

Original Research Article

## **Thyroid Cytology- Diversity of the Category “atypia of undetermined significance/ follicular lesion of undetermined significance”**

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**Abstract:** Fine needle aspiration cytology (FNAC) is a well-established diagnostic technique for the preoperative evaluation of thyroid nodules allowing a significant reduction in the number of surgical operations. Over the past few decades, FNAC has developed as the most accurate and cost effective initial method for guiding the clinical management of patients with disorders of the thyroid gland. However, the Bethesda category III (atypia of undetermined significance/ follicular lesion of undetermined significance) of thyroid cytology is somewhat heterogeneous and includes different pathological entities. A retrospective study done over a period of 2 years. Study sample included 87 patients with a cytological diagnosis of “atypia of undetermined significance/ follicular lesion of undetermined significance”. Subsequent histological assessment of the study sample showed several well distinct pathological entities. The majority of cases (80.45 %) in category III were histologically proven to be non-neoplastic while 19.52% was confirmed as neoplastic. Among the neoplastic lesions 13.78 % was benign while 5.74 % was proven to be malignant. There was no significant difference in the age, sex, site and size of the lesion between the benign and malignant categories. According to the results of the present study the category III of Bethesda classification was somewhat indefinite in arriving at a precise diagnosis to plan out the surgical management. Clinical details were not reliable in separating the benign and malignant groups of category III. Hence we recommend radiological correlation of the thyroid lesion in identifying the high risk patients.

**Keywords:** Thyroid cytology, Thyroid nodule, Fine needle aspiration

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### **INTRODUCTION:**

Diseases of the thyroid gland are diagnosed with increased frequency in clinical practice. Fine needle aspiration cytology (FNAC) is a well-established diagnostic technique for the pre-operative evaluation of thyroid nodules [1]. The first step in the management of patients presenting with thyroid enlargement is the identification of those who should be referred for early surgical management. In spite of the advances in imaging studies this basic step still heavily relies on the fine needle aspiration cytology technique [2]. In the past decade a variety of reporting systems for thyroid cytology, have been proposed by different societies and organizations [3]. The rationale of these reporting systems was to improve the understanding in terms of diagnosis, between the cytopathologist and the clinician. With the aim of standardizing the diagnostic terminology of thyroid cytology, in 2007 National Cancer Institute (NCI) of United States proposed a classification based on the NCI thyroid FNAC

consensus conference. This classification “Bethesda System for Reporting Thyroid Cytology” provided well defined diagnostic criteria and gained wide publicity all over the world [4].

### **Bethesda System for Reporting Thyroid Cytology (BSRTC):**

I. Non-diagnostic 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

**III. Atypia of undetermined significance (AUS)**

Or follicular lesion of undetermined significance (FLUS)

**IV. Follicular neoplasm or suspicious for a follicular neoplasm**

Specify if Hurthle 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's lymphoma

Fine needle aspiration cytology technique is a simple, cost effective, readily repeated and quick to perform procedure in the outpatient department with an excellent patient compliance. The sensitivity of the test is well over 90%. However, the Bethesda category III is somewhat inconclusive in terms of obtaining a cytological diagnosis [5]. The aim of this study was to assess the definitive histological diagnosis of the study sample which was cytologically categorized as “atypia of undetermined significance/ follicular lesion of undetermined significance” and determine the risk of malignancy of Bethesda category III [6, 7, 8].

**OBJECTIVES:**

1. Analyse the cytological diversity of the diagnostic category “atypia of undetermined significance or follicular lesion of undetermined significance.
2. To correlate the cytological diagnosis with the subsequent histological findings.
3. To assess the risk of malignancy in Bethesda category III.
4. To identify the limitations of FNAC.
5. To provide a feedback analysis for prospective studies.

**METHODOLOGY:**

A retrospective study had done over a period of 2 years, at the Department of pathology, Faculty of Medical Sciences, University of Sri Jayewardenepura. After perusing the laboratory reports the thyroid cytology cases with a diagnosis of “atypia of undetermined significance/ follicular lesion of undetermined significance” and those which have been followed by histological assessment were selected for the study. The cytological and histological diagnoses were reviewed by the principal investigator and the results were tabulated using a coding system. Data was collected from the laboratory reports without revealing the identification details.

**RESULTS:**

The retrospective study sample consisted of 87 cases. The initial cytological diagnosis of “atypia of undetermined significance/ follicular lesion of undetermined significance were compared with the definitive histological diagnosis.

