ISSN: 2457-0400

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

www.wjahr.com

Impact Factor: 7.675

Volume: 10, Issue: 9

Page N. 23-58

Year: 2026

Original Article

Coden USA: WJAMA3

APPLICATION OF BETHESDA SYSTEM IN CYTOLOGICAL EVALUATION AND CORRELATION TO HISTOPATHOLOGY OF SOLITARY THYROID NODULE

***Adyan Hassan Abbas, Professor Dr. Asaad Abdul-Hamza Al-Janabi M.B.Ch.B., M.Sc., PhD (Histopath.)**

University of Kufa/ Faculty of Medicine Iraq.

Article Received: 23 July 2026 **Article Revised: 13 August 2026** **Article Published: 01 September 2026**

***Corresponding Author: Adyan Hassan Abbas**

University of Kufa/ Faculty of Medicine Iraq.

DOI: https://doi.org/10.5281/zenodo.22160164

How to cite this Article: *Adyan Hassan Abbas, Professor Dr. Asaad Abdul-Hamza Al-Janabi M.B.Ch.B., M.Sc., PhD (Histopath.) (2026). Application Of Bethesda System In Cytological Evaluation And Correlation To Histopathology Of Solitary Thyroid Nodule. World Journal of Advance Healthcare Research, 10(9), 23-58.

ABSTRACT

Background: Thyroid nodules are common, and while most are benign, solitary thyroid nodule (STN) carry a risk of malignancy. Fine-needle aspiration cytology (FNAC) remains the cornerstone for preoperative evaluation. The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) was introduced to standardize reporting and improve communication, though indeterminate categories remain diagnostically challenging. **Aim of the study:** To assess the accuracy of application of Bethesda System for Reporting Thyroid Cytopathology in evaluating solitary thyroid nodules through fine-needle aspiration, and to correlate how its cytological classifications compare with final histopathological findings. **Patients and methods:** A cross-sectional study included 80 patients with STNs at Al-Kufa Training Center for Pathology between January 2025 to September 2025. FNAC samples and corresponding surgical specimens were histopathologically assessed as benign, malignant, or borderline. Associations between cytology, histology, and clinical variables were analyzed. **Results:** The study population comprised predominantly females (83.8%) with a mean age distribution peak of 20–40 years. Bethesda classification showed a significant association with histology and with benign vs malignancy status (p-value 0.001). Sensitivity, specificity, PPV, NPV, and accuracy were 97.3%, 65.2%, 81.8%, 93.8%, and 85.0%, respectively. **Conclusion:** The Bethesda system demonstrated high sensitivity and diagnostic accuracy in evaluating STNs, particularly in higher categories (IV–VI). It remains a reliable basis when combined with histopathology for guiding management decisions.

CHAPTER 1: INTRODUCTION

Thyroid nodules are among the most common endocrine problems encountered in practice, and in the vast majority of cases they are benign. Although most nodular thyroid conditions are benign but a small percentage of cases, especially solitary thyroid nodule (STN) have the risk of malignancy which forms the basis for accurate and timely diagnosis.[1] A solitary thyroid nodule can be defined as a single, well-demarcated lesion within the thyroid gland which, when felt or scanned, appears different from the surrounding tissue. Many STNs arise from benign pathologies, such as colloid nodules, cysts (including thyroid cysts and branchial cysts), and autoimmune thyroiditis. In contrast, some STNs may sometimes be an early form of thyroid cancer, mostly papillary (PTC) or follicular thyroid cancer (FTC).[2]

The main clinical challenge is discriminating malignant nodules from benign ones It is important to do this so that patients do not get an unnecessary surgery while making sure not to miss or diagnose cancers too late. In the past, clinical examination and imaging studies were the main diagnostics. While they were useful, these techniques did not possess the diagnostic specificity that could rule out a cancer diagnosis. The practice regarding nodule evaluation has radically altered with the advent of fine-needle aspiration cytology (FNAC). FNAC is a low-risk, cost-effective and generally reliable diagnostic test. Differing terminology, varying interpretations by observers and the absence of standardized malignancy risk assessment system led to diagnostic variation.[3]

With a view to address the limitations of the existing terminology, Bethesda System of Reporting Thyroid Cytopathology (BSRTC) was devised in 2007 and

further revised in 2017. The system comprises six diagnostic categories. The Bethesda system has helped greatly in standardizing reporting and helped communicate better between the pathologists and the treating physicians. Even with these benefits, we are not yet sure of the diagnosis for the patients, especially in the categories that cannot give a proven diagnosis, namely I and III. Therefore, histopathological confirmation is still mandatory for a definitive diagnosis.[4,5]

To determine the reliability of the Bethesda system, it is important to form a strong link between pre-operative cytology findings and final histopathological reports. By comparing the two, we can highlight the strengths and weaknesses of FNAC and refine clinical pathways and improve risk stratification. The development of molecular diagnosis and enhancement of imaging techniques in recent years contribute additional value especially in cases with suspicious cytology – this increased the overall accuracy of diagnosis of thyroid cancer.[6,7]

AIM OF THE STUDY

To assess the accuracy of application of Bethesda System for Reporting Thyroid Cytopathology in evaluating solitary thyroid nodule through fine-needle aspiration, and to correlate how its cytological classifications compare with final histopathological findings.

CHAPTER 2: LITERATURE REVIEW

2.1 Anatomy of the Thyroid Gland

The thyroid gland is an endocrine structure situated in the lower front part of the neck, spanning the region between the fifth cervical (C5) and the first thoracic (T1) vertebrae. It has a characteristic butterfly shape, composed of two lateral lobes joined by a slender central portion called the isthmus. Typically, the lobes are symmetrical, each measuring about 4 cm in length, 2 cm in width, and 1 to 1.5 cm in thickness. In adults, the entire gland weighs approximately 15 to 25 grams, although this can vary slightly depending on age, sex, and physiological state. An additional structure known as the pyramidal lobe, which is a remnant of the thyroglossal duct, is occasionally present. It extends superiorly from the isthmus or one of the lateral lobes.[8,9]

The thyroid gland has a rich blood supply derived primarily from two pairs of arteries: the superior thyroid arteries and inferior thyroid arteries. The superior thyroid artery, which is a branch of the external carotid artery, supplies the superior and anterior aspects of the gland. The inferior thyroid artery, which originates from the thyrocervical trunk of the subclavian artery, supplies the inferior and posterior parts. In about 10% of individuals, a thyroid ima artery maybe present from the brachiocephalic trunk or aortic arch and provides blood supply to the isthmus and inferior portions of the gland.[10,11]

Venous drainage of the thyroid gland occurs through three main veins: superior, middle, and inferior thyroid veins. The superior and middle thyroid veins drain into the internal jugular vein, while the inferior thyroid veins drain directly into the brachiocephalic veins.[10,11]

The thyroid gland receives its innervation primarily from the autonomic nervous system, this involves sympathetic fibers from the superior, middle, and inferior cervical sympathetic ganglia, and parasympathetic fibers originating from the vagus nerve. These nerves effect vascular tone and thyroid function itself is primarily regulated by hormonal mechanisms.[10]

The thyroid gland has an extensive lymphatic drainage, involving pretracheal, paratracheal, and deep cervical lymph nodes. The superior part of the gland drains predominantly into superior deep cervical nodes, whereas the inferior aspect drains into paratracheal and pretracheal nodes, which then drains to the lower deep cervical and supraclavicular nodes. This is clinically significant especially in metastatic spread from thyroid malignancies.[10]

2.2 Histology of the Thyroid Gland

The thyroid gland is mainly made up of microscopic spherical units called follicles, which serve as its essential functional structures. Each follicle is surrounded by a single layer of cuboidal epithelial cells, known as follicular cells or thyrocytes, and encloses a central lumen filled with colloid. This colloid is a gel-like material rich in thyroglobulin, which serves as the storage form and precursor for the production of the thyroid hormones T4 (thyroxine) and T3 (triiodothyronine). These hormones are crucial for maintaining metabolism and are deeply involved in growth and developmental regulation. On histological examination, follicular cells show basophilic cytoplasm, round, centrally placed nuclei, and small apical microvilli that extend toward the colloid, all reflecting their active role in hormone synthesis.[8,12] the gland also includes a smaller group of endocrine cells called parafollicular cells, or C-cells, which make up only a small fraction of the overall cell population—around 0.1%. These cells are generally found within the basement membrane of follicles or arranged in small clusters between them. Their primary role is to produce calcitonin, a hormone involved in regulating serum calcium by inhibiting osteoclasts and promoting calcium excretion by the kidneys. Morphologically, C-cells appear larger than follicular cells, with pale cytoplasm and either central or slightly eccentric nuclei. For identification, calcitonin immunostaining is often used in histopathological evaluation.[13]

The extracellular environment of the thyroid consists mainly of two key components: colloid and stromal connective tissue. The colloid appears homogeneous and eosinophilic and fills the follicular lumen, acting as a hormone reservoir. Its amount and consistency vary

depending on whether the gland is in a resting or active phase—being more plentiful when inactive and less so during active hormone release.[11]

Surrounding the follicles is a fine stromal network, made up of collagen fibers, fibroblasts, capillaries, lymphatic vessels, and nerve fibers. This connective tissue not only provides mechanical support but also plays a role in nutrient transport, signal transmission, and hormone movement within the gland. Importantly, the stroma becomes actively involved in several pathological processes, such as inflammation, tumor formation, and hyperplasia, which can directly affect how the thyroid responds to both normal physiological demands and disease conditions (Figure 2.1).[11,14]

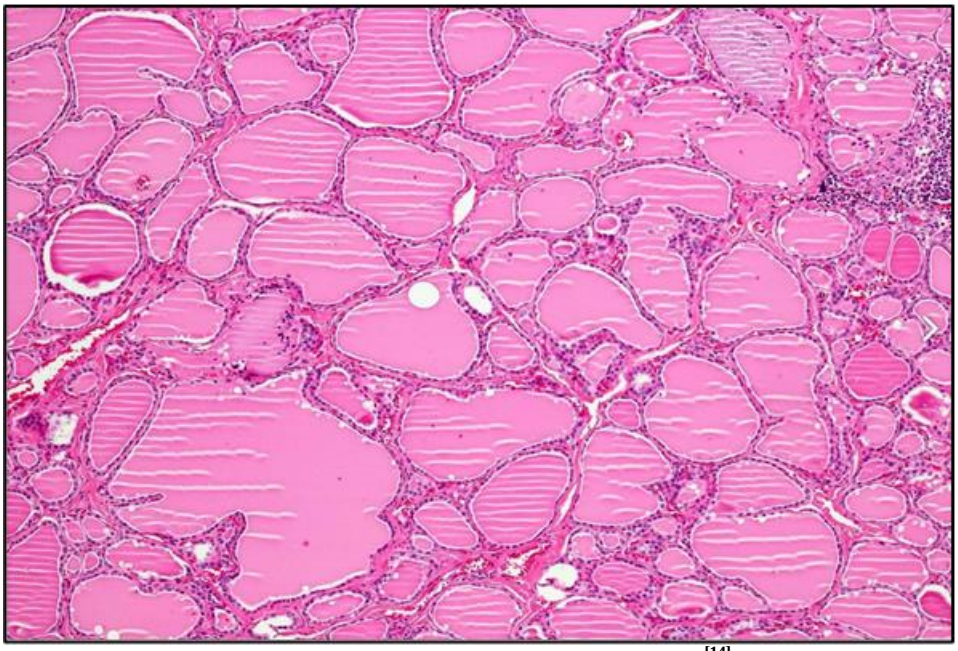

Figure 2.1: Histology of the thyroid gland.[14]

2.3 Physiological Functions of the Thyroid Gland

The thyroid gland serves as a central component of the endocrine system, exerting broad physiological effects by producing two key hormones: thyroxine (T4) and triiodothyronine (T3). These hormones are critical for maintaining basal metabolic rate, regulating thermogenesis, supporting growth, and ensuring proper neurodevelopment. Their production is governed by the hypothalamic-pituitary-thyroid (HPT) axis, a tightly controlled hormonal feedback loop. This regulatory pathway begins with the hypothalamus releasing thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary to secrete thyroid-stimulating hormone (TSH). TSH then acts directly on the thyroid follicular cells by binding to its membrane receptors, initiating the cascade of events necessary for iodine uptake and hormone synthesis. The circulating levels of T3 and T4 provide negative feedback to the hypothalamus and pituitary, thereby modulating further release of TRH and TSH and maintaining endocrine balance.[15,16]

Thyroid hormone biosynthesis takes place within the follicular cells and follows a multi-step biochemical process. Initially, iodide is actively transported from the bloodstream into the thyroid cells via sodium-iodide symporters located on the basal membrane. Inside the cell, iodide undergoes oxidation, a reaction catalyzed by the enzyme thyroid peroxidase (TPO). The oxidized iodine is then attached to specific tyrosine residues on thyroglobulin, forming monoiodotyrosine (MIT) and diiodotyrosine (DIT). Through further enzymatic coupling, two DIT molecules yield T4, while one MIT and one DIT combine to form T3. These iodinated thyroglobulin complexes are stored within the colloid of the follicular lumen as a reserve. When stimulated by TSH, the follicular cells internalize colloid material via endocytosis. The endocytosed vesicles merge with lysosomes, where proteolytic cleavage releases free T3 and T4, which then enter the circulation. Of the two, T4 is produced in larger quantities, though it functions primarily as a prohormone. Its conversion to the more active T3 occurs in peripheral tissues, particularly the liver, kidneys, and skeletal muscles, through the enzymatic action of deiodinases.[16]

2.4 Solitary Thyroid Nodule

2.4.1 Definition and Classification

A solitary thyroid nodule refers to a single, well-defined lesion within the thyroid gland that can be identified through physical examination or imaging studies, and is distinguishable from the surrounding thyroid tissue. These nodules represent a common clinical finding and may vary widely in their underlying pathology. Histologically, thyroid nodules are classified into a spectrum ranging from benign to malignant. Benign

nodules commonly include colloid nodules, simple cysts, follicular adenomas, and inflammatory nodules associated with conditions such as Hashimoto's thyroiditis. On the other end of the spectrum, malignant nodules may arise from various thyroid cell types and include papillary thyroid carcinoma—the most prevalent form—alongside follicular carcinoma, medullary carcinoma, and the more aggressive anaplastic carcinoma.[2]

2.4.2 Epidemiology

Thyroid nodules are a common finding in clinical settings, with their prevalence estimated at 4–7% when identified through physical examination. However, when high-resolution ultrasound is used, this figure dramatically rises to more than 60%, reflecting the substantial number of subclinical nodules that remain undetectable on palpation. In terms of incidence, community-based and imaging-based studies suggest that the annual detection rate of newly identified thyroid nodules (so-called "incidentalomas") is increasing, driven in part by widespread use of imaging modalities. For example, in one large Chinese health-check cohort of 15,595 adults, nodules were detected in 50.98% of subjects by ultrasound. In a global meta-analysis of more than 500 000 individuals, the overall prevalence of thyroid nodules was 27.96% when ultrasound was used as the diagnostic method.[17–19]

At the national level, the Iraqi Cancer Registry (2023) reported that thyroid cancer accounted for 2 823 cases (6.6%), ranking as the fourth most common cancer in Iraq. In Al-Najaf governorate, there were 158 newly diagnosed cases (7.9%) among all registered malignancies, indicating a particularly high local burden.[20]

The growing use of advanced imaging techniques has increased the detection of small, asymptomatic thyroid nodules that previously went unnoticed. Many factors including age, female sex, iodine deficiency, and prior exposure to neck irradiation were proposed to increase the likelihood of have such nodules. Approximately 5% to 15% of solitary thyroid nodule (STN) are found to be malignant. This relatively low incidence of cancer raised the question of how to accurately identify the small subset of malignant nodules while avoiding unnecessary interventions for those that are benign. Fine-needle aspiration cytology (FNAC) has been used as a highly valuable diagnostic tool. It offers a minimally invasive and cost-effective method for stratifying malignancy risk, reducing the number of avoidable thyroid surgeries in patients with benign lesions.[21]

A marked increase in the reported incidence of thyroid cancer has been noted worldwide in the past few decades. This trend is closely linked to the broader application of neck ultrasonography, which could reveal thyroid nodules incidentally during imaging for unrelated medical conditions. Much of this rise in diagnosis has involved small papillary thyroid microcarcinomas, which tend to have a favorable prognosis. Interestingly, despite this increase in detection, mortality rates have still remained relatively stable, this could suggest that many of these cancers are indolent and may not progress clinically. Concerns have been raised in regard to overdiagnosis and the potential for unnecessary treatment.[22]

2.4.3 Risk Factors

Several factors contribute to the formation of solitary thyroid nodule. Major risk factors include.[21,23]

- Female gender: Females are 4-6 times more likely to develop thyroid nodules compared to males.
- Age: Increasing incidence with age, especially beyond the fourth decade.
- Radiation exposure: History of ionizing radiation, especially in childhood, significantly increases malignancy risk.
- Family history: A history of thyroid cancer, familial thyroid disorders, or familial syndromes such as multiple endocrine neoplasia (MEN) types 2A and 2B increases risk.
- Iodine deficiency or excess: Both deficiency and excess iodine intake may predispose to nodular thyroid diseases.

2.5 Molecular Pathogenesis of Thyroid Nodules

2.5.1 Genetic Mutations

Molecular studies have significantly advanced the understanding of thyroid nodule behavior by identifying key genetic mutations involved in their pathogenesis and malignant transformation. The most notable of these include BRAF V600E, RET/PTC rearrangements, and RAS mutations (HRAS, KRAS, NRAS). The BRAF V600E mutation is particularly associated with papillary thyroid carcinoma, often indicating a more aggressive clinical course.[24]

2.5.2 Role of Environmental Factors

Environmental influences play a crucial role alongside genetic predisposition in the development and malignant potential of thyroid nodules. Radiation exposure, whether therapeutic or environmental (e.g., nuclear accidents), is strongly associated with chromosomal damage and gene mutations that can drive malignant transformation. Iodine intake is another key factor—deficiency promotes nodular goiter formation, while excess, particularly from dietary sources or medications like amiodarone, may trigger thyroiditis, follicular cell hyperplasia, and potentially contribute to neoplastic changes. Amiodarone, due to its high iodine content and direct toxic effects on thyroid cells, is known to cause both hypo- and hyperthyroid states, influencing thyroid structure and function.[25,26]

2.6 Diagnostic Approaches to Solitary Thyroid Nodule

2.6.1 Clinical Evaluation

The initial evaluation of a solitary thyroid nodule begins with a comprehensive clinical assessment, including a detailed medical history and physical examination. Key historical elements such as patient age, sex, family history of thyroid malignancy, prior exposure to ionizing radiation, and the rate of nodule growth are crucial in estimating the risk of cancer. Physical examination focuses on evaluating the nodule's size, texture, mobility, and tenderness, as well as the presence of cervical lymphadenopathy, all of which offer important early indicators of potential malignancy risk.[26]

The majority of solitary thyroid nodule are asymptomatic and are often discovered incidentally during routine clinical exams or imaging performed for unrelated reasons. When symptoms do occur, they may include visible neck swelling, local discomfort, difficulty swallowing or breathing, or voice changes, typically resulting from compression or invasion of surrounding structures. In some cases, patients may present with clinical signs of thyroid dysfunction, depending on whether the nodule is hyperfunctioning or associated with hypothyroid states.[27,28]

2.6.2 Imaging Techniques

Ultrasonography

Ultrasound remains the primary imaging technique for assessing solitary thyroid nodules. It allows for precise evaluation of various nodule characteristics, including dimensions, internal composition (solid, cystic, or mixed), echogenicity, border definition, calcification patterns, vascular flow, and associated cervical lymph nodes. Certain sonographic features—such as marked hypoechogenicity, irregular or infiltrative margins, microcalcifications, increased intranodular vascularity, and a taller-than-wide configuration—are highly suggestive of malignancy. These findings are critical in identifying nodules that warrant further investigation through fine-needle aspiration biopsy, and to enhance diagnostic accuracy and standardize ultrasound reporting, the Thyroid Imaging Reporting and Data System (TI-RADS) was developed by the American College of Radiology (ACR). This system stratifies thyroid nodules based on specific sonographic features into categories reflecting the estimated risk of malignancy. Each nodule is scored according to composition, echogenicity, shape, margin, and echogenic foci, with higher total scores corresponding to greater malignancy risk. The TI-RADS classification aids clinicians in decision-making regarding the need for FNAC or follow-up, thereby improving consistency and reducing unnecessary procedures.[29,30]

Radionuclide Scanning

Thyroid scintigraphy, typically using iodine-123 or technetium-99m pertechnetate, is employed in selected cases, particularly when serum TSH levels are low, raising the possibility of autonomously functioning nodules. Based on radioactive uptake, nodules are categorized as "hot" (functioning and usually benign), "warm," or "cold" (non-functioning and associated with a higher malignancy risk). Although the majority of thyroid cancers present as cold nodules, the diagnostic specificity of radionuclide scanning is limited. As a result, ultrasound-guided FNAB remains the gold standard for cytologic confirmation.[31]

2.6.3 Fine Needle Aspiration Cytology (FNAC)

FNAC is considered the cornerstone in the diagnostic workup of solitary thyroid nodule. It plays a vital role in distinguishing benign from malignant lesions and is widely valued for its simplicity, safety, low cost, and high diagnostic accuracy. This approach has significantly helped in avoiding unwarranted thyroid surgeries. The interpretation of FNAC samples is typically carried out using structured reporting systems like the Bethesda System for Reporting Thyroid Cytopathology, which enhances diagnostic consistency and supports informed clinical decision-making.[28]

2.7 Bethesda System for Reporting Thyroid Cytopathology

2.7.1 History and Development

The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) was developed to standardize the evaluation and reporting of fine-needle aspiration (FNA) findings in thyroid nodules. Its purpose is to improve clarity in communication between cytopathologists and clinicians by categorizing cytological results into defined groups, each associated with a specific risk of malignancy and a recommended course of clinical management. Introduced in 2007 through a consensus initiative led by the National Cancer Institute (NCI) in Bethesda, Maryland, the system underwent a major update in 2023 to reflect evolving evidence, enhance diagnostic reliability, and further support accurate, patient-centered decision-making in thyroid nodule care.[32,33]

2.7.2 Classification Categories

The Bethesda System organizes thyroid cytology into six categories, with each category associated with an estimated risk of malignancy and corresponding clinical management guidelines.[32]

1. Category I: Non-diagnostic or Unsatisfactory

- Inadequate sample for diagnosis (Figure 2.2).[34]
- Malignancy risk: 5–10%.

