Research Article

Cyto-histological correlation of thyroid lesions– experience at a tertiary care hospital

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Abstract

Introduction: Fine needle aspiration cytology (FNAC) is the commonly used test for thyroid nodules. FNAC is a cost effective procedure. Based on the cytology findings patients can be managed conservatively or subjected to surgery. **Objectives:** The aim of our study was to find the diagnostic accuracy of FNAC in thyroid lesions, compare it with histopathology and analyze the causes for discordance. **Materials and Methods:** A retrospective hospital- based study was conducted in our Department of Pathology. Data were collected from the records of FNAC and histopathology of thyroid lesions from January 2010 to June 2013. **Results:** FNAC was done on 1137 patients. Among them, 70 aspirates (6.16%) were sub optimal for definitive opinion. The thyroid lesions were categorized based on Bethesda system. The most common thyroid lesions were under Bethesda category II with 928 cases (81.6%).There were 14 cases (1.2%) in Bethesda III, 40 cases (3.5%) in Bethesda IV, 45 cases (5%) in Bethesda V and 40 cases (3.5%) in Bethesda VI category. The Bethesda category II lesions included nodular colloid goiter/ colloid nodule (38.79%), adenomatous nodule (15.39%), thyroiditis (21.81%), cystic lesion of thyroid (2.37%), and benign thyroid lesions (2.46%) The malignant lesions (3.5%) included papillary thyroid carcinoma and anaplastic carcinoma. Histopathology was available for 103 (9%) cases. Among them 72 benign lesions, 59 cases correlated with the excision biopsy findings. In 10 malignant lesions 8 correlated and in the 3 suspicious cases 2 of them were found to be malignant. The cytological discrepancy was noted in 16 cases (18.8%..%) and the false positive was in 3cases (3.5%) whereas the false negative was 13 (15.3%) The discordant cases were reviewed and the discrepancies in diagnosis were grouped under three categories as sampling error (47%), interpretation (40%) error and nature of lesion (13%). **Conclusions:** FNAC is a highly reliable method for the diagnosis of thyroid lesions. The discrepancies can be overcome by extensive sampling and strict adherence to the minimum set of criteria for diagnosis.

Keywords: Cytology-histology correlation, fine needle aspiration, thyroid, sampling error, interpretation error, nature of lesion.

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INTRODUCTION

Thyroid nodules are one of the common complaints of patients in the outpatient department. Being superficial in location it's amenable for direct physical examination, cytological evaluation and histopathological study. Among the various diagnostic tests like ultrasound, thyroid nuclear scan and fine needle aspiration cytology(FNAC) available, FNAC of the thyroid proves to be the most economical and gold standard screening procedure to identify cases that need surgical excision and those that can be managed conservatively. The key for the success of thyroid FNAC consists of size of the lesion, adequate and representative sample and the expertise in thyroid cytology interpretation..

MATERIALS AND METHOD

This retrospective study was conducted in the Department of Pathology at Sri Ramachandra Medical College and Research Institute, Chennai, a tertiary care institute. A total of 1137 patients with thyroid swelling were

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aspirated during a period of three and a half years from January 2010 to June 2013.FNAC was performed using 22 gauge needle. Air dried slides were stained with May Greunwald Giemsa stain and HandE was performed on absolute alcohol fixed slides. A concise clinical history, physical examination and details of relevant investigations were available. Surgical follow up was available for 103(9%) aspirations. The concordance between cytological and histological diagnoses was determined. Cases with cytohistological discrepancies were reviewed and the reasons for the same were analyzed.

RESULTS

A total of 1137 patients identified with thyroid swelling underwent fine needle aspiration. Among all the aspirates, 70 of them was sub optimal for evaluation. The criterion for adequacy was set as a minimum of 6 clusters of benign cells seen in at least 2 slides prepared from 2 needle passes[1]. The inadequate smears constituted 6.2 %.(Figure: 1).Surgical excision was done in 104 patients and thus histopathological follow up was available for 9% of the total aspirates. (Figure: 2)

