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ORIGINAL ARTICLE

Malignancy in Thyroid Nodules with Bethesda III Category on Repeat Fine Needle Aspiration Biopsy*

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Abstract

Objectives. This study aimed to evaluate the risk of malignancy for nodules repeatedly classified as Bethesda category III on fine needle aspiration biopsy (FNAB).

Methodology. A chart review on a series of 59 patients seen with thyroid nodules who underwent both initial and repeat FNAB at the Diabetes, Thyroid and Endocrine Center of St. Luke's Medical Center, Quezon City was conducted. The Thyroid Registry was utilized to collect each patient's demographic and clinical characteristics, ultrasonographic features of thyroid nodules along with the cytopathologic and histopathologic results. The subclassification of atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS) were retrieved from the cytopathology reports using the institution's electronic Healthcare-Results Management System.

Results. A total of 59 adult patients with thyroid nodules were included. Nodules which were initially AUS/FLUS turned out to be malignant on repeat FNAB in 38 patients with a prevalence of 64.41% (95% CI: 50.87-76.45%). There was no significant difference with regards to clinical, ultrasonographic and cytopathologic features of malignancy between benign and malignant nodules.

Conclusion. Findings of this study support surgical intervention as a reasonable option after a repeat Bethesda III classification on FNAB. However, the small sample size warrants confirmation in future studies with a representative sample of patients.

Key words: Bethesda III, AUS/FLUS, malignancy

INTRODUCTION

There are currently no guidelines available regarding management of repeatedly classified as Bethesda category III nodules or atypia of undetermined significance/ follicular lesion of undetermined significance (AUS/FLUS). A meta-analysis on the outcomes of repeat fine needle aspiration biopsy (FNAB) for AUS/FLUS thyroid nodules showed that the malignancy rate is about 40%.[1] To improve, diagnostic accuracy, some experts recommend core needle biopsy over repeat FNAB for this category.[2] There is no consensus regarding the treatment options for these patients, which can burden them with anxiety regarding additional costs and possible delays in definitive diagnosis and management.

The Bethesda System for Reporting Thyroid Cytopathology is a 6-category classification system created to standardize the interpretation of thyroid cytology. (Table 1) Categories I-VI include: non-diagnostic or unsatisfactory, benign, AUS/FLUS, follicular neoplasm/suspicious for follicular neoplasm (SFN), suspicious for malignancy (SFM), and malignant.[3] This system provides category-specific malignancy rates and recommends appropriate clinical management for each category.

Bethesda III has a predicted risk of malignancy that ranges from 10 – 30%.[3] The most frequently recommended management is repeat FNAB after 3 – 6 months. Even though the Bethesda System for Reporting Thyroid Cytopathology recommends repeat FNAB for AUS/FLUS,

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Table 1. Bethesda system for reporting thyroid cytopathology: diagnostic categories and risk of malignancy[3]

Bethesda category	Cytopathologic category	Approximate expected frequency	Malignancy rate	Suggested treatment (Prior to availability of molecular testing)
I	Nondiagnostic/inadequate	5-11	1-4	Repeat FNA
II	Benign	55-74	0-3	US follow up
III	Atypia/follicular lesion of undetermined significance	5-15	5-15	Repeat FNA in 3-6 months
IV	Follicular neoplasm/suspicious for FN	2-25	15-30	Lobectomy
V	Suspicious for malignancy	1-6	60-75	Lobectomy or thyroidectomy
VI	Malignant	2-5	97-99	Total thyroidectomy

the American Thyroid Association (ATA) is less clear with its weak recommendation,[4] while the American Association of Clinical Endocrinology (AACE)/Associazione Medici Endocrinologi (AME)/European Thyroid Association (ETA) favor surgery and recommend that repeat FNAB should not be performed because of the possibility of confusing results.[5] Recent studies have shown a higher risk of malignancy and higher rates of immediate surgery.[6] Although many studies have suggested a different method for management of Bethesda III nodules, such as incorporation of data from clinical history, laboratory results and ultrasonographic findings,[7-10] repeat FNAB is still frequently performed. The variability in the reported malignancy rates of repeat AUS/FLUS suggests diagnostic heterogeneity.[6,11-16] Further studies may be needed to determine the actual risk of malignancy, since a histopathologic diagnosis is only available for patients who underwent surgery, and to determine the appropriate management of an AUS/FLUS cytopathologic diagnosis.