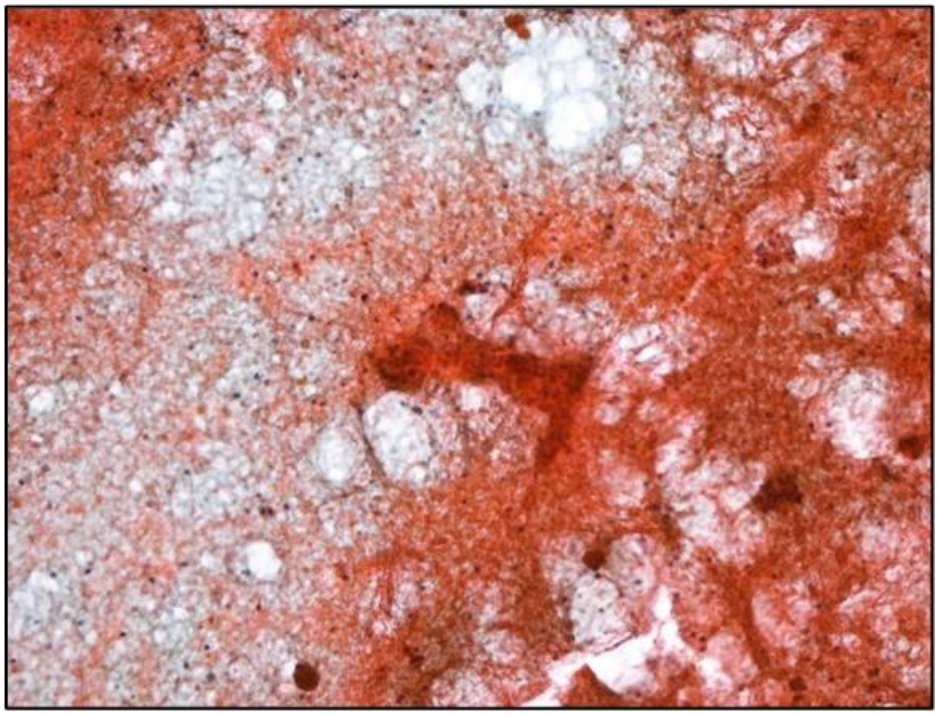

Figure 2.2: Unsatisfactory specimen of thyroid FNA, follicular cells obscured by haemorrhagic background (10x).[34]

2. Category II: Benign

- Common findings include colloid nodules, benign follicular nodules, lymphocytic thyroiditis (Figure 2.3).
- Malignancy risk: 0–3%.

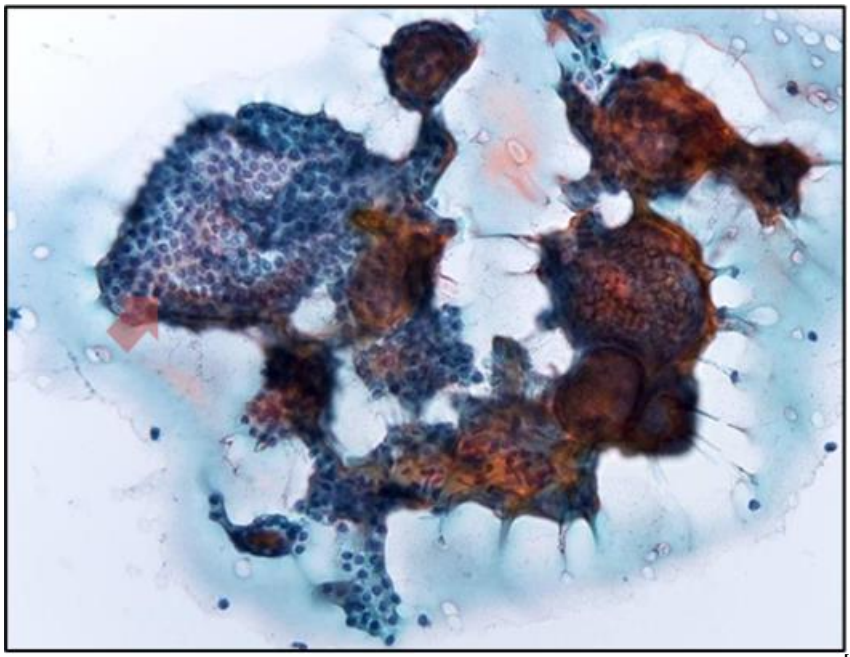

Figure 2.3: Benign follicular nodule, follicular clusters of variable size (20x).[34]

3. Category III: Atypia of Undetermined Significance (AUS)

- Indeterminate cytological features; may represent benign or malignant conditions (Figure 2.4).
- Malignancy risk: approximately 10–30%.

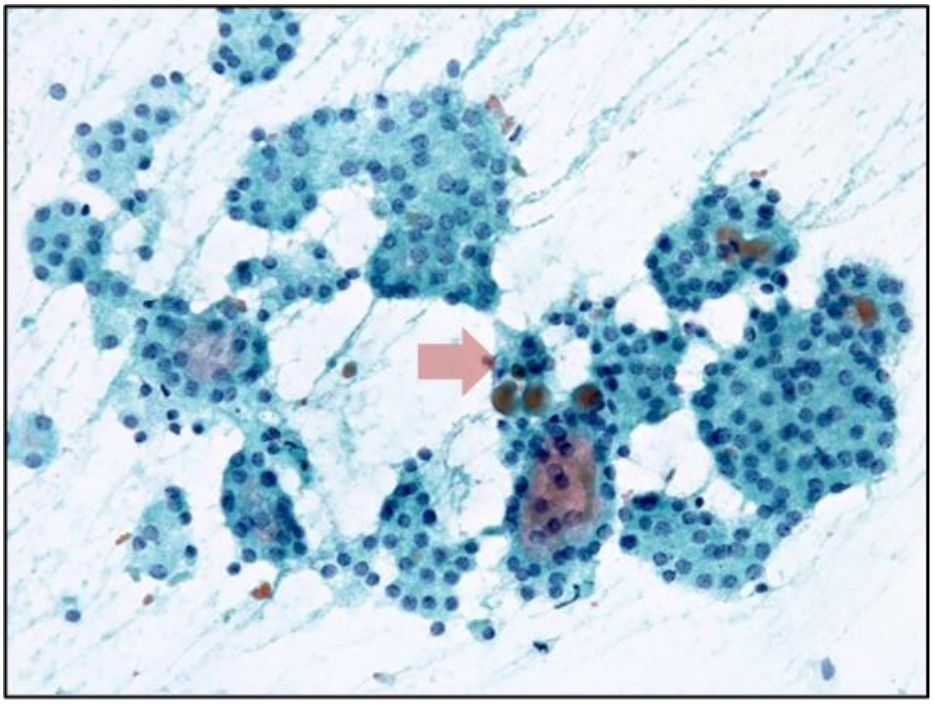

Figure 2.4: Atypia of undetermined significance with architectural atypia, thyroid FNA. (20x).[34]

4. Category IV: Follicular Neoplasm

- Suggestive of follicular adenoma or carcinoma; requires histological assessment for definitive diagnosis (Figure 2.5).

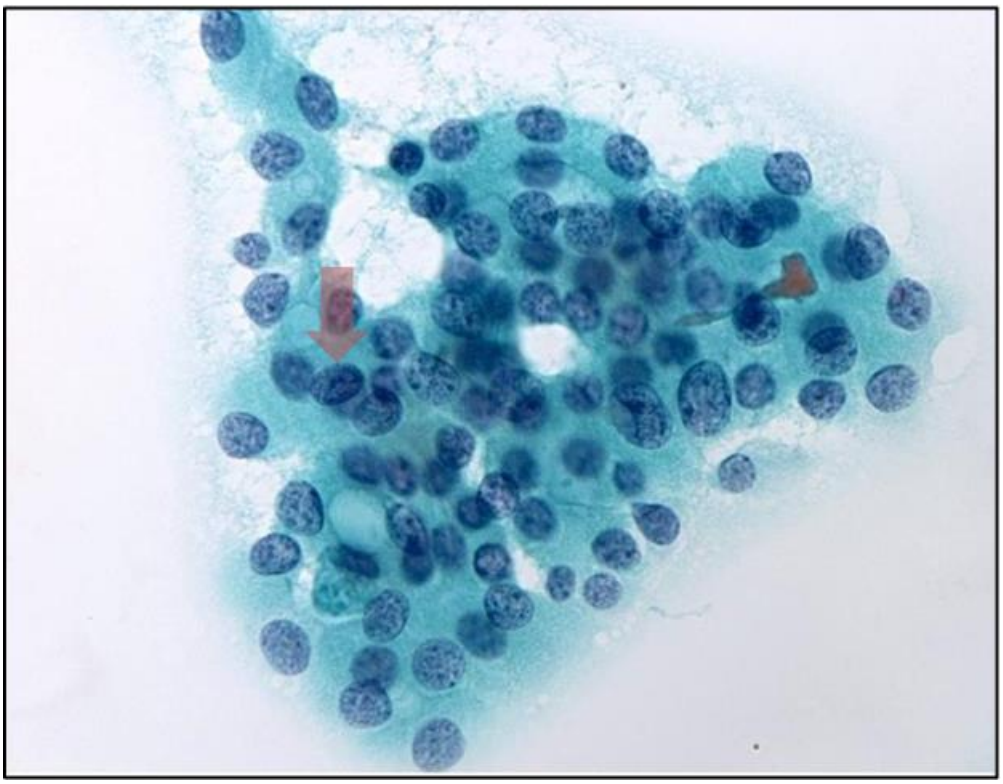

Figure 2.5: Follicular neoplasm, thyroid FNA which shows small follicles that are composed of cell with enlarged nucleus and hyperchromasia (40x).[34]

- Malignancy risk: 25–40%.

5. Category V: Suspicious for Malignancy

- Highly suggestive but not definitive for malignancy, commonly papillary thyroid carcinoma (Figure 2.6).

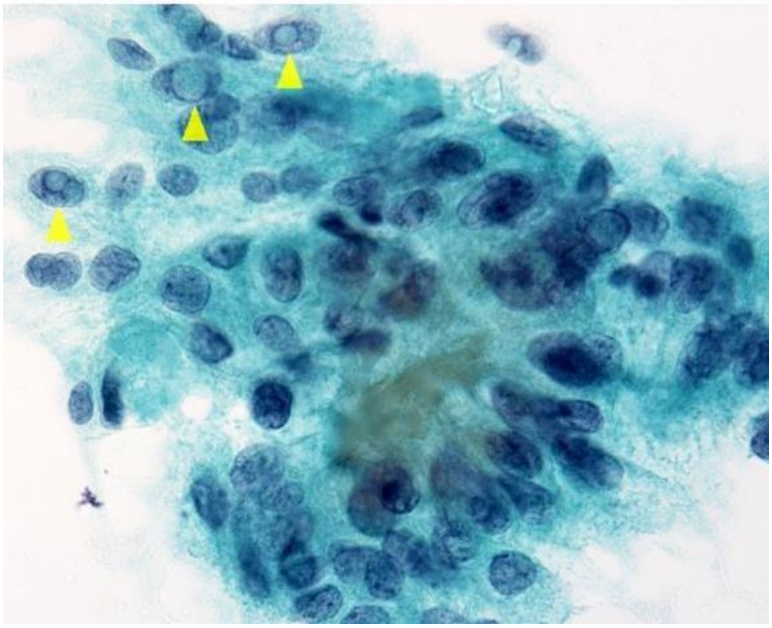

Figure 2.6: Hyalinizing trabecular tumor, thyroid FNA: cells frequent intranuclear cytoplasmic inclusions (Papanicolaou, 40x).[34]

- Malignancy risk: 50–75%.

6. **Category VI: Malignant**

- Definitive cytological evidence of malignancy (papillary, medullary, anaplastic carcinoma, lymphoma, or metastasis) (Figure 2.7).
- Malignancy risk: 97–99%.

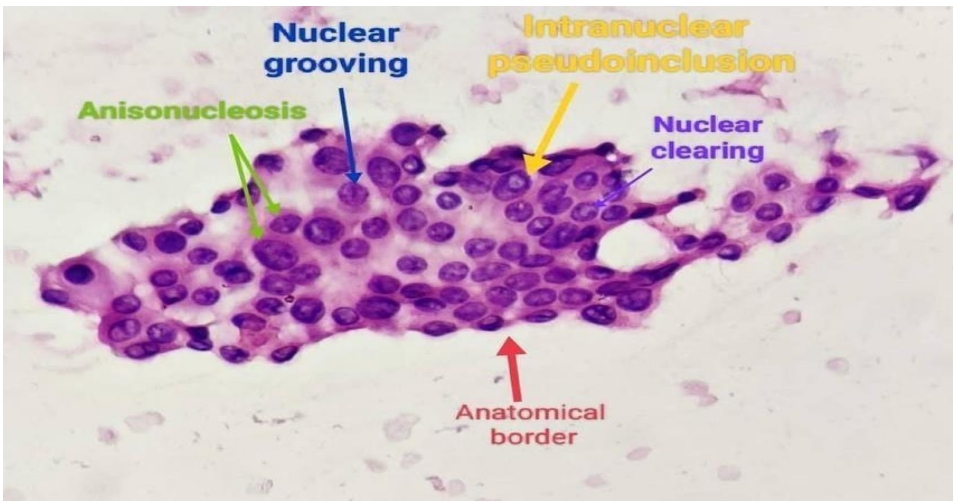

Figure 2.7: Bethesda VI, papillary carcinoma showing nuclear crowding, frequent nuclear grooves and overlapping chromatin clearing.[34]

2.7.3 Clinical Significance and Management Recommendations

Each Bethesda category guides clinicians regarding patient management[35]

- Category I typically necessitates repeat FNAC under ultrasound guidance.
- Category II usually requires clinical and ultrasonographic follow-up without immediate surgical intervention.
- Categories III necessitate repeat FNAC and molecular testing, and IV necessitate molecular testing and diagnostic surgery to clarify malignancy risk.
- Categories V and VI typically indicate surgical intervention, with category VI generally warranting total thyroidectomy due to high malignancy risk.

Accurate distinction between benign and malignant solitary thyroid nodule plays a critical role in determining appropriate treatment strategies and optimizing patient outcomes. While benign lesions are often managed conservatively with regular monitoring, malignant nodules typically require surgical intervention—ranging from total thyroidectomy to lymph node dissection, depending on the extent of disease. Reliable cytological assessment through fine-needle aspiration significantly reduces the frequency of unnecessary surgeries, lowers healthcare costs, and minimizes the risk of postoperative complications such as hypoparathyroidism and injury to the recurrent laryngeal nerve.[36,37]

Although solitary thyroid nodule are most often benign, they do carry a notable risk of malignancy, necessitating careful clinical and cytological evaluation. It is estimated that around 5% to 15% of all thyroid nodules prove to be malignant, with solitary nodules presenting a slightly increased risk compared to those occurring in the context of multinodular goiters.[37]

Age and Gender Variability

Thyroid nodules are more commonly diagnosed in females, with an estimated female-to-male ratio of approximately 4: 1. However, when a solitary nodule is present, both males and pediatric patients are statistically more likely to have an underlying malignancy. Additionally, nodules detected at the extremes of age—particularly in individuals younger than 20 or older than 70 years—are associated with an increased likelihood of cancer, highlighting the importance of age as a risk modifier in clinical assessment.[38,39]

Malignancy Rates by Bethesda Categories

The risk of malignancy varies significantly across the Bethesda System categories. Nodules classified as category V (Suspicious for malignancy) show a malignancy rate ranging from 50% to 75%, while category VI (Malignant) predicts malignancy in 97% to 99% of cases. Intermediate-risk categories, such as Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance (AUS, category III) and Follicular Neoplasm/Suspicious for a Follicular Neoplasm (category IV), carry respective malignancy risks of 10–30% and 25–40%, making cytologic interpretation and clinical correlation essential in these groups.[40]

2.8 Histopathological Evaluation of Thyroid Nodules Benign Lesions

Histopathological examination plays a pivotal role in confirming the true nature of thyroid nodules following biopsy or surgical excision. Although the majority of thyroid nodules are benign, their microscopic assessment is crucial in order to exclude malignancy, particularly in solitary thyroid nodule where the clinical suspicion of cancer may be higher.[41]

- **Colloid Nodule**

Also known as a nodular goiter, which represents one of the most frequent benign findings. Histologically, it is characterized by follicles of variable sizes, often markedly enlarged and filled with abundant colloid material. The colloid appears dense and eosinophilic, and in some areas it may show retraction cracks or scalloping margins due to resorption. The lining epithelium is generally flat or cuboidal, reflecting an inactive or low-proliferative state. Secondary degenerative changes are very common in colloid nodules, including cystic transformation, hemorrhage, fibrosis, and calcification. These degenerative changes can occasionally create diagnostic confusion, particularly when fibrosis or calcification is prominent, but they remain important features pointing toward a long-standing benign process (Figure 2.8).[1,42]

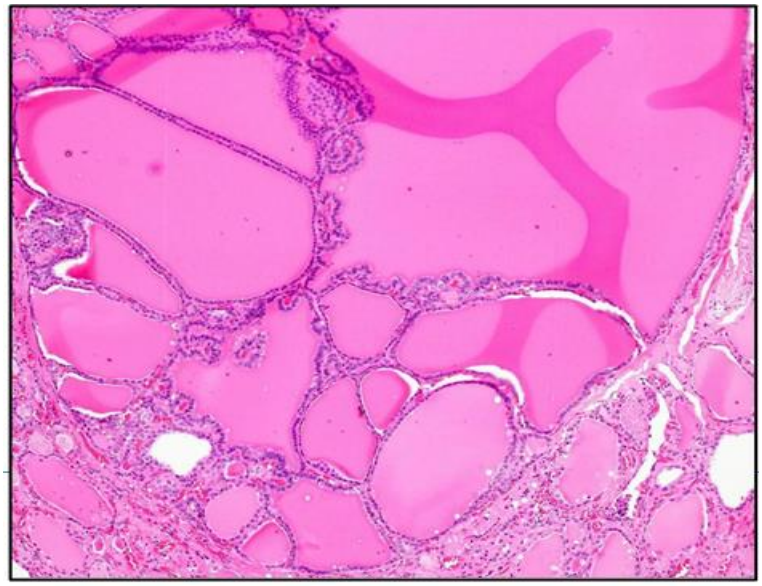

Figure 2.8: Histology of colloid thyroid nodule.[42]

