"Co-relation between TI-RADS ultrasound categories and BETHESDA cytology categories of thyroid lesions."

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" CO-RELATION BETWEEN TI-RADS ULTRASOUND CATEGORIES AND BETHESDA CYTOLOGY CATEGORIES OF THYROID LESIONS"

IN SRI DEVARAJ URS MEDICAL COLLEGE, KOLAR

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LIST OF ABBREVIATIONS

1. ATA	-	American Thyroid Association
2. ATC	-	Anaplastic thyroid carcinoma
3. AUS	-	Atypia of undetermined significance
4. BFN	-	Benign follicular nodule
5. CA	-	Carcinoma
6. CCV	-	Columnar cell variant
7. CLT	-	Chronic lymphocytic thyroiditis
8. Cms	-	Centimetres
9. CMV-PTC	-	Cribriform-morular variant of papillary thyroid carcinoma
10. C/S	-	Cut surface
11. dl	-	deciliter
12. Eg	-	Example
13. FLUS	-	Follicular lesion of undetermined significance.
14. FN	-	Follicular neoplasm
15. FNA	-	Fine needle aspiration
16. FNAC	-	Fine needle aspiration cytology
17. FTC	-	Follicular thyroid carcinoma
18. FT-UMP	-	Follicular tumor of uncertain malignant potential
19. FVPTC	-	The follicular variant of papillary thyroid carcinoma
20. GD	-	Graves' disease
21. H & E	-	Haematoxylin and Eosin
22. HPE	-	Histopathological examination

23. HTT	-	Hyalinizing trabecular tumor
24. IHC	-	Immunohistochemistry
25. INCI	-	Intranuclear cytoplasmic inclusions
26. IUL		Intrauterine life
27. LBP	-	Liquid based preparation
28. LT	-	Lymphocytic thyroiditis
29. MGG	-	May Grunwald Giemsa
30. ml	-	millilitre
31. MNG	-	Multinodular goitre
32. MTC	-	Medullary thyroid carcinoma
33. N/C ratio	-	Nuclear cytoplasmic ratio
34. ND	-	Non-diagnostic
35. NG	-	Nodular goitre
36. NIFTP	-	Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
37. NOS	-	Not otherwise specified
38. NPV	-	Negative predictive value
39. PAS	-	Periodic acid-Schiff
40. PDTC	-	Poorly differentiated thyroid carcinoma
41. pg	-	picogram
42. PPV	-	Positive predictive value
43. PTC	-	Papillary thyroid carcinoma
44. RT	-	Riedel thyroiditis
45. SFM	-	Suspicious for malignancy

46. SFN	-	Suspicious of follicular neoplasm
47. SQC	-	Squamous cell carcinoma
48. SVPTC	-	Solid variant of papillary thyroid carcinoma
49. TBSRTC	-	The Bethesda System for Reporting Thyroid Cytopathology
50. TCV	-	Tall cell variant
51. TFT	-	Thyroid function test
52. TPO	-	Thyroid peroxidase
53. TRH	-	Thyrotropin-releasing hormone
54. TSH	-	Thyroid-stimulating hormone
55. US	-	Ultrasound
56. USG	-	Ultrasonography

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ABSTRACT

Thyroid nodules are common worldwide. Preoperative evaluation is very important to distinguish between benign and malignant nodules to avoid unnecessary extensive surgery as only 4 to 7 % of Thyroid nodules are clinically palpable. Ultrasound and Cytology are the two major diagnostic modalities employed for the pre-operative evaluation of Thyroid lesions routinely. US Thyroid Imaging Reporting and Data Systems (TI-RADS) have been proposed for risk stratification of thyroid nodules. Bethesda System for Reporting Thyroid Cytopathology (BSRTC) using six diagnostic categories with a stratified risk of malignancy (ROM) in each category is employed for unambigious cytology reporting of thyroid lesions.

In literature, TI-RADS has a Sensitivity of 75% and a pooled specificity of 69%. Sensitivity of BETHESDA is 72.72 %, Specificity 95.3 %, diagnostic accuracy 90.7%, negative predictive value 93.1%, positive predictive value 80%. Combination of TI-RADS and the BETHESDA system help in improving the diagnostic accuracy of thyroid lesions. This will help in accurate patient management.

The nodules are usually divided into different categories based on TI-RADS and are then referred for Fine - Needle Aspiration Cytology (FNAC) or follow - up, according to the variable risk of malignancy.

OBJECTIVES: 1) To Co-relate between TI-RADS ultrasound categories and BETHESDA cytology categories in thyroid lesions.

2) To find the diagnostic accuracy of TI-RADS and BETHESDA systems as compared with histopathological diagnosis wherever possible.

MATERIALS AND METHODS: Present study was a prospective observational study in which 107 patients were included after obtaining their consent. Ultrasound was performed on palpable thyroid nodules, and the lesions were classified ultra-sonographically based on TI-RADS classification followed by FNAC under Ultrasound guidance. Sensitivity, specificity, Positive predictive value (PPV), Negative Predictive Value (NPV), and diagnostic accuracy were calculated in 37 cases. Chi-square test was used as a test of significance. An independent t-test was used as a test of significance for identifying the mean difference. P-value <0.05 was considered as statistically significant.

RESULTS: Among all the 107 cases, the patient's age ranged from 8-70 years, and the mean age was 41.67±14.41 years. M: F ratio was 1:5. The sensitivity, specificity, positive predictive value(PPV), negative predictive value(NPV) of TI-RADS was 50%,95.24%,88.89%,71.435 with a diagnostic accuracy of 75.68% while sensitivity, specificity, positive predictive value(PPV), negative predictive value(NPV) BETHESDA was 81.25%, 85.715,81. 25%, 85.71% as compared with the Histopathological Diagnosis. Percentage (%) of the agreement was 88%, Cohen's kappa was 0.593, so there was a moderate agreement observed in both the diagnostic modalities, with p-value (<0.001) showing statistically significant

CONCLUSION: The probability of a particular nodule being malignant can be effectively inferred from the ultrasound-based TI-RADS system, with TI-RADS having a diagnostic accuracy of 75.8% and that of BETHESDA being 83.7%. Considering our results with other literature reviews, TI-RADS and TBSRTC classification systems could be considered as feasible and effective diagnostic modalities with a moderate agreement of 88 % between both. The clinicians need to implement these diagnostic tests to tailor the treatment and estimate surgery for individual patients.

KEYWORDS: TI-RADS, PPV, BETHESDA, FNAC, US-FNA

INTRODUCTION

INTRODUCTION

Among all the Endocrine glands, the thyroid gland is unique - the only one accessible to direct physical examination and the body's largest gland. Various congenital, inflammatory, Neoplastic, and Non-neoplastic conditions affect the gland manifesting as an enlarged thyroid gland.

Most of the routinely encountered clinical conditions are Iodine deficiency and colloid goitre in most parts of India with a heavy burden of endemicity, henceforth becoming a national health issue.

Thyroid Nodule

Nodules in the thyroid are very common, but only 4 to 7 % of Thyroid nodules are clinically palpable.[1] Chance of detection of thyroid nodules has increased many folds with the use of imaging techniques, particularly ultrasound ranging from 20 to 76% in the adult population occurring in up to 70% of women and 40% of men and south India, the prevalence of palpable thyroid nodules is about 23 percent.[2]

The possibility of malignancy is the major concern for evaluating thyroid nodules because the risk of malignancy varies with the nodule's nature. The evaluation method has a wide variance in the risk of malignancy between clinically and radiographically detected nodules. The average prevalence of malignancy rates across the world in thyroid nodules, as evaluated by invasive procedures, ranges from 4.0 to 6.5%.[3,4]

As it is not advisable to go for unnecessary surgical removal of every Thyroid nodule due to potential risks of thyroidectomy, a better preoperative diagnosis will help reduce unnecessary surgical interventions, especially in the benign lesions.

DIAGNOSIS-ROLE OF IMAGING and FNAC.

Thyroid Imaging Reporting and Data System (ACR-TI-RADS).

Thyroid ultrasound is a valuable tool for the evaluation of patients with thyroid nodules. According to The American Thyroid Association, a thyroid nodule is defined as "a "discrete lesion within the thyroid gland, radiologically distinct from surrounding thyroid parenchyma." Various Ultrasound features such as the shape of the nodule being taller than wide, presence of micro calcifications, hypo-echogenicity, irregular margins, clustering of lymph nodes near the lesion, and central vascularity suggest a malignant nodule. Several stratification systems for Thyroid nodules have been developed to help clinicians triage thyroid nodules with suspicion of malignancy and subject those nodules for an FNA. To name a few K-TI-RADS (the Korean Thyroid Imaging Reporting and Data System), the American Thyroid Association nodule sonographic patterns and risk of malignancy (ATA NSP), and more recently, The American College of Radiology, for this reason, a study was done by Horvath in 2009 in which he proposed an evaluation system for Thyroid nodules called TI-RADS (Thyroid Imaging Reporting and data system).

TI-RADS (Thyroid image reporting and data systems), proposed by Horvath et al.[5], is a classification system based on ultrasound features introduced to allow for a better selection of thyroid nodules undergoing FNAC thus avoiding unnecessary

procedures. This system also unifies language between radiologists and other clinicians all over the world. However, Thyroid nodules may show highly diverse ultrasound patterns, which often impairs an accurate malignancy diagnosis. In literature, TI-RADS has a Sensitivity of 75% and a pooled specificity of 69%.

ROLE OF FNAC (Fine Needle Aspiration Cytology) It is a simple, cost-efficient modality for the Thyroid nodule assessment.

BETHESDA system of reporting thyroid cytology was introduced in 2009 in which FNAC aspirates were evaluated as per the guidelines recommended by the Bethesda System for Reporting Thyroid Cytopathology (BSRTC) to avoid the use of non-specific terminologies for accurate interpretation by the clinicians, using six diagnostic categories with a stratified risk of malignancy (ROM) in each category (0-3% in the benign category to virtually 100% for the malignant category).

Bethesda category I am non-diagnostic due to the non-representative cytology sample, whereas category II is benign thyroid lesion.

Risk of malignancy increases as we move from category III to category IV and V, whereas category VI is a biopsy-proven malignancy that is more than 90% malignant. According to the 2017 Bethesda system[6], the risk of malignancy of thyroid nodules with AUS/FLUS that is category III depends on Inclusion and Exclusion of non-invasive follicular thyroid neoplasm having papillary-like nuclear features (NIFTP) in risk assessment. In cases where NIFTP is regarded as cancer, the risk of malignancy is

10% to 30%, and when it is not considered cancerous, the risk of malignancy reduces to 6% to 18%.

BSRTC category IV comprises of follicular neoplasm (FN), Hurthle cell neoplasm (HCN), suspicious for a follicular neoplasm (SFN) is a borderline result where the cytopathologist cannot differentiate benign FNs like follicular adenomas from neoplastic thyroid neoplasms like a follicular variant of papillary thyroid carcinomas (FVPTC), follicular thyroid carcinoma (FTC), and HCNs from Hurthle cell carcinoma (HCC).[6,7] The majority of patients in Bethesda category IV Thyroid nodules undergo a therapeutic lobectomy. However, suppose histopathology turns out to be malignant, with malignancy risk stratified as per the risk of malignancy. In that case, such patients undergo complete thyroidectomy with post-operative radiation.[8] However, surgery may not be needed for many of these patients because the Risk of malignancy for Bethesda category IV nodules is estimated around 10-40%.[6] Malignancy for each BETHESDA category guides the clinician for patient management, but because of the grey zone in categories III and IV, thyroid Lesions tend to be underdiagnosed, especially in these two categories.

Combination of TI-RADS and the BETHESDA system

In order to overcome the problems of over diagnosis of imaging and Under-diagnosis of Bethesda evaluation of thyroid nodules, the combined use of both these diagnostic modalities, that is Ultrasound Guided FNAC, will be of great diagnostic help in improving the diagnostic accuracy for accurate. Patient management with Thyroid lesions. Recently, a valuable addition to standardized cytology of Bethesda

category IV patients is the development of molecular markers, but their availability and access are limited, and their cost limits their use.

Numerous risk stratification systems are proposed in the past based on sonographic features for thyroid lesions. Due to the lesser degree of correlation between the ultrasound reports and FNAC results or subjective variation in the reproducibility of various classification systems proposed, a generalization about concordance between two systems is not yet produced. Various individual research groups have proposed initial interactions like the American College of Radiology (ACR TI-RADS), the European Thyroid Association (EU TI-RADS), and the Korean Society of Thyroid Radiology (K TI-RADS), none of which gain widespread use.

Literature concluded that ACR based TI-RADS classification is reliable in predicting malignancy of focal thyroid nodule and further helps segregate patients who require follow up with ultrasound or FNAC. There was a significant relationship between ACR based TI-RADS ultrasound classification system & Bethesda cytology. Only a few studies have been conducted in India on this correlation. Therefore, carrying out this study was to assess the co-relation between TI-RADS ultrasound categories and BETHESDA cytology categories in thyroid lesions to assess the concordance between two diagnostic methods used in evaluating thyroid nodules.

AIMS & OBJECTIVES

OBJECTIVES OF THE STUDY

1) To co-relate between TI-RADS ultrasound categories and BETHESDA cytology categories in thyroid lesions.
2) To find the diagnostic accuracy of TI-RADS and BETHESDA systems as compared with histopathological diagnosis wherever possible.

REVIEW OF LITERATURE

REVIEW OF LITERATURE:

The thyroid gland is positioned anteriorly in the lower part of the neck, level with the fifth cervical to the first thoracic vertebrae. It is highly vascular, red-brown, and ensheathed by the pretracheal layer of deep cervical fascia.

Physiological Functions of the Thyroid Hormones:

- Increase metabolic activity
- Promotes growth and development

  1. Effects of Thyroid Hormone on Specific Bodily Mechanisms

  Stimulation of Carbohydrate and fat Metabolism

  -Increased Requirement for Vitamins

  -Increased Basal Metabolic Rate

  -Decreased Body Weight
- Effect of Thyroid Hormones on the Cardiovascular System

  - Increased flow of blood

  -Increased Heart Rate

  -Increased Respiration
- Increases gastrointestinal motility
- Excitatory Effects on the Central Nervous System

  Important for normal reproductive function

Thyroid function test (TFT) Comprises of estimation of Total serum thyroxine (T4), normal range being: 5-12 μg/dl, Free thyroxine (FT4): 0.7-1.9 ng/dl, Free thyroxine index (FTI): 4-11, Total tri-iodothyronine (T3): 80-180 ng/dl, Free tri-iodothyronine

(FT3): 2.3-4.2 pg/ml, Thyroid-stimulating hormone: 0.5-5 mU/L and Serum reverse T3 (rT3): 10-40 ng/dl.[10]

Terminology in thyroid disorders:

Primary hyper-/hypothyroidism: An increased or decreased thyroid gland function due to the gland's disease itself and not associated with increased or decreased TSH levels or TRH.

Secondary hyper-/hypothyroidism: Increased or decreased function of the thyroid gland due to increased or decreased TSH levels.

Tertiary hypothyroidism: Decreased function of the thyroid gland due to decreased function of the hypothalamus.

Subclinical thyroid disease: A condition with the irregularity of thyroid hormone levels in the blood but without specific clinical manifestations of thyroid disease and without any history of thyroid dysfunction or therapy.

Subclinical hyperthyroidism: A condition with normal thyroid hormone levels but with low or undetectable TSH levels.

Subclinical hypothyroidism: A condition with normal thyroxine and triiodothyronine level along with mildly elevated TSH level.[10]

Thyroid Autoantibodies: are useful for the diagnosis as well as keeping track of autoimmune thyroid diseases. The various antibodies detected are anti-TSH receptor, anti-microsomal (also called antithyroid peroxidase antibody), and antithyroglobulin antibodies.

Disorders of the Thyroid Gland:

Among all the endocrine disorders, diabetes mellitus is the most common, followed by thyroid disorders.[10,11]

The thyroid gland can be classified into non-neoplastic and neoplastic.

Non-neoplastic disorders include:[8]

a) Congenital abnormalities- Such as thyroglossal duct cyst
b) Inflammatory disorders- Such as acute thyroiditis, de Quervain thyroiditis, autoimmune thyroiditis, Riedel thyroiditis, and other granulomatous inflammations
c) Hyperplastic disorders- Dyshormonogenetic goitre, Grave's disease, and nodular hyperplasia

Neoplastic disorders: Benign

a) Malignant

PREVALENCE

According to a recent study in India, the prevalence of a palpable thyroid nodule in the community is about 12.2%. However, thyroid cancer is quite rare, and the incidence is 8.7 per 100000 people per year, though this seems to be increasing over the years.

Thyroid nodules are very frequent in the general population, and their prevalence is dependent on the method used for picking the lesion with an elevated prevalence found in ultrasound (US) examination, extending from 20% to 76% in the population of adult man and woman. Non-palpable nodules detected on the US or other imaging

examinations are called "thyroid incidentalomas" or "incidentally discovered nodules".[10]

Chen Y et al[12] in 2017 found that the prevalence of thyroid nodules was 41.4%. Thyroid nodules are common; their prevalence is largely determined by the identification method. The evaluation extends from 4% to 7% by palpation alone, whereas the US catches nodules in 20% to 76% of the adult population, especially with the ongoing trend of high-resolution US techniques. The US's reported frequencies correlate with the prevalence reported at surgery and autopsy, ranging between 50% and 65%.

Table 1: Age distribution of cases in various studies

S no	Author's Name	Mean Age (in years)
1	Vargas-Uricoechea et al.[13](2017)	57
2	Huang CC et al.[14] (2017)	54.15±13.08
3	Hong MJ et al.[15] (2018)	51.2 ± 12.2
4	Regmi S et al.[16] (2018)	50.74±17.8
5	Barbosa et al.[17] (2019)	49 ± 13
6	Kapse Pratik Siddheshwar[18] (2020)	3rd-5th decade of life

In a study done by Vargas-Uricoechea et al.[13] in 2017, participants were an average age of 57 years.

Hong MJ et al.[15] in 2018 conducted a retrospective study using data from the Thyroid Imaging Reporting and Data System (TI-RADS) multicentre retrospective study including 2000 thyroid nodules (≥ 1 cm mean age, 51.2 ± 12.2 years) having a final diagnosis.

Table 2: Gender Distribution in various studies

S No.	Authors (2017)	Female: Male
1	Vargas-Uricoechea H et al.[13] (2017)	3:1
2	Hong MJ et al.[15](2018)	2.26:1
3	Regmi S et al.[16](2018)	12:1
4	Kapse Pratik Siddheshwar[18](2020)	3:1

In a study done by Vargas-Uricoechea et al.[13] in 2017 participants were mostly women 3:1 (F: M ratio). Probably this trend is based on the significantly increased frequency of autoimmune thyroid disease in females than in males, so these patients with autoimmune thyroid disease visit the physician more often, increasing the probability of detecting the nodules either through palpation or ultrasound; clinically, this situation may be defined as a "medical surveillance bias." Hong MJ et al.[15] in 2018 observed the M: F was 1:2.26 (1387 women and 613 men); Regmi S et al.[16] in 2018 was 12:1, Kapse Pratik Siddheshwar.[18] in 2020 was 3:1.

Thyroid nodules are four times more frequent in women than men with increasing frequency with age and low iodine intake.[10] Gender discrepancy is perhaps elucidated by the influential impact of both estrogen and progesterone hormone evidenced by the increase in the size of the nodule as well as new nodule development interconnected to pregnancy and multiparity.[19]

Xiaoying Ding et al.[20] in 2017 observed that the prevalence of Thyroid nodules was one-third higher in women than in men (38.5% versus 26%, respectively) aged over 45 years. This frequency was higher with advancing age, among females and in subjects with insulin resistance.

Chen Y et al.[12] in 2017 observed that the prevalence of thyroid nodules decreased with increasing Sex hormone binding globulin levels (56.5%, 54%, 51.9%, and 46.2% in men over 60 years of age and 39%, 35.5%, 34.8%, and 30.4% in men under 60 years of age; $p<0.05$ in both age subgroups).

According to a study on Androgen receptors in normal and pathological thyroids observed that if androgens are supposed to exert an antagonist role on estrogen actions also in thyroid tissue, the presence of higher nuclear AR concentration in the male rather than in the female, normal thyroid may justify the lower incidence of thyroid diseases in men. Moreover, the lower AR levels found in males and female nodular and goitrous tissues support the hypothesis that androgens may act with an antagonist mechanism on thyroid growth.

This distribution can be explained by hormonal influences, as pregnancy is related to increased size and number of nodules.[19]

Symptoms of Thyroid Nodules: Health care workers routinely find thyroid nodules by neck examinations or due to x-ray studies done for other causes and are mostly not associated with any symptoms at all. Patients undergoing a CT scan, MRI scan, or ultrasound scan, MRI scan, CT scan of the neck for some other reason (such as

trauma, carotid artery disease, parathyroid disease, or cervical spine pain) are commonly detected thyroid nodule.

Accidentally found thyroid nodules are found to carry <1% risk of cancer transformation. Unlike other x-ray studies, PET/CT scan used in screening other types of cancers is a more advanced form of X-ray imaging found to diagnose cancerous thyroid nodules in 50% of cases.[5]

The most common symptom associated with symptomatic thyroid nodules is a lump in the neck, followed by a sense of mass during swallowing.

Very rarely, pain or discomfort is another associated symptom. Valid complaints of difficulty swallowing when a nodule is large enough and placed in a form that interferes with the normal passage of food in the esophagus (lying behind the thyroid and trachea) are even quite rare.

INVESTIGATIONS IN THYROID NODULE:

Non-invasive: Ultrasonography, TFT, Antithyroid antibodies, Radionuclide imaging, CT scan, MRI

Invasive: FNAC, Thyroidectomy

INTRODUCTION OF TI-RADS AND ITS CATEGORIES.

TI-RADS

Many investigations have focused on the US characteristics of thyroid lesions as indicators of nodule malignancy. An array of authors and institutions has developed several US systems to stratify the nodules according to malignancy risk and provide a standardized language for radiologists and endocrinologists.

In 2009, Horvath[5] was the first to propose TI-RADS as a method to stratify the estimated risk of cancer in thyroid nodules and select those nodules needing to undergo FNA.

TI-RADS is formulated after the American College of Radiology's BI-RADS, a widely accepted risk stratification system for breast lesions, further modified by ACR in 2017. However, the former has not gained equal popularity in usage among radiologists. Even when classified on ultrasound, most thyroid nodules are subjected to invasive histopathological examination. The US features considered by this classification include echogenicity, micro calcifications, shape, irregular margins, peripheral halo, and presence of suspicious lymph nodes. TI-RADS includes 10 US patterns combined into categories with the increasing risk of malignancy and nodules classified as TI-RADS score 2 to 6. This classification system's rationale is that the risk of malignancy rises in parallel with the increase of suspicious US features and the lack of benign findings. A modified version of TI-RADS that predicts malignancy risks only according to the number of suspicious US features was proposed by Kwak et al. [21] in 2011. These features include solid nodules, micro lobulated or irregular margins, hypo-echogenicity microcalcifications or mixed calcification, and taller-than-wide shape.

The American TI-RADS has five different categories for nodule appearance -- composition, echogenicity, shape, margins, and echogenic foci; each of these features is associated with a score ranging from 0 to 5 points. These points in total determine the nodule's ACR TI-RADS level, which extends from TI-RADS I, benign, to TI-RADS V, high suspicion of malignancy. Vascularity and elastography scoring are not given importance in classification. TI-RADS scores 4 and 5 were considered positive

for malignancy, while scores 1–3 were considered negative for malignancy. Ultrasound features studied by Remonti Lr et al.[22] in 2015 on thyroid ultrasound and risk of carcinoma, in which 52 observational studies were included with indeterminate cytology as a distinct category, associated with malignancy having an odds ratio varying from 1.78 to 35.7 in unselected nodules. The classification is used to differentiate thyroid swellings into benign or malignant and allow for a better selection of thyroid nodules undergoing FNAC. The proposed ten ultrasound patterns and TI-RADS 2–6 for nodules.

Table 3: Distribution of TI-RADS Category with the corresponding risk of malignancy

CATEGORY	DESCRIPTION	RISK OF MALIGNANCY
TI-RADS 1	Normal thyroid gland	
TI-RADS 2	Benign conditions	0 % risk of malignancy
TI-RADS 3	Probably benign conditions	<5% risk of malignancy
TI-RADS 4-IVA	Undetermined nodules	5-10% risk of malignancy
TI-RADS 4 -IVB	Suspicious nodules	10-50 % risk of malignancy
TI-RADS 4 -IVC	Highly Suspicious nodules	50-85 % risk of malignancy. A score of 3-4
TI-RADS 5	Probably malignant nodules	>85% risk of malignancy, score of 5 or higher
TI-RADS 6	Biopsy proven malignancy	

Russ G et al.[23] in 2013 observed the Comparison of the sensitivity of TI-RADS gray-scale score, elastography, and a combination of both methods with histopathological results

Table 4: Showing the sensitivity of TI-RADS and Elastography with Histopathology

	BASED ON TI-RADS SCORE	BASED ON ELASTOGRAPHY	COMBINATION OF BOTH COMPARING WITH HISTOPATHOLOGY
SENSITIVITY	93.2	41.9	96.7

As studied by Remonti Lr et al.[22] in 2015 on thyroid ultrasound and risk of carcinoma, in which 52 observational studies were included with indeterminate cytology as a separate category, comprising of 1851 nodules, all ultrasound features were associated with malignancy with an odds ratio varying from 1.78 to 35.7 in unselected nodules

Table 5: Showing the specificity of different Ultrasound features

Ultrasound feature	**Specificity**	**Positive likelihood ratio**
Micro calcification	87.8%	3.26
Irregular margin	83.1%	2.99
Taller than wide shape	96.6%	8.07

Remonti LR et al.[22] in 2015 studied the comparison of ultrasound feature and associated risk of malignancy-risk and affirmed the following important facts on analysis of ultrasound features associated with the risk of carcinoma. The absence of elasticity was the single feature being the best diagnostic performance with a sensitivity of 87.9%, the specificity of 86.2%, and a positive likelihood ratio of 6.39.

The most specific feature for indeterminate cytology is the presence of central vascularization, with a specificity of 96% and a positive likelihood ratio of 2.138.

Table 6: Showing the distribution of cases by TI-RADS categories in various studies.

TI-RADS CAT	M Naren Satya Srinivas et al.[24](2016)	Vargas-Uricoechea et al.[13] (2017)	Periakaruppan G et al.[25] (2020)	Kapse Pratik Siddheshwar[18] (2020)
		N=180	N=184	N=50
I	0%	(0)0%	0%	0%
II	0%	(45)25.0%	0%	58%
III	0.64%	(41)22.8%	2.2%	14%
IV	4.7 to 83.33%	(62)34.4%	38.5%	16%
V	100%	(32)17.8%	77.8%	12%

M Naren Satya Srinivas et al.[24] in 2016 studied the prospective study to evaluate the reliability of thyroid imaging reporting and data system in differentiation between Benign and malignant Thyroid lesions and revealed the risk of malignancy in TI – RADS categories I and II were found to be 0%,0.64 % in category 3,4.76% in category IVA,66.67% in category IVB,83.33% in category IVC, and 100% in category. The specificity of three sonological features (completely cystic structure, hyperechogenicity, and macro calcification) in classifying a nodule as benign was 100%.

Loss of central echogenic hilum, presence of an irregular and indistinct margin, microcalcification, and necrosis was found to have the sensitivity of 100%, 63.63%, 27.27%, and 9.09%, respectively, and specificity of 95.7%, 98.5%, 100%, and 100%, respectively for a cervical lymph node to be malignant.

Mohamed Abdulaziz Al[26] conducted a retrospective analysis in 2018 between January 2012 and December 2014, using data drawn from 1188 patients (15-90 years), 1433 thyroid nodules, and fine-needle aspiration at the Prince Sultan Military Medical City, Saudi Arabia. After reviewing all the thyroid cytopathological slides and US reports, classification was done Thyroid Imaging Reporting and Data System (TI-RADS) and the Bethesda System for Reporting Thyroid Cytology by et al. on Thyroid Nodule Management: Thyroid-Stimulating Hormone, Ultrasound, and Cytological Classification System for Predicting Malignancy by Mohamed Abdulaziz et al. which revealed:

1. The percentages of malignancy-risk for each Bethesda category found in this study are similar to the values reported in the American Thyroid Association Management Guidelines and other studies.
2. The comparisons are as follows: 25% versus 9% to 32% ("nondiagnostic or unsatisfactory" category), 10.7% versus 1% to 10% ("benign and nonneoplastic" category), 18.9% versus 6% to 48% (AUS/FLUS), 70% versus 53% to 97% ("suspicious for malignancy" category), and 88.9% versus 94% to 100% ("malignant" category)

Amongst the class Bethesda IV class, the risk of malignancy was 37.5%, which bears a close similarity to the meta-analysis recently published by Bongiovanni et al.[27] in 2012, with a 14% to 34% reported value (FN/SFN). However, in many studies, the

greatest variation for malignancy risk was seen in category 4, with a higher malignancy rate (50%-67%). From the correlation performed of the TI-RADS with the final histological findings, the probability of malignancy was found for the thyroid nodules in TI-RADS category 2 to be 15.4%, whereas, for those with TI-RADS 3, it was 13.3%; it was 26.4% for TI-RADS IVA and 48.3% for TI-RADS IVB, whereas the probability of malignancy for TI-RADS 5 was 75.6%[1]

Among the classifications proposed from all over the world, Horvath et al.[5] in 2009 projected a malignancy risk of 0% in TI-RADS II, 3.4% in TI- RADS III, 10–80% in TI-RADS IV, and 87% in TI-RADS V.

Kwak et al.[21] in 2011 retrospectively examined thyroid nodules in ultrasound and FNA using five sonological criteria to proposed a TI-RADS classification. They estimated a malignancy risk of 0% for TI-RADS II,1.7% for TI-RADS III, a risk of 3.3–72.4% for TI-RADS IV and 87.5% for TI-RADS V. Another prospective study by Srinivas et al.[24] in 2016 , and it was concluded that the risk of malignancy for TI-RADS categories I, II, III, IVA, IVB, IV C, and V was 0%, 0%, 0.64%, 4.76%, 66.67%, 83.33%, and 100%, respectively.

Ricardo et al.[28] in 2017 studied intending to assess the likelihood of malignancy from ultrasound features in 1413 thyroid nodules. A score was established by attributing different weights to each ultrasound feature evaluated. Overall, the frequency of malignancy in thyroid nodules according to the categories was 1.0% for TI-RADS III, 7.8% for TI-RADS IVA, 35.3% for TI-RADS IV B, and 84.7% for TI-RADS V.

