

THE CONTRIBUTION OF CLINICAL AND RADIOLOGICAL FEATURES TO THE DIAGNOSIS IN AUS/FLUS AND FN/SFN THYROID NODULES

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ABSTRACT

Aims: Atypical cytologies were categorized as Bethesda category III (atypia with unknown significance, follicular lesions with unknown significance, AUS/ FLUS) and Bethesda category IV (follicular neoplasm or suspicious for follicular neoplasm, FN/SFN) in Bethesda system for reporting thyroid cytopathology (BSRTC). This study was planned to define the contribution of clinical and radiological features in the course of action for AUS/FLUS and FN/SFN thyroid nodules.

Materials and methods: The age, gender, nodule size and definitive pathological results of 124 patients treated with total thyroidectomy after preoperative diagnosis of AUS/FLUS and FN/SFN lesions were recorded. Radiological features were grouped as increased vascularity, irregular borders, microcalcification, cystic component, presence of hypoechoic halo, hypoechogenicity and extraglandular involvement.

Results: The malignancy rates in AUS/FLUS and FN/SFN lesions were 8% and 16.3%, respectively. Fine needle aspiration cytology (FNAC) was repeated only in 8 patients among 75 patients diagnosed as AUS/FLUS, but the diagnosis was not changed in direction to follow-up. The presence of irregular borders at ultrasonography, increased vascularity, microcalcification, presence of hypoechoic halo and hypoechoic nodules were found to be related to the malignancy in AUS/FLUS group. On the other hand, age less than 50, presence of irregular borders, increased vascularity and presence of microcalcifications were found to be related to the malignancy in FN/SFN group.

Conclusions: The success of BSRTC in prevention of unnecessary thyroidectomies shows differences between clinics. Radiological criteria apart from patient's related factors play an important role in clinical judgement. Microcalcifications seem to be the most sensitive criteria both in AUS/FLUS and FN/SFN lesions. Irregular border was the criteria with the highest specificity in both categories.

Key words: Bethesda, Fine needle, Thyroid, Ultrasound.

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Introduction

Well differentiated thyroid carcinoma (WDTC) is the most common endocrine malignancy and its incidence has been increasing in most areas over the world during the recent three decades^(1,2). It is believed that such increase is mainly due to increased detection caused by widespread use of thyroid ultrasonography and subsequent fine needle aspiration cytology (FNAC), by increase in thyroid surgery revealing occult cancers, and by

more careful examination of surgical specimens⁽¹⁻³⁾. However, the actual reason for such increase in incidence is not clear yet. It has been shown that, serum level of oxidative stress markers is higher in patients with thyroid cancer, and the level of total antioxidant status is lower in them compared to control subjects⁽⁴⁾. Potential etiologic factors for thyroid cancer are radiation exposures, high iodine intake (papillary thyroid carcinoma, PTC), nitrates, modern life style or other environmental pollutants and endogenous factors such as high thyroid stimu-

lating hormone (TSH), the presence of Hashimoto's thyroiditis and obesity⁽⁵⁾. The main histological subtype which has been contributing to surge in thyroid cancer is PTC in Unites States⁽⁶⁾.

The presence of suspicious nodules, airway obstruction, thyrotoxicosis and cosmetic reasons are the indications for surgery in patients with multinodular goiter⁽⁷⁾. The surgical interventions for innocent thyroid nodules should be minimized to avoid from potential morbidities of thyroid surgery and hormonal imbalances. First line diagnostic tool in discrimination of thyroid nodules is FNAC. This technique is simple, quick, efficacious and cheap. It defines the clinical approach with differential diagnosis of neoplastic and non-neoplastic nodules⁽⁸⁾. Although, FNAC is being used very frequently, there is still some confusion in reporting system. The differences in nomenclature of categories, the interpretation of lesions based on description rather than categorization and differences in terminology are obstacles against the definition of accurate malignancy rates. This issue was leading to difficulties in decision making for surgery⁽⁹⁾.

