A DISSERTATION ON

PREDICTION OF THYROID MALIGNANCY BASED ON CLINICAL, RADIOLOGICAL AND BIOCHEMICAL FACTORS WITH EMPHASIS ON SERUM TSH

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BONAFIDE CERTIFICATE

Certified that this dissertation is the bonafide work of Dr**.** **G.SABARISH KUMAR** on **"PREDICTION OF THYROID MALIGNANCY BASED ON CLINICAL,RADIOLOGICAL AND BIOCHEMICAL FACTORS WITH EMPHASIS ON SERUM TSH "** during his M.S. (General Surgery) course from July 2014 to September 2015 at the Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai – 600003.

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DECLARATION

I, certainly declare that this dissertation titled, “PREDICTION OF THYROID MALIGNANCY BASED ON CLINICAL, RADIOLOGICAL AND BIOCHEMICAL FACTORS WITH EMPHASIS ON SERUM TSH”, represent a genuine work of mine . The contribution of any supervisors to the research are consistent with normal supervisory practice, and are acknowledged.

I, also affirm that this bonafide work or part of this work was not submitted by me or any others for any award, degree or diploma to any other university board, neither in India or abroad. This is submitted to The Tamil Nadu Dr.MGR Medical University, Chennai in partial fulfilment of the rules and regulation for the award of Master of Surgery Degree Branch 1 (General Surgery).

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Date :
Place:

ABSTRACT

BACKGROUND

Many patients present to the surgical department with a thyroid nodule. However not all require surgery and only 5-6% of these are malignant. There are many methods to diagnose and predict malignancy in a thyroid nodule. This study throws light on the usefulness of clinical, radiological and TSH estimation and its role in predicting malignancy.

AIMS AND OBJECTIVES

To assess whether simple clinical, radiological and biochemical parameters that can predict the likelihood of thyroid malignancy in subjects with thyroid swelling , in a tertiary care centre in south India, which caters mostly for an economically underprivileged population

MATERIAL AND METHODS

This prospective study involved 100 patients admitted to MMC, Chennai with thyroid swellings. A descriptive analysis of clinical presentation, radiological features and a correlation of TSH level and its final histopathology were done.

OBSERVATION AND RESULTS

Most patients were females. Most of the malignancy patients fall in the age group above 60. Commonest presentation was a rapidly growing thyroid swelling of short duration or development of secondary symptoms in a long standing goitre. Majority of patients presented with a SNT. The incidence of malignancy was higher in SNT compared to MNG. The incidence of neck nodes was more common malignancy patients. Most of the malignancy patients have radiological features such as hypoechoic lesion, calcification, irregular margins and invasion to adjacent structures .Mean preoperative TSH value in malignancy was higher compared to those with benign disease. Incidence of malignancy increased with higher TSH values.

CONCLUSION

There is a definite relationship between higher TSH levels and malignancy. TSH levels could be used as predictor in clinically suspicious malignant thyroid swelling with a benign FNAC report. In such cases where TSH value is high, the FNAC can be relooked to confirm the diagnosis. In addition to TSH, clinical features such as lymphadenopathy, fixity, SNT, USG features such as hypoechoic, calcification, invasion to adjacent structures are also predictors of thyroid malignancy.

LIST OF ABBREVIATIONS

ATC	:	Anaplastic Carcinoma Thyroid
CEA	:	Carcinoembryonic Antigen
EBRT	:	External beam radiotherapy
ELN	:	External Laryngeal Nerve
FNAC	:	Fine needle aspiration cytology
FN	:	Follicular Neoplasm
MIT	:	Monoiodotyrosine
MNG	:	Multinodular goitre
MTC	:	Medullary Carcinoma Thyroid
RAI	:	Radioactive Iodine
RIA	:	Radioactive Iodine Ablation
RLN	:	Recurrent Laryngeal Nerve
T3	:	Triiodothyronine
T4	:	Tetraiodothyronine/ Thyroxine
Tg	:	Thyroglobulin
TPO	:	Thyroid peroxidase
TRH	:	Thyrotropin releasing hormone
TSH	:	Thyroid Stimulating Hormone
WDC	:	Well Differented Carcinoma

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INTRODUCTION

Thyroid diseases have always been an enigma. The management of thyroid diseases has undergone a tremendous change over the ages, from the crude surgeries of the ancient times to the multidisciplinary approach of the modern era. However in the present scenario surgery still plays an important role especially in the management of thyroid malignancies.

Thyroid malignancies account for 90% of endocrinal malignancies. The incidence of thyroid malignancies has increased three fold over the past 3 decades. Many patients present to the surgical outpatient department with a thyroid nodule. However not all these patients require surgery as only 5-6% of these are malignant [26, 27]. There are many methods to diagnose and predict malignancy in a thyroid nodule.

A clinical examination is always the first step to assess a nodule. A thyroid profile is also essential. This is accompanied by certain tests which increase the rate of detection. Fine needle aspiration cytology (FNAC) is the present gold standard and

primary tool for assessing risk of malignancy [1]. Other tests include ultrasonography, thyroid scintigraphy, CT scan and MRI.

Recent studies have found levels of serum TSH to be an independent predictor of malignancy in thyroid nodules [2, 3, 5].This biochemical marker could be used as a screening test for malignancy. In this study we investigated the utility of TSH in predicting malignancy and the common clinical presentation of thyroid malignancies.

AIMS AND OBJECTIVES

Although fine-needle aspiration cytology is considered to be the reference method for evaluating thyroid nodules, the results are inaccurate in approximately 10-30% of cases. Several studies have attempted to predict the risk of malignancy in thyroid nodules based on age, nodularity, thyrotropin values, thyroid autoimmune disease, hot/cold nodule status, and ultrasound parameters. However, no consensus has been found, and none of these parameters has significantly affected patient management. The management of indeterminate thyroid nodules and re-biopsies of nodules with initially benign cytological results remain important and controversial topics of discussion.In this study the usefulness of clinical,radiological and biochemical factors in predicting the thyroid malignancy is discussed.

The main objective of this study is

1) To evaluate the utility of serum TSH estimation as a biochemical predictor of malignancy in suspicious thyroid nodules.

2) To study the clinical features, radiological findings that can predict the various thyroid malignancies.

REVIEW OF LITERATURE

HISTORY [6, 7, 8]:

The history of thyroid diseases can be traced back to ancient times. Celsus and Galen described goiters (Latin: *guttur*=throat) in 1st century A.D.

Thomas Wharton (1656) coined the term thyroid gland (Greek: *thyreoeides* =shield) because of its appearance as a shield protecting the trachea.

Andrea Vesalius (1514–1564) originally described the thyroid as "glandulae laryngis" in his inauguration of modern anatomy *De Humani Corporis Fabrica.*

Lorenz Heister of Germany first described the surgical removal of a thyroid gland.

Aniton Wölfler first called attention to the danger of injuring the recurrent nerve when ligating the inferior thyroid artery.

Theodor Billroth (1892-1894) and **Theodor Kocher** (1849-1917) were eminent surgeons who performed thyroid surgeries

in the 19th century. Kocher was awarded the Nobel Prize in 1909 for his work on thyroid physiology, pathology and surgery.

Ivar Sandström (1887) of Sweden discovered parathyroids and described the anatomy and blood supply of the glands.

C. H. Mayo of USA had tremendous experience in thyroid surgery. Reports from the Mayo Clinic had been an important factor in disseminating an understanding of the surgical technique and operative difficulties, which, in turn, greatly improved thyroid surgery.

William Halstead (1852-1922) of USA stressed the importance of preservation of parathyroids during thyroid surgery.

Saul Hertz (1905–1950) was an American physician who discovered the use of radioactive iodine for the treatment of thyroid diseases.

Martin and Ellis (1930) first described FNAC of thyroid.

Duffy et al (1950) studied relationship of papillary carcinoma of thyroid and neck irradiation in childhood.

Medullary thyroid carcinoma was recognized in the 1950s by ***Hazard et al***.

Sipple (1960) observed that medullary carcinoma thyroid was associated with pheochromocytoma.

Development in molecular medicine in the 1980s has provided major insight into the impact of genetic mutations eventually to thyroid carcinomas. This led to the recognition of the biologically different behavior of different cancer subtypes and to the introduction of differentiated surgical strategies.

EMBRYOLOGY: [6, 9]

The thyroid gland appears as an epithelial proliferation in the floor of the pharynx near the base of the tongue at a point later indicated by the foramen caecum. Subsequently the thyroid descends in front of the pharyngeal gut as a bilobed diverticulum. During this migration, the thyroid remains connected to the tongue by a narrow canal, the thyroglossal duct. This duct usually disappears by the 6^{th} week. The thyroid gland descends in front of the hyoid bone and the laryngeal cartilages and reaches its final position in front of the trachea in the

seventh week. By then it has acquired a small median isthmus and two lateral lobes.

The thyroid begins to function at approximately the end of the third month, at which time the first follicles containing colloid become visible.

The remnant of the thyroglossal duct may persist as a thyroglossal cyst which may lie at any point along the migratory path of the thyroid. Sometimes it may be connected to the outside by a fistulous track called thyroglossal fistula.

Aberrant thyroid tissue may be found anywhere along the path of descent of the thyroid gland and is subject to the same diseases as the thyroid gland itself.

Calcitonin-producing C cells or the parafollicular cells arise from the ultimobranchial body. These cells are of neuroectodermal origin migrate into the lateral and posterior upper two thirds of the thyroid lobes and are distributed among the follicles.

ANATOMY [10]:

The thyroid gland consists typically of two lobes, a connecting isthmus, and occasionally an ascending pyramidal lobe.

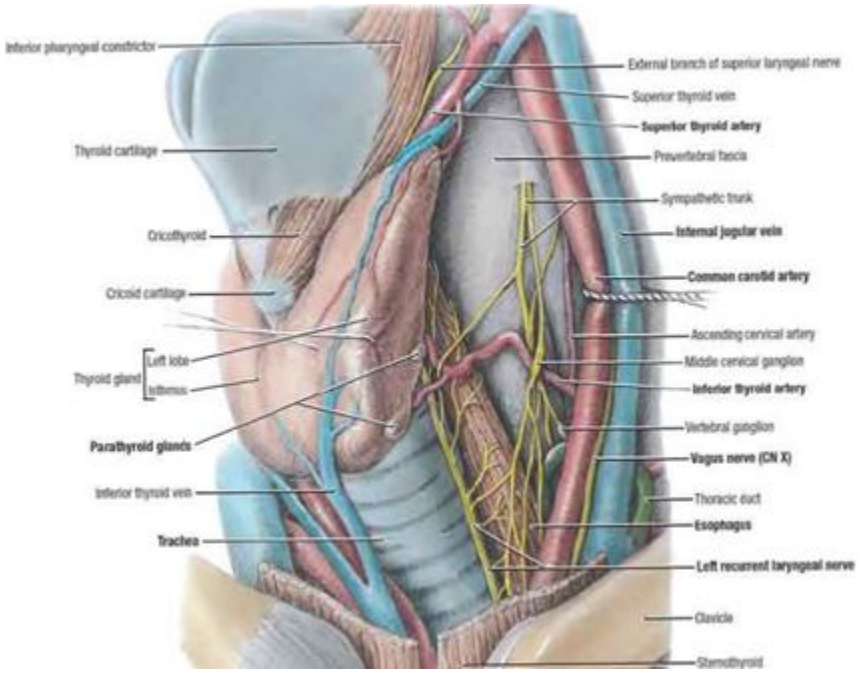
It extends from 5th cervical vertebra to 1st thoracic vertebra with the isthmus overlying the second and third tracheal ring.

The gland weighs approximately 25-30g

CAPSULES

True capsule: From condensation of connective tissue of the gland. False capsule: External to the true capsule, is well developed and derived from the pretracheal fascia. Anteriorly and laterally this fascia is well developed. Posteriorly it is thin and loose, permitting enlargement of the gland posteriorly. The false capsule, or fascia, is not removed with the gland during thyroidectomy.

Ligament of berry: This is a thickening of the fascia that fixes the back of each lobe to the cricoid cartilage. Such thickenings are the ligaments of Berry.



PARATHYROID GLANDS

The superior parathyroid glands normally lie between the true capsule and the fascial false capsule. The position of the inferior parathyroid is more variable, however, and can be along the branches of the inferior thyroid vein lateral or inferior to the lowermost portion of the thyroid lobe. The superior and inferior parathyroid glands have a single end artery that supplies them medially from the inferior thyroid artery.

VASCULAR SUPPLY

ARTERIES

The thyroid gland derives its blood supply from the external carotid system via the superior thyroid artery and the subclavian system via inferior thyroid artery. Sometimes there

may be and an additional artery the thyroid ima artery arising from brachiocephalic artery.

THE SUPERIOR THYROID ARTERY

This artery is the first branch of the external carotid artery. It passes downward and anteriorly to reach the superior pole of the gland. It usually divides into two branches at the superior pole: anterior and posterior. The anterior branch anastomoses with the contra lateral artery over the isthmus. The posterior branch anastomoses with branches of the inferior thyroid artery at the posterior border.

INFERIOR THYROID ARTERY

The inferior thyroid artery usually arises from the thyrocervical trunk. The artery divides into two or more branches as it crosses the ascending recurrent laryngeal nerve

The recurrent laryngeal nerve may pass anterior or posterior to the artery, or between its branches

THYROID IMA ARTERY

The artery is unpaired and inconstant. It arises from the brachiocephalic artery, the right common carotid artery, or the aortic arch. It occurs in about 10 percent of individuals.

VENOUS DRAINAGE:

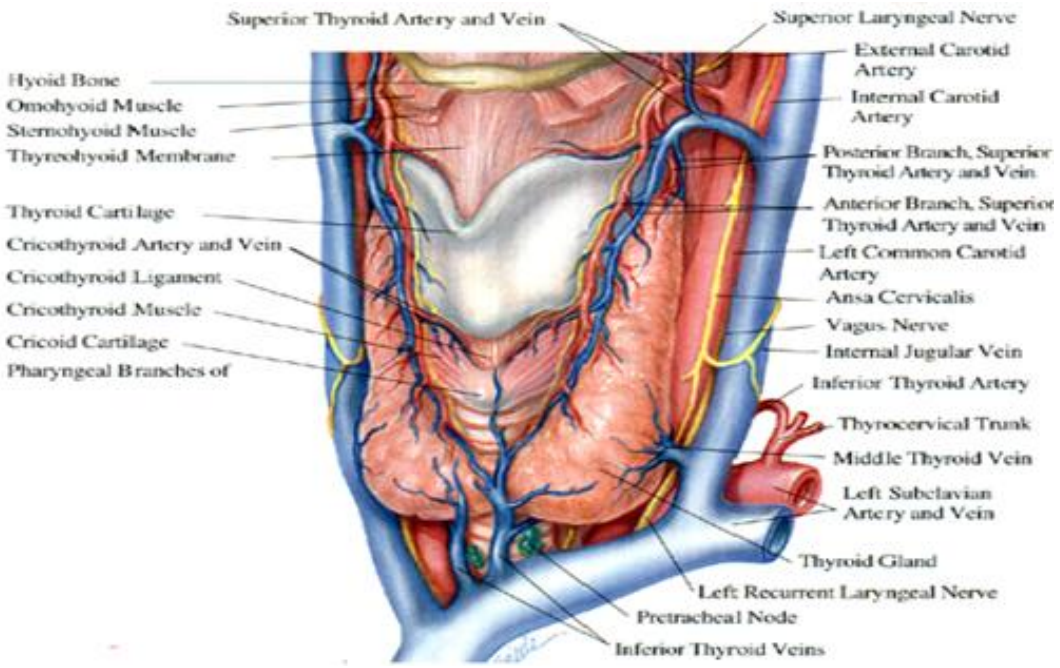
Veins of the gland form a plexus of vessels lying in the substance and on the surface of the gland. The plexus is drained by three pairs of veins, the superior, middle, and inferior thyroid veins.

Superior Thyroid vein emerges at upper pole & accompanies the artery and ends in the Internal Jugular vein.

Middle Thyroid vein leaves the middle of gland and has a short course directly into the Internal Jugular vein. It is the first vessel encountered in thyroidectomy

Inferior thyroid Vein. It is the largest and most variable of the thyroid veins; the right and left sides are usually asymmetric. The veins drain into the brachiocephalic veins.

Fourth thyroid vein [Kocher]**:** may emerge between the Middle and Inferior veins. It drains into Internal Jugular vein.



LYMPHATIC DRAINAGE

The thyroid gland has an extensive intraglandular network of lymphatic channels that allow for drainage within one lobe and from one lobe to another. The lymphatic drainage can be divided into 4 zones (Hollinshead)

MEDIAN SUPERIOR DRAINAGE

From the superior margin of the isthmus and from the medial margins of the lateral lobes. Drains primarily into the digastric lymph nodes and into one or more prelaryngeal ("Delphian") nodes just above the isthmus. Secondary drainage may be to upper jugular nodes on either side or to pretracheal nodes below the thyroid.