Concluding that newly proposed TI-RADS classification adequately assessed the likelihood of malignancy in thyroid nodules.

Hong HS, Lee, et al.[29] in 2019 observed that AUS/FLUS nodules' overall malignancy rate was 47.4% (324/683). There were significant differences in malignancy risk among the subclasses ($p = 0.001$). According to US patterns, K-TI-RADS categories, and ATA categories ($p < 0.001$). The malignancy rates in the K-TI-RADS categories of benign, low, intermediate, and high suspicion were 0%, 1.99%, 34.66%, and 89.00%, respectively ($p < 0.001$).

Table 7: Showing the diagnostic accuracy of Ultrasound TI-RADS in various studies.

	Ultrasound TI-RADS Diagnostic accuracy	
Author's Name (year)	Periakaruppan G et al.[25] (2018)	Rosario PW et al.[9](2014)
sensitivity	92.3%	79.4%,
specificity	94.15%	90.5%,
PPV	54.54%	71%
NPV	99.38%	93.75

FINE NEEDLE ASPIRATION CYTOLOGY

HISTORY OF FNAC

Kun (1847), Lebert (1851), and Menetrier (1886) in the nineteenth century employed the use of needles to obtain cellular material for the carcinoma diagnosis. The same technique was utilized to isolate pneumonic microorganisms by Leyden (1883)[7].

Involved in this pioneering work were a few early pathologists, and the development of FNAC along with exfoliative cytology was, to a large extent, performed by clinicians who used these convenient techniques as an aid to rapid diagnosis- known as 'professional hybrids.'

Dudgeon and Patrick, in 1927, advocated the needling of tumors as a means of prompt microscopic diagnosis.[7]

At the Memorial Hospital in the USA, Martin and Ellis at the same time used needles of a thicker caliber (18 gauge) than those frequently in use today. The cytopathologists at the Memorial Hospital continued to use the technique, but for a general interest in 'aspiration cytology' to develop in the USA, it took nearly 40 years.

The technique of FNAC flourished in Europe during the 1950s and 1960s. Zajdel in France, Soderstrom and Franzen in Sweden, and Lopes Cardozo in Holland (all clinicians/hematologists by training) became major proponents and studied thousands of cases each year. [7]

Among the first of pathologists to embrace FNAC, Zajicek, in collaboration with Franzen at Radiumhemmet of the Karolinska Hospital, an oncologic center, applied the requisite scientific rigor to dictate accurate diagnostic criteria and to estimate the diagnostic accuracy in a variety of lesions.

At Radiumhemmet, FNAC soon became accepted and integrated with the diagnostic routines, by which vast experience was gained rapidly. The pathologists and

oncologists from other countries came to study the technique, which eventually spread to the rest of Europe, Australia, America, and Asia. FNAC is now an integral part of the department of pathology.[7]

Cyto-pathologists who use fine-needle aspiration (FNA) are well aware of the association between microscopic examination expertise, diagnostic accuracy, and the significance of smear preparation quality.

Dr. M.S. Sukumaran in Madras and Dr. Subhash Kumari Gupta in the Postgraduate Institute of Medical Education and Research, Chandigarh, introduced FNA as a diagnostic tool for cytopathology in India.[7]

THYROID CYTOLOGY

The indications of Thyroid FNA are:

- Evaluation of solitary thyroid nodules (to distinguish malignant from benign)
- Evaluation of diffuse thyroid lesions (to differentiate between autoimmune/inflammatory lesions and nodular goiter)
- For obtaining material to perform ancillary tests.

CRITERIA FOR ADEQUACY

A smear with six groups of cells, seen in at least two slides, prepared from 2 needle passes.

Each group should contain at least ten cells.

Normal structures

Follicular epithelial cells have fragile pale blue or gray-blue cytoplasm with indistinct cell borders. Bare nuclei are commonly seen.

The thin colloid shows a cellophane-like coating, with folds and cracks due to the colloid's drying on the slide, which imparts a chicken wire or mosaic appearance. Thick colloid appears as round, dense globular masses of acellular material. It is dark, blue-violet-magenta with Romanowsky stains and green or orange-pink with Papanicolaou stain.[7]

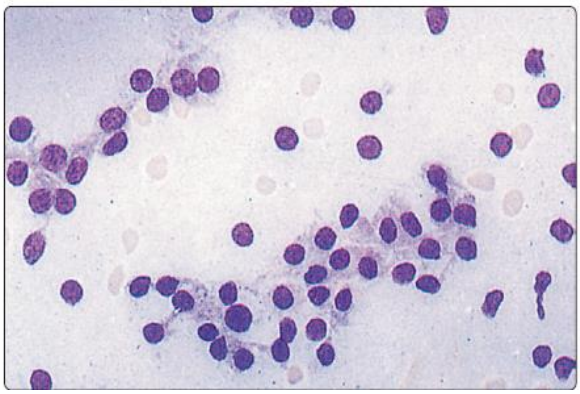


Fig 1: Normal thyroid cytology: Follicular epithelium- Uniform cells with fragile, partially disrupted cytoplasm; bare lymphocyte-like nuclei with the background showing thin colloid (May Grunwald Giemsa-MGG, 400x)[7]

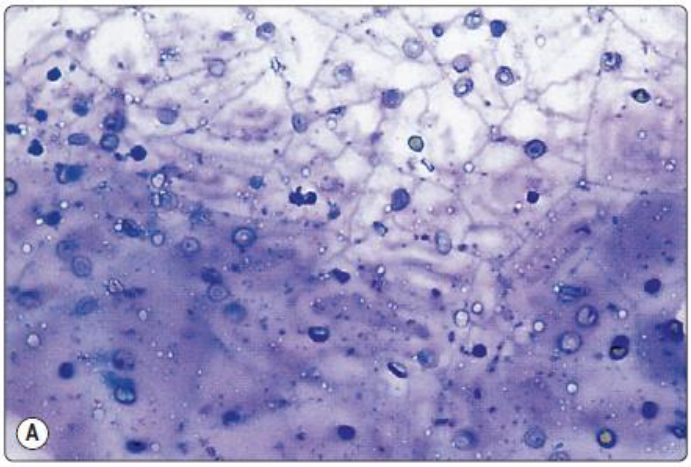


Fig 2: Thin colloid forms a varnish-like coat of homogenous material, characteristic 'crazy pavement' and cracking artifacts (MGG, 400x)[7]

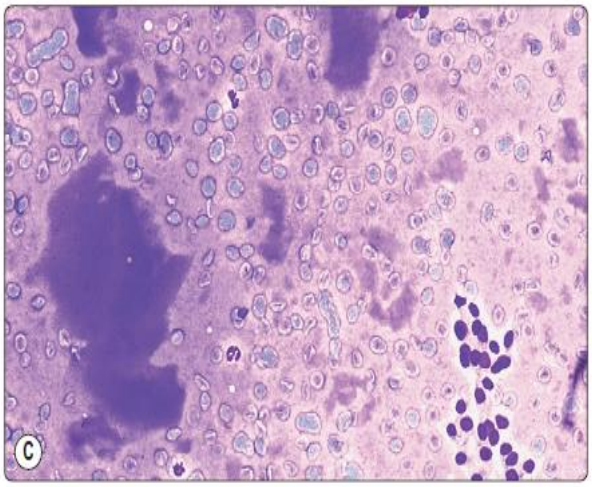


Fig 3: Thick colloid forms irregular dense clumps of material; homogeneous and violet (MGG, 400x)[7]

Complications

- Hemorrhage caused by needling can cause airway compression. Carotid hematoma is an uncommon complication.
- Occasionally, acute suppurative thyroiditis, transient vocal cord paralysis, acute transient goiter, and chemical neuritis have been noted.
- Puncture of the trachea can occur during needling, which causes coughing.
- Scans should be done before performing FNA, as needling can convert a hot nodule into a cold one and vice versa.
- Infarction following FNA is an uncommon complication.
- Granulation tissue of organizing hematoma or necrosis can mimic angiomatous tumors or sarcoma.
- Fibrosis, calcification, papillary hyperplasia, cholesterol clefts, vascular thrombosis, and capsular distortion simulating invasion are other worrisome histological features that rarely follow needling.
- Changes are proportional to the number of needle passes and the size of the needle used.

Silverman JF et al.[30] in 1986 proposed that FNAC can be used as an initial modality in evaluating palpable thyroid nodules, with a sensitivity of 93% and specificity of 95%. Well-trained pathologists can become skilled in evaluating the FNA without significant loss in accuracy and hence, provide a definite diagnosis in most cases.

Studies by Lee et al. (1987), Palombini et al. (1988), Layfield et al. (1989), and Ljung et al. (2001)[7] have stated that quality training in obtaining and preparing the smears play an important role in the efficiency of the FNA procedure.[7]

Frable WJ[33] in 1989 studied that needles of smaller gauge (25G) were more profitable thyroid nodules aspiration. It was stated that colloid, amyloid, and fire flares are better visualized in MGG stain, whereas psammoma bodies, oncocytes, and nuclear features were better appreciated in Papanicolaou stain.

Based on the materials and methods of the Karolinska Hospital, Harach HR et al.[34] in 1989 classified the follicular lesions in thyroid FNA into type I (benign), type II (atypical benign), and type III (suspicious). A rise in the surgical resection of thyroid carcinomas after FNA was reported, suggesting that FNAC of the thyroid can be used as a means for accurate diagnosis.

Hall T et al.[35] in 1989 stated that all the cases with a false negative diagnosis were ascribed to the missed sampling of inadequate smears. FNA's adequate smears showed a sensitivity of 100% in diagnosing malignant tumors, reaffirming its role as the first-line screening modality for thyroid nodules.

Burch HB et al.[36] in 1996 stated that FNA has pioneered in determining the management of thyroid nodules to conclude that the high sensitivity, specificity, and diagnostic accuracy of FNA for detecting malignant tumors has singly overshadowed other diagnostic modalities. He observed that FNA's efficiency depends on several factors, including the aspirator's experience and skillful cytological interpretation.

Zeppa P et al.[37] in 2000 stated that FNA should evaluate all the palpable nodules within the same gland because the existence of a thyroid lesion increases the risk of a 2nd pathologic process in the same gland.

In a study done by Avinash et al.[38] in 2016 , after cytological evaluation/HPE, 6 (8.57%) of the 70 nodules turned out to be malignant, and 59 (91.43%) were benign. Seventeen nodules that were given as follicular neoplasms on FNAC were diagnosed with follicular adenomas at histopathology. All the malignant nodules on FNAC turned out to be papillary carcinoma and anaplastic carcinoma

In a study done by Gautam HK et al.[39] in 2018 on FNAC, 61% of patients had colloid nodules, 17% were follicular neoplasm, and 10% were adenomatous hyperplasia, 6% of patients were hyperplastic multinodular goiter, and 4% had lymphocytic thyroiditis. Two had malignant lesions, which included 1% papillary carcinoma and 1% anaplastic carcinoma. According to the Conventional system of reporting, the cytological diagnosis was categorized into the following groups.[6]

Inadequate:

When smears contain <6 groups of thyroid follicular cells on each of at least two slides or show the only hemorrhage.

Colloid cysts:

Presence of thick or thin colloid, hemosiderin-laden histiocytes, and occasional follicular cells.

Thyroglossal cyst:

A mucinous aspirate showing anucleate, keratinized squamous cells, a few of which are metaplastic. Few ciliated columnar cells can also be seen. The background shows inflammatory infiltrate and amorphous debris.

Colloid goiter:

Smears show abundant thin and thick colloid with follicular cells arranged in monolayered sheets, clusters, and singles. Oxyphilic, involutional and hyperplastic cells can be seen with fragile cytoplasm and many bare nuclei.

Autoimmune thyroiditis (Hashimoto's thyroiditis/lymphocytic thyroiditis) Smears show impingement of follicular cells by lymphoid cells. The background shows lymphoid cells, plasma cells, and lymphohistiocytic aggregates. Askanazy cells, giant cells, and epithelioid cells are also noted. Graves' disease (Primary hyperplasia) Smears are marked to moderately cellular in a colloid-free hemorrhagic background. Follicular cells are arranged in monolayered sheets, with vacuolated cytoplasm and fire flares.

Atypical:

Smears containing cellular material having features that are neither benign nor are diagnostic of malignancy.

Follicular lesion/Neoplasm: -

Smears are marked to moderately cellular with a predominant micro follicular pattern in a colloid-free bloody background. Syncytial groups, rosettes, and equal-sized cell clusters are also noted.

Suspicious for malignancy:

Smears show some but not all features of malignancy.

Malignant lesions

a) Papillary Thyroid Carcinoma

Smears are cellular and show aggregates of cells with a distinct anatomical border, nuclear crowding, and overlapping.

Papillary tissue fragments with a fibrovascular core.

Ovoid, enlarged, pale nuclei, with finely granular, powdery chromatin

Intranuclear cytoplasmic inclusions(INCI), nuclear grooves, chewing gum colloid

Squamoid metaplastic cells

Psammoma bodies, giant cells

Debris and macrophages (suggestive of cystic degeneration),

b) Medullary Carcinoma

Cellular smears, with cells arranged in singles predominantly, showing plasmacytoid, small cell, and spindle cell variants.

Stippled nuclear chromatin, with occasional cells showing coarse red (MGG) cytoplasmic granules

Binucleation and multinucleation are common

Amorphous amyloid is seen in the background

c) Anaplastic Carcinoma

Pleomorphic malignant cells seen in a necrotic background Bizarre giant cells, multinucleation, or spindle/squamoid cells are also seen. Abnormal mitoses are commonly noted.

d) Poorly differentiated thyroid carcinoma

Hypercellular smears, showing cells arranged in singles, solid, trabecular, and insular pattern.

High N: C ratio and nuclear crowding is seen

e) Lymphoma

f) Metastatic Carcinoma

Tabaqchali et al.[40] in 2000 carried out a study comprising of 302 FNAC, of which unsatisfactory samples on initial aspiration constituted 43.1%, and on repeated aspiration constituted 32.2%. Sensitivity and specificity of 86.8% and 67% were obtained, respectively, which concluded that better pre-operative thyroid nodule assessment requires the triad of clinical examination, cytology, and imaging investigations.[40]

Sclabas et al.[41] in 2003 stated that among the 100 indeterminate FNAs, carcinoma was found in 11 (15%) of 73 follicular neoplasms, 2 (20%) of 10 Hurthle cell neoplasms, and 14 (82%) of 17 suspicious for papillary carcinoma.

A study by Garg et al.[42] in 2009 on 434 patients displayed that the most frequent thyroid lesion was colloid goiter in 250 (57.60%) cases, followed by thyroiditis in 119 (27.41%) cases, 10 (2.30%) adenomatous goiters, and 2 cases (0.004%) of thyroglossal cysts. 14 (1.38%) cases were reported as follicular neoplasms(FN) and 17(3.91%) as malignant tumors. This study was found to have a sensitivity, specificity, the positive and negative predictive value of 97%, 100%, 96%, and 100%, respectively, and concluded that FNAC aids in distinguishing lesions that require surgery from those that can be managed conservatively.

Haberal et al.[43] conducted a study on 271 patients with thyroid lesions in 2009, in which 218 (83.8%) constituted females and 42 (16.2%) constituted male patients, with a median age of 46.86 years. There were six (2.3%) false-negative cases due to an occult papillary microcarcinoma not sampled during FNA.

Kapse Pratik Siddheshwar[18] in 2020 found that Adenomatoid nodule, colloid nodule, follicular carcinoma, papillary carcinoma, and hurtle cell neoplasm of thyroid contributed 12%, 58%, 8%, 20%, and 2%, respectively. Most of the nodules fall under the TI-RADS II classification, accounting for 58% of the total nodules detected on ultrasound. he malignancy risk was 0% for TI-RADS I and TI-RADS II in our study, while the risk of cancer for TI-RADS III, TI-RADS IV, and TI-RADS V were 14.3%, 62.5%, and 100%, respectively A standardized reporting system was lacking for

thyroid FNA. The Papanicolaou Society of Cytopathology, The Royal College of Physician-British Thyroid Association, and The American Association of Clinical Endocrinologists had laid down diagnostic guidelines, none of which were universally accepted.

The National Cancer Institute in the United States hosted the State of the Science Consensus Conference on Thyroid FNAC on October 22 and 23 in 2007 in Bethesda, Maryland, to address the terminologies and other issues related to thyroid FNA.

INTRODUCTION OF BETHESDA AND ITS CATEGORIES.

The Bethesda System for Reporting Thyroid Cytopathology: diagnostic categories According to this system, the cytological diagnosis was categorized into the following six categories:[6,44]

The Bethesda system of thyroid cytopathology (TBSRTC) established a standardized, Category –based system for thyroid fine-needle aspiration cytology reporting.

(TBSRTC) classifies in categories and their risk of malignancy for

I— Non Diagnostic or unsatisfactory:

- Cyst fluid only
- Virtually acellular specimen
- Other (clotting artifact, obscuring blood).

II—benign, indeterminate

- Consisting of a benign follicular nodule (includes colloid nodule, adenomatoid nodule)

- Consistent with Hashimoto(lymphocytic) thyroiditis in the proper clinical context.
- Consistent with subacute (granulomatous) thyroiditis
- Others

III —Follicular lesion of undetermined significance (FLUS)/ atypia of undetermined significance (AUS)

- As per the Bethesda system guidelines, aspirates that were considered adequate had some atypia features but could not be categorized definitely into either of the benign, SFN, SM, or Malignancy categories were grouped under this category.

IV—follicular neoplasm (FN)/suspicious for follicular neoplasm (SFN),

- Aspirates with cytomorphologic features of moderate to high cellularity, scant or absent colloid, with a predominantly micro follicular or trabecular configuration of follicular cells, were grouped under this category.
- Specify if Hurthle cell (oncocytic) type.

V—suspicious for malignancy (SM)

- Suspicious for papillary carcinoma
- Suspicious for medullary carcinoma
- Suspicious for metastatic carcinoma
- Suspicious for lymphoma
- Other

VI—malignant

- Papillary Thyroid carcinoma
- Medullary thyroid carcinoma
- Poorly differentiated carcinoma
- Undifferentiated (anaplastic) carcinoma
- Squamous cell carcinoma
- Carcinoma having mixed characteristics (specify)
- Metastatic carcinoma
- Non-Hodgkin lymphoma

Table 8: The Bethesda System used for Reporting Thyroid Cytopathology: Risk of Malignancy [6,44]

Category	Description	Risk of malignancy in %
1) No diagnostic or unsatisfactory	Cyst fluid only, Virtually acellular specimen Others (obscuring blood, clotting artifact, drying artefact).	Nil
2) Benign	Consistent with a benign follicular nodule (includes adenomatoid nodules, colloid nodule) consistent with chronic lymphocytic (Hashimoto thyroiditis). In the proper clinical context consistent with granulomatous (subacute) thyroiditis.	0-3 % risk of malignancy
3) Atypia of undetermined	It includes follicular lesions of undetermined significance.	5-15 % risk of malignancy

significance		
4) Follicular neoplasm or suspicious for follicular neoplasm	Specify if oncocytic hurthle cell type	15-30 % risk of malignancy
5) Suspicious for malignancy	Suspicious for papillary thyroid carcinoma, suspicious for medullary thyroid carcinoma, suspicious for metastatic carcinoma, suspicious for lymphoma.	60-75% risk of malignancy
6) Malignant	Papillary thyroid carcinoma, poorly differentiated carcinoma, Medullary thyroid carcinoma, undifferentiated (anaplastic) carcinoma, squamous cell carcinoma, carcinoma with mixed features, Metastatic malignancy, Non-Hodgkin's lymphoma.	>90%

- Malignancy risk in Category 1- ND is 5-10%, for which repeat FNA with ultrasound guidance is recommended.
- Malignancy risk in Category 2- Benign is 0-3%, for which clinical and sonographic follow-up is advised.
- In Category 3-AUS/FLUS, the risk of malignancy is 10-30%, for which the recommended management is repeat FNA, molecular testing, or lobectomy.
- In Category 4-FN/SFN, the risk of malignancy is 25-40%. The management recommended is molecular testing or lobectomy.
- In Category 5-SFM, the risk of malignancy is 50-75%.

- In Category 6-Malignancy, the risk of malignancy is 97-99%.
- The recommended management for both Category 5 and 6 is near-total thyroidectomy or lobectomy.
- A study by Theohari's et al.[45] in 2009 on 3207 thyroid FNAs using TBSRTC showed: 11.1% unsatisfactory, 73.8% benign, 3.0% Atypia of Undetermined Significance(AUS), 5.5% FN, 1.3% suspicious, and 5.2% malignant, of which 378 (15%) underwent surgery. All six diagnostic categories showed excellent concordance in this study and histology in determining benign or malignant nodules.[43]

NON-DIAGNOSTIC (ND)/UNSATISFACTORY

The quality and quantity of the cellular and colloid components determine the FNA of thyroid nodules' adequacy.

Proficient FNA technique along with excellent slide preparation, processing, and staining constitutes high quality of reporting.

Criteria for Adequacy

A minimum of 6 clusters of well-visualized (unobstructed, well stained, and undistorted) thyroid follicular cells, with at least ten cells per cluster, preferably on a single slide.

Exceptions to this requirement, where a minimum number of thyroid follicular cells are not required are:

1. Cytologic atypia present in solid nodules.

2. Solid nodules showing inflammation- lymphocytic thyroiditis, granulomatous thyroiditis, or thyroid abscess can show only numerous inflammatory cells. These cases are designated as benign and not ND.
3. Colloid nodules- The presence of abundant colloid is considered benign and satisfactory for examination

Examples of cases regarded as Non-diagnostic:

1. Smears with lesser than 6 clusters of well-stained and well-preserved thyroid follicular cells with at least ten cells in each cluster.
2. Significantly obscured, poorly prepared, or poorly stained follicular cells
3. Presence of cyst fluid, with or without histiocytes, and lesser than 6 clusters with ten follicular cells in each.

BENIGN

FNA's most frequently sampled lesion is nodular goiter (NG), and the most routinely encountered form of thyroiditis is chronic lymphocytic or Hashimoto thyroiditis.

Benign follicular nodule (BFN)

The most frequently encountered entity in thyroid FNAC is Benign follicular nodule and comprises the following: nodular goitre (NG), hyperplastic (adenomatoid) nodules, colloid nodules, Graves' disease, and thyroiditis.

Definition:

Smears satisfying the criteria for adequacy comprising of benign follicular cells and colloid in varying proportions.

Criteria

- Gross examination of colloid shows a viscous, shiny, gold, or light yellow fluid (which resembles varnish or honey).
- Smears are moderately cellular and show follicular cells arranged prominently in monolayered sheets in which the cells are evenly spaced ("honeycomb-like pattern").
- Few follicular cells can also be arranged in intact, three-dimensional spheres/balls and microtissue fragments.
- The nuclei are round to oval, 7–10 microns in diameter, with finely granular chromatin.
- There is minimal nuclear crowding and overlapping. There is no significant nuclear membrane irregularity or nuclear pallor.
- Micro follicles may also be noted, but it comprises a minority of the cells.
- Occasionally, papillary hyperplasia and oncocytic cells can be seen.
- Green-black granules in the cytoplasm may be seen, which represent hemosiderin pigment or lipofuscin.
- Follicular cells can appear shrunken and degenerated in the presence of abundant colloid.
- Hemosiderin laden macrophages are commonly encountered.

Thyroglossal duct cyst

- Thyroglossal cyst must be taken into account in the category of differentials of cystic thyroid lesions when an FNA yields inflammatory cells, proteinaceous material, and occasional degenerated ciliated columnar or squamous cells.

- The patient presents with anterior midline swelling of the neck, usually above the thyroid and below the hyoid bone.

Black thyroid

- Patients on chronic treatment with antibiotics of the tetracycline group (e.g., minocycline) for acne conditions develop benign pigmentation of thyroid follicular cells.
- The abundant dark brown pigment is noted in the cytoplasm, which is darker than hemosiderin, and plausibly represents a form of melanin.

Amyloid goiter

- A rare entity associated with primary and secondary amyloidosis results in a diffuse/bilateral enlargement of the thyroid gland. Clinical features include symptoms of compression such as dyspnea, dysphagia, and hoarseness of voice.
- FNA shows abundant pink amorphous material that appears morphologically similar to colloid, but embedded fibroblasts help distinguish it from colloid goiter. Medullary thyroid carcinoma also shows amyloid deposits.

Graves' disease (GD)

- GD is most commonly seen in middle-aged women who present with hyperthyroidism. It is an autoimmune diffuse hyperplastic thyroid disorder. Aspirates are cellular, showing a variable number of follicular cells and abundant colloid.

- Follicular cells are arranged in clusters and sheets, showing abundant foamy cytoplasm.
- Nuclei are vesicular, enlarged with prominent nucleoli.
- Marginal cytoplasmic vacuoles with red to frayed pink edges known as "flame cells" are noted. Lymphocytes and hurthle cells may be seen occasionally in the background.

Lymphocytic Thyroiditis

Background:

- Lymphocytic thyroiditis (LT) includes chronic lymphocytic (Hashimoto) thyroiditis, focal lymphocytic (silent) thyroiditis, and subacute lymphocytic thyroiditis (postpartum and silent thyroiditis).
- Hashimoto thyroiditis is the most routinely found form of lymphocytic thyroiditis, which frequently affects middle-aged women but is also noted in children and adolescents.

Definition

Cytology comprises benign thyroid follicular cells along with polymorphic lymphoid cells and/or hurthle cells.

Criteria

- Frequently hyper cellular smears are seen, but dilution with blood or advanced fibrosis may reduce the cellularity.

- Oncocytic cells are seen in sheets or singles and show a large nucleus with prominent nucleoli and abundant granular cytoplasm. Anisonucleosis of these cells may be prominent, and features such as nuclear clearing and grooves can be seen.
- Polymorphous lymphoid cells are noted, comprising small mature lymphocytes, occasional plasma cells, and larger reactive lymphoid cells. These cells can be seen infiltrating epithelial cell groups or may be present in the background.
- Lymphohistiocytic aggregates and intact lymphoid follicles may also be seen.

Granulomatous (de Quervain) Thyroiditis

De Quervain thyroiditis is caused by a viral infection and is self-limited.

Criteria

- The early stage of the disease shows many eosinophils and neutrophils.
- Granulomas with numerous giant cells are noted.
- In the later stages, reduction in the cellular yield.
- Inflammatory infiltrates, and Multinucleated giant cells are absent in the involutional stage.

Acute Thyroiditis

It is an uncommon condition that is seen in immunosuppressed individuals.

Criteria

- Acute inflammatory infiltrate is noted along with fibrin, macrophages, and necrosis.

- The colloid is scant/absent.
- The background may show fungal or bacterial organisms.

Riedel Thyroiditis(RT)/Disease

The rarest form of thyroiditis is characterized by progressive fibrosis of the thyroid gland.

Criteria

- Smear consists of bland spindle cells and collagen strands with scant chronic inflammatory cells.
- Follicular cells and colloid are generally absent.

Atypia of Undetermined Significance(AUS)/ Follicular Lesion of Undetermined Significance (FLUS)

Definition

Specimens that comprise cells (follicular, lymphoid, or other) with cytologic and/or architectural atypia, insufficient to be categorized as suspicious for a follicular neoplasm, suspicious for malignancy, or malignant. The atypia is more marked and cannot be categorized in benign lesions. A provisional goal was made to limit the reporting of AUS/FLUS to 7%.

Criteria:

1. Cytologic atypia

(a) Focal cytologic atypia:

- The majority of the follicular cells appear benign, but occasional cells show irregular nuclear contours, pale chromatin, and nuclear enlargement.
- Intranuclear cytoplasmic inclusions (INCI) are absent.
- A hypo cellular smear with such cells is also diagnosed under this group.

(b) Extensive but mild cytologic atypia:

- Numerous cells show slightly pale chromatin, limited nuclear membrane irregularity, and mildly enlarged nuclei.
- Intranuclear cytoplasmic inclusions are absent.

(c) Atypical cyst-lining cells:

- Atypia (Presence of nuclear grooves, prominent nucleoli, elongated nuclei and cytoplasm, and/or occasional INCI) of cyst lining cells is categorized as AUS/FLUS.

(d) "Histiocytoid" cells-

- Aspirates from cystic papillary thyroid carcinoma(PTC) characteristically show histiocytoid cells.
- These cells are larger than histiocytes, with rounder nuclei, a higher N/C ratio, and glassier appearing cytoplasm, without the presence of hemosiderin of histiocytes, though larger, discrete vacuoles are present.

2. Architectural atypia

(a) A hypocellular specimen with scant colloid and occasional follicular cell clusters, predominantly in micro follicles or crowded three-dimensional clusters. A diagnosis FLUS/AUS is required concerning sampling limitation of a lesion that would designate an FN/SFN diagnosis if the specimen were more cellular.

(b) Smears with minimal nuclear atypia and focally prominent micro follicles - A predominant population of micro follicles can occur in a markedly or moderately cellular sample but is insufficient for a diagnosis of FN/SFN.

3. Cytologic and architectural atypia-

Smears showing both architectural and mild cytologic atypia are commonly seen in NIFTP.

4. Hürthle cell aspirates

(a) Hypo cellular smear with scant colloid, and composed exclusively of hurthle cells.

(b) Smears that are markedly to moderately cellular, comprised exclusively of hurthle cells, but the clinical plot suggests a benign hurthle cell nodule, as in lymphocytic thyroiditis or MNG.

5. Atypia, not otherwise specified (NOS)

Prominent nucleoli and nuclear enlargement is noted in occasional follicular cells.

6.Atypical lymphoid cells, rule out lymphoma

Presence of atypical lymphoid cells, the degree of atypia being inadequate to be classified as suspicious for malignancy.

Follicular Neoplasm(FN)/Suspicious for a Follicular Neoplasm(SFN)

Definition

Smears show predominant repetitive micro follicles, along with cell crowding. Hypo cellular smears with these features must be classified as AUS/FLUS. Classification of Smears with nuclear features of PTC must be done as suspicious for malignancy or malignant.

Criteria

- Smears are markedly or moderately cellular.
- Colloid is absent or minimal.
- Architectural atypia in the form of prominent micro follicles and cell crowding is noted.
- Nuclei are slightly hyperchromatic and round.
- Occasional nuclear atypia may be noted in nuclear membrane irregularity, enlarged nuclei, and prominent nucleoli.

Follicular Neoplasm, Hurthle Cell (Oncocytic) Type/Suspicious for a Follicular Neoplasm, Hurthle Cell (Oncocytic) Type

Definition

Smears show a cellular aspirate which comprises exclusively or almost exclusively of the cellular yield of oncocytic cells.