National Cancer Institute (NCI) published a guide for thyroid cytopathology, known as Bethesda system for reporting thyroid cytopathology (BSRTC), in 2007⁽¹⁰⁾. BSRTC was aimed at the standardization of thyroid fine needle cytopathologies with higher predictive values and better clinical results. The definition of treatment algorithms by common and definitive terminology between cytopathologists and clinicians were also among main objectives. In this system, atypical cytologies were re-classified as Bethesda category III (atipia with unknown significance, follicular lesions with unknown significance, AUS/ FLUS) and Bethesda category IV (follicular neoplasm or suspicious for follicular neoplasm, FN/SFN) and unnecessary thyroidectomies applied for these lesions were intended to be decreased. As the reporting and malignancy rates of these categories still varies between centers, there has been no consensus about clinical approach.

Different criteria taken into consideration by clinicians still play an important role in decision making. The age, gender, nodule size and radiological features has been the subject of investigation for a long time in clinical judgement for thyroid nodules^(11,12). This study was planned to define the contribution of clinical and radiological features in the course of action for AUS/FLUS and FN/SFN.

Materials and methods

Bethesda reporting system was started to be used in our center in 2008 and 328 patients treated with total thyroidectomy after thyroid ultrasonography (USG) and ultrasound-guided FNAC without diagnosis of malignancy (excluding Bethesda VI patients) till the end of 2013 were analyzed. Among these, the age, gender, nodule size and definitive pathological results of 124 patients treated with total thyroidectomy after preoperative diagnosis of AUS/FLUS and FN/SFN lesions were recorded. The localization of biopsied nodule and the pathologies of the other nodules detected in thyroid gland were evaluated in detail. The detection of lesions other than the nodule evaluated with FNAC was not interpreted as the failure of FNAC. Radiological features were grouped as increased vascularity, irregular borders, microcalcification, cystic component, peripheral hypoechoic halo, echogenicity (iso, hypo and hyperechoic) and extraglandular involvement. All biopsies were performed with 23-25 Gauge needles under ultrasound guidance. The smears were fixed with 90% ethanol and stained with Papanicolaou or hematoxylin. Each aspiration was repeated twice and at least four smears were prepared. The groups with minimum five to six follicular epithelial cells and aspirates with minimum 10 cells in each group were accepted as sufficient. Clinical information was extracted in a retrospective fashion from prospectively maintained databases. Fisher's exact test, chi-square test and Kruskal-Wallis nonparametric t-test were used.

Results

FNACs of 328 patients were evaluated and 75 patients were found to be diagnosed as AUS/FLUS and 49 patients as FN/SFN. The reporting rates of AUS/FLUS and FN/SFN lesions were 23.8% and 15.6%, respectively. While the mean ages and nodule sizes of patients in AUS/FLUS group were 48 ± 11.5 and 2.3 ± 1.08 cm, these numbers were 47 ± 3.1 and 2 ± 1.1 cm for FN/SFN group. The malignancy rates for AUS/FLUS and FN/SFN lesions were 8% and 16.3%, respectively. The malignancy rates for Bethesda category I, II and V lesions were 12.5%, 1.7% and 80%, respectively. FNAC was repeated only in 8 patients among 75 patients diagnosed as AUS/FLUS, but the diagnosis was not changed and they were followed-up. At the final pathology report, there were 29 follicular ade-

nomas, 19 colloidal nodules, 12 thyroiditis, 5 incidental micropapiller carcinomas, 3 papillary carcinomas, 3 papillary carcinomas with follicular variant, 3 hurthle cell adenomas and one nodular hyperplasia in AUS/FLUS group. There were 13 follicular adenomas, 10 hurthle cell adenomas, 9 incidental micropapiller carcinomas, 4 papillary carcinomas with follicular variant, 4 colloidal nodules, 3 follicular carcinomas, 3 thyroiditis, 2 nodular hyperplasia and 1 papillary carcinoma in FN/SFN group (Table 1).

	AUS/FLUS*	FN/SFN**
Papillary carcinoma	3	3
Papillary carcinoma follicular variant	3	4
Follicular carcinoma	0	1
Follicular adenoma	29	13
Hurthle cell adenoma	3	10
Colloidal nodule	19	4
Thyroiditis	12	3
Micropapillary carcinoma	5	9
Nodular hyperplasia	1	2

Table 1: Pathology results in both groups.

