OPEN ACCESS – ORIGINAL ARTICLE

Value of Cell Block Technique as an Adjunct to Smear Cytology in Thyroid Fine-Needle Aspiration Biopsy

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ABSTRACT

Background. Thyroid fine-needle aspiration biopsy (FNAB) is widely used for thyroid nodule characterization, with approximately 2.7% of samples classified as "inadequate." Non-diagnostic samples pose limitations, resulting in repeated procedures, and unnecessary diagnostic thyroidectomies. Conventional smear (CS) is commonly the method of choice for cytologic preparation of thyroid FNAB. The cell block technique is an alternative that concentrates cells providing additional material for better evaluation and ancillary testing. While conventional smears are commonly used, introducing routine complementary cell blocks could potentially lower costs associated with repeat procedures and improve patient management.

Objective. The study aimed to investigate the diagnostic value of incorporating the cell block technique as adjunct to conventional smear technique in reducing nondiagnostic rates (Bethesda Category I) in thyroid-fine needle aspiration biopsies (FNAB) conducted in two private hospitals.

Methodology. This is a multi-center, retrospective cross-sectional study with 701 samples from 528 adult patients, who underwent thyroid FNAB between January 2020 – September 2022. The primary outcome of interest is the reduction in non-diagnostic rates with the combined use of conventional smears and cell block.

Results. The non-diagnostic rates were significantly higher with cell block technique (28.10%) as compared to conventional smears (16.26%), *p*-value <0.01. The results show that conventional smears have lower non-diagnostic rates. With smear cytology alone, 114 (16.3%) of all samples were nondiagnostic. With the addition of cell block technique, 15 of these samples were reclassified as benign (n = 13), Bethesda III (n = 1) or Bethesda IV (n = 1). The rest of the non-diagnostic samples (n = 99) remained Bethesda I. Overall, the equivalent decrease in non-diagnostic rate was 2.1%

Conclusion. The combined use of cell block and conventional smears did not significantly decrease nondiagnostic rates in thyroid FNAB. In general, conventional smears demonstrated superior diagnostic efficacy across all Bethesda categories, establishing it as the preferred sampling preparation method for thyroid FNAB. Cell blocks should be considered a supplementary technique, particularly in cases where ancillary methods like immunohistochemistry or molecular testing are needed.

Key words: fine needle biopsy, thyroid nodule, Bethesda I, thyroid gland, thyroid diseases, thyroid nodules, non-diagnostic smears, cell block, Bethesda System, thyroid cytopathology

ISSN 2507-8364 (Online)
Printed in the Philippines.

Received: 1 March, 2025.
Accepted: 20 March, 2025.
Published online first: 10 June 2025.
https://doi.org/10.21141/PJP.2025.02

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INTRODUCTION

Thyroid nodules are a common clinical problem, and fine-needle aspiration biopsy (FNAB) under ultrasonographic guidance is a valuable diagnostic tool for characterizing thyroid nodules. This procedure is safe, minimally invasive, has high patient tolerability and is the most accurate and cost-effective method for selecting patients for surgery.[1]

Thyroid FNA biopsy has a positive predictive value of >97% for malignant cytology, and is the procedure of choice for evaluation of thyroid nodules.[2,3] The Bethesda system for Reporting Thyroid Cytopathology (TBSRTC) is used for standardized classification of thyroid fine needle aspiration specimens. According to this system, each report is placed under 6 possible categories: (I) nondiagnostic; (II) benign; (III) atypia of undetermined significance (AUS); (IV) follicular neoplasm; (V) suspicious for malignancy; and (VI) malignant.

Non-diagnostic/inadequate cytology is one of the most important limitations of thyroid FNAB. Non-diagnostic samples still carry a 5-20% risk of malignancy.[4] Non-diagnostic specimens (Bethesda Classification I) occur when the samples contain only cyst fluid, lacks cellular material, or contains confounding factors such as: obscuring blood, clotting/drying artifacts or specimens contaminated by gel/diluted by blood or fluid. Repeat ultrasound-guided FNAB and monitoring is recommended in these patients. This leads to repeat biopsies, increased patient anxiety, and unnecessary diagnostic thyroidectomies with its associated additional costs.

Conventional smear (CS) has traditionally been the method of choice in the cytologic preparation of thyroid FNA biopsies. Some drawbacks with this technique include presence of artifacts, variable cellularity, cellular breakdown, and limited sample preservation. The conventional smear can be used alongside other alternative and more recently introduced techniques such as cell blocks (CB) and liquid-based cytology (LBC) to improve diagnostic rates.