Criteria

- Exclusive hurthle cell population in singles or syncytial like pattern.
- Cells show abundant, finely granular cytoplasm.
- The nucleus is round, enlarged, eccentrically, or centrally placed, showing prominent nucleolus.
- Frequent binucleation
- Absent or minimal colloid.
- Intracytoplasmic "colloid" inclusions
- Small-cell dysplasia- Small cells with a high N: C ratio.
- Large-cell dysplasia- Large cells showing at least twice the variation in nuclear size.

Suspicious for Malignancy(SFM)

Definition

Smears show features that are suspicious of malignancy but are insufficient for a definite diagnosis. The atypical features are such that malignancy is considered more likely than not.

Criteria

A) Suspicious for Papillary Thyroid Carcinoma

1) Pattern A (Patchy Nuclear Changes pattern)

- The sample is markedly or moderately cellular.
- Follicular cells are admixed with cells that show nuclear contour irregularity, nuclear molding, enlargement, pallor, and grooves.

- INCI is absent or scant. Papillary architecture and psammoma bodies are absent.

2) Pattern B (Incomplete Nuclear Changes Pattern)

- Cells show mild-to-moderate nuclear enlargement with mild nuclear pallor.
- Nuclear grooves are seen.
- INCIs, nuclear molding, and membrane irregularity are minimal or absent.
- Papillary architecture and psammoma bodies are absent.

3) Pattern C (Sparsely Cellular Specimen Pattern)

- Hypocellular smear with many features of PTC.

4) Pattern D (Cystic Degeneration Pattern)

- Smears show hemosiderin-laden macrophages. Occasional atypical, histiocytoid cells with abundant vacuolated cytoplasm and enlarged nuclei are seen.
- Follicular cells show pale, enlarged nuclei and occasional grooves.
- INCIs are absent or few.
- Papillary architecture and psammoma bodies are absent.

B) Suspicious for Medullary Thyroid Carcinoma

- Smears are of moderate or scant cellularity.
- The monomorphic population of medium or small-sized cells with a high N: C ratio is noted.
- Eccentrically located nuclei with fragments of amorphous material.

- The material is inadequate to confirm a diagnosis of MTC by immunohistochemical (IHC) studies

C) Suspicious for Lymphoma

- Hypo cellular smear with atypical lymphoid cells, or,
- Cellular smear with monomorphic, intermediate to small-sized lymphoid cells.
- The material is inadequate for IHC or flow cytometry for a confirmatory diagnosis of lymphoma.

D) Suspicious for Malignancy (Not Otherwise Specified)

Comprises of thyroid malignancies like poorly differentiated carcinoma, anaplastic carcinoma, and metastases. Hypo cellular smears lead to uncertainty and result in SFM diagnosis.

Malignant

Conventional (Classic) Papillary Thyroid Carcinoma

Definition

A thyroid follicular epithelium-derived malignant tumor that shows nuclear alterations and papillary configuration.

Criteria

- Tumor cells arranged in monolayered sheets and papillae
- "Cartwheel" or "onion-skin" patterns - Cellular swirls
- Oval, enlarged, molded, crowded nuclei with membrane irregularities, thick nuclear membranes, and longitudinal nuclear grooves

- INCIs, nuclei being pale having powdery chromatin and marginally placed micro nucleoli
- Psammoma bodies and stringy, ropy, or bubble-gum colloid
- Multinucleated giant cells
- Oncocytic and squamoid metaplasia
- "Histiocytoid" cells

Cytological Features More Frequent in LBP:

Convoluted nuclei with eosinophilic nucleoli and perinuclear halo

Tall cells Collagenous stroma, naked capillaries, and intercellular spaces

Cytological Features Less Frequent in LBP:

Pale nuclei and papillary pattern

Variants of PTC:

A). Follicular Variant and NIFTP

Definition

FVPTC (Follicular variant of PTC) shows PTC's nuclear features and a predominant pattern composed of medium to small-sized follicles.

Non-invasive follicular thyroid neoplasm having papillary-like nuclear features (NIFTP) is a well-demarcated or encapsulated neoplasm with nuclear features of PTC and tumor cells predominantly follicular pattern, without vascular or capsular invasion.

Criteria

- Hypercellular smears containing micro follicles or rosettes.
- Colloid appears thick and is densely stained.
- Nuclear changes are subtle when compared to classic PTC.
- The following features are inconspicuous: papillary fragments, psammoma bodies, multinucleated giant cells, INCIs, and cystic change.

B) Macro follicular Variant

Definition

More than 50% of tumor cells are arranged as macro follicles (measuring >200microns in diameter).

Criteria

- Monolayered sheets of neoplastic epithelium and variably sized follicles with nuclear features of PTC.
- Psammoma bodies and papillary structures are absent.
- Abundant thin or thick colloid.

C) Cystic Variant

Definition

Smears show histiocytes, hyper-vacuolated tumor cells, and abundant thin, watery fluid.

Criteria

- Cells are arranged in clusters with irregular borders showing nuclear changes of PTC.
- Hyper vacuolated cells, called histiocytoid cells, are seen.
- Hemosiderin laden macrophages

- A thin colloid is present.
- Fine, powdery chromatin is inconspicuous.

D). Oncocytic Variant

Definition

Smears show predominantly oncocytic tumor cells with nuclear features of PTC.

Criteria

- Smears show polygonal cells in shape with plenty of granular cytoplasm-oncocytes, arranged in sheets, papillae, micro follicles, or in singles with PTC nuclear features.
- Lymphocytes are scant or absent.

E) Warthin-Like Variant

It is a circumscribed tumor with lymphoid follicles that resembles a Warthin tumor of the parotid gland. It arises in the background of Hashimoto thyroiditis.

Criteria

- Tumor cells show nuclear features of PTC
- Oncocytic cells are seen in singles and papillary pattern
- The background shows lymphoplasmacytic infiltrate, with the plasma cells and lymphocytes intimately associated with tumor cells and seen permeating the fibro vascular stalk.

F) Tall Cell Variant(TCV)

Definition

An aggressive form of PTC displayed classical nuclear changes and comprised predominantly of "tall" cells (their height is at least three times their width) with abundant dense granular cytoplasm.

Criteria

- Tumor cells display PTC nuclear features and are polygonal with centrally placed nuclei but can be cylindrical and elongated with an eccentrically located nucleus called "tadpole cells" or "tail-like cells."
- Few lymphocytes can be seen.

In contrast to conventional PTC:

• The nuclear chromatin is more granular and less powdery

• Prominent centrally placed nucleoli

• Presence of mitotic figures

• Few psammoma bodies

• Multiple INCIs within one nucleus, giving a "soap-bubble" appearance.

G) Columnar Cell Variant(CCV)

Definition

Smears show columnar cells with oval, hyperchromatic, pseudostratified nuclei and sub nuclear/supranuclear and cytoplasmic vacuoles, resembling secretory-type endometrium or colonic adenoma

Criteria

- Cellular smears displaying nuclear features of PTC and which lack colloid.
- Tumor cells are arranged in sheets, clusters, and papillae.

- Nuclei are pseudostratified, elongated with focal cytoplasmic vacuolization.

In contrast to conventional PTC:

• Grooves, INCIs are less prominent. • Nucleus is hyperchromatic rather than pale and powdery • Cystic change is not seen.

H) Solid Variant

Definition

Smears show solid areas that occupy at least 50% of tumors with typical nuclear features of PTC.

Criteria

- Variably cellular smears showing the typical nuclear features of PTC and lacking colloid.
- Tumor cells are seen in three-dimensional syncytial fragments, trabeculae, micro follicles, or singles.
- Papillary configuration with the fibro vascular core is absent or scant.

I) Diffuse Sclerosing Variant

Definition

There is diffuse involvement of one or both lobes of the thyroid gland, prominent lymphovascular invasion, marked lymphocytic infiltration, many psammoma bodies, squamous metaplasia, and extensive fibrosis.

Criteria

- Smears are marked to moderately cellular with absent or scant colloid.
- Tumor cells are seen in three-dimensional ball-like clusters, admixed with inflammatory cells, but monolayered and papillary configuration can also be seen.
- Cells are round, columnar, or polygonal, with well-defined cytoplasmic margins. Also noted are hobnail cells protruding from cell groups.

In contrast to conventional PTC:

• There is less nuclear pallor, INCIs, and grooves (<50% of cases). • Large septate or unilocular cytoplasmic vacuoles are frequently seen. • Squamous metaplasia, lymphocytes, and psammoma bodies are noted.

J) Cribriform-Morular Variant

The cribriform-morular variant of PTC (CMV-PTC) shows solid and cribriform architecture lacking colloid. Few nuclei within the squamoid morules show a peculiar nuclear clearing caused due to the accumulation of biotin.

Criteria

- Hypercellular smears showing a papillary configuration of tall, columnar tumor cells with eddy formation-morules.
- The cribriform pattern is noted, showing round to oval slit-like spaces formed by ovoid to spindle cells within cell groups.
- Focally, thickened nuclear membranes, pale nuclei, and grooves are seen
- The background shows spindle-shaped tumor cells, hyaline material, and hemosiderin laden macrophages.
- Colloid, multinucleated giant cells, and psammoma bodies are absent.

K) Hobnail Variant

The hobnail cells must be present in >30% of tumor cells.

Criteria

- Smears show cells in the papillary pattern or clusters with eccentric nuclei and tapering cytoplasm, “tear drop-like” or “comet-like” cells, showing loss of polarity. Nuclear features of PTC are present.
- Multiple INCIs, giving a soap-bubble appearance, is seen.
-

L) Medullary Thyroid Carcinoma

Definition

Malignant thyroid neoplasm with Neuroendocrine differentiation derived from the C cells or Para follicular cells.

Criteria

- Smears with marked or moderate cellularity, with cells arranged in syncytium-like clusters or singles.
- Cells are polygonal, round, plasmacytoid, or spindle-shaped.
- Cells show mild to moderate pleomorphism and long cell processes.
- Nuclei are round to oval, eccentrically placed, with “salt and pepper” chromatin.
- Amorphous amyloid deposition is noted.
- Occasional bizarre giant cells, binucleation, and multinucleation are common.
- INCIs are occasionally seen.
- In a few cases, small red-purple granules are seen with Romanowsky stains.
- Rarely, cytoplasmic melanin pigment can be noted.
- Fine cytoplasmic vacuolization is prominent in LBP.

Table 9: Variants of Medullary Thyroid Carcinoma (MTC)[31]

MTC variant	Differential diagnosis
Amphicrine (mucin and calcitonin-producing cells)	Secretory carcinoma, metastatic adenocarcinoma
Clear cell	Renal cell carcinoma, follicular neoplasm with clear cells
Follicular/tubular	Follicular neoplasm
Giant cell	Undifferentiated (anaplastic) thyroid carcinoma (UTC)
Melanin-producing/pigmented	Melanoma
Mixed follicular and medullary	Follicular neoplasm
Oncocytic (oxyphilic)	Oncocytic variants of follicular neoplasm and PTC
Papillary/pseudopapillary	Papillary thyroid carcinoma (PTC)
Paraganglioma-like	Paraganglioma, hyalinizing trabecular tumor
Small cell/neuroblastoma-like	Small-cell carcinoma of the lung, lymphoma
Spindle cell	Sarcoma, UTC
Squamous	Squamous-cell carcinoma, UTC, PTC with squamous differentiation/metaplasia

M) Poorly Differentiated Thyroid Carcinoma (PDTC)

Definition

The classic form of PDTC is the insular type, characterized by "cellular nests" outlined by thin fibro vascular septa.

Criteria

- Smears show cells in a solid, insular, or trabecular pattern with scant colloid.
- Uniform malignant follicular cells with scant cytoplasm are seen, with a high N/C ratio and variable nuclear atypicality.
- Mitosis, necrosis, and apoptosis are noted.

N) Undifferentiated (anaplastic) thyroid carcinoma (UTC)

Definition

UTC is a pleomorphic, high-grade epithelial malignancy with epithelioid or spindle-shaped cytologic features.

Criteria

- Smears are markedly to moderately cellular.
- Tumor cells are seen in clusters and singles.
- Cells are epithelioid, plasmacytoid, rhabdoid, or spindle-shaped and vary in size from giant to small-sized.
- Nuclei are markedly pleomorphic, with prominent nucleoli, INCIs, clumping of chromatin with Para chromatin clearing, and multinucleation.
- Mitosis (usually abnormal), necrosis, and dense inflammation comprise predominantly neutrophils, which are also seen as infiltrating tumor cell cytoplasm.
- Non-neoplastic osteoclast-like giant cells are also noted.

O) Squamous Cell Carcinoma(SCC) of the Thyroid

Definition

Malignant thyroid tumor exclusively showing squamous differentiation.

Criteria

- Smears show pleomorphic, keratinized squamous cells.
- Necrosis can be noted.

P) Metastatic Tumors, Lymphomas, and Rare Tumors of the Thyroid Metastatic Renal Cell Carcinoma.

Criteria

- Smears are hemorrhagic and are marked to moderately cellular.
- Cells are arranged in small clusters, papillae, sheets, or singles.
- Cells show abundant pale, clear, or vacuolated cytoplasm.

- Nuclei are round to oval, with prominent nucleoli.

Q) Metastatic Malignant Melanoma

Criteria

- Smears are markedly to moderately cellular.
- Cells are in singles, show variation in size, shape, and include spindle-shaped, plasmacytoid, and anaplastic types.
- Nuclei are large, eccentrically placed, and may show INCIs.
- Intracytoplasmic melanin pigment is uncommonly seen.
- IHC shows positivity for S-100, SOX-10, HMB45, and melanA.

R) Metastatic Breast Carcinomas

Criteria

- Smears are marked to moderately cellular, showing a uniform population of polygonal or oval cells present in singles or clusters.
- IHC shows positivity for estrogen and progesterone receptors, mammaglobin, GATA- 3 and are negative for PAX-8, TTF-1, and thyroglobulin.

S) Metastatic Pulmonary Carcinomas

Criteria

1) Non-small Cell Carcinomas

- Cells are arranged in clusters and singles.
- Large cells having plenty of cytoplasms are noted, with prominent nucleoli.

2) Small Cell Carcinomas

- Small cells having scant cytoplasm are seen in clusters and singles.
- Elongated to oval nuclei, nuclear molding and finely granular chromatin is seen.
- Necrosis and mitosis is frequent.

Lymphoma Involving the Thyroid Gland

Criteria

- Markedly cellular smears comprised of round to oval cells in singles.
- Nuclei have small nucleoli and vesicular chromatin.
- The background shows lymphoglandular bodies
- Cells of marginal zone lymphoma are two times the size of a small mature lymphocyte.
- Diffuse large B-cell lymphomas show cells with moderate to abundant basophilic cytoplasm.

Ali S. Z[7], in an article 'Bethesda and Beyond' in 2010 , stated that even though the majority of thyroid lesions turn out to be benign, a small percentage of carcinomas need to be accurately diagnosed for timely and optimal surgical treatment. TBSRTC has elaborate and well-founded management algorithms with a risk of malignancy in each of the six categories. The worrisome category of 'indeterminate' has led to discovering molecular markers, such as BRAF, which have displayed promising potential in recently published articles. Following the TBSRTC monogram, in 2009, the American Thyroid Association revised its clinical management guidelines for thyroid nodules.[46]

Crippa et al.[47] in 2010 stated that TBSRTC represents a major move toward reproducibility, standardization, enhanced clinical significance, and concluded that borderline lesions of the thyroid required a multidisciplinary approach.

Arul P et al.[48] in 2015 total of 603 thyroid FNAC results were retrieved retrospectively between July 2012 and January 2015 and reclassified according to TBSRTC. Of these, 392 cases had a histopathological follow-up. The FNACs results were compared to the histopathological diagnoses, and the malignancy rates of each diagnostic categories of TBSRTC were calculated. Of the 603 FNACs, nondiagnostic were 16 (2.7%), benign were 393 (65.2%), Follicular lesion of undetermined significance /atypia of undetermined significance (FLUS/AUS) were 60 (10%), follicular neoplasm/suspicious for a follicular neoplasm (FN/SFN) were 64 (10.6%), suspicious for malignancy (SM) were 32 (5.3%), and malignant were 38 (6.3%). In 392 cases, there was follow-up histopathology with the malignancy rate for non-diagnostic, benign, AUS/FLUS, FN/SFN, SM, and malignant categories were 0%, 0.8%, 24.4%, 28.9%, 70.8%, and 100%, respectively.

Hong MJ et al.[15] in 2018 proved that overall, an increase in the size of the nodule is not associated with malignancy. The malignancy rate had no association with nodule size ($p = 0.467$) in high suspicion nodules, whereas there was a trend toward an increasing malignancy risk in intermediate to low risk nodules as the nodule size increased ($p = 0.004$ and 0.002, respectively). The malignancy rate was higher in large nodules (≥ 3 cm) than that of small nodules (< 3 cm) (40.3% vs. 22.6%, respectively; $p = 0.001$) in intermediate-sized nodules and low-suspicion nodules (11.3% vs. 7.0%, respectively; $p = 0.035$). As the nodule size increased, there was a

trend toward a declining risk and proportion of papillary carcinoma and an increased risk and portion of follicular carcinoma and other malignant tumors

Out of 528 cases in a study by Naz et al.[49] in 2014, 403 cases were diagnosed as Bethesda category II, 67 were Bethesda III, while 22 cases were classified under Bethesda V and VI. Specimen for histopathology was available in 61 cases. For Bethesda categories V and VI, the concordance rate was 100%, while for Bethesda 2, 5 out of 45 cases turned out to be malignant. Sensitivity, specificity, and accuracy of FNAC were 64.3%, 85.1%, and 80.3%, respectively, in TBSRTC.

Mehra et al.[50] in 2015 stated that the BETHESDA monograph was written in an easy-to-read format, concise, and had useful color photomicrographs that helped make the diagnosis. The physicians were also benefitted because of the management guidelines it provides.

A study by Mamatha et al.[51] in 2015 on 240 patients showed a sensitivity, specificity, PPV, and NPV of 77%, 69%, 37%, and 93% respectively in the Conventional system, whereas in TBSRTC, the sensitivity, specificity, PPV and NPV were 100%, 82.5%, 45%, and 100% respectively. It was summarized that interobserver variability was lowered by utilization of TBSRTC.

A study by Gupta et al.[52] in 2016 reported that the diagnostic accuracy was overall higher in TBSRTC and stated that it has a superior edge over the Conventional System and should be incorporated in routine reporting of thyroid FNAC.

In a study done by Rossi M et al.[53] in 2016 showed that out of 460 nodules (269 Bethesda class III and 191 Bethesda IV), 344 were operated on a surgical group, and 116 followed-up conservatively (follow-up group). According to the Bethesda System for Reporting Thyroid Cytopathology, class III was divided into four subcategories based on cytomorphological features (III-1, III-2, III-3, III-4). The clinical risk was defined based on histological, cytological, and ultrasound data. In Bethesda System for Reporting Thyroid Cytopathology class III, malignancy risk was higher vs. Bethesda System for Reporting Thyroid Cytopathology class IV (34.4 vs. 26.2%; $p<0.01$). Papillary thyroid carcinoma was the Most frequently found amongst the malignant lesion. Significant nodule growth occurred in 13.7 % of nodules, belonging mostly to Bethesda class III and Bethesda class IV. The overall clinical risk was higher in Bethesda Cytopathology III-1, III-4, and IV classes. They propose differential management of Bethesda Cytopathology III and IV classes and related subcategories: surgery may be indicated in Bethesda System for Reporting Thyroid Cytopathology class III-1, III-4, and IV; a conservative follow-up avoiding repeated FNAB may be appropriated in class III-3, while repeated FNAB may be useful in class III-2.

In a study done by Anand B et al.[54] on 646 cases in 2020, it was found that out of 646 cases, 75.9% were benign, of which 34.7% were nodular goiter. Scant cellularity contributed with 7.8% of the non-diagnostic category. The distribution of cases in various TBSRTC categories is as follows: I—non-diagnostic 13.8%, II—Benign 75.9%, III—Atypia of undetermined significance (AUS)/Follicular Lesion of Undetermined significance (FLUS) 1.2%, IV—follicular neoplasm (FN)/suspicious for follicular neoplasm (SFN) 3.7%, V—suspicious for malignancy (SM) 2.6%, and VI—malignant 2.8%.

The diagnostic values (sensitivity, specificity, positive predictive value, negative predictive value, and Diagnostic accuracy) and malignancy risk for FNAs using the Bethesda system were calculated for surgical follow-up cases. The total of 99 cases was divided into two groups. One group comprised of Bethesda categories II and III, in which surgery is not recommended due to low risk of malignancy, and the other group consisted of Bethesda categories IV, V, and VI for which surgery is recommended due to high malignancy risk. The Sensitivity, Specificity, Positive predictive value, negative predictive value, and Diagnostic accuracy hence obtained are 72.4%, 94.3%, 84%, 89.2%, and 87.9%, respectively.

Table 10: Showing Distribution of cases by the Bethesda system in various studies

	BETHESDA Category	Vargas-Uricoechea et al.[13] (2017)	Periakaruppan G et al.[25](2018)	Kapse Pratik Siddheshwar[18] (2020)
Benign	Number of cases	N=180	N=184	N=50
	I	(0)0%	8.70%	0%
	II	(65)36.1%	83.15%	72%
	III	(39)21.7%	1.09%	4%
Malignant	IV	(41)22.8%	2.72%	12%
	V	(35)19.4%	3.26%	8%
	VI	0%	1.09%	4%
	Total	100%	100%	100%

The nodules classified as Bethesda I, II, and III were considered benign, and those nodules classified as Bethesda IV-VI were considered malignant.

Table 11: Percentage of Benign and Malignant cases in FNAC (BETHESDA) in various studies.

S no.	Author name (year)	
(BETHESDA)	Regmi S et al. (2018)[16]	Garg Shivani et al. (2017)[42]
Benign lesion	68.5%	83.3%
Malignant	7.4%	16.7%

Shivani Garg et al.[42] in 2017 evaluated Thyroid nodules on FNAC that is category III Patients (Follicular lesions of undetermined significance/ atypia of undetermined significance) were analyzed retrospectively over a two-year period in which a total of 1169 thyroid FNAs were done over two years in which 76 were diagnosed as category 3. Among all AUS/FLUS nodules with follow-up, malignancy was confirmed in 16.7%, whereas with nodules triaged to surgery only, the malignancy rate was 33.3%.

Regmi S et al.[16] in 2018 conducted a prospective study that evaluated a total of 54 patients with thyroid lesions presenting to Otorhinolaryngology, Surgery, and Internal Medicine out-patient departments of a tertiary hospital for nine months,the results of which on FNAC showed 68.5% were benign lesions, whereas 7.4% were malignant. Follicular Neoplasm (FN) or Suspicious for FN and Suspicious for Malignancy comprised 5.6% each. 1.9% of the lesions showed Atypia of Unknown Significance (AUS). 11.1% of the lesions were non-diagnostic or unsatisfactory for evaluation. Follicular Neoplasm (FN) or Suspicious for FN and Suspicious for Malignancy 5.6% each. 1.9% of the lesions showed AUS. 11.1% were nondiagnostic or unsatisfactory for evaluation.

TYPE OF LESION

Barbosa et al.[17] in 2019 observed that the Seventy-four (52.9%) of the 140 nodules were diagnosed as histologically benign (42 cases of nodular hyperplasia, 31 cases of follicular adenomas, and 1 case of non-invasive follicular thyroid neoplasm with papillary like features [NIFTP]). The 66 (47.1%) nodules that were malignant included 44 papillary thyroid cancers (PTC), 12 follicular-variant papillary thyroid cancers (FVPTC), 1 Warthin-like papillary carcinoma of the thyroid, four medullary thyroid cancers, four follicular thyroid carcinomas, and one poorly differentiated thyroid carcinoma.

Reddy P et al.[6] in 2018 studied all the thyroid cytology cases received between November 2012 to April 2014 and classified them according to the Bethesda system. Out of 484 cases studied, 432 (89.2%) were benign lesions, 20 (4.1%) were malignant,18 (3.7%) were Unsatisfactory/Nondiagnostic, 10 (2%) were Follicular neoplasm/Suspicious for neoplasm, 3 (0.6%) were suspicious for malignancy, and 1 (0.002%) case was reported as Atypia of undetermined significance.

A retrospective study of 140 thyroid nodules Conducted by Barbosa et al.[17] in 2019 in which 139 patients referred for ultrasound-guided (FNAC) from January 2012 to June 2016 having indeterminate cytological results (44 Bethesda III, 52 Bethesda IV, and 44 Bethesda V) were evaluated.

Comparison between the TI-RADS Categories and Bethesda System

In a study done by Vargas-Uricoechea et al.[13] in 2017 participants mostly belonged to women, with a mean age of 57. The frequency in the BETHESDA II category was

65/180 versus 45/180 in TI-RADS II. The highest frequency was found in category 4-IV 62/180 for TI-RADS 4 versus 41/180 for BETHESDA IV. Among the category 2-II classification, the highest concordance was found. The TI-RADS criteria have a good concordance with the Bethesda system. The concordance between the TI-RADS ultrasound criteria and the BETHESDA cytology criteria on the nontoxic thyroid nodule was the highest among the category 2-II classification with an observed agreement of 87.2% a linear weighted kappa of 0.69 (95% CI: 0.59-0.79). A trend towards the higher weighted kappa value in nodules ≥4 cm was seen in males and individuals aged ≥50 years on heterogenetic analysis with accelerated nodular growth, vocal folds' paralysis, extrathyroidal extension, a history of head and neck radiation therapy, and urban origin.

Ashraf M et al.[55] in 2018 included 100 patients suffering from thyroid swelling. Patients underwent ultrasound assessment using TI-RADS and FNAC biopsy using TBSRTC, and then, all patients underwent thyroidectomy operation. Specimens were sent to a laboratory for histological examination. The results of TI-RADS categories were compared with the Bethesda categories; both results matched the final histology reports. The overall concordance rate between US TI-RADS and TBSRTC is 67.6%. (82% in benign cases, 70.9% in indeterminate cases, 50% in malignant cases).

Table 12: Percentage of agreement between TI-RADS and BETHESDA in various studies.

S no.	Author Name (year)	Agreement (%)
1	Vargas-Uricoechea et al.[13] (2017)	87.2%
2	Regmi S et al.[16] (2018)	77.77%
3	Ashraf M[55](2018)	67.6%

Regmi S et al.[16] in 2018 conducted a prospective study that evaluated a total of 54 patients with thyroid lesions presenting to Otorhinolaryngology, Surgery, and Internal Medicine out-patient departments of a tertiary hospital for nine months. Overall agreement between the cases by USG and FNA using the TI-RADS and TBSRTC respectively was 77.77%. There was a substantial agreement between the diagnosis made by these systems, kappa (κ)= .633 (95% CI, 0.41 to 0.85, $p<0.05$). It was concluded in this study observed a substantial agreement between the diagnosis made by TI-RADS on USG and TBSRTC on FNA. This study advocates the stratification of thyroid lesions according to TI-RADS so that only suspicious lesions undergo FNA.

A retrospective study was conducted by Barbosa et al.[47] on a cohort of 139 thyroid nodules from January 2012 to January 2016 belonging to the category of Indeterminate cytological results with the distribution of cases as follows: -

BETHESDA III-44

BETHESDA IV-52

BETHESDA V-44

Pre FNAC images and histological results after surgery were available in all these cases. Blinded to the cytological and histological diagnosis, each nodule was

classified according to the ACR TI-RADS classification recommended by the 2015 American thyroid association guidelines, and the Ultrasound patterns were given. The risk of malignancy was calculated for TI-RADS, BETHESDA, and their combination.74 cases were found to be histologically benign on analysis of 140 Indeterminate thyroid nodules. The malignancy rate was different in Category III, IV, V, increasing according to the Ultrasound suspicion categories in TI-RADS ($p<0.001$).

BETHESDA class III thyroid nodules and the lowest risk in Ultrasound that is TI-RADS category II, III, IVA exhibited a sensitivity of 95.3% for both the classifications and Negative predictive value of (NPV) of 94.3% and 94.1%, respectively. TI-RADS category V showed a high suspicion associated with an odds ratio of 14.7 and 9.8, respectively.

Periakaruppan G et al.[25] in 2020 studied the thyroid nodules using high-resolution ultrasound in the Indian population to correlate the TI-RADS and Bethesda system for reporting thyroid cytopathology. 184 patients were studied in this prospective over two years (April 2015–April 2017). Patients with thyroid nodules in B-mode ultrasound are scheduled to get fine-needle aspiration cytology (FNAC). Bethesda classification of these nodules is tabulated in the follow-up period simultaneously. Out of the 117 TI-RADS 2 nodules, none turned out to be Bethesda IV or higher, which means none of these nodules turned out to be malignant. The risk of malignancy percentage in this study is similar to those values obtained in other prominent studies. It was concluded that the probability of a particular nodule being malignant can be effectively inferred from the ultrasound-based TI-RADS system

with a certain level of confidence. On considering results and other literature reviews, it can be safely assumed that FNAC can be deferred in patients with TI-RADS 2 nodules, contributing to most newly detected cases. In their experience, there is a remarkable correlation exists between TI-RADS ultrasound classification and Bethesda cytology, especially for benign nodules.

Hernando Vargas-Uricoechea et al.[13] in 2017 studied that ultrasounds have a low efficacy to differentiate between benign and malignant thyroid lesions. Several benign and malignant features on Ultrasound and Doppler features like TI-RADS put the risk stratification of thyroid nodules forwards. Nodules are divided into different categories based on TI-RADS and were then subjected to FNA biopsy or follow-up according to variable malignancy risk. A total of 180 subjects underwent these two diagnostic tests, and the comparison of results was made using the kappa index.

(1) Frequency of Bethesda 2 was 65/180 versus 45/180 in TI-RADS 2

(2) In contrast, the highest frequency in category four is 62/180 for TI- RADS 4 and 41/180 for Bethesda 4.

(3) Among the category two classification, the highest concordance was found Ashraf M at al[55] in 2018 included 100 patients suffering from thyroid swelling. Patients underwent ultrasound assessment using TI-RADS and FNAC biopsy using TBSRTC, and then, all patients underwent thyroidectomy operation. The overall concordance rate of results of TI-RADS versus FNAC with the final PO pathological results for predicting malignancy were (75.4%, 81.8%)with a sensitivity of (76.9 %, 81.8%) and specificity of (91.3%,98%), positive predictive values were (PPV) (71.4%, 90%), and negative predictive values were (NPV) (76.4%, 96%), respectively. It was concluded

that TI-RADS and TBSRTC classification systems could be considered feasible and effective diagnostic modalities for predicting malignant lesions in patients with thyroid nodules. The clinicians need to implement these diagnostic tests to improve their clinical performance and surgical outcomes.

