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Can Repeat Biopsies Change the Prognoses of AUS/FLUS Nodule?

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Keywords
Repeat fine-needle aspiration biopsy · Atypia of undetermined significance/follicular lesions of undetermined significance nodules · Malignancy rate · Ultrasonography

Abstract
Objective: Experience with atypia of undetermined significance/follicular lesions of undetermined significance (AUS/FLUS) showed that this category exhibited a marked variability in incidence and malignant outcome in resection specimens. We aimed to determine the utility of repeated fine-needle aspiration biopsies (FNABs) and ultrasonography to determine the malignancy rate in AUS/FLUS nodules. ***Methods:*** 23,587 nodules were biopsied, and 1,288 had at least one AUS/FLUS cytology. Ultrasonographic features including solid hypoechoic status, irregular margins, microcalcifications, nodule taller than wider, or an extrathyroidal extension were also recorded. Nodules for which only 1 FNAB revealed AUS/FLUS cytology were termed Group 1; nodules that underwent 2, 3, and 4 FNABs were termed Groups 2, 3 and 4, respectively. We compared these groups according to malignancy rates. ***Results:*** 576 of nodules underwent only 1 FNAB (Group 1); 505, 174, and 33 underwent 2 (Group 2), 3 (Group 3), and 4 FNABs (Group 4), respectively. Fifty-six (30.6%), 45 (27.3%), 18 (30%), and 5 (33.3%) of Groups 1–4 were malignant, respectively. The risk of malignancy was similar in each group ($p > 0.05$). Suspicious ultrasonographic features were encountered in malignant nodules more than benign nodules ($p < 0.05$, for each). ***Conclusion:*** Repeat biopsy of AUS/FLUS nodules did not enhance the identification of malignancy. Ultrasonographic features may be a better guide for the decision of either surveillance or diagnostic surgery.

Introduction

Thyroid nodules are a common clinical problem. Epidemiological studies have shown that the prevalence of palpable thyroid nodules is approximately 5% [1, 2]; however, the frequency of incidental discovery using ultrasound (US) or other radiological modalities ranges widely from 20 to 76% [3, 4]. Fine-needle aspiration biopsy (FNAB) is the optimal procedure for preoperative dis-

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crimination of benign from malignant nodules [5, 6]. The Bethesda System for Reporting Thyroid Cytopathology ("Bethesda System") has been widely used since 2009 for cytopathological assessment [7]. The 6 possible cytological diagnoses (I–VI) are: nondiagnostic (ND), benign, atypia of undetermined significance/follicular lesions of undetermined significance (AUS/FLUS), follicular neoplasm/suspicion of follicular neoplasm (FN/SFN), suspicion of malignancy (SFM), and malignant, respectively. A malignancy risk is assigned to each category to guide appropriate clinical management. In a literature review, Cibas and Ali [7] showed that the malignancy rates were 1–4% for ND, 0–3% for benign, 5–15% for AUS/FLUS, 15–30% for FN/SFN, 60–75% for SFM, and 97–99% for malignant nodules. Of these categories, category 3 (AUS/FLUS) features principally sparse, compromised samples with suspicious (atypical) cytological or architectural features, but the extents of such features do not permit diagnosis of FN/SFN or SFM status [8, 9]. Recent studies using the Bethesda categories found that the AUS/FLUS category exhibited marked variability in both the incidence (0.8–28%) and malignancy rate (6–48%) of resection specimens [10–14]. The AUS/FLUS management options of the current guidelines and those recommended by recent studies include repeat FNAB, molecular testing, follow-up, lobectomy, or core needle biopsy [8, 10]. However, molecular tests are not available at most centers.

High-resolution US is an excellent imaging protocol for the assessment of thyroid pathologies including abnormal nodular morphology and suspicious lymph nodes and should be used to guide FNAB and FNAB-based decision-making. The US is also valuable during follow-up of nodules and thyroid malignancies. Here, we share our experience with a large cohort of patients of Bethesda category 3 treated in a comprehensive thyroid center; all nodules were classified according to the Bethesda System. We determined whether repeat FNABs and the US more accurately estimated the malignancy rate.

