A CROSS SECTIONAL STUDY ON PREDICTORS OF MALIGNANCY IN SOLITARY THYROID NODULE

A Dissertation Submitted to

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For the Award of the Degree of

M.S. (GENERAL SURGERY) - BRANCH – I

GOVERNMENT KILPAUK MEDICAL COLLEGE

CHENNAI

MAY 2020

BONAFIDE CERTIFICATE

This is to certify that **"A CROSS SECTIONAL STUDY ON PREDICTORS OF MALIGNANCY IN SOLITARY THYROID NODULE".**is a bonafide work done by **Dr.SUJITHA.S.** Post graduate student, Department of General surgery, Kilpauk Medical College, Chennai-10, under my guidance and supervision in partial fulfillment of rules and regulations of the TamilNadu Dr. M.G.R Medical University, for the award of M.S. DegreeBranch I (General surgery) during the academic period from MAY 2017 To MAY 2020.

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DECLARATION

I solemnly declare that this dissertation **"A CROSS SECTIONAL STUDY ON PREDICTORS OF MALIGNANCY IN SOLITARY THYROID NODULE".** was prepared by me at Government Kilpauk Medical College and Hospital, Chennai, under the guidance and supervision of **Prof. Dr.V.VIJAYALAKSHMI M.S,DGO.,** Professor, Department of General surgery, Government Kilpauk Medical College and Hospital, Chennai. This dissertation is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai** in partial fulfillment of the University regulations for the award of the degree of **M.S. Branch I (General Surgery)**.

Place: Chennai-10 **Dr. SUJITHA.S**

Date:

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation titled **"A CROSS SECTIONAL STUDY ON PREDICTORS OF MALIGNANCY IN SOLITARY THYROID NODULE".** in the Department of General Surgery at Govt Kilpauk Medical College is a bonafide work done by **Dr.SUJITHA.S.** Post graduate student, Department of General surgery, Kilpauk Medical College, Chennai-10, under my guidance and supervision in my satisfaction and in partial fulfilment of requirements for the degree of **M.S General Surgery**

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Protocol ID. No.184/2019 Meeting held on 09/04/2019

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A CROSS SECTIONAL STUDY ON PREDICTORS OF MALIGNACY IN SOLITARY THYROID NODULE- AT A TERTIARY CARE HOSPITAL IN CHENNAI" submitted by Dr.S.Sujitha, 2nd Year Post Graduate Student, Department of General Surgery, Government Kilpauk Medical College, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

DEAN
Govt. Kilpauk Medical College,
Chennai-10.

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TABLE OF CONTENTS

INTRODUCTION

Thyroid nodule is a common presentation and requires a structured diagnostic approach to ascertain the risk of malignancy and determine appropriate management.[54]Thyroid nodules can be detected by palpation in 10% of women and 2% of men.[54] The prevalence of thyroid nodules can be 50% or more if ultrasonography (US) is used.1 Although thyroid nodule is a common presentation, thyroid cancer is rare representing 1% of all cancers.

Thyroid cancer has a favorable prognosis and accounts for less than 0.5% of cancer deaths.[55] The well differentiated thyroid cancer (WDTC), which includes papillary and follicular cancer, comprises the vast majority (90%) of all thyroid cancers.[56] A thyroid nodule is defined as a discrete lesion within the thyroid gland that is clinically and radiologically distinct from the surrounding thyroid parenchyma.

A thyroid nodule can be either a solitary nodule or a dominant nodule in a multinodular gland and can be clinically non-palpable. The non-palpable nodules are usually detected by incidental USG or other imaging studies and are termed incidentalomas and these non-palpable nodules have the same risk of malignancy as palpable nodules.[56] The risk of malignancy in generalized thyroid swelling is about 3% and in solitary thyroid nodule it is about 15%.[57]

The multinodular goiters (MNG), defined as an enlarged thyroid gland with multiple nodules, have historically been thought of as a benign condition with a low

risk of associated malignancy, and may be present in up to 4% of the population in iodine sufficient countries.[58]The patients with multiple thyroid nodules have the same risk of malignancy as those with solitary nodules.[59]

However, one large study found that a solitary nodule had a higher likelihood of malignancy than did a non-solitary nodule ($p<0.01$), although the risk of malignancy per patient was the same and independent of the number of nodules.[60]

Traditional risk factors for thyroid cancer in a thyroid nodule have been largely clinical and include age, gender, history of radiation exposure, family history of thyroid cancer, and cancer syndromes.

While the data refining the significance of these risks continue to evolve, recent area of research has been on several biochemical factors which are associated with the risk of malignancy in thyroid nodules.[61] Some of these biochemical factors include levels of serum thyroid stimulating hormone (TSH), thyroglobulin (Tg)

Hence, the present study is designed to evaluate the potential role of biochemical factors especially levels of serum TSH, TG as preoperative indicators of thyroid malignancy.

AIM OF THE STUDY:

To evaluate potential role of Thyroglobulin (Tg), thyroid stimulating hormone (TSH) as preoperative indicators of malignancy in thyroid nodule.

OBJECTIVE OF THE STUDY:

To measure Thyroid stimulating hormone (TSH) levels in patients presenting with Thyroid nodule

To measure Thyroglobulin (Tg) levels in patients presenting with Thyroid nodule

To classify thyroid nodular lesion into benign and malignant by HPE

Serum thyroglobulin (Tg), thyroid stimulating hormone (TSH) levels in patients with thyroid nodule are statistically analysed to establish correlation with benign and malignant lesions of thyroid nodule .

