Asian Journal of Surgery (2019) 42, 144–147

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-asianjournalsurgery.com

ORIGINAL ARTICLE

The surgery and repeat aspiration outcomes of the atypia of undetermined significance/follicular lesion of undetermined significance category in The Bethesda System for Reporting Thyroid Cytopathology

I-Shiow Jan [a,b], Ya-Ting Lee [b], Chun-Ming Wang [b], Tsu-Yao Cheng [a,b], Chih-Yuan Wang [a,c], Tien-Chun Chang [a,c,d,e], Shyang-Rong Shih [a,c,d,*]

[a] National Taiwan University College of Medicine, Taipei, Taiwan
[b] Department of Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan
[c] Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
[d] Center of Anti-Aging and Health Consultation, National Taiwan University Hospital, Taipei, Taiwan
[e] Far Eastern Polyclinic, Taipei, Taiwan

Received 4 December 2017; received in revised form 14 January 2018; accepted 1 February 2018
Available online 11 April 2018

KEYWORDS
Atypia;
The Bethesda System;
Thyroid FNA cytology

Summary *Background/Objective:* The atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) category is one of six diagnostic categories of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). In this study, we report the diagnostic distribution of thyroid fine needle aspiration (FNA) cytology and analyze the outcome of AUS/FLUS cases.
Methods: A total of 29,937 thyroid FNA results, reported between April 2012 and December 2016, were retrieved from the database of a medical center. We reviewed the electronic medical records and analyzed the management of these patients.
Results: Overall frequency of AUS/FLUS is 3.1% in our laboratory, which is at the lower limit of the recommended range. Of these, 891 reports of AUS/FLUS from 770 patients were identified. Out of the 770 patients, 367 had surgical intervention. In these 367 patients, final surgical pathology yielded 204 (55.6%) malignancies, 12 indeterminateness (3.3%), and 151 (41.1%) benignity. Among these surgical patients, 113 (30.8%) had received a repeat FNA of the thyroid before thyroid resection. The difference between the malignancy rates among patients who

* Corresponding author. Department of Internal Medicine, National Taiwan University Hospital, 7, Chung-Shan South Road, Taipei, 10002, Taiwan. Fax: +886 02 2322 4263.
E-mail address: srshih@ntu.edu.tw (S.-R. Shih).

https://doi.org/10.1016/j.asjsur.2018.02.008

directly received surgery after the first AUS/FLUS diagnosis (132 of 254, 52.0%) and patients having a repeat FNA before surgery (72 of 113, 63.7%) was not statistically significant.
Conclusion: Our results are in agreement with AUS/FLUS diagnoses in less than 7% of specimens, and confirm that it is appropriate to perform either a repeat thyroid FNA or thyroid lobectomy, with the clinical decision being subject to the standardized management protocols of the second edition of TBSRTC in the AUS/FLUS category.

1. Introduction

Goiter is the most common thyroid disease worldwide. Fine needle aspiration (FNA) of the thyroid gland is an invaluable and reliable diagnostic technique for the evaluation of patients with thyroid nodules that require either surgical excision or conservative management. The decision on the management is dependent largely on the thyroid FNA result. The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) published in 2009 has standardized the reporting of thyroid FNA, which includes six diagnostic categories; they are (1) nondiagnostic/unsatisfactory (ND/UNSAT), (2) benign, (3) atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), (4) follicular neoplasm/suspicious for a follicular neoplasm (FN/SFN), (5) suspicious for malignancy (SM), and (6) malignant.[1] This classification system defines the morphologic criteria of each category and helps to share the thyroid FNA results between different laboratories and compare the study results. It also provides estimates of the risk of malignancy and recommended management in each category.[1] Category 3 (AUS/FLUS) represents challenges in interpretation of thyroid FNA. It is a heterogeneous category including compromised specimens with cytologic or architectural atypia not sufficient to be interpreted as follicular neoplasm or suspicious for malignancy.[1] According to the TBSRTC, the most common AUS/FLUS morphologic features are as follows: (1) the cellular smear contains follicular cells arranged in microfollicular pattern, but it does not fulfill the criteria for FN/SFN; (2) the sparsely cellular smear contains exclusively Hurthle cells; (3) the poorly prepared smear shows clotting and air-dried artifacts; (4) the cellular smear contains exclusively Hurthle cells, but the clinical manifestations suggest benign Hurthle cell nodules or Hashimoto's thyroiditis; (5) the smear has focal features suggestive of papillary carcinoma, but predominance of benign follicular cells and colloid; (6) the cystic aspirate contains macrophages, cyst-lining cells, and colloid, but some enlarged cells have nuclear grooves, pale chromatin, and distinct nucleoli; (7) the smear shows focal aggregation of enlarged nuclei from patients with history of Graves' disease or history of ionizing radiation; (8) the smear contains atypical lymphoid cells; (9) the smear shows other atypical presentation where the origin of atypical cells is uncertain.[1,2] We reported the diagnostic distribution of thyroid FNA cytology, analyzed the outcome of AUS/FLUS cases, and compared our data with world literature.