MEDIAN INFERIOR DRAINAGE

Lymphatics draining the lower part of the isthmus and the lower medial portions of the lateral lobes. They end in the pretracheal and brachiocephalic nodes.

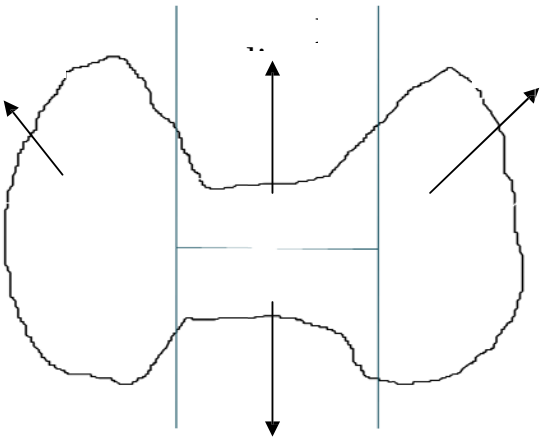
RIGHT AND LEFT LATERAL DRAINAGE

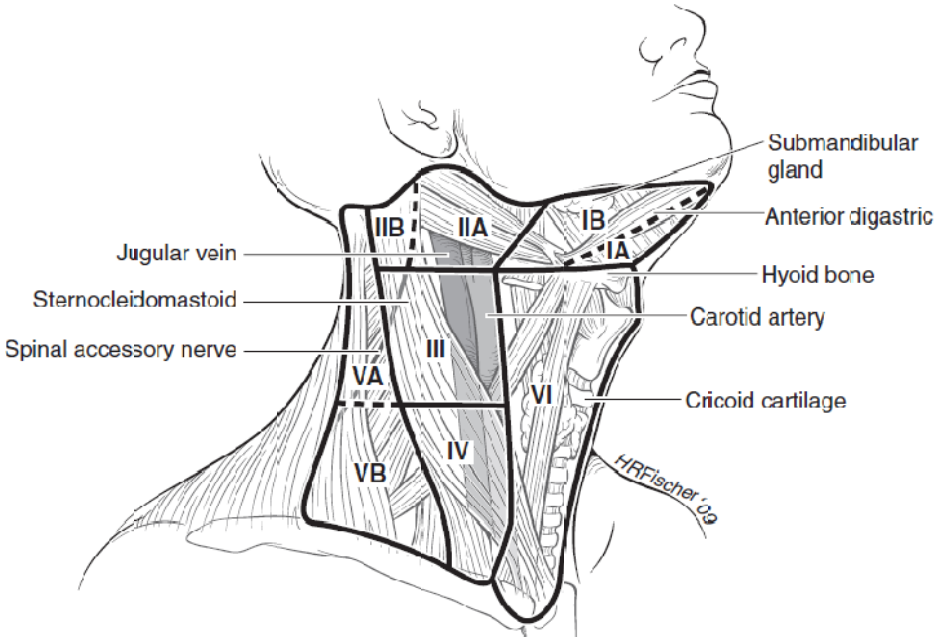
Superiorly follow superior thyroid artery and vein. Inferiorly they follow the inferior thyroid artery.

POSTERIOR DRAINAGE

Drains into nodes along the recurrent laryngeal nerve or retropharyngeal nodes.

The thyroid lymphatics typically drain first into the central compartment (level VI), which contains the pretracheal and paratracheal nodes, and subsequently into the lateral jugular regions (level II–IV).





NERVE SUPPLY

Sympathetic system from the superior, middle, and inferior ganglia of the cervical chain.

Important Relations of Thyroid

External laryngeal nerve (ELN):

It is a branch of the Superior laryngeal nerve of Vagus. It lies in lose relation with the superior vascular pedicle. It innervates the Cricothyroid muscle.

RECURRENT LARYNGEAL NERVE (RLN)

Embryonically related to 4th aortic arch vessels

On the right side the RLN crosses anterior to the right subclavian artery loops around the subclavian artery from posterior to anterior, crosses behind the right common carotid and ascends in or near the tracheoesophageal groove. It passes posterior to the right lobe of the thyroid gland to enter the larynx behind the cricothyroid articulation and the inferior cornu of the thyroid cartilage

On the left side the RLN crosses the aortic arch, just distal to the origin of the left subclavian artery from the aortic arch. It loops under the ligamentum arteriosum and the aorta, and ascends in the same manner as the right nerve. Both nerves cross the inferior thyroid arteries near the lower border of the middle third of the gland.

RLN enters the larynx behind the cricothyroid muscle and the inferior cornu of the thyroid cartilage and innervates all the intrinsic laryngeal muscles except the cricothyroid.

HISTOLOGY

The thyroid gland is divided into lobules. Each lobule contains 20 to 40 follicles. Each follicle is lined by cuboidal epithelial cells and contains a central store of colloid secreted

from the epithelial cells under the influence of the pituitary hormone, TSH. There is another group of cells in the interfollicular tissue called C cells or the parafollicular cells which produce the hormone calcitonin.

PHYSIOLOGY [11, 12]

The normal thyroid gland secretes three hormones—triiodothyronine (T3) and tetraiodothyronine (T4, thyroxine) from the follicular cells—to normalize growth and development, body temperature, and energy levels. Calcitonin, the second type of hormone produced by the parafollicular cell, is important in the regulation of calcium metabolism.

THYROID HORMONE SYNTHESIS, SECRETION, AND TRANSPORT

Iodine in diet is converted to iodides. These iodides are utilized by the thyroid gland to synthesize thyroid hormones. Thyroglobulin is a glycoprotein synthesized in the thyroid cells and secreted into the colloid by exocytosis of granule. It contains 123 tyrosine residues, but only 4 to 8 of these are normally incorporated into thyroid hormones.

STEPS OF HORMONE SYNTHESIS

IODIDE TRAPPING

Involves active (ATP-dependent) transport of iodide across the basement membrane of the thyrocyte.

OXIDATION

Oxidation of iodide to iodine and iodination of tyrosine residues on thyroglobulin (TG), to form monoiodotyrosines (MIT) and diiodotyrosines (DIT). Both processes are catalyzed by thyroid peroxidase (TPO).

COUPLING

The third step leads to coupling of two DIT molecules to form tetra-iodothyronine or thyroxine (T4), and one DIT molecule with one MIT molecule to form 3,5,3'- triiodothyronine (T3) or 3,3',5'–triiodothyronine reverse (rT3). When stimulated by TSH, thyrocytes form pseudopodia, which encircle portions of cell membrane containing Tg, which in turn, fuse with enzyme-containing lysosomes.

HYDROLYSIS

Hydrolysis of thyroglobulin to release free iodothyronines (T3 and T4) and mono- and diiodotyrosines.

In the euthyroid state, T4 is produced and released entirely by the thyroid gland, whereas only 20% of the total T3 is produced by the thyroid. Most of the T3 is produced by peripheral deiodination of T4 in the liver, muscles, kidney, and anterior pituitary, a reaction that is catalyzed by 5'-mono-deiodinase. Some T4 is converted to rT3, the metabolically inactive compound, by deiodination of the inner ring of T4.

Thyroid hormones are transported in serum bound to carrier proteins such as T4- binding globulin, T4-binding prealbumin, and albumin. Only a small fraction (0.02%) of thyroid hormone (T3 and T4) is free (unbound) and is the physiologically active component. T3 is the more potent of the two thyroid hormones, although its circulating plasma level is much lower than that of T4. T3 is less tightly bound to protein in the plasma than T4, and so it enters tissues more readily. T3 is three to four times more active than T4 per unit weight, with a half-life of about 1 day, compared to approximately 7 days for T4.

REGULATION OF THYROID HORMONES

Thyroid hormone secretion is controlled by the Hypothalamic-Pituitary-Thyroid axis. The hypothalamus

produces a peptide, the thyrotropin-releasing hormone (TRH), which stimulates the pituitary to release TSH or thyrotropin. TRH reaches the pituitary via the portovenous circulation.

THYROID STIMULATING HORMONE (TSH)

Thyroid function is regulated primarily by variations in the circulating level of pituitary TSH. TSH secretion is increased by the hypothalamic hormone thyrotropin- releasing hormone (TRH) and inhibited in a negative feedback fashion by circulating free T4 and T3. TSH secretion is also inhibited by stress, and in experimental animals it is increased by cold and decreased by warmth.

CHEMISTRY & METABOLISM OF TSH

Human TSH is a glycoprotein that contains 211 amino acid residues. It is made up of two subunits, designated α and β. The α subunit is encoded by a gene on chromosome 6 and the β subunit by a gene on chromosome 1.

TSH-α is identical to the α subunit of LH, FSH, and HCG-α. The functional specificity of TSH is conferred by the β subunit

The biologic half-life of human TSH is about 60 min. TSH is degraded for the most part in the kidneys and to a lesser extent

in the liver. Secretion is pulsatile, and mean output peaks at midnight, and then declines during the day. The normal secretion rate is about 110µg/d. The average plasma level is about 2 µg/mL.

EFFECTS OF TSH ON THE THYROID

TSH is a trophic hormone. When the pituitary is removed, thyroid function is depressed and the gland atrophies. TSH increases iodide trapping, synthesis of T3, T4, and iodotyrosines; secretion of thyroglobulin into the colloid; and endocytosis of colloid. It also increases vascularity and cellularity of the gland. Whenever TSH stimulation is prolonged, the thyroid becomes detectably enlarged.

TSH RECEPTORS

The TSH receptor is a typical G protein-coupled, seven-transmembrane segment receptor that activates adenylyl cyclase through G_S. It also activates phospholipase C. The thyroid gland also is capable of autoregulation, which allows it to modify its function independent of TSH. As an adaptation to low iodide intake, the gland preferentially synthesizes T3 rather than T4, thereby increasing the efficiency of secreted hormone. In situations of iodine excess, iodide transport, peroxide

generation, and synthesis and secretion of thyroid hormones is inhibited.

Wolff-Chaikoff effect: Excessively large doses of iodide may lead to initial increased organification followed by suppression.

THYROID MALIGNANCIES [6, 13, 14]

It is the most common endocrine malignancy i.e. 94.5% of total new endocrine cases accounting for 66% of all endocrine carcinoma related deaths.

Majority of thyroid cancers presents as thyroid nodules. Risk of malignancy: 5-10% chance of malignancy in each thyroid nodule in total population. This risk is higher for males and at extremes of age. There is a 33-37 % chance of malignancy in patients with history of childhood neck irradiation. A solitary nodule has higher incidence of malignancy (15-25%) than multinodular goitre (1-6%). A history of rapid increase in size, dyspnea, dysphagia, hoarseness is highly suspicious of malignancy.

CLASSIFICATION OF THYROID MALIGNANCIES

PRIMARY

1) Arising from the Follicular epithelium

a. Well differentiated (90%)-Papillary, Follicular

b. Undifferentiated (1-2%) - Anaplastic

2) Arising from Parafollicular cells (5-9%) - Medullary Ca

3) Lymphoid cells (1-3 %) – Lymphoma

4) Stromal cells (1%)

SARCOMAS

B.Secondary – Metastatic

ETIOLOGY & RISK FACTORS

RADIATION EXPOSURE DURING CHILDHOOD

There is an inverse relationship between risk of thyroid carcinoma and age of exposure. The risk is linearly related to exposure dose (minimum dose of 10 cGy). Latent period after childhood exposure is 3-5 yrs. Majority of cases develop between the second and third decade.

SEX

Both papillary and follicular carcinomas are approximately 2.5 times more common in females. The median age at diagnosis is earlier in women than in men for both papillary and follicular

subtypes and tends to be earlier for papillary cancer as compared to follicular cancer in either gender.

FAMILY HISTORY

Epidemiological studies have demonstrated a four to tenfold increased risk of well- differentiated thyroid cancer in first-degree relatives.

DIET

Iodine-deficient diets or diets that include a large intake of vegetables from the crucifer family may lead to increased TSH levels and are considered goitrogenic. Increased iodine intake in seafood like shellfish is associated with a higher incidence of papillary carcinoma.

THYROID ONCOGENESIS[14]

There are several oncogenes and tumor-suppressor genes which are involved in thyroid oncogenesis.

The RET proto-oncogene located on chromosome 10, encodes a receptor tyrosine kinase, which binds several growth factors. Germ line mutations in the RET proto- oncogene are known to predispose to multiple endocrine neoplasia type 2A (MEN 2A), MEN 2B, and familial medullary thyroid cancers. The

tyrosine kinase domain of RET can fuse with other genes by rearrangement. These fusion products also function as oncogenes and have been implicated in the pathogenesis of papillary thyroid cancers. BRAF (B-

type Raf kinase) mutations have recently been identified in about 40 percent of papillary thyroid cancers. Mutated ras oncogenes have been identified in up to 40 percent of thyroid follicular adenomas and carcinomas, papillary and anaplastic carcinomas. Mutations of p53 tumor suppressor gene are common in undifferentiated thyroid cancers and thyroid cancer cell lines. An oncogene resulting from the fusion of the DNA binding domain of the thyroid transcription factor PAX8 gene to the peroxisome proliferator-activated receptor gamma 1 (PPARγ 1) has been noted to play an important role in the development of follicular neoplasms.

WELL DIFFERENTIATED THYROID CARCINOMA (WDC)

PAPILLARY CARCINOMA THYROID (PTC)

This carcinoma accounts for 80% to 85% of malignant thyroid tumors. It can present as:

1) Solitary Painless nodule thyroid

2) Solitary nodule with lymph node metastasis

3) Lymph node Metastasis with occult primary

PATHOLOGY

Papillary carcinomas have a variable appearance from minute sub capsular white scars to large tumors greater than 5 to 6 cm that grossly invade surrounding structures. Areas of cystic change, calcification, and even ossification may be identified.

Microscopically, papillary carcinomas are characterized by the presence of papillae, but some variants contain no papillary areas, are totally follicular inpattern, and are identified as a follicular variant. The tumor cells have prominent ovoid nuclei with small nucleoli, (Orphan Anne eye nuclei) intranuclear grooves, and intranuclear cytoplasmic inclusions. Other

characteristic features are psammoma bodies and multicentricity. Papillary carcinoma has a propensity to invade lymphatic spaces and, therefore, leads to microscopic multimodal lesions in the gland as well as a high incidence of regional lymph node metastases. Papillary carcinomas less than 1 cm are often referred to as micro carcinoma.

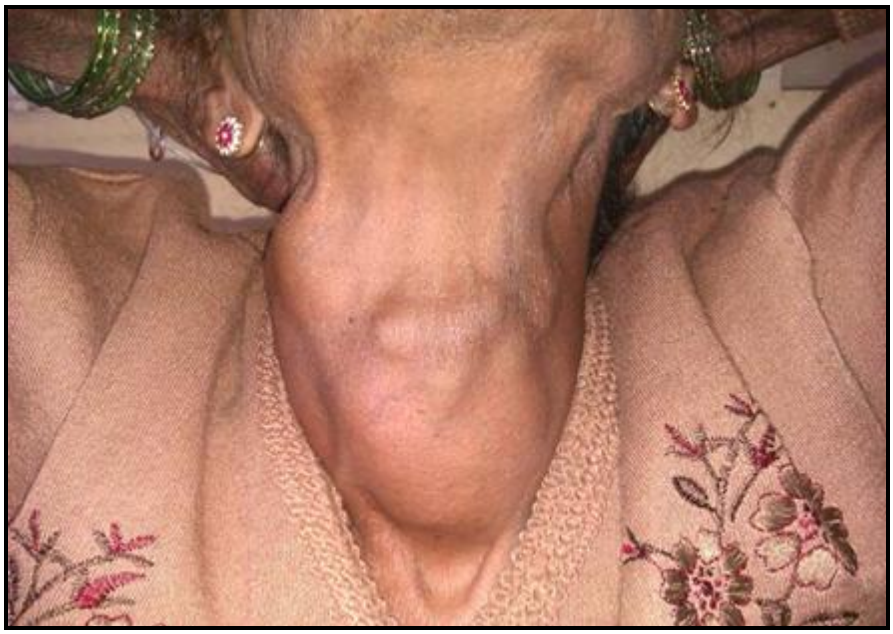
ROUTES OF SPREAD

1) Regional lymph nodes: >80%

2) Distant metastasis via blood- Rare

3) Local invasion- Trachea, Esophagus & RLN involvement.

PATIENT PRESENTING WITH MULTINODULAR GOITRE



FOLLICULAR CARCINOMA

True follicular thyroid carcinoma is an unusual tumor comprising approximately 5% to 10% of thyroid malignancies in non endemic goiter areas of the world. Follicular thyroid carcinoma is unifocal and thickly encapsulated and shows invasion of the capsule and/or blood vessels. At presentation, approximately two thirds of patients have disease localized to the thyroid. Patients may present with the following:

1) Solitary nodule

2) MNG-Rapid increase in size of a nodule.

3) Distant metastasis.

PATHOLOGY

Microscopically follicular carcinoma thyroid shows capsulated follicles with/without colloid. Based on capsular &/ or vascular invasion follicular carcinoma is divided into two types. Minimally invasive with minimal invasion of blood vessels and no breach in the capsule and the more aggressive highly invasive variety. In contrast to papillary carcinoma follicular carcinoma is unifocal in origin.

