

RESEARCH ARTICLE

Thyroid Nodules with Atypia or Follicular Lesions of Undetermined Significance (AUS/FLUS): Analysis of Variables Associated with Outcome

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Abstract

Background: The Bethesda System for Reporting Thyroid Cytopathology is one of the main classification systems for thyroid nodules. It expects that 7% of all fine needle aspiration biopsies will be reported as atypia or follicular lesions of undetermined significance, and 5-15% of these undetermined nodules are malignant. Our study is a retrospective analysis of variables that may be associated with outcome in patients with indeterminate thyroid nodules. **Materials and Methods:** Patients who underwent thyroidectomy in our institution between 2010 and 2014 were retrieved from the institutional records database. Patient demographics and medical histories were recorded. All ultrasonography reports were examined for nodule features and biochemical blood levels, hormone levels and complete blood counts were recorded. **Results:** A total of 103 patient cytopathology reports were regarded as belonging to the undetermined category. Some 35% of patients had malignant nodules. Median preoperative red cell distribution width (RDW) level was 13.6 in the benign group, while it was 14.3 in patients with malignancy, demonstrating a significant correlation ($p=0.003$). Only calcification presence was significantly different between benign and malignant groups on ultrasonography ($p=0.034$). **Conclusions:** Ultrasonography is one of the primary tools for this matter. RDW levels may become another promising tool to predict malignancy.

Keywords: Cytology - thyroid neoplasms - thyroid nodule red blood cell distribution width

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Introduction

Thyroid nodules can be seen in almost 60% of the general population (American Thyroid Association Guidelines Taskforce on Thyroid et al., 2009; Li et al., 2014). Thyroid cancer has an increasing incidence all over the world for three decades so far (Pellegriti et al., 2013; Sungwalee et al., 2013). Diagnostic management of thyroid nodules is mostly based on cytopathological assessment of fine-needle aspiration (FNA) biopsies. FNA is used for estimating malignancy risk of the nodule to decide whether patient is a candidate for surgery or not (Cibas and Ali, 2009). Therefore, malignancy risk of each cytopathology result has been determined by different organizations to recommend best treatment options for each category (Cibas and Ali, 2009; Gharib et al., 2010; Kocjan et al., 2011). Additionally, these categorizations aim to decrease the rate of indeterminate results and provide a common language in between different disciplines, such as pathology, endocrinology and surgery.

The Bethesda System for Reporting Thyroid

Cytopathology (Bethesda SRTC), created by National Cancer Institute State of the Science Conference, is one of these main classification systems. Regarding to Bethesda SRTC, six different categories are defined to be used in cytopathology reports: (1) nondiagnostic, (2) benign, (3) atypia/follicular lesion of undetermined significance (AUS/FLUS), (4) follicular neoplasm/suspicious of follicular neoplasm, (5) suspicious of malignancy, and (6) malignant (Cibas and Ali, 2009). The third category, AUS/FLUS has been the most controversial one of all. Bethesda SRTC expects that 7% of all FNAs to be reported as AUS/FLUS; and malignancy rate for this category has been estimated to be between 5% and 15%. According to Bethesda SRTC, recommended management for AUS/FLUS nodules is performing a repeat FNA and indicating the surgery in case the result is category 3 or higher (Cibas and Ali, 2009).

AUS/FLUS defines nodules with nuclear atypia or microfollicular architecture of variable degrees, which cannot fall into definite category of benign or malignant. These types of nodules are also defined as Thy3a category

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defined by The Royal College of Pathologists (TRCP) and as Class 3 (with suspicious follicular lesions also included) by the American Association of Clinical Endocrinologists/Associazione Medici Endocrinologi/European Thyroid Association (AAACE/AME/ETA) Task Force. Both guidelines recommend surgery to exclude malignancy unless the clinical, ultrasonographic, cytological and immunocytochemical features are considered favorable (Gharib et al., 2010; Kocjan et al., 2011).

