Prevalence and Outcomes of Thyroid Nodules with Atypia of Undetermined Significance (AUS) Cytology in a Tertiary Government Hospital: A Ten-year Review (2013 to 2022)

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ABSTRACT

Background and Objective. Thyroid cancer is one of the most common malignancies reported in the Philippine Cancer Registry. Fine-needle aspiration biopsy (FNAB) plays a major role in the early detection of malignant thyroid nodules and is interpreted using the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). However, Bethesda Category III, Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance (AUS/FLUS), remains a diagnostically challenging category for both clinicians and pathologists. This category represents an intermediate interpretation between benign and malignant lesions and is intended to be used as a diagnosis of last resort. This study aimed to determine whether the frequency of AUS/FLUS reporting in our institution falls within the recommended threshold of 7% and to describe the clinicopathologic characteristics of these lesions, including the reasons cited by pathologists for assigning this diagnostic category.

Methods. A retrospective descriptive review of medical records and pathology logbooks was conducted using available records from the Philippine General Hospital (PGH) and the Pathology Research Laboratory (PRL) Unit of the University of the Philippines College of Medicine (UPCM).

Results. The overall frequency of Bethesda Category III (AUS/FLUS) cases in PGH and PRL was 4.27%, which is within the recommended threshold of less than 7% specified by the Bethesda System for Reporting Thyroid Cytopathology. There was no significant difference in the proportion of Category III cases between PGH (6.56%) and PRL (1.59%). In contrast, the proportion of Category I (non-diagnostic) cases differed markedly between PGH (49.78%) and PRL (4.15%). Repeat biopsies of Category III cases were infrequent (15.38% in PGH and 18.64% in PRL). Among benign definitive diagnoses, thyroid follicular nodular disease was the most common, whereas conventional (classic) papillary thyroid carcinoma was the most frequent malignant diagnosis, followed by encapsulated angioinvasive follicular variant papillary thyroid carcinoma. The calculated risk of malignancy was high (67% in PGH, 73.9% in PRL, and 68.9% overall), although these estimates were limited by the small proportion of cases with traceable definitive surgical specimens in the PGH database. The most frequently cited reason for assigning Bethesda Category III was "focal/mild atypia," although this finding was often not further described in the pathology reports. An increasing trend in the practice of intradepartmental case review ("passing around" cases) was also observed over the study period.

Conclusions. The proportion of Bethesda Category III cases among thyroid FNAB specimens in PGH and PRL was within the recommended range. More accurate estimates of repeat biopsy rates and the risk of malignancy may be achieved through the development of a larger database that incorporates patient registries from outside the institution, thereby allowing follow-

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up of patients who receive definitive management elsewhere. Adoption of the 3rd edition of the Bethesda System for Reporting Thyroid Cytopathology is likewise recommended, as it provides a more detailed characterization of the atypia encountered in AUS cases.

Keywords: Atypia of Undetermined Significance (AUS), fine needle aspiration biopsy (FNAB), Bethesda Category III, thyroid nodule

INTRODUCTION

Thyroid cancer ranked as the ninth most common malignancy in the Philippines in the 2020 Philippine Cancer Registry and Research Annual Report.[1] The evaluation of a thyroid nodule begins with a thorough history and physical examination, followed by ultrasonography or other imaging studies, and ultimately tissue sampling or surgical resection when indicated. Fine-needle aspiration biopsy (FNAB) is the initial biopsy procedure of choice because it is relatively safe, rapid, and cost-effective. It has demonstrated high diagnostic accuracy in distinguishing benign from malignant thyroid nodules and is therefore recommended in the Philippine Clinical Practice Guidelines for Thyroid Cancer.[2]

The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), introduced in 2007, classifies thyroid FNAB specimens into six diagnostic categories, each associated with an estimated risk of malignancy and corresponding management recommendations.[3] One of these categories is Bethesda Category III: Atypia of Undetermined Significance (AUS) or Follicular Lesion of Undetermined Significance (FLUS), which is one of the three indeterminate cytologic categories. It is characterized by cytologic and/or architectural atypia that is insufficient for classification into the more suspicious categories, namely Bethesda Categories IV and V. The estimated risk of malignancy ranges from 10% to 30%, and the recommended management includes repeat FNAB, molecular testing, or diagnostic lobectomy.[4]

The principal challenge of the AUS/FLUS category lies in its inherent diagnostic uncertainty, as it does not clearly distinguish between benign and malignant lesions. Consequently, repeat FNAB is generally recommended. However, nodules with suspicious clinical or radiologic features may proceed directly to surgical resection, introducing selection bias and potentially resulting in an overestimation of the calculated risk of malignancy.

The Bethesda System recommends that AUS/FLUS be used only as a diagnosis of last resort. The original edition recommended that this category comprise less than 7% of all thyroid FNAB interpretations; however, more recent experience suggests that a threshold of approximately 10% may be more realistic in routine practice.[4] In addition, contemporary studies have demonstrated that the risk of malignancy associated with AUS/FLUS is higher than previously recognized, with reported rates ranging from 25% to 36%.[5-7]

In the Philippines, only one published study has provided a comprehensive descriptive review of AUS/FLUS cases in a private tertiary hospital.[8] That study reported a malignancy rate of 35.3% and found no significant association between the clinical or ultrasonographic characteristics of thyroid nodules and their risk of malignancy. Management of AUS/FLUS also remains heterogeneous among clinicians, pathologists, and radiologists, although most specialists follow the recommendations of the American Thyroid Association, as demonstrated in a nationwide survey.[9] The reported frequency of AUS/FLUS diagnoses likewise varies considerably among institutions, ranging from approximately 10% to more than 30%.[9] Similarly, the reported risk of malignancy differs across institutions, and many patients with an AUS/FLUS diagnosis do not ultimately undergo surgical resection. Although repeat FNAB remains the standard recommendation to obtain a more definitive diagnosis and reduce unnecessary surgery, clinical dilemmas arise when repeat aspiration remains indeterminate or when surgery becomes necessary because of compressive symptoms or other clinical indications. Therefore, the integration of cytologic findings with clinical and imaging features remains essential in the management of thyroid nodules.