REVIEW OF LITERATURE

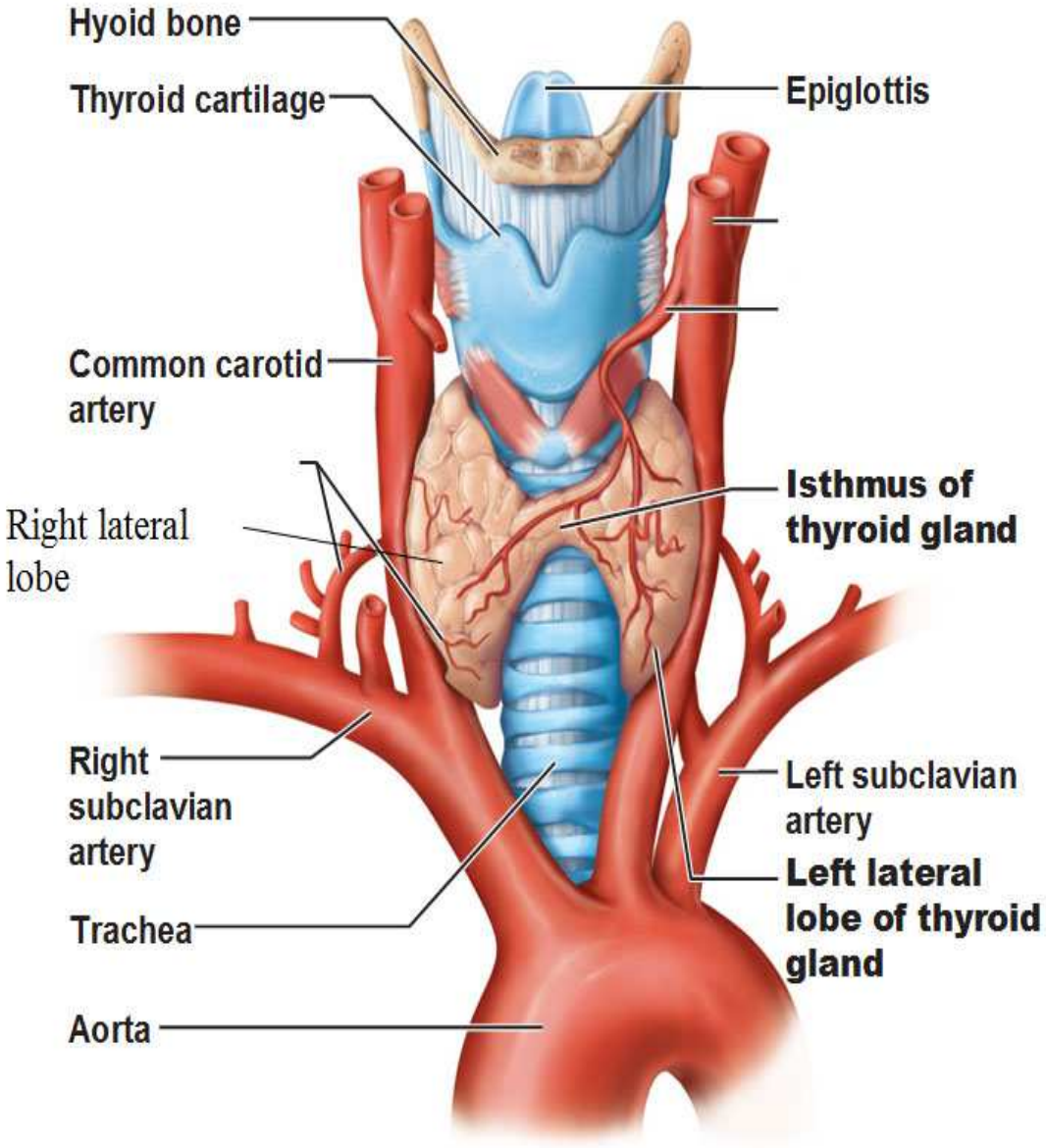
THYROID ANATOMY

The thyroid is a butterfly-shaped gland that sits low on the front of the neck. Your thyroid lies below your Adam's apple, along the front of the windpipe. The thyroid has two side lobes, connected by a bridge (isthmus) in the middle. When the thyroid is its normal size, you can't feel it.

Brownish-red in color, the thyroid is rich with blood vessels. Nerves important for voice quality also pass through the thyroid.

The thyroid secretes several hormones, collectively called thyroid hormones. The main hormone is thyroxine, also called T4. Thyroid hormones act throughout the body, influencing metabolism, growth and development, and body temperature. During infancy and childhood, adequate thyroid hormone is crucial for brain development

The Thyroid Gland



Gross anatomy of the thyroid gland, anterior view

BLOOD SUPPLY OF THYROID

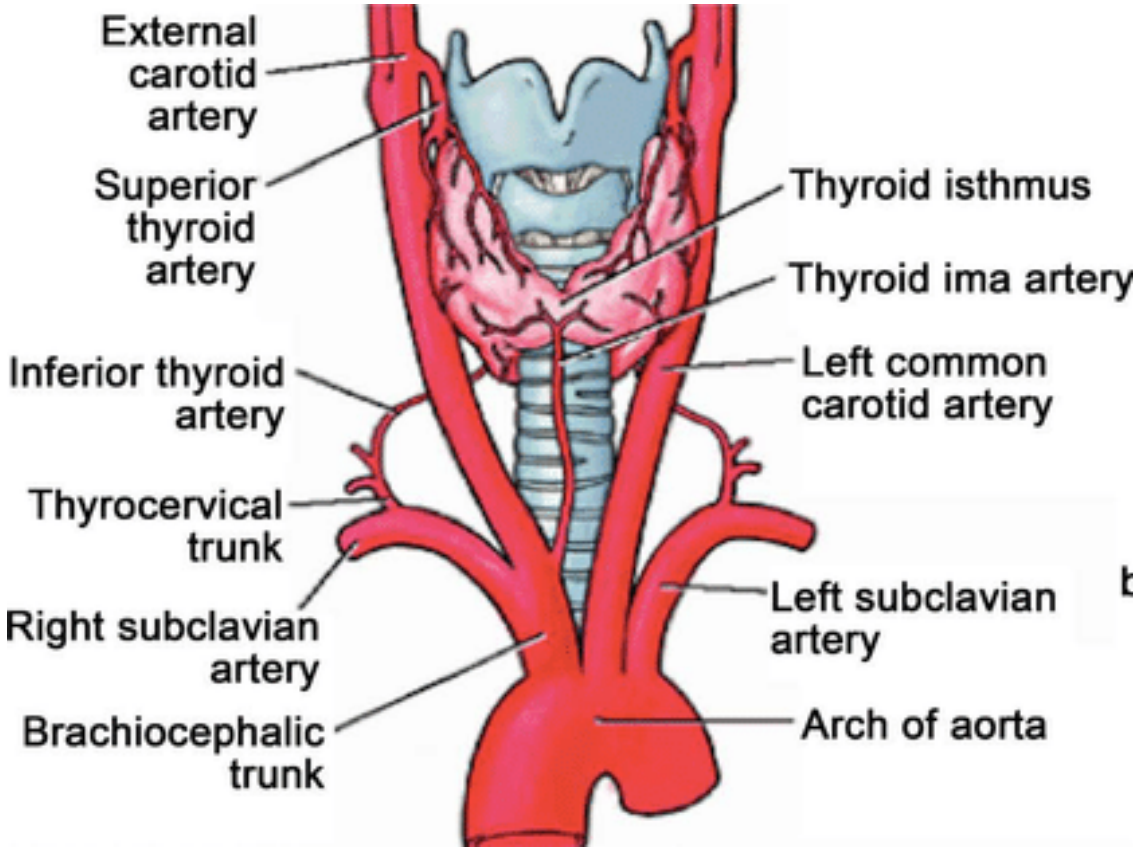
ARTERIAL SUPPLY

The thyroid has an abundant blood supply. The arterial supply comes from the inferior and superior thyroid arteries. The right and left superior and inferior thyroid arteries anastomose extensively within the gland.

The superior thyroid artery arises from the external carotid artery on each side and descends several centimetres in the neck to reach the upper pole of each thyroid lobe. It is related to the external laryngeal nerve, pierces the thyroid fascia and then divides into anterior and posterior branches. The anterior branch supplies the anterior surface of the gland, and the posterior branch supplies the lateral and medial surfaces.

The inferior thyroid artery arises from the thyrocervical trunk of the subclavian artery, crosses beneath the carotid sheath and enters the lower or middle part of each thyroid lobe and divides into superior (ascending) and inferior thyroid branches to supply the inferior and posterior surfaces of the gland. The relationship between the inferior thyroid artery and the recurrent laryngeal nerve is very important clinically because it is highly variable. Injury to the nerves supplying the larynx represents a major complication.