The cell block technique is a histological preparation method used to create a solid, tissue-like specimen from aspirated materials. It allows for better evaluation of architectural patterns and cell structures, which can be especially helpful in cases where a definitive diagnosis is challenging based on conventional cytological evaluation alone. In cases where the FNAB sample is limited or contains scant cellular material, the cell block technique can concentrate the cells, making it possible to create a more informative specimen for analysis. In cytologically indeterminate nodules, it also allows for ancillary studies such as immunohistochemistry (IHC) or molecular testing, which can provide further insights into the characteristics of the nodules. Immunohistochemical stains can help diagnose uncommon thyroid neoplasms, as well as those with uncertain histogenesis. Testing for HBME-1, GAL-3, and CK19 immunopositivity has a high sensitivity and specificity for the diagnosis of papillary thyroid cancer.[5]

Molecular testing for BRAF V600E mutation helps characterize nodules that are positive for papillary thyroid cancer.[6]

Previous reports have indicated that the use of cell blocks in combination with conventional smears have resulted in enhanced diagnostic yield and accuracy for various type of specimens.[7,8] However, there is conflicting data about the utility of the addition of cell block in FNA biopsies of thyroid nodules.

A retrospective study of 11,011 thyroid nodules from 10,206 patients examined the utility of combined cell block with conventional smears in improving diagnostic accuracy in thyroid FNAB. When CS and CB were performed in combination, the unsatisfactory rate decreased to 9.8% versus 18.1% found in samples processed with CS alone (p <0.001). This study found that the combined utilization of CS and CB can substantially reduce the unsatisfactory rate of thyroid fine needle aspirations and enhance diagnostic effectiveness. Therefore, CB should be regularly employed in the evaluation of thyroid nodules whenever possible.[9]

In another study of 328 consecutive patients who underwent ultrasound-guided thyroid FNAB, samples were processed using both CS and CB technique. Rapid on-site evaluation of all specimens was performed to evaluate adequacy. In this study, comparing the nondiagnostic/unsatisfactory rates, it was observed that the addition of the cell block to the conventional smears significantly reduced the rate of nondiagnostic samples (17.1% vs. 4.3%, P <0.001). The overall accuracy of CS with CB for detection of neoplasm was 94%, with a sensitivity and specificity of 100% and 90%, respectively. By utilizing a combination of techniques such as CS and CB, the representativeness of samples has been enhanced, leading to reduced false negative rates. This combined approach can be routinely employed in thyroid FNAB.[10]

Conversely, a small retrospective study evaluated 82 thyroid FNAB cases that underwent review of both conventional smears and cell blocks. The examination of cell block slides revealed a non-diagnostic rate of 10% (8 out of 82 cases). This study found that cell blocks did not offer significant assistance in majority of cases. They proved contributory in only 31% (25 of 82 cases), and of the neoplastic cases only 22% (5 out of 23 cases) of cell blocks contributed to the diagnosis. The minimal contribution of cell blocks in diagnosing thyroid lesions was due to the low cellularity observed.[11]

Findings from another retrospective study examining 150 cell blocks generated from 252 thyroid FNAB cases, reviewed alongside their original smears, revealed a non-diagnostic rate of 18.5%. Within this study, cell block interpretation did not demonstrate any additional benefit over cytology slides in 63% (95 out of 150) of all thyroid FNAB cases. The agreement between CS and CB interpretations based on the TBSRTC classification was observed in only 35% of cases. The generation of cell blocks provided additional diagnostic value in only 2% (3 out of 150) of FNAB samples, and this improvement was attributed to the application of immunohistochemistry in samples suspected to be of medullary thyroid carcinoma (MTC). In conclusion, this study highlights that routine processing of cell blocks in thyroid FNAB did not significantly enhance the diagnostic yield of unsatisfactory or atypical thyroid samples. Routine processing of cell blocks is time-consuming, impractical, and introduces delays in the turnaround time of results. The authors suggest generating cell blocks only in cases classified as TBSRTC Category IV and V when immunohistochemistry stains are necessary for diagnostic purposes.[12]

Despite conflicting evidence, optimized techniques in thyroid FNAB have some advantages and may have utility in our setting. In the Philippines, most samples are processed by conventional smears alone. Non-diagnostic/inadequate smears necessitate additional healthcare costs, associated with prolonged diagnostic investigations and unnecessary follow-up visits. The cell block technique may minimize the need for repeat biopsies, potentially reducing overall costs and improve patient management. However, the cost-effectiveness of this technique depends largely on the local healthcare system, the availability of resources, and the expertise of the medical staff. Further research and consideration of local factors are necessary to determine

the feasibility and appropriateness of adopting cell block technique routinely in such settings.