Molecular testing has been suggested to provide additional information for patients with Bethesda III nodules. Among the several Raf kinase isoforms, the B-type Raf kinase (BRAF) is the strongest activator of the downstream regulated kinase signaling pathway and is associated with early tumorigenesis and aggressive behavior of papillary thyroid carcinoma.[17] In a 2015 survey of clinical practice patterns in the United States, 38.8% of 820 respondents would obtain molecular testing after an initial AUS/FLUS result.[18] Its high negative predictive value of at least 95% may be used by physicians as basis for deferring surgery.[19] Molecular testing was considerably more cost-effective than diagnostic lobectomy for Bethesda III nodules.[20] It has been adopted in developed countries as it has reduced the number of surgeries with indeterminate cytopathology. Nonetheless, its routine application in our healthcare setting cannot be advocated due to its cost per case base and availability.

To date, there are a few studies that have investigated on nodules repeatedly classified as Bethesda III and there is still no consensus for the management of these cases. Therefore, this study aimed to evaluate the risk of malignancy for repeat Bethesda III nodules on FNAB and explore its correlation with the demographic and clinical patient characteristics, which may help assist in developing guidelines on the management of such nodules.

OBJECTIVES

General objective

To determine the proportion of malignancy of thyroid nodules repeatedly classified as Bethesda category III on FNAB

Specific objectives

1. To describe the clinical and ultrasonographic features of repeat Bethesda category III nodules on FNAB
2. To compare the demographic, clinical, ultrasonographic and cytopathologic characteristics between malignant cases versus benign.

METHODOLOGY

Study design and population

The design was a chart review on a series of 59 patients seen with thyroid nodules who underwent both initial and repeat FNAB at the Diabetes, Thyroid and Endocrine Center (DTEC) of St. Luke's Medical Center Quezon City (SLMC-QC), Philippines. Patients included were those who received a cytopathologic diagnosis of Bethesda Category III or AUS/FLUS at least twice within a span of 1 year from June 2017 to December 2021. Relevant clinical data of the included participants were taken from the DTEC Thyroid Registry. No patient contact was done and data were gathered retrospectively. The researchers also checked the medical records from the private Endocrinology clinics for patients who had 2 FNAB results of AUS/FLUS but had no record of surgery done at the same institution, to check for any histopathological result. Patient records which could not be retrieved were considered lost to follow-up.

Operational definition

- Fine Needle Aspiration Biopsy (FNAB) – gold standard diagnostic tool for thyroid nodules, indicated for the following:[4]
  - Patients with clinical signs of thyroid cancer
  - Nodules >1 cm with at least 2 ultrasound criteria for malignancy
  - Nodules of any size with extracapsular extension or indeterminate cervical lymph nodes
  - Nodules of any size in patients with a history of neck radiation

Table 2. Sonographic patterns, estimated risk of malignancy, and fine needle aspiration guidance for thyroid nodules[3]

Sonographic pattern	Ultrasound features	Estimated risk of malignancy	FNA size cutoff (largest dimension)
High suspicion	Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins (infiltrative, micro lobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of ETE.	>70–90	Recommend FNA at ≥1 cm
Intermediate suspicion	Hypoechoic solid nodule with smooth margins without microcalcifications, ETE, or taller than wide shape.	10–20	Recommend FNA at ≥1 cm
Low suspicion	Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or ETE, or taller than wide shape.	5–10	Recommend FNA at ≥1.5 cm
Very low suspicion	Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate, or high suspicion patterns.	<3	Consider FNA at ≥2 cm (Observation)
Benign	Purely cystic nodules (no solid component)	<1	No biopsy

    - History of well-differentiated thyroid carcinoma in more than 2 first-degree relatives
    - Medullary thyroid carcinoma or multiple endocrine neoplasia (MEN) type 2
    - Increased calcitonin levels
- Thyroid Nodule – an abnormal growth of thyroid cells that forms a lump within the thyroid gland. According to the 2015 ATA Guidelines, it can be further described based on ultrasound findings and FNA results shown in Table 2
- Bethesda III (Atypia/Follicular Lesion of Undetermined Significance) Subclassification:[21]
    - Cytologic (Nuclear Atypia) – described as having mild nuclear enlargement, membrane irregularities such as wrinkles or grooves, overlapping, or chromatin clearing
    - Architectural Atypia – described as having low cellularity, absent or minimal colloid and microfollicles (including oncocytic changes)