2. Methods

All thyroid FNAs were performed by endocrinologists or otolaryngologists, with or without ultrasound guidance. The aspirates were prepared as direct smears. Some smears were air-dried, and then a Riu stain, a kind of Romanowsky stain, was performed.[3] Immediate interpretation of specimen adequacy was not provided. Some smears were 95% alcohol fixed for Papanicolaou stain. A total of 29,937 thyroid FNAs, reported between April 2012 and December 2016, were retrieved from the database of the cytology laboratory in our medical center. We analyzed the distribution of cytologic diagnosis of thyroid FNA, and patients with an AUS/FLUS diagnosis were recruited for further analysis. Because we could not retrieve all of the thyroid FNA results not performed in our hospital, we defined the first AUS diagnosis in our institution as the first AUS diagnosis and repeat FNA was the thyroid FNA after the first AUS diagnosis in our institution. We reviewed the electronic medical records and analyzed the management following the first AUS/FLUS diagnosis. We also searched the reports of the Department of Pathology for patients treated with surgical resection.

According to the TBSRTC recommendation, repeat FNA is suggested to patients with an AUS/FLUS diagnosis.[1] However, some patients underwent surgical intervention by other indications. We determined the risk of malignancy by the final surgical pathology. We used a χ^2 test to analyze the surgical pathology results of the repeat FNA and non-repeat FNA after the first AUS/FLUS diagnosis. A p value < 0.01 was considered statistically significant.

The study was approved by the Institutional Review Board of the National Taiwan University Hospital, Taiwan (No. 201603064RINB). An informed consent from the patients was not required due to the observational and retrospective nature of this study.

3. Results

Table 1 shows the distribution of cytologic interpretation of 29,937 thyroid FNAs from 18,947 patients recruited in this study. The ND/UNSAT rate, which included cysts, was 38.6%. Benign, AUS/FLUS, FN/SFN, SM, and malignancy diagnoses were 53.1%, 3.1%, 0.4%, 2.2%, and 2.6%, respectively. From 770 patients, 891 specimens aspirated were interpreted as AUS/FLUS. Among these patients, 618

Table 1 Distribution of cytologic interpretation of thyroid FNA.

TBS category	n	%
Nondiagnostic/Unsatisfactory	11,555	38.6
Benign	15,899	53.1
AUS/FLUS	909	3.1
FN/SFN	127	0.4
Suspicious for malignancy	661	2.2
Malignant	786	2.6
Total	29,937	100.0

AUS/FLUS = atypia of undetermined significance/follicular lesion of undetermined significance; FN/SFN = follicular neoplasm/suspicious for a follicular neoplasm; TBS = The Bethesda System.

were women and 152 were men. Following AUS/FLUS diagnosis, 367 patients (47.7%) underwent subsequent surgical intervention. In these 367 patients, final surgical pathology yielded 204 (55.6%) malignancies, 12 indeterminateness (3.3%) and 151 (41.1%) benignity (Table 2). The malignancy rate of 55.6% was defined as the upper bound estimate using the following formula: total number of pathologically proven malignancies/total number of cases diagnosed as AUS/FLUS and resected.[4,5] On the contrary, the lower bound estimate of risk of malignancy in AUS/FLUS was calculated as 26.5% (204 of 770) using the following formula: total number of pathologically proven malignancies/total number of cases diagnosed as AUS/FLUS on FNA smear.[4,5] The true malignancy rate is likely to lie between the upper and lower bound estimate rates.[4,5] Among the 367 surgical patients, 113 (30.8%) had received a repeat FNA of the thyroid before thyroid resection. Of these, 9 were classified as ND/UNSAT (8.0%), and there were 59 (52.2%), 33 (29.2%), and 12 (10.6%) patients with category upgrading, category 3 (AUS/FLUS), and category downgrading results, respectively. The positive and negative predictive values for the repeat FNA were 88.1% (52 of 59) and 83.3% (10 of 12), respectively. The difference between the malignancy rates among patients who received surgical resection directly after the first AUS/FLUS diagnosis (132 of 254, 52.0%) and patients having a repeat FNA before surgical resection (72 of 113, 63.7%) was not statistically significant (Chi-square = 4.755, $p = 0.09$; Table 3).