Surgery is the recommended treatment choice for all indeterminate thyroid nodules which are reported as Thy3a (AAACE/AME/ETA), Class 3 (TRCP) or AUS/FLUS (Bethesda SRTC - in a repeat FNA), despite relatively low malignancy rates. In other words, surgery is recommended around 7% of all thyroid FNAs, although the malignancy occurs in 5-15% of the cases. Many other studies investigated malignancy rates of subgroups of indeterminate nodules to object a valid predictor of malignancy. Accumulating evidence of these thyroid nodules is focused on ultrasonographic and cytopathological features, combining with biochemical and molecular findings, to improve diagnostic accuracy.

The present study is a retrospective review of thyroidectomy cases with preoperative indeterminate thyroid nodule cytopathology reports. Demographics, laboratory findings, and ultrasonographic features of all patients in the study group are evaluated to determine the association with the histopathological outcome of the disease.

Materials and Methods

Patients who underwent thyroidectomy in our institution between May 2010 and May 2014 were retrieved from institutional records database. All preoperative cytopathology reports were examined in detail and indeterminate thyroid nodules which met cytopathological classification criteria for AUS/FLUS of Bethesda SRTC were included in the study.

Thyroid ultrasonographic examinations were performed at Endocrinology Clinic in our institution by an endocrinologist with extensive thyroid ultrasonography experience, using 11-MHz linear probe and LOGIQ 3 (General Electric Healthcare, Waukesha, WI, USA) ultrasonography device. Thyroid FNA biopsies were performed with disposable plastic syringes with 22-gauge needles.

All patients with undetermined cytopathology reports were referred to endocrinology council, which consists of senior general surgeons and endocrinologists. All surgery decisions were made by the endocrinology council.

Except the patients who had prior thyroidectomies, all patients underwent bilateral total thyroidectomy. Complimentary thyroidectomy was performed for patients who had prior thyroidectomies and recurrent thyroid nodules. All surgeries were performed by experienced surgeons of General Surgery Department in our institution.

Patient ages, gender, history of thyroiditis, radiation exposure and thyroidectomy were recorded. All ultrasonography reports examined for nodule size, presence of calcification, regularity of nodule margins,

hypoechoigenity, dominant nodule laterality, sign of tumor invasion, multi-centricity, and lymph nodes in pathological size or form, and obtained data were recorded. Biochemical blood levels, TSH, free T3, free T4 and complete blood count levels were recorded.

Our primary object is to determine malignancy rate of undetermined thyroid nodules to highlight any variable which is associated with histopathological outcome.

Statistical analysis

The SPSS 15.0 (SPSS Inc., Chicago, USA) statistics software was used for statistical analysis. Due to non-parametric distribution pattern among the groups, comparison between two groups was performed using Mann-Whitney U test. Multiple groups were compared using Kruskal-Wallis and Chi-square tests, and nominal values were compared with Fisher's exact test. Logistic regression was used to identify the factors associated with malignancy. "Receiver operator characteristic" curve analysis was used for determining cutoff value for significant variables.

Results

220 cytopathology reports were evaluated retrospectively. A total of 103 patients' cytopathology reports were regarded as AUS/FLUS category and included in study. 17 (16.5%) of the subjects were male and 86 (83.5%) were female. According to postoperative histopathological reports, 36 patients (35%) had malignant nodules and 67 (65%) patients had benign nodules. Mean age of patients in malignant and benign group are 53.64 (± 9.79) and 52.15 (± 12.33), respectively. All four patients who had prior thyroid surgery were in benign group (Two total thyroidectomies, one right lobectomy and one bilateral subtotal thyroidectomy.). No significant difference between two histopathological outcomes regarding age groups, gender or patient history was detected.

The results of biochemistry tests, complete blood count, TSH, free T3 and free T4 levels were compared with the histopathological outcome (Table 1). Median preoperative Red Cell Distribution Width (RDW) level was 13.60 (Interquartile range [IQR]: 1.20) in patients with benign thyroid, while it was 14.30 (IQR: 2.30) in patients with malignant thyroid. RDW level was found to be an independent variable correlated with malignancy ($p=0.003$). None of the other blood tests showed any significant difference between benign and malignant groups.