**Table-1: Study results of cases**

Histological diagnosis	Total number of cases	Percentage (%)
MNG	15	17.24
Hyperplastic nodule	31	35.63
Thyroiditis	24	27.58
Follicular adenoma	11	12.64
Hurthle cell adenoma	01	1.14
Follicular variant of papillary carcinoma	05	5.74
Follicular carcinoma	00	00

In thyroid cytology, a diagnosis of AUS/FLUS is given when cytologic findings cannot be characterized as benign due to the presence of follicular cells with atypical nuclear or architecture, which is not sufficient for categorization as malignant.

Fine needle aspiration cytology technique is a very popular first line investigation for the assessment of thyroid enlargement. However, cytologic

interpretation of FNAC smears requires the expertise of an experienced cytopathologist. According to the results of the present study, category III of Bethesda system was shown to include many different pathological entities. The majority of cases (80.45 %) in category III were histologically proven to be non-neoplastic while 19.52% was confirmed as neoplastic. Among the neoplastic lesions 13.78 % was benign while 5.74% was proven to be malignant.

The following variables, age, sex, site and the size of the lesion were extracted from the laboratory reports of the study sample. Results of the benign and malignant groups were tabled separately and compared. Statistical analysis was performed by SPSS statistics. P-Value < 0.05 was considered to indicate statistical significance and 95% confidence intervals were calculated to assess the precision of the obtained estimates. In the present study there was no significant difference in the age, sex, site and size of the lesion between the benign and malignant categories. Hence the clinical details were not reliable in predicting which lesions of Bethesda category III had a higher risk of malignancy.

#### **DISCUSSION:**

Several studies have shown that the risk of malignancy in AUS/ FLUS category is approximately 5 – 15% [9]. An accurate judgement of the risk of malignancy is important to plan out the management. Patients with cytologically indeterminate nodules are often referred for diagnostic surgery, though most of these nodules prove to be benign. This retrospective study was conducted to determine the diversity of Bethesda category III. Numerous studies have suggested that the age, sex and the size of the thyroid nodule of the patient was a significant predictor of malignancy [10, 11, 12]. In this study there was no statistically significant difference in the above variables between the benign and malignant categories of Bethesda III. There are some studies that have shown results similar to the current study [13, 14, 15]. In the absence of reliable clinical correlation to separate the suspicious lesions of Bethesda III, combining ultrasonographic findings may be appropriate in identifying the high risk lesions. Several studies have reported the usefulness of combining radiology with the category III of thyroid cytology [16, 17, 18].

#### **CONCLUSION:**

A possible result of FNAC in patients with thyroid disorders is “atypia of undetermined significance/ follicular lesion of undetermined significance”. However, atypical or follicular lesions of undetermined significance (AUS/ FLUS), cannot be classified as benign or malignant. It is of importance in separating the benign from malignancy. This study confirmed that the risk of malignancy in Bethesda category III is low (5.74%). The majority of the lesions in category III can be managed conservatively with regular follow-up. There was no statistically significant difference between the age, sex, site and size of the lesion between the benign and malignant categories of AUS/ FLUS group. Therefore the clinical parameters may not be helpful to identify the high risk lesions of Bethesda category III. Combining the Bethesda category III with radiological findings may be a better

option to decide which lesions have a higher risk of malignancy and consider early surgical intervention. The purpose of the present study was to determine the diversity of AUS/ FLUS category and assess the risk of malignancy. This data can be used as a feedback analysis for a prospective study which combines thyroid cytology with radiological findings.

#### **Limitations:**

This was a retrospective study done at a single centre, with a relatively small sample size. Sample consisted only the patients with AUS/ FLUS. This limitation might create a sampling bias.

#### **Recommendations:**

1. FNAC provides a cytological diagnosis while the definitive assessment of the lesion is achieved by histological evaluation.
2. Ultrasound guided FNAC should be recommended for non- palpable lesions, suspicious nodule in a MNG and cystic nodules with a solid component.
3. FNAC is recommended with a 23gauge needle. For repeatedly unsatisfactory/ inadequate samples radiological correlation is recommended. Surgery may be considered following the clinical assessment of the lesion.
4. Preparation of direct smears on glass slides from the aspirated material is the most cost effective method. Smears can be air dried or wet fixed in 95% alcohol.
5. May Grunwald Giemsa for air dried smears and H & E or Papanicolaou stain for wet fixed smears is recommended.
6. Liquid based cytology is a reliable method for centres with hands on experience.
7. The reported diagnostic accuracy of FNAC is higher than 90%. The on-site presence of an experienced cytopathologist may increase the rate of adequacy.
8. Reporting of smears according to Bethesda guidelines will enable to maintain uniformity in thyroid cytology.
9. Combining cytological features with radiological and clinical findings may be useful in cases with indeterminate results.
10. A recent advance in molecular pathology has identified genes related to the diagnosis of thyroid cancer and prognosis. The diagnostic utility of these markers is of particular importance in thyroid cytology.

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