

What Is the Malignancy Risk for Atypia of Undetermined Significance?

Three Years' Experience at a University Hospital in Turkey

Pinar Uyar Gocun, MD¹; Esra Karakus, MD²; Pinar Bulutay, MD¹; Mujde Akturk, MD³; Murat Akin, MD⁴; and Aylar Poyraz, MD¹

BACKGROUND: The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) provides uniform diagnostic terminology for communication between pathologists and clinicians. Each diagnostic category is associated with a specific risk of malignancy and a recommendation for its management. The indeterminate diagnostic categories of atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) present a major challenge for both pathologists and clinicians. We report our institution's 3 years' experience with the AUS/FLUS category and follow-up of these patients. **METHODS:** A retrospective analysis was conducted for all thyroid fine-needle aspirations (FNAs) between July 2010 and July 2013. During this period, 9242 nodules from 4916 patients were reported according to the BSRTC guidelines. We adopted the AUS terminology in our practice to refer to both AUS, and FLUS. **RESULTS:** Of the 4916 patients, 347 (7%) were diagnosed as AUS. The malignancy risk for patients who underwent surgical resection after initial diagnosis of AUS was 22.8%, whereas that for patients who underwent a second FNA and surgical resection was 36%. When we included patients with second FNA and without surgery, the malignancy risk was 15.7%. **CONCLUSIONS:** The malignancy risk for AUS reported in the present study is consistent with those reported previously and is higher than those anticipated according to the Bethesda System. This supports that a multimodal approach (clinical, radiologic, and cytopathologic) is necessary for the management of thyroid nodules diagnosed as AUS. Therefore, we suggest that the recommendation for repeat FNA following an initial diagnosis of AUS should be based on a multimodal approach for each particular patient. *Cancer (Cancer Cytopathol)* 2014;122:604-10. © 2014 American Cancer Society.

KEY WORDS: AUS, Bethesda, FLUS, FNA, malignancy risk, thyroid.

INTRODUCTION

Fine-needle aspiration (FNA) is a safe, accurate, and cost-effective method and plays an essential role in the evaluation of patients with a thyroid nodule.¹ Every patient with a thyroid nodule is a candidate for FNA. Before the decision to perform FNA, serum thyrotropin level (TSH) and thyroid ultrasound (US) should be obtained. In general, functioning thyroid nodules in the absence of clinical findings do not require an FNA because the

Corresponding author: Pinar Uyar Gocun, MD, Assistant Professor, Gazi University Medical Faculty, Department of Pathology, Gazi Üniversitesi Tıp Fakültesi, Tıbbi Patoloji AD Poliklinik 4. Kat Beşevler, Ankara 06500, Turkey; uyarpinar@yahoo.com

¹Gazi University Medical Faculty, Department of Pathology, Ankara, Turkey; ²Ankara Children's Hematology and Oncology Training and Research Hospital, Division of Pathology, Ankara, Turkey; ³Gazi University Medical Faculty, Endocrinology Service, Department of Medicine, Ankara, Turkey; ⁴Gazi University Medical Faculty, Department of Surgery, Ankara, Turkey

The preliminary study was a poster presentation at the 37th European Congress of Cytology, September 30-October 3, 2012, Dubrovnik-Cavtat, Croatia.

We thank Prof. Mustafa N. İlhan, MD, PhD, from Gazi University Medical Faculty, Department of Public Health, and Leyla Akta Akkoca from Gazi University Medical Faculty, Department of Pathology, Cytopathology Laboratory for their contributions.

Received: January 23, 2014; **Revised:** April 5, 2014; **Accepted:** April 10, 2014

Published online May 28, 2014 in Wiley Online Library (wileyonlinelibrary.com)

DOI: 10.1002/cncy.21434, wileyonlinelibrary.com

incidence of malignancy is exceedingly low. A nodule that appears either iso- or hypofunctioning on radionuclide scan should be considered for FNA based on the US findings.² FNA reduces unnecessary surgery for patients with benign nodules and appropriately triages patients with malignant nodules for timely intervention.¹ However, there was no standardized and uniform reporting system for thyroid FNA until the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) was published. The BSRTC provides uniform diagnostic terminology for communication between pathologists and clinicians. Each diagnostic category is associated with a specific risk of malignancy and a recommendation for its management.³ The undetermined diagnostic category of atypia of undetermined significance (AUS) and follicular lesion of undetermined significance (FLUS) comprise a heterogeneous group of diagnostic scenarios that are indeterminate and present a major challenge for both pathologists and clinicians.^{4,5} Some institutions use only AUS terminology for both AUS and FLUS scenarios.