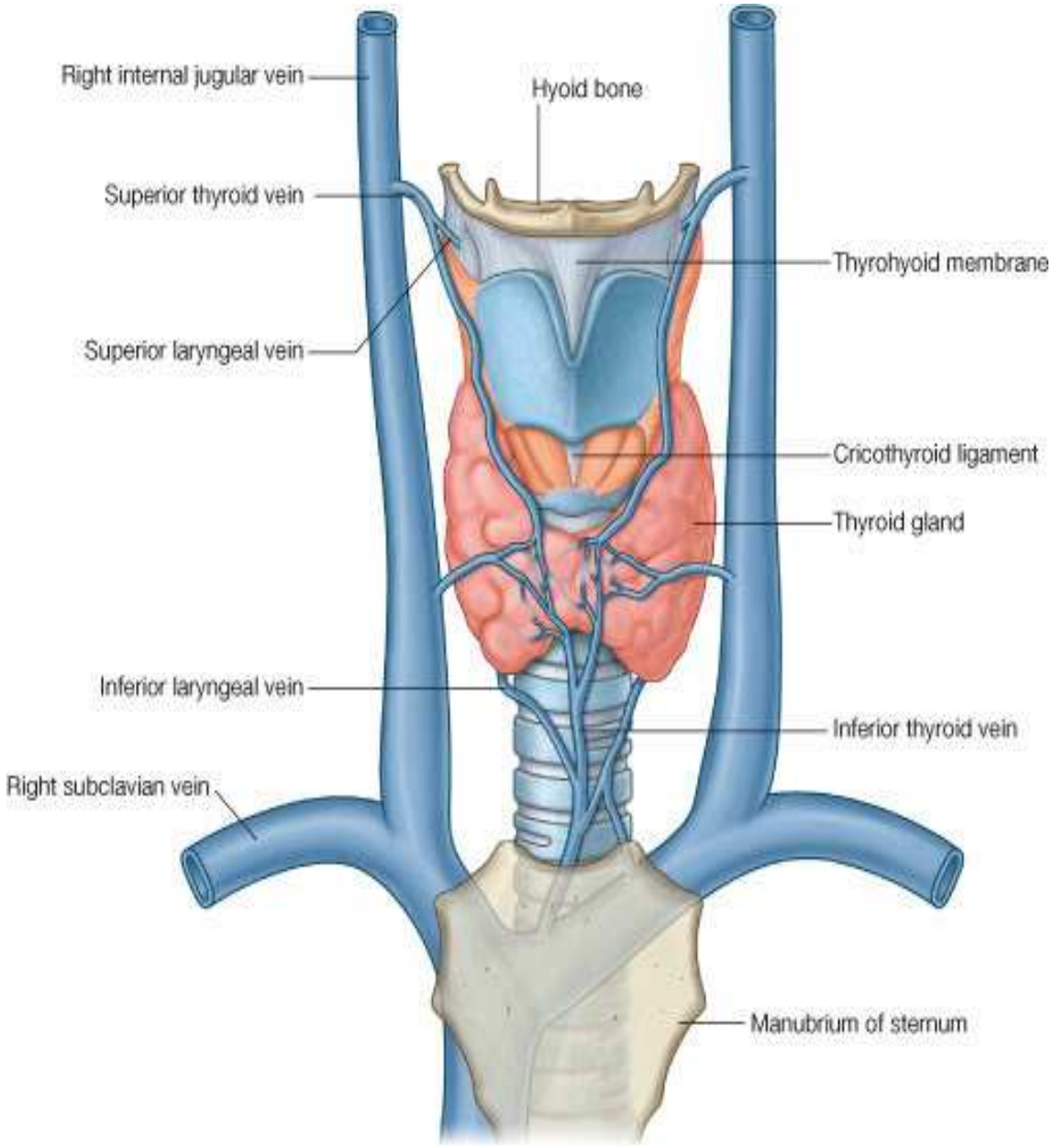
The thyroid ima artery (Latin. The arteria thyroidea ima) presents approximately in 10% of people, and may arise from the arch of the aorta, brachiocephalic trunk, or from the right common carotid, subclavian, or internal thoracic arteries. It ascends to the anterior surface of the trachea, which it supplies, and continues to the isthmus of the thyroid gland. The presence of the artery should be considered when performing procedures in the midline of the neck inferior to the isthmus, because it is a potential site of bleeding.



VENOUS SUPPLY

Three pairs of veins usually form a thyroid venous plexus on the anterior surface of the thyroid gland: the superior, middle and inferior thyroid veins.

- The superior thyroid vein emerges from the upper part of the gland, and runs with the superior thyroid artery, draining into the internal jugular vein.
- The middle thyroid vein collects blood from the lower part of the gland. It emerges from the lateral surface of the gland and drains into the internal jugular vein.
- The inferior thyroid veins arise in a glandular venous plexus which connects with the superior and middle thyroid vein.
- These veins form the paratracheal plexus from which the inferior vein descends to drain into the left brachiocephalic vein, and the right descends across the brachiocephalic artery to join the right brachiocephalic vein.
- The inferior thyroid veins often drain via a common trunk into the superior vena cava or left brachiocephalic vein. They drain the tracheal, inferior pharyngeal and oesophagus veins.


Right internal jugular vein
Hyoid bone
Superior thyroid vein
Thyrohyoid membrane
Superior laryngeal vein
Cricothyroid ligament
Thyroid gland
Inferior laryngeal vein
Inferior thyroid vein
Right subclavian vein
Manubrium of sternum

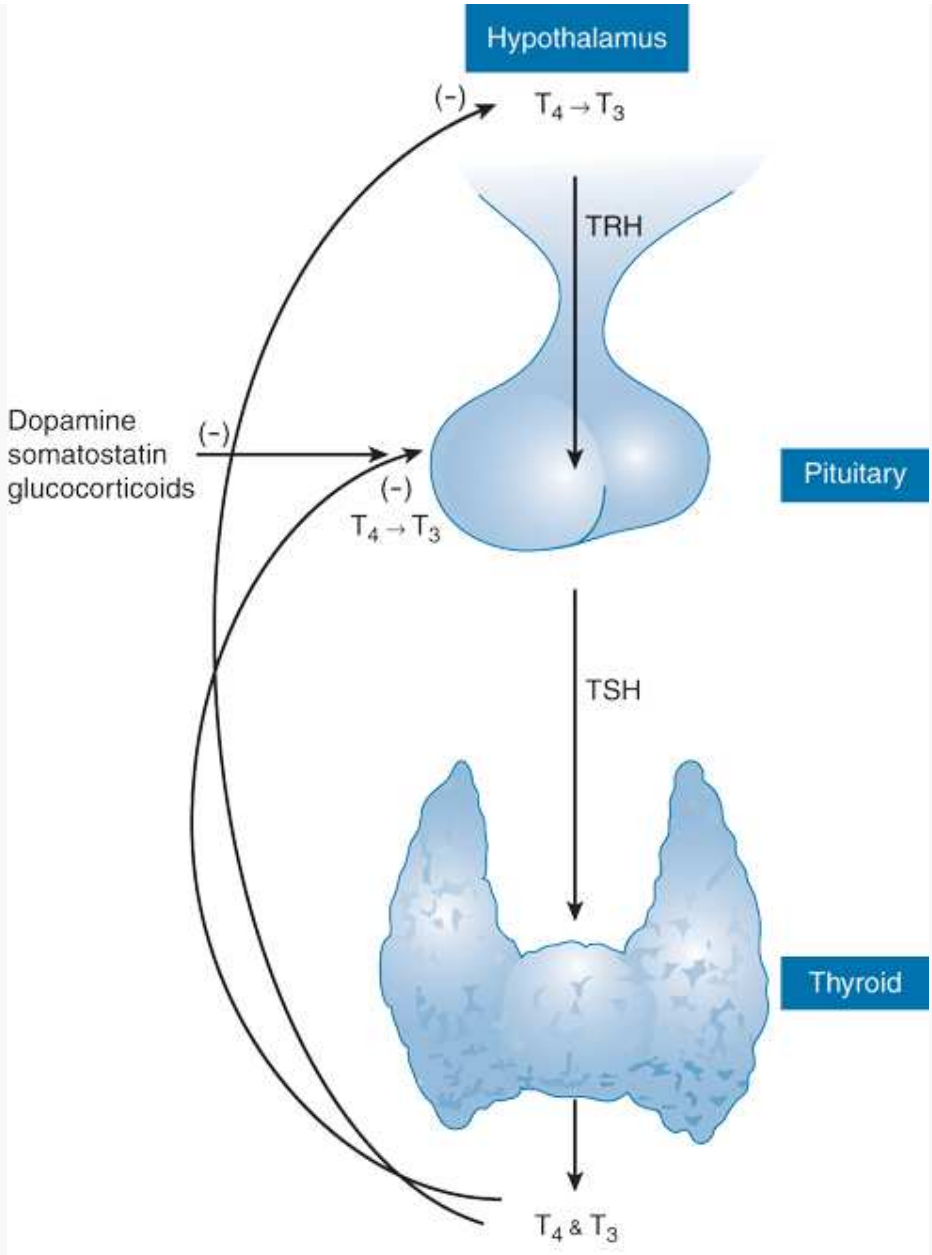
THYROID PHYSIOLOGY

Thyroid hormones play important roles in maintaining energy homeostasis and regulating energy expenditure. Their physiologic effects, mediated at multiple target organs, are primarily to stimulate cell metabolism and activity.