To date, no study has evaluated the prevalence of AUS/FLUS in the Philippine General Hospital (PGH), the country's national university hospital. This study is the first to determine whether the frequency of AUS/FLUS diagnoses in PGH falls within the recommended benchmark. Furthermore, determining the institution specific risk of malignancy may contribute to a more accurate estimate of the malignant potential of Bethesda Category III. Finally, identifying the reasons cited by pathologists for assigning an AUS/FLUS diagnosis may help reduce the subjectivity associated with this category and promote more consistent reporting within the institution.

OBJECTIVES

General Objective

To describe the clinicopathologic profile of thyroid nodules diagnosed as Atypia of Undetermined Significance/ Follicular Lesion of Undetermined Significance (AUS/ FLUS) on fine-needle aspiration biopsy and to identify the reasons cited by pathologists for assigning this diagnostic category over a 10-year period (January 2013 to December 2022) at the Philippine General Hospital (PGH) and the Pathology Research Laboratory (PRL) Unit of the University of the Philippines College of Medicine (UPCM).

Specific Objectives

1. To determine the percentage of thyroid FNAB cases diagnosed as AUS/FLUS and the proportion of these cases that subsequently underwent repeat FNAB, and to describe the outcomes of the repeat biopsies.

2. To determine the percentage of AUS/FLUS thyroid FNAB cases that subsequently underwent definitive surgery at our institution.
3. To determine the risk of malignancy associated with the AUS/FLUS diagnostic category among thyroid FNAB cases in PGH and PRL.
4. To describe the histopathologic diagnoses of the definitive surgical specimens from AUS/FLUS cases according to the 2022 WHO Classification of Thyroid Neoplasms.
5. To describe the reasons cited by pathologists for assigning an AUS/FLUS diagnosis.

METHODS

The study was approved by the Philippine General Hospital Expanded Hospital Research Office (PGH-EHRO) and the University of the Philippines Manila Research Ethics Board (UPMREB).

Study Design, Setting, Duration, Population, and Sampling

This was a retrospective descriptive observational study involving a review of records of all thyroid fine-needle aspiration biopsy (FNAB) cases diagnosed as Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance (AUS/FLUS) over a 10-year period (January 2013 to December 2022) at the Philippine General Hospital (PGH) and the Pathology Research Laboratory (PRL) Unit of the University of the Philippines College of Medicine.

The PRL was included because a proportion of PGH thyroid FNAB specimens were processed in this laboratory between 2013 and 2021. For PGH cases, FNAB was performed by clinicians from the Departments of Otorhinolaryngology–Head and Neck Surgery (ORL-HNS) and Surgery, or by radiologists. In contrast, FNAB procedures at the PRL were performed by pathology residents, allowing the use of rapid on-site evaluation (ROSE) to assess specimen adequacy during the procedure.

Total enumeration sampling was employed, and all eligible AUS/FLUS cases identified during the study period were included. Analysis of definitive histopathologic diagnoses was limited to patients who subsequently underwent surgery at PGH, where the corresponding surgical pathology records were available for review.

From 2013 to 2020, thyroid FNAB specimens obtained by residents in training from the Departments of Surgery, ORL-HNS, and Radiology at PGH were processed either at the PGH laboratory or at the PRL. During the same period, specimens obtained by pathology residents were processed exclusively at the PRL.

Data Collection, Processing, and Analysis

De-identified patient information, including demographic data and cytologic and histopathologic diagnoses, was obtained from the electronic medical records database generated by the Information Technology Division of the UP-PGH and from the thyroid FNAB logbooks maintained at the PRL of the UPCM.

Some patients underwent repeat FNAB, resulting in multiple cytology specimens from the same individual. To accurately determine the distribution of Bethesda categories among FNAB procedures, all specimens were initially analyzed individually. However, to determine the distribution of Bethesda categories among patients, duplicate specimens from the same patient were consolidated, and only the initial cytologic diagnosis was included in the final analysis.

For patients who underwent more than one FNAB procedure and whose initial result was Bethesda Category I (Nondiagnostic), the first subsequent diagnostic category higher than Category I was considered the representative cytologic diagnosis for that patient.

Data were encoded in a Microsoft Excel for Mac Version 16.64 spreadsheet. Categorical variables were summarized using frequencies and percentages.

RESULTS

A total of 15,997 thyroid FNAB records were retrieved, comprising 11,497 records from the PRL logbooks and 4,500 records from the UP-PGH Surgical Pathology database. Specimens with incomplete data were excluded, including those with an unspecified source (PGH or PRL) (n = 126), unspecified Bethesda category (n = 37), or questionable patient identifiers (illegible name and/or unspecified sex) (n = 42). After applying the exclusion criteria, 15,792 specimens remained for analysis.