Study procedures and data gathering

The Thyroid Registry of DTEC of SLMC-QC was utilized to collect each patient's demographic and clinical characteristics, ultrasonographic features of thyroid nodules (sonographic pattern, size, echogenicity, presence of vascularity and calcifications), along with the cytopathologic and histopathologic results. The ultrasound results were read by different radiologists from different institutions which were subsequently recorded in the DTEC Thyroid Registry in a standardized tabular format. The subclassification of the AUS/FLUS were retrieved from the comments section of the cytopathology reports using the electronic Healthcare-Results Management System of SLMC-QC. The slides were read by different cytopathologists from SLMC_QC, hence the cytologic diagnosis had a standardized reporting format, as it came from 1 institution.

Sampling methodology

The researcher utilized total enumeration technique wherein all eligible patients were included in the study. Based on the Thyroid Registry, only 59 patients satisfied the inclusion and exclusion criteria.

Statistical analysis

Stata MP version 17 (Stata Corp LLC, College Station, TX, US) was used for data processing and analysis. No imputation of missing data was performed. Mean and standard deviation or median and interquartile range were used to describe continuous variables depending on the data distribution. Shapiro Wilk's test was used to assess normality of data. Frequency and percent distribution were used to describe categorical variables. Comparison by histopathologic result was performed using Chi-square test or Fisher's exact test for categorical variables, and independent t-test or Mann Whitney U test for continuous variables.

An exploratory analysis on the relationship of malignancy with the patient characteristics using simple logistic regression analysis was implemented. Estimates of crude odds-ratio and 95% confidence interval were reported. P values ≤0.05 were considered statistically significant.

Ethical considerations

The Clinical Protocol and all relevant documents were reviewed and approved by the SLMC-QC Institutional Ethics Review Committee. Patient confidentiality was respected by ensuring the anonymity of patient records. Each patient document was CODED and did not contain any identifying information in order to ensure confidentiality. All study data were recorded and investigators were responsible for the integrity of the data i.e., accuracy, completeness, legibility, originality, timeliness and consistency.

RESULTS

A total of 101 patients had nodules that were classified as Bethesda III or AUS/FLUS on both initial and repeat FNAB from the Thyroid Registry from June 2017 to December 2021. Of the 101 patients, 59 underwent surgery, 6 were advised but refused surgery, 9 were advised repeat FNAB, and 27 were lost to follow-up (Figure 1).

The 59 patients who underwent surgery after repeat Bethesda III on FNAB were included in this study. The median time from repeat FNAB to surgery was 1.88 months

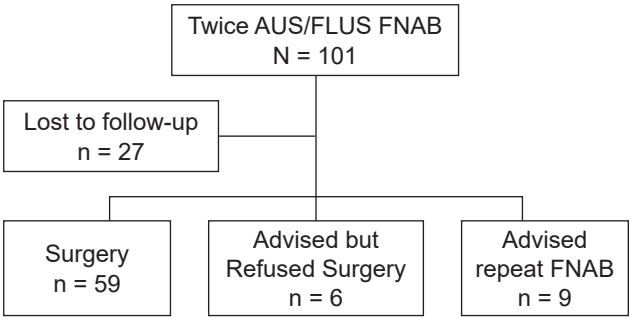

Figure 1. Management of repeat Bethesda III nodules at St. Luke's Medical Center from June 2017 to December 2021.

(range: 0.26-30.60 months). Thirty-eight patients had thyroid cancer based on histopathology, having a prevalence of 64.41% (95% CI: 50.87-76.45%).

The baseline demographic and clinical characteristics of patients by histopathology result are presented in Table 3. The mean age was 46.64 years old (range 21 to 70 years old) and the majority of the patients were females (86%). A family history of thyroid dysfunction and malignancy were reported by 14% and 8% of patients, respectively. The median thyroid stimulating hormone (TSH) was 1.25 mIU/L (range 0.27-22.66) and a majority (87%) had normal TSH. There were no reported obstructive symptoms such as hoarseness, dyspnea and dysphagia from the patients. Ten percent reported taking low dose levothyroxine for the thyroid nodules. The patients were homogenous in demographic and clinical characteristics.

There was no significant difference between the 2 groups (benign vs papillary thyroid carcinoma cytopathology) with regards to sonographic pattern, thyroid nodule size, vascularity, calcification and echogenicity (Table 4). More than half (53%) of the patients had intermediate to high sonographic pattern combined. Consequently, more than half (53%) of the nodules were hypoechoic, 44% were isoechoic and 3% were hyperechoic. The majority (90%) had a thyroid nodule size of ≥1 cm. Ten percent of nodules were vascular and 25% percent were positive for calcifications.