OBJECTIVES

This study aimed to investigate the diagnostic value of incorporating the cell block technique as an adjunct to conventional smear technique in reducing non-diagnostic rates (Bethesda Category I) in thyroid fine-needle aspiration biopsies (FNAB) conducted at a private hospital. Specifically, it sought to determine the demographic profile and pathological findings of participants; evaluate and compare the non-diagnostic rates of conventional smears and the cell block technique; analyze the distribution of benign, malignant, and other pathological findings from both methods; assess the reduction in non-diagnostic yield when using the combined approach; and compare the concordance of pathological findings between the two techniques.

METHODOLOGY

Study design and population

This is a retrospective, cross-sectional study comparing the non-diagnostic yield rates (Bethesda Category I) and other pathologic findings of combined conventional smears and cell block technique with conventional smears alone in FNA biopsies of thyroid nodules at St Luke's Medical Center Quezon City and Providence Hospital from January 2020 to September 2022. Adults 18 years of age and older, who underwent FNAB of the thyroid were included in the study. The relevant clinical data of the included participants were obtained from electronic medical health records. Patients who underwent fine needle aspiration biopsy of organs other than the thyroid (lymph nodes/parathyroid/salivary glands), biopsy done in patients post thyroidectomy and/or post radioactive iodine ablation, patients with incomplete data in the medical records, and those patients who underwent other procedures such as thyroid cyst aspiration/ethanol ablation of thyroid nodules were excluded.

Description of outcome measures

The primary outcome of this study is to determine the non-diagnostic/unsatisfactory rate (Bethesda Classification I). This will be expressed as a dichotomous variable.

"Others": those specimens with a cytologic diagnosis of either:

b.1 Benign
b.2 Atypia of undetermined significance (AUS)
b.3 Follicular neoplasm
b.4 Suspicious for malignancy
b.5 Malignant

c. Concordance rate: the rate of agreement of histologic diagnosis (as expressed by the Bethesda classification/Bethesda system for reporting thyroid cytopathology) between samples prepared by conventional smear vs cell-block technique

Study procedures and data gathering

Potential study participants who underwent thyroid fine needle aspiration biopsy were screened from the logbook and other registries of the Diabetes and Endocrine centers of St. Luke's Medical Center, Quezon City and Providence Hospital. The participants demographic, clinical characteristics, ultrasonography, histopathology, and cytopathology results were obtained from electronic medical health records.

All biopsies were performed under ultrasonographic guidance. Biopsies were performed by endocrinologists, surgeons (from ENT and General Surgery) and pathologists at the Endocrine centers of both institutions.

In cases where mixed solid and cystic nodules were present, samples were taken from the solid components. On each pass, the first half of the sample was extruded onto the glass slides for preparation of conventional smears, while the remaining material was submitted for cell block technique. The same technique was repeated on any subsequent passes. Samples were prepared using both conventional smears and cell block technique. For conventional smears, the extracted material was expelled onto a glass slide, gently spread, and then immediately fixed by immersing in 95% ethanol for fixation. For the cell block technique, needle rinses were done into a clean container with 30 mL of 10% buffered formalin solution from the material left in the hub of the needle. The packed sediment/fibrin clot was prepared by centrifugation of the test tube at 2000 revolutions per minute (RPM) for ten minutes. The sediment/fibrin clot was processed for histopathology. The clotted material was transferred into filter paper, folded and shifted into carefully labelled cassettes. The tissue cassettes were then added into a jar of formalin for fixation. The residual drops of specimen at the bottom of the previously centrifuged test tube were then gently spread on glass slides, fixed in 95% ethyl alcohol and prepared for Papanicolaou staining. Each specimen was labelled from either right, isthmus, or left nodule accordingly.

Samples were submitted to the pathology department labelled with the patient's name, age, sex, hospital pin number as well as biopsy site. For patients with samples obtained from nodules on multiple sites, samples from each site (left lobe, right lobe or isthmus) were included and analyzed as distinct data. When multiple nodules were present on one site/lobe, the first nodule biopsied with samples submitted for both conventional smear and cell block technique were chosen. No rapid on-site assessment was conducted to determine the adequacy of the specimens.

All conventional smears and cell blocks were evaluated and classified by pathologists of their respective institutions. The histopathologic diagnoses were categorized according to The Bethesda System for Reporting Thyroid Cytopathology specimens.

Sample size

Using a 5% significance level, a 5% margin of error, and 12.8% change in Bethesda I (non-diagnostic) classification as reported by de Cristo et al. (2016)[10], the required sample size was computed at 172 biopsies.

