Case Series

Diagnostic Traps in Papillary Thyroid Carcinoma: Correlation of The Bethesda System for Reporting Thyroid Cytopathology with Histopathology: A Case Series

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Abstract

Fine-needle aspiration cytology is a widely used first-line tool for evaluating thyroid lesions, with histopathology serving as the diagnostic gold standard. Despite its advantages, interpretation challenges arise due to overlapping cytomorphologic features, suboptimal sample adequacy, and inter-observer variability, occasionally leading to discordance and affecting patient management. This case series describes four diagnostically challenging cases of classical papillary thyroid carcinoma in which initial cytological interpretations differed from final histopathological findings. Each case was re-evaluated systematically with emphasis on adequacy of the aspirate, radiologic correlation, characteristic cytological features, and potential diagnostic pitfalls. Contributing factors such as papillary hyperplasia mimics, misleading ultrasound impressions, and low cellularity were analyzed to understand the basis of discordance. Final diagnoses were established through multidisciplinary collaboration among the surgeon, radiologist, and cytopathologist. Case 1 was initially reported as a benign colloid nodule (TBSRTC II) but was later confirmed as classical papillary carcinoma with nodal metastasis. Case 2 was categorized as AUS (TBSRTC III); histopathology revealed classical papillary carcinoma, infiltrating follicular subtype. Case 3 was diagnosed as follicular neoplasm (TBSRTC IV) on cytology, while final evaluation confirmed NIFTP. Case 4, also categorized as follicular neoplasm (TBSRTC IV), was ultimately diagnosed as encapsulated angioinvasive follicular variant of papillary thyroid carcinoma. TBSRTC remains a robust and standardized framework for thyroid cytology, providing consistent terminology and risk stratification. However, diagnostic limitations persist, emphasizing the need for meticulous cytologic assessment, close radiologic correlation, and interdisciplinary collaboration to minimize discordance and improve patient outcomes.

Keywords: bethesda; cytology; thyroid; papillary carcinoma; follicular variant; NIFTP

Introduction

Thyroid nodules are common in the general population, with a prevalence ranging from 4–10%. Among these, thyroid malignancies account for approximately 0.1–0.2% of all cancers in India. Evaluation of thyroid nodules measuring more than 1 cm in size is strongly recommended, as fewer than 5% of nodules are malignant; however, accurate distinction between benign and malignant lesions is essential to prevent unnecessary surgical intervention and surgery-related complications. Fine-needle aspiration cytology (FNAC) has emerged as a minimally invasive, cost-effective, and widely accepted diagnostic procedure for the initial evaluation and triaging of patients with thyroid nodules. Using FNAC, nearly 70–80% of thyroid

lesions can be accurately classified, with high diagnostic accuracy for malignancy, particularly in the higher Bethesda categories, although the predictive value varies among categories. To standardize cytopathological reporting and improve communication between pathologists and clinicians, the National Cancer Institute (NCI), along with professional bodies such as the American Thyroid Association and the Italian Society of Cytopathology, introduced The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC). This six-tiered classification system provides uniform diagnostic terminology, guides clinical management, and provides an estimated risk of malignancy for each diagnostic category.

The objective of this study is to evaluate thyroid nodules using fine-needle aspiration cytology and to categorize the lesions according to The Bethesda System for Reporting Thyroid Cytopathology, with an aim to assess its utility in differentiating benign and malignant thyroid lesions and guiding appropriate clinical management.

Thyroid nodules account for about 4–10% of the general population, among which thyroid malignancies constitute about 0.1–0.2% of all cancers in India. [1] It is highly recommended to evaluate all thyroid nodules >1 cm in size since $<5\%$ of these thyroid nodules are malignant and it is crucial to differentiate between benign and malignant lesions in order to avoid unnecessary surgical intervention and surgery-related complications. Fine-needle aspiration cytology (FNAC) proved to be a minimally invasive, cost-effective, and widely accepted procedure for triaging patients. [1, 2] By using the mode of FNAC, 70–80% of thyroid lesions can be accurately classified with high diagnostic accuracy for malignancy, particularly in higher Bethesda categories; however, positive predictive value varies across categories and is not absolute. In 2006 and 2009, the American Thyroid Association and the Italian Society proposed The National Cancer Institute (NCI) introduced The Bethesda System for Reporting Thyroid Cytology (TBSRTC); a 6-tiered system in October 2007 in Maryland in Bethesda to standardize cytopathological terminologies used in reporting thyroid nodule aspirates. It is a robust classification system to guide clinical treatment of patients and also provides an estimate of malignant potential of each individual category. [2, 3] Classical Papillary Carcinoma Thyroid (PTC) is an indolent tumor with a long-term survival rate of $>95\%$, which accounts for about 80–95% of all thyroid cancers. [3, 4] Conventional/classical PTC is usually straightforward in FNACs, where the characteristic papillary architecture is encountered. Hence, a definite awareness of the cytomorphologic spectrum of cytological features of PTC variants, especially (NIFTP) noninvasive follicular thyroid neoplasm with papillary-like nuclear features, is important to avoid pitfall diagnosis. Fine-needle aspiration has a high accuracy rate for diagnosis of classical PTC. However, a definitive diagnosis can be made only on histopathology since the architectural features of capsular/vascular invasion defining malignancy cannot be assessed cytologically akin to histopathology. [4, 5] Nevertheless, some of the architectural, cytologic, and background features are observed cytologically which ultimately diminish the risk of misdiagnosing variants and ultimately improves patient care. [6]