The general diagnostic category of AUS is reserved for specimens that contain follicular, lymphoid or other cells with architectural and/or nuclear atypia, which is not sufficient for the diagnosis of suspicious for follicular neoplasm (SFN), suspicious for malignancy (SFM), or malignant. The term *FLUS* is used when atypia consists of follicular rather than lymphoid or other cells.⁶

We have been using the BSRTC since July 2010. We adopted the AUS terminology in our practice to refer to both AUS and FLUS. In the present study, we report our institution's 3-years' experience with the AUS category and follow-up of patients who underwent repeat FNAs and/or surgery after the AUS diagnosis. We suggest that the malignancy risk of AUS/FLUS is greater than 5%-15%.

MATERIAL AND METHODS

A retrospective analysis was conducted for all thyroid FNAs between July 2010 and July 2013 at Gazi University Medical Faculty, Department of Pathology. During this period, 9242 nodules from 4916 patients were reported according to the BSRTC guidelines. However, only the AUS category is included in the present study because, as mentioned before, we prefer using AUS terminology instead of AUS/FLUS. Informed consent was obtained from patients before FNA. Patients were

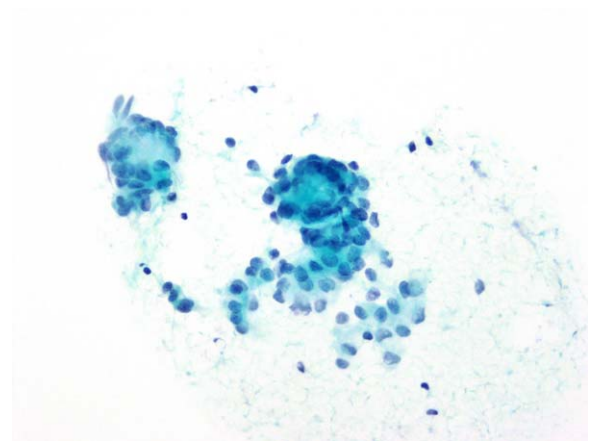


Figure 1. A group of overlapping follicular cells with slight nuclear enlargement, nuclear grooves, and microfollicle formation in otherwise benign cytology (Papanicolaou $\times 400$). Histopathology was follicular-variant papillary microcarcinoma.

informed that their archived material would be used for research purposes only. Staff endocrinologists or radiologists performed FNAs using a 25-gauge needle with ultrasound guidance (typically 3-5 passes) without on-site evaluation. All specimens were submitted as air-dried smears, and they were stained using the May-Grünwald-Giemsa (MGG), Papanicolaou, and hematoxylin-eosin (H&E) techniques. After receiving the air-dried smears, the most bloody ones were selected for MGG staining. Other smears were fixed in 97% ethanol for 5 minutes, before staining with Papanicolaou and H&E.

FNA slides were screened by all staff pathologists, and all cases, other than nondiagnostic and benign categories, were reviewed by 2 pathologists who were experienced in thyroid cytopathology (A.P. and P.U.G.) before the report was released. The 2 pathologists reported the cases as AUS, SFN, SFM, or malignant according to the BSRTC. The AUS category included the following cytologic features: cells resembling cyst-lining epithelium but cannot exclude papillary carcinoma; air-drying artifacts; small numbers of follicular epithelial cells with nuclear enlargement, overlapping, and nuclear grooves accompanying large numbers of benign follicular epithelial cells; overlapping follicular cells with nuclear grooves in a hypocellular aspirate; and small numbers of microfollicles in hypocellular aspirates. Figures 1-6 represent cases included in the AUS category.