Frequency of Thyroid FNAB Specimens Diagnosed as AUS/FLUS

A total of 11,722 thyroid FNAB specimens were collected at PGH over the 10-year study period by various clinical services, including Otorhinolaryngology–Head and Neck Surgery (ORL-HNS), Surgery, and Radiology (Figure 1). The majority of specimens were classified as Bethesda Category I (Nondiagnostic) (61.01%, n = 7,152), indicating a relatively low diagnostic yield. This finding may be related to the absence of routine rapid on-site evaluation (ROSE) during specimen collection.

In contrast, 4,070 FNAB specimens were obtained by pathology residents and processed at the PRL (Figure 1). Approximately 80% (n = 3,245) were classified as Bethesda Category II (Benign), whereas only 6.0% (n = 244) were categorized as Bethesda Category I.

The marked difference in the proportion of non-diagnostic specimens between PGH and PRL (61.01% vs. 6.00%) highlights the potential benefit of ROSE in improving specimen adequacy. No PRL cases were recorded in 2021 because laboratory operations were temporarily suspended during the COVID-19 pandemic.

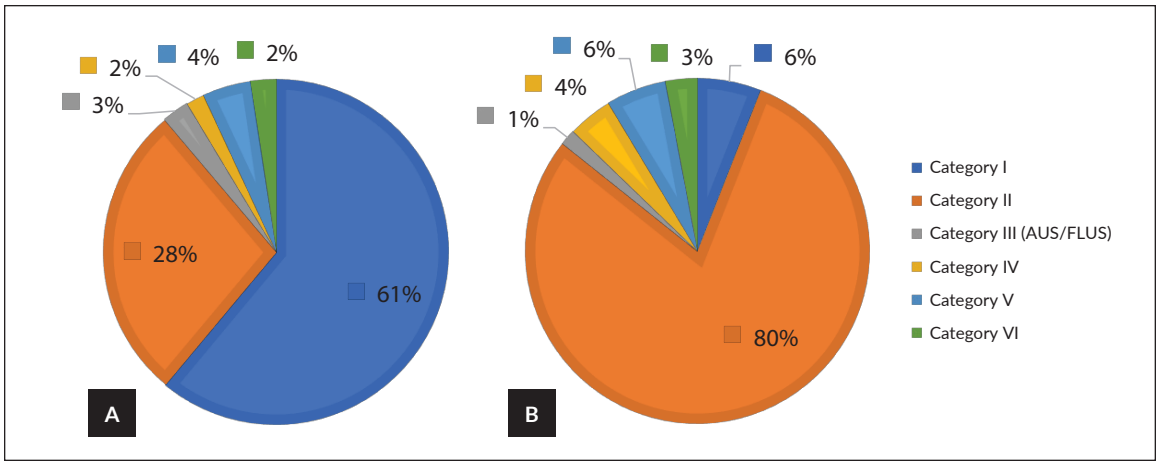

Figure 1. Overall percentages of Thyroid FNAB specimens over 10 years (2013-2022) in the PGH **(A)** (n = 11722) versus PRL **(B)** (n = 4070), according to Bethesda Categories.

PGH – Philippine General Hospital, PRL – Pathology Research Laboratory

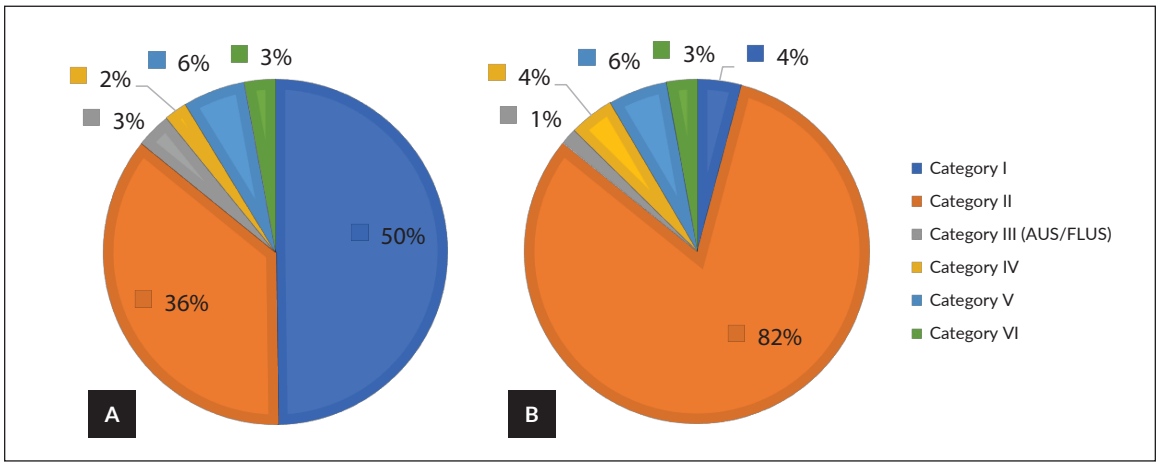

Figure 2. Percentage distribution of unique patients with Thyroid FNAB in a 10-year period in the PGH **(A)** versus PRL **(B)** according to Bethesda Categories.

PGH – Philippine General Hospital, PRL – Pathology Research Laboratory

Percentage of Patients with Thyroid FNAB Classified as AUS/FUS with Repeat Biopsies and their Outcome

After removing the repeat biopsies, a total of 12,562 unique patients remain—8,684 cases from PGH and 3,878 cases from PRL.

There is a decrease in the number of Category I cases in PGH after the removal of repeat biopsies from the original 61% (n = 7,152) to 50% (n = 4,323) (Figure 2). Most cases with repeat biopsies were initially Category I or III on their initial cytologic evaluation, which is reasonable since these two categories are the ones with repeat biopsy in the recommended management guidelines. The number of repeats also varied, the highest being six times, wherein the first five aspiration biopsies were all Category I. The cases in PRL, however, were not very much affected by the removal of repeat biopsies, and Category II (n = 3,168) is still the category with the highest percentage of 82% (Figure 2).