Stephanie A Fish[49] in 2019 observed that ACR-TI-RADS is best to stratify and evaluate Thyroid nodules. For each Ultrasound feature, ACR TI-RADS has a point system, and the sum of these points explains the risk of Malignancy. In contrast to ACR TI-RADS, the other systems depend on pattern recognition. Hence ACR-TI-RADS needs to be applied accurately and more universally. Although there is quite a possibility of clinical challenges due to interobserver variability in interpretation, the radiologists' intensive training with ACR TI-RADS can provide the most accurate results and proper care for patients with thyroid nodules. Combination of ultrasound (US) thyroid imaging reporting and data system (TI-RADS) and a new US scoring system for diagnosing thyroid nodules (thyroid nodules) with indeterminate results (Bethesda categories III, IV, and V).

He YP et al.[56] in 2017 studied to investigate the diagnostic performance of the combination of ultrasound (US) thyroid imaging reporting and data system (TI-RADS) and a new US scoring system for diagnosis of thyroid nodules (thyroid nodules) with indeterminate results (Bethesda categories III, IV, and V) on fine-needle aspiration (FNA) cytology. In this study, 453 cytologically indeterminate thyroid nodules were studied. Multivariate analyses were performed to construct the scoring system. The TI-RADS diagnostic performance and also of the combined method were evaluated and compared. Multivariate analyses revealed that marked hypoechogenicity, shape being taller than wide, and absence of halo sign were independent predictors for malignancy in cytologically indeterminate thyroid nodules.

Scoring system was thereafter defined as follows: risk score (RS) = 3.2 x (if marked hypoechogenicity) + 2.8 x (if taller than wide shape) + 1.3 x (if absence of halo sign). Compared with TI-RADS alone, the receiver operating characteristic curves (AUC) area showed a specificity, accuracy, and positive predictive value (PPV) of the combined method increased significantly with 0.731 versus 0.569, 48.5% versus 14.1%, 76.2% versus 62.3%, and 70.9% versus 59.9%, respectively (all $P < 0.05$). The combination of TI-RADS and the new US scoring system showed superior diagnostic performances in predicting malignant thyroid nodules with indeterminate FNA cytology results in comparison with TI-RADS alone.

HISTOPATHOLOGY OF THYROID LESIONS.[31]

COLLOID GOITRE

Macroscopy

The gland is enlarged with a distorted shape and stretched intact capsule. Cut surface shows multiple nodules, with a few surrounded by a partial or complete capsule. Secondary changes such as calcification, hemorrhage, and cystic degeneration are common.

Microscopy

Few nodules comprise huge follicles lined by flattened epithelium, whereas others are hyperplastic or show Hurthle cells. Sanderson pollsters and projections of papillae into the lumen are also noted.

THYROGLOSSAL DUCT CYST

Microscopy

The lining of the cyst is the pseudostratified ciliated or squamous epithelium. Thyroid follicles and mucous glands are seen in the adjacent stroma. Secondary inflammation is common, as a result of which the epithelium may be partially absent, and the stroma can show inflammatory infiltrate.

LYMPHOCYTIC THYROIDITIS

Macroscopy

The gland is diffuse, solid, white, with a vague nodular cut surface.

Microscopy

Lymphoid follicles having germinal centers scattered in the interstitium. The follicles appear normal, but some may show atrophy or oncocytic change.

FOLLICULAR ADENOMA

Macroscopy

An encapsulated solitary, oval, or round nodule, usually measuring 1-3 cm, is seen. The cut surface shows a homogeneous grey, white, or brown, fleshy tumor.

Microscopy

Tumors show a fibrous capsule, with cytological and architectural features different from those of the surrounding parenchyma. Architectural growth patterns seen are macro follicular, normo-follicular, micro follicular, solid, and trabecular. Vascular and capsular invasion is absent.

HYALINIZING TRABECULAR TUMOR(HTT)

Macroscopy

Solid, well-circumscribed, oval or round neoplasm ranging from 0.5 to 7.5 cm. Cut surface shows a lobulated, yellow/white mass.

Microscopy

Tumors are comprised of wide trabeculae or small nests surrounded by thin stromal bundles - Zellballen pattern. Abundant, hyaline, eosinophilic, amorphous material is noted within the trabeculae or seen enveloping tumor cells.

OTHER ENCAPSULATED FOLLICULAR-PATTERNED THYROID TUMORS

2017 WHO classification: recommended nomenclature for encapsulated follicular-patterned tumors based on the presence or absence of nuclear features of PTC and vascular or capsular invasion.[31]

Table 13: Encapsulated follicular-patterned thyroid tumors.[31]

		Capsular or vascular invasion		
		Present	Questionable	Absent
Nuclear features of PTC	Present	Invasive encapsulated follicular variant of PTC	Well-differentiated tumour of uncertain malignant potential	Non-invasive follicular thyroid neoplasm with papillary-like nuclear features
	Questionable	Well-differentiated carcinoma, NOS		
	Absent	Follicular carcinoma	Follicular tumour of uncertain malignant potential	Follicular adenoma

Non-invasive follicular thyroid neoplasm having papillary-like nuclear features (NIFTP)

NIFTP was formerly known as a non-invasive encapsulated follicular variant of PTC (FVPTC) or well-differentiated tumor with uncertain malignant potential.

Macroscopy

NIFTP presents as a single, well-demarcated nodule, with a thick or thin capsule. The cut surface is white-tan, homogeneous to fleshy-brown.

Microscopy

Four features required for the diagnosis are:

(1) A clear demarcation or complete capsule surrounding the tumor, delineating it from the adjacent thyroid parenchyma (2) Absence of invasion (3) Follicular growth pattern (4) PTC like nuclear changes.

PAPILLARY THYROID CARCINOMA (PTC)

Macroscopy

An invasive tumor with ill-defined margins, firm consistency, and a granular, white cut surface with calcifications.

Microscopy

Two significant features of classic PTC are nuclear changes and papillae. The papillae are arborizing and have a central fibro vascular core. The nuclei show enlargement, overlapping, irregular nuclear membrane, INCIs, longitudinal grooves, and Orphan Annie nuclei. Psammoma bodies are noted, which show concentric lamination, representing dystrophic calcification.

FOLLICULAR THYROID CARCINOMA(FTC)

Macroscopy

Completely encapsulated solid lesions with thick capsules to tumors resembling follicular adenomas can be noted, although the capsules are more prominent in carcinoma.

Microscopy

FTC is classified into three groups:

(1) Minimally invasive (capsular invasion only).

(2) Encapsulated angio-invasive- Invasion must occur in vessels within or beyond the tumor capsule.

(3) Widely invasive- into extra-thyroidal soft tissues.

HURTHLE (ONCOCYTIC) CELL TUMORS

The non-invasive tumors are called Hurthle cell adenomas, and vascular or capsular invasion tumors are called Hurthle cell carcinomas.

Macroscopy

Encapsulated tumor, appearing tan to mahogany in color. Following minor trauma, these tumors undergo infarction.

Microscopy

Hurthle cell adenoma is comprised of follicles/trabeculae of oncocytic cells without invasion. Hurthle cell carcinomas show intersecting fibrous bands between clusters and nests of tumor cells.

POORLY DIFFERENTIATED THYROID CARCINOMA (PDTC)

Macroscopy

Solid, large tumors, which are light-brown to grey. Pushing margins are noted, with the presence of satellite nodules within the thyroid parenchyma.

Microscopy

The tumor consists of well-defined solid nests- 'insulae,' with small, uniform, hyperchromatic nuclei, necrosis, and mitoses.

ANAPLASTIC THYROID CARCINOMA (ATC)

Macroscopy

Tumors are infiltrative and bulky with areas of hemorrhage and necrosis.

Microscopy

Three patterns seen are sarcomatoid, giant cell, and epithelial. Common to all three forms is an infiltrative growth pattern, necrosis, increased mitosis, acute inflammatory infiltrate, and osteoclast-like giant cells.

SQUAMOUS CELL CARCINOMA (SCC)

Macroscopy

The tumor has a firm consistency, grey-white in color, with areas of necrosis. Satellite tumor nodules are commonly seen.

Microscopy

Tumor comprises predominantly of cells with squamous differentiation and is graded similarly to SQC in other locations.

MEDULLARY THYROID CARCINOMA (MTC)

Accounts for < 2-3% of all thyroid malignancies.

Macroscopy

The tumors range from < 0.1 cm to those that replace the entire lobe and presents as a single, sharply circumscribed, tan-grey to yellow mass.

Microscopy

MTCs show a solid, trabecular, lobular, or insular growth pattern, in which cells appear round, polygonal, spindle-shaped, or plasmacytoid. Stromal amyloid deposits are present in 90% of cases.

MIXED MEDULLARY AND FOLLICULAR THYROID CARCINOMA

Primary malignant neoplasm of the thyroid, showing morphological and IHC evidence of the coexistence of follicular and C cell-derived tumor populations within the same lesion. Chetan et al. (2013)[57] and the results exhibited a higher incidence of colloid goiter (43.8%) among all the 73 solitary nodules of thyroid cases.

Gautam HK et al. (2018)[58] On final diagnosis on histopathological evaluation (HPE), 98 out of 100 patients with benign lesions included 66 patients of colloid goiter, 16 with follicular adenoma, 4 with lymphocytic thyroiditis, and 12 with adenomatous goiter. Two out of 100 patients had malignant lesions. Among malignant lesions, papillary carcinoma was found in one patient and anaplastic carcinoma in one patient.

Table 14: Diagnostic accuracy of the TI-RADS and BETHESDA System in Relation to the Final Postoperative Histopathological Diagnosis

	Ashraf M et al.[55](2018)	
	TI-RADS	FNAC
Sensitivity	76.9%	81.8%
Specificity	91.3%	98.00%
Positive predictive value	71.4%,	90%
Negative predictive value	76.4%	96%

METHODOLGY

MATERIALS AND METHODS

ETHICAL COMMITTEE APPROVAL: The Institutional ethical committee has approved this study with Ethical clearance number SDUMC/KLR/IEC/123/2019-19.

STUDY DESIGN: Prospective observational study.

DURATION OF THE STUDY: from 29-11-2018 to 20.10.2020.

STUDY POPULATION: Patients with Thyroid enlargement.

SAMPLE SIZE:

Formula

$$n = \frac{(z_\alpha + z_{1-\beta})^2}{\{\pi(1-\pi)(\rho_1-\rho_0)\}^2}\left[\frac{1}{\pi^2+\pi(1-\pi),\rho_0} + \frac{2}{\pi(1-\pi)(1-\rho_0)} + \frac{1}{(1-\pi)^2+\pi(1-\pi),\rho_0}\right]$$

Where,

ρ_0 : Null hypothesis Agreement

ρ_1 : Alternative hypothesis agreement

π : Prevalence

α : Significance level

$1-\beta$: Power

Where p0 is o.613

p1 is 0.9

prevalence-23

The sample size was calculated using the following formula:

$$n = \frac{Z^2 (p \times q)}{d^2}$$

Where,

Z = 1.96; it is standard deviation score for 95% set interval

p = assumed or estimated proportion (67%)

q = 1-P (1-0.67) = 0.33

d = allowable error (15%of P) =10.05

by putting these values in the above equation:

$$n = \frac{(1.96)^2 (0.67 \times 0.33)}{(0.10)^2} = \frac{0.101}{0.904} = 89$$

The sample size was calculated 89 subjects at 95% confidence limit and 15% allowable error assuming a correlation between TI-RADS and BETHESDA system in 67% of cases Ashraf M et al. (2018).[55]

In this study, a total of 107 patients were studied.

INCLUSION CRITERIA:

1) Thyroid enlargement in patients above 18 years of age.

EXCLUSION CRITERIA:

Patients already treated for recurrent thyroid malignancies and patients on chemotherapy.

Methods:

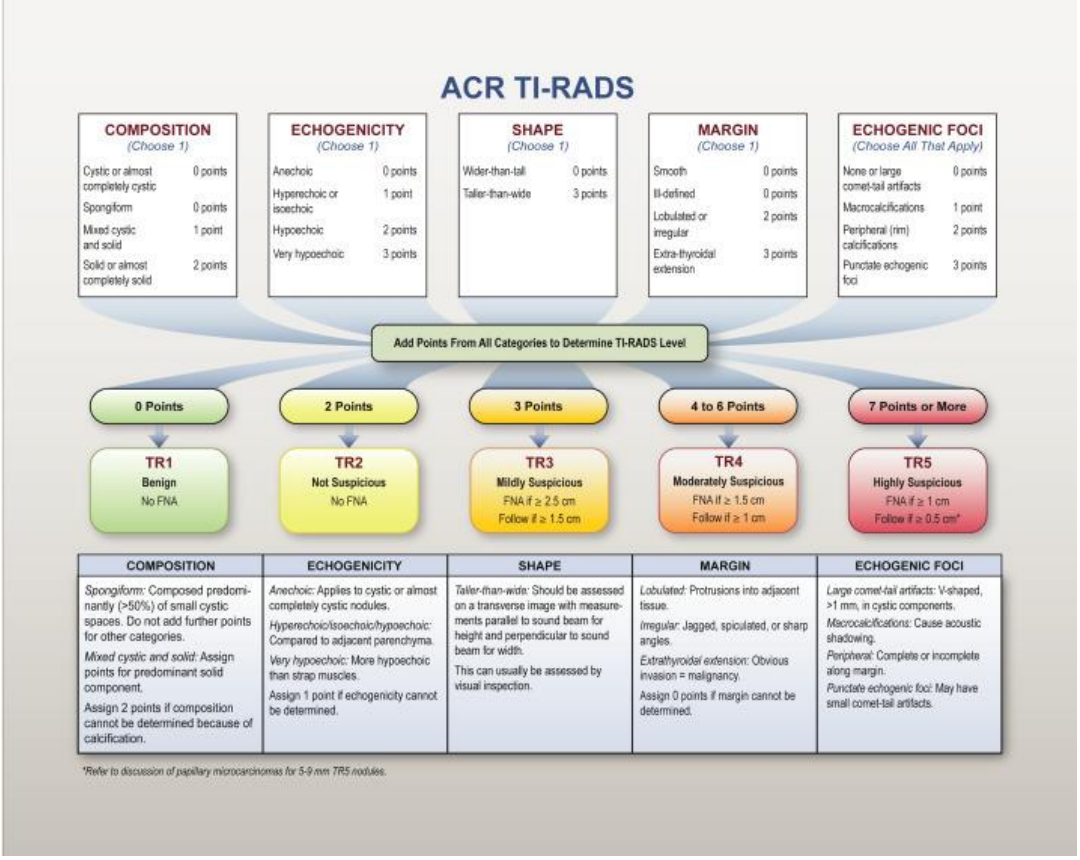
USG-guided FNAC of the suspected areas was done using a 23-gauge needle after explaining the procedure to the patient after obtaining the written consent. High-resolution B-mode ultrasound with a high-frequency probe (5-18 MHz) using a linear array transducer (PHILIPS EPIQ 5G) Ultrasound machine was used guidance. Slides planned for Haematoxylin & Eosin stain and Papanicolaou stain were subjected to ethanol fixation while slides planned for Giemsa stain were left to dry in the open air.

Methodology:

Procedure: The relevant clinical details were collected from the patient, and general physical examination and local examination of the thyroid were done. Informed written consent was obtained from the patient for FNAC. The patient is lied supine with the neck in a mild extended position, done by placing a pillow/ rolled towel below the patient's upper back. The ultrasound examination with B-mode imaging was done to examine the thyroid and the neck. The thyroid nodules, if present, were staged according to ACR TI-RADS. Images were inspected on the real-time two-dimensional grayscale and Doppler imaging. The neck was scanned in transverse, sagittal, and oblique sections to see both thyroid lobes, isthmus. The regions of the supraclavicular fossa, carotid arteries, and jugular veins, were visualized for any lymph node enlargement. The sonographic features of all saved images were

examined; such as the internal composition, echogenicity, margins, presence of calcifications, and the shape of the nodule.

Fig 4:American college of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) Tessler FN et al.[4](2018)



For patients with more than one thyroid nodule, classified as multinodular goiter (MNG) and the nodule having the most suspicious sonographic features, it was recorded as the nodule of interest. The internal structure of the nodule is demarcated as cystic, solid, or mixed. The US parameters defined the suspicion of malignancy as follows: irregular border, micro-calcifications, hypo-echogenicity. The nodule was defined as probably benign if it did not show suspicious features of malignancy.

Thyroid US was scored according to TI-RADS classification: The classification is used to differentiate thyroid swellings into benign or malignant and allow for a better selection of thyroid nodules undergoing FNAC. TI-RADS proposed ten ultrasound patterns and TI-RADS 2–6 for nodules.

Table 3: Distribution of TI-RADS Category with the corresponding risk of malignancy[5]

Category	Description	Risk of malignancy
TI-RADS I	Normal thyroid gland	
TI-RADS II	Benign conditions	0 % risk of malignancy
TI-RADS III	Probably benign conditions	<5% risk of malignancy
TI-RADS IV_IVA	Undetermined nodules	5-10% risk of malignancy
TI-RADS IV -IVB	Suspicious nodules	10-50 % risk of malignancy
TI-RADS IV -IVC	Highly Suspicious nodules	50-85 % risk of malignancy. A score of 3-4
TI-RADS V	Probably malignant nodules	>85% risk of malignancy, score of 5 or higher
TI-RADS VI	Biopsy proven malignancy	

For this study purpose, TI-RADS I, II, III, IVA were grouped as probably Benign Thyroid Lesion while TI-RADS category IVB, IVC, V, and VI were grouped as Malignant Thyroid Lesion.

FNAC PROCEDURE

Taking all aseptic precautions, all FNACs were performed under Ultrasound guidance after instructing the patient to refrain from swallowing, using a disposable syringe (10ml) and 23-gauge needle.[7,39] The skin surface at the site of needle puncture is prepared with an alcohol sponge; the needle is placed against the skin at a predetermined angle and puncture site and is then inserted through the skin and into the subcutaneous tissue in a swift, smooth motion.

The needle is advanced into the lesion after feeling for resistance when penetrating a capsule or note that the lesion moves with the needle by swing it from side to side. After the needle is within the lesion, suction is applied with the syringe. With suction, the needle is moved forward and backward in short rapid strokes in a swift cutting motion. The needle is moved in the same direction as the original needle tract while increasing the angle. The area biopsied is reminiscent of a triangle with the puncture site representing the tip of the triangle to increase the cellular yield and the area sampled. The cellular sample is acquired by the needle's cutting action and is maintained in the needle core by forwarding motion and capillary tension. An approximate dwell time of 2–5 seconds within the nodule with two or three forward and back needle strokes per second was spent to maximize cellular yield and minimizes bloody artifact. Multiple aspirates from different sites ensure the adequacy of the material. During the aspiration procedure, the needle hub is watched for the

presence of the sample. It is critical to keep the aspirated sample within the needle. After 2–5 seconds within the nodule with two or three needle strokes per second, suction should be released.

Without suction, the needle is withdrawn from the lesion in a straight line along the needle tract. The pressure is then applied to the puncture site with a sterile gauze pad. The aspirate was expelled over two clean slides (2 drops for each slide) and spread to form a film by a clean slide at 60° angle.[7]

FIXATION OF SMEARS

To retain the cytomorphologic appearance of cells, wet fixation was done by immediately immersing a slide into an alcohol fixative after smearing without air drying. The standard alcohol fixative used was 95% ethanol.

STAINING

Whenever fluid was obtained, all the contents were aspirated and centrifuged. Smears were made from the sediment and stained as follows FNAC smears were prepared, and slides were stained with PAP stain and Giemsa stain with the following procedure.

1. Procedure for rapid PAP stain[7]

Alcohol fixed smears were washed in tap water.

Dip for 2-3 minutes in Harris hematoxylin and 2-3 dips in 1% Acid alcohol.

Smears were washed in running tap water.

Equal parts of Eosin-50 and orange G, the working cytoplasm, were stained on slides for 30-45 seconds.

After washing in tap water for 20-30 seconds, slides were dried.

After drying, slides were dipped in xylene for 20 seconds, and mounting with cover glass was done using a drop of D.P.X.

2. Procedure for Hematoxylin and Eosin stain[7]

Fix the smear

Wash fixed smear using tap water

Keep in Harris hematoxylin for 5to 8 minutes and then remove excess stains in running tap water.

Differentiate in 1% acid alcohol for 2-3 minutes and well wash in Tap water until blueing and dip in Eosin for 20-30 seconds. Rinse in tap water until the excess stain is removed and dry the slides, dip in Xylene and mount in D.P.X.

3 Procedure for Giemsa stain[7]

2-3 ml of working Giemsa stain were put on air-dried smear for 20-30 seconds.

Slides were flooded with double amount of buffer solution for 10-15 minutes.

Excess stain was washed in running tap water, and slides will be dried and dipped in Xylene for 20 seconds and then mounted in D.P.X.

A Pathologist screened FNAC smear, and reporting was done using the BETHESDA system of reporting, as shown in table 7. The pathologist was blinded for the TI-RADS report.

The difficulty in distinguishing Follicular adenoma from Follicular carcinoma on FNAC majority of BETHESDA Category IV cases is taken for Thyroidectomy. Therefore, BETHESDA Category I, II, III were grouped as Benign Lesions, and BETHESDA Category IV, V, and VI were grouped as malignant lesions.

Thyroidectomy was performed in 37 out of 107 cases, after which the Thyroid specimen was fixed in 10% Neutral buffered formalin solution. After detailed gross examination, tissues were selected for Paraffin embedding and section cutting.

Histopathology reporting was done using standard guidelines. Correlations of cytology and histological diagnosis were done. Validative statistics were calculated using histopathological diagnosis as the gold standard.

STATISTICAL ANALYSIS-

Data were analyzed after entering into Microsoft Excel sheet using IBM SPSS (trial version 23) and PRIMER statistical software.

Categorical data was represented in the form of Frequencies and proportions.

Chi-square test was used as a test of significance.

Continuous data were represented as mean and standard deviation.

An Independent test was used as a test of significance for identifying the mean difference.

P-value <0.05 was considered as statistically significant.

Sensitivity, specificity, PPV, NPV, and diagnostic accuracy will be calculated by comparing with Histopathological diagnosis wherever possible using the following formula. Diagnostic accuracy measures are yielded by following formulas.

Sensitivity	Probability of a true positive test result given disease	TP/(TP+FN)
Specificity	Probability of a true negative test result given non-disease	TN/(TN+FP)
PPV	Probability of a true positive test result given a positive test result	TP/(TP+FP)
NPV	Probability of true negative test results given a negative test result	TN/(TN +FN)

TP = TRUE POSITIVE

TN = TRUE NEGATIVE

FP = FALSE POSITIVE

FN = FALSE NEGATIVE

$$\text{Test efficiency} = \frac{\text{true-positive + true-negative}}{\text{all test results}}$$

RESULTS

RESULTS

A total of 107 cases were studied in SDUMC, Kolar to find the correlation between TI-RADS ultrasound categories and BETHESDA cytology categories of thyroid Lesions.

Table 15: Showing Age group distribution of cases in the present study

Age (years)	No. of cases	%
<10	1	0.93
10 to 20	4	3.74
21 to 30	27	25.23
31 to 40	22	20.56
41 to 50	28	26.17
51 to 60	14	13.08
61 to 70	9	8.41
>70	2	1.87
Total	107	100.00

The age of patients ranged from 8 to 70 years. The mean age was 41.67±14.41years. The highest incidence was in the age group 41 to 50 years (26.17%), followed by 21 to 30 years (25.23%).

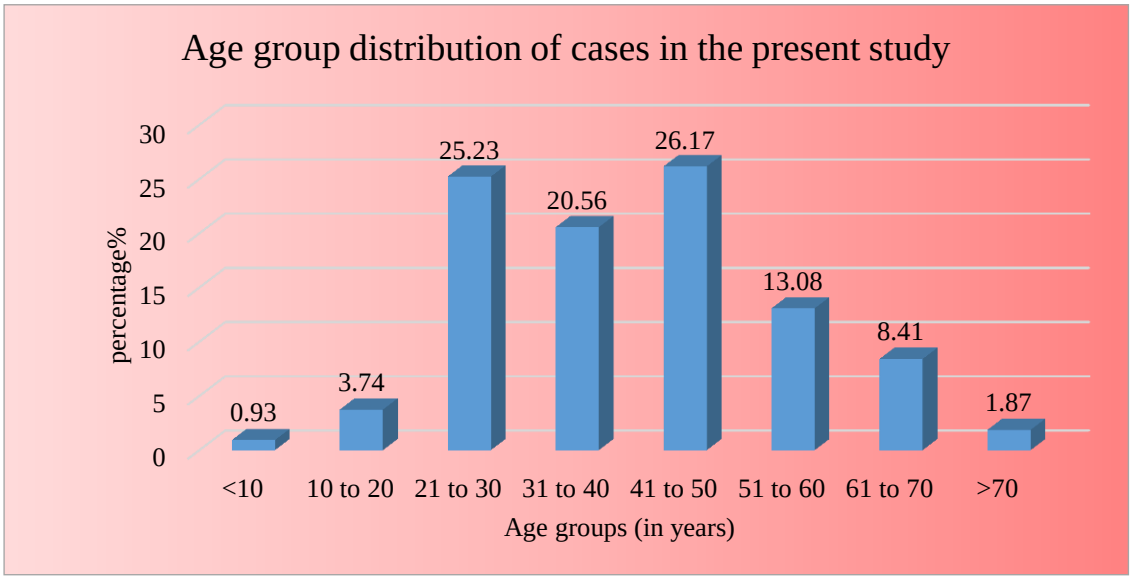


Chart 1: Bar diagram showing the percentage of age-groups in the present study

Table 16- Gender distribution of cases in the present study.

Gender	No. of cases	Percentage(%)
Female	87	81.31
Male	20	18.69
Total	107	100.00

The present study showed that females (81.31%) were affected more commonly than males (18.69%). The male to female ratio was found to be 1:4.35.

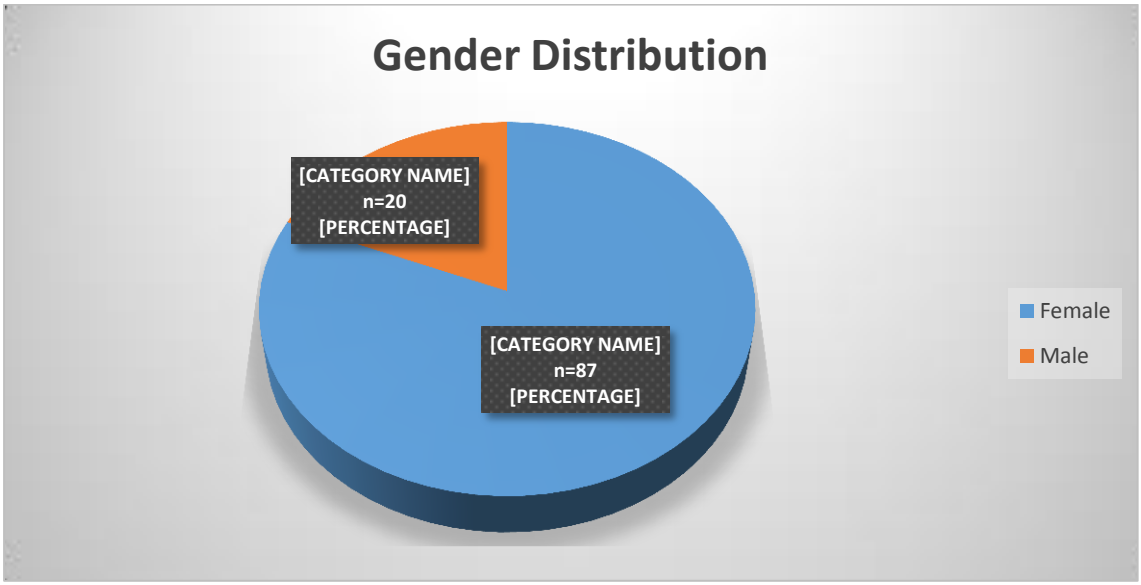


Chart 2: Pie-chart showing the percentage of distribution among males and females

Table 17: Distribution of cases by the TI-RADS categories in the present study.

TI-RADS categories	No. of cases	Percentage(%)
I	5	4.67
II	20	18.69
III	57	53.27
IVA	07	6%
IVB & IVC	07	6%
V	11	9.35
Total	107	100.00

In the present study, the most common was category III (53.27%), followed by category II (18.69%).

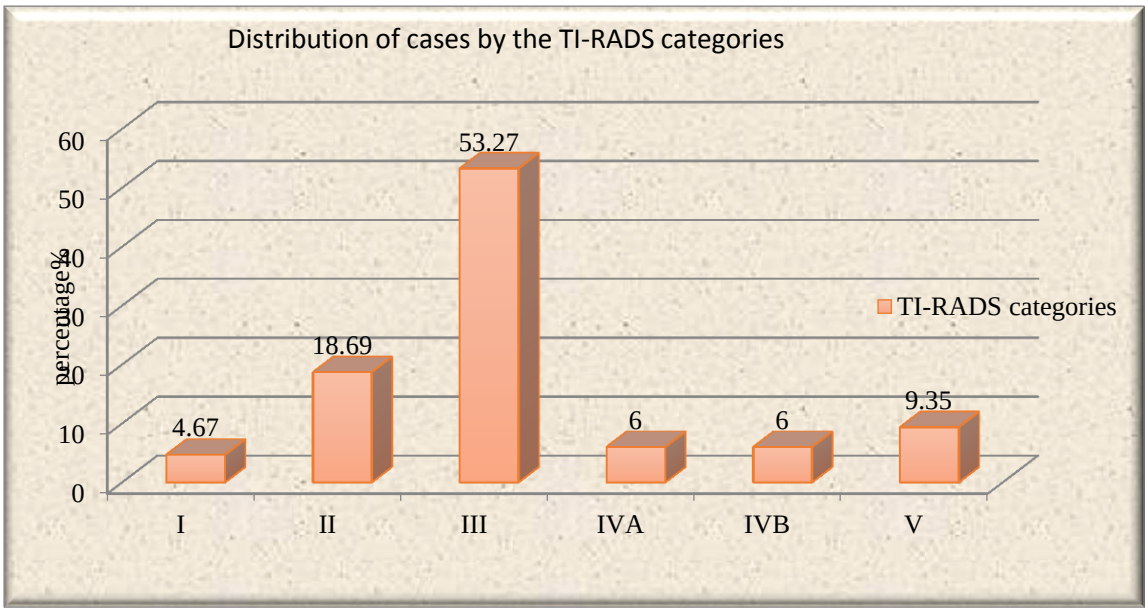


Chart 3: Bar diagram showing the percentage of distribution of TI-RADS categories

For Correlation of TI-RADS categories, I, II, III, IVA TI-RADS categories were grouped as probably Benign Thyroid Lesions while TI-RADS category IVB, IVC, and V were grouped as Malignant Thyroid Lesion.