Patients' follow-up data were collected from the archives of the hospital's automated computer system. While we were comparing the results of repeat FNAs with

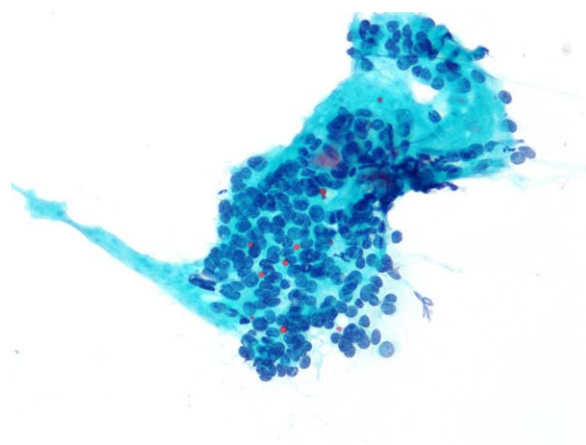


Figure 2. Overlapping follicular cells, with nuclear grooves in a hypocellular aspirate (Papanicolaou $\times 400$). Histopathology was adenomatous nodule.

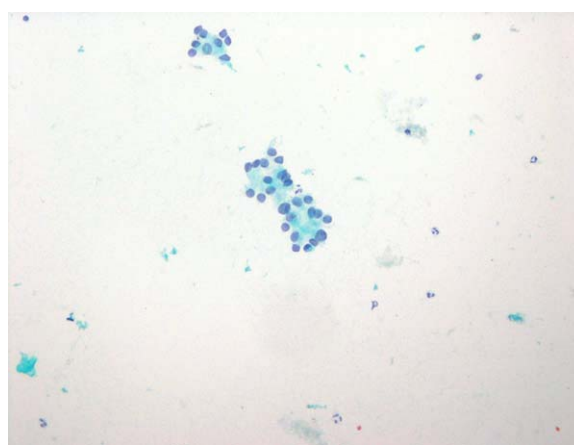


Figure 5. Microfollicles in a hypocellular aspirate (Papanicolaou $\times 100$). Histopathology was follicular-variant papillary carcinoma.

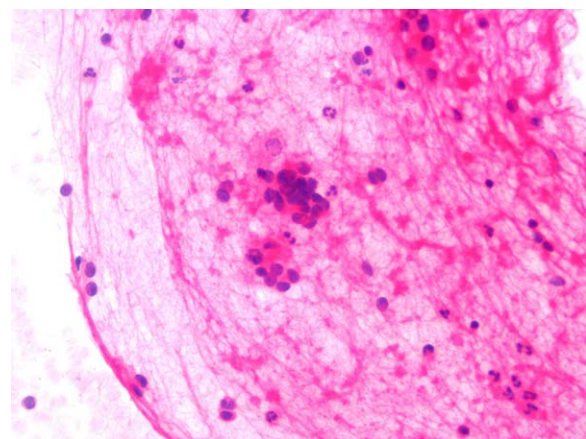


Figure 3. Hyperchromatic and overlapping nuclei with air-drying artifact (H&E $\times 200$). Histopathology was nodular goiter.

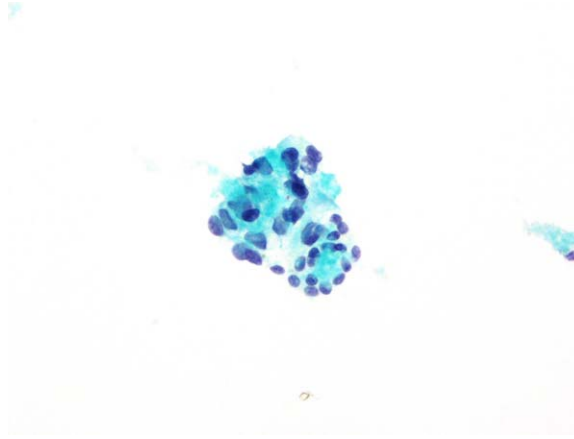


Figure 6. A small group of follicular cells with nuclear enlargement, overlapping, and rare grooves adjacent to a benign-appearing microfollicle in a hypocellular aspirate (Papanicolaou $\times 400$). Histopathology was papillary microcarcinoma.