Table 2 Distribution of surgical pathology diagnosis of thyroid surgery.

Surgical pathology diagnosis	n	%
Malignant	204	55.6
Papillary carcinoma	131	35.6
Papillary microcarcinoma	52	14.1
Follicular carcinoma	8	2.2
Hurthle cell carcinoma	4	1.1
Medullary carcinoma	1	0.3
Well-differentiated thyroid carcinoma	1	0.3
B cell lymphoma	1	0.3
Maltoma	1	0.3
Squamous cell carcinoma	2	0.5
Mixed papillary thyroid carcinoma and squamous cell carcinoma	1	0.3
Parathyroid carcinoma	1	0.3
Malignant PEComa	1	0.3
Indeterminate	12	3.3
Follicular neoplasm with uncertain malignant potential	8	2.2
Hurthle cell neoplasm of uncertain malignant potential	3	0.8
Well-differentiated tumor of uncertain malignant potential	1	0.3
Benign	151	41.1
Follicular adenoma	27	7.3
Hurthle cell adenoma	7	1.9
Oncocytoma	2	0.5
Adenomatous hyperplasia	16	4.4
Nodular hyperplasia	83	22.6
Lymphocytic thyroiditis	4	1.1
Hashimoto's thyroiditis	7	1.9
Benign thyroid gland	2	0.5
Not diagnostic of malignancy	1	0.3
Thymic cyst	1	0.3
Parathyroid adenoma	1	0.3

Table 3 Comparison of non-repeat FNA and repeat FNA groups in surgical pathology diagnosis.

	Surgical pathology diagnosis			Total number
	Malignant	Indeterminate	Benign	
Non-repeat FNA	132	8	114	254
Repeat FNA	72	4	37	113
Total number	204	12	151	367

FNA = fine needle aspiration.

4. Discussion

The FNA cytology of the thyroid is able to aid clinicians in treating patients in their practice. TBSRTC defined and distinguished six diagnostic categories for more effective communication between health providers. In our laboratory, the ND/UNSAT rate was extremely high (38.6%). The reported ND/UNSAT rate is between 1.8% and 23.6%.[6] Our high ND/UNSAT rate might be due to the lack of rapid on-site evaluation, inexperienced fellows performing thyroid FNAs, and strict criteria for specimen adequacy. Thus rapid on-site evaluation and ultrasound-guided procedure will improve the ND/UNSAT rate. TBSRTC recommends the AUS/FLUS interpretations to be limited to approximately 7% of all thyroid FNAs.[1] It was 3.1% in this study, which is less than the recommended rate by TBSRTC. However, there is a wide variation in the reported AUS/FLUS rate from different laboratories, which ranged between 0.8% and 27.2%.[2] The reason for the low AUS/FLUS rate could be the greater frequency of ND/UNSAT and benign rates in our study.[7]

Although TBSRTC recommends that the usual management of the AUS/FLUS category is a repeat FNA, the clinician may suggest the patient to receive surgical resection by some clinical or imaging feature indicating a worrisome follicular lesion. In our study, 367 patients (47.7%) underwent subsequent surgical resection in the AUS/FLUS category. Papillary carcinoma was the most frequent malignancy observed in our study and other reported studies.[8] In TBSRTC, SM, FN/SFN, and AUS/FLUS are indeterminate categories. According to the TBSRTC, the risk of malignancy is 60—75%, 15—30% and 5—15% in SM, FN/SFN and AUS/FLUS categories, respectively.[1] The malignancy rate of AUS/FLUS was between 55.6% (204 of 367) and 26.5% (204 of 770) in our study, which was higher than the risk of malignancy mentioned in the TBSRTC. The reasons for high malignancy rate in our AUS/FLUS group might be resulted from that our institution is a tertiary referral center and easy accessibility to health care is provided by universal health insurance in Taiwan. Among 204 patients with malignant surgical pathology report, 95 patients' tumor size was less than 1 cm, which was more difficult to be aspirated. In addition, 147 out of 367 (40%) patients with surgical intervention had calcification on the thyroid sonographic study. Calcification might be hinder the aspiration procedure. However, the malignancy rate of AUS/FLUS is between 6% and 96.7% in resected histologically proven cases reported in a review article by Kholová and Ludvíková.[2] Furthermore, the risk of malignancy in the majority of studies is higher than the TBSRTC implied for this category. The reasons for variability might be the heterogeneity of this category, higher risk of malignancy in some practice settings such as tertiary referral centers, subjective and controversial interpretation of cytology, and AUS/FLUS overuse.[2]