- **Hyperplastic Nodule (Adenomatous Nodule)**

It is the hallmark component of multinodular goiter. These nodules arise due to repeated cycles of hyperplasia and involution, often under the influence of prolonged TSH stimulation. Microscopically, they consist of irregularly shaped follicles that vary widely in size and colloid content. The epithelium is usually hyperplastic, with crowded cells that may project papillary infoldings into the follicular lumen. Colloid is unevenly distributed, with some follicles appearing distended while others are depleted. A key histological feature that differentiates hyperplastic nodules from follicular adenomas is the absence of a complete capsule. Instead, hyperplastic nodules often blend into the surrounding thyroid parenchyma and may coexist with other nodules, reflecting their polyclonal nature. This lack of encapsulation is a vital point in diagnosis, as it helps avoid misclassification as a neoplasm.[1]

- **Thyroiditis**

Among all inflammatory conditions, Hashimoto's thyroiditis is the most prevalent, which is considered an autoimmune disease. Histologically, Hashimoto's thyroiditis is defined by a dense and diffuse lymphocytic infiltration of the thyroid parenchyma, often forming germinal centers. The follicular epithelium undergoes oncocytic metaplasia, producing Hurthle cells with abundant granular eosinophilic cytoplasm and prominent nucleoli. Over time, there may be progressive destruction of thyroid follicles, accompanied by fibrosis. Other forms of thyroiditis include subacute granulomatous (De Quervain) thyroiditis, which is characterized by a granulomatous reaction with multinucleated giant cells surrounding pools of colloid, and Riedel's thyroiditis, a rare disorder in which dense fibrosis replaces thyroid tissue and extends into surrounding neck structures, often mimicking malignancy both clinically and radiologically.[43]

- **Follicular Adenoma**

This benign neoplasm presents as a well-encapsulated lesion composed of uniform follicular cells with minimal nuclear atypia. It is of particular clinical importance because of its close resemblance to follicular carcinoma. Follicular adenoma is a true neoplasm, usually solitary, and presents as a well-circumscribed and completely encapsulated lesion. Histologically, it is composed of uniform follicular cells arranged in architectural patterns that may be microfollicular, macrofollicular, trabecular, or solid. The nuclei are usually bland, with minimal atypia, and mitotic figures are rare. Colloid content tends to be sparse compared to hyperplastic nodules. The crucial diagnostic hallmark of follicular adenoma is the complete absence of capsular or vascular invasion, which is required to distinguish it from follicular carcinoma. Because this distinction relies on invasion, meticulous sampling and examination of the tumor capsule is mandatory. Clinically, follicular adenomas are considered benign, but their recognition is critical to avoid unnecessary aggressive treatment while maintaining vigilance against misdiagnosing carcinoma.[44]

Low-Risk Malignant and Borderline Follicular-Patterned Lesions

In recent years, thyroid pathology has witnessed a significant reclassification of certain lesions that do not behave in a strictly benign or malignant fashion. These lesions has histological features that fall between those of follicular adenoma and follicular carcinoma, or between benign follicular lesions and papillary thyroid carcinoma (PTC). Their recognition could reflect more understanding of thyroid tumor biology which aims to reduce overtreatment of indolent lesions while maintaining oncologic safety. These include.[45]

- **Follicular Tumor of Uncertain Malignant Potential (FT-UMP)**

A well-circumscribed follicular lesion in which there are foci suspicious but not diagnostic for capsular or vascular invasion. Histologically, the tumor resembles a follicular adenoma, but pathologists may identify questionable points along the capsule that raise concern for invasion without fulfilling the strict criteria required for carcinoma. Because definitive evidence of invasion is absent, these tumors are not classified as follicular carcinoma. Clinically, FT-UMP behaves in an indolent manner, and patients generally have an excellent prognosis, though careful follow-up is recommended (Figure 2.9).[45,46]

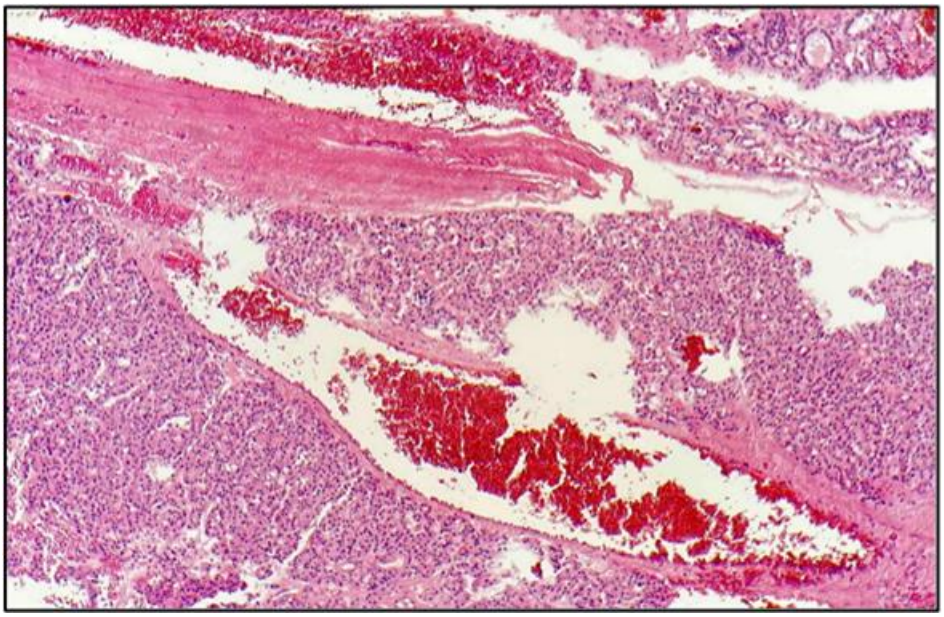

Figure 2.9: Follicular Tumor of Uncertain Malignant Potential (FT-UMP). Neoplastic follicular cells infiltrated the capsule without complete interruption of capsule (100x).[47]

- **Well-Differentiated Tumor of Uncertain Malignant Potential (WDT-UMP)**

Similar to FT-UMP but with equivocal papillary-like nuclear changes that do not meet criteria for PTC. These tumors difficulty in assessment arises not from capsular or vascular invasion, but rather from equivocal nuclear features suggestive of papillary thyroid carcinoma. These lesions display follicular growth patterns and nuclear changes that resemble those of PTC, such as chromatin clearing, grooves, or irregular nuclear contours, but the alterations are insufficient in extent or intensity to permit a definitive diagnosis of carcinoma. WDT-UMP underscores the challenge of distinguishing early papillary carcinoma from benign follicular-patterned lesions, and like FT-UMP, these tumors tend to follow a benign course.[45]

- **Non-Invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features (NIFTP)**

This entity represents one of the most impactful reclassifications in thyroid pathology. Formerly considered a variant of papillary thyroid carcinoma (encapsulated follicular variant of PTC), NIFTP was redefined in 2016 as a borderline neoplasm due to its indolent behavior and negligible risk of recurrence or metastasis. Histologically, NIFTP is characterized by a completely encapsulated or clearly demarcated follicular lesion that exhibits a follicular growth pattern with nuclear features of PTC, including clearing, grooves, and elongation. Crucially, there is no evidence of capsular or vascular invasion, nor of papillary structures, necrosis, or high mitotic activity. The recognition of NIFTP has reduced the global burden of thyroid cancer diagnoses by eliminating overtreatment of these indolent lesions while still acknowledging their neoplastic nature.[45]

- **The Hyalinizing Trabecular Tumor (HTT)**

This is another rare follicular-patterned lesion that has generated debate due to its overlapping features with papillary and medullary carcinomas. Microscopically, HTT shows a trabecular or nesting growth pattern with cells arranged around hyalinized stroma. The tumor cells often have nuclear features resembling those of papillary carcinoma, including grooves and clearing, which may cause misdiagnosis. Immunohistochemically, HTTs are usually positive for thyroglobulin and TTF-1, supporting their follicular origin, but negative for calcitonin, which helps to exclude medullary carcinoma. HTT is now recognized as a benign or borderline lesion, with excellent clinical outcomes following complete excision.[47]

Malignant Lesions

Malignant thyroid nodules display specific histopathological characteristics that are vital for accurate diagnosis, tumor staging, and prognostic assessment. The most common forms of thyroid cancer include the following major subtypes.[17]

- **Papillary Thyroid Carcinoma (PTC)**

It represents the most prevalent form of thyroid malignancy, accounting for approximately 70-80% of all thyroid cancers. It affects a wide age range, with peak incidence in young and middle-aged adults, and is more common in women. PTC is characterized histologically by distinctive nuclear changes rather than its architectural pattern. The hallmark nuclear features include enlarged, overlapping nuclei with optically clear chromatin (classically described as “Orphan Annie eye” nuclei), nuclear grooves, and intranuclear pseudoinclusions. Psammoma bodies, which are concentrically laminated calcifications, are frequently encountered and strongly support the diagnosis. PTCs are typically indolent tumors

with a favorable prognosis, though certain variants behave more aggressively.[48]

Variants for papillary thyroid carcinoma include

1. Classic Papillary Thyroid Carcinoma

The classic variant is the prototypical form of PTC and demonstrates papillary architecture in which fibrovascular cores are lined by neoplastic follicular epithelial cells exhibiting the characteristic nuclear features of PTC. The papillae may show stromal fibrosis and contain psammoma bodies. Infiltration into surrounding thyroid parenchyma is often present, and desmoplastic stromal reaction may be seen. Despite its malignant nature, the classic variant generally has an excellent prognosis with a high survival rate, especially in younger patients.[49]

2. Follicular Variant of Papillary Thyroid Carcinoma (FVPTC)

This variant on the other hand is composed almost entirely of follicles rather than papillae, yet the lining cells demonstrate the nuclear features of PTC. FVPTC is further divided into two categories: encapsulated and infiltrative. The encapsulated form has been largely reclassified, with the non-invasive encapsulated FVPTC now recognized as NIFTP, due to its indolent behavior. The infiltrative form, however, invades surrounding thyroid parenchyma and behaves more like conventional PTC. FVPTC is one of the most common variants and can be diagnostically challenging because its nuclear features may be subtle, leading to difficulty in distinguishing it from follicular adenoma or carcinoma.[50,51]

3. Tall Cell Variant (TCV)

The tall cell variant is a more aggressive subtype of PTC, typically seen in older patients. Histologically, the tumor cells are at least twice as tall as they are wide, with abundant eosinophilic cytoplasm and well-defined cell borders. Nuclear features of PTC are present, often in exaggerated form. Tall cell variant PTC tends to invade locally, shows higher rates of extrathyroidal extension, and is associated with a worse prognosis compared to the classic form. Its recognition is clinically significant because it often necessitates more aggressive therapy (Figure 2.10).[52,53]

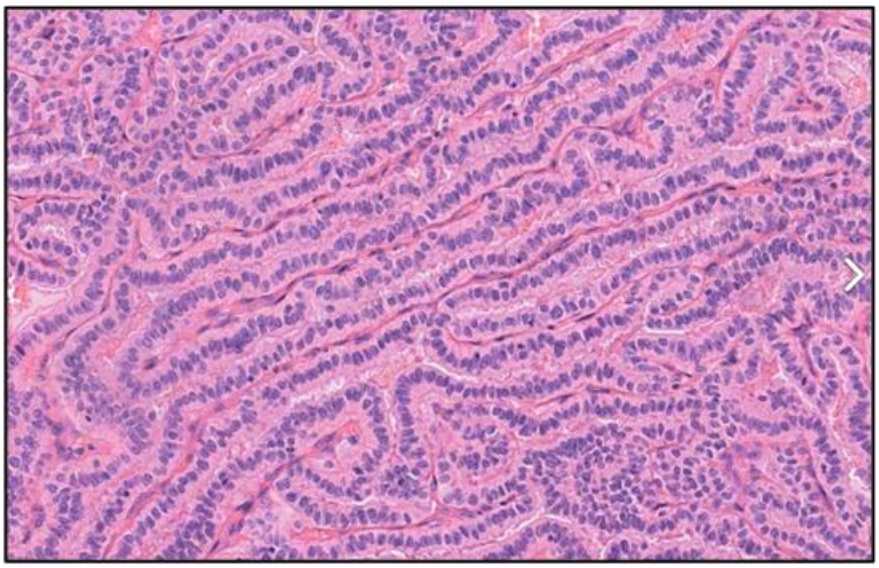

Figure 2.10: Tall cell variant, papillary thyroid carcinoma, which shows parallel cords of tumor cells.[54]

4. Columnar Cell Variant

This rare but aggressive variant consists of elongated, columnar tumor cells with nuclear stratification and pseudostratification resembling intestinal epithelium. Papillary and cribriform patterns are common, and mitotic activity may be more pronounced than in classic PTC. Columnar cell PTC is frequently associated with aggressive clinical behavior, including early extrathyroidal invasion and distant metastasis (Figure 2.11).[54]

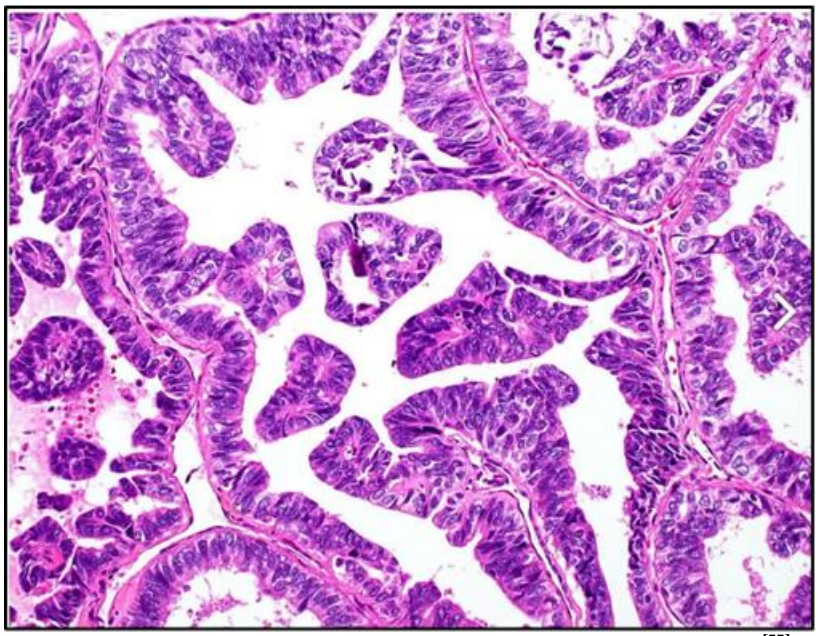

Figure 2.11: Columnar cell variant, papillary thyroid carcinoma.[55]

5. Diffuse Sclerosing Variant (DSV)

The diffuse sclerosing variant typically occurs in younger patients, including children and adolescents, and often presents with bilateral and diffuse involvement of the thyroid gland. Histologically, it is characterized by extensive stromal fibrosis and sclerosis, abundant psammoma bodies, squamous metaplasia, and dense lymphocytic infiltration resembling Hashimoto's thyroiditis. Neoplastic cells retain the nuclear features of PTC. Clinically, DSV is associated with higher rates of cervical lymph node metastasis at presentation, but long-term survival is still relatively good with appropriate treatment.[55,56]

6. Cribriform-Morular Variant

This distinctive variant is strongly associated with familial adenomatous polyposis (FAP) and germline mutations in the APC gene. Histologically, it demonstrates complex cribriform, trabecular, and morular (squamoid) growth patterns. The morules are composed of spindle to squamoid cells that often lack keratinization. Nuclear clearing typical of PTC may be absent or focal. Recognition of this variant is important not only for prognosis but also because it may serve as the first indicator of an underlying hereditary syndrome.[57,58]

7. Solid/Trabecular Variant

The solid or trabecular variant is more common in children, particularly those exposed to radiation. It is composed predominantly of solid sheets or trabeculae of tumor cells with the nuclear features of PTC. Despite the solid architecture, the presence of nuclear clearing, grooves, and pseudoinclusions confirms the diagnosis. This subtype is considered to have a higher risk of recurrence and metastasis compared with the classic form.[59]

8. Hobnail Variant

The hobnail variant is a recently described and aggressive subtype of PTC. Histologically, tumor cells display a hobnail appearance, with apically placed nuclei bulging into the lumen and high nuclear-cytoplasmic ratios. There is often significant nuclear atypia, frequent mitoses, and evidence of lymphovascular invasion. Clinically, this variant is associated with poor prognosis, higher recurrence rates, and increased mortality compared to classic PTC/.[60]

9. Warthin-like Variant

The Warthin-like variant is characterized by papillary structures lined by oncocytic tumor cells with PTC-type nuclear changes. The papillae are accompanied by dense lymphoplasmacytic infiltrates within the stroma, closely resembling Warthin tumor of the salivary gland. This variant is frequently associated with Hashimoto's thyroiditis and generally carries an excellent prognosis, similar to that of conventional PTC.[61]

10. Papillary Thyroid Microcarcinoma (PTMC)

In addition to the recognized histological variants, papillary thyroid carcinoma may also present in the form of papillary thyroid microcarcinoma (PTMC), which is defined as a tumor measuring 1 cm or less in greatest dimension. PTMC demonstrates the same histological features as conventional PTC, including the characteristic nuclear changes and, in some cases, papillary or follicular architecture. Many PTMCs are detected incidentally during imaging or histological examination of the thyroid for unrelated conditions. While most PTMCs follow an indolent course with an excellent prognosis, a subset may exhibit multifocality or regional lymph node metastasis, particularly in younger patients. Certain aggressive histological variants, such as tall cell or hobnail features, may also occur in the microcarcinoma setting and carry a less

favorable prognosis. Thus, PTMC is considered a size-based classification rather than a distinct histological subtype, but its clinical relevance lies in balancing the risk of overtreatment with the potential for metastatic disease[62] (Figure 2.12).