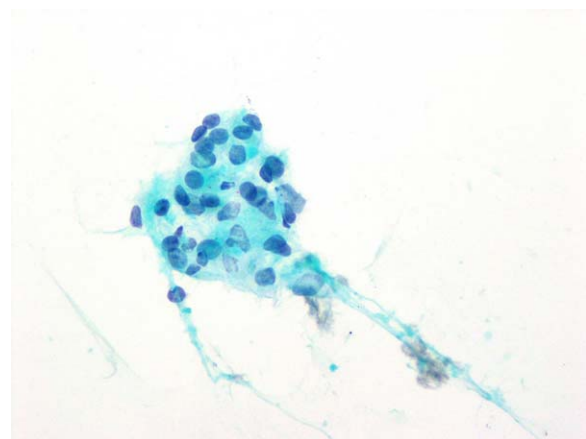


Figure 4. Nuclear enlargement, rare nuclear grooves, and air-drying artifact (Papanicolaou $\times 400$). Histopathology was papillary carcinoma.

the first AUS diagnosis or evaluating the surgical specimens, we matched each nodule to those stated in the radiologic and cytopathologic results. Incidental micropapillary carcinomas were not included.

RESULTS

Three hundred forty-seven of the 4916 patients (7%) were diagnosed as AUS. Of these 347 patients, 284 (81.8%) were women and 63 (18.2%) were men. The age of the patients ranged from 13 to 80 years (mean, 50.6 ± 12.28 years; median, 51 years).

Fifty-seven of the 347 patients (16.4%) underwent thyroidectomy after the first AUS diagnosis. The decision

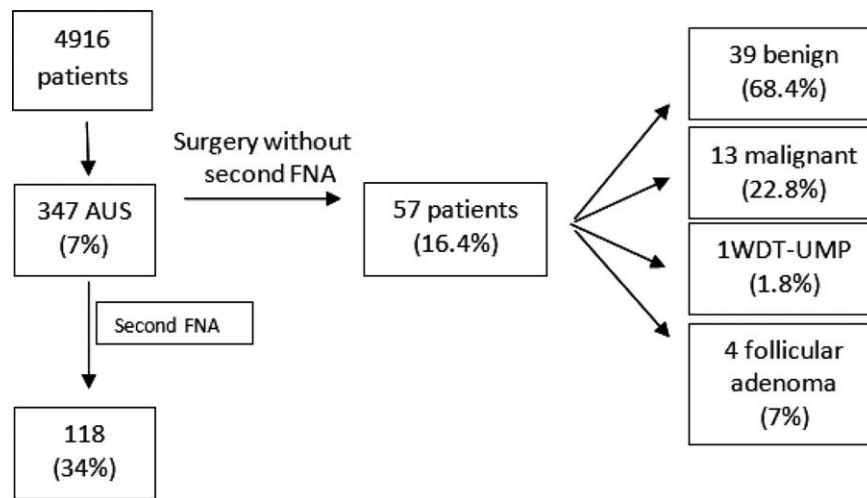


Figure 7. Histopathologic diagnostic categories of 57 patients who underwent surgery after the first diagnosis of AUS (WDT-UMP, well-differentiated tumor of uncertain malignant potential).

for surgery was based on suspicious clinical or radiologic features, mass effect, patient's choice, or in some cases, on decisions made in a multidisciplinary meeting. The lesions of the 57 patients were diagnosed as follows: 13 malignant (22.8%), 39 benign (68.4%), 4 follicular adenoma (7%), and 1 well-differentiated tumor of uncertain malignant potential (1.8%); see Figure 7.

Furthermore, 118 of the 347 patients (34%) underwent repeat FNA that was performed 3 weeks to 15 months after the first AUS diagnosis (median, 3 months). On second FNA, 65 lesions (55.1%) were reported as benign, 17 (14.4%) as AUS, 3 (2.5%) as SFN, 4 (3.4%) as SFM, 1 (0.9%) as malignant, and 28 (23.7%) as non-diagnostic. These data are summarized in Figure 8. After repeat FNAs, 25 of the 118 patients (21.2%) underwent surgical resection, with the outcomes as follows: 9 (36%) were malignant, 1 (4%) was a follicular adenoma, and 15 (60%) were benign. Histopathologic results after first and second FNAs are summarized in Tables 1 and 2. Five of 17 AUS cases underwent surgery, and all of them (100%) were benign nodules. There was no statistical differences between the malignancy risks of patients with 1 AUS diagnosis (22.8%) and second AUS diagnosis (0%) who underwent surgery. (corrected chi-square test: 0.3965; $P > .05$).

Thirty-five patients whose lesions were diagnosed as nondiagnostic ($n = 21$), AUS ($n = 12$), or SFN ($n = 2$) on second FNA and who had not undergone surgery were excluded from the study because the nature of their nodules could not be determined.