ROUTES OF SPREAD

1) Haematogenous [90%] - Bone, Lung, Liver

2) Lymph nodes [10%] – regional

HURTLE CELL CARCINOMA

It is a variant of follicular carcinoma. It is found in association with Hashimoto’s thyroiditis, Graves' disease and nodular goitre. It is clinically and histologically malignant and FNAC cannot differentiate benign from malignant. Treatment includes a total thyroidectomy with neck dissection. It is radio resistant.

MANAGEMENT OF WELL DIFFERENTIATED CARCINOMA

The mainstay in management of WDC is surgery. However, controversy still remains regarding the extent of thyroid tissue that should be removed during the initial operation.

SURGERIES FOR WDC

1) Total thyroidectomy – involves removal of the entire thyroid gland and its capsule.

2) Near-total thyroidectomy-entire gland is removed preserving a small portion near the posterior capsule of the thyroid.

3) Hemithyroidectomy- removal of the lobe ipsilateral to the lesion, and removal of the thyroid isthmus.

Total thyroidectomy may help ensure removal of all neoplastic tissue but it leaves the patient with no thyroid tissue, necessitating lifelong thyroid hormone supplementation. There is also the added to the risk of bilateral dissection of the adjacent normal neck structures and damage to important structures. Alternatively, more conservative procedures may leave inconspicuous residual cancer within the patient. Unfortunately,

there are no prospective randomized clinical trials evaluating the extent of thyroidectomy, adjuvant radioactive iodide therapy, and TSH suppressive therapy.

According to current recommendation, near-total or total thyroidectomy should be carried out in presence of any of the following:

1) Primary thyroid carcinoma more than 1 to 1.5cm in size

2) Thyroid nodules on the contra lateral lobe

3) Metastases, either regional or distant

4) History of radiation therapy to the head and neck

5) History of differentiated thyroid carcinoma in a first-degree relative

6) Age over 45 years, because of the higher recurrence in and above this age

7) Large tumours (4 cm) with marked atypia on biopsy

8) Unfavourable histology- tall cell variant, diffuse sclerosing, insular variant, poorly differentiated, Hurthle cell carcinoma and follicular cancer (except microinvasive)

Advantages of Total Thyroidectomy in WDC are

1) Higher survival rate even for lesions >1.5 cms

2) Low recurrence rate and prevention of recurrence in contra lateral lobe

3) Decreases incidence of pulmonary metastasis

4) Can be performed with same morbidity & mortality as lobectomy

5) Improved sensitivity of thyroglobulin (Tg) as marker for persistent/recurrent disease

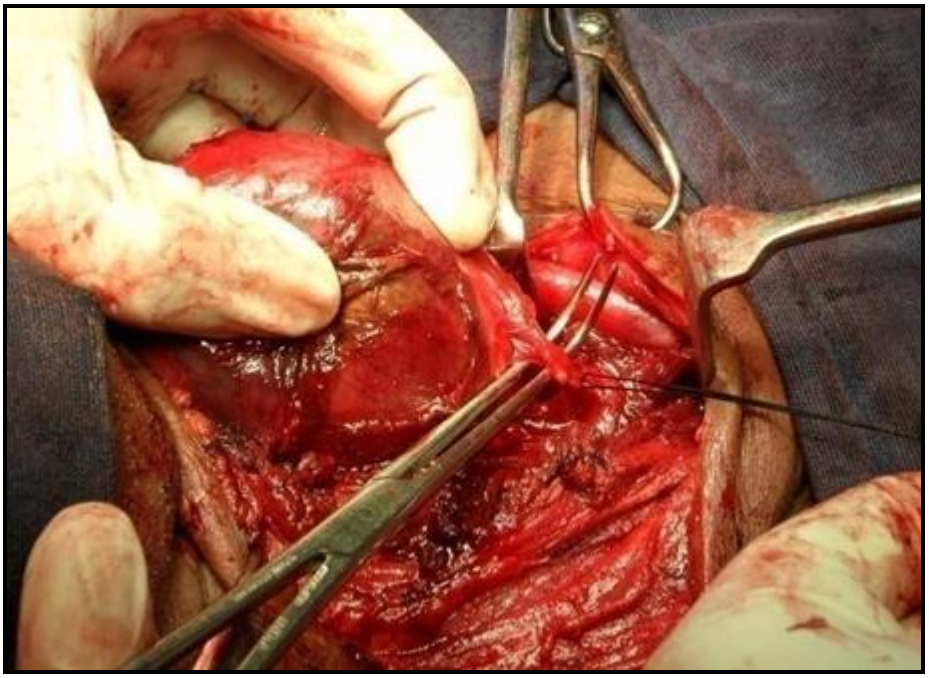
6) Radioactive iodine can be used to treat persistent/recurrent disease.

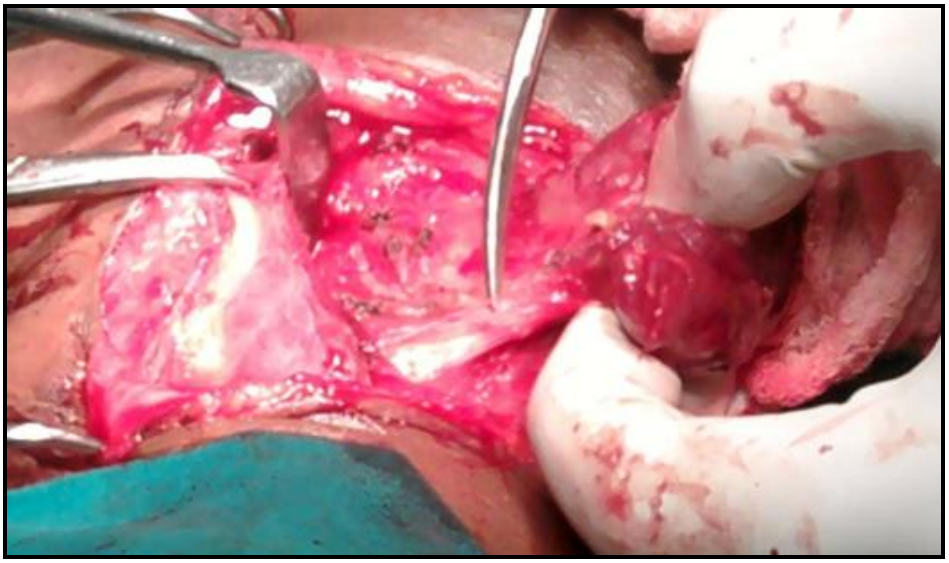
Hemithyroidectomy is done in differentiated cancers < 1.5cm in size without extrathyroidal extension (ETS) and no distant metastasis.

ARGUMENTS FAVORING HEMI-THYROIDECTOMY

1) Differentiated thyroid cancer is an indolent disease and in a majority of patients has a very low recurrence and mortality rate.

2) Permanent hypoparathyroidism and recurrent laryngeal nerve injury are potential complications of total thyroidectomy.





LYMPH NODE DISSECTION

Approximately 80% of patients with PTC have microscopic regional lymph node metastases [15]. Microscopic occult metastases may often be ablated by adjuvant radioactive iodine therapy, but they may also be a site of persistent disease that would have easily been removed at the initial operation.

Gross nodal disease occurs in 20–30% of adult cases of PTC, and is certainly justification for lymph node dissection [16]. As the central group / level VI of lymph nodes are mainly involved in thyroid malignancy it is recommended that dissection of ipsilateral central neck nodes and perithyroid lymph nodes (Delphian node and lymph nodes medial to the carotid sheath) be done in all cases of WDC. Removal of central neck lymph nodes is associated with an improvement in the regional recurrence rate, and an improved survival rate in retrospective studies [17-19]. The current American Thyroid Association Guidelines for the management of differentiated thyroid cancer now call that a staging/prophylactic level VI lymph node dissection for all

patients undergoing thyroidectomy for thyroid carcinoma should be considered [20].

LATERAL NECK NODE DISSECTION

Dissection of lateral compartment nodes (levels II–V) is important for nodes that have identifiable involvement with disease. Lymph node level based resections of lateral neck nodes are preferable to "berry-picking" if they are clinically involved.

Prophylactic lateral neck node dissection is not recommended as it is not associated with improved overall survival. However, follow-up of thyroid cancer patients by physical examination and ultrasound can identify patients with lateral neck nodal disease that can then be appropriately treated by therapeutic compartmental node dissection.

POSTOPERATIVE MANAGEMENT OF DIFFERENTIATED THYROID CANCER AND FOLLOWUP

Thyroid Hormone/ TSH Suppression

Thyroxine (T4) is given as replacement therapy in patients after total or near-total thyroidectomy. In addition it suppresses TSH and reducing the growth stimulus for any possible residual thyroid cancer cells. TSH suppression reduces tumor recurrence

rates, particularly in young patients with papillary and follicular thyroid cancer. The goal of should be to keep TSH levels at about 0.1 mU/L in low-risk patients, or less than 0.1 mU/L in high-risk patients.

THYROGLOBULIN MEASUREMENT

Thyroglobulin is a highly specific marker for follow up. Thyroglobulin levels should be below 2 ng/mL when the patient is taking T4 and below 5 ng/mL when the patient is hypothyroid. A thyroglobulin level above 2 ng/mL is highly suggestive of metastatic disease or persistent normal thyroid tissue, especially if it increases when TSH levels increase when the patient is hypothyroid during preparation for RAI scanning. Thyroglobulin and anti-Tg antibody levels should be measured initially at 6-month intervals and then annually if the patient is clinically disease free.

Rising titers of thyroglobulin or anti- Tg antibodies is highly suspicious of recurrence of the disease.

IMAGING MODALITIES

High-risk patients should also have an ultrasound of the neck and CT or MRI scan of the neck and mediastinum for early detection of any persistent or recurrent disease.

RADIOACTIVE IODINE SCAN

Post surgery screening with radioactive iodine ^{131}I is more sensitive than chest x-ray or CT scanning for detecting metastases.

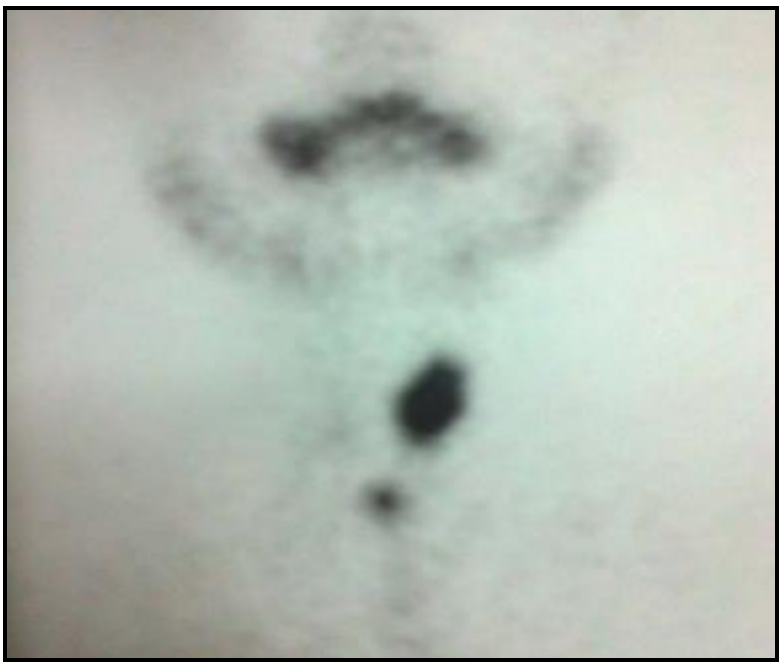
Generally, T4 therapy should be discontinued for approximately 4-6 weeks prior to scanning with ^{131}I. Patients should receive T3 during this time period to decrease the period of hypothyroidism. T3 has a shorter half-life than T4 (1 day vs. 1 week) and needs to be discontinued for 2 weeks to allow TSH levels to rise prior to treatment. A low-iodine diet is also recommended during this 2-week period. The usual protocol involves administering a screening dose of about 2 mCi of ^{131}I and measuring uptake 24 hours later. After a total thyroidectomy, this value should be less than 1%. A "hot" spot in the neck after initial screening usually represents residual normal tissue in the thyroid bed. If there is significant uptake, then a therapeutic radio ablative dose of ^{131}I should be administered to patients.

RADIOACTIVE IODINE ABLATION (RIA)

Radioiodine therapy in form of ^{131}I is the most effective non-surgical treatment for differentiated thyroid carcinoma. ^{131}I

causes cytotoxicity by the emission of short path length (1–2 mm) beta radiation. ^{131}I uptake is dependent upon adequate stimulation by TSH, and is reduced in the presence of stable iodide.

RADIO ACTIVE IODINE UPTAKE SCAN OF POST THYROIDECTOMY CASE WITH LYMPH NODE METASTASIS



Radioiodine ablation is used increasingly post operatively in treatment of well- differentiated thyroid cancer. The goals of the treatment are to destroy any residual thyroid tissue and to prevent loco regional recurrence.

Studies [20] show a benefit with ^{131}I ablation in patients with a) larger tumors (greater than 1.5 cm), b) multifocality, c) residual disease, and d) nodal metastasis.

AMERICAN THYROID ASSOCIATION GUIDELINES RECOMMENDATIONS FOR RIA

1) Patients with stage III or IV disease

2) Patients with stage II disease younger than 45 years

3) Most of those older than 45 years

4) Selected patients with stage I disease - tumours >1.5 cm, multifocality, residual disease, nodal metastasis, vascular invasion, and intermediately differentiated histology [20].

Postoperative ablation is typically performed approximately 6 weeks after near-total or total thyroidectomy.

Residual/Recurrent thyroid bed disease - 150mCi Diffuse Lung Metastasis - <150 mCi.

Patients with previously positive scans and patients with serum thyroglobulin levels greater than 2 ng/mL. usually need another ^{131}I treatment after 6 to 12 months until one or two negative scans are obtained.

SIDE EFFECTS OF RADIOIODINE

Short term complications include radiation thyroiditis, painless neck edema, sialoadenitis, nausea, tumor hemorrhage, temporary bone marrow depression and amenorrhea/oligomenorrhea. Late complications include secondary malignancies bone, soft tissue, colorectal, salivary and leukemia.[21]

THE ROLE OF RADIOTHERAPY AND CHEMOTHERAPY FOR WDC

Radiotherapy in the form of External beam radiotherapy is occasionally required to control unresectable, locally invasive or recurrent disease and to treat skeletal metastases.

Single and multidrug chemotherapy has been used with little success in disseminated thyroid cancer. Adriamycin and Taxol are the most frequently usedagents.

MANAGEMENT OF PATIENTS WITH METASTATIC DISEASE

The preferred treatment for metastatic disease includes the following:

1) Surgical excision of locoregional disease. Complete ipsilateral compartmental dissection of involved

compartments with persistent/recurrent disease while sparing vital structures is used. Surgery in conjunction with additional therapy such as external beam radiation or 131I is generally advised for tumors invading the upper aero-digestive tract.

2) External beam radiation

3) Observation of patients with stable asymptomatic disease

4) Experimental chemotherapy trials.

5) A small fraction of patients may benefit from radiofrequency ablation, ethanol ablation, or chemoembolization.

TREATMENT OF PULMONARY METASTASES

The management of patients with pulmonary metastases depends upon metastatic lesion size, avidity of radio-iodine uptake and response to prior radioiodine therapy.

Radioiodine therapy should be used to treat pulmonary micrometastases, which should be repeated every 6–12 months as long as disease continues to respond. Macronodular pulmonary metastases may also be treated with radioiodine if

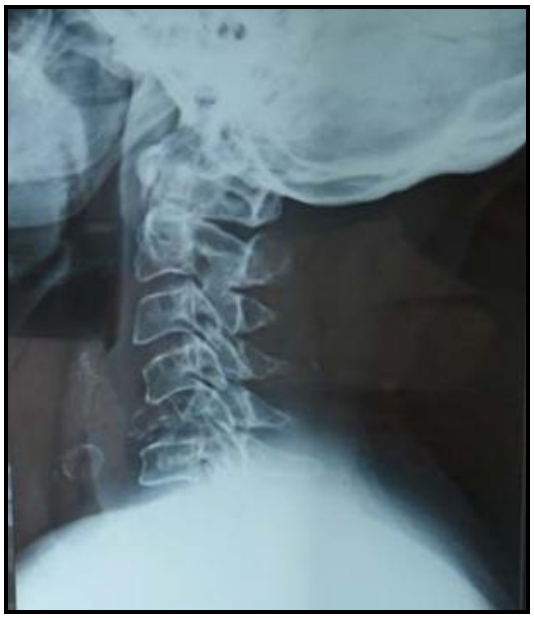
demonstrated to be iodine avid. Non radioiodine avid pulmonary disease requires chemotherapy. Traditional cytotoxic chemotherapeutic agents such as doxorubicin and cisplatin are used.