Comparing the percentages of Category III cases between the two institutions (Table 1), the percentage was higher for PGH cases (3.29%) compared to PRL (1.52%), even with the removal of the Category I cases in the total, wherein PGH (6.56%) was still higher than PRL (1.59%). The removal of Category I cases was done to demonstrate the effect on the results if there is ROSE in both settings. Nevertheless, all percentages recorded were still within the acceptable limits, which is 7% in the original Bethesda System (2nd edition) and 10% in a more realistic and present laboratory setting.[4] Overall, when adding the numbers in both institutions, the percentage of Category III cases was 2.75% (345 Category III cases over the total of 12,562 cases) and 4.27% (345 Category III cases over 8,078

Table 1. Comparing Thyroid FNAB Unique Cases from PGH and PRL with and without Category I, Highlighting the Percentages of Category III for each Institution

Category	PGH				PRL			
	Total	Percentage (%)	Total (without Cat I)	Percentage (%) (without Cat I)	Total	Percentage (%)	Total (without Cat I)	Percentage (%) (without Cat I)
I	4323	49.78%	-	-	161	4.15%	-	-
II	3132	36.07%	3132	71.82%	3168	81.69%	3168	85.23%
III	286	**3.29%**	286	**6.56%**	59	**1.52%**	59	**1.59%**
IV	188	2.16%	188	4.31%	164	4.23%	164	4.41%
V	502	5.78%	502	11.51%	216	5.57%	216	5.81%
VI	253	2.91%	253	5.80%	110	2.84%	110	2.96%
Total	8684		4361		3878		3717	

PGH – Philippine General Hospital, PRL – Pathology Research Laboratory

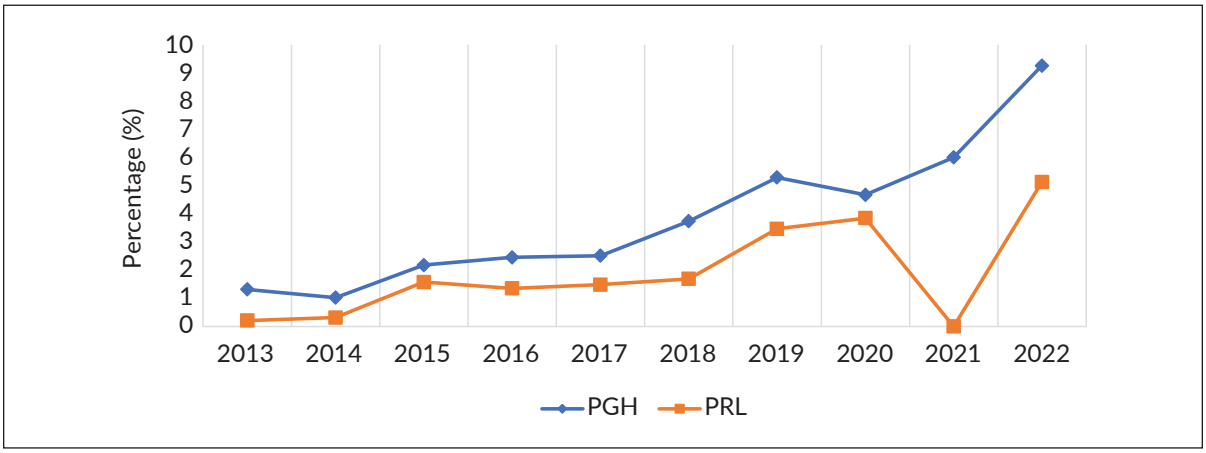

Figure 3. Percentage of Bethesda Category III (AUS/FLUS) Cases in the PGH *(blue)* and PRL *(orange)* for a 10-year period.

PGH – Philippine General Hospital, PRL – Pathology Research Laboratory

Category II-VI cases) if Category I cases were removed from the denominator.

The trend for reporting Category III (Figure 3) cases also seems to be increasing over time, both for PGH and PRL cases. This is not surprising, given the consistent updates in the Bethesda System and the introduction of new thyroid pathologic entities such as the NIFTP (Non-invasive follicular thyroid neoplasm with papillary-like nuclear features) that increase the vagueness in diagnosing thyroid entities based on morphology.[10]

Percentage of Patients who Underwent Thyroid FNAB with Repeat Biopsy

The current recommendation for Bethesda Category III cases is either a repeat biopsy, molecular testing, or lobectomy. Because molecular testing is not yet routinely performed and available in our country, and the decision for lobectomy depends on the managing surgical service and the patient, repeat biopsy is the most noninvasive way moving forward. However, it is expected that not all patients will consent to a repeat biopsy, and some will be lost to follow-up or seek a second opinion elsewhere. For all cases, the institution where the repeat biopsy was conducted varied. Some patients had it done again in PGH by surgical trainees, while some had it conducted in PRL. The decision of which institution it was conducted in was not investigated further in this study.

In PGH, out of the 286 Bethesda Cat III cases listed, only 44 (15%) underwent repeat biopsy. Three of these cases still showed Bethesda Cat III on repeat biopsy, with variable definitive outcomes. One case was eventually diagnosed with multinodular colloid goiter on the definitive specimen, while another was diagnosed with papillary microcarcinoma. The last case did not have a definitive outcome available. Fourteen repeat biopsies yielded a diagnosis of Bethesda Category II Benign, while 11 cases were Bethesda Categories V and VI, which include suspicious for malignancy and malignancy, respectively. The percentages of each are summarized in Figure 4.