Case Report

In this case series, we present 4 instances of challenging cases of thyroid lesions which showed high discordance between FNAC–histopathology report. These cases were examined with respect to comprehensive sampling adequacy, radiological intervention, clinical presentation, meticulous cytological assessment, and close histopathological correlation.

CASE-1: Classical Papillary carcinoma metastasizing to lymph node misclassified as Benign colloid nodule – TBSRTC (category 2): Case details: A 38-year-old female complained of a lump in the left side of the neck which got bigger for the last 5 months. The patient had no family history of thyroid diseases, autoimmune disorder, nor was on medications. Her lab investigations were normal with regards to T3, T4, TSH levels. Ultrasound examination revealed a nodule which is solid/cystic in the left lobe of the thyroid measuring 2×1.3 cm. Physical examination showed a well-defined nodule which is round in shape, in the left lobe of the thyroid measuring 2×1.3 cm; fixed, no tenderness and signs of inflammation noted. There were few reactive lymph nodes noted at the level 2B on the left side of the neck. She underwent USG-guided FNAC which later underwent total thyroidectomy was performed where the external surface was grey-brown in colour. Cut surface of which showed multiple polypoidal fragments. USG-guided FNAC: FNAC yielded sparsely cellular smears composed of few clusters of benign follicular epithelial cells with background showing thin colloid, blood and foamy macrophages. The 2023 Bethesda system revealed TBSRTC–Category 2, which is consistent with Benign colloid nodule. [12] Histopathology: On subsequent total thyroidectomy, the final pathology report revealed a tumor arranged in papillary pattern having papillae with central fibrovascular core. The individual tumor cells are enlarged, thickened nuclear membrane, pale/acidophilic cytoplasm, ground glass nuclear clearing (orphan Annie nuclei), glassy intranuclear inclusions, margination of chromatin, nuclear grooving (coffee bean nuclei), nuclear pseudoinclusions. Areas of necrosis and few round, concentric laminated calcification around necrotic tumor (psammoma bodies) consistent with classical papillary carcinoma was confirmed. On beyond examination of adjacent lymph node, showed similar histological features as that of the thyroid tissue suggesting the primary lesion metastasizing to lymph node on the left side.

Case- 2: Papillary microcarcinoma - follicular variant misinterpreted as AUS (Atypia of undetermined significance); TBSRTC category -III on FNAC: A 51-year-old female complaints of swelling in the right side of the neck which moves on swallowing for the past 5 years which increased in size for the past 3 months. USG showed a hypoechoic nodule with microcalcification. Physical examination revealed a well-defined solid mass round in shape measuring $12\times7\times4$ cm;

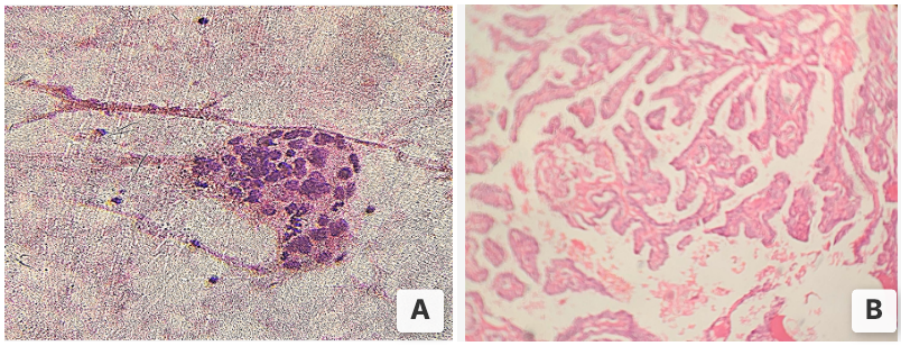

Figure 1: (A) Fnac smear (H&E, 40×) showing mild cellularity with benign-appearing follicular cells. Low cellularity contributed to malignancy underestimation. (B) Thyroidectomy specimen (H&E, 40×) showing classical PTC nuclear features, micropapillary architecture, and psammoma bodies, explaining the discordance.