In this study, malignancy rates among patients who directly went to surgical resection and patients having repeat thyroid FNA after the first AUS/FLUS diagnosis were 52.0% (132 of 254) and 63.7% (72 of 113), respectively. There was no statistically significant difference in the malignancy rate between these two groups of patients. Our findings correspond to findings of Ho et al and VanderLaan et al[5,9] However, Üstün et al reported that the malignancy rate in AUS/FLUS patients with and without repeat FNA was 29% and 14%, respectively.[10] They suggested AUS/FLUS patients were best managed by repeat FNA. Therefore, Cibas and Ali revised the usual management of the AUS/FLUS category to a repeat FNA, molecular testing, or lobectomy, and implied risk of malignancy was around 10—30% based on the meta-analysis of the post-2007 literature.[11]

In conclusion, overall frequency of this category is 3.1% in our laboratory, which is at the lower limit of the recommended range. The estimated risk of malignancy is between 26.5% and 56.5%. The difference between the malignancy rates of non-repeat FNA and repeat FNA patients after the first AUS/FLUS diagnosis is not statistically significant. This result confirms that for AUS/FLUS patients, either a repeat thyroid FNA or thyroid lobectomy is indicated, with the clinical decision being subject to the standardized management protocols of the second edition of TBSRTC.

Author contributions

Dr. Shih contributed to the study design, specimen sampling, and critical revision of the manuscript. Dr. Jan contributed to the study design, recognition of cytology report, analysis and interpretation of data, and manuscript writing. Miss Lee contributed to the collection and analysis of data. Mr. Wang contributed to the collection and analysis of data. Dr. Cheng contributed to recognition of cytology report. Dr. Wang contributed to specimen sampling. Dr. Chang contributed to specimen sampling and critical revision of the manuscript.

Declarations of interest

None.

Acknowledgements

We thank the Cytology Laboratory, Department of Laboratory Medicine, National Taiwan University Hospital for the support during the study.

References

1. Cibas ES, Ali SZ. The Bethesda system for reporting thyroid cytopathology. *Thyroid*. 2009;19:1159—1165.
2. Kholová I, Ludviková M. Thyroid atypia of undetermined significance or follicular lesion of undetermined significance: an indispensable Bethesda 2010 diagnostic category or waste garbage? *Acta Cytol*. 2014;58:319—329.
3. Riu CH. A study of staining blood film (Romanowsky system). *J Niigata Med Assoc*. 1956;70:635—643.
4. Mahajan S, Srinivasan R, Rajwanshi A, et al. Risk of malignancy and risk of neoplasia in the Bethesda Indeterminate Categories: study on 4,532 thyroid fine-needle aspirations from a single institution in India. *Acta Cytol*. 2017;61:103—110.
5. Ho AS, Sarti EE, Jain KS, et al. Malignancy rate in thyroid nodules classified as Bethesda category III (AUS/FLUS). *Thyroid*. 2014;24:832—839.
6. Krane JF, Vanderlaan PA, Faquin WC, Renshaw AA. The atypia of undetermined significance/follicular lesion of undetermined significance:malignant ratio: a proposed performance measure for reporting in the Bethesda System for thyroid cytopathology. *Cancer Cytopathol*. 2012;120:111—116.
7. VanderLaan PA, Renshaw AA, Krane JF. Atypia of undetermined significance and nondiagnostic rates in the Bethesda System for Reporting Thyroid Cytopathology are inversely related. *Am J Clin Pathol*. 2012;137:462—465.
8. Bongiovanni M, Krane JF, Cibas ES, Faquin WC. The atypical thyroid fine-needle aspiration: past, present, and future. *Cancer Cytopathol*. 2012;120:73—86.
9. VanderLaan PA, Marqusee E, Krane JF. Clinical outcome for atypia of undetermined significance in thyroid fine-needle aspirations: should repeated fna be the preferred initial approach? *Am J Clin Pathol*. 2011;135:770—775.
10. Üstün H, Astarci HM, Altunkaya C, et al. Fine-needle aspiration of follicular patterned lesions of the thyroid: diagnosis, management, and follow-up according to thyroid Bethesda system. *Acta Cytol*. 2012;56:361—369.
11. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. *Thyroid*. 2017;27:1341—1346.