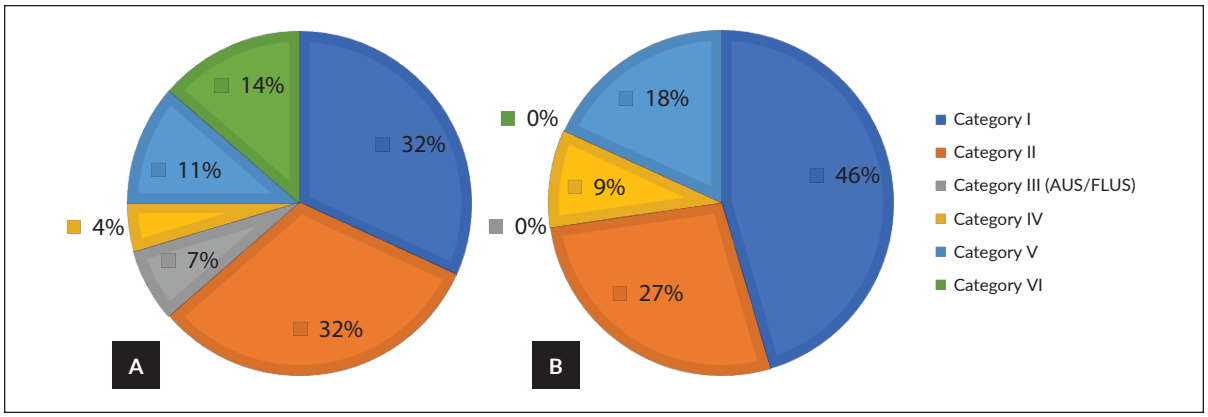

Figure 4. Categories of the repeat biopsies of Category III cases for a 10-year period in the PGH **(A)** versus PRL **(B)** divided according to Bethesda Categories.

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In PRL, out of the 59 Bethesda Cat III cases, only 11 (19%) underwent repeat biopsy. 3 cases fell under Bethesda Category II, while 3 cases fell under Bethesda Categories IV and V. The remaining 5 were Category I on their repeat biopsies, the percentages of which are also summarized in Figure 4.

When the PGH and PRL cases are combined, the category of the repeat biopsies with the highest frequency is Category I (34.5%), followed by Category II (30.9%). The lowest frequency is observed for Categories III and IV (both 5.45%). A significant percentage of repeat biopsies was downgraded from Category III to Category I, which may be explained by the fact that the repeat biopsy was done routinely without the utilization of rapid onsite evaluation (ROSE). This may be improved by the implementation of the said evaluation in subsequent repeat biopsies.

Risk of Malignancy

The risk of malignancy of Bethesda Category III cases can be computed by dividing the number of malignant definitive cases by the total number of Category III cases whose definitive outcomes are available. Unfortunately, our computation for this study is very much limited by the traceable definitive specimens from the database of PGH, meaning only those who had the definitive surgery done in PGH were accounted for. These are enumerated in Tables 2 and 3.

Out of the 286 PGH Bethesda Category III cases, only 67 cases (23.43%) had definitive specimens available. 22 (33%) of these definitive specimens were benign, while the rest (67%) were malignant. Thyroid follicular nodular disease, previously called multinodular colloid adenomatous goiter, remains the top outcome for the benign category, while papillary carcinoma, conventional/classic subtype, is the top diagnosis under the malignant category. Not all malignant entities are thyroid carcinomas. There was one case of diffuse

Table 2. Outcomes of Definitive Specimens of the Category III Cases in PGH

Definitive specimen	No.
Benign	
Thyroid Follicular Nodular Disease/ Multinodular Colloid Adenomatous Goiter	16
Hashimoto thyroiditis	2
Follicular adenoma	2
Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)	1
Hürthle cell adenoma	1
Total (Benign)	22
Malignant	
Papillary carcinoma, conventional/classic subtype	13
Encapsulated, angioinvasive, follicular variant papillary carcinoma	8
Papillary carcinoma, infiltrative follicular subtype	4
Papillary carcinoma, multifocal	4
Papillary carcinoma, encapsulated classic subtype	2
Medullary thyroid carcinoma	2
Papillary microcarcinoma	2
Papillary carcinoma, oncocytic classic subtype	1
Minimally invasive follicular variant papillary carcinoma	1
Papillary carcinoma, solid subtype	1
Papillary carcinoma, follicular, encapsulated, noninvasive	1
Diffuse Large B-cell Lymphoma (DLBCL)	1
Poorly differentiated carcinoma, probably squamous cell carcinoma	1
Minimally invasive Hürthle cell carcinoma	1
Widely invasive follicular variant papillary carcinoma	1
Poorly differentiated thyroid carcinoma	1
Anaplastic thyroid carcinoma	1
Total (Malignant)	45
Total	**67**

large B-cell lymphoma and one case of a poorly differentiated carcinoma, probably squamous cell carcinoma.

On the other hand, 23 (38.98%) out of 59 PRL cases had definitive specimens traced in the PGH database. Only 5 (21.7%) cases have benign definitive specimens, 1 (4.3%) case is borderline, while the rest, which were 17 (73.9%) cases, had a malignant diagnosis. The top diagnosis in both the benign and malignant categories was similar to the PGH cases. The only borderline case was in 2018, diagnosed with Oncocytic Well-Differentiated Tumor of Unknown Malignant Potential (WDT-UMP), the specimen capsule being extensively sampled, and the case was also shown to another consultant before sign-out.