Statistical analysis

Descriptive statistics were used to summarize the general and clinical characteristics of the patients. Frequency and proportion were used for categorical variables such as sex,

nodule laterality, and Bethesda classification, median and range for non-normally distributed interval/ratio variables such as age.

For categorical variables, Fisher's Exact test was used to determine the difference in frequencies between groups (Conventional Smear (CS) vs Cell block technique (CB)). Cohen's Kappa was used to determine the concordance rate or the agreement of nominal/ordinal variables such as the Bethesda classification of the Conventional Smear and Cell block. Missing variables were neither replaced nor estimated. The null hypothesis was rejected at a significance level of 0.05α.R-4.1.3 was used for data analysis.

Ethical considerations

The Clinical Protocol and all relevant documents were reviewed and approved by the SLMC Institutional Ethics Review Committee. Patient confidentiality was respected by ensuring anonymity of patient records. Each patient document was CODED and did not contain any identifying information 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. The study abided by the Principles of Declaration of Helsinki and was conducted along the Guidelines of the International Conference on Harmonization-Good Clinical Practice (ICH-GCP). The authors declare that there was no conflict of interest with study collaborators, and subjects.

RESULTS

This study presents the clinicodemographic profile of 528 patients who underwent fine-needle aspiration biopsy of thyroid nodules (Table 1). The median age of the patients was 51.50 years, ranging from 18 to 85 years. In terms of sex distribution, females predominated the study, comprising 86.17% (455 out of 528) of the participants, while males constituted a smaller fraction of 13.83% (73 out of 528).

When considering the laterality of the nodules, right-sided nodules were slightly more common, with a frequency of 51.50% (361 out of 528), while left-sided nodules accounted for 44.51% (312 out of 528) of the cases. Isthmic nodules, found in the narrow part of the thyroid gland connecting the two lobes, were relatively rare, representing only 3.99% (28 out of 528) of the patients.

The cross-tabulation table (Table 2) provides a comparative overview of the Bethesda classifications for conventional smears and cell block techniques. It highlights the distribution of results across the different Bethesda categories, offering an insight into the concordance and discordance of diagnoses made by these two methods.

We observed a high concordance rate for category II (Benign), with 355 out of 434 cases (81.56%) being classified as benign by both techniques. However, there is a notable discordance in Category I (Nondiagnostic), where the cell block technique resulted in a much higher frequency (28.10%) compared to conventional smears (16.26%).

In Table 3, the concordance rate of Bethesda classification between conventional smears and cell block technique was evaluated using Cohen's Kappa, a statistical measure of agreement. The study included a total of 701 cases.

The overall Kappa value obtained for all Bethesda classifications combined was 0.679, indicating a substantial level of agreement between conventional smear and cell block technique interpretations. This suggests that there is consistency between the two methods in classifying cases into different Bethesda categories.

The study results revealed individual Kappa values for each Bethesda classification, ranging from 0.533 to 0.892. These values indicate varying degrees of agreement between conventional smear and cell block technique for specific categories. The Kappa values of 0.533, 0.677, and 0.749, corresponding to Bethesda I (Nondiagnostic), Bethesda II (Benign), and Bethesda III (Atypical cells of undetermined significance - AUS), respectively, demonstrate moderate to substantial agreement.

For the categories Bethesda IV (Follicular CA/ Suspicious for follicular CA), Bethesda V (Suspicious for malignancy), and Bethesda VI (Malignant), the Kappa values of 0.894, 0.865, and 0.892, respectively, indicate near-perfect agreement between the two methods. All the Kappa values had p-values less than 0.01, confirming that the observed agreements between conventional smear and cell block technique classifications are statistically significant.

Table 4 provides a comparison of the results obtained using conventional smears and cell block techniques for the assessment of thyroid nodules. The results are classified according to the Bethesda System for Reporting Thyroid Cytopathology, and a total of 701 samples were analyzed for each technique.