Table 18: Ultrasound diagnosis in the present study.

Category of Lesion	No.	Percentage(%)	Percentage out of the total number of cases = 107(%)
Benign	89		83
Descriptive findings of Benign Lesions			
Benign	47	52	43
Benign multinodular goitre	16	17	14
Benign thyroid lesion(lymphocytic thyroiditis)	17	19	15
Adenomatous hyperplastic nodule	1	1.22	0.93
Benign – Solitary nodule +colloid degeneration	8	8.9	7.4
Malignant	18		17
Descriptive findings of malignant Lesions			
Malignant	08	44	39
Suspicious for malignancy	7	38	65
Multiple nodules-one nodules likely neoplastic	2	4	0.93
Malignant lesion-Stiff lesion	1	4	0.93

Out of 107 cases in TI-RADS, 83.18% were diagnosed benign, and 16.82% were malignant.

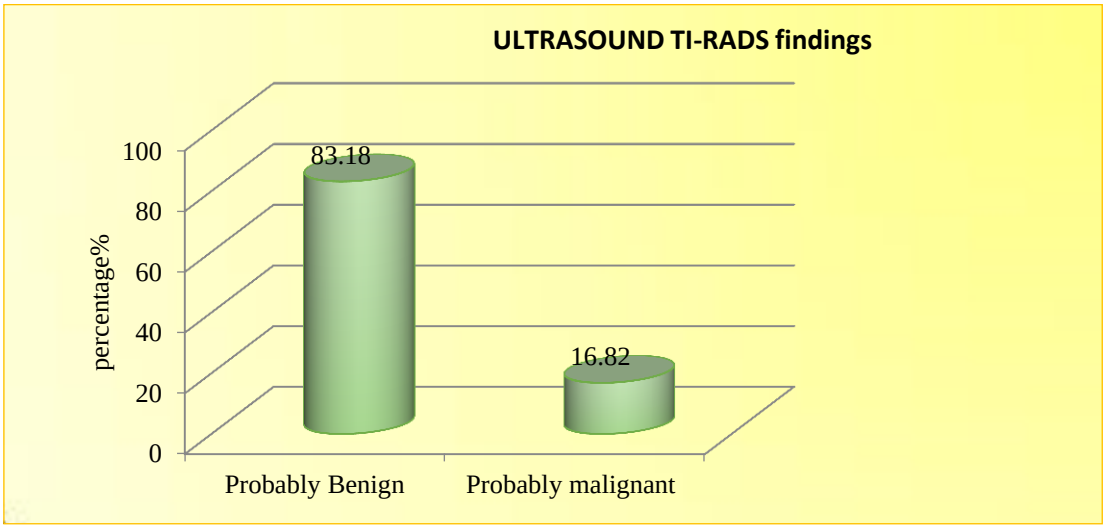


Chart 4: Column diagram showing Ultrasound TI-RADS findings

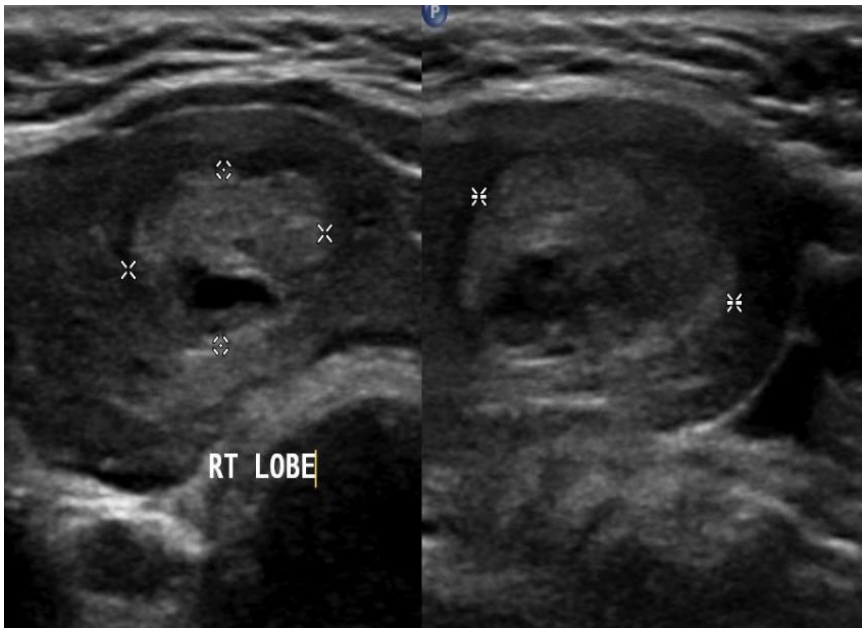


Fig 5: Showing TI-RADS I lesion (U/S No. :- 2501/19)

Shape -Wider than taller

Margin-Smooth

Composition-spongiform

Echogenicity-hyperechoic

Echogenic Foci-Nil

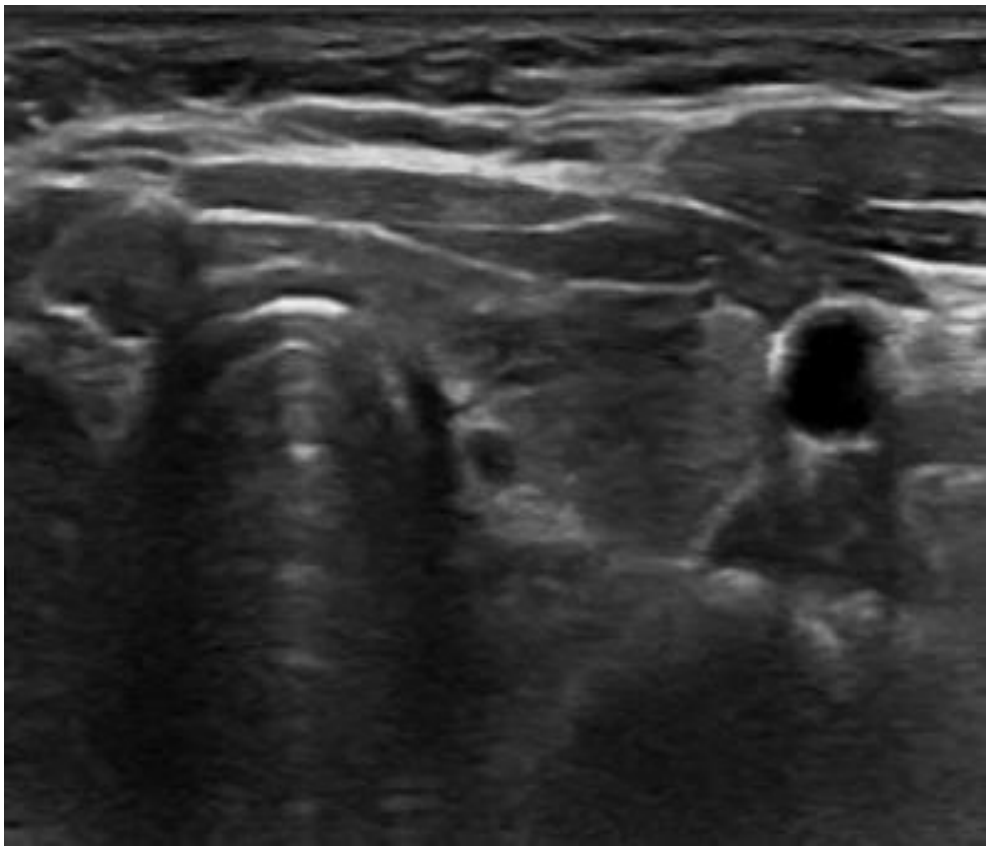


Fig 6: Showing TI-RADS II Lesion (U/s No :- 524/19)

Shape-Wider than taller

Margin-Smooth

Composition – Mostly solid and cystic component with colloid degeneration

Echogenicity-Anechoic.

Echogenic Foci-Nil

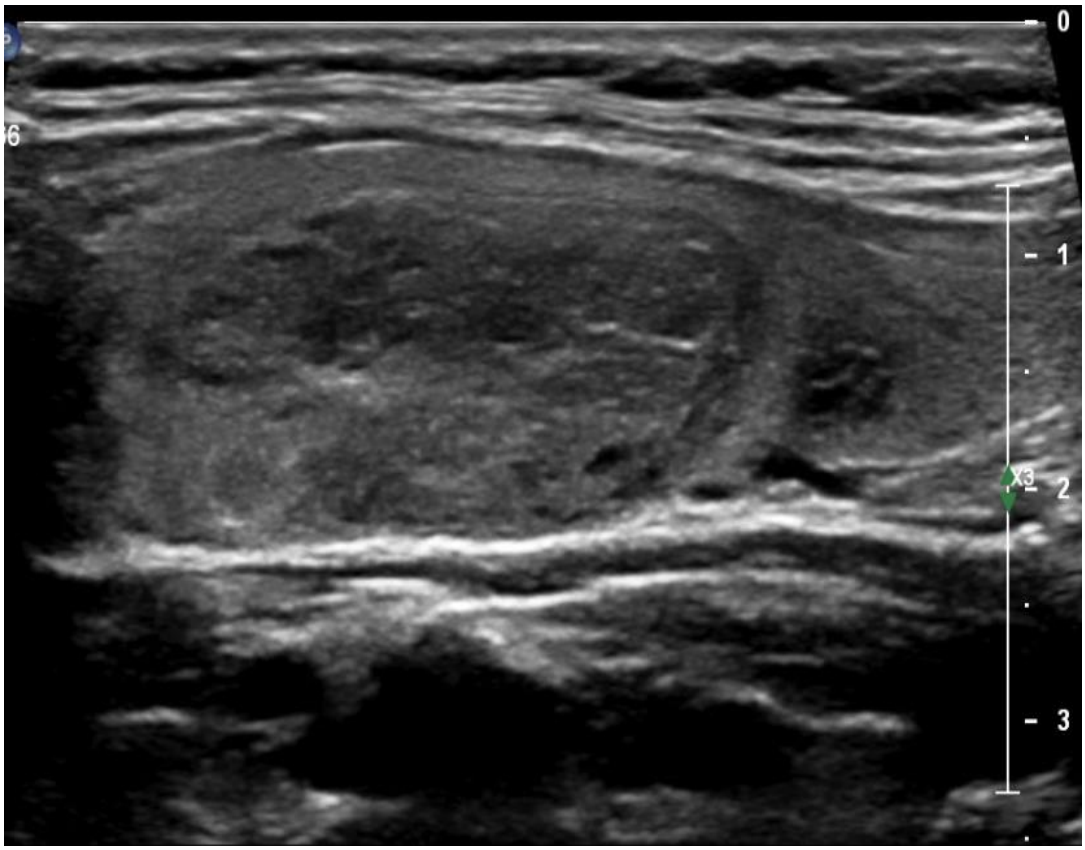


Fig 7: Showing TI-RADS III Lesion with (U/S No. :- 10035/19)

Shape - Wider than taller

Margin- Smooth

Composition – Mostly solid

Echogenicity – Iso-hypoechoic.

Echogenic foci – Nil

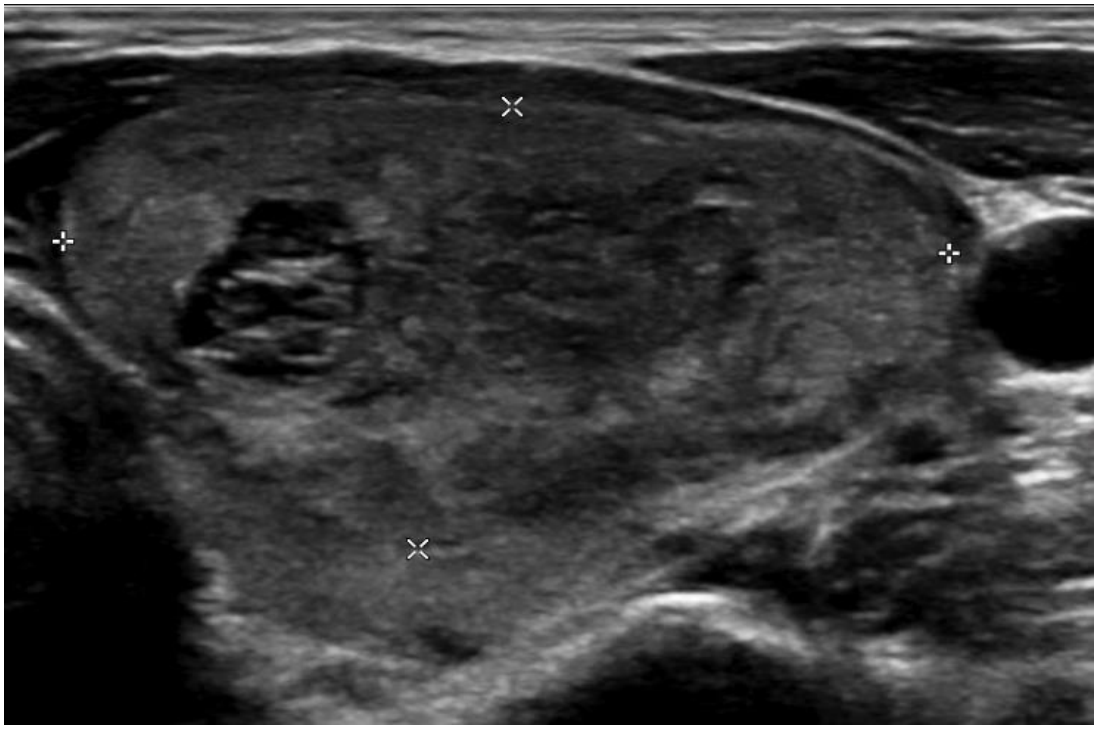


Fig 8: Showing TI-RADS IVA Lesion (U/S No. :- 3740/19)

Composition: Solid and cystic component

Echotexture: Heterogeneously hyperechoic with multiple areas of anechoic cystic / colloid degeneration. Shape: Wider than taller

Margin: Smoothly marginated

Echogenic foci: Tiny calcific foci.

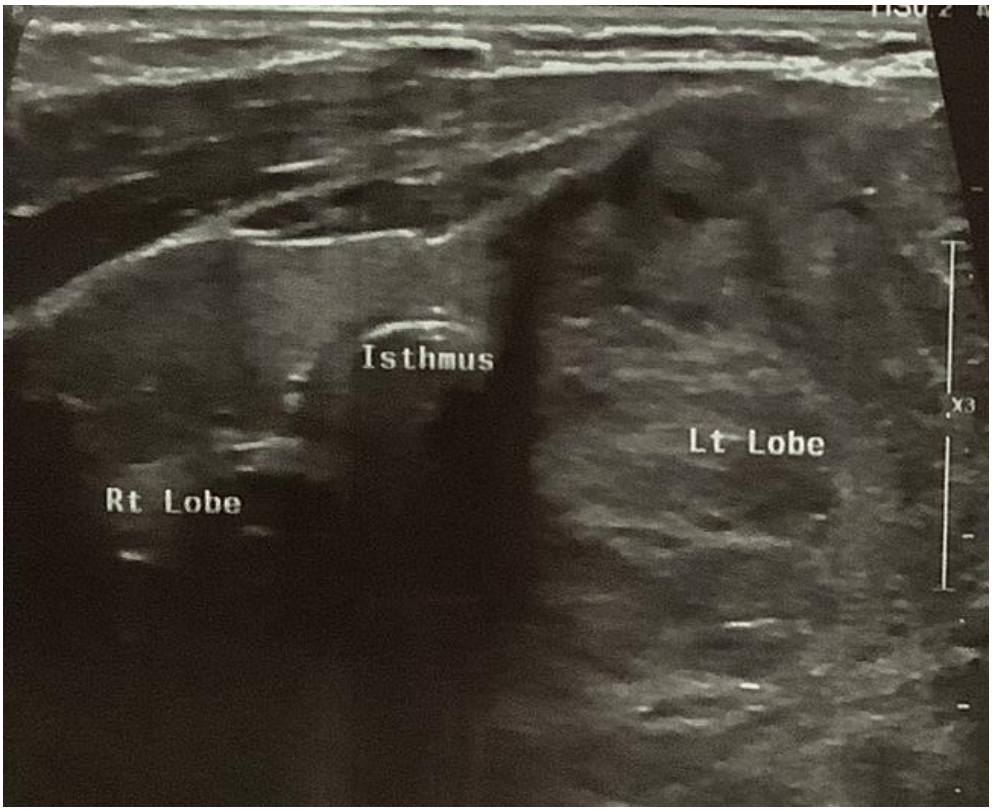


Fig 9: Showing TI-RADS IVB (U/S No. : - 7968/19)

Composition: Solid

Echotexture: Hypoechoic

Shape: Taller than wide

Margin: Irregular margins

Echogenic foci: Tiny calcific foci.

Table 19: Distribution of cases by the BETHESDA system in the present study.

BETHESDA categories	No. of cases	Percentage(%)
I	2	1.87
II	79	73.83
III	5	4.67
IV	11	10.28
V	6	5.61
VI	4	3.74
Total	107	100.00

In the present study, the most common category was II (73.83%), followed by IV (10.28%).

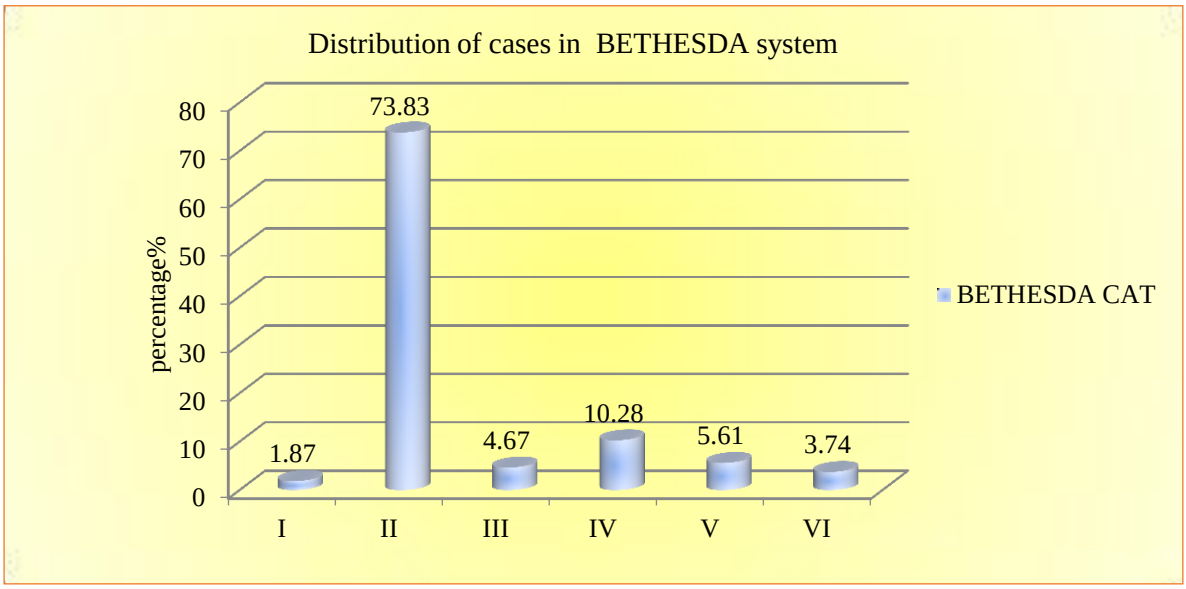


Chart 5: Column diagram showing the distribution of cases in the BETHESDA system

Table 20: FNAC diagnosis in the present study.

Category of Lesion	No.	Percentage(%)	Percentage out of a total number of cases = 107(%)
Benign	85		79
Descriptive findings of Benign Lesions			
Benign Nodular lesions nodular hyperplasia, follicular lesion, colloid goitre, follicular nodule, nodular goitre, adenomatoid nodule, nodular hyperplasia, colloid adenoma, follicular hyperplasia, nodular goitre +cystic degeneration	35	41	32
Benign Colloid lesion Colloid nodule Colloid nodule with cystic degeneration Colloid cyst	16	18	14

Benign thyroiditis Lymphocytic thyroiditis Hashimoto thyroiditis Autoimmune thyroiditis	34	40	31
Malignant	22		21
Descriptive findings of malignant Lesions			
Medullary carcinoma	3		28
Follicular neoplasm	6		56
Hurthle cell neoplasm	2		18
Malignant-papillary thyroid carcinoma	10		9.34
Anaplastic thyroid carcinoma	1		0.93

BETHESDA Category I, II, and III were categorized as Benign lesions, whereas BETHESDA Category IV, V, and VI were categorized as Malignant lesions.

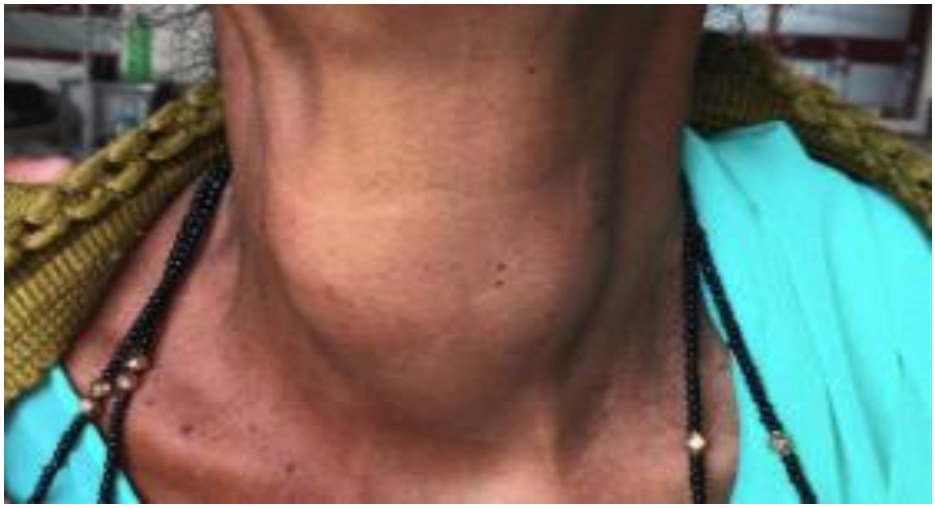


Fig 10: Clinical photograph of a patient with Hashimoto's' thyroiditis having butterfly-shaped swelling.

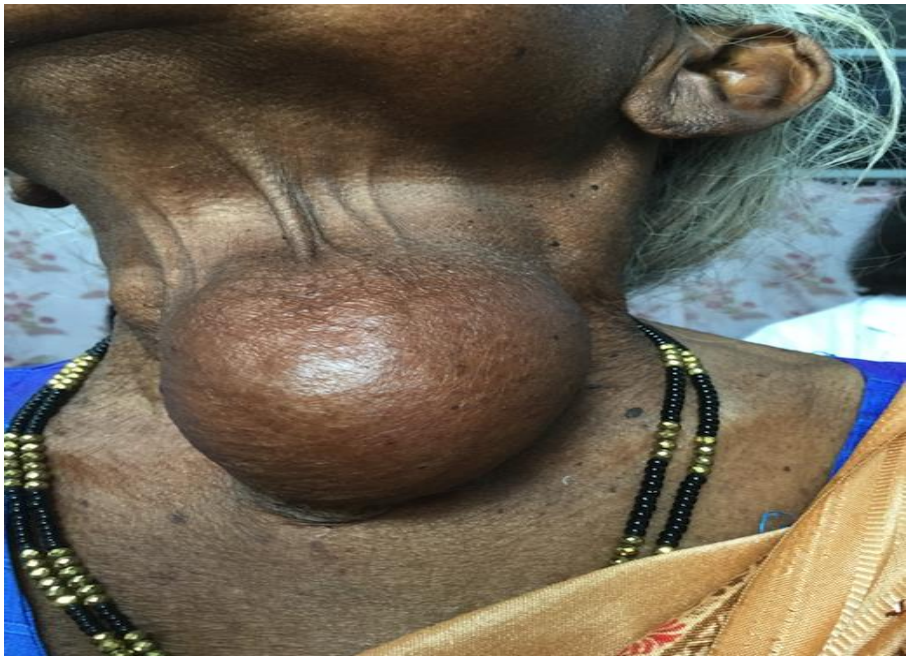


Fig 11: Clinical photograph of a patient with large single solitary swelling.

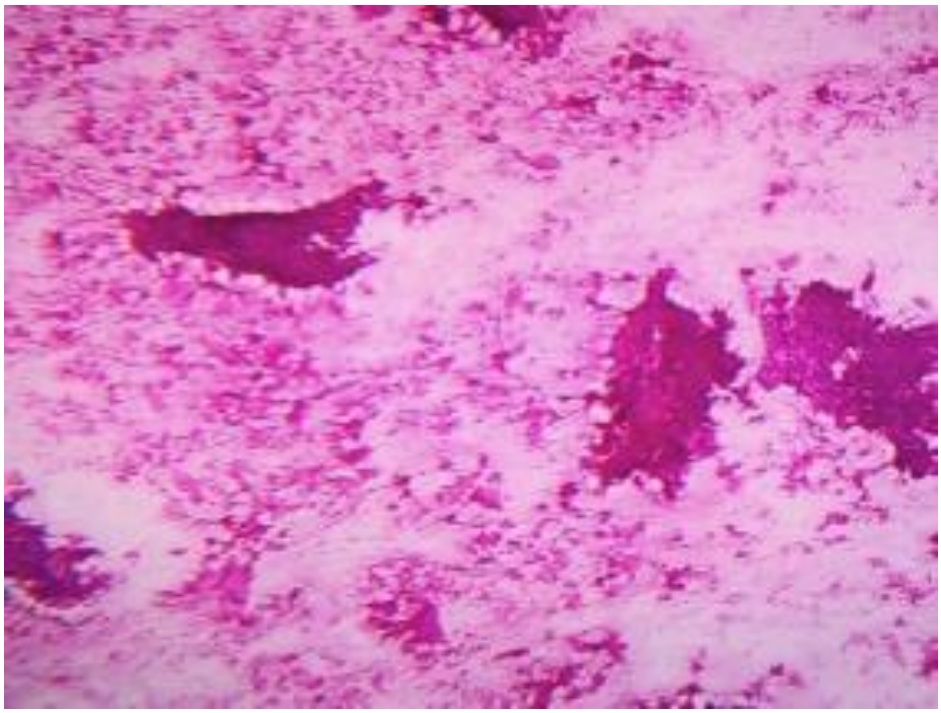


Fig 12/C-1065-19: Photomicrograph of FNAC smear showing benign thyroid follicular cells arranged in clusters and sheets. The background shows colloid mixed with blood- BETHESDA Category II (Benign thyroid lesion, H & E, 40 x)

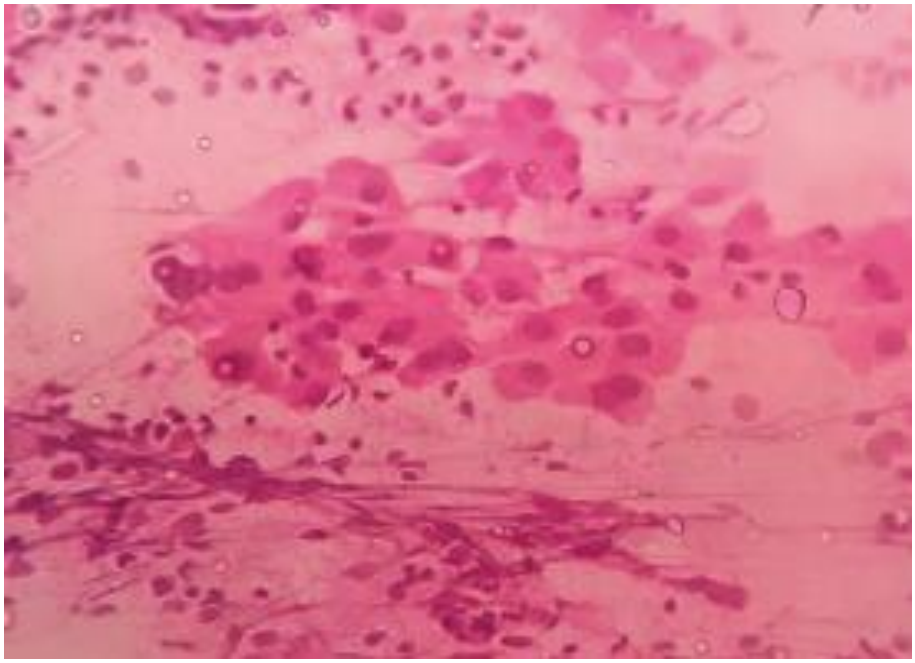


Fig 13/C-2159-19: Photomicrograph of FNAC smear showing thyroid follicular cells with Hurthle cell change. The background shows lymphocytes- BETHESDA Category II (Hashimoto thyroiditis, H & E,100x)

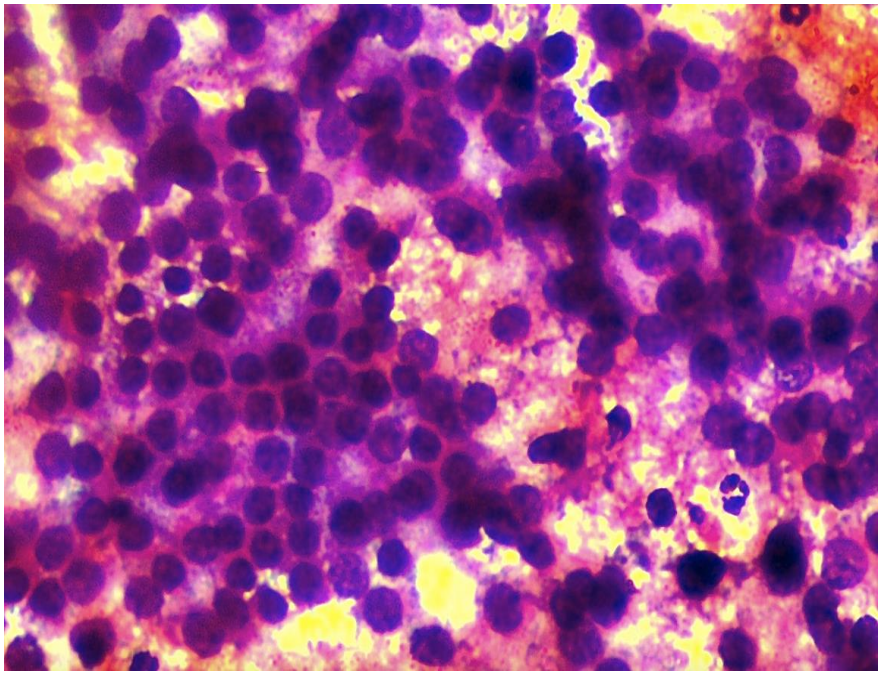


Fig 14 /C-692-20: Photomicrograph of FNA smear showing high cellularity with pleomorphism and cytological atypia with intranuclear inclusions-BETHESDA Category III (Atypia of undetermined significance (AUS, H &E stain-100x)