* Atipia with unknown significance, follicular lesions with unknown significance, **Follicular neoplasm or suspicious for follicular neoplasm

	AUS/FLUS* (P value)	FN/SFN** (P value)
Age <50 years	0.4	0.031
Gender	0.6	0.3
Irregular border	0.001	0.001
Extraglandular extension	0.1	0.1
Increased vascularity	0.001	0.005
Presence of peripheral halo	0.004	0.19
Microcalcification	0.001	0.001
Cystic nodule	0.4	0.1
Hypoechoogenicity	0.001	0.1

Table 2: The parameters related to malignancy.

* Atipia with unknown significance, follicular lesions with unknown significance, **Follicular neoplasm or suspicious for follicular neoplasm

The mean sizes of tumors and benign nodules were 2.35±1.23 cm and 2.66±1.17 cm, respectively. The presence of irregular borders at ultrasonography, increased vascularity, microcalcifications, presence of peripheral halo and hypoechoic nodules

were found to be related with the malignancy in AUS/FLUS group. On the other hand, age less than 50 years, the presence of irregular borders, increased vascularity and microcalcifications were found to be related to the malignancy in FN/SFN group. Gender and the size of nodule were not found to be related with malignancy in both groups (Table 2). The sensitivity, specificity, negative and positive predictive values of ultrasonographic parameters in both groups were summerized in Table 3.

		Sensitivity	Specificity	PPV***	NPV****
Irregular border	AUS/FLUS*	36%	100%	100%	90%
	FN/SFN**	47%	96.80%	88%	77%
Increased vascularity	AUS/FLUS*	63%	98.40%	87.50%	94%
	FN/SFN**	41%	93%	77%	75%
Microcalcification	AUS/FLUS*	81.80%	98.40%	90%	100%
	FN/SFN**	100%	75%	68%	100%
Peripheral halo	AUS/FLUS*	54.50%	87.50%	42%	91.80%
	FN/SFN**	41%	78%	50%	71%
Hypoechoogenicity	AUS/FLUS*	54%	89%	50%	90%
	FN/SFN**	39%	84%	54%	71%

Table 3: Diagnostic value of ultrasonographic parameters.

* Atipia with unknown significance, follicular lesions with unknown significance, **Follicular neoplasm or suspicious for follicular neoplasm, *** Positive predictive value, **** Negative predictive value

Discussion

The incidence of thyroid cancer has been seen to be increased worldwide and this increase is also applicable for tumor sizes⁽¹³⁾. Despite technical advances in radiology and routine use of ultrasound- guided FNAC, the preoperative diagnosis still is not certain in many patients and this brings about unnecessary thyroidectomies. The success of BSRTC in prevention of unnecessary thyroidectomies shows differences between clinics. There are six diagnostic categories in BSRTC. The risk of malignancy and suggestions for clinical approach for each category is presented⁽¹⁰⁾. The distinction between benign and malignant lesions with FNAC is possible in 70-80% of thyroid nodules. Negative predictive value for benign lesions and positive predictive value for malignant lesions were reported as 92% and almost 100%, respectively⁽¹⁴⁾. In these groups, there is no debate in clinical approach. Prior to BSRTC, there was no certain diagnostic

criteria for atypical cytologies like follicular neoplasia, follicular lesion and Hurthle cell metaplasia.

The most important change and novelty brought with BSRTC was AUS/FLUS and FN/SFN categories in which atypical cytologies has been described. The diagnosis of “atypia with unknown significance” and “follicular lesion with unknown significance” has been introduced in AUS/FLUS group. Histologically, this group has been consisted of atypical findings like high cellularity, laminated or small follicular cells, the presence of multinuclear giant cells or Hurthle cells, intranuclear pseudoinclusions and nuclear pleomorphism. The malignancy risk for this group was reported as 5-15% and the repeat of FNAC was recommended. The diagnosis of “follicular neoplasia” and “suspicion for follicular neoplasia” was introduced in FN/SFN group. Histologically, this group was consisted of cytomorphological findings with high cellularity, absence of colloid, repetition of trabecular or microfollicular configuration of follicular cells. The malignancy risk for this group was reported as 15-30% and lobectomy was recommended.