Ultrasonographic features were evaluated separately: dominant nodule size, presence of calcification, sign of tumor invasion, and presence and size of swelled lymph nodes. Nodes with a greatest diameter of 10 mm or higher are regarded as swelled lymph nodes. Detailed information about ultrasonographic findings is available in Table 1. Calcification presence was the only finding that differed significantly between benign and malignant groups. Preoperative ultrasound imaging showed calcifications in 52.8% of patients in the malignant group, whereas only 31.3% of patients in benign group

Table 1. Blood Test Results and Ultrasonic Findings

Pre-operative Status	Benign	Malignant	p value
TSH (Median [IQR])	1.26 (1.70)	1.29 (1.45)	
fT3 (Mean±SD)	3.11±0.53	3.04±0.43	
fT4 (Mean±SD)	1.10±0.24	1.09±0.21	
Thyroglobulin (Median [IQR])	51.25 (189.37)	145 (277.90)	
Anti TPO (Median [IQR])	7.92 (138.61)	7.13 (6.18)	
CEA (Median [IQR])	1.03 (0.07)	1.60 (0.57)	
Total Calcium (Median [IQR])	9.40 (0.60)	9.35 (0.40)	
Albumin (Mean±SD)	4.73±0.34	4.48±0.37	
ALP (Median [IQR])	70 (38)	63.50 (26.50)	
Platelet (Mean±SD)	275.64±62.79	274.95±61.70	
RDW (Median [IQR])	13.60 (1.20)	14.30 (2.30)	0.007
Dominant nodule size	20 (8.5)	17 (18)	
Presence of swelled lymph node	43/67 (64.2%)	27/36 (75%)	
Swelled lymph node size	13 (7)	15 (8)	
Calcifications presence (Number of patients)	21/67 (31.3%)	19/46 (52.8%)	0.034
Sign of tumor invasion (Number of patients)	2/67 (3%)	0/36 (0%)	
Solitary nodule (Number of patients)	16/67 (23.9%)	13/36 (36.1%)	

*aTSH: Thyroid Stimulating Hormone, fT3: Free T3, fT4: Free T4, Anti TPO: Anti-thyroid peroxidase, CEA: Carcinoembryonic antigen, ALP: Alkaline Phosphatase, RDW: Red cell distribution width, SD: Standard Deviation, IQR: Inter-quartile Range

Table 2. Diagnostic Measures for RDW and calcification presence

	Sensitivity	Specificity	PPV	NPV
RDW (cutoff 14,1)	52.78%	74.63%	52.78%	74.63%
Calcification presence	52.78%	68.66%	47.50%	73.02%
Both Combined (“One positive and one negative” result is regarded as Negative)	30.56%	97.01%	84.62%	72.22%

*RDW: Red cell distribution width, PPV: Positive Predictive Value, NPV: Negative Predictive Value

had presented calcification in dominant nodule. Other ultrasonographic findings were not found to be associated with histopathological outcome.

With the aim to understand the ability of RDW and calcification presence to predict malignancy, sensitivity, specificity and other diagnostic values were calculated. 14.1 was set as the cutoff value for RDW levels, as a result of ROC curve analysis. Values below 14.1 were regarded as negative; whereas 14.1 and higher values were regarded as positive RDW result. Diagnostic measures for RDW and calcification presence are listed on Table 2.

To increase the accuracy in prediction, we calculated combined diagnostic value of RDW levels and calcification presence on ultrasonography. The sensitivity, specificity, positive and negative predictive values were calculated under the assumption of whether these test results are opposing as one is negative and the other is positive, or both are yielding in the same direct. During the interpretation of combined factors, opposing results were considered as negative.