There was no significant difference between the 2 groups (benign vs papillary thyroid carcinoma cytopathology) with regards to the subclassification of AUS/FLUS on FNAB (Table 5). Most patients had cytologic atypia on the first (71%) and second (63%) FNAB.

Table 3. Demographic and clinical characteristics of Bethesda III patients by histopathologic result (n = 59)

Characteristics	All patients (n = 59), N(%)	Malignant (n = 38), N(%)	Benign (n = 21), N(%)	*P*
Age (in years), mean ± SD	46.64 ± 11.52	46.68 ± 12.34	46.57 ± 10.14	0.972
Sex				0.438
Female	51 (86)	34 (67)	17 (33)	
Male	8 (14)	4 (50)	4 (40)	
Past medical history				
Malignancy				
Without	54 (92)	35 (65)	19 (35)	1.000
With	5 (8)	3 (60)	2 (40)	
Malignancy: Head and neck				
Without	59 (100)	38 (100)	21 (100)	
With	0	0	0	
Thyroid disease				
Without	58 (98)	37 (64)	21 (36)	1.000
With	1 (2)	1 (100)	0	0.438
Family history: Thyroid dysfunction				
No	51 (86)	34 (67)	17 (33)	0.438
Yes	8 (14)	4 (50)	4 (50)	0.646
Family history: Thyroid malignancy				0.646
No	54 (92)	34 (63)	20 (37)	
Yes	5 (8)	4 (80)	1 (20)	
TSH (in mIU/L)[a]				
median	1.25	1.24	1.63	0.7840
IQR	0.81-1.94	0.86-1.9	0.69-2.69	
Low	5 (10)	3 (60)	2 (40)	0.085
Normal	44 (87)	32 (73)	12 (27)	-
High	2 (4)	0	2 (100)	
History of radiation				
No	59 (100)	38 (64)	21 (36)	1.000
Yes	0	0	0	
Presence of obstructive symptoms				1.000
No	54 (92)	35 (65)	19 (35)	0.733
Yes	5 (8)	3 (60)	2 (40)	
Thyroid Medications				
No	49 (83)	32 (65)	17 (35)	
Yes	10 (17)	6 (60)	4 (40)	

[a]Only 51 patients have data for TSH

Table 4. Ultrasonographic features of Bethesda III patients by histopathologic result (n = 59)

Characteristics	All patients (n = 59), N(%)	Malignant (n = 38), N(%)	Benign (n = 21), N(%)	*P*
Sonographic pattern				0.584[a]
Very low/low	28 (48)	17 (61)	11 (39)	
Intermediate	15 (25)	9 (60)	6 (40)	
High	16 (27)	12 (75)	4 (25)	
Size of thyroid nodule				0.407[b]
≥1 cm	53 (90)	33 (62)	20 (38)	
<1 cm	6 (10)	5 (83)	1 (17)	
Vascularity				1.000[b]
Non-vascular	53 (90)	34 (64)	19 (36)	
Vascular	6 (10)	4 (67)	2 (33)	
Calcification				0.403[a]
Negative	44 (75)	27 (61)	17 (39)	
Positive	15 (25)	11 (73)	4 (27)	
Echogenicity				0.901[b]
Isoechoic	26 (44)	17 (63)	10 (37)	
Hypoechoic	31 (53)	20 (67)	10 (33)	
Hyperechoic	2 (3)	1 (50)	1 (50)	

Table 5. Cytopathologic features of Bethesda III patients by histopathologic result (n = 59)

Characteristics	All patients (n = 59), N(%)	Malignant (n = 38), N(%)	Benign (n = 21), N(%)	*P*
First FNAB				0.108[a]
Cytologic atypia	42 (71)	29 (69)	13 (31)	
Architectural atypia	5 (8)	1 (20)	4 (80)	
Both cytologic and architectural atypia	12 (20)	8 (67)	4 (33)	
Second FNAB				0.211[a]
Cytologic atypia	37 (63)	24 (65)	13 (35)	
Architectural atypia	6 (10)	2 (33)	4 (67)	
Both cytologic and architectural atypia	16 (27)	12 (75)	4 (25)	

The results on insufficient evidence of differences between the 2 groups were consistent with the lack of statistical significance in the crude association of the patient characteristics with malignancy (Table 6).