Table 1. Clinicodemographic profile of patients who underwent thyroid fine needle aspiration

	Median (Range); Frequency (%)
Age, years	51.50 (18 - 85)
Sex	
Male	73 (13.83)
Female	455 (86.17)
Nodule laterality	
Left	312 (44.51)
Right	361 (51.50)
Isthmus	28 (3.99)

Table 2. Cross tabulation of the Bethesda classification of conventional smear and cell block technique (n = 701)

		Cell Block						
		I	II	III	IV	V	VI	Total
Conventional Smear	*I*	99 (14.1)	13 (1.9)	1 (0.1)	1 (0.1)	0	0	114 (16.26)
	II	78 (11.1)	355 (50.6)	1 (0.1)	0	0	0	434 (61.91)
	III	16 (2.3)	12 (1.7)	55 (7.8)	0	0	0	83 (11.84)
	IV	1 (0.1)	1 (0.1)	0	13 (1.9)	0	0	15 (2.14)
	V	2 (0.3)	3 (0.4)	2 (0.3)	0	27 (3.9)	0	34 (4.85)
	VI	1 (0.1)	2 (0.3)	0	0	1 (0.1)	17 (2.4)	21 (3.00)
	Total	197 (28.1)	386 (55.06)	59 (8.42)	14 (2.00)	28 (3.99)	17 (2.43)	701 (100)

Table values are in frequency (%).

Table 3. Concordance rate of Bethesda classification of conventional smear vs cell block technique (n = 701)

	Kappa	Interpretation	*p*
Overall	.679	Substantial	<.01
Bethesda I – Nondiagnostic	.533	Moderate	<.01
Bethesda II – Benign	.677	Substantial	<.01
Bethesda III – AUS	.749	Substantial	<.01
Bethesda IV – Follicular CA	.894	Near Perfect	<.01
Bethesda V – Suspicious for malignancy	.865	Near Perfect	<.01
Bethesda VI – Malignant	.892	Near Perfect	<.01

Statistical analysis used: Cohen's Kappa.
Kappa interpretation; 0, no agreement; 0.1-0.2, slight agreement; 0.21-0.4, fair agreement; 0.41-0.6, moderate agreement; 0.61-0.8, substantial agreement; 0.81-0.9, near perfect agreement; 1, perfect agreement.

Table 4. Differences in Bethesda classification using smear alone and combined smear-cell block interpretation (n = 701)

Bethesda category	Smear	Smear + Cell block	No change	Stepped up	Stepped down	Total
	Frequency (%)					
I	114 (16.26)	99 (14.12)	99 (14.12)	15 (2.14)	0	114 (16.26)
II	434 (61.91)	433 (61.77)	355 (50.64)	1 (0.14)	78 (11.13)	434 (61.91)
III	83 (11.84)	83 (11.84)	55 (7.85)	0	28 (3.99)	83 (11.84)
IV	15 (2.14)	15 (2.14)	13 (1.85)	0	2 (0.29)	15 (2.14)
V	34 (4.85)	34 (4.85)	27 (3.85)	0	7 (1.00)	34 (4.85)
VI	21 (3.00)	21 (3.00)	17 (2.43)	0	4 (0.57)	21 (3.00)
Total	701 (100)	685 (97.72)	566 (80.74)	16 (2.28)	119 (16.98)	701 (100)

The non-diagnostic rates were significantly higher with cell block technique (28.10%) as compared to conventional smears (16.26%). Conventional smears alone yielded a higher percentage of benign results (61.91%) than cell block technique (55.06%). For category III (Atypia of Undetermined Significance, AUS), conventional smears reported a higher percentage (11.84%) compared to cell block technique (8.42%). Furthermore, very slight differences were observed in the categories IV (Follicular Neoplasm/ Suspicious for a Follicular Neoplasm), V (Suspicious for Malignancy), and VI (Malignant) between the two techniques, with conventional smear generally reporting slightly higher percentages.

The results show that conventional smears have lower non-diagnostic rates when compared to cell block technique. While differences were observed in the categories suggestive of or confirming malignancy, these differences were minimal. With smear cytology alone, 114 (16.3%) of all samples were non-diagnostic. With the addition of cell block technique, 15 of these samples were reclassified as benign (n=13), Bethesda III (n=1) or Bethesda IV (n=1). The rest of the non-diagnostic samples (n=99) remained Bethesda I. Overall, the equivalent decrease in non-diagnostic rate was 2.1% (Table 4).

Conventional smears tagged 434 (61.9%) of biopsies as benign, but the addition of cell block recategorized only 1 sample to Bethesda III (AUS). In contrast, adding cell block technique to conventional smear cytology did not increase the risk category of any of the samples initially graded as Bethesda III - VI. Hence, overall, cell block technique as an adjunct to conventional smear resulted in a higher risk category for only 3 in 701 samples (0.4%), or 3 in 528 patients (0.6%).

DISCUSSION

Fine-needle aspiration biopsy plays a crucial role in the initial screening of suspicious thyroid nodules. It has demonstrated reproducibility, high diagnostic accuracy, and has also resulted in improved patient selection for conservative management or surgical treatment. Despite its clinical significance, FNAB has certain limitations, such as inadequate sampling and limited cellularity of obtained samples.