Discussion

Bethesda SRTC points that; approximately %5-15 of all thyroid nodule cytopathology reports are not able to favor definite diagnosis of benign or malignant, where these nodules are considered as undetermined (Cibas and Ali, 2009). Undetermined thyroid nodules are one of the major challenges in making diagnosis for thyroid nodules. The Bethesda SRTC recommends performing a second consecutive FNA to reevaluate these nodules. In case of cytopathological outcome to be the same or higher risk group, surgery is recommended. However, only 15-30%

of this group is expected to be malignant, which means; approximately 70% of this group of patients undergo surgery with non-malignant thyroid tissue (Cibas and Ali, 2009). This condition leads to two plausible questions: [1] What is the exact rate of malignancy in undetermined thyroid nodules? [2] Can we predict malignancy in undetermined thyroid nodules more accurately? Today, there is a remarkable global effort to seek an answer for these questions.

In this study, malignancy rate in undetermined thyroid nodules is found 35%. We were expecting a slightly higher malignancy rate. Increasing number of recent studies assess the malignancy rate among undetermined thyroid nodules, where two different patient selection criteria were used to evaluate these rates. One of these criteria includes all patients with undetermined thyroid nodules in to the study group and requires follow-up for all of the patients with surgery, FNAs, or ultrasonography. On the other hand, the second study design accepts only patients who have already underwent surgery and received histopathology reports, respectively, as the way we designed our study. Both perspectives have different pros and cons. First group of studies, evaluating the patients regardless of surgical intervention, lack certain information about follow-up patients, hence, malignancy rates are expected low. In contrast, post-surgery studies are equipped with the certain information about each sample's histopathological outcome, which leads to an unfortunate patient selection bias and higher malignancy rates. The literature contains quality studies for both groups with varied results. Malignancy rates that were reported by first group studies, including all undetermined patients for follow-up, are found between 15.7% and 44.1% (Horne

et al., 2012; Dincer et al., 2013; Chen et al., 2014; Ho et al., 2014; Hyeon et al., 2014; Rosario, 2014). In contrast, these rates are reported between 22.8% and 54% in the second group of studies that have only selected the patients who underwent surgery (Alexander et al., 2012; Jeong et al., 2013; Chen et al., 2014; Cuhaci et al., 2014; Ho et al., 2014; Park et al., 2014; Ryu et al., 2014). In our study, as a consequence of our patient selection, there is a predictable selection bias, caused by including the patients who only underwent thyroidectomy.

A recent study by Ho et al., including patients with Bethesda Category 3 thyroid nodules, reported a malignancy rate of 37.8%. The researchers evaluated all bias possibilities and re-calculated the lower bound of the malignancy rate of undetermined nodules. Even if all nodules that were followed up without surgical intervention, were considered as benign, the malignancy rate would only decline to 26.6% (Ho et al., 2014). According to this brief review of literature, even the lowest of the claimed malignancy rates seem to be higher than Bethesda SRTC estimation. In the near future, recommendations about undetermined thyroid nodules may be altered in favoring surgical intervention, regarding to accumulating evidence.

In our study, we analyzed features of preoperative patient, to reveal any association with outcome as a potential predictor of malignancy. Patient age or gender didn't show any statistically significant difference between histopathological outcome groups. In contrast to our results, some studies have shown age as an independent variable effective to malignancy rates. The aforementioned study by Ho et al. has investigated 541 patients with AUS/FLUS and age was found reversely related with malignancy (Ho et al., 2014). Another retrospective study, including 116 thyroidectomy patients, were also consistent with these results and malignancy rate was reported significantly higher for those who are older than 40 years of age (Ryu et al., 2014). Additionally, in our study, similar with the age and gender, there was no correlation with history of thyroiditis, thyroid hormone levels, calcium levels, albumin levels, or alkaline phosphatase levels considering histopathological outcome.