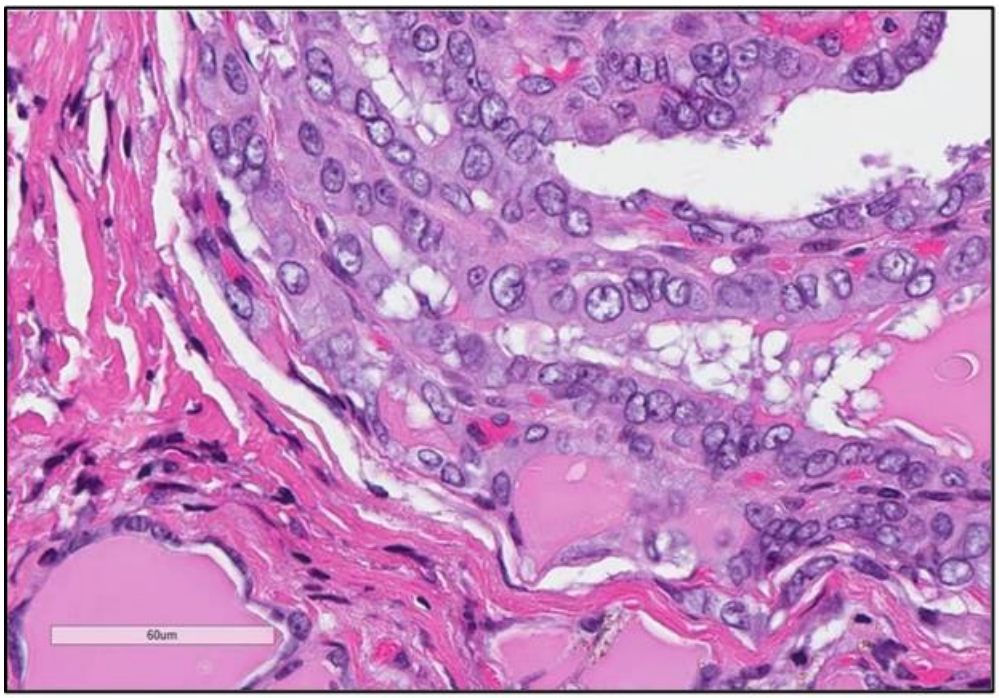

Figure 2.12: Micro-papillary PTC, 1 mm PTMC showing characteristic nuclear features including nuclear enlargement, overlapping, chromatin clearing, irregular nuclear membrane, grooves and occasional pseudo inclusions; background nonneoplastic thyroid follicles for comparison (H&E, 100x).[63]

- **Follicular Thyroid Carcinoma (FTC)**

FTC is the second most common malignant tumor of the thyroid, accounting for approximately 10–15% of thyroid cancers. It arises from follicular epithelial cells and is more frequent in areas of iodine deficiency. FTC is more often seen in middle-aged adults and has a female predominance, similar to papillary thyroid carcinoma (PTC). Unlike PTC, the diagnosis of FTC is not based on nuclear features but rather on the demonstration of capsular and/or vascular invasion. For this reason, distinguishing follicular adenoma from carcinoma can only be made by thorough histological examination of the entire tumor capsule, as cytology alone cannot reliably differentiate the two. Clinically, FTC tends to spread hematogenously, most commonly to bone, lung, and liver, rather than through lymphatic spread as in PTC.[63]

Variants for follicular thyroid carcinoma include

1. Minimally Invasive Follicular Carcinoma

The minimally invasive form of FTC is characterized by a tumor that is usually well-circumscribed and encapsulated, with only microscopic evidence of capsular and/or vascular invasion. Histologically, these tumors may appear deceptively similar to follicular adenomas, with uniform follicles and scant colloid, but careful evaluation reveals foci of invasion. The extent of invasion is limited, usually focal, and not widely destructive. Prognosis for minimally invasive FTC is excellent, with very low recurrence or metastasis rates, particularly in the absence of vascular invasion. Patients usually do well after surgical excision, and radioactive iodine therapy is considered only in select cases.[64,65]

2. Widely Invasive Follicular Carcinoma

Widely invasive FTC represents the more aggressive counterpart of minimally invasive disease. These tumors show extensive infiltration beyond the capsule into adjacent thyroid tissue and often demonstrate prominent vascular invasion, sometimes involving large-caliber veins. Histologically, they are composed of follicles arranged in variable patterns, sometimes solid or trabecular, with destruction of surrounding structures. Clinically, widely invasive FTC carries a significantly worse prognosis than the minimally invasive type, with higher risks of recurrence, distant metastasis, and mortality. Management requires total thyroidectomy and radioactive iodine therapy, with close long-term surveillance.[64,66]

3. Hurthle Cell (Oncocytic) Carcinoma

Hurthle cell carcinoma, now considered a distinct variant of FTC, is composed predominantly of oncocytic (Hurthle) cells, which are large polygonal cells with abundant granular eosinophilic cytoplasm packed with mitochondria. Histologically, the tumor is encapsulated, but unlike a Hurthle cell adenoma, it demonstrates capsular and/or vascular invasion. Hurthle cell carcinoma is more aggressive than conventional FTC, with a higher

likelihood of recurrence and distant metastasis. Importantly, Hurthle cell tumors are less responsive to radioactive iodine due to reduced iodine uptake capacity, making surgical resection the mainstay of treatment. Prognosis is variable but generally less favorable than that of classic FTC.[67,68]

4. Insular and Poorly Differentiated Follicular Carcinoma

A subset of FTCs shows intermediate features between well-differentiated follicular carcinoma and anaplastic carcinoma. These are often referred to as insular carcinoma or poorly differentiated thyroid carcinoma. Histologically, they exhibit solid nests ("insulae") or trabecular arrangements of cells with increased mitotic activity, necrosis, and reduced colloid production. While they retain some follicular differentiation, their clinical behavior is more aggressive, with early recurrence and higher mortality. They are therefore recognized as part of the poorly differentiated thyroid carcinoma spectrum, carrying a worse prognosis than classic FTC but better than anaplastic carcinoma.[69]

- **Medullary Thyroid Carcinoma (MTC)**

Derived from parafollicular C-cells, MTC typically consists of polygonal or spindle-shaped cells arranged in nests, sheets, or trabecular patterns. A hallmark feature is the presence of amyloid deposits in the stroma, which can be confirmed histochemically using Congo red staining.[70]

- **Anaplastic Thyroid Carcinoma (ATC):**

ATC is a rare but extremely aggressive thyroid cancer composed of undifferentiated tumor cells. Histology reveals marked cellular pleomorphism, spindle or giant cells, extensive necrosis, and numerous mitoses. Due to its rapid progression and early metastasis, ATC carries a very poor prognosis.[71]

World Health Organization (WHO) 2022 (5th edition) classification (for the chapter Tumours of the Thyroid Gland).

Category / Family	Tumour type (WHO 2022)
Follicular cell-derived neoplasms	**Benign tumours**
	Thyroid follicular nodular disease
	Follicular thyroid adenoma
	Follicular thyroid adenoma with papillary architecture
	Oncocytic adenoma of the thyroid
Low-risk neoplasms	Non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)
	Thyroid tumour of uncertain malignant potential: Follicular tumour of uncertain malignant potential (FT-UMP)
	Thyroid tumour of uncertain malignant potential: Well-
	differentiated tumour of uncertain malignant potential (WD-UMP)
	Hyalinizing trabecular tumour (HTT)
Malignant neoplasms (follicular cell-derived)	Follicular thyroid carcinoma (FTC), NOS
	Invasive encapsulated follicular variant papillary thyroid carcinoma
	Papillary thyroid carcinoma (PTC) – classical type
	Oncocytic carcinoma of the thyroid
	High-grade follicular-derived carcinomas: "Differentiated high-grade thyroid carcinoma" & "Poorly differentiated thyroid carcinoma"
Salivary gland-type carcinomas of the thyroid	Mucoepidermoid carcinoma of the thyroid
	Secretory carcinoma of salivary gland-type in the thyroid
Thyroid tumours of uncertain histogenesis	Sclerosing mucoepidermoid carcinoma with eosinophilia (SMECE)
	Cribriform morular thyroid carcinoma
C-cell (parafollicular) derived neoplasms	Medullary thyroid carcinoma (MTC)

Correlation between Cytology and Histopathology

Establishing a reliable correlation between cytological interpretations based on the Bethesda System and the final histopathological diagnosis is critical for guiding appropriate patient care. While cytology provides valuable preoperative insights, discrepancies can occasionally arise, this highlights the need for histological evaluation to validate cytologic findings and support informed clinical decision- making.[32,72]

2.9 Correlation Studies between Bethesda Cytological Categories and Histopathological Findings Clinical Outcomes and Management Decisions

The cytological diagnosis via the Bethesda System and final histopathological findings both play crucial role in determining clinical management strategies. When cytological results fall into Bethesda categories V (suspicious for malignancy) and VI (malignant), the high concordance with histopathologic malignancy which would justifies proceeding directly to definitive surgical treatment, such as total thyroidectomy. In comparison, the indeterminate categories—such as Category III (AUS) and Category IV (Follicular Neoplasm/Suspicious for a Follicular Neoplasm)—often result in diagnostic surgical procedures due to the uncertainty surrounding their malignancy risk. This highlights the importance of selecting patients carefully and incorporating additional tools, such as molecular testing and comprehensive risk stratification, to reduce unnecessary surgical interventions. Ideal clinical outcomes can be achived more when cytological findings are evaluated alongside the patient's clinical profile, imaging characteristics, and final histopathological results.[72,73]

Sensitivity, Specificity, and Accuracy

Multiple studies have assessed the diagnostic performance of the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) in predicting thyroid malignancy. The system has demonstrated consistently high sensitivity and specificity, especially for nodules classified as benign (category II) or malignant (category VI). Reported sensitivity values typically range from 65% to 98%, while specificity varies between 60% and 96%, influenced by population characteristics and the level of cytological expertise. Category VI consistently shows strong correlation with malignancy on histology, often yielding sensitivity and specificity rates between 97% and 99%. However, the intermediate categories, III (AUS) and IV (follicular neoplasm/suspicious for follicular neoplasm), are associated with lower specificity due to their inherent diagnostic ambiguity. In such cases, additional tools like repeat FNAC, molecular assays, or diagnostic surgery are often necessary to reach a conclusive diagnosis.[74,75]

Limitations of Cytological Evaluation

Despite high overall accuracy, FNAC evaluation using the Bethesda system presents limitations. Significant challenges include.[76,77]

- Non-diagnostic samples (category I), which require repeat biopsy.
- Atypia of undetermined significance (AUS) (category III), which demonstrates considerable inter-observer variability.
- Difficulty distinguishing follicular adenoma from follicular carcinoma on cytology due to reliance on histological evidence of capsular and vascular invasion for definitive diagnosis.
- Potential sampling errors, inadequate specimen quality, or interpretative variability among pathologists, emphasizing the importance of multidisciplinary approaches and complementary diagnostic tools (2,3).

Chapter 3: Patients and methods

3.1 Study Design and study population

This study was a cross-sectional analysis conducted in Al-Kufa Training Center for Pathology, Iraqi Board of Medical Specializations during the period from 1st of January 2025 to 1st of September 2025. The Fine-Needle Aspiration (FNA) samples of patients presented with solitary thyroid nodule with corresponding subsequent histopathological results collected from surgical specimens (lobectomy or total thyroidectomy) collected from medical records performed during the peroid from January 2023 to September 2025 in department of pathology of Al- Sader medical city.

3.2 Sample Selection and Study Groups

A total of 80 thyroid FNA samples were retrieved from the laboratory archives. These selected cases underwent analysis to determine the association between cytological classification and final histological diagnosis.

Criteria of inclusion.

1. Cases with solitary thyroid nodule with their ultrasound reports.
2. Same cases with complete histopathological confirmation following surgical excision.

Exclusion criteria included:

- Incomplete histopathology reports.
- Unavailability of histological slides.

3.3 Sample Assessment

3.3.1 Cytological Classification

FNA smears were stained using the standard techniques of smearing and fixation in 95% alcohol. Cytological assessment of old cases was carried out by pathologists while new cases were assessed under supervision of my supervisor and all were categorized according to the Bethesda System (BSRTC 2023). the steps of standards technique involve.[78]

1- Preparation

Already smeared slides aspirated under U/S departments or those aspirated under manual technique were fixed in 95 % alcohol for at least 20 minutes

2- staining with Hematoxylin and Eosin (H&E) Staining protocol

1. Rinse the fixed slides in distilled water for 1–2

minutes.
2. Stain with Harris Hematoxylin for 5–10 minutes.
3. Rinse in running tap water for 5 minutes.
4. Differentiate in 1% acid alcohol for a few seconds until nuclei appear light blue.
5. Wash in tap water for 1–2 minutes.
6. Dip in ammonia water or lithium carbonate solution for 30 seconds to "blue" the nuclei.
7. Rinse again in tap water for 5 minutes.
8. Counterstain with Eosin for 30 seconds to 1 minute.
9. Rinse quickly in tap water to remove excess Eosin.

3- Dehydration, Clearing, and Mounting

1. Dehydrate through ascending grades of alcohol (70%, 90%, and 100%), 2 minutes each.
2. Clear the slides in xylene, two changes for 2 minutes each.
3. Mount the slides with DPX mounting medium and place a cover slip.
4. Allow to dry before microscopic examination.

3.3.2 Histopathological evaluation

When histopathology was available, corresponding tissue blocks were sectioned and stained with Haematoxylin and eosin (H&E) and reviewed by pathologist blinded to the cytological findings.

Deparaffinization: Keep the sections in xylene for 10 min each and three changes. Rehydration.
Absolute alcohol: 1-2 min 95% alcohol: 1-2 min
80% alcohol: 1-2 min
60% alcohol: 1-2 min Rinse in tap water.
Nuclear stain by haematoxylin: Harris haematoxylin 15 min (keep according to the type of haematoxylin).
Differentiation: In case of regressive staining, one to two dips in acid alcohol (1% HCl in 70% alcohol) for differentiation are necessary. Please check by microscope for the desired staining of nucleus.
Rinse in water.
Bluing: Wash by running tap water for 10-15 min.
Counterstain by eosin: 1% aqueous eosin Y for 2-3 min.
Dehydration:
95% alcohol: 3 min

- Absolute alcohol: 3 min
- Absolute alcohol: 5 min

Clearing: Xylene 5 min each in twe Mount in DPX.

Histopathological diagnoses were stratified as benign or malignant. Colloid nodules and Follicular adenomas were classified as benign. Malignant lesions included follicular carcinoma, papillary carcinoma variants, medullary carcinoma and anaplastic carcinoma. While tumors of uncertain malignant potential (such as NIFTP, WDTUMP, FTUMP, and hyalinizing trabecular tumor), were classified according to updated WHO and ATA guidelines.

3.4 Data Collection and Variables

For each case, the following data were recorded.

- Patient age and gender.
- Size and anatomical location of the thyroid nodule.
- Cytological category (Bethesda I–VI).
- Final histopathological diagnosis.

3.5 Ethical Considerations

Prior to data collection, the research protocol was reviewed and approved by the institutional ethical committee in accordance with the regulations of the Iraqi Board for Medical Specializations. Patient confidentiality was preserved by anonymizing all personal identifiers throughout the research process.

3.6 Statistical analysis

Data analysis was performed using IBM SPSS software (version 27). Categorical variables were expressed as counts and percentages. Associations between categorical variables (e.g., Bethesda category and histological outcome) were assessed using the Chi-square test or Fisher's exact test, as appropriate. A p-value less than 0.05 was considered statistically significant.[79]

Additionally, a performance assessment of the cytological findings was conducted which compared the Bethesda classifications with final histological outcomes. Diagnostic parameters including sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were all calculated using 2×2 contingency analysis.

Chapter 4: RESULTS

4.1 Demographic characteristics for study sample

A total of 80 patients were included in this study. For distribution of sex among patients of the study, the study population was predominantly female, comprising 67 (83.75%) patients, whereas male patients represented only 13 (16.25%) patients. (Figure 4.1).

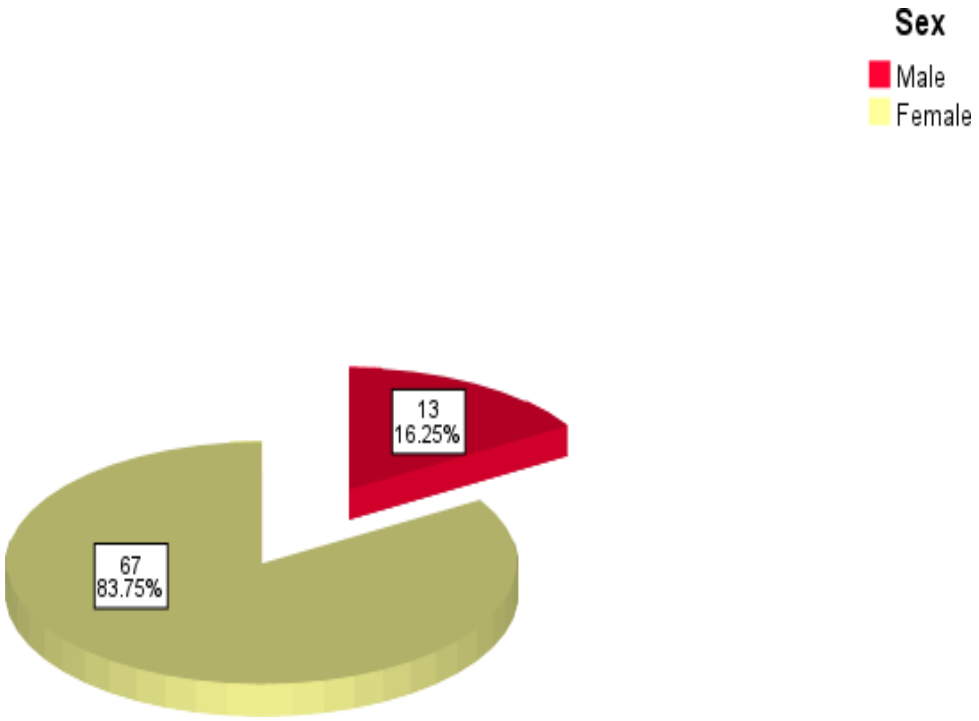

Figure 4.1: The distribution of sex among patients of the study.

Meanwhile, the age distribution demonstrated that the largest proportion of patients were between 21 and 30 years old with 24 patients (30.0%), followed closely by those aged 31–40 years with 23 (28.75%) patients. Patients aged 41–50 years constituted 19 (23.75%) patients, while those less than 20 years old accounted for 7 (8.75%) patients. In contrast, older patients were less represented, with 4 (5.0%) patients in the 51–60 years age group and 3 (3.75%) patients aged more than 60 years (Figure 4.2).

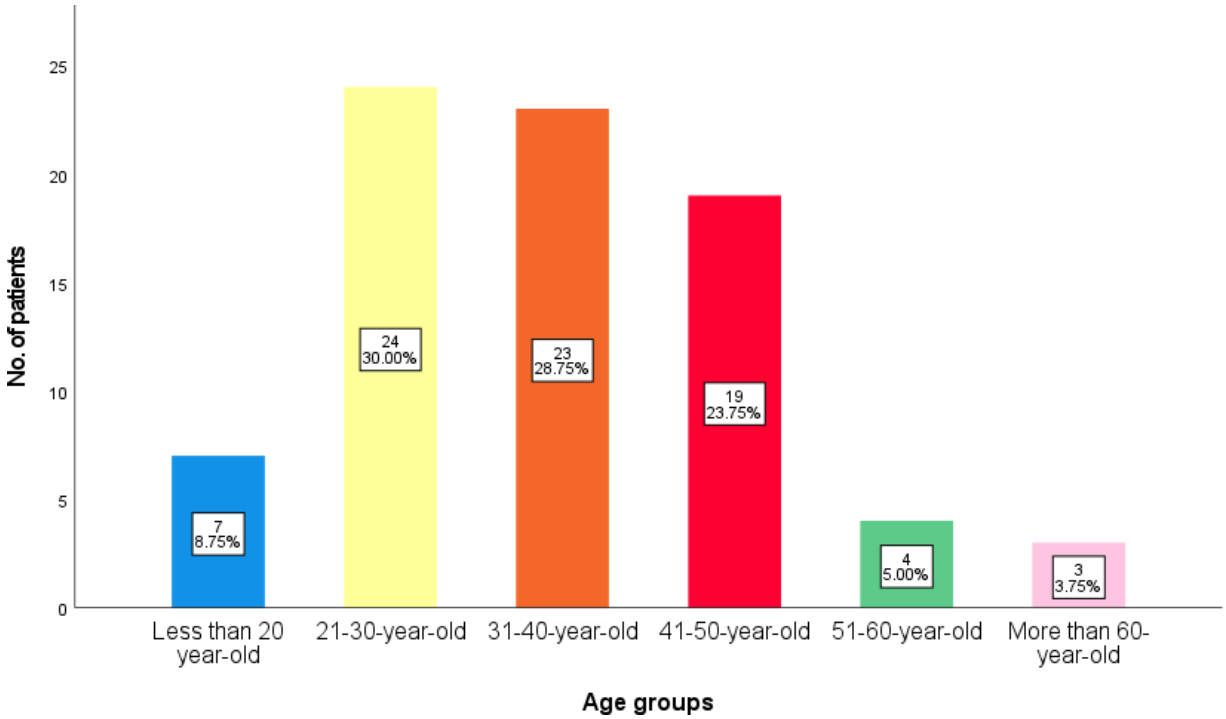

Figure 4.2: The distribution of age among patients of the study.

For the association of sex with age among patients of the study, there was no statistically significant association with p-value of 0.18. (Table 4.1)

Table 4.1: The association of sex with age among patients of the study.

		Sex		Total	P-value*
		Male	Female		
Age groups					
Less than 20-year-old	No.	0	7	7	0.187
	%	0.00	8.75	8.75	
21-30-year-old	No.	3	21	24	
	%	3.75	26.25	30.00	
31-40-year-old	No.	2	21	23	
	%	2.50	26.25	28.75	
41-50-year-old	No.	6	13	19	
	%	7.50	16.25	23.75	
51-60-year-old	No.	1	3	4	
	%	1.25	3.75	5.00	
More than 60-year-old	No.	1	2	3	
	%	1.25	2.50	3.75	

*Fisher exact test.

4.2 Thyroid nodule characteristics

Thyroid nodules were located on the right lobe in 45 (56.25%) patients and on the left lobe in 35 (43.75%) patients (Figure 4.3).