MANAGEMENT OF THE PATIENT WITH BONE METASTASES

The management of patients with bone metastases depends on risk for pathologic fracture, particularly in a weight-bearing structure, risk for neurologic compromise from vertebral lesions, presence of pain, avidity of radioiodine uptake and potential significant marrow exposure from radiation arising from radioiodine-avid pelvic metastases. Complete surgical resection of isolated symptomatic metastases has been associated with improved survival and should be considered, especially in patients less than 45 years old. Radioiodine therapy of iodine-avid bone metastases has been associated with improved survival and should be used. External radiation and the concomitant use of glucocorticoids should be considered when skeletal metastatic lesions arise in locations where acute swelling may produce severe pain, fracture, or neurologic complications. Unresectable painful lesions can be treated by a combination of options or individual therapy that includes radioiodine, external beam

radiotherapy, intra-arterial embolization, radiofrequency ablation, periodic pamidronate or zoledronate infusions or bone-seeking radiopharmaceuticals such as strontium-8 or samarium-153.

CERVICAL VERTEBRA METASTASIS



TREATMENT OF BRAIN METASTASES

Brain metastases typically occur in older patients with more advanced disease at presentation, and are associated with a poor prognosis. Surgical resection and external beam radiotherapy traditionally have been the mainstays of therapy. Targeted approaches (such as radiosurgery) are employed to limit the radiation exposure of the surrounding brain tissue. Radioiodine can be considered for CNS metastases that concentrate radioiodine.

AMERICAN JOINT COMMITTEE ON CANCER (AJCC) CLASSIFICATION OF THYROID CANCER[22]

PRIMARY TUMOR (T)

TX Primary tumor cannot be assessed T0 No evidence of primary tumor

T1 Tumor < 2 cm confined to the thyroid

T2 Tumor >2 cm and <4 cm confined to the thyroid T3 Tumor >4 cm confined to the thyroid

T4a Tumor of any size with extra thyroid extension to subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve *or* Intrathyroidal Anaplastic carcinoma

T4b Tumor invading prevertebral fascia or encases carotid artery or mediastinal vessels *or* Extrathyroidal Anaplastic carcinoma

REGIONAL LYMPH NODES (N)

(Central Compartment, Lateral Cervical, And Upper Mediastinal)

NX Regional lymph nodes cannot be assessed N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

N1a Metastasis to level VI (pre- or paratracheal, and prelaryngeal)

N1b Metastasis to contra lateral cervical or superior mediastinal lymph nodes

DISTANT METASTASIS (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

STAGE GROUPINGS

PAPILLARY AND FOLLICULAR

Under 45 years of age

Stage I Stage II	Any T Any T	Any N Any N	M0 M1
45 years of age and over Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3 T1 T2 T3 T4a T4a	N0 N1a N1a N1a N0 N1a	M0 M0 M0 M0 M0 M0

Stage I Stage II	Any T Any T	Any N Any N	M0 M1
Stage IVA	T	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
	T4a	N1b	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

MEDULLARY CARCINOMA

Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage III	T1	N1a	M0
	T2	N1a	M0
	T3	N1a	M0
Stage IVA	T4a	N0	M0
	T4a	N1a	M0
	T1	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N1b	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

ANAPLASTIC CARCINOMA

Stage IVA	T4a	Any N	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

PROGNOSIS OF WDC

In the overall population with papillary thyroid cancer, there is a 90% to 95% long- term disease-free survival; there is a 70% to 80% long-term disease-free survival for patients with follicular cancers. 20% of patients in this group who develop recurrent disease include a majority with local cervical recurrences either in lymph nodes or the thyroid bed and a minority of patients with distant metastases to the lung, bone, and liver.

PROGNOSTIC FACTORS

AMES criteria (Lahey Clinic) based on age, metastatic disease, Extrathyroidal extension and size.

	Low Mortality Risk	**High Mortality Risk**
A: Age	Men <41years Women <51 years	Men > 41 years Women >51years
M: Metastasis	Absence of distant metastasis	Presence of distant metastasis
E: Extent of primary tumor	Intrathyroidal papillary cancer Follicular cancer with minor capsular Involvement	Extrathyroidal papillary cancer Follicular cancer with major capsular involvement
S: Size of primary tumor	< 5cm	≥ 5 cm (regardless of extent)

Low-risk patients can be identified as those who have a long-term overall survival rate of 98% and overall disease-free survival of 95% as compared to 54% and 45%, respectively, for high-risk patients.

AGES Criteria (Mayo Clinic) **-** A mathematical formula based on weighted risk factors was developed to yield a prognostic score. Based on age, tumor grade,tumor extent and tumor size

Score= 0.05 x Age [if age >40]+ 1[if Grade 2] +3 [if Grade 3 or 4]+1 [if extra thyroid]

+ 3 [if distant metastasis]+ 0.2x tumour size[maximum diameter in cm] 20yr survival score:

<3.99- 99%

4-4.99- 80%

5-5.99 – 67%

> 6 – 13%

The MACIS scale is a more sophisticated postoperative system modified from the AGES scale. This scale incorporates distant metastases, age at presentation, completeness of original surgical resection, extrathyroidal invasion, and size of original

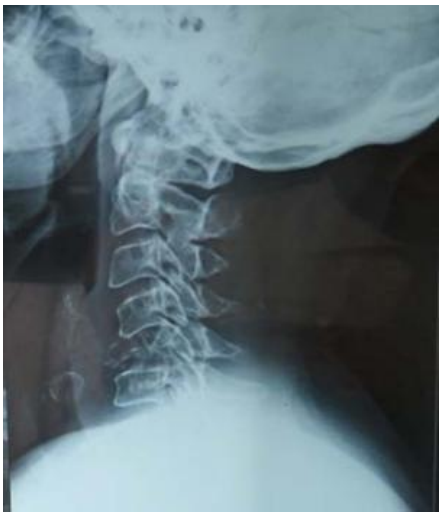
lesion (in centimeters) and classifies patients into four risk-groups based on their scores

OTHER PROGNOSTIC SCORING SYSTEMS

Ohio State Size, cervical metastases, multiplicity, invasion, distant metastases Sloan-Kettering Age, histology, size, extension, metastases NTCTS Size, multifocality, invasion, differentiation, cervical metastases, extracervical metastases

METASTASIS

Approximately 33% to 61% of patients with PTC will have involvement of cervical lymph nodes at the time of diagnosis. Whereas in follicular cancers is lower, ranging between 5% and 20%. Only a small minority of patients have distant metastatic hematogenous disease at the time of diagnosis. Having distant metastases at the time of presentation is a strong predictor of very poor outcome.



POORLY DIFFERENTIATED THYROID CARCINOMA

ANAPLASTIC CARCINOMA

It is a lethal malignancy with the worst prognosis of all thyroid malignancies. The median survival is 4 to 5 months from diagnosis. The mean age of diagnosis is the sixth and seventh decade with male to female ratio of 1: 1.5. It usually develops via dedifferentiation of prior well differentiated carcinoma. 25-50% have pulmonary metastases at the time diagnosis. Other organs of metastasis include bone and liver.

Microscopy shows anaplastic cells with marked cytologic atypia and high mitotic activity. Tumour necrosis and vascular invasion are common. A third of cases show coexisting areas of well differentiated thyroid carcinoma

CLINICAL FEATURES

The patients present with a palpable mass that is rapidly increasing in size. Invasion into the trachea, larynx, or recurrent laryngeal nerve leads to obstructive symptoms, hemoptysis, dysphagia, and hoarseness, which are often present at diagnosis.

The majority of patients with ATC die from aggressive local-regional disease, primarily with upper airway respiratory failure.

TREATMENT

Aggressive local therapy is indicated in all patients who can tolerate it and in whom it is technically possible. Survival after the diagnosis of ATC is very poor. External radiation has been used with limited success to treat locally recurrent ATC. Doxorubicin is the single most effective chemotherapeutic for ATC, and it has been shown that doxorubicin plus platinum is more effective than doxorubicin alone.

MEDULLARY THYROID CARCINOMA (MTC).

This variety arises from the parafollicular (‘c cells’). It has an incidence of 3-12% of thyroid cancers. There are two types of MTC namely sporadic/non familial (60-70%) and Familial(30%)

There are 3 distinct syndromes associated with familial MTC- MEN 2A, MEN 2B and Familial non MEN MTC. All these variants are known to result secondary to germline mutations in the *RET* proto-oncogene.

PATHOLOGY

MTCs typically are unilateral (80%) in patients with sporadic disease and multicentric in familial cases, with bilateral tumors occurring in up to 90% of familial patients. Familial cases also are associated with C-cell hyperplasia, which is

considered a premalignant lesion. Microscopically, tumors are composed of sheets of infiltrating neoplastic cells separated by collagen and amyloid. The presence of amyloid is a diagnostic finding, but immunohistochemistry for calcitonin is more commonly used as a diagnostic tumor marker. These tumors also stain positively for CEA and calcitonin gene–related peptide.

CLINICAL FEATURES

Most patients present between 50 and 60 years old, although patients with familial disease present at a younger age. Patients with MTC often present with a neck mass that may be associated with palpable cervical lymphadenopathy (15 to 20%). Pain or aching is more common in patients with these tumors, and local invasion may produce symptoms of dysphagia, dyspnea, or dysphonia. Distant blood-borne metastases to theliver, bone (frequently osteoblastic), and lung occur later in the disease. Patients with extensive metastatic disease frequently develop diarrhea, which may result from increased intestinal motility and impaired intestinal water and electrolyte flux. About 2 to 4% of patients develop Cushing's syndrome as a result of ectopic production of adrenocorticotropic hormone (ACTH).

TREATMENT

If patients are found to have a pheochromocytoma, this must be operated on first. Total thyroidectomy is the treatment of choice for patients with MTC. Central compartment nodes frequently are involved early in the disease process, so that a bilateral central neck node dissection should be routinely performed. In patients with palpable cervical nodes or involved central neck nodes, ipsilateral or bilateral, modified radical neck dissection is recommended. In patients with tumors >1 cm, ipsilateral prophylactic modified radical neck dissection is recommended because >60% of these patients have nodal metastases. In the case of locally recurrent or metastatic disease, tumor debulking is advised not only to ameliorate symptoms of flushing and diarrhea, but also to decrease risk of death from recurrent central neck or mediastinal disease.

Radiotherapy -External beam radiotherapy is controversial, but is recommended for patients with unresectable residual or recurrent tumor.

There is no effective chemotherapy regimen.

In patients who have hypercalcemia at the time of thyroidectomy, only obviously enlarged parathyroid glands should be removed.

Patients are followed by annual measurements of calcitonin and CEA levels, in addition to history and physical examination.

THYROID LYMPHOMA

Thyroid Lymphoma is rare constituting < 1% of all lymphomas. Majority are non- Hodgkin's lymphoma of intermediate grade. Many are considered mucosa-associated lymphoid tissue lymphomas (MALTomas) that show plasmacytic differentiation and may be associated with similar lesions in extranodal sites especially in the gastrointestinal tract. The majority have thyroid disease plus cervical or mediastinal lymph nodes. Thyroid lymphomas have a strong female predominance, ranging from 3:1 up to 8:1 in the 6^{th} and 7^{th} decade of life. Symptoms include hoarseness, dyspnea with stridor, or dysphagia. Patients may be hypothyroid with Hashimoto's thyroiditis. Treatment includes combination of surgery, EBRT combined with a chemotherapy regimen based on the histopathological subtype of lymphoma.

METASTATIC CARCINOMA TO THYROID [23, 24]

Comprises less than 1% of thyroid malignancies. The most common primary site is renal cell carcinoma, accounting for 23% of cases. The next most common sites are breast (16%), lung (15%), melanoma (5%), and colon and larynx (4.5% each). Diagnosis is by FNAC. Treatment is mainly palliative. Surgery maybe indicated in case of obstructive symptoms.

MATERIALS AND METHODS

This prospective study included 100 patients presenting with thyroid swellings clinically suspicious of malignancy at the Institute of general surgery,Madras medical college. Duration of study was June 2014 to Dec 2015 which included a 6 month follow up.

INCLUSION CRITERIA

The patients admitted with thyroid swelling in various surgical wards in RGGGH.

All cases must be clinically and biochemically euthyroid

EXCLUSION CRITERIA

Those cases not in euthyroid state.

All patients were admitted and a detailed history and clinical examination was done and investigated as per the written proforma. Informed consent was taken and thyroid profile and ultrasonogram ,FNAC was done in all cases. All cases that gave consent for surgery were explained about risk and complications of surgery and anesthesia. Preoperatively investigations were sent according to protocol. A preoperative indirect laryngoscopy was

done in all cases to check for the status of vocal cords. The type of surgery depended on the clinical diagnosis and FNAC report. Correlation of the clinical diagnosis, preoperative TSH levels,radiological,cytology and the final histopathological diagnosis was done. Patients were followed up regularly over a minimum period of 6 months. Follow up was done at regular interval by clinical examination, serum thyroglobulin estimation, serum TSH levels and thyroid scan.

STATISTICAL METHODS

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters. Leven1s test for homogeneity of variance has been performed to assess the homogeneity of variance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

SIGNIFICANT FIGURES

+ Suggestive significance (P value: $0.05<P<0.10$)

* Moderately significant (P value: $0.01<P \leq 0.05$)

** Strongly significant (P value: $P \leq 0.01$)

Statistical software: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Microsoft Excel have been used to generate graphs, tables etc.

OBSERVATION AND RESULTS

This was a prospective study done in the Department of General Surgery at Madras medical college,Chennai. The study period was June 2014 to June 2015.

Total number of cases - 100

Total number of confirmed malignancy – 25

Cases who were histopathologically proven to be malignant were retrospectively studied.Their clinical features,radiological findings and pr operative serum TSH levels were analysed.

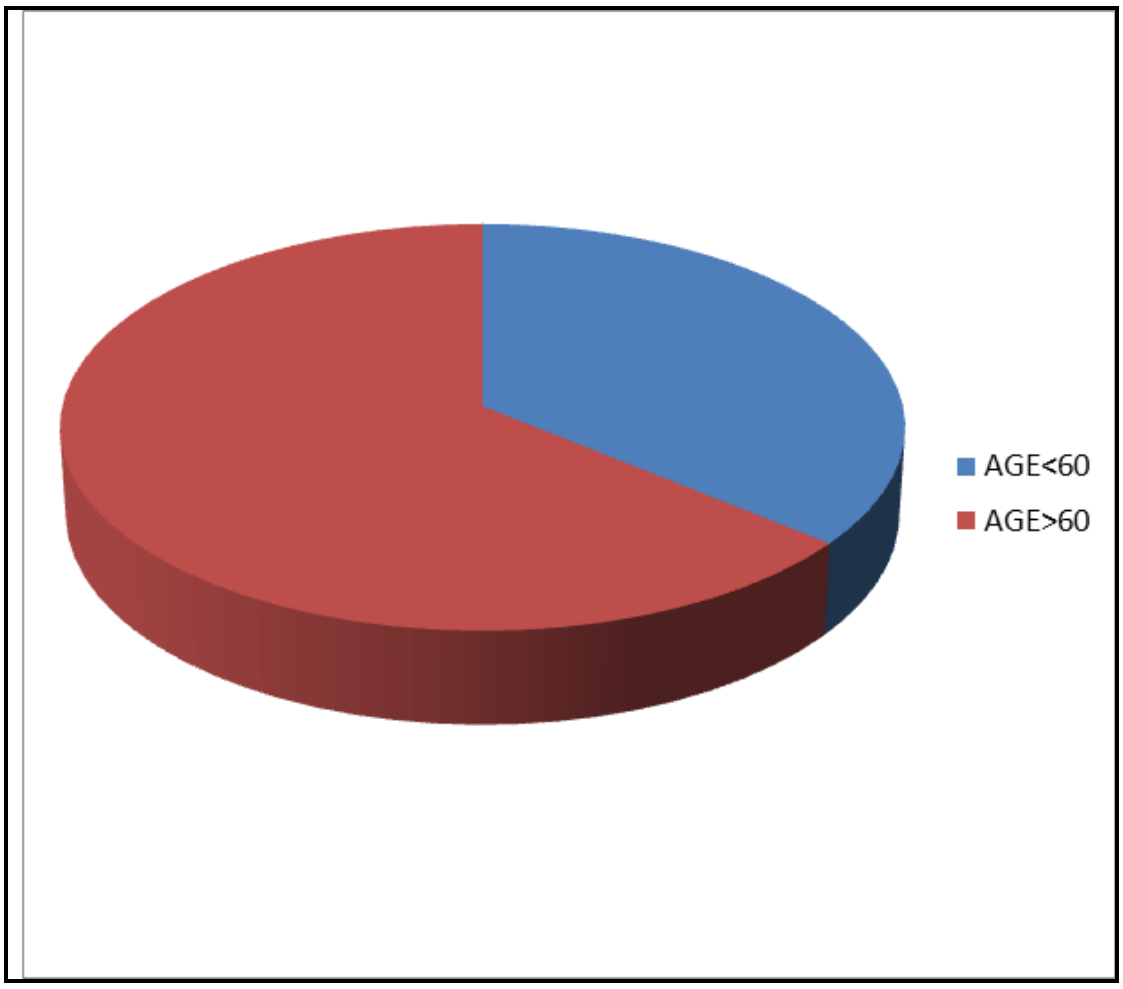
STUDY DESIGN

A prospective study with a sample size of 100 patients was conducted at the Institute of General surgery,Madras Medical College,Chennai . Patients with clinical features suggestive of thyroid malignancy were included. The preoperative clinical,radiological and TSH levels were analyzed to check for any relationship between them and the likelihood of a thyroid nodule being malignant. At the same time a clinical study of those patients with confirmed thyroid malignancy was done. The observed results were subjected to statistical analysis. The following observations were made.

