 37.9 in resected cases
vanderlaan et al	4,691/512	10.9	27 in all cases;46 in resected cases
Present study	1,057/57	5.39	3.52 in all cases; 6.9 in resected cases

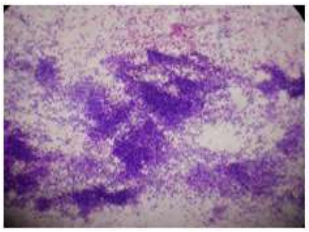

Fig. 3: Hashimotos Thyroiditis: Plenty Of lymphocytes, hurthle cells And histiocytes.

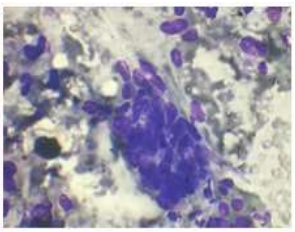

Fig. 4: AUS: Due to delayed smearing artefact, cells were arranged in overlapping clusters Showing atypia.

In the study done by Mohammad Jaragh et al. [29], Of the 76 cyst fluid only cases with subsequent thyroidectomy, 10 cases had an ipsilateral diagnosis of papillary carcinoma measuring >1.0 cm.

Majority of our lesions are Benign, which constituted 85.71% of the total cases, which is comparable with the other studies.

This benign group according to TBSRTC includes Nodular goitre, Hashimotos Thyroiditis (Fig. 3) and Graves' disease.

The commonest benign lesion in the present study is Hashimotos Thyroiditis which is comparable to other Indian studies like the study by I.V. Renuka et al. [21].

In contrast, Nodular goitre is the commonest benign lesion in the studies by Vickie Y. Jo et al. [1], Granados Garcia M et al. [15].

Some of these benign lesions are correlated with ultrasound [30] and hormonal study wherever available. 57/1,057 (5.39%) cases in the present study were included in Atypical follicular lesion of undetermined significance/atypia of undetermined significance (Fig. 4). This is a heterogeneous group [31-37] and should be followed by repeat aspiration [38-42] U/S correlation and sometimes surgical intervention as it has limited reported follow-up and outcome data. This indeterminate diagnostic category is intended to represent a low-risk category for malignancy for which a repeat FNA would be the appropriate management in most cases, which usually result in a more definitive interpretation [43]. 24/57 cases were subjected to repeat aspiration, which significantly changed the final diagnosis. Out of these, 14 cases turned out to be nodular goitre, 6 as SFN/FN, 1 as adenomatoid nodule and 1 as papillary carcinoma. Whereas 3 cases remained as AUS. These results were compared with the study by Andrew [40] and were found to be correlated with that study. Follow up histology is available for 29 cases, yielding the following diagnoses: Nodular goitre (12), Follicular Adenoma (8), Adenomatoid goitre (7), Papillary carcinoma (1) and FVPC (1).

Malignancy risk in AUS is usually ranges from 5-15%. In the present study it is 3.52% in all cases; 6.9% in resected cases and is comparable with other studies [44] as shown in the Table 7.

Table 8: Comparison of malignancy risk among various studies [1]

Diagnostic category	Present study	Vickie. Y. Jo et al.	Yassa et al	Yang et al	Nayar& Ivanovic
ND/US	12.5%	8.9%	10%	10.7%	9%
Benign	0.9%	1.1%	0.3%	0.7%	2%
AFLUS/AUS	6.9%	17%	24%	19.2%	6%
SFN/FN	27.8%	25.4%	28%	32.2%	14%
Suspicious for malignancy	50%	70%	60%	64.8%	53%
Malignant	100%	98.1%	97%	98.4%	97%

Overall, our data and those of others, support the usefulness of the AUS designation for risk stratification with a risk of malignancy intermediate between that of the benign (2.5%-3%) and suspicious for malignancy (60%-75%) categories [38].

Our findings support that classifying thyroid lesions into AFLUS category will have an important role in triaging patients with thyroid nodules, because patients with AFLUS are found to have lower risk of malignancy on surgical follow up than patients with an initial diagnosis of SFN on cytology. In present study the risk of malignancy for AFLUS/AUS and SFN/FN is 6.9% and 27.8% respectively [1].

The Bethesda System (TBS) for reporting thyroid cytopathology is the one which introduced the atypia of undetermined significance / follicular lesion of undetermined significance (AUS/AFLUS) category. In a study by Krane JF et al. [45], the authors sought to identify an appropriate measure for AUS use based on experience to date with TBS. Based on these studies, an AUS: M ratio of 1 to 3 is recommended. AUS: M ratio > 3 are likely because of over-diagnosis of AUS or under-diagnosis of M. AUS: M ratios < 1.0 are mostly due to low AUS rates, at the likely expense of sensitivity. In present study AUS: M is 3:1.