solitary, fixed, painful on palpating. She had low TSH, free T3 levels. USG-guided FNAC was performed then. Aspiration cytology/FNAC: Moderately cellular smear yielded mono-layered/multilayered epithelial cell clusters few arranged in microfollicular pattern in a background of pigment laden macrophages and hemorrhage. Some nuclei of cell clusters demonstrated nuclear crowding, nuclear overlapping and mild anisonucleosis having fine chromatin. With these features, this case was classified as Bethesda category III - AUS. Histopathological Examination: A total thyroidectomy was performed which revealed a cellular neoplasm formed of tumor cells arranged near exclusively in a follicular pattern (microfollicles). The individual tumor cells show all nuclear features characteristic of classical papillary carcinoma thyroid (nuclear crowding, mild nuclear enlargement, chromatin clearing, grooving, focal nuclear membrane irregularity). Mitotic rate was found to be < 3 mitosis/HPF. Lymphatic invasion was present. With these nuclear features and pattern of tumor cell arrangement, the diagnosis was as Infiltrative follicular -subtype of papillary carcinoma.

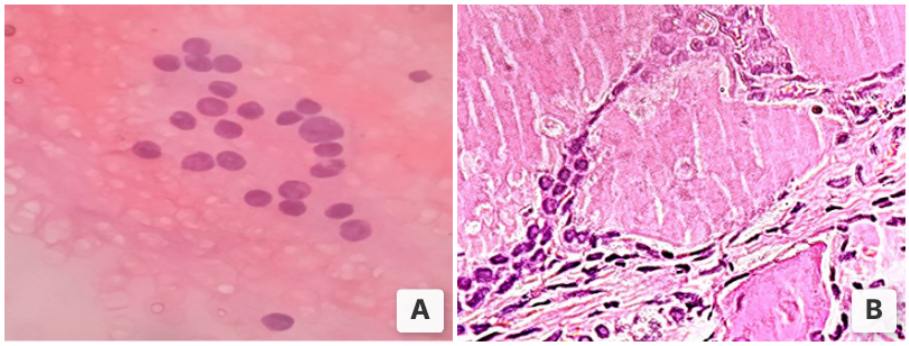

Figure 2: (A) Fnac smear (H&E, 40×) showing microfollicular pattern with nuclear crowding, raising suspicion for neoplasia. (B) Specimen (H&E, 40×) showing follicular patterns with classical PTC nuclear features, establishing definitive diagnosis.

Case -3: NIFTP miscategorized as follicular neoplasm: (TBSRTC-4): A 41-year-old female presented with solitary thyroid nodule – right lobe which seems to be euthyroid on investigations, having painless episodes and feel uncomfortable while eating. USG showed predominately solid and homogeneous internal echoes. Physical examination revealed a well-defined cystic mass, round in shape, with a diameter of 9×5×2 cm, solitary, which moved on swallowing, signs of inflammation–nil, No family history/autoimmune diseases noted. To diagnose the lesion, an ultrasound–guided fine needle aspiration cytology (FNAC) was performed. On FNAC, the smears were moderately cellular displaying thyroid follicular cells arranged in microfollicles, trabeculae, mono-layered sheets and occasionally as isolated single cells with few showing focal nuclear crowding and anisonucleosis. No evidence of colloid noted in the smears examined. Based on this cytomorphological features, it was classified into Bethesda category IV indicating a follicular neoplasm. On subsequent total thyroidectomy, a well encapsulated nodule measuring about 8.3×5×2 cm; periphery of which is thinned out with, cut surface of the lesion showing grey white areas with a focal central friable lesion noted. Histopathologic examination: On histopathological examination, the thyroid tissue shows a lesion arranged predominantly in a closely packed microfollicular pattern and less than 1% as papillae and focal areas of cystic degeneration. Nuclear enlargement, clearing and grooving noted, pseudoinclusions. Mitosis 1–2 /10 HPF noted. No capsular/vascular invasion identified. The case was diagnosed finally as NIFTP (Non invasive follicular thyroid neoplasm with papillary-like nuclear features).