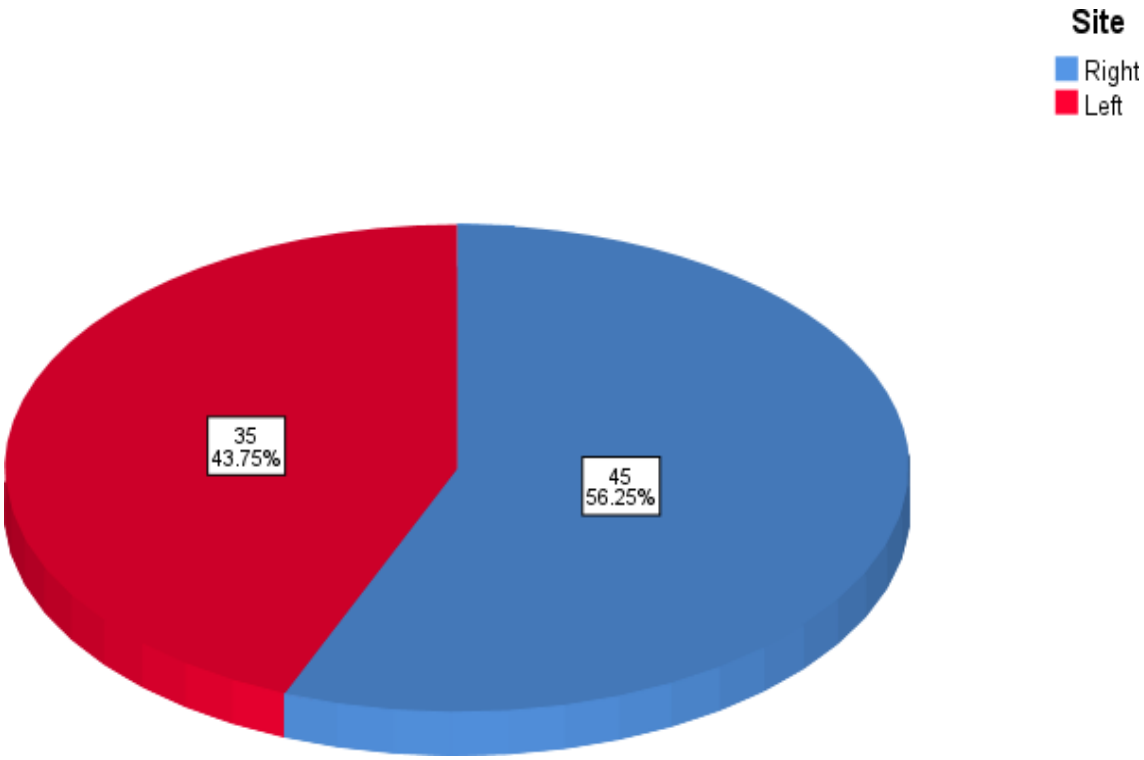

Figure 4.3: The site of thyroid nodule among patients of the study.

Nodules size showed that those measuring 20–40 mm was the most frequent, reported in 60 (75.0%) patients, followed by nodules <20 mm in 12 (15.0%) and nodules >40 mm in 8 (10.0%) (Figure 4.4).

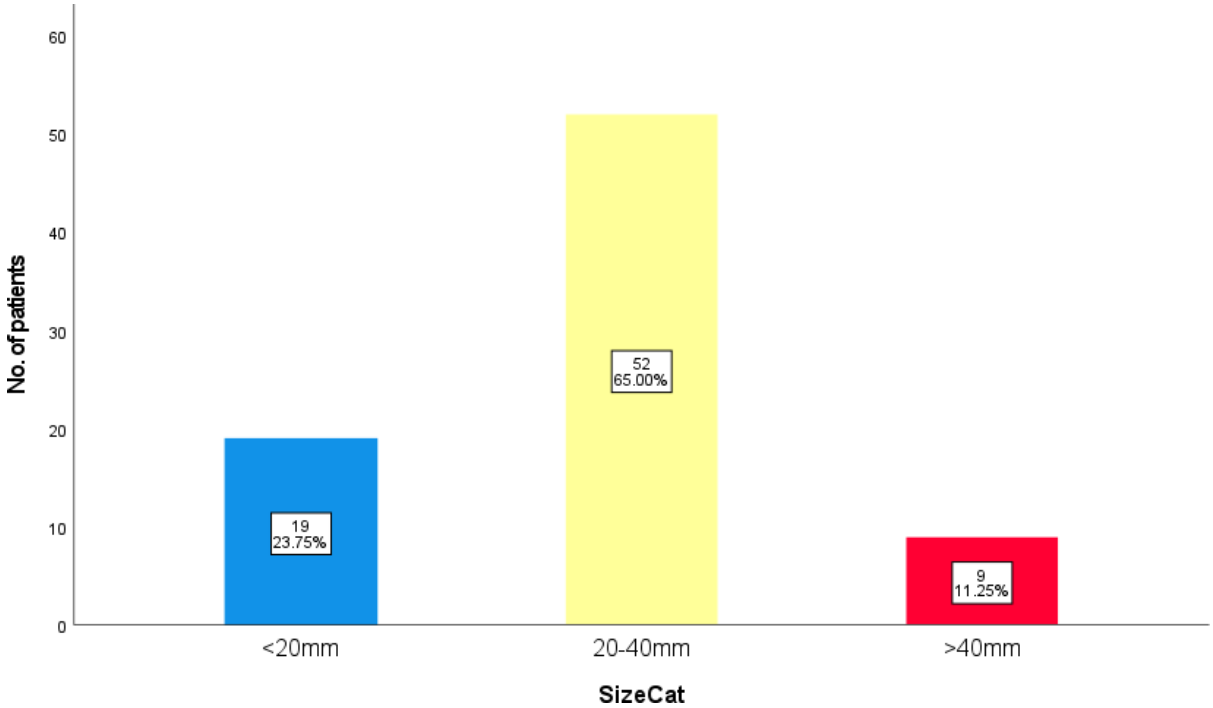

Figure 4.4: The size of nodules among patients of the study.

Out of 40 patients with malignant thyroid nodules, most nodules were classified as T2 in 24 (60.0%) patients, followed by T1 in 14 (35.0%) and T3 in 2 (5.0%) (Figure 4.5).

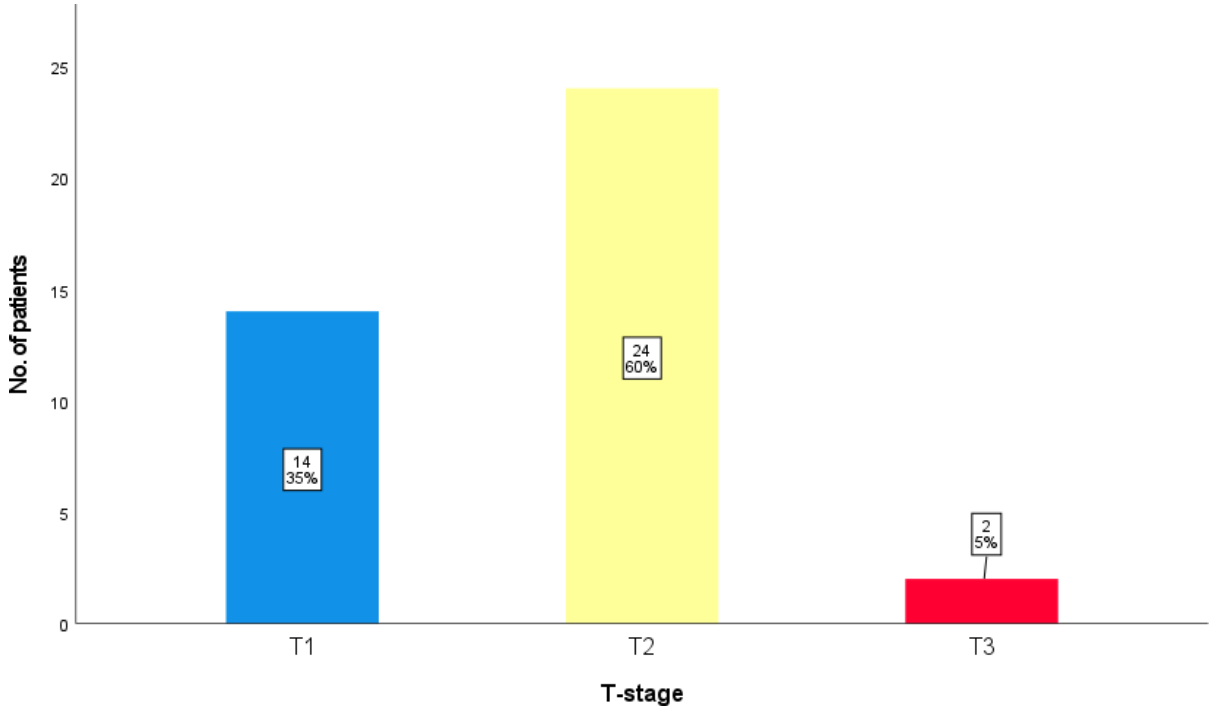

Figure 4.5: The T-stage for patients with malignant nodules among patients of the study.

The association for sex with site, size and FNA method showed no statistically significant association with p-value>0.05 (Table 4.2).

Table 4.2: Distribution of patients according to demographic and clinical characteristics among patients of the study.

		Sex		Total	P-value
		Male	Female		
Site					
Right	No.	6	39	45	0.308
	%	7.50%	48.75%	56.25%	
Left	No.	7	28	35	
	%	8.75%	35.00%	43.75%	
Size by US					
<20mm	No.	1	18	19	0.249
	%	1.25%	22.5%	23.75%	
20-40mm	No.	11	41	52	
	%	13.75%	51.2%	65.0%	
>40mm	No.	1	8	9	
	%	1.25%	10.0%	11.25%	
Total	No.	13	67	80	
	%	16.25%	83.75%	100.00%	

4.3 Cytological Findings (Bethesda System)

Cytological evaluation of FNA specimens which was classified according to the Bethesda System for Reporting Thyroid Cytopathology showed that Category VI (malignant) was the most frequent, found in 24 (30.0%) cases (Figure 4.17 & 4.18), followed by Category III (atypia of undetermined significance / follicular lesion of undetermined significance) in 19 (23.75%) cases (Figure 4.11 & 4.12). Both Category II (benign) and Category V (suspicious for malignancy) were reported in 16 (20.0%) cases each (Figure 4.9, 4.10, 4.15 & 4.16). Category IV (follicular neoplasm/suspicious for follicular neoplasm) was identified in 4 (5.0%) cases (Figure 4.13 & 4.14), whereas Category I (nondiagnostic) was the least frequent, seen in only 1 (1.25%) case (Figure 4.6).

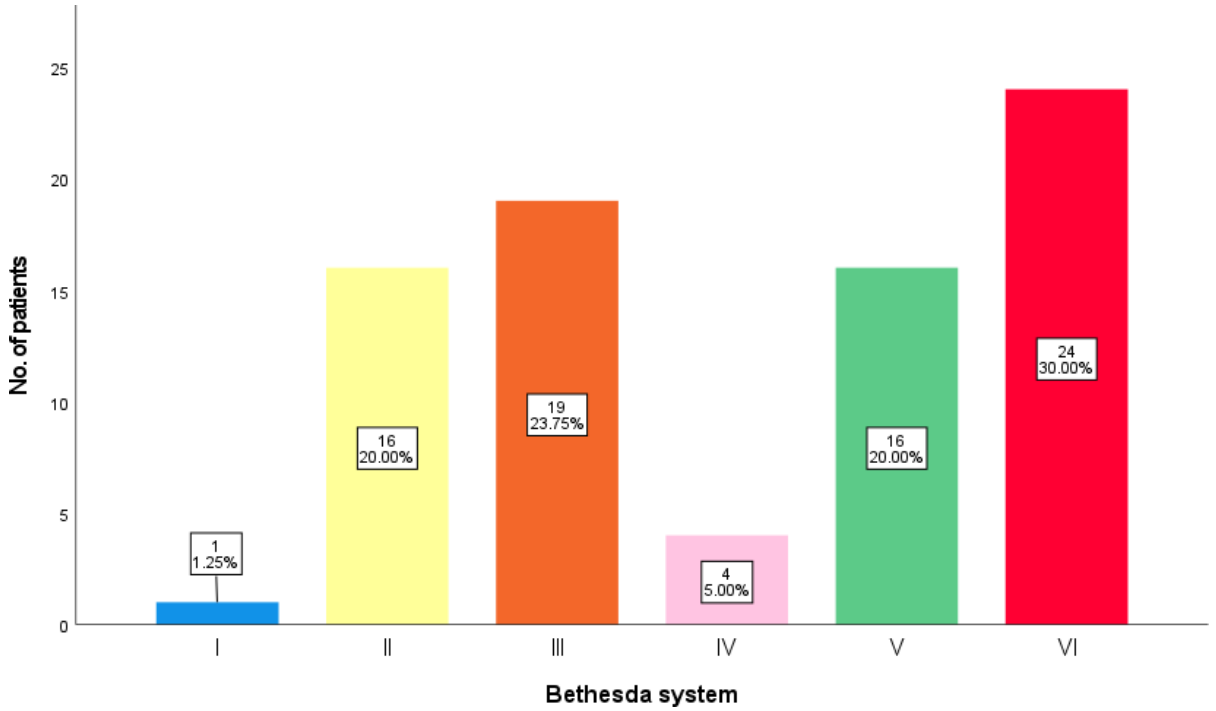

Figure 4.6: Cytological categories based on the Bethesda system among patients of the study.

There was no statistically significant association between Bethesda classification and patient sex (Fisher's exact test, p = 0.33), as shown in table 4.3 below.

Table 4.3: The association of Bethesda system categories with patient sex among patients of the study.

Bethesda system categories		Sex		Total	P-value*
		Male	Female		
Class I	No.	0	1	1	0.33
	%	0.00%	1.25%	1.25%	
Class II	No.	0	16	16	
	%	0.00%	20.00%	20.00%	
Class III	No.	4	15	19	
	%	5.00%	18.75%	23.75%	
Class IV	No.	1	3	4	
	%	1.25%	3.75%	5.00%	
Class V	No.	3	13	16	
	%	3.75%	16.25%	20.00%	
Class VI	No.	5	19	24	
	%	6.25%	23.75%	30.00%	
Total	No.	13	67	80	
	%	16.25%	83.75%	100.0%	

*Fisher exact test.

Similarly, there was no statistically significant association between Bethesda classification and patient age group (Fisher's exact test, p = 0.341) as shown in table 4.4 below.

Table 4.4: The association of Bethesda system categories with age groups among patients of the study.

Age groups		Bethesda system						Total*
		I	II	III	IV	V	VI	
Less than 20-year-old	No.	0	3	1	0	1	2	7
	%	0.00%	3.75%	1.25%	0.00%	1.25%	2.50%	8.75%
21-30-year-old	No.	1	2	6	3	4	8	24
	%	1.25%	2.50%	7.50%	3.75%	5.00%	10.00%	30.00 %
31-40-year-old	No.	0	2	6	0	5	10	23
	%	0.00%	2.50%	7.50%	0.00%	6.25%	12.50%	28.75 %
41-50-year-old	No.	0	6	5	0	5	3	19
	%	0.00%	7.50%	6.25%	0.00%	6.25%	3.75%	23.75 %
51-60-year-old	No.	0	2	1	0	0	1	4
	%	0.00%	2.50%	1.25%	0.00%	0.00%	1.25%	5.00%
More than 60-year-old	No.	0	1	0	1	1	0	3
	%	0.00%	1.25%	0.00%	1.25%	1.25%	0.00%	3.75%
Total	No.	1	16	19	4	16	24	80
	%	1.25%	20.00%	23.75%	5.00%	20.00%	30.00%	100%
P-value		0.341						

*Fisher exact test.

There was also no statistically significant association between Bethesda classification and nodule site (Fisher's exact test, p = 0.648) as shown in table 4.5 below.

Table 4.5: The association of Bethesda system categories with nodule site among patients of the study.

Bethesda system categories		Site		Total	P-value*
		Right	Left		
Class I	No.	1	0	1	0.648
	%	1.25%	0.00%	1.25%	
Class II	No.	8	8	16	
	%	10.00%	10.00%	20.00%	
Class III	No.	11	8	19	
	%	13.75%	10.00%	23.75%	
Class IV	No.	1	3	4	
	%	1.25%	3.75%	5.00%	
Class V	No.	11	5	16	
	%	13.75%	6.25%	20.00%	

Class VI	No.	13	11	24	
	%	16.25%	13.75%	30.00%	
Total	No.	45	35	80	
	%	56.25%	43.75%	100.0%	

*Fisher exact test.

The association between Bethesda classification and T-stage not statistically significant (Fisher's exact test, p = 0.594) as shown in table 4.6 below.

Table 4.6: The association of Bethesda system categories to T-stage among patients of the study.

Bethesda system categories		T-stage			Total	P-value*
		T1	T2	T3		
Class II	No.	1	0	0	1	0.594
	%	2.5%	0.0%	0.0%	2.5%	
Class III	No.	0	3	0	3	
	%	0.0%	7.5%	0.0%	7.5%	
Class IV	No.	0	1	0	1	
	%	0.0%	2.5%	0.0%	2.5%	
Class V	No.	5	5	1	11	
	%	12.5%	12.5%	2.5%	27.5%	
Class VI	No.	8	15	1	24	
	%	20.0%	37.5%	2.5%	60.0%	
Total	No.	14	24	2	40	
	%	35.0%	60.0%	5.0%	100.0%	

*Fisher exact test.

There was a statistically significant association between Bethesda classification and malignancy status (Fisher's exact test, p = 0.001) (Table 4.7).

Table 4.7: The association of Bethesda system categories with malignancy status among patients of the study.

Bethesda system categories		Malignancy status		Total	P-value*
		Malignant	Non-malignant		
Class I	No.	0	1	1	0.001**
	%	0.00%	1.25%	1.25%	
Class II	No.	1	15	16	
	%	1.25%	18.75%	20.00%	
Class III	No.	3	16	19	
	%	3.75%	20.00%	23.75%	
Class IV	No.	1	3	4	
	%	1.25%	3.75%	5.00%	
Class V	No.	11	5	16	
	%	13.75%	6.25%	20.00%	
Class VI	No.	24	0	24	
	%	30.00%	0.00%	30.00%	
Total	No.	40	40	80	
	%	50.0%	50.0%	100.0%	

*Fisher exact test, **Statistically significant at p-value<0.05.

4.4 Histopathological Findings

Histopathological examination of surgically excised nodules revealed that papillary thyroid carcinoma (all variants) was the most common diagnosis, observed in 38 (47.5%) patients. Benign nodules were identified in 27 (33.75%) cases, while follicular/Hürthle cell adenoma accounted for 7 (8.75%) cases.

Additionally, non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) was detected in 4 (5.0%) cases, and well-differentiated tumors of uncertain malignant potential (WDT-UMP) were reported in 2 (2.5%) cases. Less frequent malignancies included medullary carcinoma (1; 1.25%), and follicular tumor of uncertain malignant potential (FT-UMP) (1; 1.25%) while follicular carcinoma was present in none of the cases (Figure 4.7).