The category Follicular neoplasm/Suspicious for a Follicular neoplasm or Hurthle cell neoplasm/ Suspicious of Hurthle cell neoplasm typically showed scant colloid, a monotonous population of either follicular or Hurthle cells in a predominantly (>80%)microfollicular pattern, and cells with nuclear crowding and overlap (Fig. 5). Andrew et al. [46] gave criteria for microfollicle which is made up of < 15 cells arranged in a circle that is at least 2/3 complete and flat. This category constituted 2.7% of all thyroid FNAC in present study which is comparatively less when compared with other studies which may be due to differences in geographic distribution.

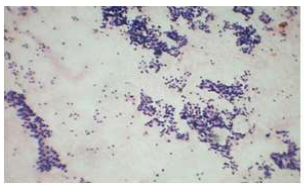

Fig. 5: SFN / FN: Plenty of repeatitive follicles with overlapping nuclei

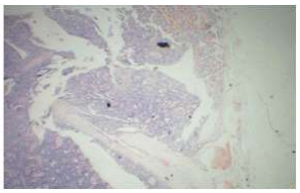

Fig. 6: Follicular carcinoma: mushroom shaped invasion into capsule

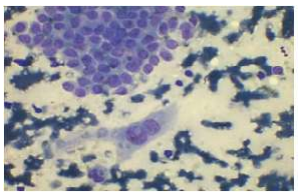

Fig. 7: Suspicious of Papillary carcinoma: Follicular cells showing intranuclear cytoplasmic inclusions

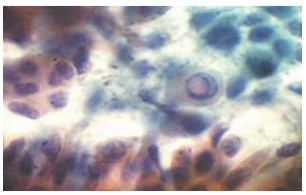

Fig. 8: Papillary carcinoma: Intranuclear cytoplasmic inclusions

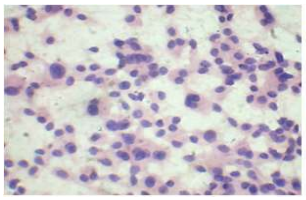

Fig. 9: Medullary carcinoma: Isolated cells, Syncytial clusters, plasmacytoid cells, bi and multinucleation.

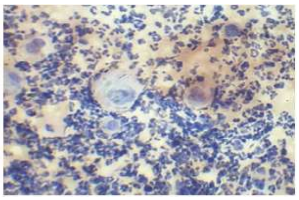

Fig. 10: Anaplastic carcinoma: Discrete large bizarre/ epithelioid cells with plenty of neutrophilic inflammatory infiltrate

Follow-up histology is available for 18 cases which includes: Follicular adenoma (7); Adenomatoid goitre (5); MNG (1); Follicular carcinoma (2) (Fig. 6); FVPC(1); Papillary carcinoma(1); Hurthle cell neoplasm(1). 2.74% of cases are grouped as suspicious for malignancy, which correlated with the other studies.

The suspicious for malignancy category demonstrated the following features: cells with grooves and/or intranuclear cytoplasm inclusions (Fig. 7), nuclear elongation, and chromatin clearing. These changes are worrisome but not diagnostic of papillary carcinoma.

In the suspicious category, Grant et al. [13] defined suspicious as suggestive but nonconclusive for malignancy but containing significant nuclear atypia.

2 out of 11cases diagnosed as suspicious of malignancy are subjected to surgical resection. Of which one case is diagnosed as MNG and another as PC. The reasons for over diagnoses [47] of suspicious cases include pseudopapillae, syncytial sheets and nuclear grooves. The primary reasons for under diagnoses [47] of PTC as suspicious include cystic aspirates with minor features of PTC. 1 case in present study showed cells with abundant cytoplasm resembling Hurthle cells and occasional intranuclear inclusions [47].

In the present study, 19 malignant cases are diagnosed. They are (17) Papillary carcinoma (Fig. 8); (1) Anaplastic carcinoma (Fig 10); and (1) medullary carcinoma (Fig. 9).

In the benign category, 8 cases showed discrepancy with histopathology due to sampling error, lack of clinical information and imaging studies. 1 more case reported as SM showed discrepancy with histopathology due to misinterpretation and sampling error.

Multiple passes to cover all areas, U/S guided aspiration and thorough clinical examination may reduce the sampling errors [48].

Distinguishing hyperplastic nodules from Follicular neoplasm is difficult because they have similar cytomorphological features [48].

We found that classification of thyroid lesions according to proposed standardized nomenclature yields similar results for risk of malignancy reported by others using the proposed Bethesda or comparable systems (Table 8).

Conclusion

1. The results of the present study are comparable to most of the others.
2. Standard reporting system will help to reduce different diagnostic schema used by different institutions.
3. Patients with AFLUS are found to have lower risk of malignancy on surgical follow up when compared to patients with initial diagnosis of SFN on cytology.
4. Most of the AFLUS may turn out to be benign on repeat FNAC. Repeat FNA is the initial recommended management. This will reduce unnecessary surgeries.
5. FNAC is a supplementary but not a substitute for Histopathological examination.
6. Applying a standard terminology reporting system for thyroid FNA may enhance the communication between pathologists and clinicians and assists them to find out the rate of malignancy in each cytologic group, and facilitating a more consistent approach for patients management.
7. Rigorous cytopathology to histopathology correlation is needed to accurately reflect the malignancy rates of the different BSRTC categories at each individual institution.

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