Materials and Methods

Patients with at least 1 AUS/FLUS nodule treated between January 2016 and December 2018 at Yildirim Beyazit University Hospital were reviewed. We biopsied 23,587 nodules, of which 1,288 exhibited AUS/FLUS cytology. Some nodules were biopsied only once, but others were biopsied repeatedly to refine the diagnoses. This was a retrospective study of the patients defined above, and was performed in a single, large academic institution serving as a tertiary referral center for patients with thyroid neoplasms. Our Institutional Ethics Committee approved the study. The Bethesda System (6 categories) was used for cytological evaluation [7]: ND (category 1), benign (category 2), AUS/FLUS (category 3), FN/SFN (category 4), SFM (category 5), and malignant (category 6). All patients underwent thyroid US in our hospital and were recommended for surgery on suspicion of malignancy, or repeat FNAB or other follow-up, at the discretion of the attending thyroid surgeon/endocrinologist, with consideration of patient preference. If the second FNAB of AUS/FLUS nodules revealed ND, FN/SFN, SFM, or malignant status, surgery was recommended. If a repeat FNAB of an AUS/FLUS nodule was also of AUS/FLUS status, surgery was offered. When the second FNAB was benign, re-biopsy was performed if nodule growth (20% increase in at least two nodule dimensions with a minimal increase of 2 mm or more than a 50% change in volume) [11] or suspicious sonographic features was/were evident. Surgery was recommended if a nodule benign on FNAB was ≥4 cm in diameter. In addition, some patients were operated upon to treat suspicious nodules (other than the index AUS/FLUS nodule) in the thyroid parenchyma. Additional operative criteria included a large multinodular goiter, sonographic features that were of concern [11], nodules that were growing, clinical suspicion, or patient/physician preference. Patients who accepted thyroidectomy underwent total/near-total thyroidectomy or lobectomy-plus-isthmectomy. Despite the suggestion of surgery, some patients requested re-biopsies or other follow-up and others were lost to follow-up. A carcinoma in a nodule other than the investigated index nodule was defined as an incidental carcinoma and was not reported as a carcinoma associated with AUS/FLUS status in our present series.

Demographic characteristics and thyroid autoantibody status were recorded. Thyroid peroxidase antibody (anti-TPO) and thyroglobulin antibody (anti-Tg), were measured with a chemiluminescent immunoassay method (CMIA) (Architect i2000 system, Abbott, USA) between the years 2014 and 2016. Positive anti-TPO, and anti-Tg were defined as a value greater than 5.61 and 4.11 IU/mL, respectively. After this period, samples were analyzed for anti-TPO and anti-Tg using the Roche Cobas 8000 Modular e602 electrochemiluminescence immunoassay. The reference ranges were 0–34 IU/mL and 0–115 for anti-TPO and anti-Tg, respectively. Levels higher than the reference values were considered positive and all other levels were considered negative. Esaote color Doppler ultrasonography (Model 796FDII; MAG Technology Co. Ltd., Yung-Ho City, Taipei, Taiwan) using a superficial probe (Model LA523 13–4, 5.5–12.5 MHz) was performed by endocrinologists. Preoperative US nodular findings (location, diameters [anteroposterior (AP), transverse (T), and longitudinal], the AP/T ratio, echogenicity, texture, marginal [ir]regularity, micro- and macro-calcification status, and halo status) were recorded. According to the recent ATA guideline, high suspicion is appropriate if any of the following features are present: solid hypoechoic status, irregular margins, microcalcifications, nodule taller than wider, or an extrathyroidal extension [11]. FNAB was performed using a 27-G needle and a 20-mL syringe under US guidance (Logic Pro 200 GE fitted with a 7.5-MHz probe; Kyunggi-Do, South Korea). All patients gave written informed consent before their procedures. FNAB samples were smeared, air-dried, and Giemsa-stained.