The vital roles of these hormones, particularly in development, differentiation, and maturation, are underscored by the severe mental retardation observed in infants with deficient thyroid hormone function during gestation.

Thyroid hormones are derived from the amino acid tyrosine and are produced by the thyroid gland in response to stimulation by thyroid-stimulating hormone (TSH) produced by the anterior pituitary.

TSH, in turn, is regulated by the hypophysiotropic peptide thyrotropin-releasing hormone (TRH). Thyroid hormone production is also under regulation by dietary iodine.



The hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) is synthesized in parvicellular neurons of the paraventricular nucleus of the hypothalamus and released from nerve terminals in the median eminence, from where it is transported via the portal capillary plexus to the anterior pituitary. TRH binds to a G protein–coupled receptor in the anterior pituitary, leading to an increase in intracellular Ca^{2+} concentration, which in turn results in stimulation of exocytosis and release of thyroid-stimulating hormone (TSH) into the systemic circulation.

TSH stimulates the thyroid gland to increase the synthesis and secretion of tetraiodothyronine (T_4) and triiodothyronine (T_3) into the circulation. T_4 and T_3 inhibit the secretion of thyrotropin both directly and indirectly by inhibiting the secretion of TRH. Additional factors that inhibit TSH release are glucocorticoids, somatostatin, and dopamine.

The thyroid gland is a highly vascular, ductless alveolar (acinar) gland located in the anterior neck in front of the trachea. The gland weighs 10–25 g and consists of a right and left lobe connected by the isthmus. The cellular composition of the thyroid gland is diverse, including the following:

- Follicular (epithelial) cells, involved in thyroid hormone synthesis
- Endothelial cells lining the capillaries that provide the blood supply to the follicles
- Parafollicular or C cells, involved in the production of calcitonin, a hormone involved in calcium metabolism
- Fibroblasts, lymphocytes, and adipocytes

THYROID NODULES

Thyroid nodules have been defined by the American Thyroid Association (ATA) as "discrete lesions within the thyroid gland, radiologically distinct from surrounding thyroid parenchyma."[1] They may be discovered by palpation during a general physical examination or with radiographic studies performed for medical evaluations, such as carotid duplex ultrasound (US), computed tomography (CT) scans, magnetic resonance imaging (MRI) studies, or 18FDG-PET scanning.

The latter entities are called "thyroid incidentalomas" and they generally do not correspond to palpable thyroid lesions. Conversely, clinicians may identify palpable thyroid lesions that do not correspond to distinct radiological entities, and therefore would not be defined as thyroid nodules.[2]

The natural history of benign nodules is unclear, but most palpable nodules probably reduce in size, with up to 38% disappearing altogether [3, 4]. The concern with thyroid nodules is the possibility of malignancy. Thyroid cancers are rare, accounting for only 1.0% of all cancers in most populations and 0.5% of all cancer deaths [5].

Nonetheless, thyroid cancers occur in approximately 5% of all thyroid nodules independent of their size. With thyroid nodules being so prevalent in the general population, it is important to have a clear strategy of assessing nodules and determining which of these will require surgery or can be managed conservatively.

BENIGN & MALIGNANT LESIONS OF SOLITARY NODULE

BENIGN LESIONS:

Common types are,

1)Adenomas

2)Thyroid cyst

3)Hashimotos thyroiditis

Uncommon types of benign thyroid nodules,

1)subacute thyroiditis

2)painless thyroiditis

3)unilateral lobe agenesis

4)riedel's struma

MALIGNANT LESIONS:

1) papillary (85%).
2) follicular (11%).
3) Hürthle cell (3%). and
4) anaplastic (1%).
5) Medullary carcinoma of thyroid

THYROID ADENOMA

Thyroid adenoma is usually slow-growing and is very benign; it does not metastasize. Progression from hyperplasia to adenoma and then to adenocarcinoma has been reported in rodents, but this progression is not reported in the horse.[2]

[6] However, rapid expansion of the thyroid mass can occur, suggesting that these tumours may remain dormant or quiescent, but can suddenly enlarge. Prognosis is good.[2]

THYROID CYSTS

Thyroid cysts represent enlarged fluid-filled regions of the thyroid that may be small (less than 1 cm) or quite large and sometimes arise very suddenly.

A cyst, by definition, contains fluid. Thyroid nodules may be entirely cystic, in which case there are no solid components detectable within the fluid

.

Alternatively, the nodule may be **complex**, and contain both fluid and solid components. Cystic nodules may expand and enlarge suddenly sometimes due to hemorrhage or bleeding within a smaller pre-existing nodule. In some cases, rapidly enlarging cysts may produce symptoms in the neck, including pain, trouble swallowing, and rarely, compression of vocal cords leading to a change in voice quality.

Cysts that are entirely fluid filled have a much lower risk of harboring a small thyroid cancer compared to cysts that have solid components. Diagnosis of a cystic thyroid lesion may be made at the time of ultrasound, or following a thyroid aspiration biopsy, when fluid is obtained from the thyroid lesion.

Complete spontaneous resolution of a thyroid cyst may occur, but is uncommon (~ 15 % of cases). Most large cysts or complex cysts should be aspirated with a fine needle to rule out the possibility of malignancy.

Ultrasound-guided biopsies of complex cystic nodules may be particularly useful for ensuring that the biopsy material contains thyroid cells, and not just cystic fluid

HASHIMOTO'S THYROIDITIS

Hashimoto's thyroiditis (chronic lymphocytic thyroiditis) is an autoimmune disorder that causes inflammation of the thyroid gland. Hashimoto's thyroiditis is the most common cause of hypothyroidism (low thyroid hormone levels in the blood) in the United States.

- Symptoms of Hashimoto's thyroiditis are the same as hypothyroidism, and include
    - feeling cold,
    - depression,
    - dry skin,
    - constipation,

- fatigue,
- sleepiness, and
- weight gain.

- Hashimoto's thyroiditis is diagnosed by blood tests that measure thyroid gland function and blood tests that look for antibodies against proteins found in the thyroid gland.
- Treatment options for Hashimoto's thyroiditis are oral thyroid hormones to maintain normal thyroid hormone levels.
- Since Hashimoto's thyroiditis is an autoimmune disorder it cannot be prevented.
- The prognosis for someone with Hashimoto's thyroiditis is excellent with proper treatment.
- The condition was named after Dr. Hakaru Hashimoto, the doctor who described it in 1912.

RIEDEL'S THYROIDITIS

INVASIVE fibrous thyroiditis, first described by Riedel[1] in 1896, is also known as Riedel's struma, woody or ligneous thyroiditis, and "eisenhart" goiter.

It is characterized by the slowly progressive invasion of part of or all the thyroid and adjacent cervical tissues by dense fibrous or collagenous connective tissue. It is an uncommon disease, and its etiology remains unknown.

