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### Mini Review

## The Gray Zone in Thyroid Nodules: Atypia of Undetermined Significance/ Follicular Lesion with Unknown Significance

### Abstract

Major purpose of the management of thyroid nodules is to distinguish between malignant nodules and the benign ones. Nodules with the cytology result Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance are still a diagnostic challenge. Initial presentation of the Bethesda System was based on 7% diagnosing rate and around 5-15% malignancy rate for these nodules; however, clinical practice presents with higher rates for both variables. Recent studies showed that when these nodules are grouped by cytological features; compared with the architectural atypia group, the cytological atypia group has a significantly higher risk of malignancy. Cytological sub-classification, ultrasonographic evaluation and genetic tests in selected cases should be used in the management of these nodules.

### Introduction

Management of thyroid nodules is still one of the main topics in endocrine surgery. Nodules can be detected in the thyroid glands of around 60% of the population according to the American Thyroid Association [1]. Major purpose of the management of these nodules is to distinguish between malignant nodules and the benign ones. At this point, fine needle aspiration biopsy is the most valuable tool we currently have. Although it is massively used around the world for a significant time, there are still gray zones that put us in a difficult decision making when evaluating the results. The Bethesda System for Reporting Thyroid Cytopathology is the main source for this decision making process. According to this classification there are 6 main diagnostic categories, 4 of which have relatively less controversy going on around. These diagnostic categories are non-diagnostic, benign, suspicious for malignancy and malignant. "Do"s and "Don't"s are quite clear with these categories. However, it is not the same way with the "Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance (AUS/FLUS)" and the "Follicular Neoplasm or Suspicious for a Follicular Neoplasm" category. Here, we are discussing the AUS/FLUS category.

When evaluating a fine needle aspiration biopsy patient, category 3 – AUS/FLUS may be the most unwanted result for many clinicians. According to Bethesda statement in 2009, only around 7% of fine needle aspirations are expected to

be interpreted as AUS/FLUS by cytopathologists. However, there are multiple studies that state higher rates. A five-year multi-institutional analysis with 6,872 cases evaluated by 28 cytopathologists showed that use of FLUS category varied among pathologists from 2.5 to 28.8% and among institutions from 3.3 to 14.9% [2]. Another study from a respected center with almost 4000 patients reported the overall rate of AUS as 9.8% [3]. Another significant and also important fact that the further studies on Bethesda System point out is that the malignancy rates are higher than it was expected. It was stated on 2009 that the risk of malignancy is probably close to 5% to 15% in all AUS patients [1]. However, this rate is reported as 28.3% for FLUS and 32% for AUS patients in the above mentioned studies [3]. In a similar study of ours, we found that 35% of patients who undergone surgical resection due to AUS/FLUS were diagnosed malignant [4]. Initial presentation of the Bethesda System was based on 7% diagnosing rate and around 5-15% malignancy rate; however, clinical practice does not seem to tone with these expectations.

Standart approach to patients with AUS/FLUS is repeat fine needle biopsy [5]. Due to uncertainty of the diagnosis and heterogeneity among AUS/FLUS patients cytopathologists and clinicians focused on this issue recently to clarify the diagnoses and classify this group of patients to increase homogeneity. Sub-classification of AUS/FLUS nodules is being made based on detailed cytopathological features. A recent study grouped these patients into two groups as cytological atypia and architectural

atypia, and showed that compared to the architectural atypia group, the cytological atypia group had a 2.64-fold increase in the risk of malignancy [6]. Similarly, a prospective study with 98 patients showed that 41.5% of AUS/FLUS nodules with nuclear atypia were malignant, whereas only 15.5% of AUS/FLUS nodules with architectural atypia were so [7]. This relatively new and striking information makes one think that routine use of further sub-classification may be inevitable in the near future.

As one of the most valuable tools of thyroid imaging, ultrasound is highly relied on by clinicians. Lately, there has been increasingly more evidence on the valuable assistance of Thyroid Image Reporting and Data System (called TIRADS) in management of thyroid nodules with AUS [8]. A meta-analysis of fourteen studies showed that ultrasound has significant sensitivity and specificity rates in AUS/FLUS patients: 75% and 48%, respectively [9]. It is clear that ultrasound should support the diagnosis process.

Another suggested supportive tool in the diagnosis process of AUS/FLUS nodules are genetic tests. Genetic tests are mostly based on micro RNAs and used to predict malignancy in specific lesions. Although molecular tests are quite expensive and relatively inaccessible, AUS/FLUS nodules may be fair candidates for these tests. Recent findings promote the selective use of genetic testing of patients with AUS/FLUS nodules as a complementary method for prediction of malignancy [10,11].

In conclusion, management of thyroid nodules is mostly based on fine needle aspiration cytology findings. Bethesda category 3 – AUS/FLUS nodules are the most dreadful ones, due to their potential of malignancy that one cannot underestimate. Today, ultrasound is accepted as an important diagnostic tool to help prediction of malignancy, alongside cytopathology. Consequently, working in a team with trained and experienced cytologists and radiologists seems essential to provide decent prediction rates in AUS/FLUS nodules.

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