Case 4: A 42-year female presented with constant swelling in front of the neck. USG showed a partially cystic nodule and a solid component in the right lobe which further on performing guided FNAC showed TBSRTC category -4 (follicular neoplasm). On FNAC: Showed moderately cellular smears of thyroid follicular cells arranged in monolayered sheets/papillaroid clusters and microfollicular pattern in a background of hemosiderin laden macrophages, lymphocytes colloid and blood. Few cells show nuclear enlargement, nuclear crowding, powdery chromatin, occasional nucleoli and rare pseudoinclusions. Based on this view, TBSRTC–category 4 (follicular neoplasm) was considered. Histopathological examination: Following

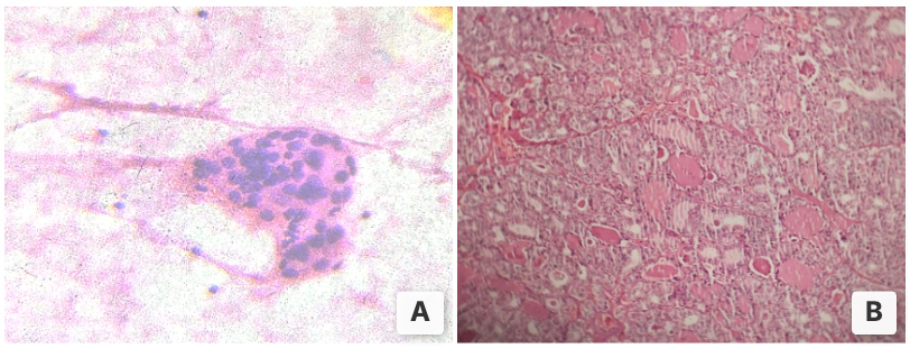

Figure 3: (A) Fnac smear (H&E, 40×) showing focal nuclear crowding and anisonucleosis. Subtle atypia contributed to diagnostic uncertainty. (B) Histopathology (H&E, 40×) showing microfollicular pattern with cytological atypia, supporting neoplastic diagnosis.

total thyroidectomy, multiple sections taken from thyroid tissue shows a thin capsulated cellular neoplasm formed of tumor cells arranged predominantly in closely packed microfollicles with individual cells showing nuclear clearing, crowding, overlapping and nuclear grooving. Capsular invasion not identified. Angioinvasion was noted with few blood vessels (4 in number) showing luminal free floating tumor cell fragments in both lobes. Lymphatic invasion also identified. Mitotic rate < 3 per HPF noted. Based on these histopathological features malignant follicular cell derived thyroid neoplasm – Encapsulated angioinvasive follicular variant of papillary carcinoma was diagnosed.

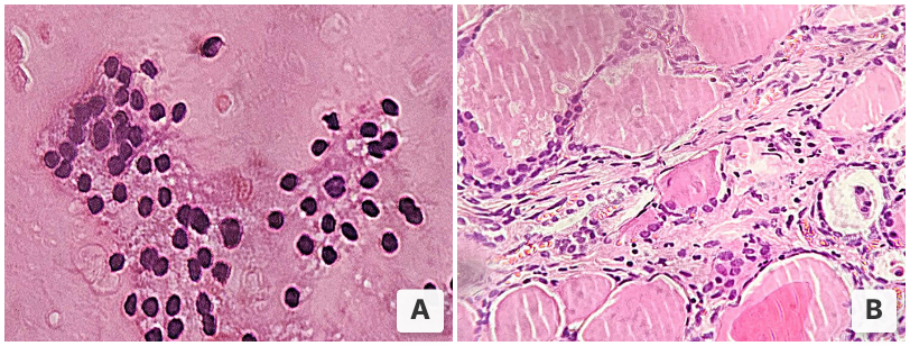

Figure 4: (A) Fnac smear (H&E, 40×) showing microfollicular pattern with characteristic nuclear features suggestive of malignancy. (B) Histopathology (H&E, 40×) showing microfollicles and vascular tumor emboli indicating invasive behavior and confirming malignancy.