Due to increasing interest especially in RDW levels in inflammatory and malignant diseases, we decided to include RDW levels for statistical analysis. Among the histopathological outcome groups, significant difference was found between median RDW levels ($p=0.007$). To our knowledge, there is no such study investigating the association between RDW levels and thyroid malignancies. Dorgalaleh et al., has shown that RDW levels are correlated with both hypothyroidism and hyperthyroidism (Dorgalaleh et al., 2013), whilst other studies have shown this correlation with primary and subclinical hypothyroidism (Bashir et al., 2012; Yu et al., 2014). In literature, there are also studies reported high RDW levels as a predictor of malignancy. Beyazit et al. has studied 194 patients with obstructive jaundice, retrospectively. RDW levels that are higher than 14.8%, was associated with malignancy ($p<0.001$) (Beyazit et al., 2012). Early mortality rates in patients with acute dyspnea (Hong et al., 2012) and acute pulmonary embolism (Zorlu

et al., 2012) were also found associated with high levels of RDW. To obtain more compelling evidence and disclose the true value of RDW levels in specific conditions, more studies are needed with higher volume samples.

Due to limitations of retrospective study design, we were not able to evaluate all ultrasonographic features among our study group. Obtained retrospective data included information about nodule size and count, lymph node size, calcification presence and sign of tumor invasion. None of these ultrasonographic features were found to be associated with histopathological outcome, except calcification presence in the suspected nodule. Calcification presence was noticed in 31.3% of benign nodules, and 52.8% of malignant nodules. This difference was found to be statistically significant ($p=0.034$). This finding is consistent with recent similar studies (Jeong et al., 2013; Lee et al., 2014). Taller-than-wide shape (antero-posterior radius is greater than transvers radius), irregular margins and hypoechogenicity are also shown to be associated with malignancy in undetermined nodules (Jeong et al., 2013; Lee et al., 2014; Yu et al., 2014). In a study by Rosario et al, an original definition for "suspicious ultrasonographic findings" was used for AUS/FLUS nodules, which already has demonstrated the value for benign, follicular neoplasm and suspicious for malignancy groups (Rosario and Purisch, 2010; Rosario et al., 2010; Rosario, 2014). According to this definition, presence of marked hypoechogenicity or microcalcifications or hypoechogenicity is considered as suspicious for malignancy when it is combined with any of the following; microlobulation, irregular margins, taller-than-wide shape and predominantly or exclusively central vascularization. In this study, malignancy rate of nodules with suspicious ultrasonographic findings was 76.2%, whereas significantly higher than the malignancy rate of non-suspicious nodules (Rosario, 2014). Similarly, Yoon et al. defined a nomogram which is formed of same ultrasonographic features combined with age and nodule size, and showed that it can be used for prediction of malignancies (Yoon et al., 2014). An eastern China based recent study also showed that, a scoring system which was developed on the basis of different ultrasonographic features of thyroid nodules can be used for predicting histopathological outcome (Cheng et al., 2013). Not only ultrasonography seems to be a legit tool for predicting malignancy, but also more studies and meta-analyses are needed to define a universally viable set of criteria.

After considering our results, we decided to evaluate diagnostic value of RDW levels and calcification presence in nodules, both separately and combined together. Specificity for combined evaluation is found as 97.01%, while positive predictive value is 84.6% and sensitivity is 30.56%. Patients with low RDW levels and calcification free nodules appear to be benign and don't require surgery. This evidence may be too weak to claim this test as a predictor, but can be used as a guide for further approaches.

This study is limited by its retrospective design, relatively low sample size and patient selection bias. Prospective studies with both operated and non-operated patients may give better information about malignancy

rate and same predictor variables. On the other hand, we included all undetermined thyroid nodules, regardless to the initial diagnosis of BETHESDA SRTC Category 3-AUS/FLUS that was performed by cytopathologist. Additionally, we did not investigate nodules separately according to their cytological subcategory. Another limitation of this study is that, gathered ultrasonographic information about nodule margins, nodule shape and nodule vascularization was not adequate for proper statistical analysis. Similarly, calcification presence in nodules could not be grouped into subcategories. An imperative point for this group of patients is that; with a futuristic perspective, further prospective study designs must include molecular and genetic evaluation.

In conclusion, predicting malignancy in undetermined thyroid nodules is an important challenge. Ultrasonography is one of the primary tools for this matter. RDW levels may become another promising tool to predict malignancy in this group of patients. Further prospective and larger-scale studies are needed.

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