We divided all nodules into two groups based on histopathology: benign (Group B) and malignant (Group M). Nodules for which only 1 FNAB revealed AUS/FLUS cytology were termed

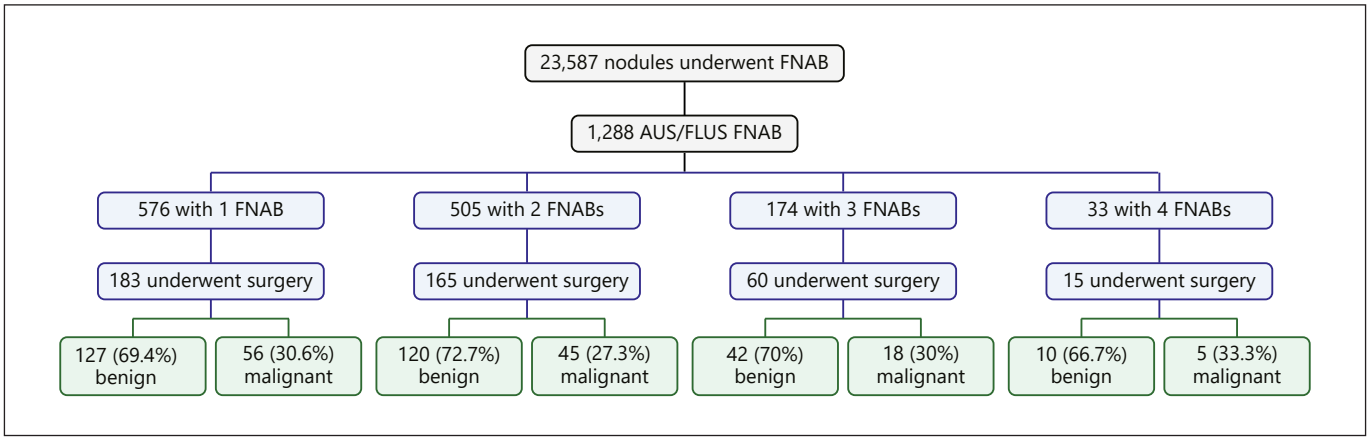

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Fig. 1. Outcome of AUS/FLUS nodules according to the number of FNABs performed.

Group 1; nodules with a recent AUS/FLUS cytology that underwent 2, 3, and 4 FNABs (samples were taken on different occasions) were termed Groups 2, 3, and 4, respectively. We evaluated groups in terms of preoperative US findings, demographic features, and FNAB results. Estimation of the malignancy risk for AUS/FLUS nodules was subject to bias because not all such nodules were surgically removed; thus, not all were subjected to definitive histopathological analyses. Calculation of the risk for malignancy (ROM) based only on patients undergoing follow-up would overestimate the ROM, assuming that some AUS/FLUS nodules were benign nodules and/or inclusion of all patients regardless of follow-up status would underestimate the ROM. The real ROM lies somewhere between these two extreme values. Therefore, we provide a ROM range for each value. The upper and lower ROM bounds of AUS/FLUS patients were calculated. The lower bound was derived by dividing the number of malignancies evident histologically by the number of AUS/FLUS nodules diagnosed using FNAB. The upper bound was calculated by dividing the number of malignancies evident histologically by the number of AUS/FLUS nodules that underwent surgery. As nodules selected for surgery may have other clinical or ultrasonographic features that increase suspicion, this number would overestimate the prevalence of malignancy. The true prevalence probably lies between the lower and upper bounds.

Statistical Analyses

All statistical analyses were performed using the IBM Statistical Package for Social Sciences for Windows ver. 25.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was evaluated using the Kolmogorov-Smirnov test. Fisher's exact test was employed to assess the statistical significance of categorical variables. Between-group comparisons were performed using Student's *t* test to compare parametric variables and the Mann-Whitney U test to compare nonparametric variables. The Kruskal-Wallis test was employed to assess the significance of differences among the means of 3 or more independent groups. All p values were two-sided, and a $p < 0.05$ level was considered statistically significant.