DISCUSSION

AUS/FLUS is a heterogenous cytopathologic category that was neither definitively benign nor definitively malignant.[22] Three possible management options are recommended by current guidelines for AUS/FLUS follow-up: (1) Clinical observation; (2) Repeat FNAB with management being based on the result of the last exam; or (3) Surgery (lobectomy/thyroidectomy).[11] The approach to the management of these Bethesda III nodules differs among physician-specialists, although the majority adhere to the clinical practice guidelines of the ATA.[23] There were a few studies that have investigated on repeatedly classified as Bethesda III nodules and there is no consensus on the treatment options for these patients.

In this study, a repeat Bethesda III on FNAB had a 64% risk of malignancy. This is lower than the risk of malignancy (73.1%) after repeat Bethesda III by Yoo et al.[24] On the other hand, the malignancy risk in this study is higher than the risks of malignancy after repeat Bethesda III in the studies of Bayona et al.,[1] Wong et al.,[16] Ogmen et al.,[12] and Ho et al.,[6] at 40%, 39%, 32.4% and 26.3%, respectively. Whether this higher risk reflects a more aggressive nature of lesions among Filipinos remains debatable. It is important to note that these reported rates are higher than the risk of malignancy (5-15%) of Bethesda III as adopted by the Bethesda System.

The risk of malignancy in this study may also be higher since only those patients who underwent surgery were included. Surgery was most probably performed on patients considered high risk for malignancy. Those patients who were advised but refused surgery, advised repeat FNAB and lost to follow-up were excluded. Thereby, a 64% risk of malignancy in this study may reflect the higher baseline risk of patients and may not estimate the true rate of malignancy after repeat Bethesda III among patients with lower baseline risk.

With the wide range of malignancy rates found in these studies, the variability in the reported risks may be due to different rates of repeat FNAB versus surgery from the conflicting management guidelines for AUS/FLUS. In the Philippines, the survey of Abelardo et al., revealed that the management of patients with AUS/FLUS diagnosis is heterogenous within and across different specialties, at the same individualized depending onthe patient's clinical and ultrasonographic features.[23] Greater management differences in practice may be seen after repeat Bethesda III owing to the lack of concrete guidelines. In addition, the variability might come from the heterogeneity and subjectivity of the reported AUS/FLUS being read, since technical issues including adequacy of sample and optimization of cellular preservation from slide preparation may have greatly affected the results.[25,26] This highlights the value of interpreting AUS/FLUS results with caution

and combining it with clinical correlation to arrive at a clinical decision.

There were no clinical characteristics correlated with malignancy in this study, which is in congruence with the previous studies. In several studies, age and sex were not considered predictors of malignancy for thyroid nodules with AUS/FLUS.[8-10] However, other studies found that the malignancy rate was higher in younger patients.[12,27] Furthermore, neither a family history of papillary thyroid carcinoma nor a history of radiation exposure increases the risk of malignancy in patients with AUS/FLUS.[8-10] Even though several known clinical risk factors in patients with thyroid nodules for thyroid cancer include immobility with swallowing, pain, cough, voice change, growth and lymphadenopathy, these have not been included in multivariate analyses of ultrasonographic features and thyroid cancer risk.[3]

Table 6. Exploratory results on the association of patient characteristics with malignancy

Characteristics	Crude OR (95% CI)	*P*
Age (in years)	1.00 (0.96-1.05)	0.967
Sex		
Female	Ref	Ref
Male	0.51 (0.12-2.11)	0.351
Past medical history		
Thyroid disease		
Without	Ref	Ref
With	1.72 (0.07-44.10)	0.743
Family history: Thyroid dysfunction		
No	Ref	Ref
Yes	0.51 (0.12-2.11)	0.351
Family history: Thyroid malignancy		
No	Ref	Ref
Yes	1.78 (0.26-12.24)	0.557
Smoking status		
No	Ref	Ref
Yes	0.53 (0.09-3.35)	0.504
Alcohol consumption		
No	Ref	Ref
Yes	1.26 (0.31-5.07)	0.746
Presence of obstructive symptoms		
No	Ref	Ref
Yes	0.77 (0.14-4.27)	0.764
Thyroid medications		
No	Ref	Ref
Yes	0.78 (0.20-2.96)	0.712
Sonographic pattern		
Very low/low	Ref	Ref
Intermediate	0.96 (0.28-3.33)	0.949
High	1.83 (0.49-6.76)	0.368
Size of thyroid nodule		
≥1 cm	Ref	Ref
<1 cm	2.24 (0.34-14.81)	0.401
Vascularity		
Non-vascular	Ref	Ref
Vascular	1.02 (0.20-5.26)	0.984
Calcification		
Negative	Ref	Ref
Positive	1.63 (0.47-5.64)	0.443
Echogenicity		
Isoechoic	Ref	Ref
Hypoechoic	1.17 (0.40-3.41)	0.771
Hyperechoic	0.60 (0.06-6.54)	0.675
First FNAB		
Cytologic atypia	Ref	Ref
Architectural atypia	0.11 (0.01-1.10)	0.061
Both cytologic and architectural atypia	0.90 (0.23-3.52)	0.876
Second FNAB		
Cytologic atypia	Ref	Ref
Architectural atypia	0.27 (0.04-1.68)	0.161
Both cytologic and architectural atypia	1.63 (0.44-6.07)	0.470