Table 3. Outcomes of Definitive Specimens of the Category III Cases in PRL

Definitive specimen	No.
Benign	
Thyroid Follicular Nodular Disease/ Multinodular Colloid Adenomatous Goiter	4
Follicular adenoma	1
Total (Benign)	5
Borderline	
Oncocytic well-differentiated thyroid tumor of unknown malignant potential	1
Malignant	
Papillary carcinoma, conventional/classic subtype	7
Encapsulated, angioinvasive, follicular variant papillary carcinoma	5
Papillary carcinoma, infiltrative follicular subtype	1
Medullary thyroid carcinoma	1
Anaplastic thyroid carcinoma	1
Follicular thyroid carcinoma	1
Widely invasive oncocytic carcinoma	1
Total (Malignant)	17
Total	**23**

When combined, out of the 90 definitive specimens, 27 (30%) were benign, 62 (68.9%) were malignant, and 1 (1.11%) was borderline. With the disclaimer that the population was small and the limited available data, the risk of malignancy of Bethesda Category III cases in this institution is 68.9%. Papillary carcinoma, conventional/classic subtype, is the most frequent type of malignancy observed in these cases, followed by encapsulated, angioinvasive, follicular variant papillary carcinoma.

Diagnostic Concordance of Repeat Biopsy and Definitive Specimen

For cases wherein a repeat biopsy was performed (Tables 4 and 5) and a definitive specimen is available, the diagnostic concordance of the repeat biopsy is evaluated. There were only 12 cases from PGH and 5 cases from PRL with diagnostic concordance of the repeat biopsy and the definitive specimen. Excluding those whose repeat biopsies were Category I and III, whose diagnoses in the definitive specimen were neither concordant nor discordant, there was

Table 4. Specimens with Repeat Biopsy and Definitive Specimens from Category III Cases in PGH

Year	Repeat Biopsy	Definitive Specimen	Diagnostic Concordance
2013	Category V	Papillary carcinoma, conventional/classic subtype	Yes
2015	Category III	Multinodular colloid adenomatous goiter	Not applicable
2017	Category I	Papillary carcinoma, conventional/classic subtype	Not applicable
2019	Category I	Papillary carcinoma, conventional/classic subtype	Not applicable
2019	Category V	Anaplastic thyroid carcinoma	Yes
2019	Category V	Papillary carcinoma, follicular, encapsulated, noninvasive	Yes
2019	Category III	Papillary microcarcinoma	Not applicable
2021	Category VI	Papillary carcinoma, multifocal	Yes
2021	Category V	Papillary carcinoma, conventional/classic subtype	Yes
2021	Category IV	Minimally invasive Hurthle cell carcinoma	Yes
2022	Category II	Hurthle cell adenoma	Yes
2022	Category I	Minimally invasive follicular variant papillary carcinoma	Not applicable

Table 5. Specimens with Repeat Biopsy and Definitive Specimens from Category III Cases in PRL

Year	Repeat Biopsy	Definitive Specimen	Diagnostic Concordance
2015	Category I	Multinodular colloid adenomatous goiter	Not applicable
2018	Category V	Medullary thyroid carcinoma	Yes
2018	Category II	Follicular adenoma	Yes
2019	Category V	Papillary carcinoma, conventional/classic subtype	Yes
2019	Category I	Multinodular colloid adenomatous goiter	Not applicable

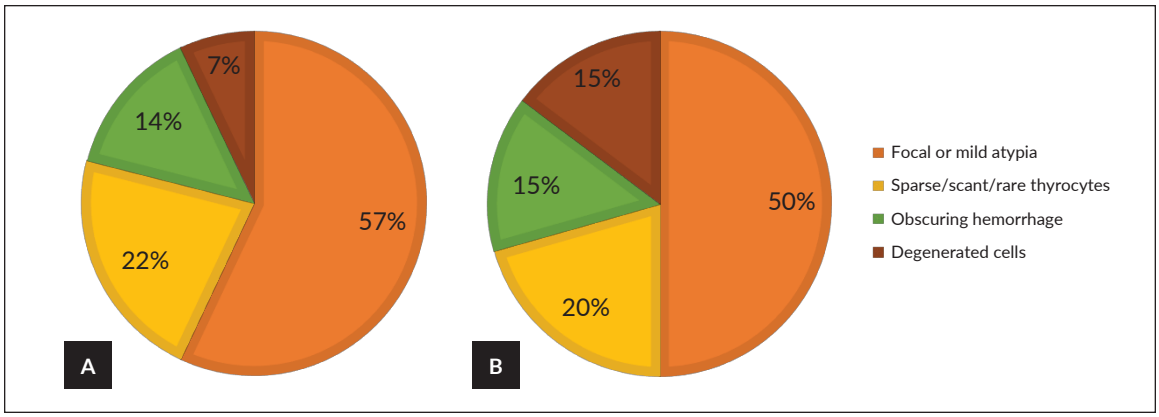

Figure 5. Reasons for Category III diagnosis for a 10-year period in the PGH **(A)** versus PRL **(B)**.
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100% diagnostic concordance between the category of the repeat biopsy and the diagnosis of the definitive specimen.

Reason for Category III

Because Bethesda Category III is intentionally defined as a diagnosis of exclusion, assignment to this category is inherently subjective. It is helpful if the reason for choosing this Category by the pathologist is listed or enumerated in the diagnosis; however, this was not always the case. There were cytopathology reports wherein this category was reported without further elaborating the reason for the diagnosis. Given the limited data available, a review of the reports was done to extract the possible reasons for the pathologists in choosing this category, taken from the "diagnosis", "comments", "remarks", and "note" sections. From here, common terms mentioned, such as "focal/mild atypia" and "obscuring hemorrhage," are listed and enumerated. The number of passed-around Category III cases in both PGH and PRL was also tallied.