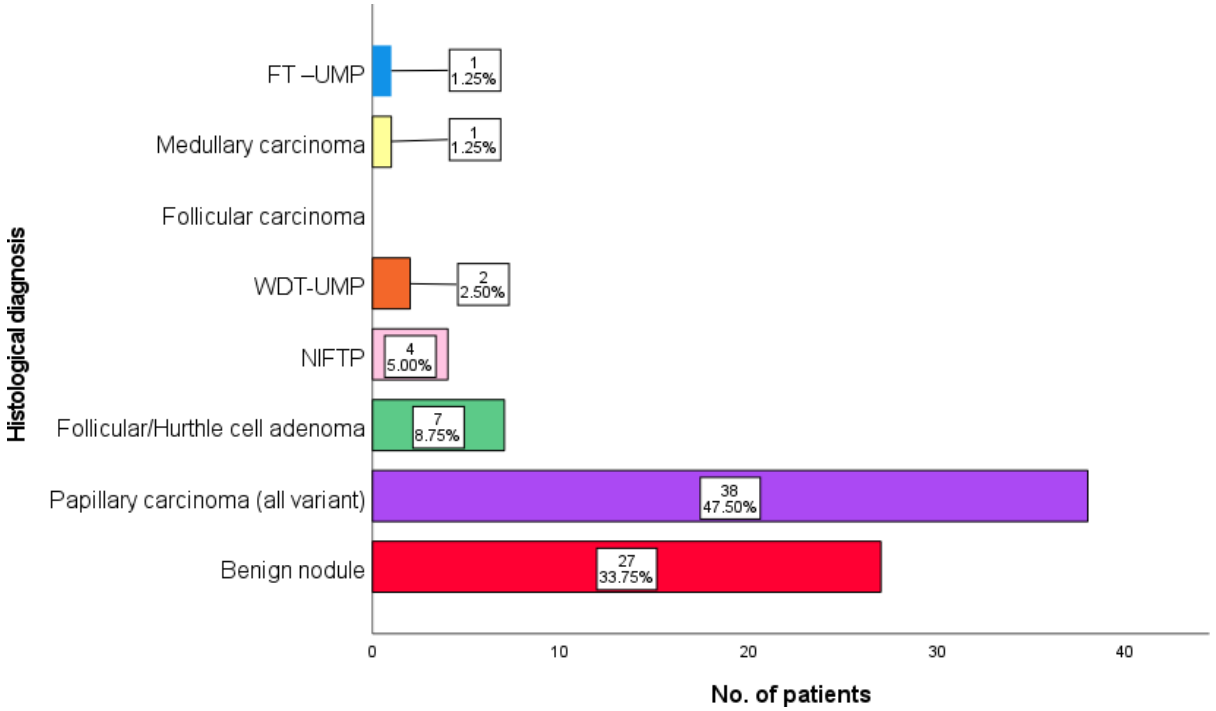

Figure 4.7: Histological diagnosis for thyroid nodules among patients of the study.

Malignancy status assessment showed that 40 (50.0%) were malignant and 40 (50.0%) were non-malignant as shown in figure 4.8 below.

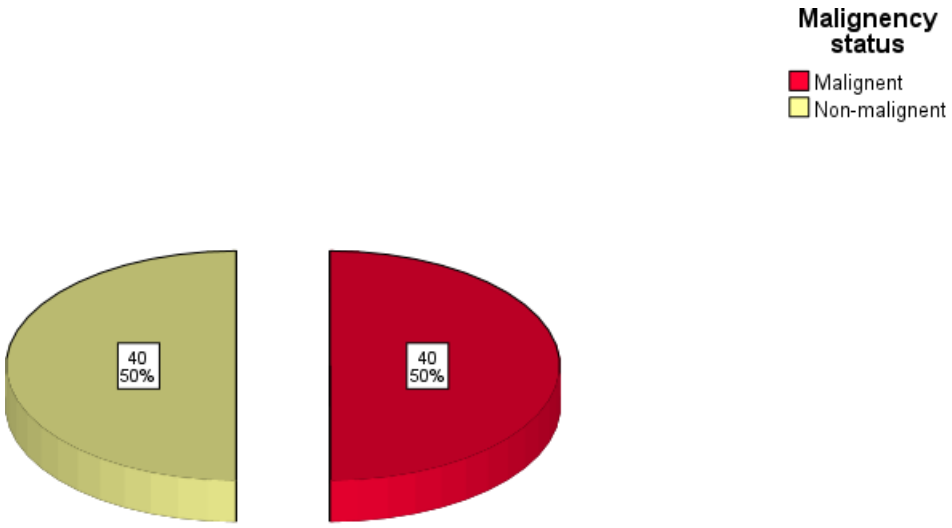

Figure 4.8: Malignancy status among patients of the study.

There was no statistically significant association between histological diagnosis and patient sex (Fisher's exact test, p = 0.654) as shown in table 4.8.

Table 4.8: The association of histological diagnosis with patient sex among patients of the study.

Histological diagnosis		Sex		Total	P-value*
		Male	Female		
Colloid / Hyperplastic nodule	No.	3	24	27	0.654
	%	3.75%	30.0%	33. 75%	
Papillary carcinoma (classic variant, encapsulated follicular variant, microcarcinoma, follicular variant)	No.	7	31	38	
	%	8. 75%	38. 75%	47.5%	
Follicular/Hurthle cell adenoma	No.	1	6	7	
	%	1.25%	7.5%	8.75%	

NIFTP	No.	1	3	4	
	%	1. 25%	3. 75%	5.0%	
WDT-UMP	No.	1	1	2	
	%	1. 25%	1.3%	2.5%	
Medullary carcinoma	No.	0	1	1	
	%	0.0%	1. 25%	1. 25%	
FT –UMP	No.	0	1	1	
	%	0.0%	1. 25%	1. 25%	
Total	No.	13	67	80	
	%	16. 25%	83. 75%	100.0%	

*Fisher exact test

The association between histological diagnosis and Bethesda classification showed a statistically significant difference (Fisher's exact test, p = 0.001) as shown in table 4.9 below.

Table 4.9: The association of histological diagnosis according to Bethesda system categories among patients of the study.

Histological diagnosis		**Bethesda system**						**Total**
		I	**II**	**III**	**IV**	**V**	**VI**	
Colloid / Hyperplastic nodule	No.	1	11	10	1	4	0	27
	%	1.25%	13.75%	12.50 %	1.25%	5.00%	0.00%	33.75 %
Papillary carcinoma (classic variant, encapsulated follicular variant, microcarcinoma, follicular variant)	No.	0	1	3	0	11	23	38
	%	0.00%	1.25%	3.75%	0.00%	13.75 %	28.75 %	47.50 %
Follicular/Hurthle cell adenoma	No.	0	2	2	1	1	1	7
	%	0.00%	2.50%	2.50%	1.25%	1.25%	1.25%	8.75%
NIFTP	No.	0	1	3	0	0	0	4
	%	0.00%	1.25%	3.75%	0.00%	0.00%	0.00%	5.00%
WDT-UMP	No.	0	1	0	1	0	0	2
	%	0.00%	1.25%	0.00%	1.25%	0.00%	0.00%	2.50%
Medullary carcinoma	No.	0	0	0	1	0	0	1
	%	0.00%	0.00%	0.00%	1.25%	0.00%	0.00%	1.25%
FT –UMP	No.	0	0	1	0	0	0	1
	%	0.00%	0.00%	1.25%	0.00%	0.00%	0.00%	1.25%
Total	No.	1	16	19	4	16	24	80
	%	1.25%	20.00%	23.75%	5.00%	20.00%	30.00%	100.00%
P-value*	0.001**							

*Fisher exact test, **Statistically significant at p-value<0.05.

4.5 Performance assessment

Benign cytology (Bethesda II) was reported in 16 cases, of which 1 (1.3%) proved malignant and 15 (18.8%) were benign on histology. Cytological findings including (Bethesda I and III) was reported in 20 cases, with 3 (3.8%) malignant and 17 (21.3%) benign. Malignant cytology (Bethesda IV–VI) was reported in 44 cases, of which 36 (45.0%) were malignant and 8 (10.0%) were benign as shown in table 4.10 below.

Table 4.10: Distribution of cytology groups and histology outcomes among patients of the study.

Cytology group	**Malignant**	**Benign**	**Total**
Class (II)	1 (1.3%)	15 (18.8%)	16 (20.0%)
Class (I & III)	3 (3.8%)	17 (21.3%)	20 (25.0%)
Class (IV, V, VI)	36 (45.0%)	8 (10.0%)	44 (55.0%)
Total	40 (50.0%)	40 (50.0%)	80 (100.0%)

When only benign cytology (Bethesda II) and malignant cytology (Bethesda IV–VI) were considered, malignant histology was correctly identified in 36 of 37 malignant cases, yielding a sensitivity of 97.3%. Benign histology was correctly identified in 15 of 23 benign cases, with a specificity of 65.2%. The positive predictive value was 81.8%, and the negative predictive value was 93.8%. Overall diagnostic accuracy was 85.0% as shown in table 4.11 below.

Table 4.11: Diagnostic performance of Bethesda cytology (Benign vs Malignant groups only).

	Value	95% CI
Sensitivity	97.3% (36/37)	86.2% – 99.5%
Specificity	65.2% (15/23)	44.9% – 81.2%
Positive predictive value (PPV)	81.8% (36/44)	68.0% – 90.5%
Negative predictive value (NPV)	93.8% (15/16)	71.7% – 98.9%
Accuracy	85.0% (51/60)	73.9% – 91.9%

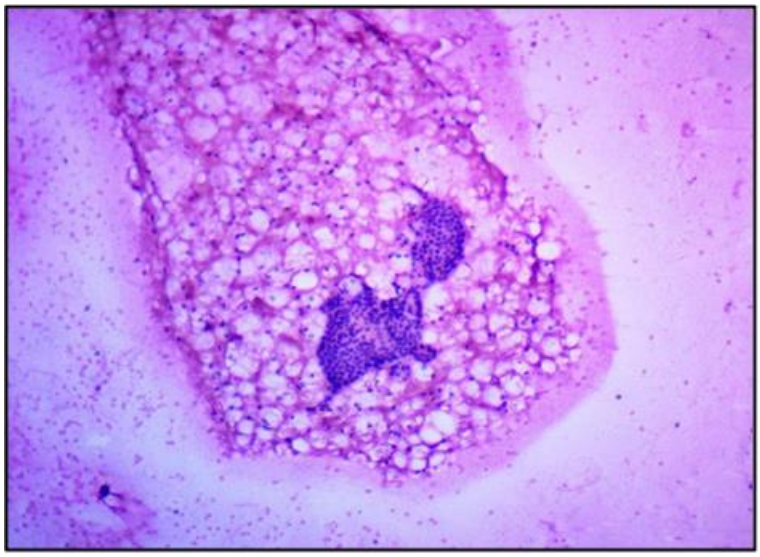

Figure 4.9: Class II: Benign follicular nodule thyroid fine needle aspiration: follicular clusters of variable size (H&E stain, 10x).

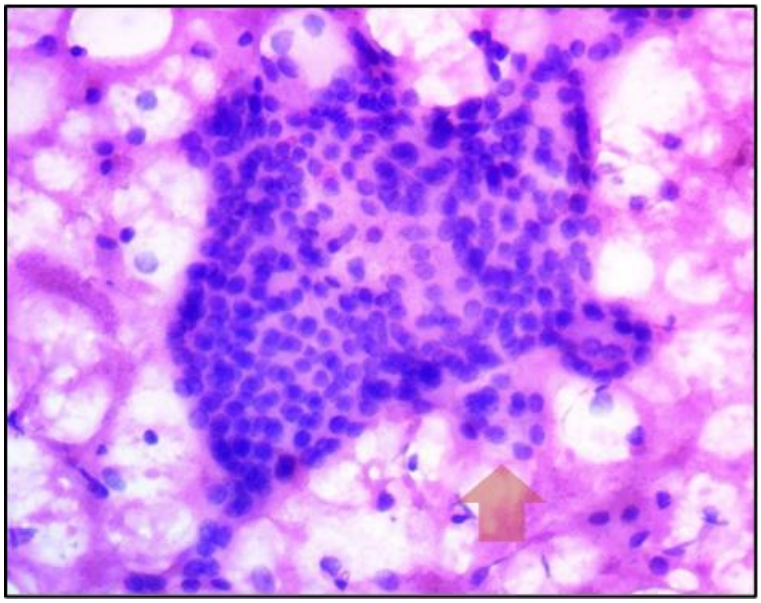

Figure 4.10: Class II: Benign follicular nodule, thyroid fine needle aspiration, arrow points to microfollicular pattern (H&E stain, 40x).

4.6 FNA findings

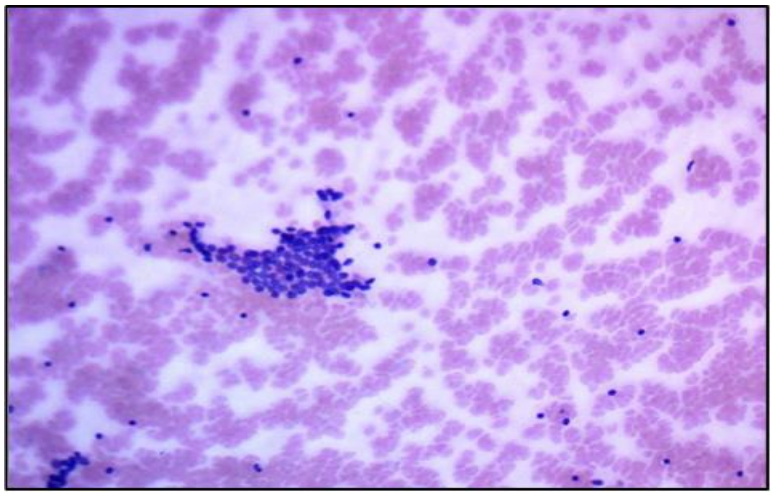

Figure 4.11: Class III: Atypia of undetermined significance (AUS) with nuclear atypia, (H&E stain, 10x).

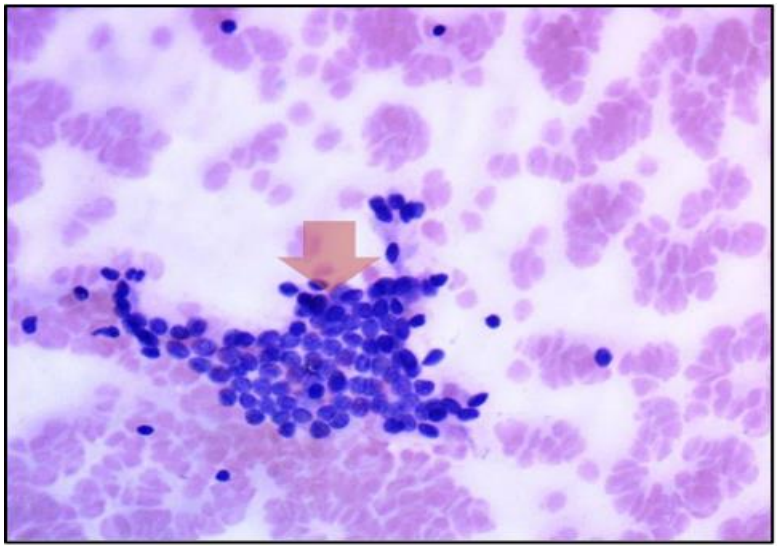

Figure 4.12: Class III: Atypia of undetermined significance (AUS), atypical cell with nuclear change (enlargement, hyperchromasia and irregular nuclear contours), (H&E stain 40x).

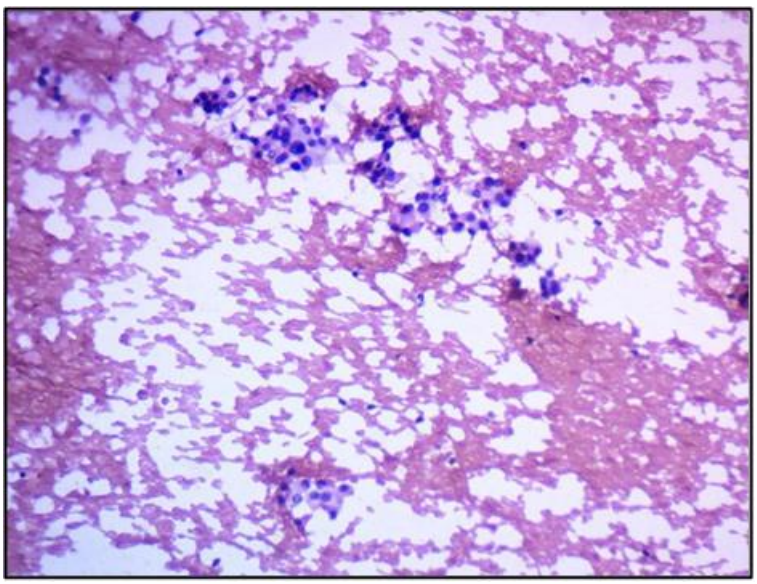

Figure 4.13: Follicular Neoplasm (Bethesda Category IV). Moderately cellular smear showing microfollicles groups of follicular cells. H&E stain 10x.

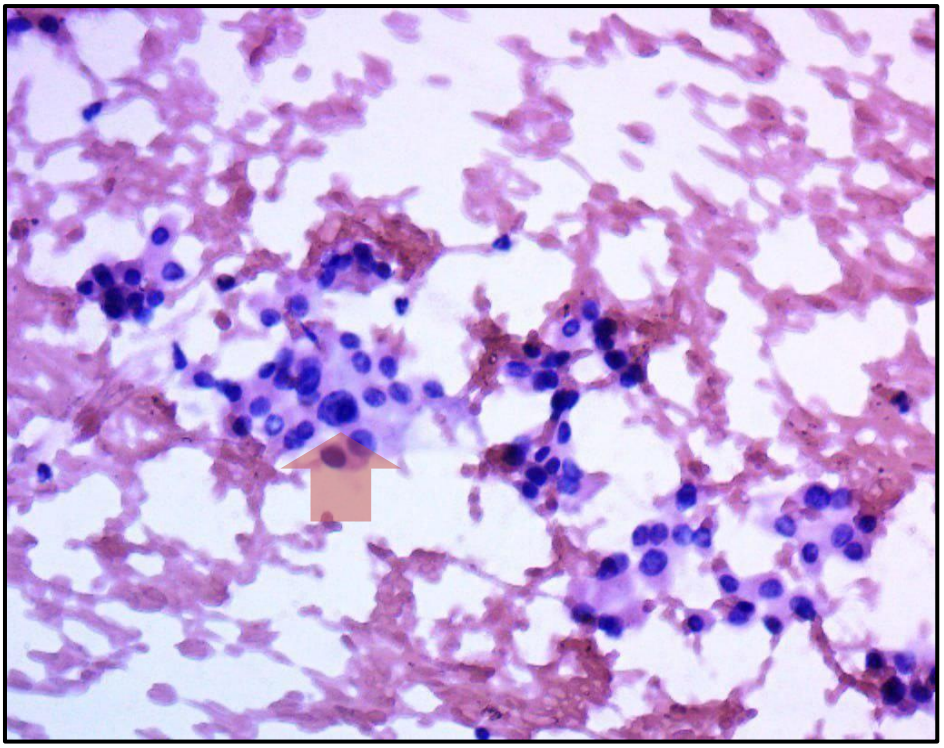

Figure 4.14: Follicular neoplasm Bethesda IV. Cluster of follicular cells with nuclear atypia, arrow shows microfollicular pattern (H&E stain 40x).

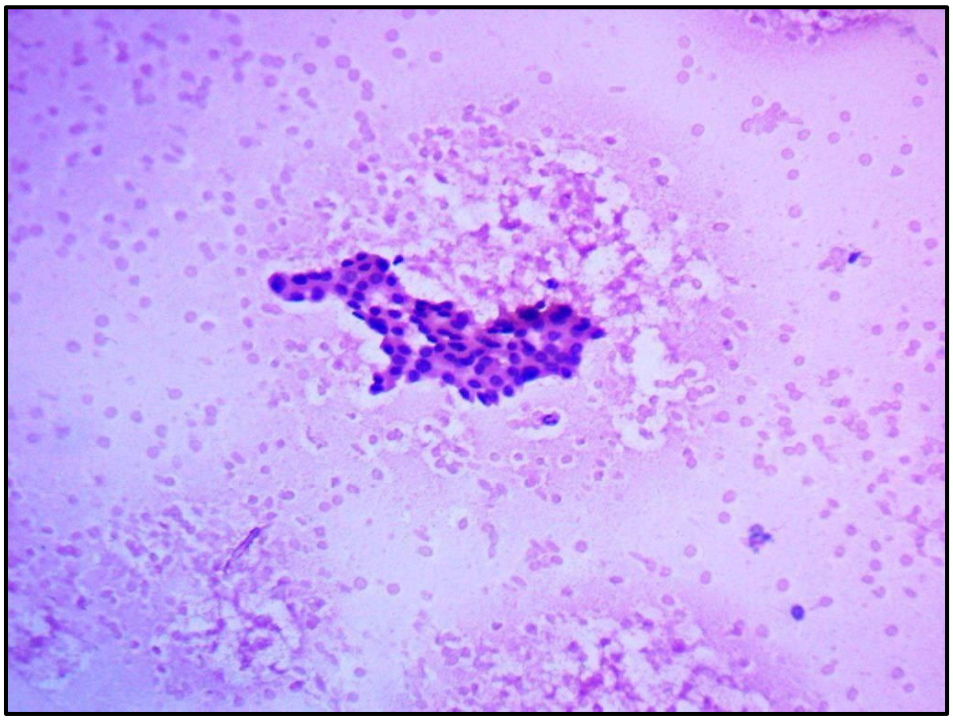

Figure 4.15: Suspicious for papillary thyroid carcinoma, class V. Slide showing cluster and papillary fragment with scant colloid. (H&E stain 20x).