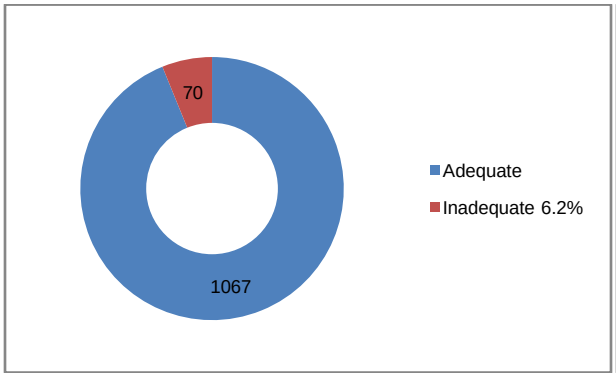

Figure 1: Efficacy of Adequacy Checking

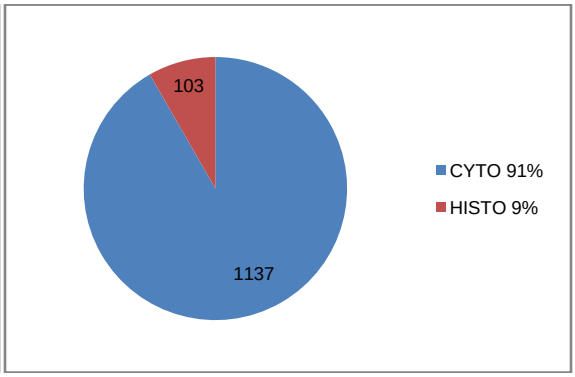

Figure 2: FNAC (Cyto) and Excision (Histo)

The thyroid lesions were categorized based on Bethesda system(Table:1).The most common thyroid lesions were under Bethesda II category with 928 cases(81.6%). There were 14 cases(1.2%) in Bethesda III, 40 cases (3.5%) in Bethesda IV, 45 cases(5%) in Bethesda V and 40 cases(3.5%) in Bethesda VI category. The Bethesda category II lesions included nodular colloid goiter/ colloid nodule (38.79%), adenomatous nodule (15.39%), thyroiditis (21.81%), cystic lesion of thyroid (2.37%), and benign thyroid lesions (2.46%)The malignant lesions (3.5%) included papillary thyroid carcinoma and anaplastic carcinoma. (Figure: 4). Surgical excision was done for 72 cases and histopathologic correlation was performed. 59cases (79.2%) were in concordance with aspirate findings. However 13cases (20.8%) did not.

Table 1: The Bethesda System for Reporting Thyroid Cytopathology recommended diagnostic categories[2]

- **I. Nondiagnostic or Unsatisfactory**
  - Cyst fluid only
  - Virtually acellular specimen
  - Other (obscuring blood, clotting artifact, etc.)
- **II. Benign**
  - 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
- **III. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance**
- **IV. Follicular Neoplasm or Suspicious for a Follicular Neoplasm**
  specify if Hürthle cell (oncocytic) 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

