Diagnostic Thyroidectomy May Be Preferable in Patients With Suspicious Ultrasonography Features After Cytopathology Diagnosis of AUS/FLUS in the Bethesda System

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INTRODUCTION

Thyroid cancer is the first leading cancer accounting for 17.8% of all new cancers diagnosed in the Korean population.1

Cervical ultrasonography (US) is mandatory before surgery for thyroid cancer and is recommended for thyroid nodule evaluation. Fine-needle aspiration cytology (FNAC) under ultrasonography guidance represents the critical initial diagnostic test used to evaluate thyroid nodules and stratify the risk of malignancy. FNAC plays a key role in disease management.2,3

Traditionally, cytological interpretations categorize the specimen into 1 of the 4 diagnostic categories: negative, positive, nondiagnostic, and indeterminate.

As thyroid nodules are evaluated and treated, the first question the cytopathologist encounters is regarding specimen adequacy. If the cytopathologist encounters cellular paucity, most diagnose the nodules as nondiagnostic. The second question that clinicians encounter is indeterminate diagnoses. Indeterminate cytological diagnoses occur in follicular patterned thyroid lesions owing to overlapping cytomorphologic characteristics of benign and malignant lesions.4

The distinction between benign and malignant thyroid nodules has remained challenging for clinicians.

To improve the classification, a revised classification system for reporting thyroid FNAC was proposed at the National Cancer Institute State of Science conference in 2007. This led to the Bethesda System for Reporting Thyroid Cytopathology (BSRTC), which was adopted in 2009 and comprised the following 6 classifications: unsatisfactory/non-diagnostic (category I), benign (category II), atypia or follicular lesion of undetermined significance (AUS/FLUS) (category III), follicular neoplasm/suspicious for follicular neoplasm (category IV), suspicious for malignancy (category V), and positive for malignancy (category VI) (Table 1).5

The traditional indeterminate group was further divided into the AUS/FLUS (category III) and follicular neoplasm (category IV) categories in BSRTC. AUS/FLUS is a new category in the BSRTC, with malignancy rates of ~5% and 15%, for which repeat FNAC is recommended.6 According to the BSRTC, the reported rates of AUS/FLUS have been between 3% and 18% of thyroid FNAC. Furthermore, the frequency of AUS/FLUS diagnosis should be ~7% or less of all thyroid FNAC.6–8

As per the synopsis of the NCISSC, patients with AUS/FLUS FNAC should undergo a second FNAC after 3 months based on clinical correlations and/or ultrasound findings.5,9–11

Performing a repeat FNAC before 3 months is hypothesized to increase the chance of reparative atypia of follicular cells,
These nodules.

FLUS at our institution and optimal surgical treatment of thyroid nodules associated with cytology diagnoses of AUS/FLUS require surgical intervention, the benefit for patients with a repeated diagnosis of AUS/FLUS and surgical intervention is not yet clearly established.

Second, although patients with a repeated diagnosis of AUS/FLUS require surgical intervention, the benefit for patients between repeated FNAC and surgical intervention is a heterogeneous category that contains follicular cells and/or nuclear atypia that exceed benign changes, but the changes are not enough to justify classification into any of the other diagnostic categories. Thus, it has been suggested that AUS could be further subclassified into more distinct subtypes that consulting a distinct consequence for the risk of malignancy.

The aim of this study was to identify specific ultrasonography and clinical predictors of malignancy in a subset of thyroid nodules associated with cytology diagnoses of AUS/FLUS at our institution and optimal surgical treatment of these nodules.

MATERIALS AND METHODS

Patient Cohort and Selection

This study was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine, and was conducted according to the principles of the Helsinki Declaration (IRB No.3-2013-0246). Between January 2011 and December 2012, a total of 8244 FNAC were performed at the Thyroid Cancer Center, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. Of these, 757 FNACs (9.2%) were interpreted as AUS/FLUS, follicular neoplasm/suspicious for follicular neoplasm, suspicious for malignancy, or nondiagnostic/factory/nondiagnostic, benign, AUS/FLUS, follicular neoplasm or unsatisfactory. BSRTC categories were comprised of the following: unsatisfactory, hypercellular, follicular, suspicious for malignancy, or unsatisfactory.

Between January 2011 and December 2012, a total of 8244 FNAC were performed at the Thyroid Cancer Center, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. Of these, 757 FNACs (9.2%) were interpreted as AUS/FLUS in BSRTC. Patients who underwent thyroid surgery for recurrent thyroid cancer were excluded.

Patients with typical features for thyroid cancer on ultrasonography imaging were recommended thyroidectomy, and patients with controversial ultrasonography findings who wanted repeated FNAC received repeated FNAC. If patients had controversial ultrasonography findings repeatedly, they were recommended for the same process.