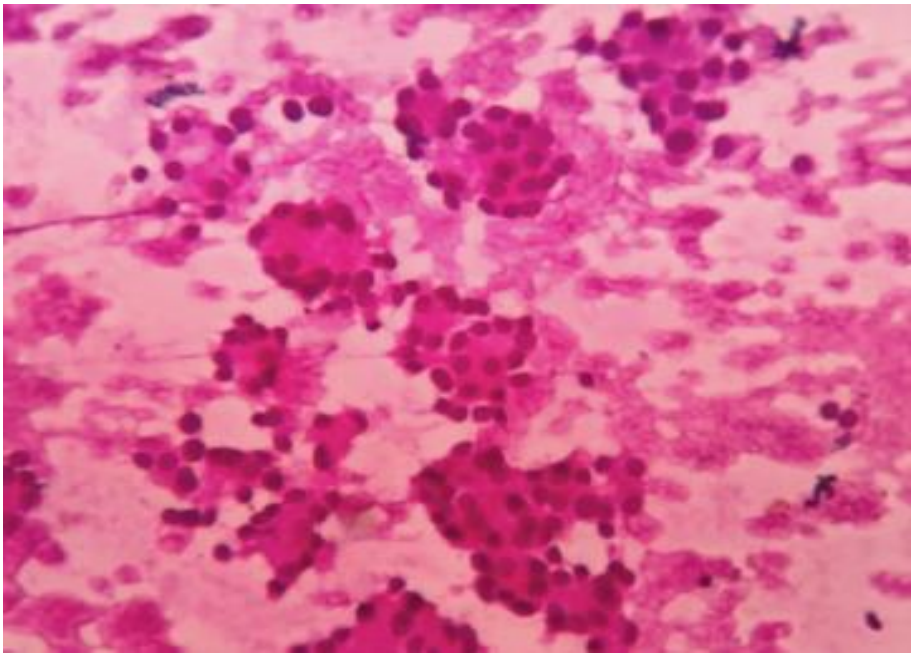


Fig 15/C-1127-20: Photomicrograph of FNA smear showing high cellularity consisting of micro follicles BETHESDA Category IV (Follicular Neoplasm H & E 40 x)

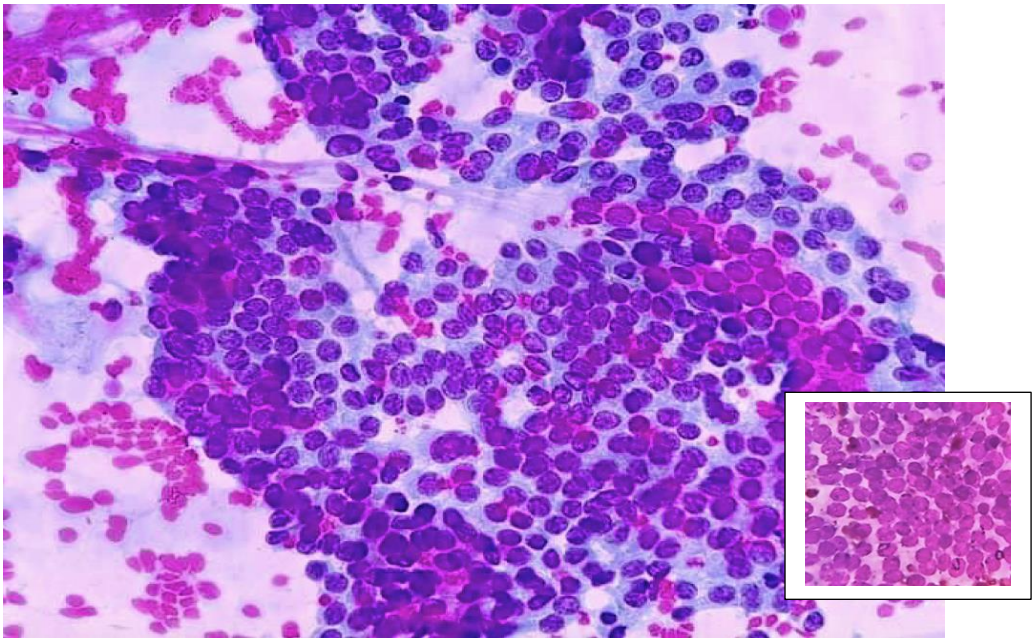


Fig 16/C-2053-19: Photomicrograph of FNA smear of Papillary thyroid carcinoma showing a finger-like three-dimensional tissue fragment with a distinct anatomical border. Ovoid nuclei are seen with crowding and overlapping(H & E, 40x) Inlet showing nuclear grooves and intranuclear cytoplasmic pseudo inclusions.(H & E,100x)

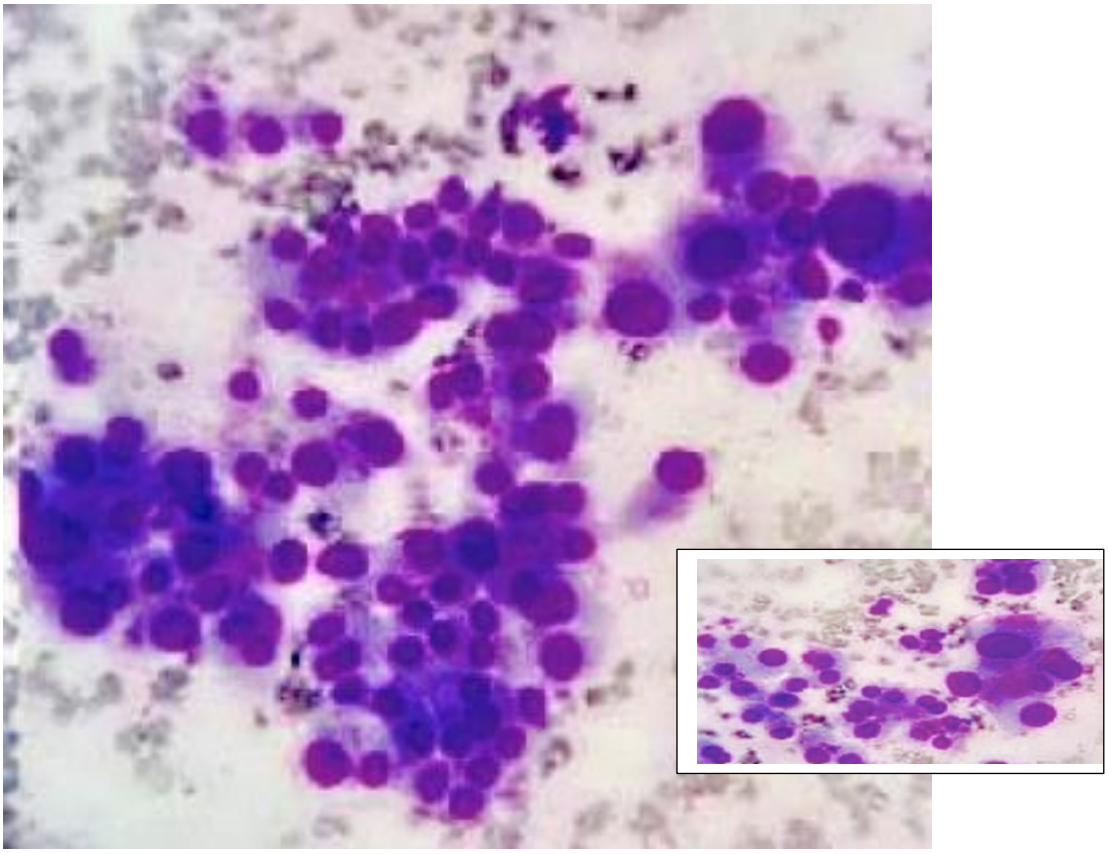


Fig 17/C-580-20: Photomicrograph of FNA smear of Medullary Thyroid Carcinoma-Spindle cell variant. Cellular smear with moderate anisonucleosis and stippled chromatin(MGG stain, 40x),inlet showing a plasmacytoid cell with cytoplasmic granularity (MGG stain, 100x)

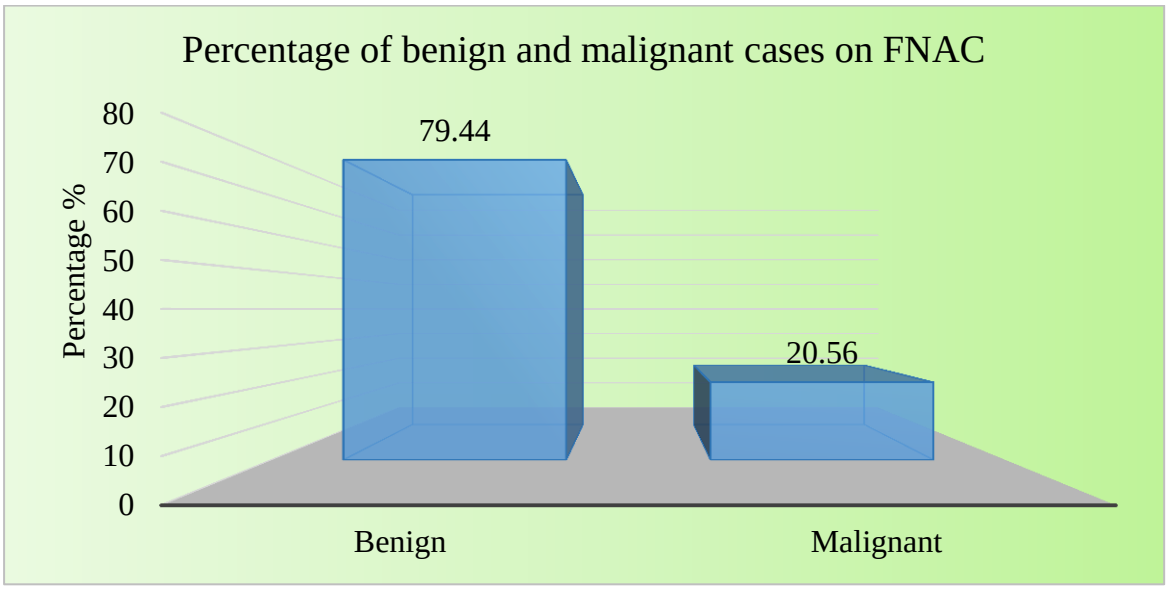
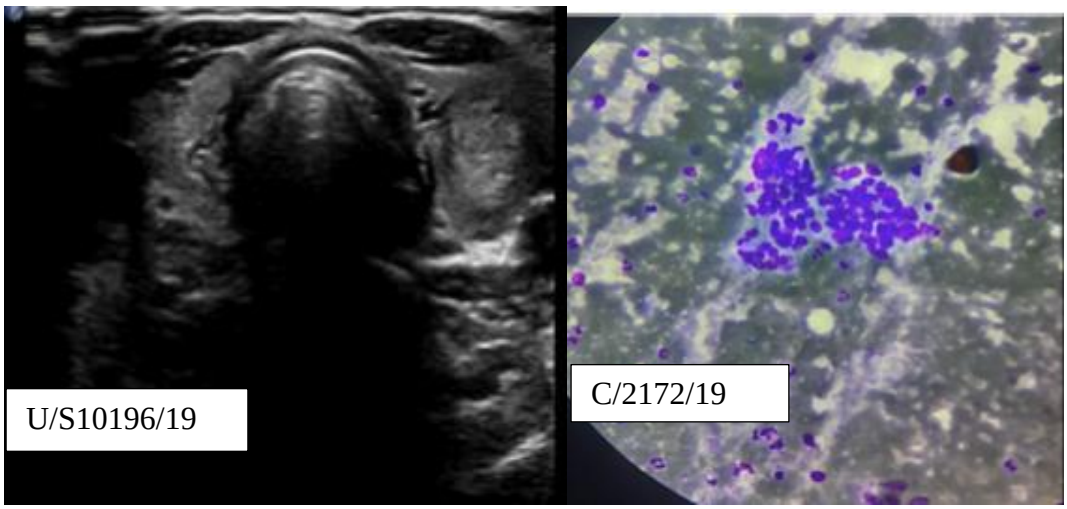


Chart 6: Bar diagram showing the percentage of benign and malignant cases on FNAC

Table 21: Comparison between the TI-RADS category and the BETHESDA System in the present study.

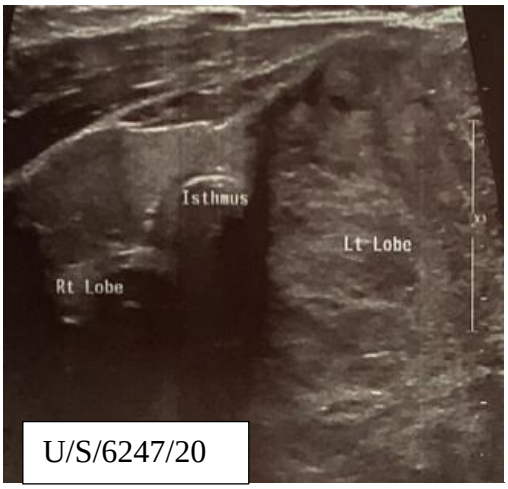
TI-RADS category	BETHESDA Category							Number of concordant cases	Concordance rate in %
	I	II	III	IV	V	VI	Grand Total		
I	0	4	0	1	0	0	5	4/5	80%
II	2	18	0	0	0	0	20	20/20	100%
III	0	47	4	3	3	0	57	51/57	89.47%
IVA	0	6	0	1	0	0	07	6/7	85%
IVB and C	0	1	0	5	1	0	07	6/7	85%
V	0	3	1	1	2	4	11	7/11	63.64%
Total	2	79	5	11	6	4	107	94/107	87%

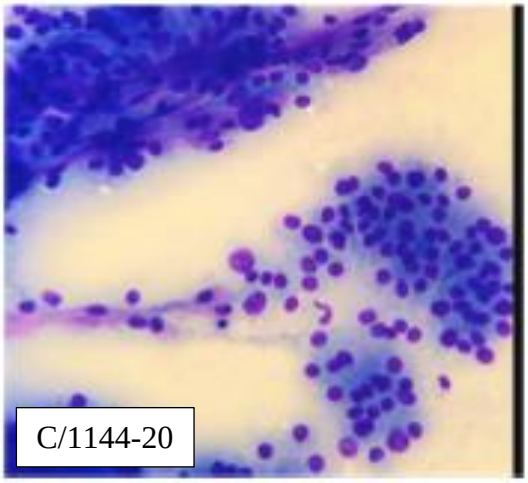
Note- Out of the total 107 cases, 94 cases were concordant while a total of 13 cases were discordant, which are marked in red.



TI-RADS score III Points-3 Solid composition-2 points Heterogenously hyperechoic-1 point Wider than tall-o point	Microphotograph showing Small cluster of Thyroid follicular cells with monomorphic nuclei and moderate amount of cytoplasm(Giemsa stain-40x)-Benign Thyroid Lesion

Fig 18: Concordance between TI-RADS III and BETHESDA –II.

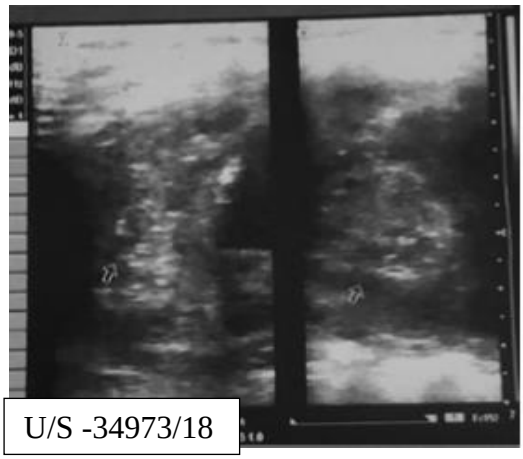


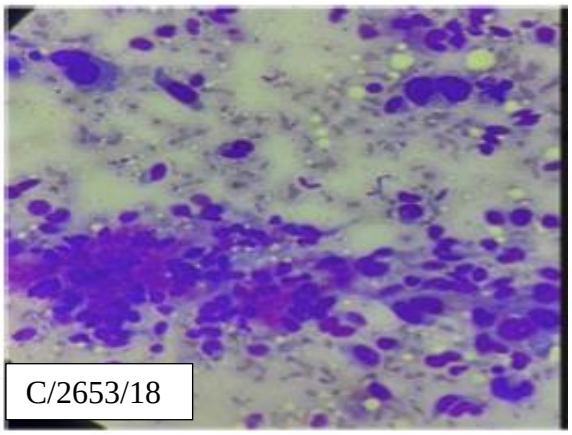


TI-RADS score IV Points-6
Solid composition-2 points
Heterogenously hyperechoic-1 point
Taller than wide-3point
Smooth margin-o point
No calcification -0 point

Microphotograph showing Cellular smears showing multiple microfollicles and solid sheets of cells with discrete hurthle cells in Hurthle cell neoplasm-Giemsa stain-40x

Fig 19: Concordance between TI-RADS IV and BETHESDA –IV.





TI-RADS score V

Points-12 points

Solid composition-2 points

Hypoechoic-2 points

Taller than wide-3points

Irregullar margin-2points

Microcalcification(rim)-3 point

Microphotograph showing highly Pleomorphic cells with some round cells and few spindle shaped cells with hyperchromatic nuclei-Giemsa stain-40x

Fig 20: Concordance between TI-RADS V and BETHESDA –V.

Table 22: Distribution of discordant cases in TI-RADS category and the BETHESDA system in the present study.

TI-RADS CATEGORY	BETHESDA CATEGORY	TOTAL
1	IV	01
III	IV-(3), V-(3)	06
IVA	IV-(1)	01
IVB	II-(1)	01
V	II-(3), III-(1)	04

Table 23: Findings of discordant cases in the present study.

S No.	TI-RADS CATEGORY	BETHESDA CATEGORY	Histopathology	Total number of cases
1	I-Spongiform nodule, Wider than tall Smooth margin Isoechoic No echogenic foci	IV-Follicular neoplasm -Micro follicular cell clusters, rosettes with nuclear hyperchromasia	Follicular variant of Papillary thyroid carcinoma	01
2	2ai) III-solitary hypoechoic nodule, comet-tail artefact underdiagnosed the lesion	V-Suspicious for malignancy(PTC) Cellular smears with cells having enlarged, ovoid, strikingly pale nuclei, finely granular, powdery chromatin	Papillary thyroid carcinoma	06
	2aii) III-solid Isoechoic Wider than tall	V-Suspicious for malignancy(PTC) Cellular smears with cells having	Papillary thyroid carcinoma	

	Smooth No echogenic foci	enlarged, ovoid, strikingly pale nuclei, finely granular, powdery chromatin		
	2aiii) III-solid Variable echogenicity Wider than tall	V-Suspicious for malignancy(PTC)Cellular smears with cells having enlarged, ovoid, strikingly pale nuclei, finely granular, powdery chromatin	Not available	
	2bi)III-solitary hypoechoic nodule	IV- Follicular neoplasm smears showing moderate cellularity with prominent micro follicular pattern with blood colloid free background.	Not available	
	2bii) III-solid Variable echogenicity Wider than tall ESI-<1(Less stiff lesion)	IV- Follicular Neoplasm Cellular smears showing micro follicular cell clusters with nuclear hyperchromasia Follicular neoplasm	Metastatic thyroid carcinoma Papillary Thyroid Carcinoma	
	2biii) III-solid Isoechoic Wider than tall Smooth No echogenic foci	IV-Follicular neoplasm smears are showing moderate cellularity with a prominent micro follicular pattern with a blood colloid free background.	Not available	
3	IVA-Solid and cystic Taller than wide Hyperechoic Smooth margin No echogenic foci	IV-Follicular neoplasm Cellular smears showing small intact follicles with the basement membrane, small uniform nuclei.	Not available	01
4	IVB-Solid +cystic- Hypoechoic lesion	II-Nodular hyperplasia	Not available	01

	Taller than wide shape- Lobulated margins- and Echogenic foci - nil			
5	5ai) V-Solid nodule Hypoechoic halo Multiple calcifications	II-Adequate cellularity with thyroid follicular cells in micro follicles, clusters, and singles in a background of scanty thin colloid -Lymphocytic thyroiditis	Not available	04
	5aii) V-Solitary solid lesion Taller than wide Hypoechoic	II-Adequate cellularity with thyroid follicular cells in micro follicles, clusters, and singles in a background of scanty thin colloid -Lymphocytic thyroiditis	Not available	
	5aiii) V-Hypoechoic Lobulated margins, Punctate calcification,	II- Adenomatoid nodule Scant cellularity showing thyroid follicular cells in the follicular pattern in a background of colloid.	Not available	
	5b) V-Solitary solid lesion Taller than wide Hypoechoic	III-Moderately cellular smears showing thyroid follicular cells in the micro follicular pattern, clusters with a round to oval nucleus, showing mild anisonucleosis with a moderate amount of cytoplasm in the background of abundant colloid.	Not available	

On further analysis of these 13 discordant cases,8 cases were underdiagnosed on TI-RADS.

Histopathology was available in 3 cases out of a total of 8 underdiagnosed cases, in which 2 of them turned out to be a Follicular variant of Papillary thyroid carcinoma on histopathology, another case being classical Papillary Thyroid Carcinoma.

The remaining 5 cases out of 13 discordant cases were described as probably malignant on TI-RADS; hence these cases were over-diagnosed on TI-RADS.

Out of these five over-diagnosed cases, 1 case belongs to TI-RADS category IVB and BETHESDA category II, remaining 4 cases belongs to TI-RADS V and BETHESDA category II (3 cases) and III (1 case), respectively.

Table 24: Correlation of TI-RADS with BETHESDA system

TI-RADS		BETHESDA		Total	Chi-Square	kappa	p-Value
		Malignant	Benign				
Malignant	Count	13	4	17	34.718	0.594	<0.001S*
	Row %	76%	24%	100%			
	Column %	59%	4.71%	15%			
Benign	Count	9	81	90			
	Row %	10%	90%	100%			
	Column %	40%	95%	84%			
Total	Count	22	85	107			
	Row %	20.56%	79.44%	100%			
	Column %	100%	100%	100%			

Chi-square = with 1 degree of freedom; P <0.001(statistically significant).

Number of observed agreements: 94 (87.85% of the observations)

Number of agreements expected by chance: 75.1 (70.08% of the observations).

Kappa= 0.594 (Moderate agreement)

SE of kappa = 0.101

95% confidence interval: From 0.394 to 0.791

S*=Significant

Table 25: Comparison of rate of malignancy of FNAC with Histopathology in each category

Histopathological diagnosis	I	II	III	IV	V	VI	Grand Total
Benign	**1**	**16**	**1**	**1**	**2**	**-**	**21**
Adenomatous hyperplasia	0	1					
Follicular adenoma	0	2		1			
Hashimoto's thyroiditis	0	2					
Multinodular goiter	0	4			2		
Nodular hyperplasia with cystic degeneration	1						
Nodular hyperplasia	0	7	1				
Malignant	**0**	**3**	**0**	**6**	**4**	**3**	**16**
Follicular carcinoma-metastasis	0	0	0	2	0	0	
Follicular variant of papillary Thyroid carcinoma	0	2	0	1	1	0	
Hurthle cell Carcinoma	0	0	0	1	0	0	
Non-invasive follicular thyroid neoplasm with papillary like nuclear features.	0	1	0	0	0	0	
Papillary thyroid carcinoma	0	0	0	1	3	3	
Classical papillary thyroid carcinoma	0	0	0	1	0	0	
Total	1	19	1	7	6	3	37
Risk of malignancy(%)	0	15.79	0.00	85.71	66.67	100.00	43.24

Fig 21: Gross specimen of follicular adenoma which is well circumscribed.(B/72/19)

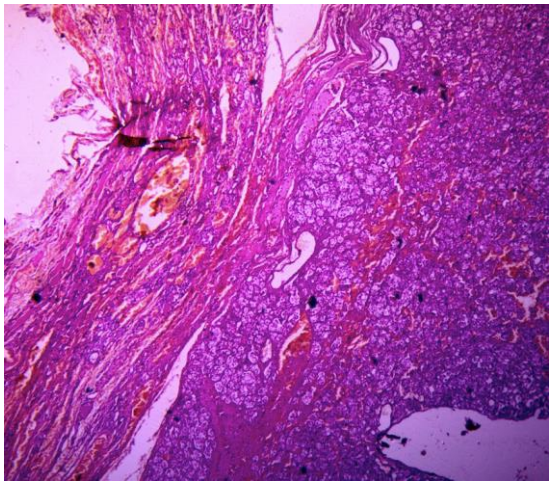


Fig 22: Histopathology of Follicular adenoma. The tumor is well encapsulated and shows repetitive microfollicles. Surrounding normal thyroid tissue is also seen.(H & E, 40x)

Fig 23/B-373-19: Gross specimen of Papillary thyroid carcinoma showing a hard grey white mass.

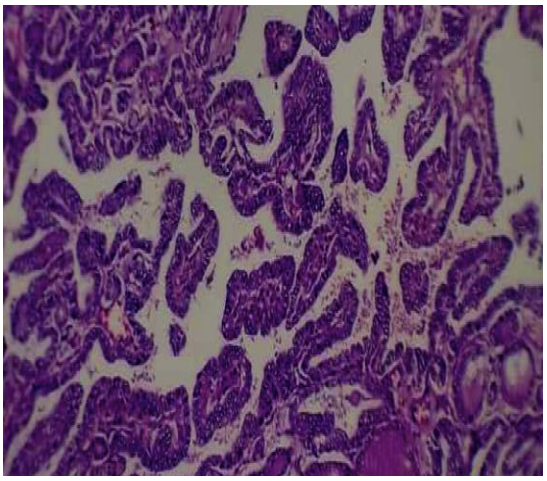


Fig 24/B-373-19: Histopathology of Papillary thyroid carcinoma showing papilla lined by a single layer of cuboidal cells. The nuclei is optically clear (Orphan Annie Eye). Psammoma body is also noted. The stroma of the papilla is oedematous and shows lymphocytes.(H & E, 40x).

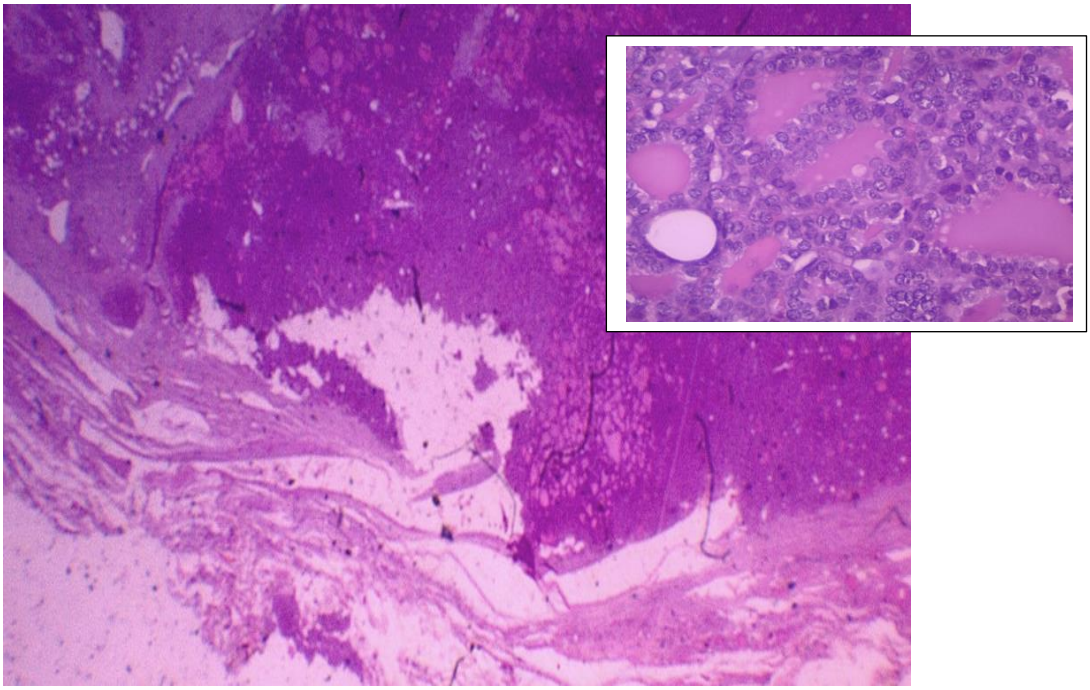


Fig 25/B-1055-19: Histopathology of Follicular Carcinoma showing capsular invasion (H & E, 40x) with inlet showing follicular cells with tall columnar epithelium (H & E, 100x).

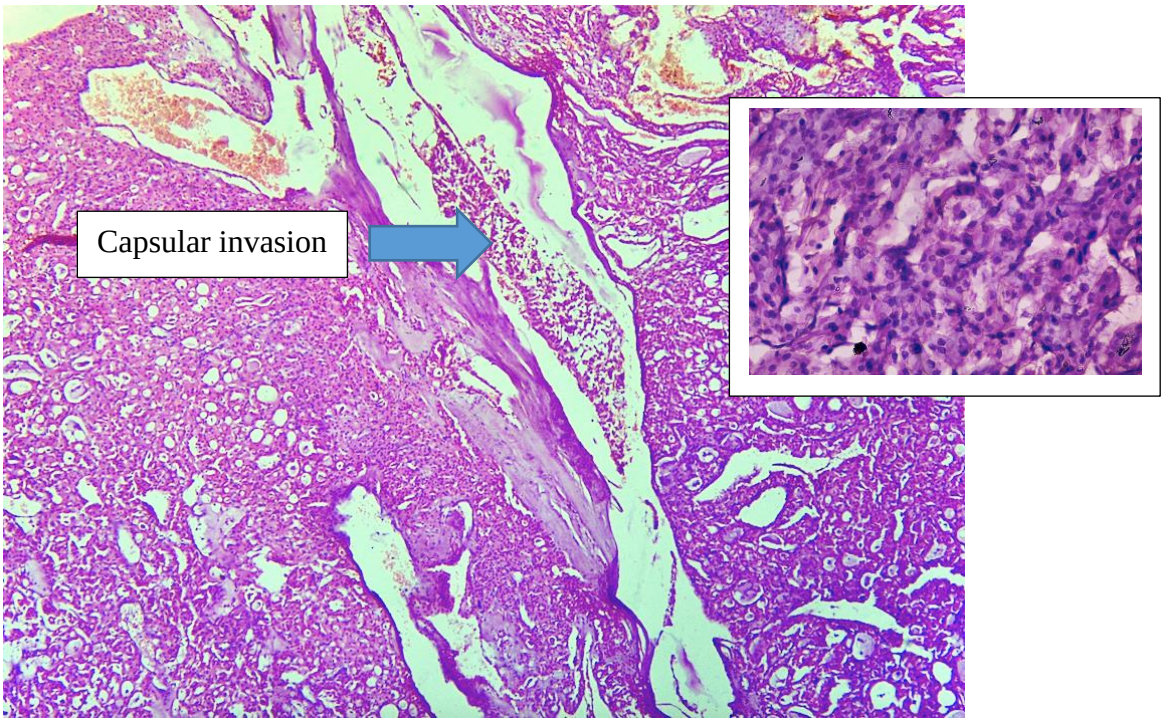


Fig 26/B-1548-20: Histopathology of Hurthle cell carcinoma with capsular invasion (H & E, 40x) and inlet showing hurthle cells with granular oxyphilic cytoplasm and few oncocytes (100x).