Although, there has been some clear clinical suggestions in this manual, there are still some indeterminate areas. Unnecessary thyroidectomies were tried to be decreased with repeat FNAC in AUS/FLUS lesions, but its effect on the incidence of change in diagnosis is not clear. Correct diagnosis can not be obtained even with repeat FNAC. Chen et al. were reported that the diagnosis could be changed in 65% of the cases with repeat FNAC⁽¹⁵⁾. Faguin et al. had shown that the need for surgery could be decreased from 60% to 43% with repeat FNAC⁽¹⁶⁾. On the other hand, there are some papers in literature that repeat FNAC did not change the decision about to perform surgery⁽¹⁷⁾. In our series, FNAC was repeated only in 8 patients among 75 patients diagnosed as AUS/FLUS and the diagnosis and treatment selected was not changed. The significant changes in the rates of surgical interventions between clinics for AUS/FLUS lesions reveal this discrepancy⁽¹⁸⁾. Completion thyroidectomy might also be needed after lobectomy for FN/SFN lesions.

As more than 40% of the AUS/FLUS lesions with actual 5-10% risk of malignancy has been treated with surgery, there is a need for some other criteria for clinical judgement. The greater vertical dimension than horizontal dimension, central vascularity, microcalcifications, hypoechogenicity and the presence of suspicious lymph nodes at the neck

area were described as suspicious radiological findings for thyroid nodules^(19,20). It was also stated that, liquid-base cytology and immunohistochemical studies in preparations with atypical cells might be helpful for diagnosis, but calcifications, irregular borders and abnormal vascularization at ultrasonography were the most useful criteria for decision making⁽²¹⁾. The diagnostic value of suspicious radiological findings for each category should be introduced. Gulcelik et al. were evaluated the contribution of clinical and radiological findings to the diagnosis in patients with follicular neoplasia before the era of BSRTC. While the age, gender and nodule size were not significant, hypoechogenicity and the presence of microcalcification at USG were found to be significant with high sensitivity and specificity⁽²²⁾. The contributions of hypoechogenicity^(23,24) and microcalcifications^(11,25) to the diagnosis were also expressed by other authors. But all these studies were again reported before the era of BSRTC and in most of them, the nodules were not categorized. In our study, the criteria like irregular borders and the presence of peripheral halo were also evaluated.

Among these criteria, microcalcifications seems to be the most sensitive criteria for both AUS/FLUS and FN/SFN categories. Irregular borders was also defined as a criterion with highest specificity for both categories. All these criteria, namely irregular borders, increased vascularity and microcalcifications were re-evaluated on condition that all present in the same patient. All 24 patients with none of these criteria in FN/SFN group were reported to be benign at final pathology report. Negative predictive value was 100%. Among 25 patients with any of these criteria, 17 patients were reported to have malignancy at final pathology report. Among 64 patients with none of these criteria in AUS/FLUS group, 62 patients were reported to be benign at final pathology report. Negative predictive value was 96%. Among 11 patients with anyone of these criteria, 9 patients were reported to have malignancy at final pathology report.

In literature, it has been reported that, advanced and early age, male gender, nodular disease, small and large nodule size were all associated with cancer^(7,26-28). But these factors might change with factors like race, diet and environment. Additionally, when considering the different biological features of endemic goiters, the restricted contribution of these factors to the diagnosis might be better understood. Radiological criteria, indepen-

dently from patient related factors, might be helpful for clinical decision making. Retrospective design and unknown results of patients followed after FNAC were the weak points of our study.

Further prospective studies are needed to clarify this issue. In this way, the success of BSRTC in prevention of unnecessary thyroidectomies in AUS/FLUS lesions might be increased and total thyroidectomy might be suggested more reliably in FN/SFN lesions.

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