It has been well-established that a thyroid nodule has a highly suspicious sonographic pattern when it has these features: solid consistency, hypoechogenicity with one or more of the following; irregular margins (infiltrative, microlobulated, or spiculated), microcalcifications, taller than wide shape, disrupted rim calcifications with small extrusive soft tissue component, and evidence of extrathyroidal extension.[3] Nodules measuring ≥1 cm with this sonographic pattern should undergo diagnostic FNAB to confirm malignancy.[3] Nodule size has not been correlated with malignancy in most studies.[7,8,10] This study showed that these high-risk ultrasound features were not statistically different between benign and malignant nodules. However, further studies of a larger scale are necessary to confirm these non-significant findings.

In cytopathology reports, AUS/FLUS can be classified into 3 categories: cytologic (nuclear) atypia, architectural atypia, or both. Some of the common situations where AUS/FLUS is used are in samples with occasional follicular cells that have enlarged, pale, grooved, nuclei in an otherwise benign appearing aspirate (cytologic atypia); prominent microfollicles in a sparsely or only moderately cellular aspirate (architectural atypia); or when evaluation of follicular cell atypia is less than optimal because of an artifact produced from sample preparation.[28]

Many studies reported that the malignancy rate of cytologic atypia is higher than that seen with architectural atypia. In the study of Gan et al., cytologic atypia had a malignancy rate of 36.8% compared to 14.7% in architectural atypia.[29] Furthermore, the meta-analysis by Ahn et al., revealed the overall malignancy rate of cytologic atypia (24.3 – 65.8%) to be significantly higher than in architectural atypia (5.95 – 38.8%).[30] In spite of that, this study showed that the subclassification of AUS/FLUS on FNAB was not statistically different between benign and malignant nodules. As mentioned earlier, the interpretation of FNAB results may be influenced by the subjective reading of the individual cytopathologists, which could have produced the heterogeneity.[24,25] Similarly, the non-significant findings require confirmation in future studies with larger sample size.

Limitations

This study was limited to a chart review on a series of patients. There may have been a selection bias since patients with thyroid nodules initially classified as Bethesda III who were eventually lost to follow-up were excluded. In addition, the individualized approach of the physician

and preference of the patient have affected the decision to proceed with surgery or not after a repeat Bethesda III. In the same way, both the initial and repeat cytopathologic reports were read by different cytopathologists, and is subjective.

Due to the small population of 59 patients, the findings of this study cannot be used to make inferences to a larger population, and thus warrants confirmation in future studies with a representative sample of patients.

CONCLUSION AND RECOMMENDATION

Based on the results of this study, a second FNAB result of AUS/FLUS carries a 64% risk of malignancy. This suggests an elevated risk of malignancy compared with a single FNAB result of Bethesda III (5 – 15%). Therefore, this study supports surgical intervention (lobectomy/ thyroidectomy) as a reasonable option after a second Bethesda III classification on FNAB as recommended by AACE/AME/ETA.

The researchers recommend future studies with larger sample size to confirm the findings of this study. It is also recommended to explore the significance of cytologic and architectural atypia to the risk of malignancy. Therefore, we likewise recommend to include a pathologist be a study co-author.

Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
JLN: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration; **LME:** Conceptualization, Methodology, Validation, Writing – original draft preparation, Visualization, Supervision, Project administration; **OAD:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration.

Author Disclosure
The authors declared no conflict of interest.

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