Table 26: Histopathology diagnosis of benign and malignant cases.

	No. of cases = 37	Percentage(%)
Benign	21	56.76
Malignant	16	43.24

Histopathological specimens were available in 37 cases out of a total of 107 cases (34.58%), of which 21 cases (56.76%)were diagnosed benign, and 16 cases (43.24%) were malignant.

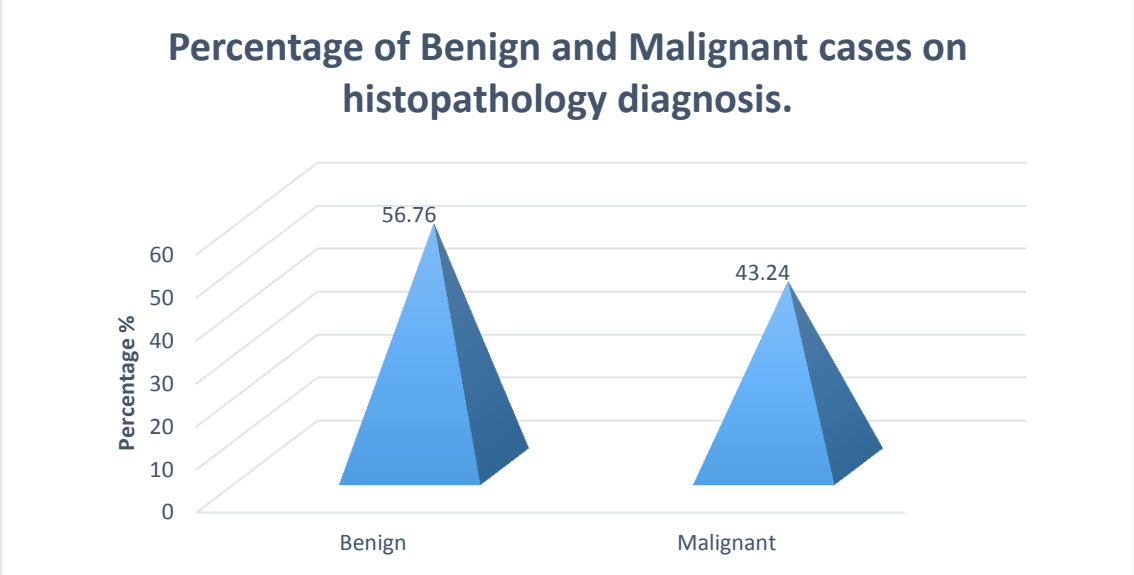


Chart 7: Column diagram showing the percentage of benign and malignant cases on Histopathology.

Table 27: Comparison of TI-RADS with Histopathology diagnosis.

		Histopathology		Total
TI-RADS		Malignant	Benign	
	Malignant	08(True Positive)	01(False Positive)	16
	Benign	08(False Negative)	20(True Negative	21
	Total	16	21	37

The significance level for tests was determined as 95% ($p < 0.05$).

Table 28: Accuracy of TI-RADS reporting.

Category	**Percentage(%)**
Sensitivity	50.00
Specificity	95.24
Positive predictive value	88.89
Negative predictive value	71.43
Accuracy	75.68

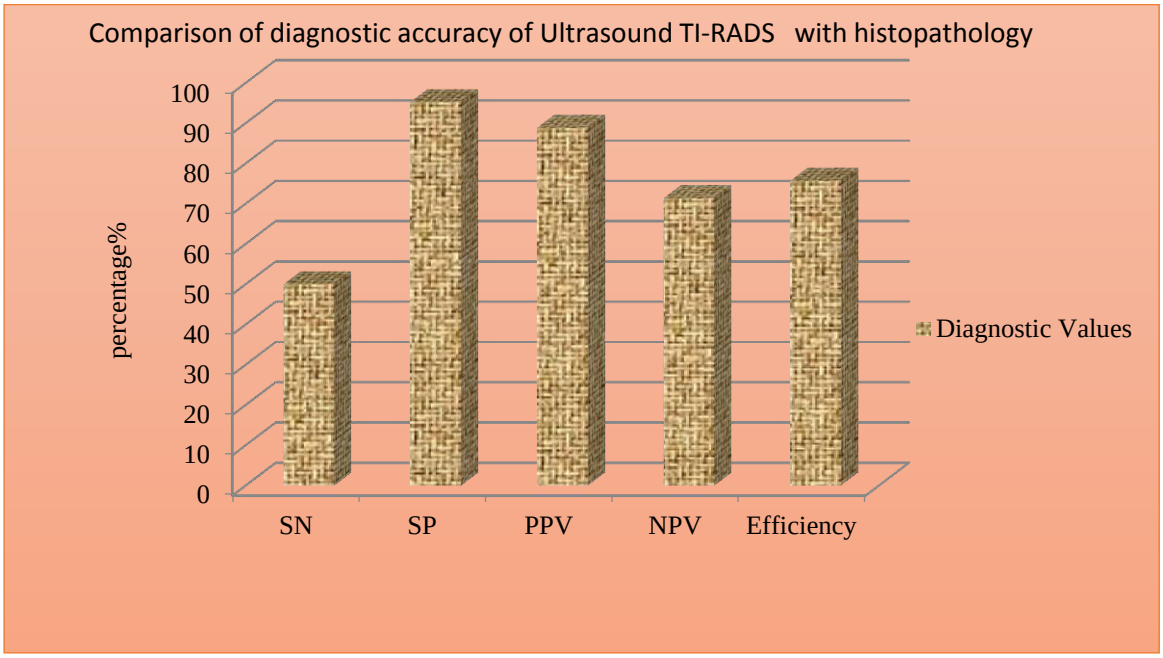


Chart 8: Bar diagram showing the comparison of diagnostic accuracy of Ultrasound TI-RADS with Histopathology.

Table 29: Comparison of BETHESDA with histopathology Diagnosis.

		Histopathology		Total
Cytology		Malignant	Benign	
	Malignant	13(True Positive)	3(False Positive)	16
	Benign	3(False Negative)	18(True Negative	21

Table 30: Accuracy of BETHESDA Reporting.

Diagnostic Values	Percentage(%)
Sensitivity	81.25
Specificity	85.71
Positive predictive value	81.25
Negative predictive value	85.71
Accuracy	83.78

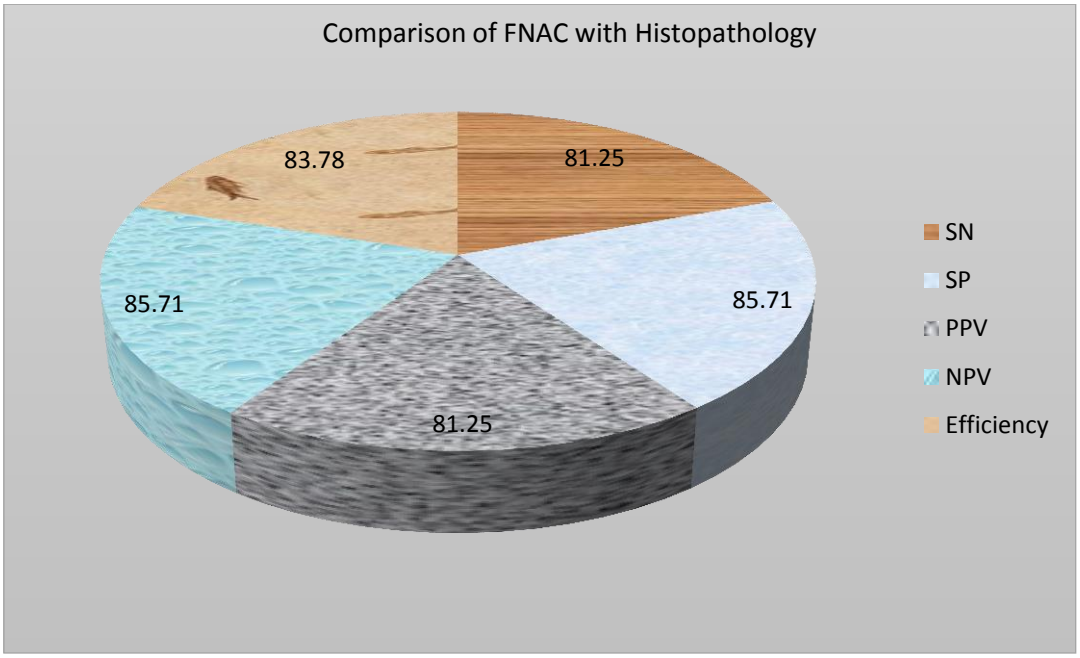


Chart 9: Pie chart showing the comparison of diagnostic accuracy of FNAC with Histopathology.

Table 31: Comparison of TI-RADS and BETHESDA with Histopathological diagnosis.

Histopathological Diagnosis					
	Malignant		Benign		Total
	No	%	No	%	
Malignant	13	81.25	3	18.75	16
Benign	3	14.29	18	85.71	21
Total	16	43.24	21	56.76	37

Table 32: Combined diagnostic accuracy of TI-RADS and BETHESDA on comparison with Histopathology

Sensitivity	81.25%
Specificity	85.71%
Positive predictive value	81.25%
Negative predictive value	85.71%
Accuracy	83.78%

DISCUSSION

DISCUSSION

This was an observational study conducted on 107 patients with Thyroid enlargement to study the co-relation between TI-RADS ultrasound categories and BETHESDA cytology categories of thyroid lesions.

AGE WISE DISTRIBUTION

In this study, the age of patients ranged from 8 to 70 years. The mean age was 41.67±14.41years. The highest incidence was in the age group 41 to 50 years (26.17%), followed by 21 to 30 years (25.23%). Our findings were consistent with other studies, as shown in Table 33.

Table 33: Comparison of mean age of clinical presentation of the present study with other studies

S No.	Author's Name	Mean Age (in years)
1	Vargas-Uricoechea et al (2017)[13]	57
2	Chen Y et al. (2017)[12]	54.15±13.08
3	Hong MJ et al. (2018)[15]	51.2 ± 12.2
4	Regmi S et al. (2018)[16]	50.74±17.8
5	Barbosa et al. (2019)[17]	49 ± 13
6	Kapse Pratik Siddheshwar et al. (2020)[18]	3rd-5th decade of life
7	**The present study (2020)**	41.67±14.41years

GENDER WISE DISTRIBUTION

In this study, females (81.31%) were more commonly affected than males (18.69%). Male to female ratio was 1:4.35; similar findings were observed in the literature as follows: -

Table 34: Comparison of the gender-wise distribution of cases of the present study with other studies

S No.	Authors	Male: Female ratio
1	Hong MJ et al. (2018)[15]	1:2.26
2	Vargas-Uricoechea et al (2017)[13]	1:3
3	Regmi S et al. (2018)[16]	1:12
4	Kapse Pratik Siddheshwar et al. (2020)[18]	1:3
5	**The present study (2020)**	1:4.35

Females were affected more than the males because autoimmune thyroid disease is significantly more frequent in females than in males, so patients with autoimmune thyroid disease visit the physician more often, increasing the probability of detecting the nodules either through palpation or ultrasound; clinically, this situation may be defined as a "medical surveillance bias"[10] Females detect thyroid enlargement early and seek medical attention due to cosmetic reasons.

TI-RADS REPORTING SYSTEM

Many investigations have focused on the ultrasound characteristics of thyroid lesions as indicators of nodule malignancy. An array of authors and institutions has developed several ultrasound systems to stratify the nodules according to malignancy risk and provide a standardized language for radiologists and endocrinologists.

In 2009, Horvath[5] was the first to propose TI-RADS as a method to stratify the estimated risk of cancer in thyroid nodules and select those nodules needing to undergo FNAC.

TI-RADS is formulated after the American College of Radiology (ACR) BI-RADS, a widely accepted risk stratification system for breast lesions, further modified by ACR in 2017.

This classification system's rationale is that the risk of malignancy rises in parallel with the increase of the number of suspicious ultrasound features and the lack of benign findings.

The American TI-RADS has five different categories for nodule appearance: composition, echogenicity, shape, margins, and echogenic foci; each of these features is associated with a score ranging from 0 to 5 points.

These points in total determine the nodule's TI-RADS level, which extends from TRI, benign, to TRV, high suspicion of malignancy. Vascularity and elastography scoring are not given importance in classification. TI-RADS scores IVB, IVC and V, were considered positive for malignancy, while scores I-III and IVA were considered negative for malignancy.

M Naren Satya Srinivas et al. (2016) [24] studied in 2016 to evaluate the reliability of thyroid imaging reporting and data system in differentiation between benign and malignant thyroid lesions. It revealed the risk of malignancy in TI –RADS categories one and II were found to be 0%, 0.64 % in category 3, 4.76% in category IVA, 66.67% in category IVB, 83.33% in category IVC, and 100% in category V. The specificity of three sonological features (completely cystic structure, hyper-echogenicity, and macro calcification) in classifying a nodule as benign was 100%.

Loss of central echogenic hilum, presence of an irregular and indistinct margin, micro calcification, and necrosis was found to have the sensitivity of 100%, 63.63%, 27.27%, and 9.09%, respectively, and specificity of 95.7%, 98.5%, 100%, and 100%, respectively for a cervical lymph node to be malignant.

Ricardo[28] studied in 2017, intending to assess the likelihood of malignancy from ultrasound features in 1413 thyroid nodules. A score was established by attributing different weights to each ultrasound feature evaluated. Overall, the frequency of malignancy in thyroid nodules according to the categories was 1.0% for TI-RADS III, 7.8% for TI-RADS IVA, 35.3% for TI-RADS IVB, and 84.7% for TI-RADS. This study concluded that the newly proposed TI-RADS classification adequately assessed the likelihood of malignancy in thyroid nodules.

In a study done in 2019 by Stephanie [50], it was observed that TI-RADS is best to stratify and evaluate thyroid nodules. For each ultrasound feature, TI-RADS has a point system, and the sum of these points explains the risk of malignancy. In contrast to TI-RADS, the other systems depend on pattern recognition. Hence, TI-RADS

needs to be applied accurately and more universally. Although there is quite a possibility of clinical challenges due to interobserver variability in interpretation, the radiologists' intensive training with TI-RADS can provide the most accurate results and proper care for patients with thyroid nodules.

TI-RADS CATEGORIES

In the present study, the most common TI-RADS category was III (53.27%), followed by II (18.69%).

Table 35: Distribution of TI-RADS categories of the present study with other studies

TI-RADS category	Vargas-Uricoechea et al. (2017)[13]	Periakaruppan G et al. [25]	Kapse Pratik Siddheshwar et al. (2020)[18]	**The present study (2020)**
Total number of cases	180	184	50	107
I	40%	0%	0%	4.67%
II	25.0%	63.59%	58%	18.69%
III	22.8%	24.46%	14%	53.27%
IV	34.4%	7.07%	16%	13.08%
V	17.8%	4.89%	12%	9.35%

As compared with the other studies, cases in category III were observed more in the present study as compared to category II. This could be due to geographic variation and the Patient referral system.

Thyroid cytology reporting

The technique of FNAC flourished in Europe during the 1950s and 1960s.[7]

Among the first of pathologists to embrace FNAC, Zajicek, in collaboration with Franzen at Radiumhemmet of the Karolinska Hospital, an oncologic center, applied the requisite scientific rigor to dictate accurate diagnostic criteria and to estimate the diagnostic accuracy in a variety of lesions.

FNAC is now an integral part of the department of pathology. Dr. M.S. Sukumaran in Madras and Dr. Subhash Kumari Gupta in the Postgraduate Institute of Medical Education and Research, Chandigarh, introduced FNA as a diagnostic tool in cytopathology in India.[7]

Silverman JF et al. (1986) proposed that FNAC can be used as an initial modality in the evaluation of palpable thyroid nodules, with a sensitivity of 93% and specificity of 95%.[30]

Studies by Lee et al. (1987), Palombini et al. (1988), Layfield et al. (1989), and Ljung et al. (2001) have stated that quality training in obtaining and preparing the smears play an important role in the efficiency of the FNA procedure.[7]

Hall T et al. (1989) stated that all the cases with a false negative diagnosis were ascribed to missed sampling or because of inadequate smears. Inadequate smears, FNA showed a sensitivity of 100% in diagnosing malignant tumors, reaffirming its role as the first-line screening modality for thyroid nodules.[35]

Burch HB et al. (1996)[36] stated that FNA has pioneered in determining the management of thyroid nodules to conclude that the high sensitivity, specificity, and diagnostic accuracy of FNA, for the detection of malignant tumors has singly overshadowed other diagnostic modalities. He observed that FNA's efficiency depends upon several factors, including the experience of the aspirator and skillful cytological interpretation.

A standardized reporting system was lacking for thyroid FNA. The Papanicolaou Society of Cytopathology, The Royal College of Physician-British Thyroid Association, and The American Association of Clinical Endocrinologists had laid down diagnostic guidelines, none of which were universally accepted.

BETHESDA reporting system

The National Cancer Institute in the United States hosted the State of the Science Consensus Conference on Thyroid FNAC on October 22 and 23 in 2007 in Bethesda, Maryland to address the terminologies and other issues related to thyroid FNA where the Bethesda System for Reporting Thyroid Cytopathology with its six diagnostic categories was introduced, and each category was stratified with the risk of malignancy.

Ali S.Z[46], in an article 'Bethesda and Beyond' (2010) stated that even though the majority of thyroid lesions turn out to be benign, a small percentage of carcinomas need to be accurately diagnosed for timely and optimal surgical treatment. TBSRTC (Bethesda system for reporting thyroid cytology) has elaborate and well-founded management algorithms with a risk of malignancy in each of the six categories. The

worrisome category of 'indeterminate' has led to discovering molecular markers, such as BRAF, which have displayed promising potential in recently published articles. Following the TBSRTC monogram, in 2009, the American Thyroid Association revised its clinical management guidelines for thyroid nodules.

Crippa et al.[47] (2010) stated that TBSRTC represents a major move toward reproducibility, standardization, enhanced clinical significance, and concluded that borderline lesions of the thyroid required a multidisciplinary approach.

Mehra et al.[50] (2015) stated that the BETHESDA monograph was written in an easy-to-read format, concise, and had useful color photomicrographs that helped make the diagnosis. The physicians were also benefitted because of the management guidelines it provides.[9]

A study by Mamatha et al. [51] (2015) on 240 patients showed a sensitivity, specificity, PPV, and NPV of 77%, 69%, 37%, and 93% respectively in the Conventional system, whereas in TBSRTC, the sensitivity, specificity, PPV and NPV were 100%, 82.5%, 45%, and 100% respectively. It was summarized that interobserver variability was lowered by utilization of TBSRTC.

A study by Gupta et al.[52] (2016) reported that the diagnostic accuracy was overall higher in TBSRTC and stated that it has a superior edge over the Conventional System and should be incorporated in routine reporting of thyroid FNAC.

Table 36: Comparison of the distribution of the number of patients in each of the BETHESDA categories of the present study with other studies.

	BETHESDA category	Vargas-Uricoechea et al.[13] (2017)	Periakaruppan G et al [25](2018)	Kapse Pratik Siddheshwar et al[18] (2020)	Theohari's et al [45](2009)	Arul P et al [48](2015)	Anand B et al [54](2020)	**The present study (2020)**
Benign	Total no of cases	180	184	50	3207	209	646	107
	I	0%	8.70%	0%	11.1%		13.8%	1.87%
	II	36.1%	83.15%	72%	73.8%	65.2%	75.9%	73.83%
	III	21.7%	1.09%	4%	3.0%	10%	1.2%	4.67%
Malignant	IV	22.8%	2.72%	12%	5.5%	10.6%	3.7%	9.35%
	V	19.4%	3.26%	8%	1.3%	5.3%,	2.6%	6.54%
	VI	0%	1.09%	4%	5.2%	6.3%.	2.8%	3.74%
	Total	100	100	100				100

When compared to other studies, cases in category II were observed high in the present study. The most common category was ll (73.83%), followed by IV (9.35%). So it is concluded that Benign Thyroid Lesions are more common than malignant thyroid Lesion.

A study by Garg et al[42] in 2009 on 434 patients showed that the most frequent thyroid lesion was colloid goiter in 250 (57.60%) cases, followed by thyroiditis in 119 (27.41%) cases, 10 (2.30%) adenomatous goiters, and 2 cases (0.004%) of thyroglossal cysts. 14 (1.38%) cases were reported as follicular neoplasms(FN) and 17(3.91%) as malignant tumors.

Gautam HK et al[39] FNAC findings in 2018 showed that 61% of patients had a colloid nodule, 17% of patients were follicular neoplasm, 10% were adenomatous hyperplasia, 6% of patients were hyperplastic multinodular goiter, and 4% had lymphocytic thyroiditis. Two had malignant lesions, which included 1% papillary carcinoma and 1% anaplastic carcinoma.

Out of 528 cases studied by Naz et al.[49] (2014), 403 cases were diagnosed as benign (Bethesda II) and 67 were Bethesda III (follicular lesion of undetermined significance, FLUS), while 22 cases were categorized as either malignant or suspicious for malignancy (Bethesda V and VI). BETHESDA Category II is considered benign in patient management; BETHESDA category V and VI are treated as malignant. BETHESDA category III and IV are considered gray zones posing challenges in diagnosing and managing cases.

BETHESDA CATEGORY III

Architectural/nuclear atypia not sufficient to be classified as follicular neoplasm (or suspicious for follicular neoplasm), suspicious for malignancy or malignant, a heterogeneous category In the context of follicular-patterned lesions.

Following cytological features are graded under Category III-

(i) A sparsely cellular aspirate with scant colloid and mainly consisting of micro follicles with dense colloid, raising the possibility of an FVPTC.

(ii) A specimen containing some follicular cells exhibiting focal nuclear atypia such as nuclear grooves and clearing, suggesting FVPTC or papillary thyroid carcinoma.

(iii) A hypocellular aspirate showing focal oncocytic features.

(iv) Atypical cyst-lining cell clotting.

BETHESDA CATEGORY -IV

FN or SFN corresponds to diagnostic category IV of TBSRTC and refers to a cellular aspirate consisting of follicular cells, mostly arranged in an altered architectural pattern characterized by significant cell crowding /micro follicle formation or syncytial fragments.

The predominant non-macro follicular architectural pattern, characteristics of most follicular-patterned thyroid lesions, is usually seen in the FN/SFN category. The colloid is scant or absent.

Micro follicles consisting of 5 to 15 cells are variably admixed with trabecular or ribbon-like groups of follicular cells, rarely cantered by a droplet of dense colloid. Follicular cells are normal-sized or enlarged and uniform with scant to moderate amounts of cytoplasm. Nuclei are round and slightly hyperchromatic with inconspicuous nucleoli and regular nuclear contour.

BETHESDA Category III patients are managed conservatively with follow up. BETHESDA Category IV includes both Follicular adenoma and Follicular Carcinoma because it is difficult to identify capsular /vascular invasion on cytology. Hence most of the BETHESDA Category IV are treated like malignant cases. Therefore, for this study purpose, Category III is grouped under benign lesions and Category IV as malignant cases and are taken for Thyroidectomy.

Similar to other studies, benign Thyroid lesions are observed more in the present study. A total of 16 cases (14%) cases are found in Bethesda category III and Bethesda category IV, which fall into the category of gray zones in cytology of Thyroid Lesions were found in the present study.

Table 37: Comparison of Benign and Malignant cases with other studies of the present study with other studies

(BETHESDA)	Regmi S et al. (2018)[16]	Shivani Garg et al. (2017)[42]	Avinash et al. (2016)[38]	The present study (2020)
Probably Benign categories	68.5%	66.7%	91.43%	79%
Probably malignant categories	7.4%	16.7%	8.57%	21%

Analysis of TI-RADS and BETHESDA correlation showed the following findings: -

Number of observed agreements: 94 (87.85% of the observations)

Number of agreements expected by chance: 75.1 (70.08% of the observations).

Kappa= 0.594 (Moderate agreement)

SE of kappa = 0.101

95% confidence interval: From 0.394 to 0.791

S*=Significant

In 2007 Vargas-Uricoechea et al.[13] conducted a study with predominantly female participants, with an average age of 57. The frequency of BETHESDA II was 65/180 versus 45/180 in TI-RADS 2. The highest concordance was found among the category II 36% (65/180) classification on the nontoxic thyroid nodule found among the category II classification compared to TI-RADS category IV 25% (45/180). The observed agreement was 87.2% with a linear weighted kappa of 0.69 (95% CI: 0.59-0.79).

The heterogeneity analysis showed a trend towards a higher weighted kappa value in nodules ≥4 cm in males and individuals aged ≥50 years, with accelerated nodular growth, binding to adjacent structures, vocal folds' paralysis, urban origin, and a history of head and neck radiation therapy.

Out of 528 cases in a study by Naz et al.[49] in 2014, For BETHESDA categories V and VI, the concordance rate with TI-RADS categories was100%, while for Bethesda II, the Concordance rate was 88%.

We have observed a good correlation between TI-RADS and BETHESDA categories in 88% of cases with kappa value =0.593 showing moderate agreement between the two diagnostic modalities with a statistically significant P value <0.001.

Table 38: Comparison of the percentage of agreement between TI-RADS and BETHESDA with other studies.

S NO	Author Name(year)	Agreement(%)
1	Vargas-Uricoechea et al.[13] (2017)	87.2%
2	Regmi S et al.[16] (2018)	77.77%
3	Ashraf M.[55] (2018)	67.6%
4	**The present study (2020)**	88%

- Out of a total of 107 cases,13 cases are discordant out of which 08 Cases have been designated as probably benign on TI-RADS, out of which 1 case in total belongs to TI-RADS category I, 6 cases belong to TI-RADS category III, and only 1 case belongs to TI-RADS category IVA.

  The remaining 5 cases reported as probably malignant on TI-RADS are as follows: -

  a) One case of TI-RADS IVB turned out to be BETHESDA II.
  b) Four cases of TI-RADS V (3 Cases turned out to be BETHESDA II, 1 Case of BETHESDA III).
  c) Hence for the nodules categorized as TI-RADS 3 or 4, USG-Guided FNAC should be done.

In the present study, Histopathology correlation was available only in 37(34.55%) cases out of 107 cases. Other cases are managed conservatively or lost for follow up.

Table 39: Comparison of Sensitivity and specificity of TI-RADS with Histopathological diagnosis.

TI-RADS	Remonti et al .[22] (2015)	Ashraf et al. [55] (2018)	**Present study (2020)**
Sensitivity	87.9%	76.9%	50%
Specificity	86.2%	91%	95.24%
Positive predictive value	30.6%	71.4%	88.89%
Negative predictive value	98.6%	76.4%	71.43%
Diagnostic accuracy	76.4%	75.3%	75.68%

A study was done by Bruno Mussoi de Macedo et al [59] in 2018 on Reliability of Thyroid Imaging Reporting and Data System (TI-RADS). Ultra sonographic classification of the American Thyroid Association (ATA) in differentiating benign from malignant thyroid nodules when compared with cytological results, sensitivity, specificity, negative predictive value (NPV), and accuracy were 100%, 61.1%, 100, and 63%, respectively for TI-RADS; and 100%, 75%, 100%, and 76%, respectively for ATA. Compared with histopathological results, sensitivity, specificity, NPV, and accuracy were 90%, 51.4%, 94.7%, and 60%, respectively, for TI-RADS; and 100, 60, 100, and 68%, respectively, for ATA. According to the ATA system, all patients

with malignant nodules were classified in the categories IV or V of TI-RADS and in the intermediate or high suspicion risk.

Low sensitivity is due to 2 cases of Follicular variant of PTC, known to have a lower

TI-RADS score.

- On further analysis of these cases, histopathology was available in 3 cases out of a total of 13 discordant cases, which belong to the category of 8 underdiagnosed cases on TI-RADS, and it was found that 2 of them belong to the Follicular variant of PTC.
- In literature studies done by Zhang F, Chen W et al. (2020)[61]on Sonographic features of follicular variant of papillary thyroid carcinoma (FV-PTC) and diagnostic performance of the TI-RADS in 2017 on FV-PTC, it was found that on comparison of C-PTC with FV-PTC, FV-PTC had lower percentages of a taller-than-wide shape (11.3% vs. 46.6%) and lobulated or irregular margin (33.0% vs. 61.8%), and a higher percentage of extrathyroidal extension (20.8% vs. 8.2%). FV-PTC featured macro calcifications, whereas punctate echogenic foci were more frequently seen in the C-PTC group. Other characteristic US appearances of FV-PTC included uneven hypoechoic halo and peripheral vascularity. The mean TI-RADS score of FV- PTC cases was lower in the FV-PTC group, 11.3%, 44.3%, and 42.5% categorized as TI-RADS 3, 4, and 5, respectively.

Table 40: Comparison of Sensitivity and Specificity of FNAC with Histopathological diagnosis.

BETHESDA	Garg et al.[42] (2009)	Tabaqchali et al.[40] (2000)	Mamtha et al.[51] (2015)	Anand et al.[54] (2020)	Naz et al.[49] (2014) (2014)	**Present study (2020)**
Sensitivity	97%	86.8%	77%	72.4%	64.3%	81.25%
Specificity	100%	67%	69%	94.3%	85.1%	85.71%
PPV	96%	-	37%	84%		81.25%
NPV	100%	-	93%	89.2%		85.71%
Efficiency	-	-		87.9%	80.3%	83.78%

The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy hence obtained are 72.4%, 94.3%, 84%, 89.2%, and 87.9%, respectively, in the study done by Anand Bakiarathana et al. in 2020.[54]

In a study done by Zhu Y et al.[62] in 2020 on Causes of misdiagnoses by thyroid fine-needle aspiration cytology when BETHESDA Category V and VI were both considered cytologic-positive, the sensitivity, specificity, PPV, NPV, and diagnostic accuracy of FNAC were 98.0%, 84.0%, 99.4%, 58.3%, and 97.5% respectively. The main cause of false-negative diagnoses was sampling error (86.7%), while interpretation error led to most false-positive diagnoses (80.9%). Overlapping cytological features in adenomatous hyperplasia, thyroiditis, and cystic lesions were the major factors contributing to interpretation errors, while the size and number of

nodules may have led to false-negative diagnoses because of heterogeneity and unsampled areas.