RESULTS

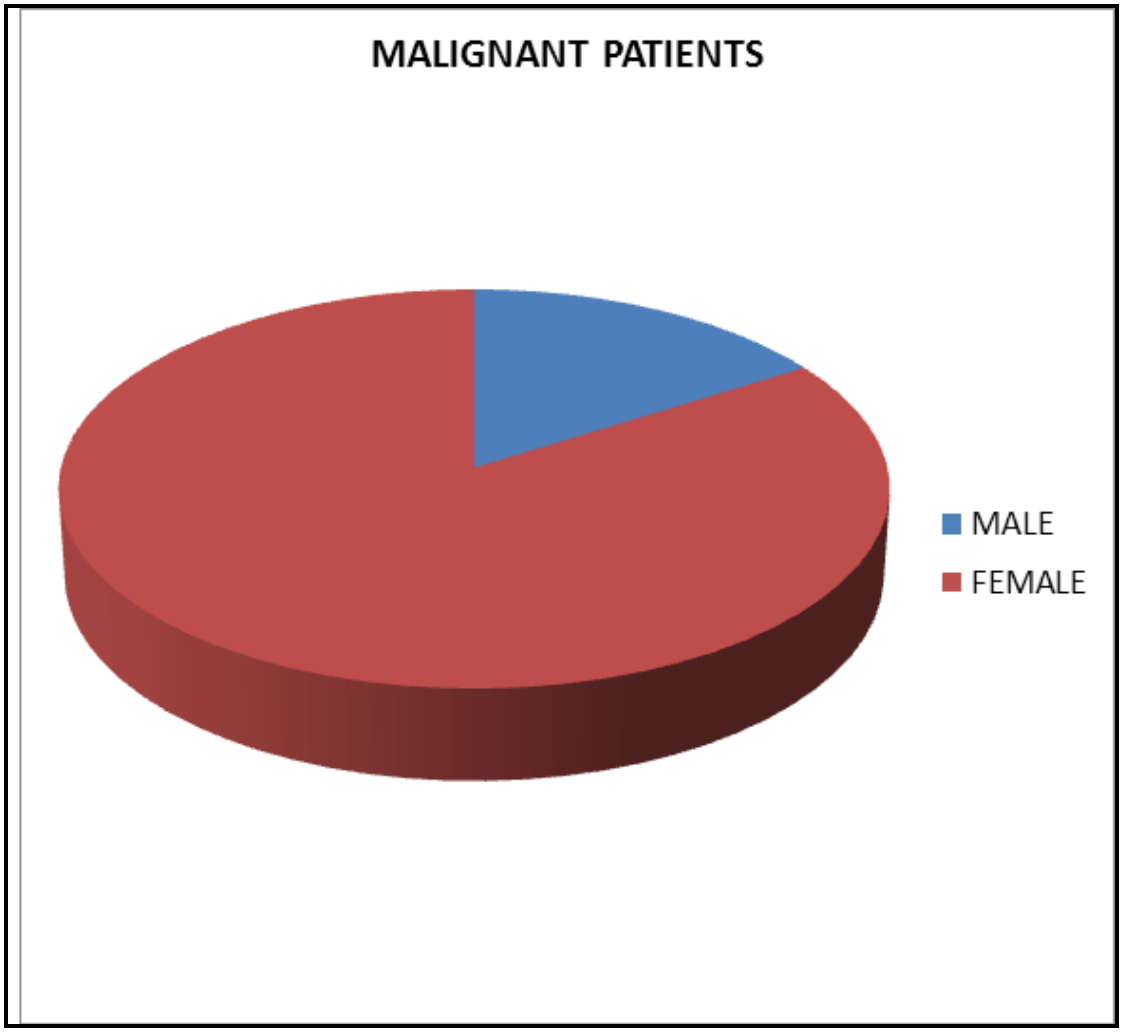
AGE DISTRIBUTION AMONG MALIGNANCY PATIENTS

Age in years	Malignant (n=25)	Percentage (%)
<60	9	36%
>60	16	64%



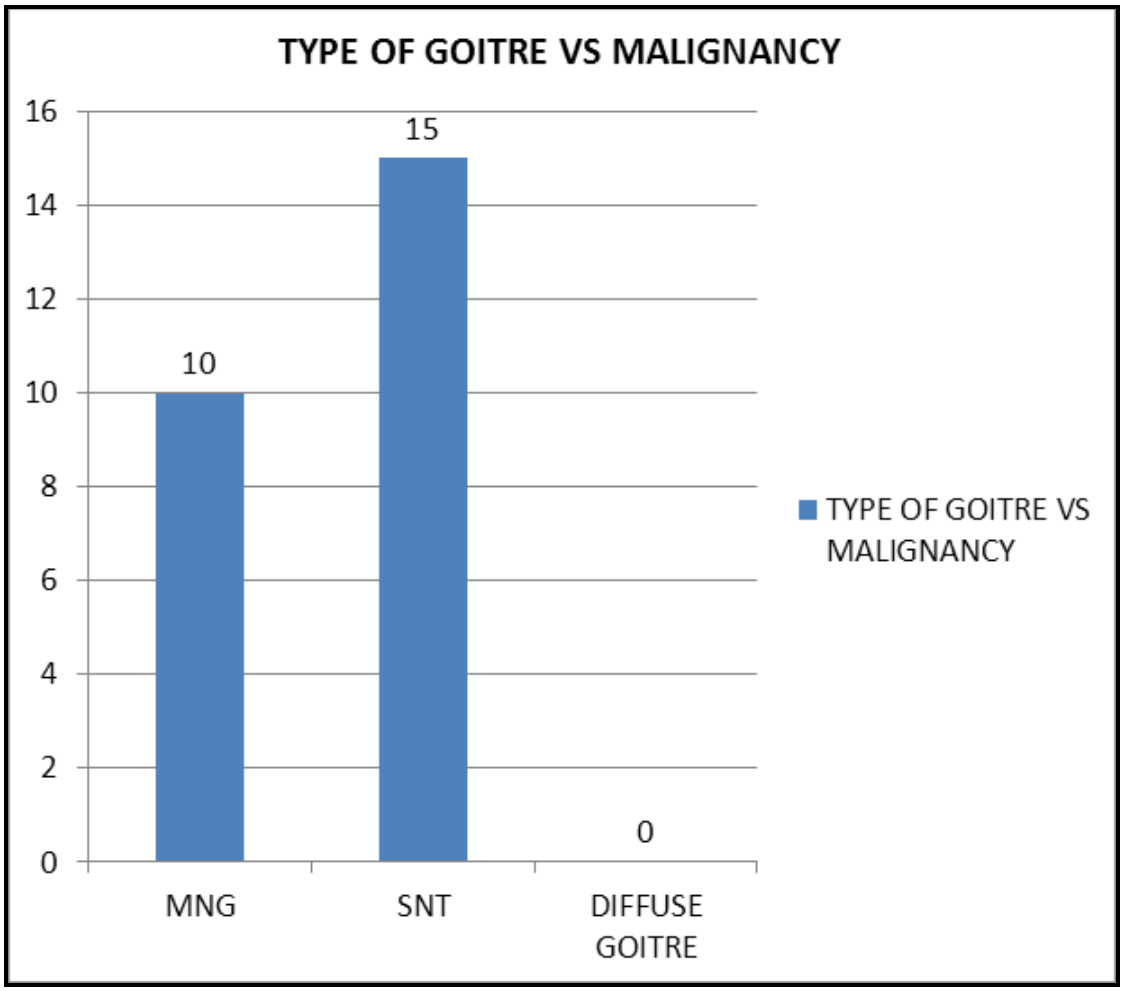
SEX DISTRIBUTION AMONG MALIGNANCY PATIENTS

Sex	Malignant (n=25)	Percentage
Male	4	16%
Female	21	84%



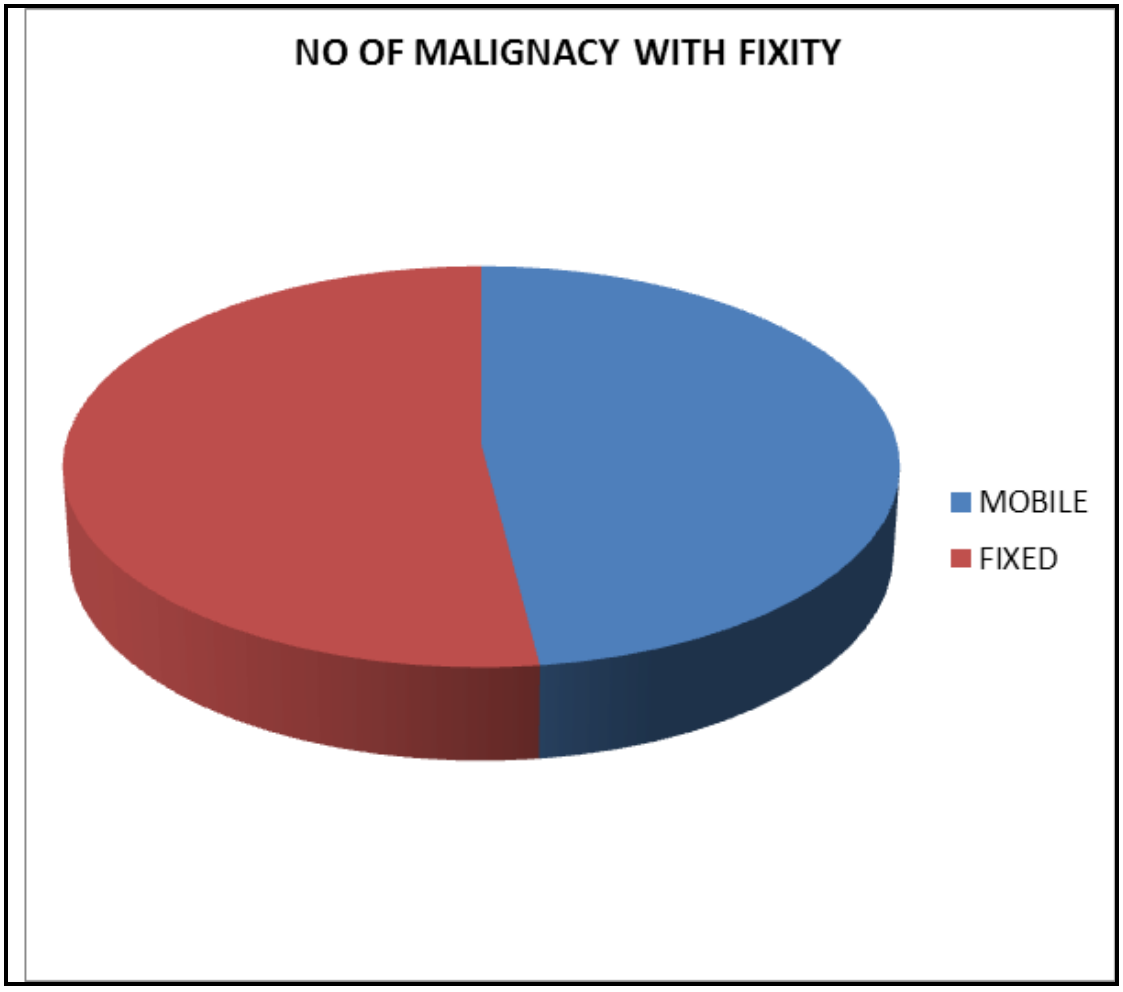
TYPE OF GOITRE AND MALIGNANCY

Type of Goitre	No of Malignancy Patients	Percentage
MNG	10	40%
SNT	15	60%
DIFFUSE	0	0%