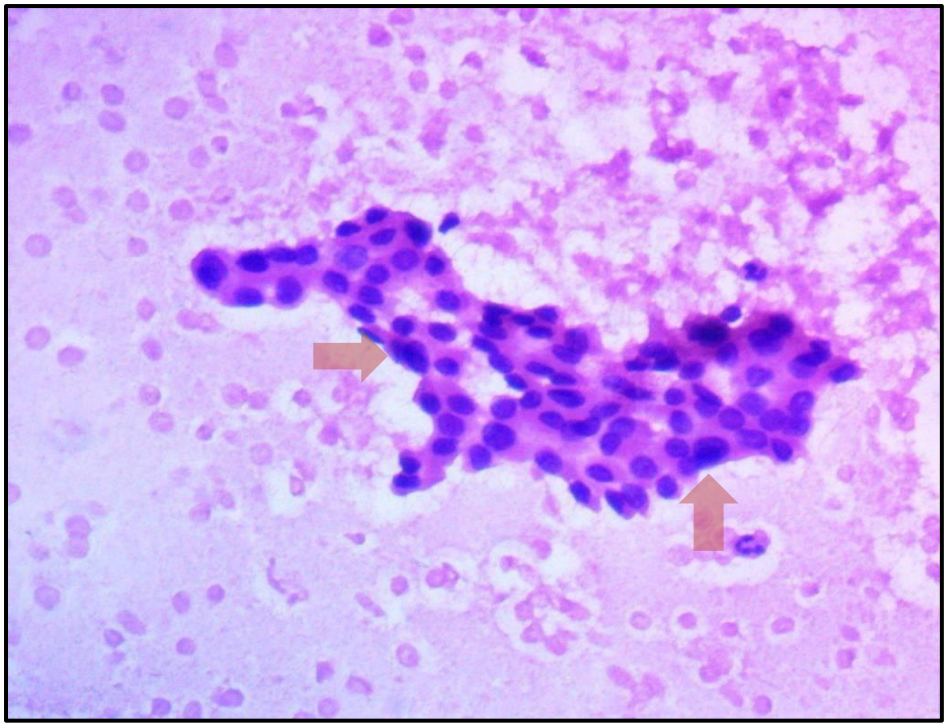

Figure 4.16: Suspicious for papillary thyroid carcinoma, thyroid FNA: mixture of benign follicular cells and cells with nuclear enlargement, membrane irregularities and grooves (H&E stain, 40x).

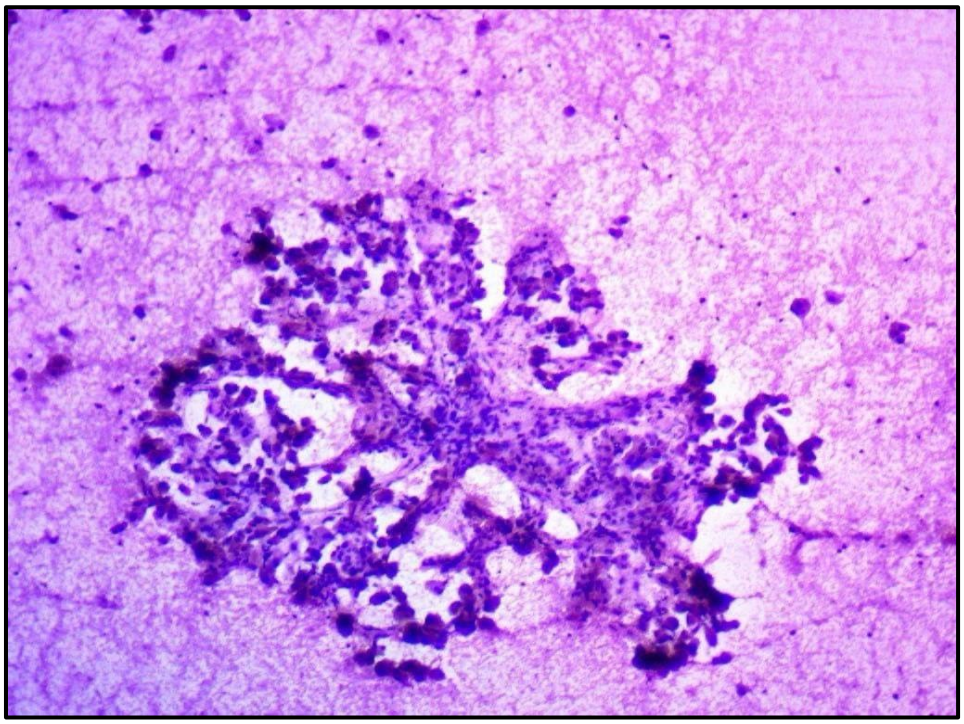

Figure 4.18: Oncocytic varant of papillary thyroid carcinoma class VI. Cellular smear, large papillary fragments branching 3D cluster (H&E stain 10x).

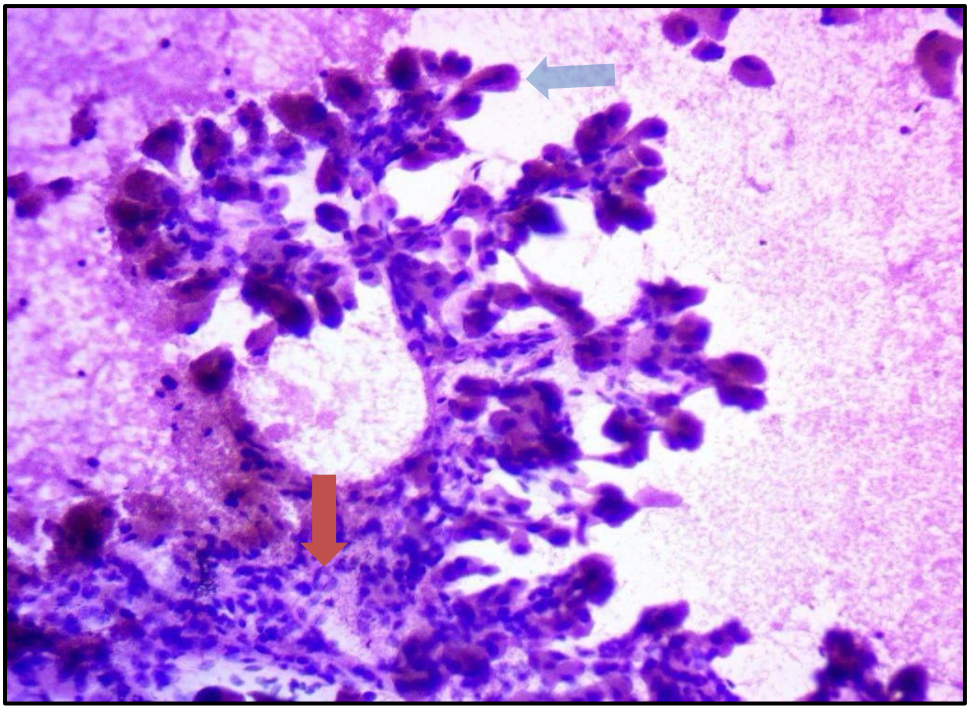

Figure 4.17: Oncocytic varant of papillary thyroid carcinoma class VI. Oncocytic cell a with abundant cytoplasm, nuclear groove, inclusion clear chromatin, blue arrow oncocytic changes, red arrow shows inclusions bodies. (H&E stain 40x).

Chapter 5: DISCUSSION

Thyroid nodules are common clinical findings, and fine-needle aspiration cytology (FNAC) remains the primary diagnostic tool for preoperative evaluation. The Bethesda System for Reporting Thyroid Cytopathology standardizes cytological interpretation and provides an evidence-based framework for estimating malignancy risk and guiding management.[6,35] In this study, the aim is to assess the association between Bethesda categories and various clinicopathological parameters, including demographic characteristics, tumor features, and histological outcomes, with the objective of evaluating its diagnostic performance and relevance in the population.

The findings of this study showed no statistically significant association between Bethesda categories and patient sex. This was consistent with the findings of Ali-Jasim G et al. (2024)[80], Najeeb DF et al. (2022) both in Iraq[81] and Ghandurah, SE. et al. (2018) in Saudi Arabia[82] all showed no statistically significant between Bethesda classification and patient's sex. Although the prevalence of thyroid nodule predominates among females, as seen in the results which showed a female-to-male ratio of approximately 5: 1 which reflect the well-established higher prevalence of thyroid nodules in women, but sex alone does not influence Bethesda categorization. The lack of statistically association with Bethesda classification in this study and previous literature confirm that this demographic characteristic is not a determinant of cytological category.

Similarly, there was no significant relationship between Bethesda classification and patient age group. the absence of a significant association between Bethesda category and age group mirrors the observation by Ali-Jasim G et al. (2024)[80], who found that age distribution does not significantly impact the probability of a nodule being assigned to a particular Bethesda class. Meanwhile, Najeeb DF et al. (2022)[81] showed a statistically significant association between Bethesda classification with age groups distribution. Although this study demonstrated higher case frequencies in the 21–40-year age range, the cytological spectrum remained broadly distributed across all age groups, suggesting that age alone was not a predictive variable for cytological severity among patients of this study. The differences between this study and previous studies[80,81] could be due to the patients of this study had a high concentration of younger patients from 20 to 40-year range, while other studies had included older patients with 50% above 40 years of age, which could influence the statistical association. The differences could also be due to sample size differences and difference in patients' characteristics and methodologies used in these studies.

No significant association was found between Bethesda category and nodule site. The lack of statistical significance with laterality of thyroid nodule is in agreement with earlier study by Najeeb DF et al. (2022) in Iraq[81] and Sengul I et al. (2020) in Brazil[83], which showed that laterality does not significantly influence cytological outcomes or malignancy risk. This reinforces the concept that pathological processes in the thyroid are not inherently side-specific, the right and left thyroid lobes share similar embryological origins, vascular

supply, and exposure to systemic hormonal influences[84], providing no inherent biological predisposition for one side to develop more severe cytological changes than the other.

Likewise, Bethesda classification was not significantly associated with tumor T-stage. The absence of a statistically significant correlation between Bethesda classification and T-stage is also in line with the work of Park H et al. (2024) in Korea[85], who found that cytological category does not necessarily reflect the pathological stage at diagnosis. Several factors could explain this, first, the Bethesda system is designed to assess the likelihood of malignancy based on cytomorphological features rather than to evaluate tumor size or extrathyroidal extension, which may could be key determinants of T-stage. As a result, a small but aggressive carcinoma and a large but indolent tumor could both fall into the same Bethesda category. Second, the preoperative cytological sample represents only a small portion of the lesion, which may not capture features related to tumor extent or invasion. Third, tumor stage is influenced by anatomic growth patterns, patient-specific factors, and the duration of disease before diagnosis, variables that are independent of cytological appearance.

In contrast, a statistically significant association was noted between Bethesda category and type of imaging used for FNA. The majority of patients of the study (more than 90%) were obtained under ultrasound guidance, and higher Bethesda categories (IV–VI) were mostly identified in this group, which could suggest a possible influence of imaging guidance on cytological yield. This is consistent with the findings of Yan C et al. (2021) in China.[86] This pattern could suggest that ultrasound guidance may enhance the cytological yield by enabling more precise targeting of suspicious areas within the nodule, particularly in lesions with heterogeneous echotexture, microcalcifications, or partially cystic composition. Ultrasound guidance could also allow for real-time visualization of the needle path, ensuring accurate sampling from solid components and avoiding cystic or necrotic areas, which can yield inadequate or misleading cytological specimens and facilitates the sampling of small, deep, or posteriorly located nodules that might otherwise be missed or under-sampled with palpation-guided techniques. This may increase the likelihood of capturing the cellular and architectural features characteristic of higher Bethesda categories.

When histological diagnosis was examined, a high statistically significant association was observed with Bethesda categories. The higher Bethesda classes (V and VI) predominantly corresponded to malignant lesions (such as papillary carcinoma), while lower Bethesda class (class II) corresponded to benign nodules (colloid and hyperplastic nodules). The findings of this study contrast with the results of Ali-Jasim G et al. (2024)[80] which showed no statistically significant association of the two. The discrepancy could be due to differences in the study population characteristics, sample size, and diagnostic practices. For example, differences in cytopathologist expertise, FNA sampling techniques, and case selection for surgery may influence the degree of concordance between cytology and histology. Additionally, the proportion of categories (III and IV) and their subsequent surgical follow-up rates could markedly impact the statistical strength of the association.

Meanwhile, the current findings are in agreement with an Egyptian study by Fawzy MM *et al.* (2021)[87], which demonstrated a statistically significant association between Bethesda category and final histopathology. The concordance observed in both this study and that of Fawzy *et al.*[87] could support the predictive validity of the Bethesda System when applied in settings where FNAs are performed with high-quality imaging guidance and reported by experienced cytopathologists.

For malignancy status, a statistically significant association was found between Bethesda classification and malignancy status. Malignant cytology was highly predictive of malignancy in this study, with Bethesda VI cases exclusively malignant. This aligns with the findings of George NA et al (2022) in India[88], Yan C et al. (2021) in China[86] and Ali-Jasim G et al. (2024) in Iraq.[80] Ali-Jasim G et al. study[80] showed no statistically significant association when comparing Bethesda categories with specific histological subtypes, but showed a statistically significant association between Bethesda category and malignancy status when histological outcomes were grouped simply as malignant versus non-malignant. This indicates that, in that study setting, the Bethesda system was effective in broadly differentiating malignant from benign disease but less reliable in predicting the exact histopathological type.

The strong association between Bethesda classification and malignancy status in this study is further reflected in the diagnostic performance of the two dichotomized Bethesda groups (II vs. IV–VI) which included only clearly benign (Bethesda II) and malignant (Bethesda IV–VI) categories, while cytological findings including (Bethesda I and III) were excluded due to their inconclusive nature and limited diagnostic definitiveness. The analysis showed a very high sensitivity of 97.3%, indicating that almost all malignant cases were correctly identified as positive cytology, and a moderate specificity of 65.2%, meaning that while most benign cases were correctly classified, a proportion were overcalled as malignant. When these findings were placed in the comparison to previous literature, this study sensitivity exceeded that reported by most previous studies, including Ali-Jasim *et al.* (2024) in Iraq (90%)[80], George NA *et al.* (2022) in India (78%)[88], Patel K *et al.* (2023) in India (70%)[89], Fawzy MM *et al.* (2021) in Egypt (77.8%)[87], Yan C *et al.* (2021) in China

(79.4%)[90], and Avior G *et al.* (2020) with (91%).[91] In contrast, the specificity in this study was comparable to that of Ali-Jasim *et al.* (64.6%)[80] and Avior G *et al.* (73%)[91], but lower than the perfect specificities reported by Patel K *et al.* and George NA *et al.* (100%)[88,89], and the higher specificities were observed by Yan C *et al.* (90.5%) and Fawzy MM *et al.* (88.9%).[87,90]

The notably higher sensitivity in this study compared to most previous studies could be attributed to several factors. First, all FNAs in this study were performed in solitary thyroid nodule, which could inherently have a higher probability of malignancy than multiple nodules, this can potentially enhance the cytologist's ability to detect suspicious features. Second, more than 90% of aspirations were performed under ultrasound guidance, which increases the likelihood of having precise targeting of the most suspicious solid components, minimizing sampling error and increasing the likelihood of identifying cytological features consistent with malignancy. Third, cytological interpretation was carried out by experienced cytopathologists in a tertiary care setting, further improving malignant case detection rates.

Conversely, the moderate specificity compared with the higher values reported by previous studies could be explained by cytological overcalling which is the tendency to classify borderline or atypical features conservatively as malignant in order to avoid false negatives. This approach could improve sensitivity but can lower specificity by increasing false-positive rates. Finally, differences sample size, and diagnostic thresholds between institutions may further account for the variability in specificity across studies.

The positive predictive value (PPV) of 81.8% in this study indicates that the majority of cytologically malignant cases were confirmed as malignant on histology, while the negative predictive value (NPV) of 93.8% underscores the strong reliability of a benign cytology result in excluding malignancy. The overall diagnostic accuracy was 85.0%, supporting the Bethesda system's robust performance in distinguishing benign from malignant solitary thyroid nodule in this cohort.

When compared with previous reports, the PPV of this study was slightly higher than that reported by Zarif H *et al.* (2018) in Saudi Arabia (79%)[82], but considerably higher than that of Ali-Jasim *et al.* (2024) in Iraq (46%).[80] The NPV was also higher than Zarif H *et al.* (84%)[82] and slightly lower than Ali-Jasim *et al.* (95%).[80] For the overall accuracy, the result (85.0%) exceeded both Zarif H *et al.* (81%) and Ali-Jasim *et al.* (71%).[80,82] These differences may be explained by variations in patient selection, with this study focusing exclusively on solitary thyroid nodule and employing ultrasound-guided FNA in more than 90% of cases, factors that likely enhanced sampling accuracy and improved both predictive values and overall diagnostic performance.

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

1. The Bethesda System demonstrated strong diagnostic performance in solitary thyroid nodules in this study, with high sensitivity (97.3%), high NPV (93.8%), and overall accuracy (85.0%).
2. A statistically significant association was observed between Bethesda category and both histological diagnosis and malignancy status, with Bethesda VI cases exclusively malignant, this emphasizes its predictive validity for identifying malignant disease.
3. No significant association was found between Bethesda category and sex, age group, laterality, or tumor T-stage.
4. Ultrasound-guided FNAs were strongly associated with higher Bethesda categories (IV–VI), which could suggest that imaging guidance enhances sampling accuracy and increases the likelihood of detecting cytological atypia.
5. This study findings support the notion that the Bethesda system is a valuable and clinically applicable tool in the evaluation of solitary thyroid nodules.

Recommendations

1. Further research with larger, multicenter cohorts should be undertaken to validate these findings, assess performance across diverse populations, and explore integration with molecular testing to improve specificity.
2. Adopt the Bethesda System as the standard cytological reporting framework in thyroid nodule evaluation, given its high diagnostic accuracy and ability to reliably exclude malignancy in benign cases.
3. Interpret Bethesda results in conjunction with clinical and imaging findings, especially in indeterminate categories (III and IV), to optimize patient management and avoid unnecessary surgeries. Encourage multidisciplinary collaboration between endocrinologists, surgeons, radiologists, and cytopathologists to ensure high-quality sample acquisition, accurate interpretation, and consistent follow-up.

ACKNOWLEDGEMENT

All praise is due to Allah for granting me the strength, patience, and perseverance to complete this work.

I would like to express my heartfelt thanks to my supervisor, Dr. Asaad Abdul-Hamza, for his valuable guidance, continuous support, and insightful comments throughout every stage of this study. His encouragement and supervision have been instrumental in bringing this work to completion.

I am also deeply grateful to the patients who were part of this study. Their cooperation and trust played a crucial role in the success of this research, and I hold their

contribution in the highest regard.

My sincere appreciation extends to everyone who offered assistance, support, or encouragement during this journey, both academically and personally. This achievement would not have been possible without the collective efforts of those around me.