In total, 140 patients with follow-up (82 patients with surgical resection and 58 patients with repeat FNA without surgical resection) were included in the study.

The malignancy risk for patients who underwent surgical resection after initial diagnosis of AUS was 22.8% (13 of 57), whereas that for patients who underwent second FNA and surgical resection was 36% (9 of 25). When we included patients with second FNA without surgery (58 patients), the malignancy risk was 10.8% (9 of 83); see Table 3. There is a wide range of malignancy risk for AUS as listed in Table 3, which is caused by calculation differences. A more accurate risk for malignancy on AUS aspirates is the number of resected cases along with the number of FNA follow-up cases; therefore, a more accurate risk is 15.7% (22 of 140 cases), as listed in Table 3.

Twenty-two of the 140 patients (15.7%) were diagnosed with malignancies, of which 17 of 22 (77.3%) were papillary thyroid carcinomas (Table 4). Eleven of the 17 papillary carcinomas (64.7%) were follicular variant (Table 5).

DISCUSSION

According to the BSRTC recommendations, AUS is a category of last resort and should not be used indiscriminately. The frequency of AUS is advised to be in the range of approximately $\leq 7\%$ of all thyroid FNA interpretations.¹ The literature published after the BSRTC reported a rate of AUS between 2% and 18%.⁷⁻¹⁸ Our institution's

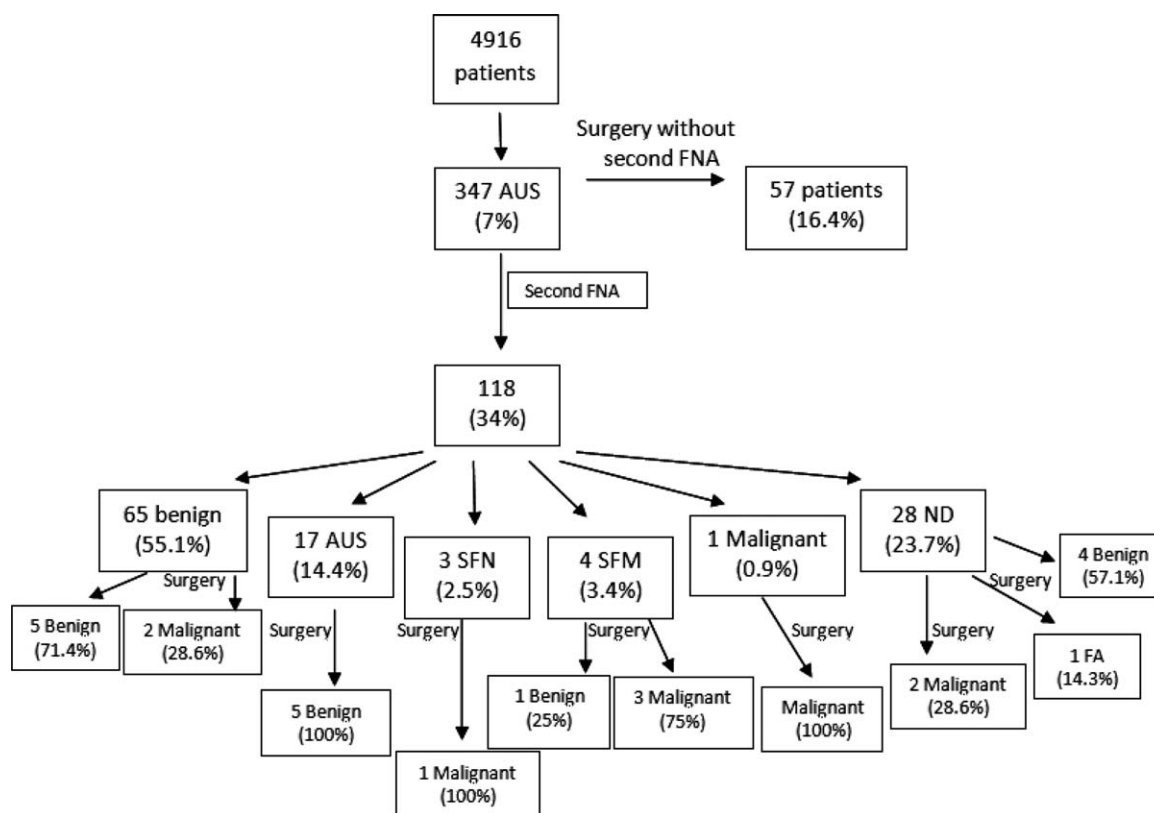


Figure 8. Results of second FNA of 118 patients and histopathologic diagnostic categories of 25 patients who underwent surgery (SFN, suspicious for follicular neoplasm; SFM, suspicious for malignancy; ND, nondiagnostic; FA, follicular adenoma).

diagnostic rate of AUS is 7%, consistent with that reported in the literature.