THYROID HEMIAGENESIS

Thyroid hemiagenesis (THG) is a rare congenital anomaly in which one lobe of thyroid gland fails to develop. Agenesis may be unilateral, total or isthmic. Left thyroid lobe is commonly involved than right lobe in hemiagenesis.

Clinically patients can be euthyroid, hypothyroid or hyperthyroid. Often it is diagnosed as an incidental finding during ultrasonography (USG) study of neck, which easily diagnose this condition.

Actual incidence of THG is unknown, most cases are diagnosed in patients admitted for thyroid scan or thyroid surgery because of suspicion of other thyroid abnormalities.

This explains high frequency of association of hemiagenesis with other thyroid abnormalities such as multinodular goiter, adenoma, hyperthyroidism, hypothyroidism, chronic thyroiditis, and carcinoma.

PAPILLARY CARCINOMA OF THYROID

Papillary thyroid cancer (carcinoma) can occur in people of all ages from early childhood to advanced ages although it is most common in people between age 30 and 50. Papillary thyroid cancer affects women more commonly than men, and

it is most common in young women. the most common way papillary thyroid cancer is found is by a patient noticing a lump in their throat, or a doctor feeling a lump or nodule when examining a patient's thyroid gland.

Surgery for papillary thyroid cancer is filled with a number of choices. If the cancer is big (over 1.5 cm or 3/4 inch) then the entire thyroid needs to be removed. However, there is controversy over how much thyroid should be removed if the cancer is small.

Some expert thyroid surgeons contend that if the cancer is small and not invading other tissues (the usual case) then simply removing the half of the thyroid (called the thyroid lobe) which contains the cancer will provide as good a chance of cure as removing the entire thyroid. Other surgeons prefer the older method of removing the entire thyroid for all papillary thyroid cancers.

Almost all people who had surgery for papillary thyroid cancer will need to see a doctor for many years to have exams and certain blood tests to make sure the cancer has been cured, and to detect any return of the cancer as soon as possible should it return. Many people with papillary thyroid cancer will need to take radioactive iodine to help cure the cancer.

FOLLICULAR CARCINOMA OF THYROID

- Females more common than males by 3 to 1 ratio
- Peak onset ages 40 through 60
- Prognosis directly related to tumor size [less than 1.0 cm (3/8 inch) good prognosis]

- Rarely associated with radiation exposure
- Spread to lymph nodes is uncommon (~12%)
- Invasion into vascular structures (veins and arteries) within the thyroid gland is common
- Distant spread (to lungs or bones) is uncommon, but more common than with papillary cancer
- Overall cure rate high (near 95% for small lesions in young patients), decreases with advanced age

HURTHLE CELL CARCINOMA

Hurthle cell cancer doesn't always cause symptoms, and it's sometimes detected during a physical examination or an imaging test done for some other reason. Signs and symptoms of Hurthle cell cancer may include:

- A lump in your neck, just below your Adam's apple
- Pain in your neck or throat
- Hoarseness or other changes in your voice
- Shortness of breath
- Swallowing difficulty

ANAPLASTIC CARCINOMA

Accounts for 1percent of all thyroid malignancies.most aggressive form.mortality rate is 100 percent.

Manifestations include: Dysphagia

Cervical tenderness

Painful rapidly enlarging neck mass.

Findings also includes superior venacava syndrome.situation deteriorates rapidly into tracheal obstruction and local invasion of surrounding structures.

Treatment of ATC is usually tempered by its rapidly progressive course.distant spread will be present in 90percent cases.mostly conservative approach like tracheostomy will be needed

MEDULLARY CARCINOMA

MTC accounts for 4percent of thyroid cancer. Originates from parafollicular cells. Occurs most commonly as sporadic form.manifests as:
1)palpable mass,
2)elevated calcitonin level

Treatment includes complete resection of primary tumour with local and regionl metastses

EVALUATION OF THYROID NODULE:

As with all assessments, a thorough history and examination is required in patients who present with a thyroid nodule. Most nodules are asymptomatic and are often discovered serendipitously by the patient or their primary medical practitioner when being examined for another problem [6]. With the increasing use of diagnostic imaging, thyroid nodules are not infrequently detected as an incidental finding on ultrasounds and computed tomography (CT) scanning.

History and Examination

Regardless of the way in which thyroid nodules are discovered, a detailed patient history is requisite. Information that needs to be ascertained includes: the presence of symptoms, a change in nodule size, previous head/neck radiation exposure, and a family history of thyroid or endocrine diseases. The patient may report a history of pain, which may follow hemorrhage into a colloid nodule, or a sudden increase in the size of a neck lump, which would raise concern of malignancy. Voice change or hoarseness may also be a progressive symptom associated with an invasive tumor. Symptoms of dysphagia, coughing, choking, and dyspnea should be asked about.

Exposure of the thyroid gland to ionizing radiation is known to contribute to a higher incidence of both benign and malignant thyroid nodules, with malignancy rates in a palpable nodule in a previously irradiated thyroid in the range of 20%–50% [7, 8].

Thyroid carcinomas are classified according to the cell type from which they develop.

A) Non medullary thyroid cancers

B) Medullary thyroid cancers

The majority are non medullary thyroid cancers (NMTCs), which arise from the thyroid epithelial cells. These account for approximately 95% of tumors and are divided into four histologic subtypes:

1)papillary (85%),

2) follicular (11%),

3)Hürthle cell (3%), and

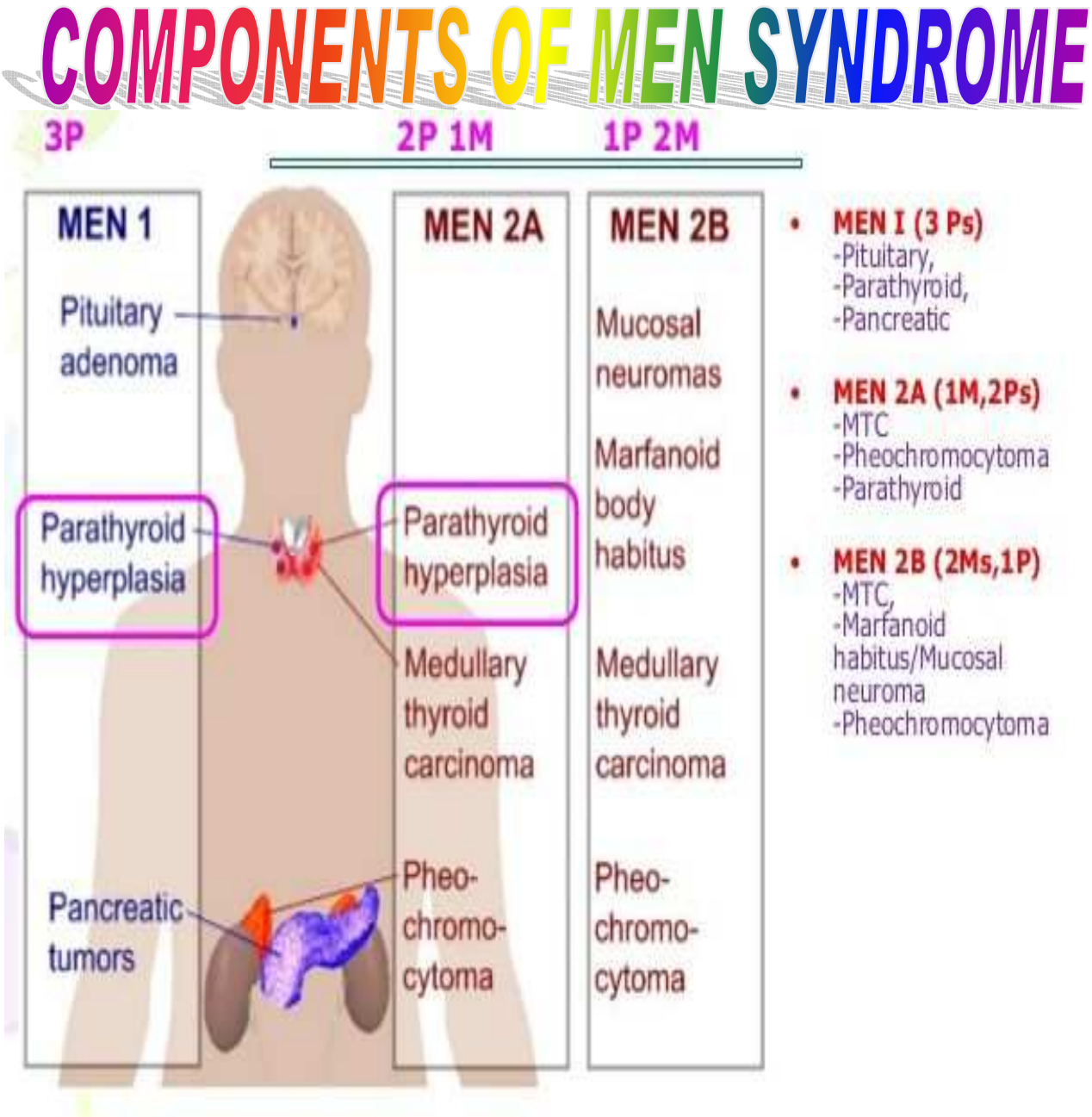
4) anaplastic (1%).