Results

Of the 23,587 nodules, 1,288 (5.4%) of 1,234 patients exhibited AUS/FLUS cytology at least once. A total of 414 (33.5%) patients with 423 nodules underwent surgery, and 124 (29.3%) nodules were histopathologically malignant. The ROM lower bound was 9.6%. The mean age of Group B patients was higher than that of Group M patients (49.99 ± 12.12 vs. 47.13 ± 12.38 years, respectively [$p = 0.031$]). Most patients (79.09%) were female; the female/male ratios were similar in Groups B and M ($p = 0.85$). Most patients who underwent surgery were anti-Tg-negative (78.7%) and anti-TPO-negative (72.6%). These rates were similar in patients with benign and malignant histopathological findings ($p > 0.05$). The malignancy rates of AUS/FLUS patients who underwent surgery, with and without repeat FNAB, were 28.3 and 30.6%, respectively ($p > 0.05$).

Nodular outcomes are shown in Figure 1; 576 (44.7%) of nodules underwent only 1 FNAB (Group 1); 505 (39.2%), 174 (13.5%), and 33 (2.6%) underwent 2 (Group 2), 3 (Group 3), and 4 FNABs (Group 4), respectively. Of the Group 1 nodules, 183 (31.8%) were surgically removed; 56 (30.6%) were malignant. In Group 2, 165 (32.7%) nodules were surgically removed, and 45 (27.3%) were malignant. In Group 3, 60 (34.5%) nodules were surgically removed, and 18 (30%) were malignant. In Group 4, 15 (45.45%) nodules were surgically removed, and 5 (33.3%) were malignant. The ROM upper bounds were similar in all groups ($p = 0.89$). The lower ROM bounds were 9.7, 8.9, 10.3, and 15.2% in Groups 1, 2, 3, and 4, respectively, which again were similar among the groups ($p = 0.6$). Of the second biopsies, 324 (45.5), 221 (31), 142 (19.9), 4 (0.6), 14 (2), and 7 (1%) were of Bethesda catego-

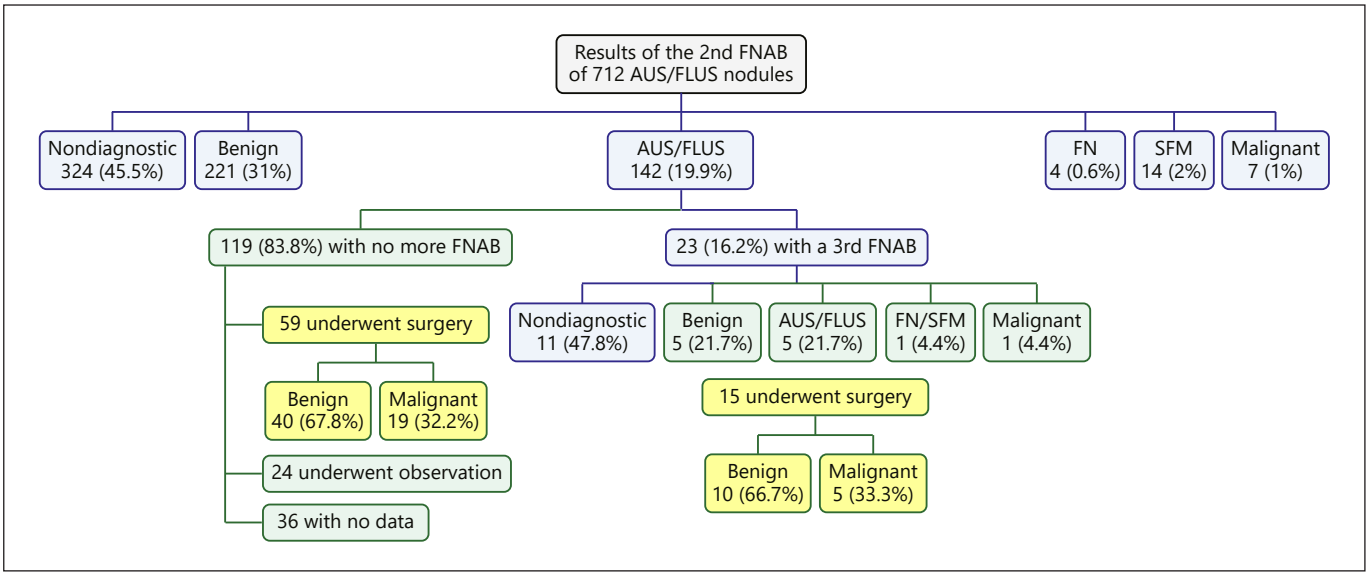

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Fig. 2. Results of the second FNAB of 712 AUS/FLUS nodules.