REFERENCES

1. Alexander EK, Doherty GM, Barletta JA. Management of thyroid nodules. Lancet Diabetes Endocrinol, 2022; 10(7): 540–8.
2. Enny LE, Singh KR, Mishra A. Solitary Thyroid Nodule. In: Surgical Management of Thyroid and Parathyroid Diseases. Springer, 2024; 9–29.
3. Stewardson P, Eszlinger M, Paschke R. Diagnosis of endocrine disease: usefulness of genetic testing of fine-needle aspirations for diagnosis of thyroid cancer. Eur J Endocrinol, 2022; 187(3): R41–52.
4. Hassan TM, Hegazy AM, Mosaed MM, Alzahrani N, El-Enizi AT. Thyroid Nodules: Cytopathological Correlations with the Update Bethesda System 2017: Our Experience and a Systematic Review, 2021; 9(12): 1233.
5. Nguyen TPX, Truong VT, Kakudo K, Vuong HG. The diversities in thyroid cytopathology practices among Asian countries using the Bethesda system for reporting thyroid cytopathology. Gland Surg, 2020; 9(5): 1735.
6. Anand B, Ramdas A, Ambroise MM, Kumar NP. The Bethesda system for reporting thyroid cytopathology: A cytohistological study. J Thyroid Res, 2020; 2020(1): 8095378.
7. Yaprak Bayrak B, Eruyar AT. Malignancy rates for Bethesda III and IV thyroid nodules: a retrospective study of the correlation between fine-needle aspiration cytology and histopathology. BMC Endocr Disord, 2020; 20: 1–9.
8. Al-Suhaimi EA, Khan FA. Thyroid glands: Physiology and structure. In: Emerging concepts in endocrine structure and functions. Springer, 2022; page 133–60.
9. Liddy W, Bonilla-Velez J, Triponez F, Kamani D, Randolph G. Principles in thyroid surgery. In: Surgery of the Thyroid and Parathyroid Glands. Elsevier, 2021; page 272-293. e5.
10. Assi MH. Thyroid Gland Basics: A Comprehensive Review. Mustansiriya Med J., 2023; 22(2): 172–81.
11. Nair CG. Anatomy of Thyroid and Parathyroid Glands. In: Surgical Management of Thyroid and Parathyroid Diseases. Springer, 2024; page 37–65.
12. Karabaeva ME, Kozlov SV, Kolotova NA, Verkhutina MK, Kalinichenko EB. Influence of dietary supplements Iodcasein on the functional activity of the thyroid gland in lambs. In: AIP Conference Proceedings. AIP Publishing, 2023.
13. Al-Suhaimi EA, Khan FA. Thyroid glands: Physiology and structure. In: Emerging concepts in endocrine structure and functions. Springer, 2022; page 133–60.
14. Islam S. Thyroid & parathyroid histology [Internet]. Pathol, 2024 [cited 2025 Sept 3]; Available from: https: //www.pathologyoutlines.com/topic/thyroidhistology.html
15. Bhardwaj S, Yadav S. Thyroid Physiology. Endocr Surg, 2022; 2–9.
16. Hall JE, Hall ME. Guyton and Hall Textbook of Medical Physiology E-Book: Guyton and Hall Textbook of Medical Physiology E-Book. Elsevier Health Sciences, 2020.
17. Grani G, Sponziello M, Filetti S, Durante C. Thyroid nodules: diagnosis and management. Nat Rev Endocrinol, 2024; 1–14.
18. Li X, Chen Z, Wu L, Tu P, Mo Z, Xing M. Prevalence of thyroid nodule and relationship with physiological and psychosocial factors among adults in Zhejiang Province, China: a baseline survey of a cohort study. BMC Public Health, 2024; 24(1): 1854.
19. Mu C, Ming X, Tian Y, Liu Y, Yao M, Ni Y, et al. Mapping global epidemiology of thyroid nodules among general population: A systematic review and meta-analysis. Front Oncol, 2022; 12: 1029926.
20. Al-Musawi JM, Al-Shadeedi F, Shakir NA, Ibrahim SQ. Epidemiological Characteristics of Lung Cancer Patients in the Middle Euphrates Region of Iraq: Retrospective Analysis from the Middle Euphrates Cancer Center (2018-2023). Al-Rafidain J Med Sci ISSN 2789-3219, 2025; 8(2): 63–70.
21. Rehman AU, Ehsan M, Javed H, Ameer MZ, Mohsin A, Aemaz Ur Rehman M, et al. Solitary and multiple thyroid nodules as predictors of malignancy: a systematic review and meta-analysis. Thyroid Res, 2022; 15(1): 22.
22. Chooi JE, Ravindiran A, Balasubramanian SP. The influence of incidental detection of thyroid nodule on thyroid cancer risk and prognosis—A systematic review. Clin Endocrinol (Oxf), 2022; 96(2): 246–54.
23. Berinde GM, Socaciu AI, Socaciu MA, Cozma A, Rajnoveanu AG, Petre GE, et al. Thyroid cancer diagnostics related to occupational and environmental risk factors: an integrated risk assessment approach. Diagnostics 2022; 12(2): 318.
24. Romei C, Elisei R. A narrative review of genetic alterations in primary thyroid epithelial cancer. Int J Mol Sci, 2021; 22(4): 1726.
25. Kruger E, Toraih EA, Hussein MH, Shehata SA, Waheed A, Fawzy MS, et al. Thyroid carcinoma: A review for 25 years of environmental risk factors studies. Cancers, 2022; 14(24): 6172.
26. Kitahara CM, Schneider AB. Epidemiology of thyroid cancer. Cancer Epidemiol Biomarkers Prev, 2022; 31(7): 1284–97.
27. Bernet VJ, Chindris AM. Update on the evaluation of thyroid nodules. J Nucl Med, 2021; 62(Supplement 2): 13S-19S.
28. AlSaedi AH, Almalki DS, ElKady RM, ElKady R. Approach to thyroid nodules: diagnosis and treatment. Cureus, 2024; 16(1).

29. Boers T, Braak SJ, Rikken NE, Versluis M, Manohar S. Ultrasound imaging in thyroid nodule diagnosis, therapy, and follow- up: current status and future trends. J Clin Ultrasound, 2023; 51(6): 1087–100.
30. Fresilli D, David E, Pacini P, Del Gaudio G, Dolcetti V, Lucarelli GT, et al. Thyroid nodule characterization: How to assess the malignancy risk. update of the literature. Diagnostics, 2021; 11(8): 1374.
31. AlSaedi AH, Almalki DS, ElKady RM, ElKady R. Approach to thyroid nodules: diagnosis and treatment. Cureus, 2024; 16(1).
32. Ali SZ, VanderLaan PA. The Bethesda system for reporting thyroid cytopathology: definitions, criteria, and explanatory notes. Springer Nature, 2023.
33. Sengul I, Sengul D. The 2023 Bethesda system for reporting thyroid cytopathology: novi sub sole, subdivision is no more debatable, in thyroidology. Rev Assoc Médica Bras, 2023; 69(12): e20231124.
34. Suzuki A, Bychkov A. Bethesda system diagnostic categories [Internet]. Pathol. Website [cited 2025 Sept 1]; Available from: https: //www.pathologyoutlines.com/topic/thyroiddiagnostic .html.
35. Ali SZ, Baloch ZW, Cochand-Priollet B, Schmitt FC, Vielh P, VanderLaan PA. The 2023 Bethesda system for reporting thyroid cytopathology. Thyroid, 2023; 33(9): 1039–44.
36. Nie W, Zhu L, Yan P, Sun J. Thyroid nodule ultrasound accuracy in predicting thyroid malignancy based on TIRADS system. Adv Clin Exp Med, 2022; 31(6): 597–606.
37. Shi M, Nong D, Xin M, Lin L. Accuracy of ultrasound diagnosis of benign and malignant thyroid nodules: a systematic review and meta-analysis. Int J Clin Pract, 2022; 2022(1): 5056082.
38. Erkan S, Yabanoğlu H, Avci T, Gündoğdu R, Kuş M, Erkent M, et al. The necessity of fine-needle aspiration biopsy in surgical decision-making for thyroid nodules larger than 3 cm. Medicine (Baltimore), 2024; 103(51): e40373.
39. Makani AD, Nangre N, Nerlekar A. Patient Demographics and Characteristics Associated with Solitary Thyroid Nodules. Azerbaijan Pharm Pharmacother J., 2023; 22(2): 63–5.
40. Azzam EZ, Salah MA, Aboelwafa WA, Essam RM, Bondok ME, Ahmed Sr MAS, et al. Rates and Predictors of Malignancy in Bethesda III and IV Thyroid Nodules: A Prospective Study. Cureus, 2024; 16(12).
41. Cozzani F, Bettini D, Rossini M, Bonati E, Nuzzo S, Loderer T, et al. Thyroid nodules with indeterminate cytology: Association between nodule size, histopathological characteristics and clinical outcome in differentiated thyroid carcinomas—A multicenter retrospective cohort study on 761 patients. Updat Surg, 2021; 73(5): 1923–30.
42. Satturwar S, Aly Z. Thyroid follicular nodular disease [Internet]. Pathol, 2023 [cited 2025 Sept 3]; Available from: https: //www.pathologyoutlines.com/topic/thyroidnodular.html.
43. Avramidou E, Gkantaras A, Dermitzakis I, Sapalidis K, Manthou ME, Theotokis P. Histological Alterations in Hashimoto's Disease: A Case-Series Ultrastructural Study. Medicines, 2023; 10(9): 51.
44. Auger M, Callegari F, Fadda G, Hirokawa M, Rooper L. Follicular neoplasm. In: The Bethesda System for Reporting Thyroid Cytopathology: Definitions, Criteria, and Explanatory Notes. Springer, 2023; 81–95.
45. Misra S, Dhawan S, Badwal S, Sengupta A, Khosla A, Agarwal SK, et al. Evaluation of the follicular patterned thyroid lesions based on the WHO 2022 criteria with an emphasis on the grey-zone lesions. Ann Diagn Pathol, 2024; 71: 152282.
46. Asgari-Karchekani S, Ghasemi M, Tavangar M. Low risk thyroid tumors (FT-UMP) [Internet]. Pathol, 2025 [cited 2025 Sept 3]; Available from: https: //www.pathologyoutlines.com/topic/thyroidftump.html
47. Huang Y, Liu S, Wen Y. Hyalinizing trabecular tumor of the thyroid: A comprehensive review of clinicopathological features, diagnostic dilemmas, and emerging molecular insights. Ann Diagn Pathol, 2025; 152539.
48. Pusztaszeri M, Stelow E, Westra W, Zakowski M, Mastorakis E. Papillary thyroid carcinoma, subtypes, and related tumors. In: The Bethesda System for Reporting Thyroid Cytopathology: Definitions, Criteria, and Explanatory Notes. Springer, 2023; page 135–76.
49. Scappaticcio L, Trimboli P, Bellastella G, Ferrazzano P, Clery E, Cozzolino I, et al. Prediction of classical versus non classical papillary thyroid carcinoma subtypes from cytology of nodules classified according to TIRADS. Endocrine, 2024; 84(2): 560–70.
50. Halada S, Baran JA, Bauer AJ, Ricarte-Filho JC, Isaza A, Patel T, et al. Clinicopathologic characteristics of pediatric follicular variant of papillary thyroid carcinoma subtypes: a retrospective cohort study. Thyroid, 2022; 32(11): 1353–61.
51. Demir H, DAĞLAR ADAY A, Yol C, ÖZTÜRK T. Comparison of the Classical and Follicular Variants of Papillary Thyroid Carcinomas in Terms of the Clinicopathological Prognostic Parameters. Firat Tip Derg, 2024; 29(2).
52. Parvathareddy SK, Siraj AK, Qadri Z, Al- Rasheed M, Haqawi W, Siraj N, et al. Tall Cell Variant Histology Predicts Poorer Disease- Free Survival in Papillary Thyroid Carcinoma: A Propensity-Matched Cohort Study. World J Surg, 2025.
53. Samankan S, Militello L, Seo G, Everest S, O'Malley Q, Spaulding SL, et al. Tall cell variant papillary thyroid carcinoma impacts disease-free

survival at the 10% cut-point on multivariate analysis. Pathol-Res Pract, 2022; 236: 154012.
54. Higgins KE, Sadow PM, Johnson DN, Wang P, Wanjari P, Cipriani NA. Columnar cell thyroid carcinoma: a heterogeneous entity demonstrating overlap between papillary thyroid carcinoma and follicular neoplasms. Head Neck Pathol, 2024; 18(1): 39.
55. Crayton H, Wu K, Leong D, Bhimani N, Gild M, Glover A. Diffuse sclerosing variant papillary thyroid carcinoma has worse survival than classic papillary thyroid carcinoma: a meta-analysis. Endocr Relat Cancer., 2023; 30(6).
56. Cavaco D, Martins AF, Cabrera R, Vilar H, Leite V. Diffuse sclerosing variant of papillary thyroid carcinoma: outcomes of 33 cases. Eur Thyroid J., 2022; 11(1).
57. Sharma KL, Singh RB, Fidda N, Lloyd RV. Cribriform-morular variant of papillary thyroid carcinoma with poorly differentiated features: report of a case and review of the literature. Surg Exp Pathol, 2022; 5(1): 1.
58. Yang J, Yu J, Zhang Y. Cribriform-morular variant of papillary thyroid carcinoma: a case report and literature review. Chin J Med Ultrasound Electron Ed, 2022; 19(06): 597.
59. Ohashi R. Solid/Trabecular Subtype of Papillary Thyroid Carcinoma. In: Thyroid FNA Cytology: Differential Diagnoses and Pitfalls. Springer, 2024; page 377–82.
60. Zhang M, Duan HL, Wang LM, Gao W, Yao YY, Teng LH. Clinicopathological features and molecular characteristics of tall cell and hobnail variants of papillary thyroid carcinoma. Zhonghua Bing Li Xue Za Zhi, 2021; 50(11): 1234–9.
61. Sanyal K, Diwaker P, Garg N, Gogoi P. Warthin like variant of papillary thyroid carcinoma: a rare variant. Saudi J Pathol Microbiol, 2022; 7(2): 54–8.
62. Shaha AR, Tuttle RM. Active surveillance for micropapillary thyroid carcinoma: a clinical review. Gland Surg, 2023; 13(1): 100.
63. Ohori NP, Nishino M. Follicular neoplasm of thyroid revisited: current differential diagnosis and the impact of molecular testing. Adv Anat Pathol, 2023; 30(1): 11–23.
64. Basolo F, Macerola E, Poma AM, Torregrossa L. The 5th edition of WHO classification of tumors of endocrine organs: changes in the diagnosis of follicular-derived thyroid carcinoma. Endocrine, 2023; 80(3): 470–6.
65. Chen DW, Rob FI, Mukherjee R, Giordano TJ, Haymart MR, Banerjee M. Variation in the diagnosis of noninvasive follicular thyroid neoplasm with papillary-like nuclear features. J Clin Endocrinol Metab, 2022; 107(10): e4072–7.
66. Yamamoto FM, Liano LC, Camilo- Júnior DJ, Xavier- Junior JCC. Digital analyses of nuclear features can help discriminate among non- invasive follicular thyroid neoplasm with papillary- like nuclear features, papillary thyroid carcinoma follicular subtype, and follicular carcinoma in cytological specimens. Cytopathology, 2024; 35(1): 98–104.
67. Sakr M. Oncocytic (Hürthle Cell) Neoplasm: Controversy of Pathological Classification. In: Oncocytic (Hürthle Cell) Thyroid Lesions: From Diagnosis to Treatment. Springer, 2025; 83–105.
68. Matsuura D, Yuan A, Wang L, Ranganath R, Adilbay D, Harries V, et al. Follicular and Hurthle cell carcinoma: comparison of clinicopathological features and clinical outcomes. Thyroid, 2022; 32(3): 245–54.
69. Thompson LD. High grade differentiated follicular cell-derived thyroid carcinoma versus poorly differentiated thyroid carcinoma: A clinicopathologic analysis of 41 cases. Endocr Pathol, 2023; 34(2): 234–46.
70. Liu CY, Chen CC. Diagnosis of Medullary (C Cell) Thyroid Carcinoma. In: Thyroid FNA Cytology: Differential Diagnoses and Pitfalls. Springer, 2024; page 475–85.
71. Jannin A, Escande A, Al Ghuzlan A, Blanchard P, Hartl D, Chevalier B, et al. Anaplastic thyroid carcinoma: an update. Cancers, 2022; 14(4): 1061.
72. Han M, Fan F. Bethesda system for reporting thyroid cytopathology–an updated review. J Clin Transl Pathol, 2023; 3(2): 84–98.
73. Rao KN, Randolph GW, Lopez F, Zafereo M, Coca-Pelaz A, Piazza C, et al. Assessment of the risk of malignancy in Bethesda III thyroid nodules: A comprehensive review. Endocrine, 2024; 85(2): 473–92.
74. Guan W, Zheng J, Nie L, Yang J, Cui X, Miao S. Diagnostic value of BRAF V600E mutation detection in BSRTC categories Ⅰ and Ⅲ thyroid nodules. Chin J Nucl Med Mol Imaging, 2023; 166–70.
75. Gokozan HN, Dilcher TL, Alperstein SA, Qiu Y, Mostyka M, Scognamiglio T, et al. Combining molecular testing and the Bethesda category III: VI ratio for thyroid fine- needle aspirates: a quality-assurance metric for evaluating diagnostic performance in a cytopathology laboratory. Cancer Cytopathol, 2022; 130(4): 259–74.
76. Mohammad A, Khan T, Uzair M, Abbas W. Diagnostic accuracy of fine-needle aspiration cytology in thyroid and head and neck lesions: A retrospective analysis with histopathological correlation. J Med Health Sci Rev, 2025; 2(1).
77. Rahman M, Bhuyan G, Duarah B, Saikia P. Comparison of diagnostic accuracy of conventional method and Bethesda system for reporting thyroid cytopathology in the diagnosis of various lesions of the thyroid: Experience from a tertiary care center of northeastern India. Thyroid Res Pract, 2024; 20(1): 26–33.
78. Bahattin E, Emine D, Çivi ÇK, Fatih Y. Inter-and Intra-observer Reproducibility of Thyroid Fine Needle Aspiration Cytology: An investigation of Bethesda 2023 Using Immunohistochemical

BRAFV600E Antibody. J Cytol, 2024; 41(4): 221–8.
79. Di Leo G, Sardanelli F. Statistical significance: p value, 0.05 threshold, and applications to radiomics—reasons for a conservative approach. Eur Radiol Exp, 2020; 4: 1–8.
80. Ali-Jasim G, Abdulwahab-Mirza S. Histopathological study of solitary thyroid nodules in a sample of Iraqi patient. Libri Oncol Croat J Oncol, 2024; 52(1): 25–32.
81. Najeeb DF, Ali HH. The Bethesda system of reporting cytopathology of thyroid nodules in correlation with radiological and clinicopathological findings. Int J Health Sci, 2022; 6(S9): 957–67.
82. Zarif HA, Ghandurah SE, Al-Garni MA, Binmahfooz SK, Alsaywid BS, Satti MB. Thyroid nodules cytopathology applying the Bethesda system with histopathological correlation. Saudi J Med Med Sci, 2018; 6(3): 143–8.
83. Sengul I, Sengul D, Egrioglu E, Ozturk T. Laterality of the thyroid nodules, anatomic and sonographic, as an estimator of thyroid malignancy and its neoplastic nature by comparing the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) and histopathology. J BUON, 2020; 25: 6.
84. Balasubramanian SP. Anatomy of the thyroid, parathyroid, pituitary and adrenal glands. Surg Oxf, 2024; 42(4): 204–8.
85. Park H, Oh YL, Kim MK, Hahn SY, Choe JH, Chung MK, et al. Prognostic Implications of the Bethesda System in Fine-Needle Aspiration for Follicular Thyroid Carcinoma. Arch Pathol Lab Med, 2024.
86. Yan C, Luo Z, Lin Z, Xu S, Luo Y, Chen J. Value of Thyroid Imaging Reporting and Data System in Initial Bethesda Category III Thyroid Nodules. Sci Program, 2021; 2021(1): 3482111.
87. Fawzy MM, Harb D, Sheta H. Accuracy of Bethesda system in the diagnosis of thyroid nodules: Utility of combined histopathological and radiological reporting systems. Egypt J Cancer Biomed Res, 2021; 5(4): 147–58.
88. George NA, Suresh S, Jiji V, Renu S, Thomas S, Janardhan D, et al. Correlation of TIRADS and Bethesda scoring systems with final histopathology of thyroid nodules–an institutional experience. Indian J Otolaryngol Head Neck Surg, 2022; 74(Suppl 3): 5753–8.
89. Patel KA, Anandani G, Sharma BS, Parmar RA, Parmar R. Study of fine needle aspiration cytology (FNAC) of thyroid gland according to the Bethesda system. Cureus, 2023; 15(4).
90. Yan MT, Chao CT, Lin SH. Chronic kidney disease: strategies to retard progression. Int J Mol Sci, 2021; 22(18): 10084.
91. Avior G, Dagan O, Shochat I, Frenkel Y, Tessler I, Meir A, et al. Outcomes of the Bethesda system for reporting thyroid cytopathology: Real- life experience. Clin Endocrinol (Oxf), 2021; 94(3): 521–7.