The cell block technique has been routinely employed as a technique for evaluating tissue from fine-needle aspirations or fluid aspirations. While the smear technique has been universally used for detection of malignancy in thyroid FNAB, the use of cell blocks has been adopted to enhance diagnostic accuracy. Cell blocks offer diagnostic architectural information that complements fine-needle aspiration smears and allows for the application of ancillary tests such as immunohistochemistry and molecular testing on the preserved cellular material. This can provide additional diagnostic information and aids in characterizing certain thyroid nodules. This can lead to definitive diagnoses, providing crucial information for developing targeted treatment strategies.

It has been established that the diagnostic accuracy of FNAB is significantly improved when performed under ultrasonographic guidance, alongside an accompanying onsite cytopathologist.[13,14] Similarly, lower FNAB sampling inadequacy is associated with operator experience.[15] Non-diagnostic rates are lower in specialty groups with high procedural volumes (>600 within a group practice/year) than those with low volumes (<105/year).[16] All thyroid FNA biopsies in this study were done with ultrasound guidance, but without the presence of an onsite cytopathologist to

assess for sample adequacy. Also, thyroid FNA biopsies in this study were done by various specialists with differing levels of experience. Specimens were collected from specialists from Endocrinology, General surgery, Ear, Nose and Throat (ENT), as well as Pathology.

The results of this study offer a detailed comparison of the conventional smear and cell block technique using the Bethesda System for Reporting Thyroid Cytopathology. The key finding is the high level of concordance between the two methods across most Bethesda categories, as indicated by substantial to near-perfect Kappa values. This high concordance, particularly in categories IV, V, and VI, which indicate potential malignancy, suggests a robust reliability of both techniques in detecting malignant or suspicious thyroid nodules. Clinicians can thus have confidence in the diagnostic consistency of these two methods.

However, a notable discordance was observed in the Bethesda I (non-diagnostic) category, with higher frequency of non-diagnostic samples in the cell block technique compared to conventional smears. The addition of cell block to conventional smears meanwhile, yielded a non-significant decrease in the non-diagnostic rates. This suggests that the routine addition of cell blocks to conventional smears in thyroid FNAB does not improve diagnostic accuracy.

Given these findings, the routine addition of cell block to conventional smears for thyroid nodule evaluation should also consider other factors such as turnaround time, cost, and local expertise. The turnaround times for histopathologic diagnosis for thyroid FNAB samples with conventional cytology smears and cell blocks of 2321 specimens from 1826 patients were evaluated. Of the 2321 samples, 933 had cell block smears prepared. The study found that cases with cell blocks had longer turnaround times compared to those without. Cases with cell blocks were more likely to have a turnaround time more than 1 day (65%, $P < 0.0001$) or greater than 3 days (25.4%, $P < 0.0001$). This led to a longer workaround time, increasing patient's waiting time and increased hospital billing costs. The longer turnaround time, increased utilization of resources and workforce allocation could be potentially reduced if cell blocks were produced only as needed, particularly when smear results are inconclusive or if ancillary tests are necessary to confirm the diagnosis.[17]

Sample processing via the cell block technique require technical skills. This entails specialized machinery and staff who are trained to handle, process and interpret the cell block smears for an accurate histologic diagnosis. Currently, cell blocks are not consistently valuable in improving diagnostic rates, with insufficient sample cellularity being the primary factor.

The greater proportion of inadequate samples with the cell block technique compared to conventional smears in this study, could also be attributed to the sampling method or improper triage of the sample. At our institutions, cell block material is currently obtained through a needle rinse after each pass. To enhance the diagnostic yield of cell block preparations, an alternative approach is to perform a dedicated needle pass with the specific purpose to obtain cell block material. This method offers a higher probability of obtaining an adequately cellular specimen, compared to relying solely on a needle rinse at the end of each pass.[18]

Ensuring careful and strategic allocation of samples among smears and cell blocks is also important.[19] Lastly, close collaboration between the pathologists and interventionalists to develop effective specimen processing protocols may lead to better diagnostic outcomes. These practices may increase the probability of obtaining sufficient samples for histologic diagnosis, ancillary testing and help avoid the need for repeated procedures.

Limitations

This study has several limitations. First, data was collected by retrospective chart review, and a secondary examination of each conventional smear and cell block slide to determine their contributory status to histopathologic diagnosis could not done. In this study, FNA biopsies were conducted by various interventionalists, each having different levels of expertise and procedural volume. Likewise, the evaluation of the conventional and cell block smears for each participant was performed by different cytopathologists, and the readers were unblinded.