Of these, 95% are sporadic tumors ,

5% are thought to represent a familial origin, that is, familial nonmedullary thyroid cancer (FNMTC).

Medullary thyroid cancers (MTCs) arise from the calcitonin-producing parafollicular cells of the thyroid and account for about 5% of all thyroid malignancies. In 20% they are familial and occur as part of the multiple endocrine neoplasia (MEN) syndromes. It is important to identify these patients, as pheochromocytomas are associated with MEN II and need to be excluded prior to the patient receiving an anesthetic.

MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES



FNMTCs are rare. Based on epidemiologic studies and kindred analysis, this group of tumors is believed to result from a genetic inheritance, although environmental influences cannot be excluded. Inheritance is probably autosomal dominant with incomplete penetrance and variable expressivity. The diagnosis of FNMTC is made when thyroid cancer occurs in two or more first-degree relatives [9].

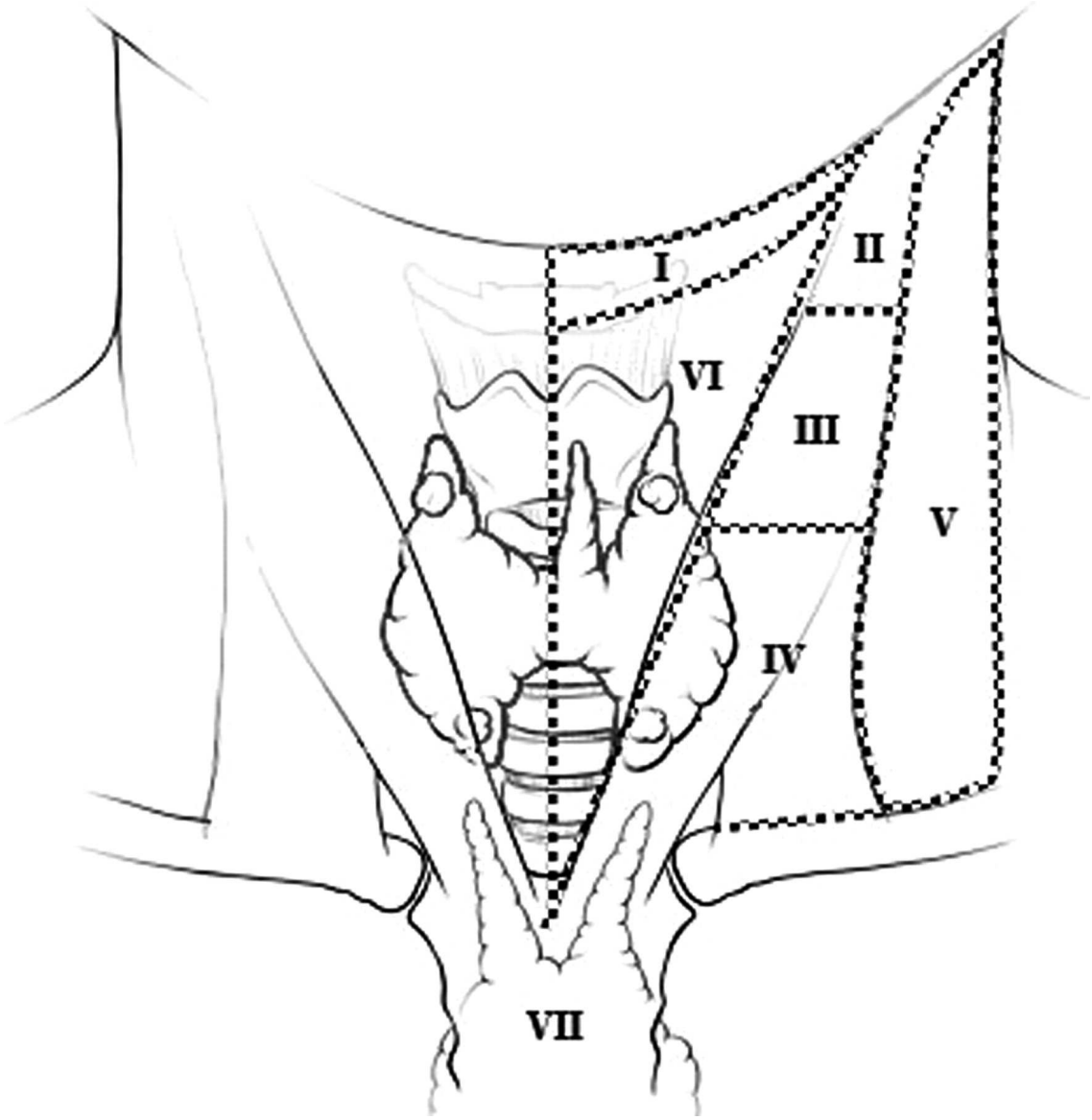
Clinically, FNMTCs can be divided into two groups.

The first group includes familial tumor syndromes characterized by a preponderance of nonthyroidal tumors. These cancer syndromes include familial adenosis polyposis (Gardner syndrome), familial hamartoma syndrome (Cowden syndrome), and the Carney complex type 1.

In the second group, NMTC predominates [10]. Compared with sporadic NMTC, patients with FNMTC appear to present at an earlier age, have more benign thyroid nodules, have multifocal disease, and have a higher rate of locoregional recurrence [11, 12].

Clinical examination of the thyroid should focus on whether the nodule is solitary or dominant in a multinodular goiter. The characteristics of the nodule, including size, consistency (e.g., soft, firm, woody, or hard), and involvement with adjacent structures, should also be defined.

Examination of the cervical lymph nodes, including the central compartment (level VI) and the lateral neck (levels I–V), should also be performed (Fig. 1). Suggestion of involvement of lateral neck lymph nodes will change the extent of preoperative investigation required in these patients.



INVESTIGATIONS

Biochemical Evaluation

Investigation of thyroid nodules should begin with assessment of the functional status of the thyroid. Tests include serum thyroid-stimulating hormone (TSH), free thyroxine, and free tri-iodothyronine.

Measurement of TSH is the most useful initial step. With the availability of highly sensitive TSH assays, it is possible to detect subtle thyroid dysfunction with this test alone [13]. If the TSH is abnormal, free thyroid hormones and thyroid antibodies should be the next investigations.