Table 1. Comparison of all the 2nd cytology results according to histopathologies

	Benign	Malignant	Total
Nondiagnostic	105 (81.4%)	24 (18.6%)	129
Benign	13 (76.5%)	4 (23.5%)	17
AUS/FLUS	50 (67.6%)	24 (32.4%)	74
FN	1 (33.3%)	2 (66.7%)	3
SFM	2 (16.7%)	10 (83.3%)	12
Malignant	1 (20%)	4 (80%)	5
Total	172 (71.7%)	68 (28.3%)	240

p value for this comparison is <0.001.

ries 1–6, respectively (Fig. 2). A total of 24 (18.6%) ND nodules, 4 (23.5%) benign nodules, and 24 (32.4%) AUS/FLUS nodules that were surgically removed were malignant (Table 1). The ROM upper bounds were similar for nodules of Bethesda categories 1 and 2 ($p = 0.74$) but were higher for nodules of category 3 ($p = 0.026$). The lower ROM bounds of the second FNABs were 7.4, 1.8, 16.9, 50, 71.4, and 57.1% for nodules of Bethesda categories 1–6, respectively, being highest for Bethesda category 3 among the first 3 Bethesda categories ($p < 0.001$).

One hundred and nineteen of the nodules with double AUS/FLUS cytology did not undergo a third FNAB (Fig. 2). Fifty-nine were surgically removed, and 19 (32.2%) were malignant. The lower ROM bound was 16%. Twenty-three of the nodules with double AUS/FLUS cytology underwent a third FNAB (Fig. 2). Eleven (47.8%), 5 (21.7%), 5 (21.7%), 1 (4.4%), 0 (0%), and 1 (4.4%) were of Bethesda categories 1–6, respectively. Fifteen were surgically removed, and 5 (33.3%) were malignant. The lower ROM bound was 21.7%. The upper and lower ROM bounds in these 2 groups (double AUS/FLUS nodules biopsied twice and three times) were similar ($p = 0.9$, $p = 0.54$, respectively). Four of the nodules ($n = 5$ in all) with triple AUS/FLUS cytology were surgically removed, and 2 (50%) were malignant. One of the nodules with triple AUS/FLUS cytology was also biopsied a fourth time due to patient preference and remained of AUS/FLUS status. The nodule was surgically removed and was malignant (malignancy rate 100%).

Of the 414 patients, the preoperative US features of 124 histopathologically malignant nodules were compared to those of 299 histopathologically benign nodules (Table 2). The AP diameter did not significantly differ ($p = 0.17$), but the T ($p = 0.02$) and longitudinal diameters ($p = 0.027$) were higher in Group B. The AP/T ratio was significantly higher in Group M than in Group B ($p = 0.006$). Presence of macrocalcification was similar in Groups B and M ($p = 0.21$). An irregular margin, microcalcification, and absence of a halo were more common in Group M than in Group B (12.9 vs. 1.5%, $p < 0.001$, 15.5 vs. 5.1%, $p = 0.001$, and 81 vs. 71%, $p = 0.038$, respectively). Nodule echogenicity differed between Groups B and M; hypoechoic nodules were more common in Group M (49.1 vs. 25.3%, $p < 0.001$).

