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The Utility of Clinical Findings Including Serum TSH and Neck Ultrasonography for Predicting Thyroid Malignancy in Atypia of Undetermined Significance/Follicular Lesions of Undetermined Significance

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Purpose: Neck ultrasonography (NUS) is one of the most commonly used methods for evaluating thyroid nodules and preoperative higher TSH levels are known to be associated with differentiated thyroid cancers. This study was conducted to assess whether serum TSH levels and neck ultrasonography are of value in predicting malignancy in patients with atypia of undetermined significance/follicular lesions of undetermined significance (AUS).
Methods: A total of 62 patients (7 men, 55 women; mean age 48.4±11.9 years) who had indeterminate cytologic results indicating AUS underwent thyroidectomy. Preoperative clinical data including serum TSH and the findings of NUS were analyzed retrospectively between malignant and non-malignant groups.
Results: The final pathologic results of malignancy were reported in 53 of 62 (85.5%) patients with AUS. There was no significant difference in the mean value of preoperative serum TSH between malignant and non-malignant groups (1.5±1.3 vs. 1.9±1.2, P=NS). In NUS, the patients diagnosed with malignancy in histology showed a higher proportion of calcification, taller-than-wide shape, hypoechoic texture and irregular margin (58.5% vs. 22.2%, P=0.044; 34% vs. 0%, P=0.038; 98.1% vs. 44.4%, P＜0.01; 47.2% vs. 0%, P=0.008).
Conclusion: Serum TSH was not related to malignancy in thyroid nodules showing AUS. However, ultrasonographic features including calcifications, taller-than-wide shape, hypoechoic pattern and irregular margin could be used to predict malignancy. Ultrasonography should be the first useful methods when making decisions regarding management of thyroid nodules showing indeterminate cytologic results as AUS.

Key Words: Atypia of undetermined significance/follicular lesion of undetermined significance, Neck ultrasonography, TSH

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INTRODUCTION

Despite the high number of thyroid nodules in normal population, the occurrence of malignancy in population with thyroid nodules remains relatively low, ranging between 5～7%.(*1,2*) Fine needle aspiration cytology (FNAC) with or without ultrasonography guidance is an essential part of the assessment of a solitary thyroid nodule. The Bethesda system for reporting thyroid cytopathology (BSRTC) was formulated as a means to better standardize the cytologic interpretation of thyroid lesions.(*2*) Table 1 shows the BSRTC and implication of risk of malignancy with recommending clinical management. The creation of a new category, atypia of undetermined significance/

Table 1. The Bethesda System for Reporting Thyroid Cytopathology: implied risk of malignancy and recommended clinical management

Diagnostic category	Risk of malignancy (%)	Usual management
I. Nondiagnostic or unsatisfactory	1~4	Repeat FNAC* with ultrasound guidance
II. Benign	0~3	Clinical follow-up
III. Atypia of undetermined significance or follicular lesion of undetermined significance	5~15	Repeat FNAC*
IV. Follicular neoplasm or suspicious for a follicular neoplasm	15~30	Surgical lobectomy
V. Suspicious for malignancy	60~75	Near-total thyroidectomy or surgical lobectomy
VI. Malignant	97~99	Near-total thyroidectomy

Modified from Ali SZ, Cibas ES, eds. The Bethesda System for Reporting Thyroid Cytopathology: Definitions, Criteria and Explanatory Notes. New York: Springer; 2010. *FNAC = fine needle aspiration cytology.

follicular lesion of undetermined significance (AUS) was designated for use when the cytologic and/or architectural appearance displays sufficiently atypical features to exclude it from a benign diagnosis, that is, of uncertain significance.(*2,3*) The BSRTC estimates a 5~15% risk of malignancy for AUS and 15~30% for follicular neoplasm.(*1,4*) Also, recent publications have corroborated the risk incidence of malignant disease ranging from 5 to 15% in this category,(*5,6*) but definitive statistical data can be difficult to ascertain due to absence of postsurgical follow-up in a significant number of cases.

Several factors including age, sex, nodule size, and a previous history of radiation have been evaluated for their potential in predicting thyroid malignancy. Various ultrasonographic characteristics of thyroid nodules have been associated with a higher likelihood of malignancy, and certain clinical features may also increase the likelihood of malignancy in patients.(7-*9*) However, other authors have reported the relative lack of accuracy of the clinical parameters in predicting malignancy in indeterminate thyroid nodules.(*10-12*)

Recently, Boelaert et al. reported the preoperative serum thyroid-stimulating hormone (TSH) level as an independent predictor of thyroid malignancy in euthyroid patients with a nodular or diffuse goiter.(*13*) But their study, which was completed in the United Kingdom, had a disproportionably high incidence of follicular carcinoma, which is different from our epidemiology that papillary carcinoma accounts for greater than 90% of all thyroid cancers.