Finally, of the 757 cases of AUS/FLUS, 284 cases (37.5%) that were reported as suspicious for follicular neoplasm (category IV), suspicious for malignancy (category V), or malignant (category IV) underwent thyroidectomy, 213 cases (28.1%) underwent thyroidectomy after a diagnosis of AUS/FLUS, and 260 cases (34.4%) were closely observed.

During the same period, a total of 5440 patients underwent thyroid surgery. Of these, 213 (3.9%) patients were AUS/FLUS at preoperative cytopathology diagnosis.

After identification of the enrolled patients, medical records including patient demographics, subsequent clinical outcomes, imaging studies such as ultrasonography, FNAC results, and surgical pathology results, were retrospectively reviewed. The surgical extent for thyroid cancer was decided by the American Thyroid Association (ATA) and Korean Thyroid Association (KTA) guidelines.

Classification of Ultrasonography Findings of Nodules With AUS/FLUS

US features were described based on the “Guidelines for Thyroid US” by the Thyroid Study Group, Korean Society of Head and Neck Radiology.

US findings of the thyroid nodules were evaluated for the following categories: shape, margins, echogenicity, and calcification. Nodule shape was described as oval-to-round, taller than wide or irregular. The margin was described as well defined, ill defined, or speculated. The presence of calcification was described as none, microcalcification (<1 mm), or macrocalcification (≥1 mm). The echogenicity of the nodule was described as hyper-, iso-, or hypoechogenic compared with the thyroid gland or as markedly hypoechogenic compared with the adjacent strap muscle. US criteria for malignant nodules were taller-than-wide, speculated margin, marked hypoechogenicity, and the presence of micro- or macrocalcifications.

FNAC and Cytology Interpretation

FNAC were performed under ultrasound guidance using 3 to 4 passes with 22-gauge needles. Syringes with FNAC were rinsed in a methanol–water solution (ThinPrep CytoLyt, Hologic).

A board-certified cytopathologist made cytology interpretations and classifications based on the BSRTC. The transition to BSRTC took place in December 2009 at our institution. The BSRTC categories were comprised of the following: unsatisfactory/ nondiagnostic, benign, AUS/FLUS, follicular neoplasm/suspicious for follicular neoplasm, suspicious for malignancy, and positive for malignancy (Table 1).

Statistical Analyses

Student t tests were used for univariate analyses when comparing selected variables. Pearson’s chi squared tests were

| TABLE 1. The Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy a Recommended Clinical Management |
|---------------------------------------------------------------|
| Diagnostic Category | Risk of Malignancy (%) | Usual Management |
|----------------------|------------------------|-----------------|
| Nondiagnostic or unsatisfactory | 1–4 | Repeat FNAC |
| Benign | 0–3 | Clinical follow-up |
| Atypia of undetermined significance or follicular lesion of undetermined significance | ~5–15 | Repeat FNAC |
| Follicular neoplasm or suspicious for follicular neoplasm | 15–30 | Surgical lobectomy |
| Suspicious for malignancy | 60–75 | Near-total thyroidectomy or surgical lobectomy |
| Malignant | 97–99 | Near-total thyroidectomy |

FNAC = fine-needle aspiration cytology.

increasing the potential for false-positive diagnoses of malignancy (Table 1).

Some concerns and confusion were encountered when adapting the AUS diagnosis according to the BSRTC. First, AUS/FLUS is a heterogeneous category that contain follicular cells and/or nuclear atypia that exceed benign changes, but the changes are not enough to justify classification into any of the other diagnostic categories. Thus, it has been suggested that AUS could be further subclassified into more distinct subtypes that consulting a distinct consequence for the risk of malignancy.

Second, although patients with a repeated diagnosis of AUS/FLUS require surgical intervention, the benefit for patients between repeated FNAC and surgical intervention is not yet clearly established.

The aim of this study was to identify specific ultrasonography and clinical predictors of malignancy in a subset of thyroid nodules associated with cytology diagnoses of AUS/FLUS at our institution and optimal surgical treatment of these nodules.

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used to analyze categorical and nonparametric data. Multiple logistic regression analyses with a forward stepwise variable selection procedure were used to select significant variables and identify independent predictors of malignancy. A P value of < 0.05 was considered statistically significant.

RESULTS

There were 757 AUS/FLUS on preoperative FNAC. Of these, 213 cases (28.1%) underwent thyroidectomy under the preoperative diagnosis of AUS/FLUS. Of the 213 patients, 158 (74.2%) were diagnosed with thyroid carcinoma at the final pathology reports.

In univariate analyses, repeated times of FNAC did not correlate with cancer risk. Patients with repeated FNAC (> 2 times) were similar to patients with single FNAC (Table 2, P = 0.573).