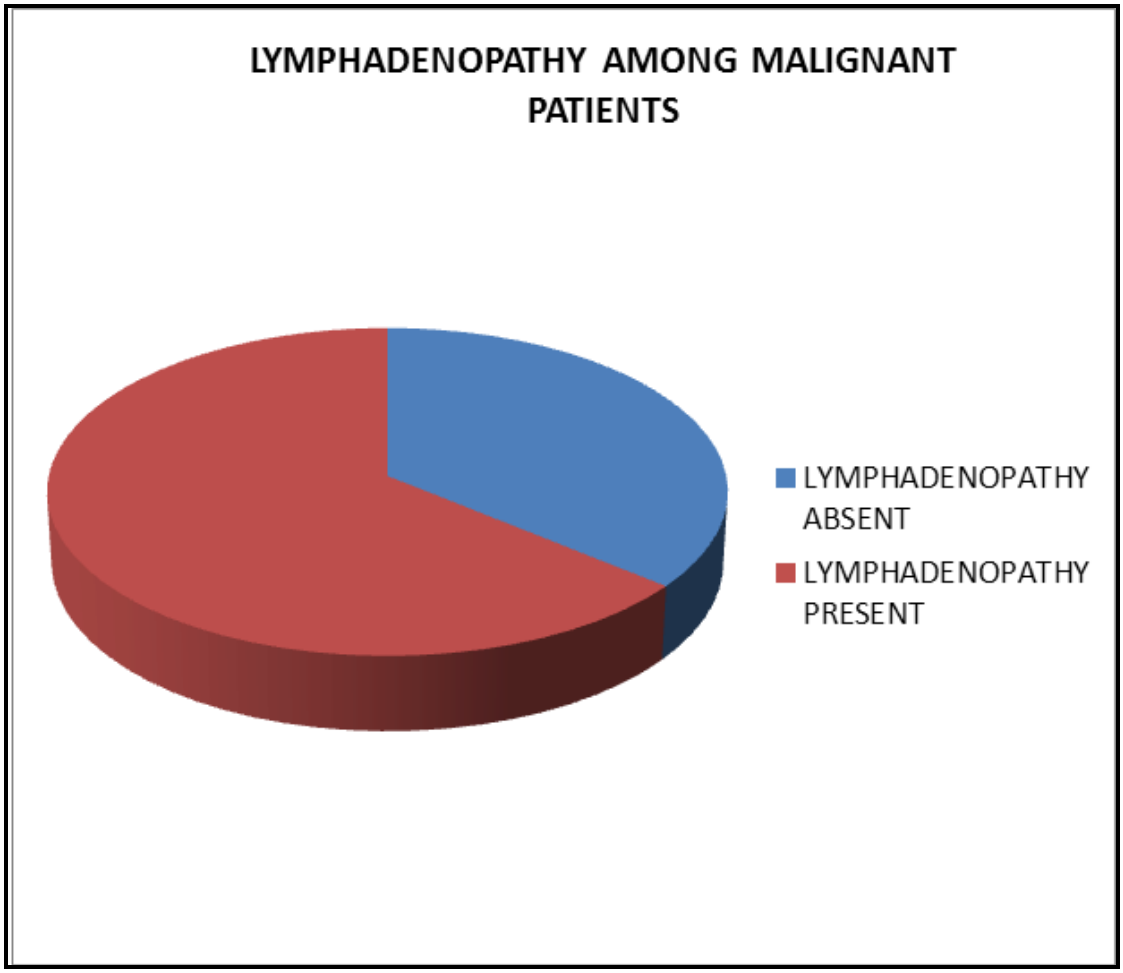
FIXITY AMONG MALIGNANCY PATIENTS

Fixity	Malignant (n=25)	Percentage
MOBILE	12	48%
FIXED	13	52%



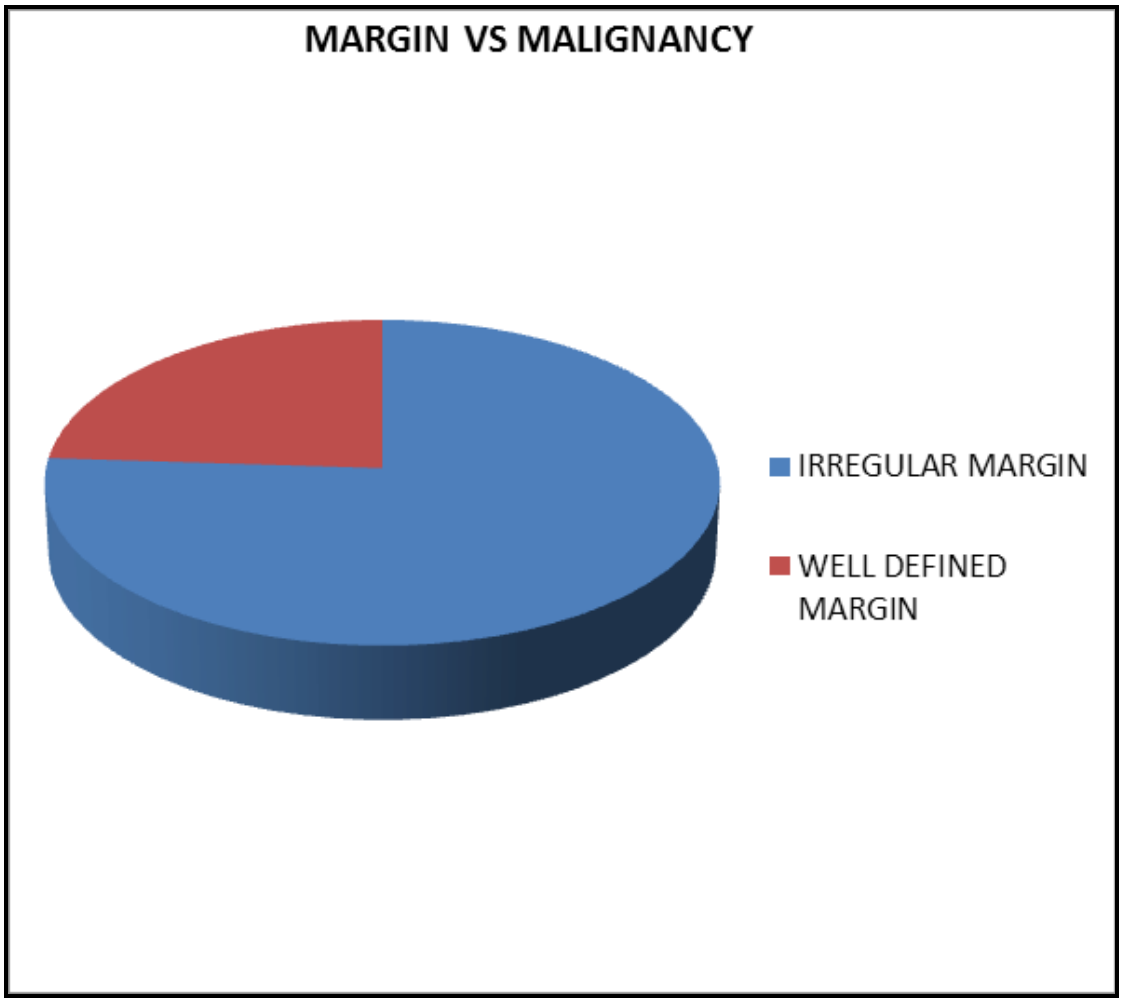
LYMPHADENOPATHY IN MALIGNANCY

Lymphadenopathy	Malignant(n=25)	Percentage
ABSENT	9	36%
PRESENT	16	64%



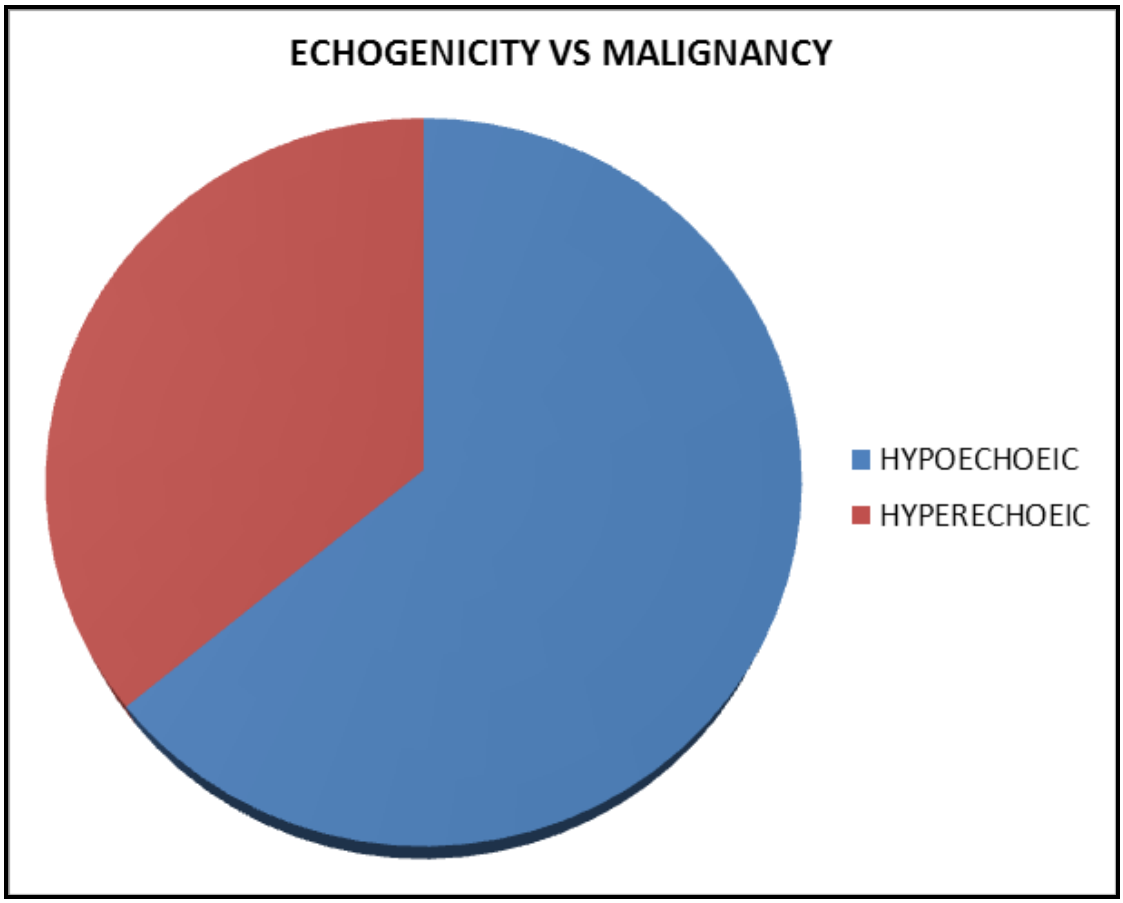
SONOGRAPHIC FINDINGS MARGINS IN USG AMONG MALIGNANCY PATIENTS

Margin	Malignant(n=25)	Percentage
IRREGULAR	19	76%
WELL DEFINED	6	24%



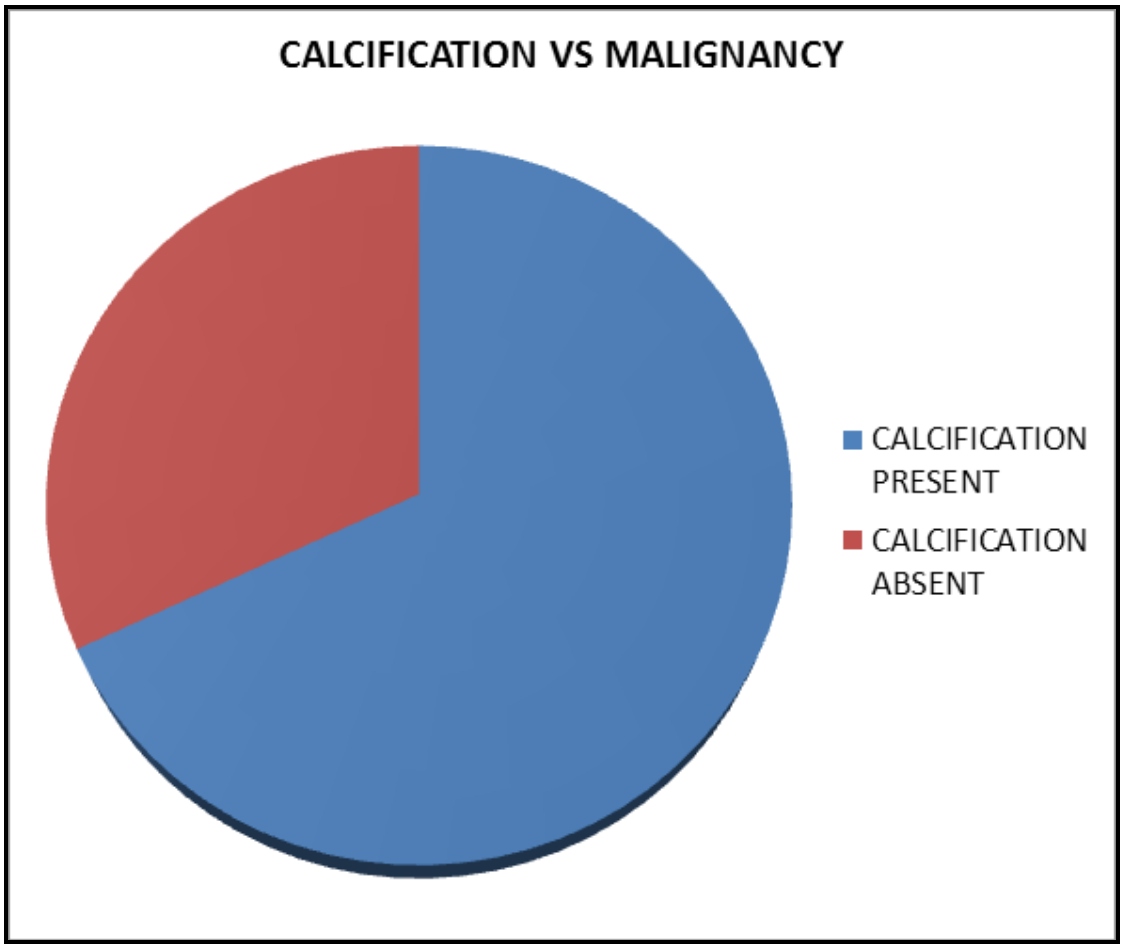
ECHOGENICITY IN SONOGRAPHY AMONG MALIGNANCY PATIENTS

Echogenicity	Malignant(n=25)	Percentage
HYPOECHOEIC	16	64%
HYPERECHOEIC	9	36%



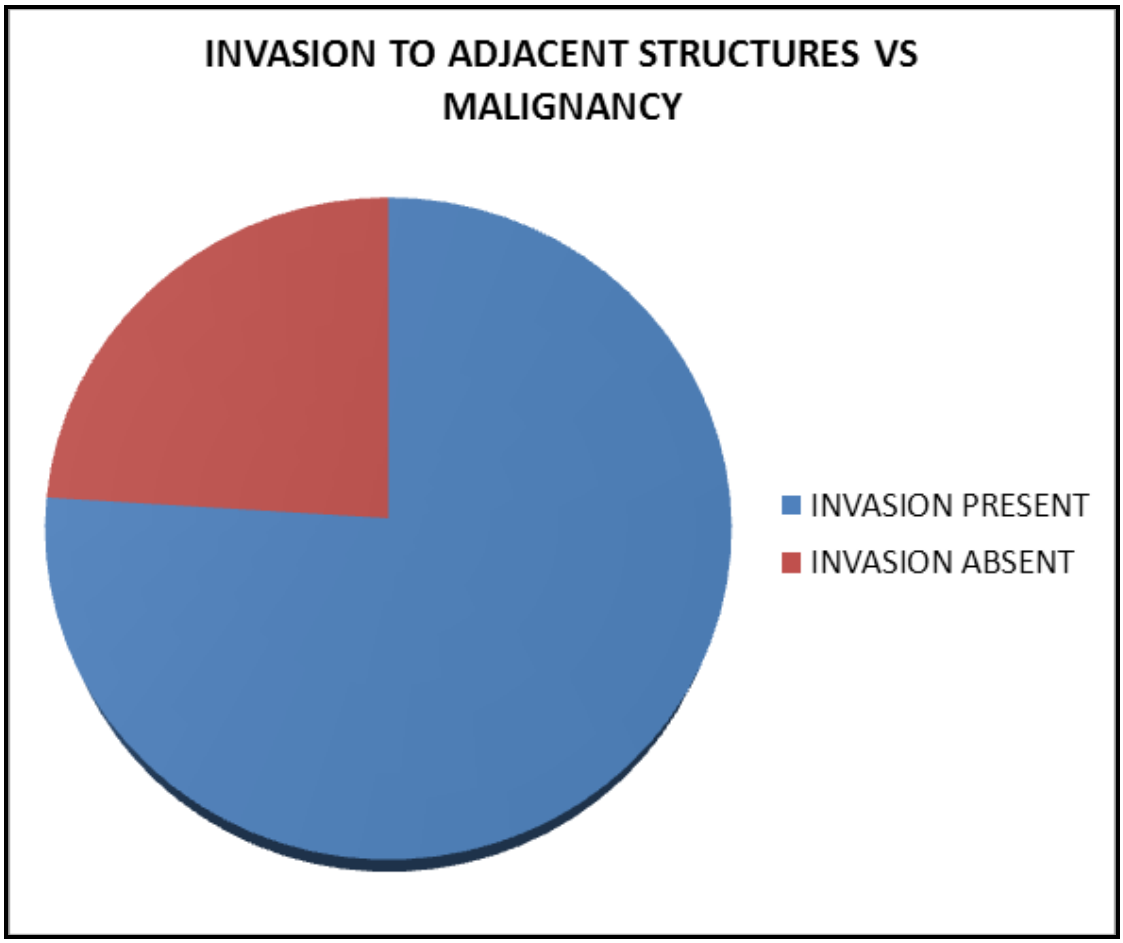
CALCIFICATION IN USG AMONG MALIGNANCY PATIENTS

Calcification	Malignant (n=25)	Percentage
PRESENT	17	68%
ABSENT	8	32%



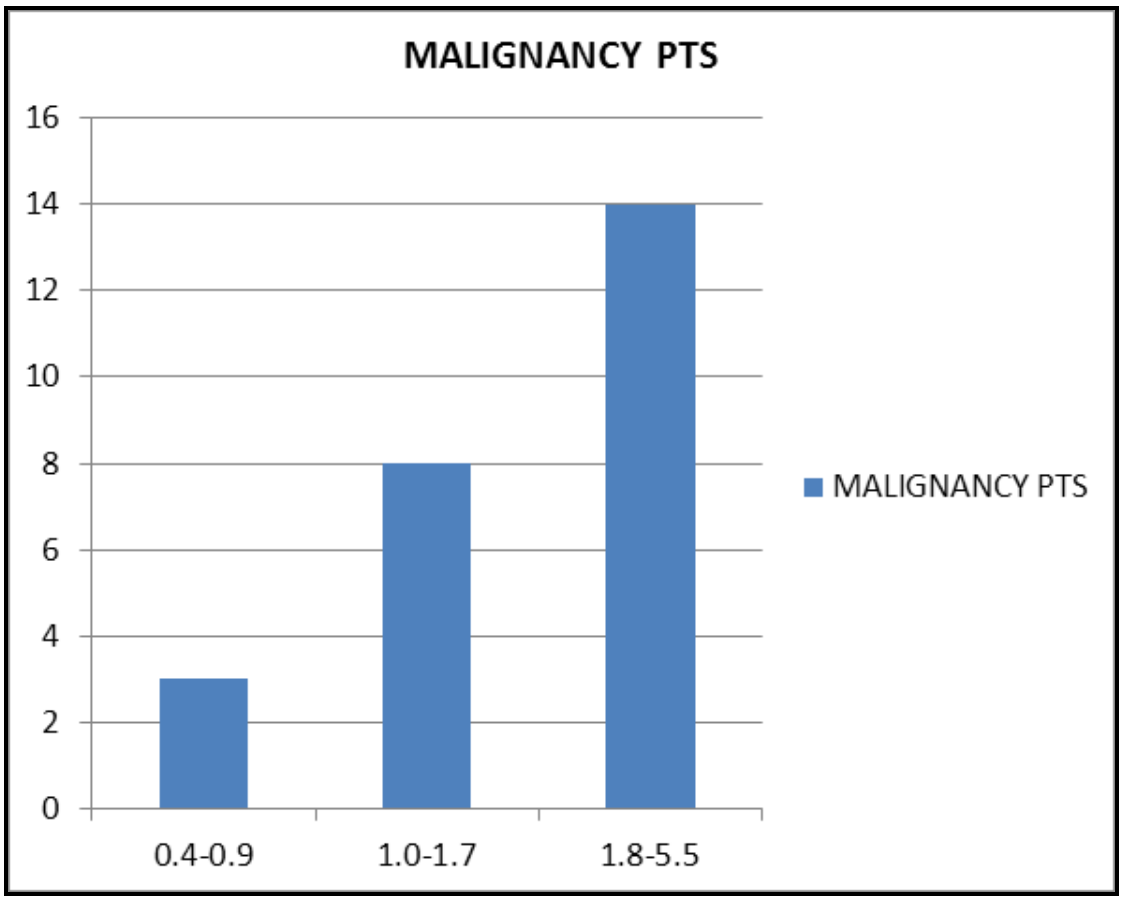
INVASION TO ADJACENT STRUCTURES SEEN IN USG AMONG MALIGNANCY PATIENTS

Invasion to adjacent structures	Malignant(n=25)	Percentage
PRESENT	19	76%
ABSENT	6	24%



SERUM TSH LEVELS AMONG MALIGNANCY PATIENTS

TSH levels	Malignant(n=25)	Percentage
0.4-0.9	3	12%
1.0-1.7	8	32%
1.8-5.5	14	56%



DISCUSSION

PREDICTORS OF MALIGNACY IN THYROID NODULES

There are many predictors of malignancy in a thyroid nodule. A history of prior radiation exposure especially during childhood is known to be found in many cases of papillary carcinoma. Similarly, exposure to certain environmental risk factors such as excess dietary intake of iodine, retinol and vitamin E has shown to have an increased chance of malignancy.