Certain features of neck ultrasonography (NUS) such as hypoechogenicity, irregular margins, microcalifications, and intranodular hypervascularity have been determined to be predictive of thyroid malignancy.(*7,9,14,15*) A recent study showed that a combination of solid nodules, nodules with irregular contours, symptomatic nodules, and positive BRAF mutation had high predictive value for malignancy in patients with a cytologic diagnosis of AUS.(*16*) However another study reported that ultrasonographic features, including thyroid nodule margin, consistency, contour, shape, and presence or absence of calcifications, have failed to consistently predict malignancy in cytologically indeterminate lesions.(*17*)

The objective of our study was to evaluate the use of the clinical characteristics including age, gender, and tumor size, and TSH level and ultrasonographic characteristics for predicting thyroid malignancy in patients with AUS cytologic diagnosis.

METHODS

At first, total 99 patients was diagnosed as AUS in FNAC and underwent thyroid surgery between Jan 2011 and June 2012. The indications of operation of 99 patients were that patients had the suspicious findings on NUS, and/or wanted to undergo surgery voluntarily.

The cytologic diagnosis of AUS was reported by several pathologists of our institute or outside institutes. One pathologist reviewed all over the cases retrospectively, and 37 of 99 cases were excluded because of inadequate diagnosis of AUS. Then total 62 patients diagnosed as AUS were enrolled finally.

44 patients of 62 (70.9%) underwent only one test of FNAC, and 14 patients (29.1%) had second FNAC test before surgery. BRAF mutation test was not performed routinely in that period. FNAC was performed at our institute in 55 patients of 62 (88.7%), and 7 patients fetched the cytologic result from outside clinics. In 64.5% (40/62), the preoperative NUS was performed by endocrine surgeons. On NUS, if the nodules had any of the findings of calcifications, taller-than-wide shape, irregular margin, and hypoechoic characteristics, the nodules were considered as abnormal findings suggesting malignancy.

The final pathology was reported as thyroid cancer in 53 patients (85.5%) and as benign in 9 patients (14.5%). The clinical findings including preoperative TSH level and sonographic findings were analyzed and compared between the malignant and benign group retrospectively.

For statistical analysis, Chi-square analysis and Student t-test were performed to evaluate quantitative variables, with a value of $P \leq 0.05$ indicating statistical significance. The statistic analysis was performed by SPSS software (Version 17, SPSS Inc, Chicago, IL).

Informed consent was omitted because of the retrospective character of the study, and the Institutional Review Board approved this retrospective study.

Table 2. Demographic and basic clinicopathologic data of 62 patients diagnosed as AUS

Variables, N=62	
Age, yrs*	48.4±11.9 (24~72)
Preoperative TSH, μIU/ml, n=61*	1.6±1.3
M : F	1 : 8
FNAC†, our clinic : outside	55 (88.7) : 7 (11.3)
Preoperative USG findings	
Calcification, No : Yes	29 (46.8) : 33 (53.2)
Shape, ovoid : taller-than-wide	44 (71) : 18 (29)
Echo texture, not hypoechoic : hypoechoic	6 (9.7) : 56 (90.3)
Margin, not irregular : irregular	37 (59.7) : 25 (40.3)
Extent of surgery, TT‡ : less than TT‡	34 (54.8) : 28 (45.2)
Intraoperative pathology, malignancy : benign	36 (58) : 26 (42)
Pathology	
Permanent pathologic result, malignancy : benign	52 (85.5) : 9 (14.5)
Thyroiditis, No : Yes	38 (61.3) : 24 (38.7)

*Presented as Mean±Standard deviation, Others: n (%); †FNAC = fine needle aspiration cytology; ‡TT = total thyroidectomy.

RESULTS

53 of 62 patients (85.5%) diagnosed as AUS showed thyroid malignancy and all malignancy was papillary carcinoma. The mean age of 62 patients was 48 (24~72) years, and the ratio of male to female patients was 1 : 8 (Table 2). There was no statistical difference in mean age, gender, tumor size, and preoperative free T4 between the malignant and benign group.

The mean TSH level checked before surgery was 1.6 μIU/ml, and there was no significant difference in mean value of preoperative serum TSH between the malignant and benign group (1.5±1.3 vs. 1.9±1.2, P=NS). And also, the existence of lymphocytic thyroiditis affecting the TSH level was not related with the malignancy (P=0.523).