Discussion

The misdiagnosis in this case arose from paucicellular aspirates, which masked the characteristic nuclear features of classical papillary carcinoma. [2, 3] Given, the low cellularity associated with high cystic degenerative changes of a lesion made diagnosing the nuclear features by FNA difficult. Hence, awareness regarding overlapping of nuclear features with regard to inadequate sampling is essential to avoid misclassification and enhance diagnostic accuracy. This can be improved through ultrasound-guided sampling, thus upgrading the detection of nuclear features. [2, 3, 4]

The fine needle aspiration cytology diagnosis of tumors with follicular pattern presents a considerable diagnostic challenge for pathologists. [4] Despite the recent WHO classification of tumors categorizing infiltrative FVPTC versus invasive FVPTC as two distinct neoplastic entities, the differentiation between the two in cytological smears remains quite challenging. [4, 5] Infiltrative FVPTC is believed to have more distinct and well-defined nuclear characteristics, resulting in a higher total nuclear score than the subtle nuclear features found in invasive encapsulated FVPTC. Moreover, The Bethesda system categorizes AUS/FLUS – Category 3 carrying an overall malignancy risk of 30%. Still, the crucial method to confirm PTC is to search for capsular and vascular invasion by histopathological examination. [6]

Follicular neoplasm is a general term for thyroid nodules with follicular cell appearance, can be benign or malignant, risk of metastasis varies depending on the type, pattern of histology can be follicular growth pattern. [7, 8] NIFTP fits into a specific type of thyroid neoplasm. It has low-risk borderline lesion. The risk of metastasis is very low. Histology shows a follicular growth with added PTC nuclear features. NIFTP includes $< 1\%$ true papillae, no psammoma bodies, no capsular/vascular invasion and lack of cytomorphological features. [7, 8]

According to the 5th edition of recent World Health Organization Classification of Endocrine and Neuroendocrine Tumors, invasive encapsulated follicular variant of papillary thyroid carcinoma was reclassified as its own entity. [9] Thyroid nodules displaying follicular histological characteristics include a variety of conditions, ranging from benign to malignant subtypes, such as Follicular adenoma, FTC, NIFTP, WDT-UMP, and IEFVPTC. [10] Distinguishing these nodules, when they appear as isolated occurrences with follicular morphology, presents considerable diagnostic challenges for pathologists

in histopathologic evaluations. FVPTC is recognized as malignant and is categorized into three subtypes: minimally invasive, encapsulated angioinvasive, and widely invasive. Minimally invasive tumor, which possesses low risk, might only require local excision, whereas tumors with widely invasive or extensive vascular invasion (more than 4 foci) often necessitate complete thyroidectomy. Therefore, precise diagnosis of IEFVPTC is crucial to avoid unnecessary or potentially detrimental surgical procedures. [11]

Patient Management and Follow-up Outcomes: All patients underwent definitive surgical management based on multidisciplinary discussion integrating FNAC findings, radiological assessment, and clinical suspicion. Postoperative histopathological diagnosis guided further management, including the need for completion surgery, lymph node dissection, radioactive iodine therapy, and surveillance. Cases initially underdiagnosed on FNAC were upgraded following histopathological confirmation, leading to appropriate escalation of treatment. Patients diagnosed with papillary thyroid carcinoma received risk-stratified postoperative management and were followed up clinically and radiologically for evidence of recurrence or metastasis. The case diagnosed as NIFTP was managed conservatively following surgery, without adjuvant radioactive iodine therapy, and remained disease-free on follow-up. These outcomes highlight the clinical impact of FNAC–histopathology discordance and emphasize the importance of histopathological confirmation in guiding optimal patient management and avoiding both overtreatment and undertreatment.

Conclusion

This case series underscores the critical importance of a multimodal diagnostic framework for accurately stratifying the malignant potential of thyroid nodules through the integration of ultrasonographic evaluation using the Thyroid Imaging Reporting and Data System (TI-RADS), fine-needle aspiration cytology (FNAC) interpreted according to the Bethesda system, and comprehensive histopathological examination. Rigorous assessment of nuclear features on FNAC remains fundamental to enhancing diagnostic reliability. Furthermore, molecular analysis for mutations such as BRAF and RAS has emerged as a valuable adjunct in differentiating benign from malignant thyroid lesions and in facilitating precision-based therapeutic strategies for advanced thyroid carcinomas. Meticulous histopathological sampling, with particular emphasis on evaluation of capsular invasion, is indispensable for establishing a definitive diagnosis and optimizing clinical decision-making. Despite its role as the primary diagnostic modality, FNAC in isolation demonstrates inherent limitations, particularly in indeterminate lesions. This study highlights several diagnostic pitfalls, including morphological overlap between papillary hyperplasia and classical papillary thyroid carcinoma, atypical or non-classical ultrasonographic characteristics leading to erroneous TI-RADS categorization, and suboptimal cellularity of FNAC smears that compromises cytological interpretation. Recognition of these challenges reinforces the necessity of comprehensive clinicoradiological-cytopathological-histopathological correlation to minimize diagnostic discordance and to avert inappropriate overtreatment or undertreatment of patients with thyroid nodules.