Thyroid antibodies such as thyroid peroxidase and antithyroglobulin antibodies are found in most patients with Graves' disease or Hashimoto's thyroiditis. TSH receptor autoantibodies are detectable in the majority of patients with Graves' disease [14].

Thyroglobulin (Tg) is the major constituent of colloid and precursor of thyroid hormones. Serum Tg can be elevated in most thyroid diseases and is therefore not recommended as a routine initial assessment of thyroid nodules [15].

Calcitonin is produced from the parafollicular cells of the thyroid. Serum levels are usually elevated in patients with MTCs. The calcitonin assay as a screening test is not cost-effective; however, in patients with a history suggestive of MEN, it may aid in the diagnosis of MTC.

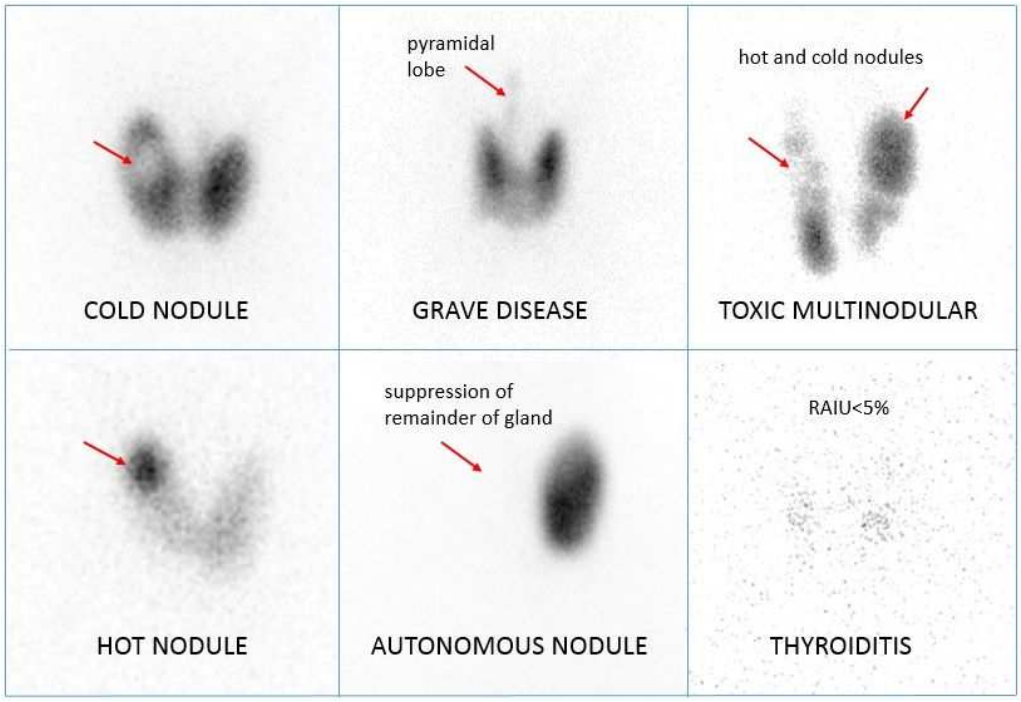
These are the common biochemical investigations done in evaluation of solitary thyroid nodule.

Thyroid Scintigraphy

Thyroid scintigraphy has a limited role in the evaluation of a solitary thyroid nodule. It has been relied upon in the past to assist in risk stratification of nodules as being benign or malignant based on their ability to take up isotope. Depending on the pattern of uptake, nodules are classified as hyperfunctioning (hot), hypofunctioning (cold), or normal functioning (warm).

Hot nodules are seen in about 5% of scans and are malignant in 5% of cases [16]. Approximately 80%–85% of nodules are cold and 10%–15% of these are malignant [17]. The incidence of malignancy in warm nodules is reported to be 9%. This information on its own is unlikely to change the subsequent management of the nodule and further decision making [18].

Thyroid scintigraphy does have a place in the investigation of a thyroid nodule when serum TSH is suppressed. In this setting, it is useful to determine if the nodule is an autonomously toxic nodule, if it is part of a toxic multinodular goiter or a single nodule in a patient with Grave's disease [18, 19].



Ultrasonography

All patients who present with a thyroid nodule should undergo ultrasound evaluation of the nodule, thyroid gland, and cervical lymph nodes, if indicated. Ultrasound is an inexpensive, readily available, and noninvasive investigation.

The superiority of ultrasound examination of the thyroid over clinical examination has been described, with one study showing ultrasonography leading to a change in management of 44% of patients who had been referred for a solitary nodule on physical examination [20].

As has been eloquently described, "The ultrasound machine to the endocrinologist evaluating a thyroid nodule is analogous to the stethoscope of the cardiologist" [21].

An ultrasound examination should focus on the size of the nodule, its composition, the presence of additional nodules, and any sonographic appearance suggestive of

malignancy. Patients with multiple thyroid nodules have the same risk for malignancy as those with solitary thyroid nodules [20, 22] or even diffuse goiters [23], and it is recommended that all patients who have a nodular thyroid undergo ultrasound evaluation [15].

Numerous studies have attempted to define which ultrasound characteristics are most predictive of malignancy. To date, no single feature carries a high sensitivity and high positive predictive value for thyroid cancer [24].

However, there are a number of ultrasound qualities that, when they occur in combination, are associated with a higher risk for malignancy [24, 25].

Nodule Size

Nodule size in not predictive of malignancy, and the risk for cancer in a thyroid nodule has been shown to be the same regardless of the size on ultrasound [22, 24, 26]. Previous guidelines had recommended that the decision to perform a fine-needle aspiration biopsy (FNAB) should be based on nodules >10 mm. It has now been demonstrated that cancer in nodules <10 mm is not less frequent, and if this value is used as a cutoff, then a significant proportion of cancers will be missed [22].

The prevalence of extracapsular or metastatic growth was shown to be similar in nodules >10 mm and <10 mm [22, 27]. The lower size limit of a nodule that should be biopsied is currently under debate [24], but nodules <10 mm with associated microcalcifications or a history of neck irradiation should undergo FNAB [13].

Composition

Nodules can be descriptively classified depending on their predominant composition, for example,

solid,

cystic or

mixed, or

complex.

Papillary thyroid cancer (PTC) is identified in 87% of solid nodules, 7% of mixed composition nodules, and 6% of predominantly cystic nodules [28]. Large cystic or mixed lesions may represent large PTCs that have undergone cystic degeneration. The cystic component is often at the periphery of the nodule, with the solid epithelial portion potentially representing only a small, compressed part of the lesion. It is important to direct the FNAB to this solid component to rule out malignant disease.

Calcification

The presence of any calcification within a nodule increases the likelihood of malignancy. Microcalcifications are defined as multiple, small intranodular punctate hyperechoic spots, with scanty or no posterior acoustic shadowing [13]. They are thought to represent the superimposition of Psammoma bodies upon one another [28]. These lesions are most indicative of PTC and have a specificity of up to 95% [29].

When microcalcifications are seen in a predominantly solid nodule, there is an approximately threefold higher cancer risk, and coarse calcifications are associated with a twofold higher risk, as compared with solid nodules without calcifications [24]. Coarse calcifications are common and can be found in PTCs as well as benign nodules, but their presence in a solitary nodule in a young patient should raise concern for PTC [29].

Solitary Versus Multiple Nodules

The prevalence of thyroid cancer has been shown to be similar in patients with a solitary nodule and patients with multiple nodules [30]. In glands with multiple nodules, the recommendation of the American Thyroid Association (ATA) is to biopsy nodules that are >10 mm and those that have suspicious features [15].