Lastly, there was no correlation of thyroid FNA biopsy results with histology. To further determine diagnostic accuracy, a comparison of both conventional smear and cell block with the gold standard of post-surgical histopathology is ideal. Such a comparison would provide a more comprehensive and accurate evaluation of their diagnostic accuracy.

CONCLUSION

The routine addition of cell block to conventional smears did not significantly decrease non-diagnostic rates in thyroid FNA biopsies. In general, conventional smears demonstrated superior diagnostic efficacy, establishing it as the preferred sampling preparation method for thyroid FNAB. Cell block should be considered as a supplementary technique in establishing the diagnosis in equivocal cases, and when ancillary methods like immunohistochemistry or molecular testing are required. The authors recommend that cell block be used as a supplementary technique in establishing the diagnosis specifically in equivocal cases, particularly when ancillary methods such as immunohistochemistry or molecular testing are required.

ACKNOWLEDGMENTS

The authors acknowledge Dr. Venus Cloma-Rosales and her team, under 101 Health Research who provided invaluable technical assistance; and Dr. Gabriel Jasul Jr., the chair of the Section of Endocrinology, Diabetes and Metabolism of SLMC-QC for his support and encouragement throughout the course of this research.

STATEMENT OF AUTHORSHIP

All authors certified fulfilment of ICMJE authorship criteria.

AUTHOR DISCLOSURE

The authors declared no conflict of interest.

FUNDING SOURCE

The authors received a grant in 2023 from the Philippine College of Endocrinology, Diabetes and Metabolism.

REFERENCES

1. Galera-Davidson H, Gonzalez-Campora R. Thyroid in: Bibbo M, Wilbur: Comprehensive cytopathology, 3rd ed, chapter 23. Philadelphia, PA: Saunders Elsevier. 2008. NLM ID: 101487642
2. Yassa L, Cibas ES, Benson CB, et al. Long-term assessment of a multidisciplinary approach to thyroid nodule diagnostic evaluation. Cancer. 2007;111(6):508-16. PMID: 17999413. DOI: 10.1002/cncr.23116
3. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. Thyroid. 2016; 26(1): 1–133. PMID: 26462967 PMCID: PMC4739132 DOI: 10.1089/thy.2015.0020
4. Ali SZ, Baloch ZW, Cochand-Priollet B, Schmitt FC, Bielh P, VanderLaan PA. The 2023 Bethesda System for reporting thyroid cytopathology. J Am Soc Cytopathol. 2023;12(5):319-25. PMID: 37438235 DOI: 10.1016/j.jasc.2023.05.005
5. Crescenzi A, Baloch Z. Immunohistochemistry in the pathologic diagnosis and management of thyroid neoplasms. Front Endocrinol (Lausanne). 2023; 14:1198099. PMID: 37324272 PMCID: PMC10266214 DOI: 10.3389/fendo.2023.1198099
6. Poller D, Glaysher S, Agrawal A, Caldera S, Kim D, Yiangou C. BRAF V600 co-testing in thyroid FNA cytology: short-term experience in a large cancer centre in the UK. J Clin Pathol. 2014;67(8):684-9. PMID: 24873948 DOI: 10.1136/jclinpath-2014-202348
7. Khan S, Omar T, Michelow P. Effectiveness of the cell block technique in diagnostic cytopathology. J Cytol. 2012;29(3):177-82. PMID: 23112458 PMCID: PMC3480766 DOI: 10.4103/0970-9371.101167
8. Demirci NY, Dikmen AU, Abdullayeva Z, Öztürk C. Contribution of cell blocks obtained through endobronchial ultrasound-guided transbronchial needle aspiration for the determination of lung cancer subtypes. Clin Respir J. 2018;12(4):1623-7. PMID: 28976111 DOI: 10.1111/crj.12719
9. Jiang K, Zhou J, Lei J, et al. Cell block is a valuable adjunct to conventional smear for thyroid fine needle aspiration: 2395 cases with histological correlation. Cytopathology. 2018;29(6). 525-30. PMID: 30238537 DOI: 10.1111/cyt.12633
10. De Cristo AP, Goldstein HF, Faccin CS, Maia AL, Graudenz MS. Increasing diagnostic effectiveness of thyroid nodule evaluation by implementation of cell block preparation in routine US-FNA analysis. Arch Endocrinol Metab. 2016;60(4):367-73. PMID: 27533613 PMCID: PMC10118724 DOI: 10.1590/2359-3997000000180
11. Sanchez N, Selvaggi SM. Utility of cell blocks in the diagnosis of thyroid aspirates. Diagnostic Cytopathol. 2006;34(2):89-92. PMID: 16514670 DOI: 10.1002/dc.20385
12. Saharti S. The diagnostic value of add-on thyroid cell block in the evaluation of thyroid lesions. Cytojournal. 2023;20:3. PMID: 36895260 PMCID: PMC9990845 DOI: 10.25259/Cytojournal_9_2022
13. Bongiovanni M, Spitale A, Faquin WC, Mazzucchelli L, Baloch ZW. The Bethesda System for reporting thyroid cytopathology: a meta-analysis. Acta Cytologica. 2012; 56(4):333-9. PMID: 22846422 DOI: 10.1159/000339959
14. Pastorello RG, Destefani C, Pinto PH, et al. The impact of rapid on-site evaluation on thyroid fine-needle aspiration biopsy: a 2-year cancer center institutional experience. Cancer Cytopathology, 2018;126(10). 846–52. PMID: 30317695 DOI: 10.1002/cncy.22051
15. Gursoy A, Anil C, Erismis B, Ayturk S. Fine-needle aspiration biopsy of thyroid nodules: comparison of diagnostic performance of experienced and inexperienced physicians. Endocr Pract. 2010;16(6): 986-91. PMID: 20570813 DOI: 10.4158/EP10077.OR
16. Houdek D, Cooke Hubley S, Puttagunta L, Morrish D. Factors affecting thyroid nodule fine needle aspiration non-diagnostic rates: a retrospective association study of 1975 thyroid biopsies. Thyroid Research. 2021;14(1):2. PMID: 33568168 PMCID: PMC7874649 DOI: 10.1186/s13044-021-00093-2
17. Edens J, Chand M, Asghar I, Bhatt M, Anderson I, Miller S. Practical diagnostic utility of thyroid fine-needle aspiration cell blocks: Is always too much? J Am Soc Cytopathol. 2021;10(2):164–7. PMID: 32978096 DOI: 10.1016/j.jasc.2020.07.136
18. Knoepp SM, Roh MH. Ancillary techniques on direct-smear aspirate slides: a significant evolution for cytopathology techniques. Cancer Cytopathol. 2013; 121(3):120-8. PMID: 22786714 DOI: 10.1002/cncy.21214
19. Saqi A. The state of cell blocks and ancillary testing: past, present, and future. Arch Pathol Lab Med. 2016; 150(12):1318-22. PMID: 27557411 DOI: 10.5858/arpa.2016-0125-RA