Table 2. Comparison of the preoperative ultrasonographic features of AUS/FLUS nodules with malignant and benign final histopathology

	Benign (n = 299)	Malignant (n = 124)	p
Irregular margin	4 (1.5%)	16 (12.9%)	<0.001
Microcalcification	15 (5.1%)	19 (15.5%)	0.001
Hypoechogenity	75 (25.3%)	60 (49.1%)	<0.001
Absence of a halo	212 (71%)	99 (81%)	0.038
Macrocalcification	44 (14.7%)	24 (19.8%)	0.21
Anteroposterior diameter, cm (median)	11.9 (3.9–46.4)	10.1 (3.7–34.9)	0.17
Transverse diameter, cm (median)	14.8 (4.4–142.2)	13.1 (3.9–53.4)	0.02
Longitudinal diameter, cm (median)	16.7 (5–150)	14.7 (4.8–63.3)	0.027
AP/T ratio (median)	0.7 (0.3–1.28)	0.78 (0.41–1.27)	0.006

AP, anteroposterior; T, transverse.

Discussion

Of all nodules, 1,288 (5.4%) were of AUS/FLUS status; 423 (32.8%) were surgically removed, and the malignancy rate was 29.3%. Our AUS/FLUS frequency of 5.4% was within the literature range (1–27%; average 10%) [12, 13], and close to the frequency (7%) commonly recorded using the Bethesda System [7]. Our malignancy rate of 29.3% in resected AUS/FLUS patients was also within the literature range (6–48%) [10–14]. As the malignancy rate varies among institutions, we believe it is useful to present our figures. The risk for AUS/FLUS nodular malignancy as defined by the Bethesda System is lower than our results; the usual range is 5–15% [7]. The malignancy rates of AUS/FLUS nodules subjected or not to repeat biopsy differed in different patient series [14–23].

In our series, the malignancy rates of resected patients with AUS/FLUS nodules were 30.6, 27.3, 30, and 33.3% in Groups 1–4, respectively. Malignancy rates were similar between groups regardless of the number of recurrent biopsies. To the best of our knowledge, this is the first study consisting of a substantial number of third (n = 174) and fourth biopsies (n = 33) of an AUS/FLUS nodule. We compared our results with the studies reporting the outcome of AUS/FLUS nodules with a second FNAB. Our results support the findings of the studies suggesting that repeat biopsy does not affect the malignancy rates [17, 21, 22]. Broome et al. [22], VanderLaan et al. [21], and Nagarkatti et al. [17] reported that the malignancy rate did not change with repeat FNAB, whereas Ho et al. [16] and Stanek-Widera et al. [24] disagreed. It was previously suggested that the recommended repeat biopsy for most patients with initial AUS/FLUS diagnoses should be reconsidered. However, some reports do not support this suggestion. Ho et al. [16] found that of 541 AUS/FLUS nodules, 350 (64.7%) that were immediately surgically removed exhibited a malignancy rate of 38.6%. The malignancy rate of 31 patients with AUS/FLUS nodules removed after repeat biopsy was 29.03%. Stanek-Widera et al. [24] reported that the cancer risk in patients with FLUS nodules was 2.78%, but that risk fell to 2.43% on subsequent biopsy. Conversely, Gweon et al. [15] found that the malignancy rate of patients with AUS/FLUS nodules increased from 78 to 89% on repeat biopsy. Wong et al. [14] showed that, of cases diagnosed with AUS/FLUS nodules on initial biopsy, the malignancy rates were 39% for those who underwent repeat biopsy but 26% for those who underwent surgery without repeat biopsy. Although the Bethesda System recommends biopsy of AUS/FLUS nodules, the American Thyroid Association (ATA) is less clear on this topic ("weak" recommendation) [11], and the AACE/AME/ETA guidelines recommend that repeat biopsy should not be performed because the results may be confusing [25, 26].

In this study, repeat biopsies were benign in 31% (221/712) of patients, suggesting that the Bethesda recommendation of repeat biopsy may be beneficial for some cases. Sullivan et al. [13] reviewed many studies that demonstrated the benefits of repeat biopsy for "reclassifying" AUS/FLUS cases into categories other than AUS/FLUS or nondiagnostic. The reclassification rates ranged from 50 to 100% [13]. Our results do not support a useful role for repeat biopsy; the reclassification rate was 34.6%.