The terms "focal atypia" and "mild atypia" remain the top reasons for pathologists in reporting Bethesda Category III (Figure 5). These are followed by the terms "rare thyrocytes", "sparse thyrocytes", and "scant thyrocytes". The trend is similar for both PGH and PRL cases. This is in keeping with the definition of Bethesda Category III cases which is "reserved for specimens that contain cells (follicular, lymphoid, or other) with architectural and/or nuclear atypia that is not sufficient to be classified as suspicious for a follicular neoplasm, suspicious for malignancy, or malignant, and the atypia is more marked than can be ascribed confidently to benign changes". Other reasons listed include "obscuring hemorrhage" and "degenerated cells".

It is also noted that the reasons for choosing category III were being listed or enumerated more by the pathologists in their reports over time. This implies that pathologists are seeing the need to put their histologic description as to why the cases are under Bethesda Category III in their diagnosis from 2016 onwards. Initially, Bethesda Category III cases were signed out only as "Bethesda Category III: Atypia of Undetermined Significance" without further elaboration on why they were under this category. This translates to better practices and communication between pathologists, especially if the cases are to be reviewed, since the histopathologic report is more descriptive and complete in interpretation.

The number of cases that were shown by the main pathologists to other pathologist/s increased throughout the years, from 2 out of 17 (12%) cases in 2013 to 25 out of 72 (35%) cases in 2019—the highest numbers for both PGH and PRL were in 2019, before the COVID19 pandemic hit. Then, the numbers declined, but this is consistent with the small number of specimens processed during the pandemic. The number of patients as well as the number of pass-around cases gradually increased starting in 2022 (Figure 6). While the process of passing around challenging cases usually lengthens the turnaround time, this is also a safe and effective practice since it may reduce the subjective bias in interpreting FNAB cases.

DISCUSSION

This study demonstrated that the overall frequency of Bethesda Category III (AUS/FLUS) diagnoses in our institution (4.27%) is within the recommended limits. This finding is consistent with the recommendations of the 3rd edition of The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC), published in 2023. At the time this study was initiated, however, the 2nd edition of TBSRTC was still in use. Both editions recommend that Bethesda Category III diagnoses should comprise less than 7% of all thyroid FNAB interpretations, although a threshold of up to 10% is considered acceptable in routine laboratory practice.[4]

Although not included among the original objectives of this study, we also demonstrated the impact of rapid on-site evaluation (ROSE) on the frequency of Bethesda Category I (Nondiagnostic) cases. At the PRL, ROSE is routinely

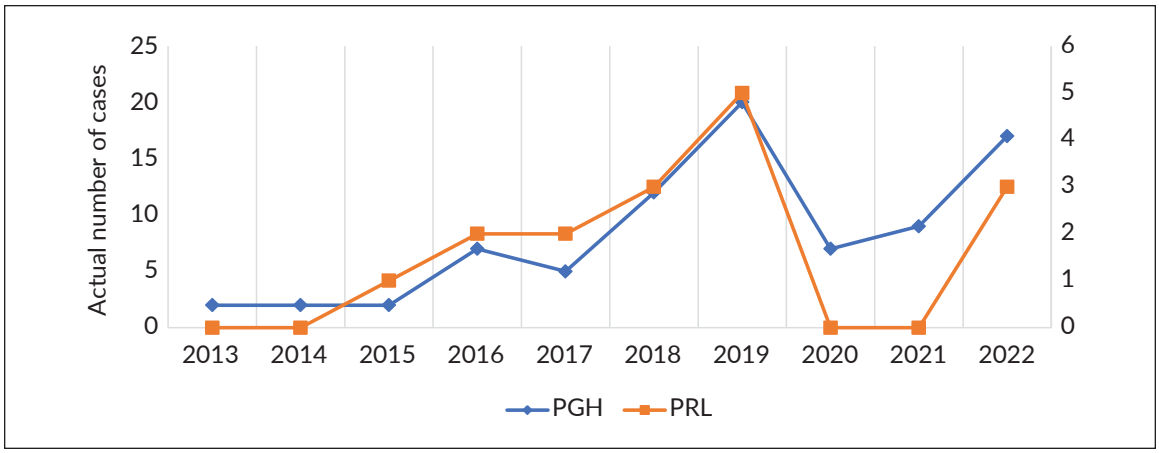

Figure 6. Number of Category III cases that underwent intradepartmental consultations in the PGH *(blue)* and PRL *(orange)*.

PGH – Philippine General Hospital, PRL – Pathology Research Laboratory

performed by pathology residents during FNAB procedures, allowing additional aspirations to be obtained immediately when the initial smears are inadequate. Consequently, the proportion of Category I cases was markedly lower in PRL than in PGH (4.15% vs. 49.78%). In contrast, the difference in the frequency of Bethesda Category III cases between PGH (6.56%) and PRL (1.59%) was considerably smaller, suggesting that although ROSE substantially improves specimen adequacy, its effect on the frequency of AUS/FLUS diagnoses appears to be less pronounced.