Recommended management for an initial diagnosis of AUS is clinical correlation, and for most cases, FNA should be repeated at an appropriate interval.¹⁹ Repeat FNA usually yields a more definitive diagnosis; only approximately 20%-25% of nodules are repeatedly interpreted as AUS.^{7,20} In the present study, 14.4% of patients (17 of 118) were diagnosed as AUS after repeated FNAs. Because surgery is performed only on a subset of AUS cases, it is difficult to ascertain the risk of malignancy of AUS. The resected cases represent a selected population with multiple AUS results or patients with worrisome clinical or sonographic findings. In this selected population, 20%-25% of patients with AUS prove to have histopathologically confirmed cancer; however, this is an overestimate for all AUS nodules.^{20,21} Extrapolating for all AUS nodules (including patients with negative follow-up without surgery), the risk of malignancy is possibly close to 5%-15%.⁶ The malignancy risk in the present study was 15.7% (22 of 140) including 82 patients with surgical resection, and 58

patients with repeat FNA without surgical resection. In the literature, the malignancy risk for AUS ranges from 6% to 48% for resected cases and 5% to 27% for all cases.^{5,7-18} This wide range is generated by calculating the malignancy risk in all cases or only in resected cases. In the present study, the malignancy rate was 26.8% (22 of 82) for resected cases, 15.7% (22 of 140) for patients with either resection or FNA follow-up, and 6.34% (22 of 347) for all AUS cases, consistent with those reported previously.

The proposed Bethesda classification algorithm for clinical follow-up of most patients with an initial AUS diagnosis recommends repeat FNA after 3-6 months, with subsequent surgical resection if the follow-up FNA results in a diagnosis of AUS or worse.²² VanderLaan et al reported malignancy rates of 52.3% and 41% for patients who had undergone surgery after repeat FNA and those who had undergone surgery after the first diagnosis of AUS, respectively, although the difference was not statistically significant. In the present study, the malignancy risk of patients with repeat FNA followed by surgery was 36% (9 of 25), whereas that for patients who underwent

TABLE 1. Histopathologic Diagnostic Categories of Patients Who Underwent Surgery After First or Second FNA

Surgery	Benign, n (%)	Follicular adenoma, n (%)	WDT-UMP, n (%)	Malignant, n (%)	Total, n (%)
After the first AUS diagnosis	39 (68.4)	4 (7)	1 (1.8)	13 (22.8)	57 (100)
After second FNA	15 (60)	1 (4)	0	9 (36)	25 (100)

Abbreviations: AUS, atypia of undetermined significance; FNA, fine-needle aspiration; WDT-UMP, well-differentiated tumor of uncertain malignant potential.

TABLE 2. Histopathologic Results of 82 Patients Who Underwent Surgery With or Without Repeat FNA

Histopathologic Diagnosis	n (%)
Malignant	22 (26.83)
WDT-UMP	1 (1.22)
Follicular adenoma	5 (6.01)
Adenomatous nodule	8 (9.8)
Nodular goiter	32 (39.02)
Diffuse hyperplasia	1 (1.22)
Hashimoto thyroiditis	13 (15.9)
Total	82 (100)

Abbreviations: FNA, fine-needle aspiration; WDT-UMP, well-differentiated tumor of uncertain malignant potential.

surgery after initial diagnosis of AUS was 22.8% (13 of 57). This increase was not statistically significant, indicating minimal additional benefit to repeat FNA. VanderLaan et al reported an overall malignancy rate of 23.7% when they included patients with benign lesions after follow-up FNA.¹⁶ In the present study, this rate was 10.8% (9 of 83) including diagnosis of benign lesions after repeat FNA follow-up. Therefore, cytologic, clinical, and radiologic findings should be evaluated together when deciding to perform surgery or repeat FNA.