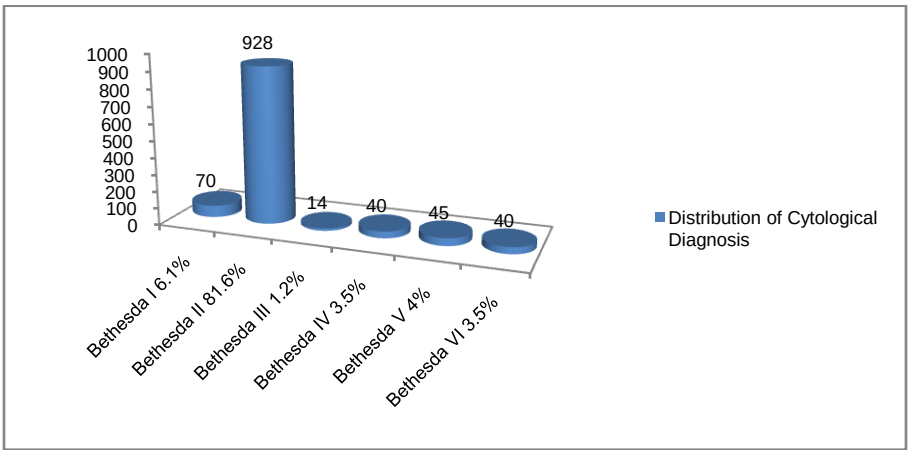

Figure 3: Distribution of Cytological Diagnosis

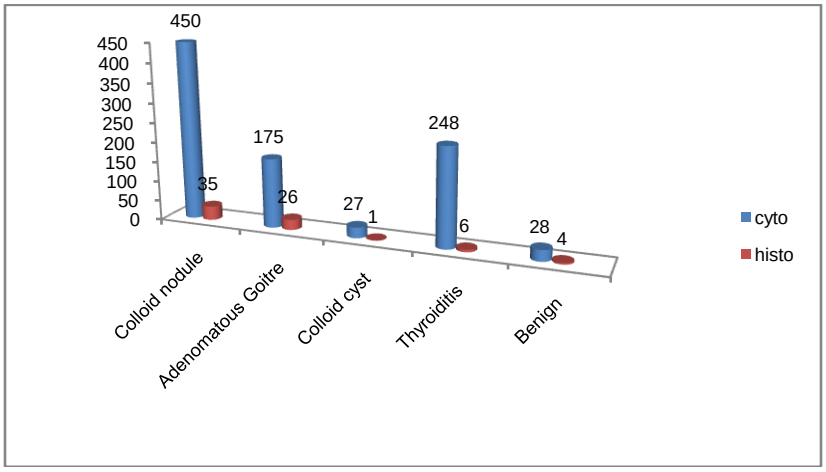

Figure 4: Benign Cases

Under Bethesda category III, there were 14 cases and in Bethesda category IV were 40 cases. Histopathologic correlation was available for 7 cases of category III and 11 of category IV. In the 7 cases, there were 3 nodular colloid goiter, 2 adenomatoid nodule, 1 micropapillary carcinoma and 1 follicular adenoma. The category IV lesions (follicular neoplasms) in FNAC were found to be histologically the following 2 follicular adenoma,1 follicular carcinoma,1 hurthle cell carcinoma , 5 papillary thyroid carcinoma with 2 classical and 3 follicular variant and 2 adenomatous goiter.. (Figure: 5)

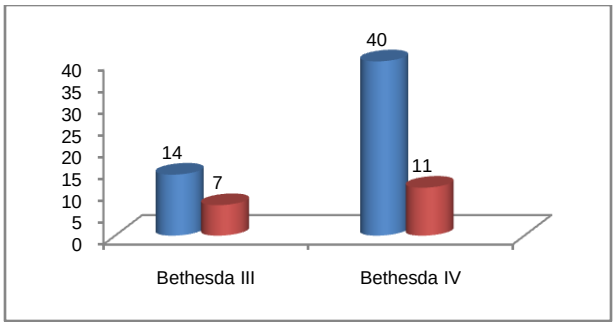

Figure 5: Cases under Bethesda III and IV

There were 45 suspicious cases in Category V and 40 malignant cases in Category VI. The malignant cases included 39 Papillary thyroid carcinoma and one Anaplastic thyroid carcinoma. Biopsy correlation was available for 3 of the suspicious cases and 10 of the malignant cases. (Figure:6) 77% correlated with cytology findings. The non-correlation was 23%.

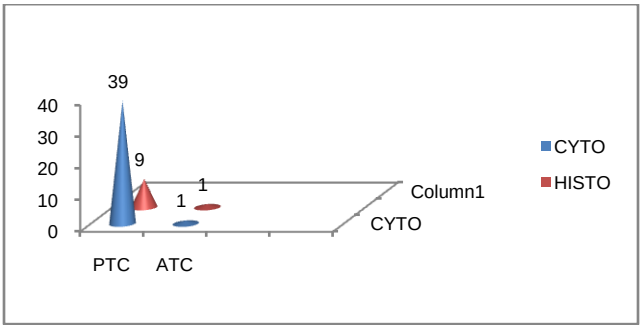

Figure 6: Cases under Bethesda VI -Malignant

The Bethesda Category III includes lesions with atypia of undetermined significance or follicular lesions of undetermined significance. A definitive opinion is not inferred. Similarly Category IV includes follicular neoplasm which may be follicular adenoma, follicular carcinoma and follicular variant of papillary thyroid carcinoma. Follicular adenoma and carcinoma cannot be differentiated cytologically, since the differentiating feature being capsular and vascular invasion can be appreciated only in excised specimens. Hurthle cell adenomas and carcinomas too have similar criteria. Hence we grouped these two categories as indeterminate lesions and were excluded in the statistical analysis. Statistical Analysis of our data gives the sensitivity, specificity, positive predictive value, negative predictive value for benign and malignant cases as 95%, 43%, 81%,77% and 44%, 95%,77%, 82% respectively.(Table :2)