The calculation of the risk of malignancy (ROM) for Bethesda Category III remains challenging because of selection bias, as described in both the 2nd and 3rd editions of TBSRTC. Patients with AUS/FLUS are more likely to undergo surgical resection when they have suspicious clinical or radiologic findings, thereby enriching the surgical cohort with malignant cases and potentially overestimating the ROM.[11] In the present study, the calculated ROM was high (67% in PGH, 73.9% in PRL, and 68.9% overall). However, these estimates should be interpreted cautiously because only a relatively small proportion of patients had traceable definitive surgical specimens in the PGH database (23.43% in PGH and 38.98% in PRL). Furthermore, the introduction of noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) in 2016 has influenced the reported ROM across Bethesda categories.[12] In our series, only one case of NIFTP was identified; therefore, its effect on the calculated ROM could not be adequately assessed.

Bethesda Category III has long been recognized as one of the most challenging diagnostic categories in thyroid cytopathology because of its intentionally broad definition, its nature as a diagnosis of exclusion, and its susceptibility to interobserver variability. Nevertheless, successive editions of TBSRTC have sought to improve diagnostic reproducibility by providing more refined subclassifications and clearer morphologic criteria.[12] The 3rd edition of TBSRTC (2023) addresses this issue by subdividing Bethesda Category III into two categories: (1) AUS with nuclear atypia, which raises a low level of concern for papillary thyroid carcinoma or NIFTP, and (2) AUS–Other, in which the atypia is predominantly architectural or attributable to other non-nuclear features. This refinement encourages pathologists to describe the specific type of atypia present rather than relying on nonspecific terms such as "focal atypia" or "mild atypia." In the present study, these nonspecific descriptors were the most commonly documented reasons for assigning Bethesda Category III, and several reports provided no explanation beyond the diagnostic category itself. Adoption of the 3rd edition of TBSRTC may therefore improve the consistency, reproducibility, and clinical utility of thyroid cytology reports by promoting more precise characterization of atypical cytologic findings.

Intradepartmental consultation, or review of challenging cases by one or more additional pathologists ("pass rounds") has long been an established quality assurance practice in pathology. Such consultation promotes diagnostic consensus and increases confidence in difficult interpretations. In the present study, the frequency of intradepartmental consultation for Bethesda Category III cases increased over time. This trend is encouraging and may reflect greater recognition among pathologists of the value of collaborative review in reducing subjectivity and improving diagnostic consistency for one of the most challenging categories in thyroid cytopathology.

According to the 2015 American Thyroid Association (ATA) Guidelines, recommended management options for Bethesda Category III include repeat FNAB, molecular testing, or diagnostic lobectomy, depending on the overall clinical context.[13] Although molecular testing may reduce the need for diagnostic surgery, its routine use remains limited in the Philippines because of its high cost and limited availability. At the time of writing, comprehensive

molecular testing is generally performed through referral to laboratories outside the country. The decision to proceed with surgery is multifactorial and should incorporate clinical findings, ultrasonographic features, laboratory results, patient preference, and the estimated risk of malignancy. Close communication between pathologists and treating clinicians remains essential to ensure appropriate interpretation and management of Bethesda Category III lesions.

Limitations of the Study

This study has several limitations. Patient identifiers, including names and case numbers, were excluded from the study database to preserve confidentiality, and patients were neither contacted nor interviewed during the study period. Consequently, follow-up was limited to the information available in the institutional medical records. Incomplete or unavailable clinical and surgical data may have affected the completeness of the dataset and the accuracy of the calculated repeat biopsy rates and risk of malignancy.

CONCLUSIONS

The frequency of Bethesda Category III (AUS/FLUS) diagnoses in our institution (4.27%) is within the recommended limits of the Bethesda System for Reporting Thyroid Cytopathology.

Only a small proportion of Bethesda Category III cases underwent repeat FNAB (15.38% in PGH and 18.64% in PRL). Among these repeat biopsies, a substantial proportion were reclassified as Bethesda Category I (Nondiagnostic) (31.8% in PGH, 45.4% in PRL, and 34.5% overall), limiting their ability to provide a more definitive cytologic diagnosis.

Among cases with both repeat FNAB and corresponding definitive surgical specimens, the diagnostic concordance between the repeat biopsy and the final histopathologic diagnosis was 100%. However, this finding should be interpreted cautiously because several repeat biopsies remained classified as Bethesda Category I or III, categories that are inherently nondiagnostic or indeterminate and therefore less informative in predicting the final diagnosis.

The calculated risk of malignancy (ROM) for Bethesda Category III was high (67.0% in PGH, 73.9% in PRL, and 68.9% overall). However, these estimates are likely influenced by selection bias, as only a relatively small proportion of patients had traceable definitive surgical specimens in the PGH database (23.43% in PGH and 38.98% in PRL). Among malignant outcomes, papillary thyroid carcinoma was the most common diagnosis, whereas thyroid follicular nodular disease (TFND) was the most frequent benign diagnosis. The most commonly documented reason for assigning Bethesda Category III was focal atypia.

Recommendations

Continued efforts to improve specimen sampling and smear quality, together with ongoing education and training of pathologists, are recommended to maintain the low frequency of Bethesda Category III diagnoses while ensuring diagnostic accuracy.

Implementation of the recommendations in the 3rd edition of the Bethesda System for Reporting Thyroid Cytopathology, particularly the subclassification of AUS into AUS with nuclear atypia and AUS–Other, together with documentation of the specific cytomorphologic features prompting an AUS interpretation, is strongly encouraged. These refinements may improve diagnostic consistency and provide clinicians with more meaningful information for patient management.

The establishment of a larger multicenter database or national thyroid cytopathology registry is likewise recommended to enable more complete follow-up of patients and more accurate estimation of repeat biopsy rates, definitive histopathologic outcomes, and the risk of malignancy associated with Bethesda Category III.

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Statement of Authorship

Both authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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