VanderLaan et al reported a malignancy risk of 27.5% for lesions diagnosed as AUS, which included 89% papillary carcinomas.¹⁶ Similarly, Layfield et al and Marchevsky et al reported 77%, and 90%, respectively, of the AUS nodules of their patient populations were papillary carcinomas.^{8,15} In the present study, 22 of 140 patients (15.7 %) were diagnosed with a malignancy, and 17 of the lesions (77.3%) were papillary thyroid carcinomas. Eleven of the 17 papillary carcinomas (64.7%) were diagnosed as follicular variant. The cytologic features of follicular variant papillary carcinomas (FVPTCs) may be subtle, leading to a diagnosis of benign, SFM, or malignant. In the present study, most of the AUS cases were FVPTCs. These findings emphasize that it is essential to evaluate clinical, radiologic, and cytopathologic findings when making decisions to perform surgery.

TABLE 3. Malignancy Risk of Lesions Diagnosed as AUS Generated Using Different Calculations

	Malignancy Risk
Patients who underwent surgery after first AUS diagnosis	13/57 (22.8%)
Patients who underwent surgery after second FNA	9/25 (36%)
All resected cases	22/82 (26.83%)
Resected cases + FNA follow-up cases	22/140 (15.7%)
Patients who underwent second FNA with or without surgery	9/83 (10.8%)
All AUS cases	22/347 (6.34%)

Abbreviations: AUS, atypia of undetermined significance; FNA, fine-needle aspiration.

TABLE 4. Malignant Histopathologic Diagnoses of 22 Cases

Malignancy	n (%)
Papillary carcinoma	17 (77.3)
Minimally invasive follicular carcinoma	2 (9.1)
WDT-CA (NOS)	2 (9.1)
Carcinoma ^a	1 (4.5)
Total	22 (100)

Abbreviations: WDT-CA (NOS), well-differentiated carcinoma, not otherwise specified.

^aCarcinoma was diagnosed at another center. We do not know the exact tumor type.

TABLE 5. Subtypes of Papillary Carcinoma

Malignancy	n (%)
Papillary carcinoma/microcarcinoma, follicular variant	11 (64.7)
Papillary carcinoma/microcarcinoma, classical type	6 (35.3)
Total	17 (100)

One criterion used to diagnose AUS is sample preparation artifacts, which hinder interpretation of follicular cell atypia. For example, air-drying artifacts causes slight nuclear and cytoplasmic enlargement, pale and slightly smudgy chromatin, and/or mildly irregular nuclear contours.⁶ In our institution, all thyroid FNAs are sent to our laboratory as air-dried, but despite this, all cases are stained with MGG, H&E, and Papanicolaou because the pathologists are familiar with interpreting such preparations. Air-dried slides should be stained with MGG, and

those fixed with alcohol should be stained with Papanicolaou. Moreover, H&E is not used in routine cytology practice; however, we suggest using the stain that the pathologist is most familiar with. Although some air-drying artifacts were frequently present in our cases and some led to a diagnosis of AUS, our AUS rate was lower than expected. If we can overcome the air-drying artifacts, our AUS rates will be less than 7%. Technical issues affecting quality of smears are greatly improved when the cytopathologist performs the procedure, either by palpation or ultrasound guidance, prepares the smears, and renders the preliminary (rapid on-site evaluation) and final diagnosis.

In conclusion, in the literature, there is a wide range of malignancy rates for thyroid lesions diagnosed as AUS that may be accounted for by differences in calculations as well as other clinical and/or radiologic features of the nodules. The malignancy risk for AUS reported in the present study is consistent with those reported previously and is higher than those anticipated according to the Bethesda System. This suggests that a multimodal approach (clinical, radiologic, and cytopathologic) is very important in the management of thyroid nodules diagnosed as AUS. Therefore, we suggest that the recommendation for repeat FNA following an initial diagnosis of AUS should be based on a multimodal approach for each particular patient.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