Based on US findings, thyroid nodules that were confirmed as carcinoma on the final pathology reports showed significantly more malignant features than benign confirmed nodules: taller than wide (12.7% vs 0%, P = 0.003), ill-defined margins (58.2% vs 38.2%, P = 0.012), hypoechogenicity (75.9% vs 52.7%, P = 0.002), and microcalcification (17.1% vs 12.7%, P = 0.001) (Table 2).

In multivariate analyses, the frequency of FNAC was not significantly correlated with cancer diagnosis. From the US findings, hypoechogenicity (odds ratio 2.521, P = 0.007) and microcalcification (odds ratio 3.247, P = 0.005) were significantly correlated with cancer risk (Table 2).

Scoring using variables that were statistically significant in Table 2 (taller than wide, ill-defined margin, hypoechogenicity, and microcalcification) showed that as the number of malignant US characteristics of cancer increased, the possibility of cancer is increased (Pearson’s correlation coefficient = 0.990, P < 0.001) (Table 3).

DISCUSSION

FNAC has an essential role in the evaluation of thyroid nodules. Traditionally, the cytological interpretation categorizes the specimen into 1 of the 4 diagnostic categories: negative, positive, nondiagnostic, and indeterminate.

However, some thyroid FNACs are not easily classified into the benign, suspicious, or malignant categories. Indeterminate diagnoses have been used to represent follicular patterned thyroid lesions due to the overlapping cytomorphologic characteristics of benign and malignant lesions.

After the National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference took place in October 2007, the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) was proposed. BSRTC was adopted worldwide in 2009 and our institution adopted in 2009.

In BSRTC, some thyroid FNACs that are not easily classified into benign or malignant were reported as “Atypia of Undetermined Significance (AUS)” or “Follicular Lesion of Undetermined Significance (FLUS)” in the Bethesda System for Reporting Thyroid Cytopathology. AUS/FLUS are included in the indeterminate diagnoses.

The risk of malignancy for all AUS/FLUS cases including those patients with benign results at follow-up and who did not undergo surgery is presumably 5% to 15%. The malignancy rates in recently published studies using the BSRTC show a

| TABLE 2. Univariate and Multivariate Analyses of Times of FNAC and Ultrasonographic Features |
|-----------------------------------------------|-------------------|-----------------------|-----------------|-----------------|
| Variables                                      | Times of FNAC     | Ultrasound features   |                                            |
| Benign (n = 55)                                | Malignant (n = 158)| Taller than wide      | Ill-defined margin | Hypoechogenicity | Microcalcification |
| 1 (n = 179)                                    | 48 (26.8%)        | 20 (12.7%)            | 120 (75.9%)     | 67 (42.4%)      | 20 (12.7%)    |
| 2 (n = 24)                                     | 4 (16.7%)         | 92 (58.2%)            | 120 (75.9%)     | 67 (42.4%)      | 20 (12.7%)   |
| 3 (n = 10)                                     | 3 (30.0%)         | 7 (70.0%)             | 120 (75.9%)     | 67 (42.4%)      | 20 (12.7%)   |
| Odds Ratio (95% CI)                            | 1.139 (0.443–2.932)| 1.482 (0.402–2.947) | 2.521 (1.393–5.431) | 3.247 (1.533–8.027) |
| P Value                                       | 0.573             | 0.003                 | 0.012            | 0.001            | 0.005        |

CI = confidence interval, FNAC = fine-needle aspiration cytology.

| TABLE 3. Scoring Using Variables that Have Statistical Significance in Table 2 |
|-----------------------------------------------|-------------------|-----------------|-----------------|
| Number of Variables | Benign (n = 55) | Malignant (n = 158) | Pearson’s Correlation Coefficient (ρ) | P Value |
| 0                 | 16 (51.6%)     | 15 (48.4%)        | 0.990           | <0.001          |
| 1                 | 22 (36.1%)     | 39 (63.9%)        |                 |                 |
| 2                 | 14 (19.2%)     | 59 (80.8%)        |                 |                 |
| 3                 | 3 (7.3%)       | 38 (92.7%)        |                 |                 |
| 4                 | 0 (0%)         | 7 (100%)          |                 |                 |

Variables: taller than wide, ill-defined margin, hypoechogenicity, and microcalcification.
CONCLUSIONS

Repeated AUS/FLUS results in preoperative FNAC are challenging for pathologists and clinicians. If indications for thyroidectomy, regardless of AUS/FLUS results, were established, repeat biopsies do not appear necessary. Although AUS/FLUS in cytopathology is recommended for repeating FNAC in BSRTC, thyroidectomy with diagnostic intent may be recommended for thyroid nodules with US findings that suggest the possibility of cancer.

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