The findings of calcifications, taller-than-wide shape, irregular margin, and hypoechoic texture on NUS were

Table 3. Comparison of clinical features and NUS findings between malignant and benign group of cytologic diagnosis of AUS

Variables, N=62	Carcinoma group, n=53	Benign group, n=9	P value
Age, yrs*	47.7±10.8	52.6±17.2	0.425
M : F	1 : 9	2 : 7	0.262
Size, cm	0.93	2.15	0.065
Preop. TSH, μIU/ml, n=61*	1.5±1.3	1.9±1.2	0.481
Preoperative USG findings			
Calcification, No : Yes	22 (41.5) : 31 (58.5)	7 (77.8) : 2 (22.2)	0.044
Shape, ovoid : taller-than-wide	35 (66) : 18 (34)	9 (100) : 0	0.038
Echo texture, not hypoechoic : hypoechoic	1 (1.9) : 52 (98.1)	5 (55.6) : 4 (44.4)	<0.01
Margin, not irregular : irregular	28 (52.8) : 25 (47.2)	9 (100) : 0	0.008
Thyroiditis on histology, No : Yes	31 (58.5) : 22 (41.5)	7 (77.8) : 2 (22.2)	0.523

*Presented as Mean±Standard deviation, Others: n (%).

Table 4. Accuracy of intraoperative pathology and NUS in predicting malignancy in AUS

	Sn*	Sp†	PPV‡	NPV§
Intraoperative pathology	67.9	100	100	34.6
Ultrasonographic findings				
Hypoechogenicity	98.1	55.6	92.9	83.3
Calcifications	58.5	77.8	93.9	24.1
Taller than wide shape	34	100	100	20.5
Irregular margin	47.2	100	100	24.3

*Sn = sensitivity; †Sp = specificity; ‡PPV = positve predictive value; §NPV = negative predictive value.

considered as suspicious for malignancy, and 11.3% (7/62) patients had all four characteristics, otherwise 6.5% (4/62) had not any of these. The patients group diagnosed as malignancy in histology showed higher proportion of calcifications, taller-than-wide shape, hypoechoic texture and irregular margin (58.5% vs. 22.2%, P=0.044; 34% vs. 0%, P=0.038; 98.1% vs. 44.4%, P＜0.01; 47.2% vs. 0%, P=0.008, respectively) (Table 3).

Intraoperative pathology using frozen section and touch imprint cytology made a correct diagnosis of thyroid cancer in 36 among the 53 patients with PTC (69.7%). The sensitivity and specificity of intraoperative pathology was 67.9%, 100% respectively. And of NUS findings, the hypoechogenicity had the highest sensitivity (98.1%), and the taller-than-wide shape and irregular margin had the highest specificity (100%) (Table 4).

In 9 patients with benign pathology, nodular hyperplasia, follicular adenoma, and lymphocytic thyroiditis was diagnosed in 6, 2, and 1 patient respectively.

DISCUSSION

Preoperative management of thyroid nodules typically relies upon the FNAC and cytologic interpretation of the aspirate specimen with or without concomitant ultrasonographic evaluation.(*3*) These techniques represent the most effective means by which clinical management is determined due to its rapid interpretation, relative cost-effectiveness, and ability to stratify the risk for malignancy in targeted thyroid nodules.(*1,18*) Although FNAC is an effective means of evaluating thyroid nodules, the cytologic interpretation cannot be easily classified as benign, suspicious for carcinoma, or malignant in as many as 10～30% of cases.(*1*) The BSRTC classifies the indeterminate categories based on their differing risks of malignancy, as AUS/FLUS, follicular neoplasm/suspicious for follicular neoplasm, and suspicious for malignancy.

A diagnosis of AUS is intended to represent a lower risk of malignancy when compared to the diagnostic categories of suspicious for malignancy and malignant. The Bethesda classification provides an estimated risk for malignancy at 5～15%, but the incidence of malignancy in large case series can reach as high as 28～48% in those treated by surgical management.(*2,4,5,19,20*) Carr R et al. reported up to 48.9% of malignant rate in 140 cases of AUS.(*16*) In our study, the malignancy rate of AUS was 85.5% which is extraordinary incidence because we selected the patients having the suspicious findings on NUS despite including cases of patient preference.

Utilization and reproducibility of AUS continue to vary amongst experienced cytopathologists and institutions due to inter-observer variability and differing interpretations of these cytologic criteria. Difficulty is also encountered when applying these criteria to distinguish between atypical cells of undetermined significance and atypical cells most consistent with malignancy.(*21*) Therefore, to preserve uniformity in our study, one pathologist reviewed all over the cases of AUS retrospectively, and 37 cases with cytologic diagnosis of 'suspicious for malignancy' and 'malignancy' were excluded.