- Baloch ZW, Alexander EK, Gharib H, Raab SS. Overview of diagnostic terminology and reporting. In: Ali SZ, Cibas E, eds. *The Bethesda System for Reporting Thyroid Cytopathology. Definitions, Criteria and Explanatory Notes*. New York: Springer; 2010:1.
- Layfield LJ, Cibas ES, Baloch Z. Thyroid fine needle aspiration cytology: a review of the National Cancer Institute state of the science symposium. *Cytopathology*. 2010;21:75-85.
- Wu HH, Rose C, Elsheikh TM. The Bethesda system for reporting thyroid cytopathology: an experience of 1,382 cases in a community practice setting with the implication for risk of neoplasm and risk of malignancy. *Diagn Cytopathol*. 2012;40:399-403.
- VanderLaan PA, Marqusee E, Krane JF. Usefulness of diagnostic qualifiers for thyroid fine-needle aspirations with atypia of undetermined significance. *Am J Clin Pathol*. 2011;136:572-577.
- Dincer N, Balci S, Yazgan A, et al. Follow-up of atypia and follicular lesions of undetermined significance in thyroid fine needle aspiration cytology. *Cytopathology*. 2013;24:385-390.
- Krane JF, Nayar R, Renshaw AA. Atypia of undetermined significance/follicular lesion of undetermined significance. In: Ali SZ, Cibas ES, eds. *The Bethesda System for Reporting Thyroid Cytopathology. Definitions, Criteria and Explanatory Notes*. New York: Springer; 2010:37-38.
- Nayar R, Ivanovic M. The indeterminate thyroid fine-needle aspiration: experience from an academic center using terminology similar to that proposed in the 2007 National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference. *Cancer Cytopathol*. 2009;117:195-202.
- Layfield LJ, Morton MJ, Cramer HM, Hirschowitz S. Implications of the proposed thyroid fine needle aspiration category of "follicular lesion of undetermined significance": a five-year multi-institutional analysis. *Diagn Cytopathol*. 2009;37:710-714.
- Theoharis CG, Schofield KM, Hammers L, Udelsman R, Chheng DC. The Bethesda thyroid fine-needle aspiration classification system: year 1 at an academic institution. *Thyroid*. 2009;19:1215-1223.
- Shi Y, Ding X, Klein M, et al. Thyroid fine-needle aspiration with atypia of undetermined significance: a necessary or optional category? *Cancer Cytopathol*. 2009;117:298-304.
- Faquin WC, Baloch ZW. Fine needle aspiration of follicular patterned lesions of the thyroid: diagnosis, management, and follow-up according to National Cancer Institute (NCI) recommendations. *Diagn Cytopathol*. 2010;38:731-739.
- Renshaw AA. Should "atypical follicular cells" in thyroid fine needle aspirates be subclassified? *Cancer Cytopathol*. 2010;118:186-189.
- Jo VY, Stelow EB, Dustin SM, Hanley KZ. Malignancy risk for fine-needle aspiration of thyroid lesions according to the Bethesda System for Reporting Thyroid Cytopathology. *Am J Clin Pathol*. 2010;134:450-456.
- Somma J, Schlecht NF, Fink D, Khader SN, Smith RV, Cajigas A. Thyroid fine needle aspiration cytology: follicular lesions and the gray zone. *Acta Cytol*. 2010;54:123-131.
- Marchevsky AM, Walts AE, Bose S, et al. Evidence-based evaluation of the risks of malignancy predicted by thyroid fine-needle aspiration biopsies. *Diagn Cytopathol*. 2010;38:252-259.
- 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.
- Ustun 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 Cytologica*. 2012;56:361-369.
- Tepeoglu M, Bilezikci B, Bayraktar SG. A histological assessment of the Bethesda system for reporting thyroid cytopathology (2010) abnormal categories: a series of 219 consecutive cases. *Cytopathology*. 2014;25:39-44.
- Layfield LJ, Abrams J, Cochand-Priollet B, et al. Post-thyroid FNA testing and treatment options: a synopsis of the National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference. *Diagn Cytopathol*. 2008;36:442-448.
- Yassa L, Cibas ES, Benson CB, et al. Long term assessment of a multidisciplinary approach to thyroid nodule diagnostic evaluation. *Cancer Cytopathol*. 2007;111:508-516.
- Yang J, Schnadig V, Logrono R, Wasserman PG. Fine needle aspiration of thyroid nodules: a study of 4703 patients with histologic and clinical correlations. *Cancer*. 2007;111:306-315.
- Cibas ES, Ali SZ. The Bethesda System for Reporting Thyroid cytopathology. *Thyroid*. 2009;19:1159-1165.