Table 1: Case-wise FNAC–histopathology correlation.

Case No.	FNAC Diagnosis (TBSRTC)	Final Histopathological Diagnosis	Concordance Status	Type of Discordance
Case 1	Benign colloid nodule (Bethesda II)	Classical papillary thyroid carcinoma with nodal metastasis	Discordant	Underdiagnosis
Case 2	AUS/FLUS (Bethesda III)	Classical papillary thyroid carcinoma, infiltrating follicular subtype	Discordant	Underdiagnosis
Case 3	Follicular neoplasm (Bethesda IV)	NIFTP	Discordant	Category shift (non-malignant outcome)
Case 4	Follicular neoplasm (Bethesda IV)	Encapsulated angioinvasive follicular variant of papillary thyroid carcinoma	Discordant	Discordant

Abbreviations: TBSRTC The Bethesda System for Reporting Thyroid Cytopathology
TI-RADS Thyroid Imaging Reporting and Data System
FNAC Fine-Needle Aspiration Cytology
AUS Atypia of Undetermined Significance
NIFTP Noninvasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features
NCI National Cancer Institute
PTC Papillary Thyroid Carcinoma
T3 Triiodothyronine
T4 Thyroxine
TSH Thyroid-Stimulating Hormone
USG-guided FNAC Ultrasound-Guided Fine-Needle Aspiration Cytology
FVPTC Follicular Variant of Papillary Thyroid Carcinoma

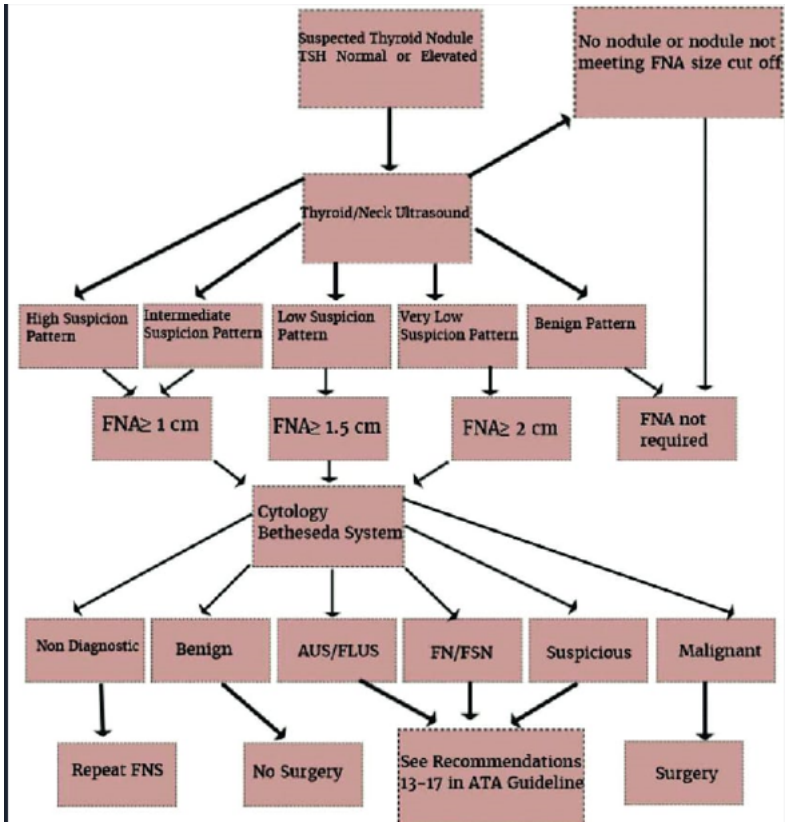

Figure 5: Flow chart of this case series study.

AUS/FLUS Atypia of Undetermined Significance / Follicular Lesion of Undetermined Significance
HPF High Power Field
FTC Follicular Thyroid Carcinoma
WDT-UMP Well Differentiated Tumor of Uncertain Malignant Potential
IEFVPTC Infiltrative Encapsulated Follicular Variant of Papillary Thyroid Carcinoma
RAS Rat Sarcoma Viral Oncogene
BRAF v-Raf Murine Sarcoma Viral Oncogene Homolog B

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Conflicts of Interest: The authors declare no conflict of interest related to this study.

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