Table 2:

sensitivity	specificity	PPV	NPV
Benign	95.1%	43.5%	81.9%
Malignant	43.5%	95.1%	77%

The false positive and false negative cases (Table: 3and4) were analyzed to find the cause of non-correlation. The causes for non-concordance in diagnosis are grouped under the following: Sampling error, Interpretation error and Nature of lesion**.** (**Table 5:** Figure 7:)

Table 3: False positive cases

Sr. No.	Cyto No	CytoDx	Histo No.	HistoDx
1	C220/10	PTC	S 504/10	Adenomatous goiter
2	C 259/10	PTC	S 635/10	FA
3	C 589/10	PTC	S 1364/12	Nodular colloid Goiter

PTC- Papillary Thyroid Carcinoma, FA- Folliculae adenoma

Table 4: False negative cases

Sr. No.	Cyto No.	CytoDx	Histo No.	Histo DX
1	C 765/10	CN	S 1656/10	PTC
2	C 770/10	AG	S 1588/10	PTC-Follicular
3	C 763/10	AG	S 1834/10	PTC
4	C 938/10	CN	S 1874/10	PTC-Micro
5	C 965/10	CN	S 2028/10	PTC
6	C 1984/10	Cystic lesion	S 4094/10	PTC
7	C 1047/10	AG	S 2182/10	FTC—Hurthle
8	C 1447/10	AG	S 2951/10	PTC
9	C 484/12	AG	S 1108/12	PTC
10	C 949/12	AG	S 2119/12	PTC
11	C 916/12	CN	S 2113/12	FTC-Hurthle
12	C 805/13	AG	S 2011/13	PTC
13	C 1012/13	Benign	S 2651/13	PTC-Micro

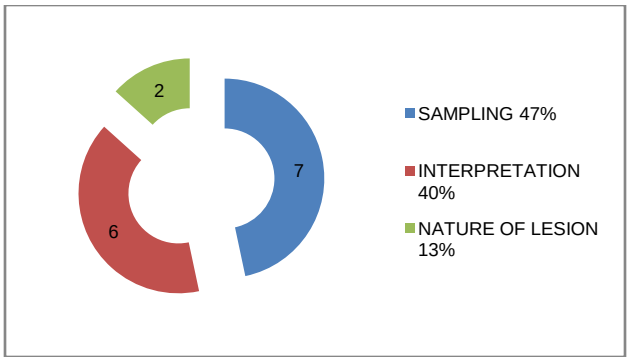

Figure 7: Errors

AG- Adenomatous Goiter, CN-Colloid nodule, FN-Follicular neoplasm, FL-Follicular lesion Sampling error**.** The inadequate smears constituting 6.2% is comparable with those in other series which range from 0 to 25 %[6,7] Among the 16discrepant cases, 7cases (47%)were found to be sampling error. Thyroid nodules that are highly vascular, small lesions, lesions with large areas of cystic degeneration and necrosis may not yield representative aspirate. In such cases, repeat aspirates with ultrasound guidance may help.

Interpretation Error

6 out of 16 (40%) cases fall under interpretation error. Among which three of them diagnosed as papillary thyroid carcinoma two of them turned out to be adenomatoid nodule and the other a follicular adenoma. The 3 cases diagnosed as adenomatoid nodule were found to be papillary thyroid carcinoma

Nature of Lesion

3 cases come under this category and 2 showed micro PTC in the surgical specimen and the one reported as cystic lesion in FNAC was found to be PTC with cystic changes. Micro PTC being a subcentimetric lesion can easily be missed on FNAC. The 3.5% incidence of false positivityand 15.3% of false negativity is comparable with that reported by previous studies.[5,6]

Table 5

Sr. No	Errors	False Positive	False Negative
1	Sampling Error	-	7
2	Interpretation Error	3	3
3	Nature of Lesion	-	3