Age factors: Younger age group (<20 years) and older age group (>70years) have a higher risk of malignancy.

Associations with other inherited syndromes such as familial polyposis coli, Gardner's syndrome and Cowden's syndrome is seen with medullary carcinoma thyroid.

In the presence of certain clinical signs and symptoms i.e. hard and fixed nodules, large nodules (>4cm) with presence of neck lymph nodes,solitary thyroid nodule, rapid increase in size of thyroid nodules, associated hoarseness of voice, dysphagia, dyspnea and Horner's syndrome malignancy should always be suspected.

Suspicious criteria by ultrasound include central hypervascularity, microcalcifications smaller than 2mm in diameter, irregular borders,hypoechoic lesions and invasion into surrounding tissues. [28, 29] Ultrasound scan is more sensitive than clinical examination in the detection of enlarged cervical nodes. Cervical lymph nodes, infiltrated by papillary carcinoma may be entirely cystic and mimic other cystic masses of the neck, such as a branchial cyst, while calcification may be seen within nodes invaded by medullary carcinoma.

SERUM TSH LEVELS – A NOVEL METHOD IN PREDICTING MALIGNANCY

Many studies have shown a definite relation between preoperative serum TSH levels and thyroid malignancy. Furthermore, preoperative serum TSH concentrations are higher in patients with more aggressive tumors. Thus a baseline TSH would predict which nodules require a more aggressive approach and surgery.

RATIONAL BEHIND CHOOSING TSH LEVELS AS A PREDICTOR OF MALIGNANCY

TSH is a known thyroid growth factor. Well-differentiated thyroid cancers express TSH receptors [30, 31]. Although oncogenes and other growth factors are involved in thyroid cancer growth and

development [32, 33], it seems probable that TSH can act as a cancer stimulus. This hypothesis is supported by improved survival in thyroid cancer patients treated with suppressive doses of levothyroxine [34] and by cases of tumor growth post-T4 withdrawal or recombinant TSH [35]. Some studies have showed higher serum TSH levels associated with advanced stages of thyroid cancer. These findings suggest that TSH may play a central role in the development and /or progression of thyroid carcinomas.

Supportive of the TSH receptor's role in cancer are the data on autoimmune thyroid disease and thyroid cancer. An increased incidence of thyroid cancer is seen in patients with antibody evidence of Hashimoto's thyroiditis.

Our Study: In this study we had a total of 100 patients who presented with thyroid swelling. The main objective was to evaluate the role of TSH as a biochemical predictor of malignancy and also study about the clinical radiological features that can predict thyroid malignancy. Only patients that were euthyroid were included.

Of those patients with confirmed malignancy a descriptive analysis of the clinical presentation and management was done.

The observations and results were subjected to statistical analysis and compared with other studies.

GENDER DISTRIBUTION:

There were 21 female patients and 4 male patients in this study histopathologically proven malignancy. This distribution is comparable to other studies

COMPARISONOF GENDER DISTRIBUTION OF MALIGNANT CASES

Study	Year	Male: Female Ratio
Jemal et al	2003	1:3
Dorairajan et al	2002	1:3.5
Our study	2015	1:5.5

It is well established that thyroid disorders including thyroid malignancies are more common among women than men.But still the cause of this increased prevalence of thyroid cancers among women is unclear .In our study,incidence of malignancy is more common among females as compared with previous studies.Application of genomic and proteomic approaches to the study of thyroid cancer gender disparity could be helpful for better understanding the molecular basis for gender differences in thyroid cancers (Rahbari R,Zhang L,Kebebew E)

AGE DISTRIBUTION

The mean age for thyroid malignancy was 50 years which was comparable to other studies [3, 37, 38].Mean age in males was 59 years whereas in females was 55.

Study	Year	Mean age
Haymart et al(3)	2008	46
Fiore et al (42)	2009	45
Our study	2015	50

Thyroid cancer incidence in males is strongly related to age with highest incidence rates being in older men.However incidence in females does not entirely follow the pattern of increasing incidence in age seen in males(and in most other cancers).Hormonal factors may be implicated in the association with age in females.

In our study,most of the malignant patients fall in age group >60 years.The mean age of malignancy was found to be lower in females than in males as shown in previous studies.

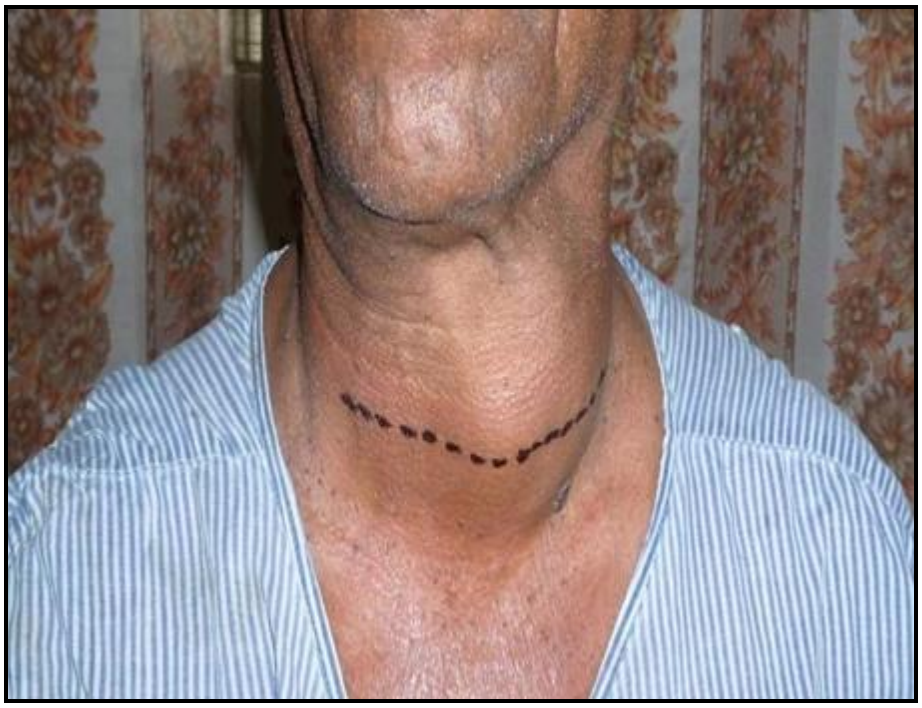
TYPE OF GOITRE AND ITS INCIDENCE OF MALIGNANCY

Clinically recogonised thyroid cancer constitutes less than 1% of human malignancies.Risk of malignancy in solitary nodule

thyroid is greater than other swellings. Risk of malignancy in generalized swelling is about 3% and in solitary nodule thyroid is about 15%.In a study done by :Lema,L.E.K.; M.R. Aziz; N.A. Mbembati; H.A. Mwakyoma: malignancy was found in 10% of solitary nodule thyroid and 5% of multinodular goiter.

Well differentiated cancers are common among thyroid cancers.Among the well differentiated cancers papillary carcinoma is more common which usually presents as solitary nodule.Hence

In our study among the malignancy patients 60% are SNT and remaining had multinodular goiter.



CERVICAL LYMPH NODE INVLOVEMENT

Cervical lymphadenopathy is a common presentation in thyroid malignancy.

Approximately 33% to 61% of patients with papillary carcinoma will have involvement of clinically apparent cervical lymph nodes at the time of diagnosis as per previous studies.

COMPARISION OF INCIDENCE OF CERVICAL LYMPH NODE INVOLVEMENT

Study	Year	Percentage
Mazzaferri et al (41	2001	53-61%
Dorairajan et al(37)	2002	26-50%
Our study	2015	64%

Appeareance of enlarged cervical lymph nodes on ultrasound boosted the predictive value of diagnosing thyroid cancer in suspicious nodules.

- The incidence of neck nodes in our study was 64%
- Presence of neck lymph nodes was a significant clinical indicator of malignancy Hence assessment of enlarged cervical lymph nodes by ultrasound is feasible and should be studied further to determine the exact clinical and

pathological implications of cervical lymph nodes found on pre operative ultrasound

RADIOLOGICAL FEATURES PREDICTING THYROID MALIGNANCY

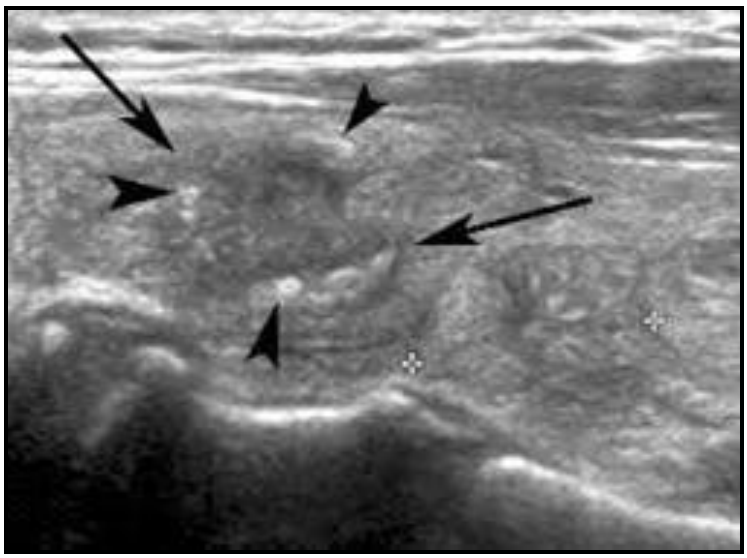
According to *Leenhardt et al* ,the incidence of malignancy is 4% when a solid thyroid nodule is hyperechoic. If the lesion is hypoechoic, the incidence of malignancy rises to 26% . However, hypoechogenicity alone is inaccurate in predicting malignancy, and if used as a sole predictive sign, it has a relatively poor specificity (49%) and positive predictive value (40%) .

In our study,64% of the malignancy patients have hypoechoic lesion.

A malignant thyroid nodule tends to have ill-defined margins on ultrasound. A peripheral halo of decreased echogenicity is seen around hypoechoic and isoechoic nodules and is caused by either the capsule of the nodule or compressed thyroid tissue and vessels. The absence of a halo has a specificity of 77% and sensitivity of 67% in predicting malignancy.

In our study,19 out of 25 malignancy patients have irregular margins in ultrasound.

Fine punctate calcification due to calcified psammoma bodies within the nodule is seen in papillary carcinoma in 25%–40% of cases. If used as the sole predictive sign of malignancy, microcalcification is the most reliable one with an accuracy of 76%, specificity of 93% and a positive predictive value of 70%. Coarse, dysmorphic or curvilinear calcifications commonly indicate benignity.



In our study,68% of the malignancy patients have micro calcification on sonography.

Invasion to adjacent structures such as trachea,oesophagus and major vessels such as carotid is a important featrure of malignancy and is considered as a key predictor of thyroid malignancy.

In this study 19 out of 25 patients have invasion to adjacent structures.

TSH LEVELS AND THE RISK OF MALIGNANCY

In this study the mean preoperative TSH value was: 2.39±1.42mU/L. All patients were euthyroid. The mean TSH value was significantly higher in malignancy than in benign disease i.e. 3.71±1.22mU/L vs. 1.80±1.03mU/L. This is comparable to the results of Haymart et al [3], Fiore et al [42] and Jonklaas et al [34]

TABLE 24 COMPARISON OF MEAN TSH VALUE IN BENIGN VS MALIGNANT DISEASE

	Benign disease	Malignant disease	P value
Our Study	1.80±1.03	3.71±1.22	P<0.001
Haymart et al (3)	1.4±0.4	3.7±2.3	P<0.001
Fiore et al (42)	0.70 ± 0.41	1.10±0.6	P<0.0001

On analysis of the preoperative TSH values it was observed that TSH level was an independent predictor of malignancy. Patients with values of 0.40-1.39 mU/L had 0% chance of malignancy. Those with range of 1.40-4.99mU/L had

36.7% chance of malignancy whereas those with TSH levels >5mU/L had 75% chance of malignancy

The following table shows the various studies that have shown a relationship between serum TSH concentration and thyroid cancer.

SUMMARY OF STUDIES INVESTIGATING THE RELATIONSHIP BETWEEN SERUM TSH CONCENTRATION AND THYROID CANCER [2]

Authors	Journal	No. of patients	Country	Significant findings
Boelaert et al. (2006)(2)	Journal of Clinical Endocrinology and Metabolism	1500	UK	Serum TSH is independent predictor of malignancy in thyroid nodules. Risk of malignancy rises in parallel with serum TSH within normal range.
Haymart et al. (2008a)(3)	Journal of Clinical Endocrinology and Metabolism	843	US	Likelihood of thyroid cancer increases with higher TSH concentration. Higher serum TSH associated with advanced stage-differentiated thyroid cancer

Authors	Journal	No. of patients	Country	Significant findings
Jonklaas et al. (2008)(34)	Thyroid	50	US	Higher TSH concentrations are associated with diagnosis of thyroid cancer. Patients with thyroid cancer have lower serum total T3 Concentrations
Polyzos et al. (2008)(5)	Journal of Cancer Research and Clinical Oncology	565	Greece	Higher rates of thyroid malignancy in patients with TSH in upper tertile of normal range
Haymart et al. (2008b)(3)	Clinical Endocrinology	1361	US	Thyroid cancer incidence correlates with serum TSH independent of age. Higher TSH is associated with Extrathyroidal extension of disease.
Fiore et al. (2009) (42)	Endocrine-Related Cancer	10 178	Italy	Higher TSH in patients with T3–T4 disease and in those with lymph node metastases. Autonomously functioning thyroid nodules are less likely to be malignant

SUMMARY

This was a prospective study involving 50 patients admitted to our hospital with thyroid swellings. The aim was to evaluate the utility of serum TSH estimation as a biochemical predictor of malignancy in suspicious thyroid nodules and to study the clinical presentation of thyroid malignancies.Also other predictors such as clinical features and radiological features were studied. The observations of this study can be summarized as follows:

- Most patients were females with mean age of 44.62±15.12 years. Mean age of malignancy was 4o years with a higher mean age in males (59 years) as compared to females (38 years).

- Commonest presentation was a rapidly growing thyroid swelling of short duration. In some cases there was history of a longstanding goitre with sudden development of secondary symptoms such as pain and compressive symptoms.

- Majority of malignancy patients presented with a SNT. 60% of the malignancy patients presented with SNT.
- Most of the malignancy patients presented with lymphadenopathy.64% of malignancy patients had cervical lymphadenopathy.
- Papillary carcinoma was the most common histopathological type.
- The mean preoperative TSH value was 2.39±1.42 mU/L.
- Mean TSH value in malignancy was higher (3.71±1.22mU/L) compared to those with benign disease 1.80±1.03mU/L)
- Incidence of malignancy increased with higher TSH values.

CONCLUSION

Thyroid malignancies have a varied clinical presentation. The commonest presentation being that of a solitary thyroid nodule.

Though there are many predictors of thyroid malignancy, none of them can conclusively predict the nature of a thyroid nodule.

In our study we evaluated the utility of preoperative serum TSH levels as a predictor of malignancy and it did show a statistically significant correlation (P=<0.01) between higher TSH levels and malignant nodules. However this relationship between higher TSH levels was not seen in those presenting with no primary thyroid swelling and only cervical lymph node metastasis. The utility of TSH in poorly differentiated carcinoma could not be assessed as all the patients in this series had well differentiated carcinoma.

However, as all patients with a thyroid swelling undergo a thyroid function test it is important to pay special attention to the TSH values. . TSH levels could be used as predictor in

clinically suspect malignant thyroid swelling with a benign FNAC report. In such cases where TSH value is high, the FNAC can be relooked to confirm the diagnosis.