The presence of nuclear grooves in benign and malignant thyroid lesions lowers the diagnostic accuracy of FNAC.

Table 41: Comparison of the rate of malignancy in each BETHESDA Category with other studies.

BETHESDA CATEGORY		Naz et al.[49] (2014)	Mohamed Abdulaziz et al.[26] (2018)	**Rate of malignancy in the present study (2020)**
I	Unsatisfactory/Nondiagnostic	----	--	0%
II	Benign	11.1%	10.7%	15.79%
III	AUS/FLUS	33.4%	25%	0%
IV	Follicular neoplasm/suspicious for a follicular neoplasm	25%	70%	85.71%
V	Suspicious for malignancy	100%	88.9%	66.67%
VI	Malignant	100%	100%	100%

In the present study, since histopathology was available only in 37 cases, the rate of malignancy is underestimated as compared to other studies in BETHESDA Category V and VI.

In a study done by Mohamed Abdulaziz et al.[26] in 2018 , the percentages of malignancy-risk for each Bethesda category are similar to the values reported in the American Thyroid Association Management Guidelines and other studies. The comparisons are as follows: 25% versus 9% to 32% (“nondiagnostic or unsatisfactory” category), 10.7% versus 1% to 10% (“benign and nonneoplastic” category), 18.9% versus 6% to 48% (AUS/FLUS), 70% versus 53% to 97%

("suspicious for malignancy" category), and 88.9% versus 94% to 100% ("malignant" category).

Bethesda category IV shows marked variation in malignancy rate due to the limitation of cytology in assessing the capsular/vascular invasion.

Table 42: Comparison of combined diagnostic accuracy of TI-RADS and BETHESDA with Histopathology.

Combined TI-RADS and BETHESDA Diagnosis	Ashraf M[55] (2018)	Singapore Walla et al.[63] (2017)	The present study (2020)
Sensitivity	76.9%	70.6%	81.25%
Specificity	91.3%	90.4%	85.71%
Positive Predictive value	71.4%,	91.3%	81.25%
Negative Predictive value	76.4%	93.8%	85.71%
Diagnostic Efficiency	75.3%	83%	83.78%

On comparing the combined diagnostic accuracy of both TI-RADS and BETHESDA with histopathology, the present study results are in complete concordance with studies done by Singapore wala[63] in 2017 and Ashraf et al.[55] in 2018.

The combination of TI-RADS and BETHESDA system plays a major role in the management of Thyroid lesions.

SUMMARY

SUMMARY

The following are the key observation and findings from our research study done in a detailed way (total no. of cases considered are N=107):

- A total of 107 cases have been studied, the patient's age ranged from 8-70 years, and the mean age was 41.67±14.41 years. The highest incidence was in the age group 41-50 years (26.17%), followed by 21-30 years (25.23%).
- In the present study, female patients were more common than males with an M: F ratio of 1:4.35.
- As per the TI-RADS category, the most common category was III (53.27%), followed by II (18.69%).In the Ultrasound investigation for 107 cases, 89 (83%) were benign lesions, while 18 (17%) were malignant lesions.
- In FNAC, 79.44 % were diagnosed as benign and 20.56% as malignant lesions. As per the BETHESDA category, the most common category was II (73.83%), followed by IV (9.35%). Among benign lesions, Nodular Hyperplasia was observed in 47.37%, followed by Nodular Goitre (26.32%). Among malignant lesions, PTC-CLASSICAL was observed in 33.33%, followed by FV-PTC (27.78%).
- There was 80 % Concordance between TI-RADS I and BETHESDA II, 100 % between TI-RADS II and BETHESDA II, 89.47% between TI-RADS III and BETHESDA II and III, 85% between TI-RADS IVA and BETHESDA II, 85% between TI-RADS IVB and IVC and BETHESDA IV and V, 63.64% between TI-RADS V and BETHESDA IV, V and VI.
- Histopathological specimens were available in 37 cases (34.58% across N cases), of which 57% were diagnosed benign, and 43% were malignant.

- On histopathology correlation, TI-RADS reporting accuracy turned out to be 75.68% with a sensitivity of 50%, a specificity of 95.24%, a positive predictive value of 88.89%, a negative predictive value of 71.43%.
- On histopathology correlation, the accuracy of BETHESDA reporting turned out to be 83.78% with a sensitivity of 81.25%, the specificity of 85.71%, the positive predictive value of 81.25%, the negative predictive value of 85.71%.
- Out of 107 cases studied, 94 cases were concordant, whereas 13 cases were discordant between TI-RADS and BETHESDA. One case was concordant on both TI-RADS and BETHESDA, but it was missed on both the diagnostic modalities as the actual diagnosis of FV-PTC was confirmed on histopathology it was missed on TI-RADS being the FV-PTC but and false negative in BETHESDA because of the Non-representative sample.
- The percentage of the agreement between both TI-RADS and BETHESDA was 88% with Cohen's k 0.593, so there was a moderate agreement observed in both the diagnostic modalities, with p-value (<0.001) showing statistically significant results.
- On analysis of Combined diagnostic accuracy of both TI-RADS and BETHESDA with histopathology, the diagnostic accuracy of both the diagnostic modalities was found to be 83.78 % with a sensitivity of 81.25%, the specificity of 85.71%, the positive predictive value of 81.25%, and negative predictive value of 85.71%.

CONCLUSION

CONCLUSION

This study shows a remarkable correlation between TI-RADS ultrasound classification and Bethesda cytology, especially for benign nodules.

TI-RADS and TBSRTC classification systems should be considered feasible and effective diagnostic modalities for predicting malignant lesions in patients with thyroid nodules.

The probability of a particular nodule being malignant can be inferred from the ultrasound-based TI-RADS system with a certain level of confidence. It will help avoid many unnecessary thyroid-related surgical procedures in cases where both TI-RADS and BETHESDA Categories are low and warrant early intervention in higher scores with increased risk of malignancy.

The combination of both TI-RADS and TBSRTC can also be of great help to surgeons in deciding the extent of surgical procedure. Research with a large sample size will make the pre-operative assessment of thyroid more accurate.

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ANNEXURE

ANNEXURES

STUDY PROFORMA

Co-relation between BETHESDA cytology categories of thyroid lesions and TI-RADS ultrasound categories.

Serial No:

Cytology No:

NAME: I.P.NO:

AGE: Hosp. No:

SEX: D.O.A:

OCCUPATION: D.O.D:

ADDRESS:

CHIEF COMPLAINTS & DURATION

1)

2)

3)

4)

HISTORY OF PRESENTING ILLNESS

1) SWELLING:

2) PAIN

Aggravating/relieving factors

3. PRESSURE EFFECTS

4. TOXIC SYMPTOMS/HYPERTHYROID SYMPTOMS

HYPOTHYROID SYMPTOMS

PAST HISTORY:

Radiation to neck in childhood

Pre-existing goitre

Drug history

Any surgery

TB/DM/THYROID NODULES/ASHMA

FAMILY HISTORY

Family members/neighbours suffering from similar complaints

PERSONAL HISTORY

GENERAL PHYSICAL EXAMINATION

Built/nutrition

Pallor/icterus/cyanosis/lymphadenopathy/clubbing

Vital signs

Temp

Pulse

B.P

Respiratory rate

Eye signs

Examination of hands

Tremors

LOCAL EXAMINATION

1. INSPECTION:

Site

Size

Shape

Extent: vertical

horizontal

borders (lower border): surface:

the surrounding area (lymph nodes):

movement of deglutition/protrusion of tongue:

dilated veins:

2. PALPATION:

Tenderness & temperature:

Confirmation of inspection findings:

Consistency;

Mobility:

Position of the trachea:

Carotid pulsations/thrill over the swelling

Regional lymph nodes

SYSTEMIC EXAMINATION

CVS

RS

Per abdomen

CLINICAL DIAGNOSIS

INVESTIGATIONS;

ROUTINE INVESTIGATIONS:

Blood: HB % TC- DC- ESR-

URINE: Alb- Sugar- Micro-

ECG-

Chest X-ray PA-

Blood urea/S. Creatinine-

SPECIFIC INVESTIGATIONS:

Sleeping pulse rate-

X-ray neck AP/Lateral-

Serum T3 T4, TSH

USG Thyroid: TI-RADS Category

Radiology No

FNAC No

BETHESDA Category

Cytological features

TREATMENT:

1. PRE-OPERATIVE TREATMENT-

2. POST-OPERATIVE PERIOD-

OPERATIVE NOTES-

POSTOPERATIVE PERIOD:

3.HISTOPATHOLOGICAL REPORT:

4.FOLLOW UP:

CONSENT FORM

Study title: "Co-relation between BETHESDA cytology categories and TI-RADS ultrasound categories of thyroid lesions."

Chief researcher/ PG guide's name: DR. SONIA KUMARI

Under the guidance of DR. T. N. SURESH

Name of the subject:

Age :

Address :

a. I have been informed in my vernacular language of the purpose of the study, the necessity of relevant investigations to be carried out, and photographs to be taken.
b. I understand that this study's medical information will become part of the institutional record and will be kept confidential by the said institute.
c. I understand that my participation is voluntary and may refuse to participate or may withdraw my consent and discontinue participation at any time without prejudice to my present or future care at this institution.
d. I agree not to restrict the use of any data or results that arise from this study, provided such use is only for the scientific purpose(s).
e. I confirm that _____ (chief researcher/ name of PG guide) has explained to me the purpose of research and the study procedure that I will undergo, and the possible risks and discomforts that I may experience in my language. I hereby agree to give valid consent to participate as a subject in this research project.

Participant's signature

Signature of the thyroid nodules: Date:

I have explained to _____ (subject) the purpose of the research, the possible risk and benefits to the best of my ability.

Chief Researcher/ Guide signature Date:

ರೋಗಿಯ ಮಾಹಿತಿ ಮತ್ತು ಸಮ್ಮತಿ ಪತ್ರ

ಕ್ರಮ ಸಂಖ್ಯೆ:

ರೋಗಿಯ ಹೆಸರು:

ಮೊಬೈಲ್ ನಂಬರ್:

ಶೀರ್ಷಿಕೆ: **"Co-relation between BETHESDA cytology categories and TI-RADS ultrasound categories of thyroid lesions."**

ಈಕೆಳಗೆ ರುಜು ಮಾಡಿರುವ ನಾನು, ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು, ಅಧ್ಯಯನ ನಡೆಸಲು ಮತ್ತು ಈ ಸಮ್ಮತಿ ನಮೂನೆಯಅಂಶಗಳಂತೆ ನನ್ನ ವೈಯಕ್ತಿಕ ಮಾಹಿತಿಯನ್ನು ಬಹಿರಂಗಪಡಿಸುವ ಒಪ್ಪಿಗೆ ನೀಡಿರುತ್ತೇನೆ.

ನನಗೆ ಈ ಅಧ್ಯಯನದ ಉದ್ದೇಶ ಹಾಗು

ಗೋಪ್ಯತೆಯ ವಿಚಾರವನ್ನು ನನ್ನ ಭಾಷೆಯಾದ ಕನ್ನಡದಲ್ಲಿ ವಿವರಿಸಲಾಗಿದೆ.

ಈ ಅಧ್ಯಯನದ ಕುರಿತಾದ ನನ್ನ ಎಲ್ಲ ಪ್ರಶ್ನೆಗಳಿಗೂ ಸಮಾಧಾನಕರ ಉತ್ತರ ನನಗೆ ದೊರಕಿರುತ್ತದೆ. ಎಲ್ಲ ಮಾಹಿತಿಗಳುಸಂಶೋಧಗೆಗಾಗಿಯೇ ಬಳಸಲಾಗುವುದು.

ಎಲ್ಲಾ ಮಾಹಿತಿಯನ್ನು ಗೌಪ್ಯವಾಗಿ ಇಡಲಾಗುತ್ತದೆ ಮತ್ತು ಯಾವುದೇ ಹೊರಗಿನವರ ಬಹಿರಂಗ ಮಾಡಲಾಗುವುದಿಲ್ಲ

ಈ ಅಧ್ಯಯನದಿಂದ ನನ್ನ ಜೀವಕ್ಕೆ ಯಾವುದೇ ಹಾನಿ ಇರುವುದಿಲ್ಲ ಮತ್ತು ಹೆಚ್ಚು ಅನುಕೂಲಕರವಾಗಿದೆ ಎಂದು ನನಗೆಅರ್ಥವಾಗಿರುತ್ತದೆ.

ನಾನು ಯಾವಾಗ ಬೇಕಾದರೂ ಈ ಅಧ್ಯಯನದಿಂದ ಹೊರನಡೆಯಬಹುದು ಮತ್ತು ನನಗೆ ಯಾವುದೇ ರೀತಿಯ ಅಧಿಕಖರ್ಚಾಗಿರುವುದಿಲ್ಲವೆಂದು ನಾನು ಒಪ್ಪಿಕೊಂಡಿರುತ್ತೇನೆ.

ರೋಗಿಯ ಹೆಸರು ಮತ್ತು ರುಜು/ಬೆರಳುಗುರುತು

ಸಾಕ್ಷಿಗಳ ಹೆಸರು ಮತ್ತು ರುಜು

1.

2.

ಪ್ರಮುಖ ಸಂಶೋಧಕರ ಹೆಸರು ಮತ್ತು ರುಜು: ಡಾII SONIA KUMARI

PATIENT INFORMATION SHEET

STUDY TITLE: "Co-relation between BETHESDA cytology categories and TI-RADS ultrasound categories of thyroid lesions."

STUDY SITE: R.L Jalappa Hospital and Research Centre, Tamaka, Kolar.

AIM-.

To study Co-relation between BETHESDA cytology categories and TI-RADS ultrasound categories in thyroid lesions.

Please read the following information and discuss it with your family members. You can ask any question regarding the study. If you agree to participate in this study, we will collect information (as per proforma). This information collected will be used for dissertation and publication only.

All information collected from you will be kept confidential and will not be disclosed to any outsider. The subject's identity will not be revealed. The Institutional Ethics Committee has reviewed this study, and you are free to contact the member of the Institutional Ethics Committee. There is no compulsion to agree with this study. The care you will get will not change if you do not wish to participate. You are required to sign/ provide a thumb impression only if you voluntarily agree to participate in this study.

For any further clarification, you can contact the study investigator:

Dr. SONIA KUMARI

Mobile no: 8826052826

E-mail id: soniaarora26789@gmail.com

KEY TO MASTER CHART

SN	Solitary nodule
LL	Left lobe
RL	Right lobe
D	Diffuse
MN	Multinodular
AUS	Atypia of undetermined significance
HPE	Histopathological Examination
S No	Serial No
Yr	year
CYTO NO	Cytopathological Number
AGE	Age (in years)
sex	m- Male ; f- Female
TI-RADS CAT	TI-RADS category
ULTRASOUND findings	M=Malignant B =Benign
BETHESDA CAT	BETHESDA CATEGORY
FNAC REMARKS	M=Malignant B =Benign
HISTOPATH DIAGNOSIS	M=Malignant B =Benign

Sl No.	YEAR	CYTO NO	AGE	Age	Age	sex	HOSPITAL NO	TI-RADS CAT	ULTRASOUND FINDINGS	BETHESDA CAT	FNAC FINDINGS	HISTOPATH DIAGNOSIS
1	2019	395	32 y/F	32	31 to 40	F	689686	III	BEN-Multi Nodular G	II	BEN-Lymphocytic Thyroditis	Follicular Adenoma
2	2019	377	32 y/F	32	31 to 40	F	686831	III	BEN-THROIDITIS	II	BEN-Lymphocytic Thyroditis	Not done
3	2019	324	20 y/M	20	10 to 20	M	685278	II	BEN-CL	II	BEN-Cystic lesion	Not done
4	2019	292	18y/F	18	10 to 20	F	683485	III	BEN-THROIDITIS	II	BEN-Lymphocytic Thyroditis	Not done
5	2019	281	55y/F	55	51 to 60	F	683492	II	BEN TL	II	BEN-Follicular lesion	Nodular goitre
6	2019	1994	37/f	37	31 to 40	f	714763	II	COLLOID DEG	II	COLLOID CYST	NOT DONE
7	2019	269	25y/F	25	21 to 30	F	682550	III	LIKELLY MALIG	III	Atypia Undetermined Significance	NODULAR HYPERPLASIA
8	2019	254	42 y/F	42	41 to 50	F	682191	II	BEN-THROIDITIS	II	FOLL NODULE	Not done
9	2019	247	55y/F	55	51 to 60	F	681563	III	LIKELLY MALIG	II	BEN-Nodular Hyprplsia	Nodular goitre
10	2019	326	27/F	27	21 to 30	F	823551	III	LIKELY BENIGN	II	BEN-Lymphocytic Thyroditis	Not done
11	2019	221	25y/F	25	21 to 30	F	679675	III	BEN-INFL	II	BEN-Lymphocytic Thyroditis	Not done
12	2019	206	42 y/F	42	41 to 50	F	679934	IVA	BEN-Multi Nodular G	II	BEN-Lymphocytic Thyroditis	FV-PTC
13	2019	160	58 y/M	58	51 to 60	M	677521	III	CYSTIC NOD	II	Benign Nodular -Goiter	NODULAR HYPERPLASIA
14	2019	136	48y/F	48	41 to 50	F	670747	III	MOD SUS NEO	II	BEN-Nodular Hyprplsia	Not done
15	2019	638	27/F	27	21 to 30	F	705464	III	ADEnomatous HPERplasia NOD	II	BEN-Lymphocytic Thyroditis	Not done
16	2019	92	30 y/M	30	21 to 30	M	673541	V	MALIGNANT	VI	Medullay Carcinoma - MALIG	Papillary Carcinoma
17	2019	1574	31 y/F	31	31 to 40	F	756973	I	BEN-THROIDITIS	IV	MAL-Follicular Nodule	FV-PTC
18	2019	535	35y/M	35	31 to 40	M	690326	III	BEN-THROIDITIS	II	BEN-Aiutoimmune thyoiditis	Not done
19	2019	1201	56Y/F	56	51 to 60	F	735283	II	MALIGNANT	II	BEN-Lymphocytic Thyroditis	HT

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20	2019	373	55y/F	55	51 to 60	F	687300	I	BENIGN	II	BEN-Cystic lesion	Not done
21	2019	272	70y/F	70	61 to 70	F	682643	III	MNG	II	BEN-Nodular Hyprplsia	Not done
22	2019	256	46Y/F	46	41 to 50	F	682413	III	BORDERLINE	II	BEN Follicular Lyesion	Not done
23	2019	45	40 y/F	40	31 to 40	F	670888	II	CYS NOD DEG	II	BEN Colloid NOD	Not done
24	2019	479	58y/F	58	51 to 60	F	661962	II	BENIGN	II	BEN Colloid NOD	Not done
25	2019	422	25/F	25	21 to 30	F	541540	I	BEN-Solitary nodule +Colloid Degenration	II	BEN-Nodular Hyprplsia	Not done
26	2019	1225	45/F	45	41 to 50	F	566895	II	BENIGN	II	BEN-Lymphocytic Thyroditis	Not done
27	2019	127	30y/F	30	21 to 30	F	670909	III	MNG-BENIGN	II	BEN-Lymphocytic Thyroditis	Not done
28	2019	218	60y/F	60	51 to 60	F	680620	IVA	BEN TL	IV	MAL-Follicular Nodule	NOT DONE
29	2019	595	30y/F	30	21 to 30	F	700484	I	BEN-NOD+Colloid Degenration	II	BN-COLLGOIT	Not done
30	2019	524	30y/F	30	21 to 30	F	695038	II	BENIGN	II	BEN-CN +CS	Not done
31	2019	400	35y/F	35	31 to 40	F	689887	III	MNG	II	BEN-COLL ADENoma	Not done
32	2019	441	53y/F	53	51 to 60	F	692244	III	BENIGN	II	BEN Colloid NOD	Not done
33	2019	858	50/F	50	41 to 50	F	410506	III	BORDERLINE	II	BEN-Follicular lesion	Not done
34	2019	624	35/F	35	31 to 40	F	701257	II	BEN-Multi Nodular G	I	BEN-CN +CS	Not done
35	2019	660	45/M	45	41 to 50	M	666010	V	MALIGNANT	II	BEN Colloid NOD	Not done
36	2019	946	26/F	26	21 to 30	F	713466	III	BEN-Multi Nodular G	IV	MAL-SuPcious for folloicular Neoplasm	PTC
37	2019	1270	45/F	45	41 to 50	F	739547	V	BEN-THROIDITIS	II	BEN-Lymphocytic Thyroditis	Not done
38	2019	2172	50/F	50	41 to 50	F	637624	III	BEN-Multi Nodular G	II	BEN-Colloid Goiter with cystic	Not done
39	2019	773	45/F	45	41 to 50	F	712481	III	BENIGN	II	BEN thyoid lesion	Not done
40	2019	1730	32/F	32	31 to 40	F	756964	III	BORDERLINE	II	BEN-Lymphocytic Thyroditis	Not done
41	2019	1333	56/M	56	51 to 60	M	742330	II	BEN-Multi Nodular G	II	BEN-NOD GOITer with cystic change in rl lobe	Not done

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42		580	52/F	52	51 to 60	F	701946	IVC	LIKELLY MALIG	V	Medullay Carcinoma - MALIG	Not done
43		573	80/F	80	>70	F	607882	III	BORDERLINE	II	BEN-Aiutoimmune thyoiditis	Not done
44		753	27/F	27	21 to 30	F	679376	III	BENIGN	II	BEN-Nodular Hyprplsia	Not done
45		868	13/F	13	10 to 20	F	717397	III	BEN-THROIDITIS	II	BEN thyoid lesion	Not done
46		2309	34/M	34	31 to 40	M	643806	III	LIKELLY MALIG	II	BEN-Lymphocytic Thyroditis	Not done
47		1864	43/F	43	41 to 50	F	771295	II	BEN-Multi Nodular G	II	BEN-Lymphocytic Thyroditis	Not done
48		2625	20/F	20	10 to 20	F	661494	III	MOD SUS NEO	II	BEN-Lymphocytic Thyroditis	Not done
49		1914	35/F	35	31 to 40	F	778860	III	BORDERLINE	III	Atypia Undetermined Significance	Not done
50		348	30/M	30	21 to 30	M	673541	V	MALIGNANT	VI	Medullay Carcinoma - MALIG	PTC
51		2159	50Y/F	50	41 to 50	F	789719	III	BENIGN	II	BEN-Hashimoto thyroditis	Not done
52		2471	30Y/F	30	21 to 30	F	652394	II	BENIGN	II	BEN-Lymphocytic Thyroditis	Not done
53			60/f	60	51 to 60	f	762900	III	benign	II	BENIGN-NODULAR HYPERPLASIA	NOT DONE
54		1981	45/M	45	41 to 50	M	782199	V	MALIGNANT	VI	ANAPLASTIC Medullary Thhyoid Crcinoam	Not done
55			40/F	40	31 to 40	F	655772	III	BENIGN	II	BEN-Lymphocytic Thyroditis	Not done
56		314	75/F	75	>70	F	685122	IVA	BENIGN	II	BEN-Hashimoto thyroditis	Not done
57		1939	38/F	38	31 to 40	F	768024	III	BEN-Multi Nodular G	II	BEN-FOLL NOD	Not done

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58		1065	30/f	30	21 to 30	f	728975	II	SOLID CYSTIC LESION-MALIGNANT	II	BENIGN follicular nodule	Not done
59		2159	50Y/F	50	41 to 50	F	789719	III	BENIGN	II	BEN-Hashimoto thyroditis	Not done
60		151	41/M	41	41 to 50	M	676887	III	BEN -NOD GOIT	II	Benign Nodular -Goiter	Not done
61		2077	70y/F	70	61 to 70	F	632163	III	PROBABLY BENIGN	II	BEN-FOLL HPERplasia	Not done
62		692	45/F	45	41 to 50	F	708187	III	LIKELLY MALIG	III	Atypia Undetermined Significance	Not done
63		2236	45/F	45	41 to 50	F	640575	III	BEN-Multi Nodular G	IV	MAL-Follicular Nodule	Not done
64		1365	42/F	42	41 to 50	F	742625	III	BEN-Multi Nodular G	II	BEN-Colloid Goiter with cystic	NODULAR HYPERPLASIA
65		2053	30Y/F	30	21 to 30	F	785597	III	BENIGN	V	MALIG-SuPcious Papillary thyoidC	PTC
66	2020	188	31/F	31	31 to 40	F	821037	II	MALIGNANT	II	BEN-Lymphocytic Thyroditis	Not done
67	2020	152	65/F	65	61 to 70	F	795602	III	LIKELLY MALIG	II	BEN-Lymphocytic Thyroditis	Not done
68	2020	221	67/f	67	61 to 70	f	819936	III	BEN-Multi Nodular G	II	BEN Follicular Lyesion	Not done
69	2019	2493	65/M	65	61 to 70	M	809454	III	MALIGNANT	II	BEN Colloid NOD	NODULAR HYPERPLASIA
70	2019	772	37/F	37	31 to 40	F	710215	V	MALIGNANT	IV	MALIGNANT	FC-METS
71	2019	2240	49/M	49	41 to 50	M	794556	III	BENIGN	II	BEN Colloid NOD	NOT DONE
72	2020	326	27/F	27	21 to 30	F	823551	IVA	PROBABLY BENIGN	II	ChronicLymphocystic Thyroiditis-BENIGN	NIFTP
73	2020	666	65/F	65	61 to 70	F	844120	III	MALIGNANT	IV	Metastatic Follicular Neoplsam	METS-FC
74	2020	502	30/M	30	21 to 30	M	834665	V	BENIGN	VI	MALIGNANT	PTC
75	2020	433	50/M	50	41 to 50	M	830312	III	BENIGN	V	MALIGNANT	Nodular goitre
76		150	40/F	40	41 to 50	F	676642	IVA	BENIGN	II	BENIGN	Nodular goitre
77		996	43/F	43	41 to 50	F	856905	V	MALIGNANT	II	Adenomatoid NODule	Not done
78		219	30/M	30	21 to 30	M	822629	III	BENIGN	II	BENIGN colloid nodule	NODULAR HYPERPLASIA

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79		1065	30/F	30	21 to 30	F	728975	IVB	MALIGNANT	II	BEN-Nodular Hyprplsia	Not done
80		714	45/F	45	41 to 50	F	845734	III	MALIGNANT	II	BEN Follicular NOD	Not done
81		152	65/F	65	61 to 70	F	795602	III	LIKELLY MALIG	II	BEN-Lymphocytic Thyroditis	Not done
82		2653	32/M	32	31 to 40	M	662716	V	MALIGNANT	V	MALIGNANT	Not done
83			23/F	23	21 to 30	F	823175	III	LIKELLY MALIG	II	BEN Colloid NOD	Not done
84			29/F	29	21 to 30	F	831569	III	LIKELY BENIGN	II	BEN-Lymphocytic Thyroditis	Not done
85			26/F	26	21 to 30	F	838912	II	MNG-CYSTIC DEGENERATION	II	BENIGN-COLLOID NOD +CYSTIC DEGENERATION	Not done
86			31/F	31	31 to 40	F	714763	II	COLLOID NODULE WITH SPONGIFORM DEGEN	II	BENIGN TL -COLLOID CYST	NODULAR HYPERPLASIA
87			50/F	50	41 to 50	F	833014	III	BEN-THROIDITIS	II	BENIGN-HASHIMOTOS THYROIDITIS	Not done
88			35/F	35	31 to 40	F	762617	IVA	BEN-THROIDITIS	II	BENIGN TL WITH NODULAR HYPERPLASIA	FOLL ADENO+ADEN HY
89		1144	23/F	23	21 to 30	F	867449	IVB	NEOPLASTIC	IV	hurthle CELL NEOPLASM	Hurthle cell carcinoma
90		1127	60/F	60	51 to 60	F	867037	IVB	NEOPLASTIC	IV	FOLLICULAR NEOPLASM	NOT DONE
91			45/F	45	41 to 50	F	813847	III	BEN-THROIDITIS	II	BENIGN-HASHIMOTOS THY	Not done
92			45/F	45	41 to 50	F	716786	III	LIKELLY MALIG	II	BENIGN-LT	HASHIMOTOS THYROIDITIS
93			61/F	61	61 to 70	F	741643	II	BENIGN	II	BENIGN FOLLICULAR LESION	Not done
94			50/F	50	41 to 50	F	821408	III	LIKELY BENIGN	II	COLLOID NODULE	NODULAR HYPERPLASIA
95			68/F	68	61 to 70	F	763079	III	LIKELY BENIGN	II	BENIGN-NODULAR HYPERPLASIA	Not done
96		1034	29/F	29	21 to 30	F	862190	V	MALIGNANT	III	FOLL-AUS	NOT DONE
97		1064	29/F	29	21 to 30	F	864534	III	BENIGN	III	AUS	NOT DONE

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98	2018	2518	54/M	54	51 to 60	M	655377	II	BENIGN	I	CYSTIC THYROID LESION	NODULAR HYPERPLSIA +CYST DEG
99		2415	40/M	40	31 to 40	M	640269	V	MALIGNANT	V	MALIGN-PTC	PTC
100		2049	40/M	40	31 to 40	M	629899	IVC	MALIGNANT	IV	HURTHLE CELL NEOPLASM	PTC-CLASSICAL
101		2574	21/F	21	21 to 30	F	658306	III	MALIGNANT	V	SUSPICIOUS FOR MALIGNANCY-PTC	FV-PTC
102		2332	36/F	36	31 to 40	F	645665	IVA	LIKELY BENIGN	II	BENIGN	ADENOMATOYS HYPERPLASIA+DOMINANT NODULE
103		1771	8Y/F	8	<10	F	615747	III	SPNGIFORM NOD-BEN	II	BENIGN	NODULAR GOITRE
104		2110	40/F	40	31 to 40	F	633088	IVC	MULTIPLE NODU	IV	FOLLICULAR NEOPLASM	Follicular carcinoma
105		2507	57/F	57	51 to 60	F	643259	IVC	STIFF LESION	V	PTC	MNG
106		1850	30/F	30	21 to 30	F	620514	I	SOL NOD +COL DEG	II	COLLOID GOITRE	NODULAR HYPERPLASIA
107		2276	48/M	48	41 to 50	M	641499	II	MNG	II	COLLOID GOITRE	FV-PTC