DISCUSSION

FNAC being minimally invasive, cost effective, having high sensitivity and specificity has been applied routinely as a useful and indispensable method to diagnose thyroid lesions. There is some` grey zone' of thyroid cytology where the diagnostic efficacy of FNAC declines sharply, rendering it difficult to exactly categorize the nature of the lesion leading to discrepant cases. The reported pitfalls in FNAC thyroid are those related to size and nature of the lesion, specimen adequacy, sampling techniques, the skill of the aspirator, the experience of the cytopathologists interpreting the aspirate and the overlapping cytological features between benign and malignant follicular neoplasms. The sensitivity, specificity, positive predictive value, negative predictive value for benign and malignant cases are95%, 43%, 81%,77% and 44%, 95%,77%, 82% respectively.(Table:2) This is comparable to the sensitivity and specificity of thyroid FNACs in other studies ranging from 43 to 99% and 72 to 100% respectively in other studies[1,3-5,7-14] Adhering to the criterion of presence of minimum 6 groups of benign cells in at least 2 slides from 2 needle passes, slides are termed diagnostic or satisfactory for interpretation.[1]The method of adequacy checking i.e. staining the slides immediately after aspiration while the patient is waiting, to see if sufficient material is there in the slide, helps to obtain a better diagnostic sample. If the sample is inadequate, a repeat aspirate can be done immediately. Sampling error is one of the common causes of false negative results. In our study, 47% of non-correlation was due to sampling error. Since most benign nodules of thyroid don't undergo surgical excision, the exact incidence of false negativity is difficult to assess. The size of the lesion a plays a role; needle can easily miss a lesion less than 1 cm. Similarly, it's difficult to increase the number of passes to get the most representative sample in larger lesions. This paves way for misdiagnosis. The coexistence of more than one lesion in thyroid is a frequent occasion. Adenomatous goiter, Hashimoto Thyroiditis, PTC coexisting with each other is not uncommon. In such conditions missing of one lesion in FNAC is a possibility. Microscopic misinterpretation constituted to 40% of misdiagnosis in our study. There is considerable overlap of cytological features between adenomatous goiter and a follicular neoplasm. Cytological atypia doesn't account for neoplasm in thyroid. The commonly termed endocrine atypia is frequently seen among patients on anti-thyroid medications. Though high cellular yield suggest a neoplastic process, the presence of monolayered sheets of

thyroid follicular cells with abundant colloid and hemosiderin laden macrophages, are in favor of adenomatous goiter (Figure 11:). In follicular neoplasms generally there are more cells, arranged in repetitive acinar pattern or syncytial groups with nuclear overlapping and scant colloid.[1,8] (Figure 12)

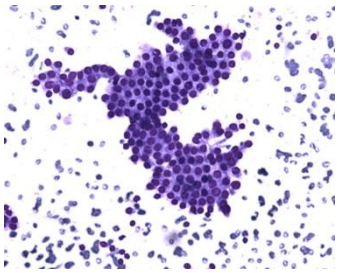

Figure 11: Monolayered sheets of thyroid follicular epithelial cells in an adenomatous goiter. x200, MGG

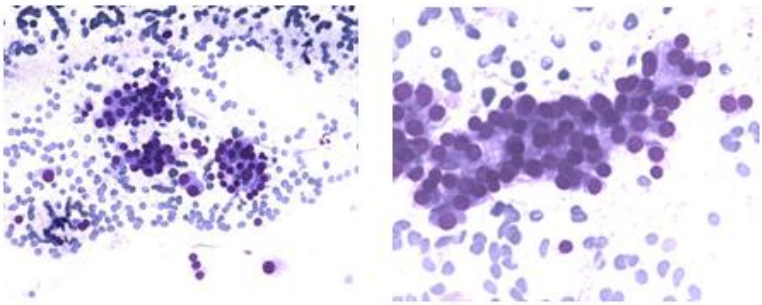

Figure 12: Microacinar pattern of thyroid follicular cells with mild atypia in Follicular neoplasm.x200, MGG