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ANNEXURE
DATA COLLECTION SHEET

I.Patient particulars:

Name	DOA	Case No.
Age	DOS	I.p.No.
Sex	DOD	

Address

Occupation:

CHIEF COMPLAINTS

HISTORY OF PRESENTING ILLNESS

Duration /Progression

Pressure symptoms-dyspnoea/dysphagia

Symptoms of hyperthyroidism/hypothyroidism

Symptoms suggestive of malignancy

Other symptoms

PAST HISTORY

History of previous thyroid disorder

History of goitrogen intake

Drug history

Radiation exposure

MENSTRUAL HISTORY

FAMILY HISTORY

PERSONAL HISORY

Diet

Sleep

Apetite

Bladder/Bowel habits

EXAMINATION

Appearance,build,nutritional assessment

Pallor/Icterus/Cyanosis/Clubbing/Edema/Lymphadenopathy

Vitals:Pulse rate/BP/Respiratory rate

LOCAL EXAMINATION

Inspection

a.Site
b.Size
c.Shape
d.Surface
e.Extent
f.Margins
g.Skin over the swelling
h.Pulsation
i.Movement with deglutition
j.Position of trachea

Palpation

a.Local temperature
b.Tenderness
c.Site, size, shape and extent
d.Surface
e.Borders
f.Consistency
g.Mobility
h.Fixity to skin
i.Plane of the swelling
j.Examination of lymph nodes
k.Tracheal position
l.Carotid pulsation

Percussion

Auscultation

SYSTEMIC EXAMINATION

INVESTIGATIONS:

Blood routine

Chest x ray/Xray neck AP and lateral view

Indirect laryngoscopy

Thyroid profile-TSH,T3,T4

FNAC

FINAL DIAGNOSIS

MANAGEMENT

Operated /Non operated-

POST OPERATIVE COURSE

Recovery

Complications

FOLLOW UP

TSH concentration

Thyroglobulin

NAME	AGE	SEX	TYPE OF GOITRE	FIXITY	LYMPHADENOPATHY	MARGINS	ECHOES	CALCIFICATION	INVASION	TSH	MALIGNANCY
SARASWATHY	64	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.3	NO
KAMATCHI	34	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	YES	1.9	NO
JAGAN	36	M	SNT	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.8	NO
VALLI	65	F	SNT	MOBILE	NEGATIVE	IRREGULAR	HYPO	YES	YES	1.7	YES
VANATHI	45	F	DIFFUSE	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.5	NO
SURESH	51	M	MNG	MOBILE	NEGATIVE	REGULAR	HYPO	NO	NO	1.23	NO
MUNIAMMAL	60	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	0.8	NO
MEENAKSHI	48	F	SNT	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.54	NO
MARY	54	F	MNG	MOBILE	POSITIVE	IRREGULAR	HYPER	NO	NO	1.38	NO
JOTHI	22	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	YES	NO	1.41	NO
AARTHI	40	F	MNG	FIXED	POSITIVE	IRREGULAR	HYPER	NO	NO	1.6	YES
ARUN PRASATH	34	M	SNT	MOBILE	NEGATIVE	REGULAR	HYPO	NO	YES	0.85	YES
ANITHA	26	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.27	NO
JAYALAKSHMI	61	F	SNT	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.11	NO
BHAIRAVI	36	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	0.5	NO
MUTHULAKSHMI	62	F	SNT	MOBILE	NEGATIVE	IRREGULAR	HYPER	YES	NO	2.9	YES
FATHIMA	27	F	DIFFUSE	MOBILE	NEGATIVE	REGULAR	HYPER	YES	NO	1.56	NO
BHANU	34	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPO	NO	NO	2.2	NO
VIGNESH	26	M	SNT	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	0.9	NO
RAJESHWARI	63	F	MNG	MOBILE	NEGATIVE	IRREGULAR	HYPER	NO	NO	1.64	NO
SHANTHI	33	F	SNT	FIXED	NEGATIVE	REGULAR	HYPER	YES	NO	3.1	YES
VIJAYA	38	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.32	NO
JANAKI	41	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.27	NO
SANTHOSH	21	M	SNT	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	0.64	NO
ARASI	62	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.48	NO
VENDA	65	F	MNG	MOBILE	NEGATIVE	IRREGULAR	HYPO	NO	NO	2.1	NO
RAJALAKSHMI	49	F	SNT	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.57	NO
MUNIYANDI	70	M	MNG	MOBILE	POSITIVE	IRREGULAR	HYPO	NO	YES	1.4	YES
LAKSHMIPRIYA	66	F	SNT	FIXED	NEGATIVE	IRREGULAR	HYPO	NO	NO	3.8	YES
NOOR JAHAN	54	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	0.82	NO
ARJUN	19	M	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.65	NO
GOPIKA	29	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPO	NO	NO	2.8	YES
JAYA	61	F	SNT	FIXED	POSITIVE	IRREGULAR	HYPO	YES	NO	1.5	YES
VARALAKSHMI	24	F	SNT	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.31	NO
MIRUNALINI	28	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	YES	NO	0.74	NO
MANGAYARKARASI	62	F	SNT	MOBILE	NEGATIVE	IRREGULAR	HYPER	NO	NO	4.1	YES
KANCHANA	64	F	DIFFUSE	MOBILE	NEGATIVE	IRREGULAR	HYPO	NO	NO	2.2	NO
MALA	27	F	SNT	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	0.69	NO
NAGESH	65	M	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.27	NO

AMIRTHA	34	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.19	NO
FARIDA	44	F	SNT	FIXED	NEGATIVE	REGULAR	HYPER	NO	NO	0.76	YES
KHURSHID	67	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.65	NO
VIMALA	38	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.39	NO
LAKSHMI	68	F	SNT	MOBILE	NEGATIVE	IRREGULAR	HYPER	NO	NO	0.75	NO
NARAYANAN	41	M	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.52	NO
VENKATESAN	55	M	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	3.1	NO
GEETHA	29	F	DIFFUSE	MOBILE	NEGATIVE	REGULAR	HYPO	YES	NO	0.71	NO
JANANI	30	F	SNT	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.49	NO
GAYATHRI	27	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.47	NO
ANBARASI	50	F	MNG	MOBILE	POSITIVE	IRREGULAR	HYPO	YES	YES	2.2	YES
GOMATHI	41	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	3.4	NO
RAZIYA BHANU	49	F	SNT	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.11	NO
JANNATH	51	F	MNG	FIXED	NEGATIVE	IRREGULAR	HYPER	NO	NO	1.29	NO
VIJAYAKUMAR	64	M	SNT	MOBILE	POSITIVE	IRREGULAR	HYPO	NO	NO	1.2	YES
MEENA	47	F	MNG	FIXED	NEGATIVE	REGULAR	HYPO	YES	NO	0.81	YES
KALPANA	35	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPO	NO	NO	0.88	NO
KUMARI	62	F	SNT	MOBILE	NEGATIVE	REGULAR	HYPO	YES	NO	1.37	NO
LATHA	65	F	SNT	MOBILE	NEGATIVE	IRREGULAR	HYPER	NO	NO	2.4	YES
JEEVITHA	39	F	DIFFUSE	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	0.54	NO
MURUGAN	40	M	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.49	NO
SUBBALAKSHMI	61	F	SNT	FIXED	NEGATIVE	IRREGULAR	HYPER	NO	NO	2.3	YES
VANITHA	61	F	SNT	FIXED	NEGATIVE	IRREGULAR	HYPO	NO	NO	3.8	YES
VIJAYAPRIYA	62	F	MNG	MOBILE	POSITIVE	IRREGULAR	HYPO	YES	YES	1.35	YES
MALAR	27	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.38	NO
PREM	31	M	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	0.61	NO
VASANTH	37	M	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	3.4	NO
RENUKA	44	F	SNT	MOBILE	NEGATIVE	REGULAR	HYPO	NO	NO	2.8	NO
SUBHASHINI	63	F	SNT	MOBILE	NEGATIVE	IRREGULAR	HYPER	NO	NO	1.44	NO
ANJALI	21	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	YES	NO	0.85	NO
AROKIAMARY	52	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.47	NO
ESWARI	56	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.67	NO
YOGAMAL	54	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.71	NO
SULOCHANA	62	F	SNT	MOBILE	NEGATIVE	IRREGULAR	HYPER	NO	NO	2.6	NO
RAJARAJAN	47	M	MNG	FIXED	NEGATIVE	REGULAR	HYPER	NO	NO	1.59	NO
VANI	61	F	MNG	MOBILE	POSITIVE	IRREGULAR	HYPER	YES	NO	3.2	YES
MALATHI	31	F	DIFFUSE	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	0.77	NO
YASODHA	39	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPO	NO	NO	3.1	NO
SUBHA	40	F	SNT	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	0.64	NO
SENTHIL	40	M	SNT	FIXED	NEGATIVE	REGULAR	HYPO	NO	NO	1.6	YES

TAMIL SELVI	66	F	SNT	FIXED	NEGATIVE	IRREGULAR	HYPO	NO	NO	3.7	YES
SULTHANA	38	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.33	NO
NITHYA	24	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.44	NO
LATHA	41	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	4.4	NO
RAJAMANIKAM	69	M	SNT	MOBILE	NEGATIVE	IRREGULAR	HYPO	NO	NO	0.58	NO
RAMYA	34	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	3.3	YES
SARADHA	50	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.32	NO
NASREEN	60	F	MNG	FIXED	POSITIVE	IRREGULAR	HYPER	YES	NO	1.8	YES
RAMESH BABU	35	M	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.37	NO
ANUSYA	26	F	DIFFUSE	MOBILE	NEGATIVE	REGULAR	HYPO	NO	NO	0.59	NO
LOGAPRIYA	31	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.55	NO
GAYATHRI	21	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.61	NO
SURESH	32	M	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.29	NO
SUNDAR	49	M	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.31	NO
KALAIVANI	33	F	SNT	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	0.78	NO
PADMA	60	F	SNT	FIXED	POSITIVE	IRREGULAR	HYPO	NO	NO	2.1	YES
MONISHA	21	F	DIFFUSE	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.42	NO
KANNAGI	71	F	MNG	FIXED	NEGATIVE	REGULAR	HYPER	NO	NO	2.7	NO
DIVYAMBIGAI	28	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	0.85	NO
CHITRA	60	F	MNG	FIXED	NEGATIVE	IRREGULAR	HYPO	NO	NO	2.7	YES
ILAKIYA	34	F	MNG	MOBILE	NEGATIVE	REGULAR	HYPER	NO	NO	1.37	NO

PATIENT CONSENT FORM

STUDY TITLE:

" PREDICTION OF THYROID MALIGNANCY BASED ON CLINICAL,RADIOLOGICAL AND BIOCHEMICAL FACTORS WITH EMPHASIS ON SERUM TSH"

STUDY CENTRE:
Rajiv Gandhi Government General hospital and Madras Medical College.

PARTICIPANT NAME: **AGE:** **SEX:** **I.P. NO :**

I confirm that I have understood the purpose of interventional procedure for the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I have been explained about the possible complications that may occur during the interventional and interventional procedure. I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason.

I understand that the investigator, regulatory authorities and the ethical committee will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from the study.

I hereby consent to participate in this study of the " PREDICTION OF THYROID MALIGNANCY BASED ON CLINICAL,RADIOLOGICAL AND BIOCHEMICAL FACTORS WITH EMPHASIS ON SERUM TSH"

Date: signature / thumb impression of patient

Place:

Patient's name:

Signature of the Investigator: _____

Name of the investigator:

INFORMATION SHEET

We are conducting a study on " PREDICTION OF THYROID MALIGNANCY BASED ON CLINICAL,RADIOLOGICAL AND BIOCHEMICAL FACTORS WITH EMPHASIS ON SERUM TSH" among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your information is valuable to us.

The purpose of this study is to assess clinical,radiological,and biochemical parameters can predict the likelihood of thyroid malignancy in RGGGH , Chennai.

We are selecting certain cases and if you are found eligible, we may be using your information which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of the Participant

Signature of the Investigator

Date

Place

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு
மருத்துவ, கதிரியக்க மற்றும் உயிர்வேதியியல் காரணிகளின் அடிப்படையில் தைராய்டு புற்றுநோயை கண்டறிதல்

பெயர்	:	தேதி	:
வயது	:	உள் நோயாளி எண்	:
பால்	:	ஆராய்ச்சி சேர்க்கை எண்	:

இந்த ஆராய்ச்சின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன்.

மேற்கண்ட பரிசோதனையின் போது ஏற்படக்கூடிய பின்விளைவுகளையும் முழுவதும் உணர்ந்து இந்த பரிசோதனைக்கு மனமார சம்மதிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின்பேரில் பங்கு பெறுகின்றேன். இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.

நான் என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக்கொள்ள சம்மதம்.

ஆராய்ச்சியாளர் கையொப்பம்
தேதி

பங்கேற்பாளர் கையொப்பம்
தேதி

ஆய்வு தகவல் தாள்

ஆய்வின் தலைப்பு
முன்கழுத்து கழலை வீக்கம் கொண்ட நோயாளிகளின் இரத்த TSH அளவிற்கும் அதில் ஏற்படும் புற்றுநோய்க்கும் உள்ள தொடர்பை கண்டறிதல்

சென்னை ராஜீவ் காந்தி அரசு பொது மருத்துவமனைக்கு வரும் முன்கழுத்து கழலை வீக்கம் கொண்ட நோயாளிகளில் ஏற்படும் புற்றுநோய்க்கும் இரத்த TSH அளவிற்கும் உள்ள தொடர்பை கண்டறிதல் பற்றிய பரிசோதனை நடைபெறுகிறது.

நீங்களும் இந்த ஆய்வில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆய்வில் உங்களுடைய இரத்தத்தை எடுத்து சில சிறப்பு பரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆய்வின்போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதை தெரிவித்துக்கொள்கிறோம்.

இந்த ஆய்வில் பங்கேற்பது தங்களுடைய விருப்பத்தின்பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆய்விலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆய்வின்போது அல்லது ஆய்வு முடிவின்போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

ஆய்வாளர் கையொப்பம்
தேதி

பங்கேற்பாளர் கையொப்பம்
தேதி

INTRODUCTION

Thyroid diseases have always been an enigma. The management of thyroid diseases has undergone a tremendous change over the ages, from the crude surgeries of the ancient times to the multidisciplinary approach of the modern era. However in the present scenario surgery still plays an important role especially in the management of thyroid malignancies.

Thyroid malignancies account for 90% of endocrinal malignancies. The

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.G.Sabarish Kumar
Post Graduate M.S.(General Surgery)
Madras Medical College
Chennai 600 003

Dear Dr.G.Sabarish Kumar,

The Institutional Ethics Committee has considered your request and approved your study titled **"Prediction of thyroid malignancy based on clinical, radiological and biochemical factors with special emphasis on serum TSH levels" No.16062015.**

The following members of Ethics Committee were present in the meeting held on 09.06.2015 conducted at Madras Medical College, Chennai-3.

1.	Prof.C.Rajendran, M.D.,	: Chairperson
2.	Prof.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3.	Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4.	Prof.B.Vasanthi, M.D., Prof. of Pharmacology, MMC	: Member
5.	Prof.P.Raghumani, M.S., Professor of Surgery, MMC	: Member
6.	Prof.Md.Ali, M.D., DM., Prof. & HOD of MGE, MMC	: Member
7.	Prof.Baby Vasumathi, Director, Inst.of O&G, Ch-8	: Member
8.	Prof.Ramadevi, Director, Inst.of Bio-chemistry, MMC	: Member
9.	Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
10.	Prof.K.Srinivasagalu, M.D.,Director, I.I.M. MMC, Ch-3	: Member
11.	Thiru S.Rameshkumar, B.Com., MBA	: Lay Person
12.	Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
13.	Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

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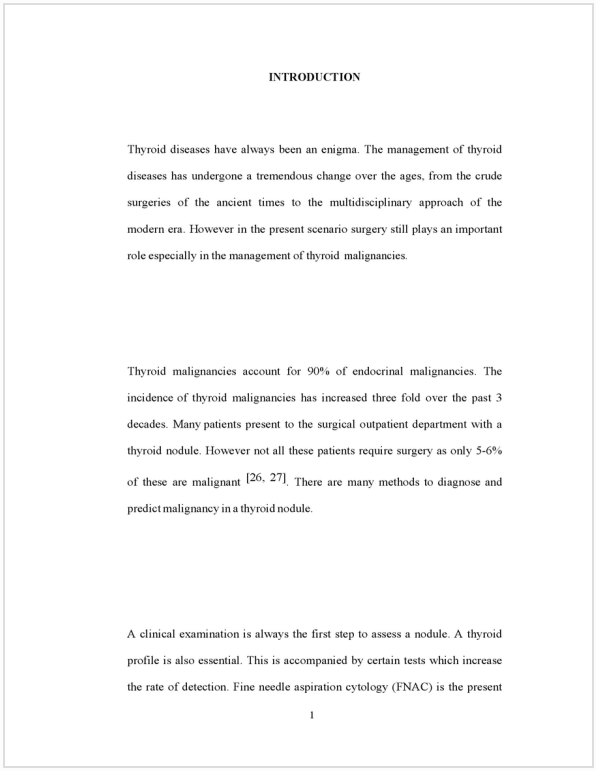

INTRODUCTION

Thyroid diseases have always been an enigma. The management of thyroid diseases has undergone a tremendous change over the ages, from the crude surgeries of the ancient times to the multidisciplinary approach of the modern era. However in the present scenario surgery still plays an important role especially in the management of thyroid malignancies.

Thyroid malignancies account for 90% of endocrinal malignancies. The incidence of thyroid malignancies has increased three fold over the past 3 decades. Many patients present to the surgical outpatient department with a thyroid nodule. However not all these patients require surgery as only 5-6% of these are malignant [26, 27]. There are many methods to diagnose and predict malignancy in a thyroid nodule.

A clinical examination is always the first step to assess a nodule. A thyroid profile is also essential. This is accompanied by certain tests which increase the rate of detection. Fine needle aspiration cytology (FNAC) is the present

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