ANNEX

Operational Definitions

Fine needle aspiration biopsy of the thyroid: diagnostic tool which is a simple procedure that involves passing a thin needle through the skin to sample fluid or tissue from a cyst or solid mass in the thyroid

Conventional smear: technique in the preparation of samples of thyroid fine-needle aspiration biopsies which is done by gently expelling extracted material from the syringe onto a glass slide, gently spreading, and then immediately fixed by immersing in 95% ethanol for fixation

Cell-block technique: a technique in the preparation of samples of thyroid fine-needle aspiration biopsies which is done by injecting the extracted material from the syringe into a container with 30 mL of 10% buffered formalin solution or 95% ethanol, then subjected to cytospin (centrifuged for 10 min. at 2000 rpm), then stained with hematoxylin and eosin (H&E).

Bethesda classification/Bethesda system for reporting thyroid cytopathology: a standardized, category-based reporting system for thyroid fine-needle aspiration biopsy (FNAB) specimens. It is composed of 6 categories, namely:

Nondiagnostic or unsatisfactory: specimen containing cyst fluid only, virtually acellular specimen, or other (with obscuring blood or clotting artifact)

Benign: specimen consistent with a benign follicular nodule (includes adenomatoid nodule, colloid nodule, etc.), consistent with lymphocytic (Hashimoto) thyroiditis in the proper clinical context, consistent with granulomatous (subacute) thyroiditis

Atypia of undetermined significance (AUS): specimen that contains few cells that have distinct but mild nuclear atypia or with more extensive but very mild nuclear atypia

Follicular neoplasm: specimens with most of the follicular cells arranged in cell crowding or microfollicle formation

Suspicious for malignancy: specimen suspicious of papillary thyroid carcinoma, suspicious for medullary carcinoma, suspicious for metastatic carcinoma, suspicious for lymphoma

Malignant: specimen showing features of Papillary thyroid carcinoma, Poorly differentiated carcinoma, Medullary thyroid carcinoma, Undifferentiated (anaplastic) carcinoma, Squamous-cell carcinoma, Carcinoma with mixed features, Metastatic carcinoma, Non-Hodgkin lymphoma, or others