Errors due to nature of lesion constituted 13 % in our study. Micropapillary thyroid carcinoma being a subcentimetric can be an incidental finding, coexisting with another lesion. Papillary thyroid carcinoma is known to undergo cystic degenerative changes. Hence if only the cystic fluid is aspirated, representive sample of PTC can be missed. Follicular adenoma and carcinoma cannot be differentiated cytologically, since the differentiating feature being capsular and vascular invasion can be appreciated only in excised specimens. Hurthle cell adenomas and carcinomas too have similar criteria. The most common malignant tumor of the thyroid is Papillary thyroid carcinoma (PTC). The classical cytological features include high cellularity with papillary clusters with anatomic bordering, nuclear enlargement and overlapping, powdery chromatin, nuclear grooving, cytoplasmic intrusions, multinucleated giant cells, scant gummy colloid and psammoma bodies. Of all, the most important features include papillary clusters, nuclear enlargement with powdery chromatin, nuclear grooving and intranuclear cytoplasmic intrusions.[1,8] (Figure:13).However none of the criteria in isolation or in low frequency is diagnostic. Misdiagnosis happens when cellular criteria is present in few clusters without papillary formations. Similarly air drying artefacts may lead to enlargement and hypochromasia, with chromatin change in some assuming a circumferential shape with sharp borders mimicking intranuclear intrusions. In hemorrhagic aspirates, the peripheral blood hinders fixation resulting in pseudoclearing of follicular cells. Nuclear grooving can be found in other lesions of thyroid also. In PTC longitudinal grooves must be present in a minimum of 20% of cells examined.[1] Cystic change can occur in PTC leading to aspiration of cystic fluid lacking diagnostic cellular material.

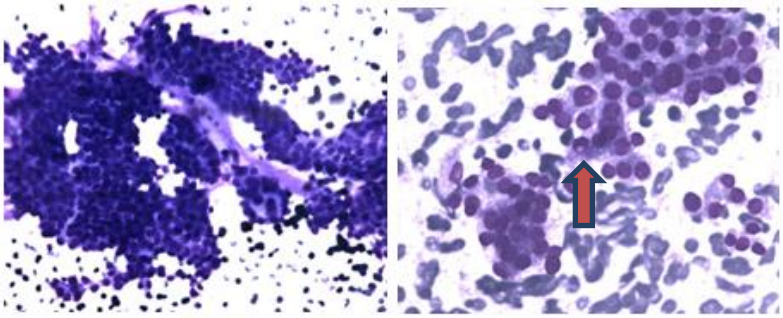

Figure 13: Follicular epithelial cells in papillary architecture with nuclear overlapping. Nuclear intrusion is shown by arrow. 200XMGG.

We categorized Bethesda III and IV as indeterminate group since a definitive opinion of benign or malignant is not given. The reporting of these categories are highly subjective. In our institute, 71% of category III turned out to be non- neoplastic, whereas 82% of category IV was neoplastic. The overlapping features of adenomatoid goiter with follicular neoplasms are the main source of concern. As said previously cytological atypia doesn't account for neoplasm in thyroid. The commonly termed endocrine atypia is frequently seen among patients on anti-thyroid medication. The presence of monolayered sheets of thyroid follicular cells with abundant colloid and hemosiderin laden macrophages, are more in favor of adenomatous goiter. In follicular neoplasms generally there are more cells, arranged in repetitive acinar pattern or syncytial groups with nuclear overlapping and scant colloid.[1,8] . By following the criterias strictly, the reporting of category III can be minimized, thus avoiding unnecessary surgery. However when cytologically a definitive opinion cannot be arrived, then a clinical and radiological correlation is very essential.

CONCLUSIONS

Inadequate and indeterminate FNAC in addition to false positive and false negative diagnosis are the major limitations of thyroid FNAC. Our recommendations to avoid these discrepancies are:

1. Nature of lesion- Ultrasound guided aspirations easily locates the lesion when they are subcentimeter in size. Also solid component in a cystic lesion also need US guided FNAC.
2. Sampling errors- Adequacy checking immediately after procedure limits the incidence of sub optimal aspirates. Also repeat multiple aspirates may be attempted when representative sample is not obtained.
3. Interpretation errors: Meticulous screening of all slides with strict adherence to the criteria for diagnosis helps in correct interpretation.

The discrepancies can be overcome by extensive sampling with multiple passes or under ultrasound guidance when needed and strict adherence to the minimum set of criteria for diagnosis. Clinical, radiological and pathological correlation is very essential to reduce false positive and false negative result. In cases of benign thyroid lesions diagnosed by FNAC, excision is requested if the lesion recurs, persists or enlarges in size.

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