The official Bethesda classification recommendation in the context of a diagnosis of AUS is repeat FNAC due to low malignancy rate.(*2,19,21*) In present study, a significant proportion of AUS diagnoses (44 patients, 70.9%) proceeded directly to surgical intervention without repeat FNAC because they had suspicious findings on NUS. The decision regarding whether to proceed with lobectomy or total thyroidectomy or to proceed with repeat FNAC is dictated by clinical context and patient preference as well as the Bethesda classification recommendations.

It has been known that TSH stimulates the growth or development of thyroid malignancy and higher serum TSH has association with both thyroid cancer incidence and advanced tumor stage. In patients with nodular thyroid

disease, the risk of thyroid malignancy increases with serum TSH, and even within normal ranges, higher TSH values are associated with a higher frequency of thyroid cancer.(*22*) In addition, there are reports that higher TSH values are even associated with more advanced stage of thyroid cancer such as extrathryoidal extension, and lateral lymph node metastasis.(*23*)

The serum TSH level may be useful in not only predicting the probability of cancer but also optimizing the extent of thyroidectomy in patients with nodular thyroid disease.(*22*) However, the role of TSH was not fully evaluated especially in patients with AUS. Our study showed there was no difference in TSH level between malignant and benign group in patients with AUS. But the present study contained limited number of patients to evaluate the TSH level for the prediction of malignancy in AUS.

Despite the increased utilization of FNAC and ultrasound, cytologically indeterminate thyroid nodules continue to present a major diagnostic issue for clinicians.(*3*) Several authors have attempted to subclassify nodules based on several clinical, ultrasonographic, and cytologic characteristics to better predict malignancy in indeterminate nodules,(*8,9,24*) while others have reported limited accuracy for those clinical parameters regarding their predictive power.(*11,12*) The clinical factors, including family history, radiation exposure, and symptomatic nodules, were each found to have no statistically significant impact on risk of malignancy.(*16*) Also, in our study, the clinical findings such as gender, age, and tumor size have not failed to predict the malignancy in cytologic result as AUS.

A few reports were skeptical about the using the NUS to predict malignancy in cytologic diagnosis of AUS. Ultrasonographic features, including thyroid nodule margin, consistency, contour, shape, and presence or absence of calcifications, have failed to consistently predict malignancy in cytologically indeterminate lesions.(*17*) A recent study showed that when the clinical and radiologic findings were correlated with the final surgical pathology diagnosis in 140 cases of AUS, there was no single clinical or ultrasonographic feature or combination of features was adequately sensitive or specific to identify all malignant nodules. However, a combination of solid nodules, nodules with irregular contours, symptomatic nodules, and positive BRAF mutation had high predictive value for malignancy in patients with a cytologic diagnosis of AUS.(*16*) But in our study, the ultrasonographic features such as calcifications, taller-than-wide shape, hypoechoic texture and irregular margin were significantly associated with the malignancy in patients with AUS (58.5% vs. 22.2%, P= 0.044; 34% vs. 0%, P=0.038; 98.1% vs. 44.4%, P＜0.01; 47.2% vs. 0%, P=0.008, respectively) Therefore we suggest that NUS may well be a strong tool to evaluate the nodules with cytologic result of AUS.

However, in present study, BRAF mutation analysis was not performed. A certain study reported BRAF mutation analysis was helpful in evaluating the AUS lesions. The sensitivity and specificity of BRAF mutation in detecting PTC in FNAC specimens with indeterminate diagnosis was 59.3 and 100%, respectively, while the positive and negative predictive values were 100 and 65.6%, respectively.(*25*) Otherwise, there were a few reports that BRAF mutations were uncommon in nodules with AUS or FLUS, or follicular neoplasm. BRAF was positive in only 2 of 95 subcategorized as AUS or FLUS (2.1%, 95% CI, 0～7). Most cytologically indeterminate nodules that proved to be malignant were also BRAF negative.(*26*) AUS lesions with significant cytological and/or architectural atypia and negative BRAF mutation analysis still portend a significant risk of malignancy in suspected thyroid nodules.(*27*) Therefore, preoperative BRAF mutation analysis should not be viewed in isolation as a definitive predictor of malignancy, and should be used as an adjunct criterion in association with available clinical and radiologic criteria in order to make an accurate determination of clinical risk.(*27,28*)

This study, like many others addressing the same topic, has its shortcomings. This case series was limited to AUS cases with corresponding surgical intervention.

Based on our findings, clinical findings such as gender, age, tumor size, and preoperative serum TSH level have not failed to predict the malignancy in AUS of cytologic diagnosis. Otherwise, ultrasonographic features such as calcifications, taller-than-wide shape, irregular margin, and hypoechogenicity are adequately sensitive or specific

to identify malignant nodules diagnoses as AUS.

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