In the patient series of VanderLaan et al. [21] and Renshaw et al. [27], nodules of initial Bethesda category 3 biopsy status followed by benign status on a second biopsy, and which were then surgically removed, exhibited malignancy in 28.5% (2/7) and 9.4% (3/32) of cases, respective-

ly. In our series, 23.5% (4/17) had malignancies. Ho et al. [16] reported that none of the 2 patients exhibited malignancy, but most patients (39/41) did not proceed to surgery. Given the small number of patients in the subsets under discussion, the question of whether repeat biopsy is useful is difficult to answer; it is not clear whether a benign diagnosis on repeat biopsy should be accorded greater or lesser weight than the index AUS/FLUS diagnosis. The risk for malignancy of a nodule of initial AUS/FLUS status followed by benign status may lie somewhere between the risks of malignancy for the 2 individual categories.

In this study, the malignancy rates were 30.6% (n = 183), 32.4% (n = 59), 50% (n = 4), and 100% (n = 1) for 1–4 consecutive AUS/FLUS reports, respectively. The numbers of nodules with 3 and 4 consecutive AUS/FLUS reports were very low; the statistics are not robust.

Any association between thyroid malignancy and Hashimoto thyroiditis remains controversial. Gabalec et al. [28] found no relationship between the presence of autoantibodies against thyroid peroxidase or thyroglobulin, and malignancy rate. Topaloglu et al. [29] reported that the anti-TPO and anti-Tg positivity rates were significantly higher in a malignant compared to a benign group of patients with AUS/FLUS cytology, but found no association between histopathological Hashimoto thyroiditis status and an increased malignancy risk. We found that the anti-thyroid antibody positivity rates were similar in patients with benign and malignant histopathologies.

We also found that the malignancy rate was higher in younger patients. The effects of age on the risk for thyroid malignancy varied in different reports. Likewise, Mileva et al. [30] reported that younger age was a significant risk factor for malignancy in patients with thyroid nodules of Bethesda category 3. Conversely, Ryu et al. [31] found that older age (≥40 years) was associated with an increased risk, but others found that age did not significantly predict malignancy of AUS/FLUS nodules [15, 32].

We found that US findings predictive of malignancy were more common in malignant than benign nodules. Similarly, Park et al. [33] reported that suspicious US findings were more common in indeterminate nodules with malignancy. Rago et al. [34] conversely reported that the gray-scale US alone did not distinguish malignant from benign lesions in indeterminate cytology.

Our work had several limitations. The study was retrospective in nature, and surgical decision-making (excision or repeat biopsy) was often influenced by patient preference rather than the recommendations of surgeons or endocrinologists. As patient decisions must be respected, particularly regarding surgical outcomes, it was difficult to derive a true malignancy rate. Moreover, most patients with category 3 cytology were advised to accept follow-up without operation. Malignancy rates of only operated patients may be associated with patient selection bias. To reduce such bias, we also calculated lower ROM bounds.

In addition, the ultrasonography is a subjective procedure although done by experienced endocrinologists and the data were evaluated retrospectively.

Conclusions

We evaluated a large number of repeat AUS/FLUS nodular biopsies. Very few studies have analyzed data from third and fourth biopsies, in addition to those from earlier biopsies. Repeat (2, 3, or 4) biopsies of AUS/FLUS nodules do not enhance the identification of malignancy risk. US findings and, if possible, molecular testing may be a better guide for the decision of either surveillance or diagnostic surgery. In addition, AUS/FLUS diagnoses are associated with a higher risk for malignancy than anticipated by the Bethesda System.

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Statement of Ethics

Patients signed an informed consent form to participate in the study. The protocol was approved by the Ethics Committee of the Yildirim Beyazit University Hospital.

Disclosure Statement

None of the authors has any potential conflict of interest associated with this research.

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Author Contributions

All authors contributed to the study design, recruited the subjects, and discussed the results. B.E.O. wrote the first draft of the manuscript. All authors revised and approved the final version.

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