Other Ultrasound Features

Ultrasound with color Doppler evaluates nodule blood flow as a possible predictor of thyroid malignancy. Benign nodules are thought to demonstrate peripheral flow, with malignant lesions showing flow predominantly in the central portion. Results have failed to conclusively support this. Hypoechogenicity and the absence of a halo around the nodule are nonspecific markers of thyroid cancers [28].

A nodule that is shaped more tall than wide (defined as being greater in its anteroposterior dimension than its transverse dimension) has been shown to be suggestive of malignancy [31].

Cervical Lymphadenopathy

Ultrasound is an accurate and sensitive imaging modality for the detection of cervical lymph node metastasis and recurrence [28]. The ultrasound features associated with the highest risk for cancer include a heterogeneous echotexture, calcifications, no hilus, a rounded appearance, cystic changes, and chaotic hypervascularity. These lymph nodes should always be biopsied even in the absence of a malignant-appearing thyroid nodule [13].

Other Imaging Modalities

CT, magnetic resonance imaging (MRI), and positron emission tomography (PET) scanning are not recommended in the routine workup of thyroid nodules. CT is useful in providing additional anatomical information, such as the presence of a retrosternal goiter, compressive symptoms attributable to a posteromedially placed nodule, and the relationship of a goiter to adjacent structures. MRI can do the same, but at a greater cost.

With the advent of the increased use of PET scanning in the staging and surveillance of various malignancies, the phenomenon of the PET-identified thyroid incidentaloma is becoming more prevalent. These PET-detected nodules have been shown, in some studies, to harbor a higher malignancy risk [32–34]. Until more information is collected on the significance of these nodules, it seems prudent to have a low threshold for biopsying these lesions.

FNAB

FNAB is the most crucial step in the evaluation of a thyroid nodule and is the procedure of choice in the workup of thyroid nodules [15, 35]. It is able to provide specific information about the cellular composition of a nodule that directs subsequent management decisions.

FNAB can be performed by palpation or with ultrasound guidance. In our institution, it is performed exclusively with ultrasound guidance. This technique has been shown to decrease false negatives resulting from needle misplacement and reduce the rate of nondiagnostic smears from 15% to 3% [36–39]. The use of FNAB has led to a reduction in the number of patients requiring surgery and increased the diagnostic yield of cancers at thyroidectomy [5, 40, 41].

For FNAB to be regarded as a useful diagnostic tool, it must have a low false-negative rate. The false-negative rate is reported in the literature to be in the range of 1%–11%, with a value ≤5% being acceptable [42, 43]. A number of strategies, including aspirating multiple nodule sites, submitting cyst fluid for cytologic examination, and reviewing slides with an experienced cytopathologist [35], have been suggested to minimize false negatives.

Procedure

The technical aspects of FNAB are well described in numerous publications [35, 40, 42–45] and are not repeated here. It is generally well tolerated, with minor complications of local pain and, rarely, a hematoma.

Interpretation

"An accurate diagnosis depends on an adequate and representative sample interpreted correctly in the clinical context" [43]. A diagnostic sample is generally defined as when there are at least two slides that have six or more groups of >10 well-preserved follicular epithelial cells in each group [13, 40]. The four categories that are commonly used to describe FNAB results and their reported incidences are: benign, 70%; indeterminate, 10%; malignant, 5%; and nondiagnostic, 15% [13].

Benign

The majority of aspirates are benign and represent colloid, adenomatous or hyperplastic nodules, simple thyroid cysts, autoimmune thyroiditis, and lymphocytic thyroiditis. Colloid nodules demonstrate abundant colloid with benign follicular cells arranged in sheets, clusters, and spherules [43]. In contrast, hyperplastic nodules have less colloid with more follicular epithelial cells. The cells seen in thyroiditis will depend on the stage of the disease, with lymphoid cells predominating in the early stages and the later showing extensive fibrosis.

Malignant

The most frequent malignant biopsy is that of PTC, with a sensitivity and specificity approaching 100%. The diagnosis is based on the arrangement of the cells and their cellular features. Typically, many neoplastic follicular epithelial cells are seen with or without fibrovascular cores in a papillary configuration. The nuclei are enlarged and show crowding with irregular shapes and pale chromatin [44]. Intranuclear "holes"

(pseudoinclusions) and Psammoma bodies are the most important diagnostic features of PTC. The follicular variant of PTC is a source of false-negative diagnosis. This variant has been described as a "pathological paradox" because it does not demonstrate papillae and the diagnosis is made on the nuclear changes seen in the neoplastic cells [46].

MTCs often demonstrate spindle-shaped or plasmacytoid neoplastic cells. Binucleation is common and intranuclear pseudoinclusions may be seen. FNAB may reveal the presence of amyloid, which is associated with MTC. Because these tumors arise from the calcitonin-producing C cells, immunoperoxidase staining for this marker is essentially diagnostic of MTC [40]. A cytological diagnosis of anaplastic thyroid carcinoma can be made when smears show abundant blood, necrotic debris, pleomorphic cells with large irregular nuclei, and the presence of mitotic figures. Metastatic lesions to the thyroid are uncommon and are usually from primary renal, breast, lung, colon, melanoma, and prostate cancers. These are usually diagnostic on FNAB [40].

Indeterminate

This category covers two subgroups. First, "suspicious for malignancy," in which malignancy is suspected but there is not enough information from the smear to make a definitive diagnosis. Second, "follicular neoplasm," when it is not possible to make a diagnosis of a follicular adenoma or carcinoma because this depends on the absence or presence of capsular or lymphovascular invasion, which can only be determined on

histology. Approximately 20% of these indeterminate nodules are malignant. Therefore, these lesions should be excised to allow for a definitive diagnosis.

Nondiagnostic

Nondiagnostic smears occur when there are insufficient follicular cells to make a cytological diagnosis. Reaspiration yields satisfactory smears in 50% of cases [13]. An interval of at least 4 weeks should be allowed between repeat FNABs, because inflammation and bleeding from the initial biopsy may limit the ability to adequately interpret the second biopsy. Aspirates of cystic nodules are a source of unsatisfactory specimens and are thought to be a result of sampling error, when only the fluid is examined and the solid component of a cystic lesion is not biopsied. Malignancy rates of the solid component of cystic lesions are thought to approach those of solitary cold nodules [40].

MANAGEMENT

Management of thyroid nodules is based on the combination of history, examination, ultrasound evaluation, and ultimately cytology results.

Benign Nodules

Nodules diagnosed as benign on FNAB, and which are biochemically normal, do not need specific treatment. If the nodule is large and is causing compressive symptoms, then it may require surgery. Toxic nodules require medical management and/or radioactive iodine administration, and occasionally surgery.

Benign nodules require follow-up with annual clinical examinations and repeat ultrasound, because of the small false-negative rate of approximately 5% on FNAB [4]. Most benign nodules grow slowly over time [47], but there is no consensus as to what constitutes significant growth warranting rebiopsy [24]. One reasonable definition of growth is a 20% increase in nodule diameter with a minimum increase in two or more dimensions ≥2 mm. According to the ATA recommendations, if there is evidence of nodule growth either by palpation or on sonography, ultrasound-guided repeat FNAB should be carried out [15]. Any new features on ultrasound suggestive of malignancy (as described earlier) should also prompt repeat FNAB. If nodule size remains stable, the interval until the next follow-up may be increased [15].

Malignant Nodules

A positive result of malignancy on FNAB almost certainly warrants surgery. Total thyroidectomy for PTC is the preferred treatment option. In one landmark paper with the longest follow-up of patients with PTC [48], mortality and recurrence rates were compared in patients who underwent thyroid lobectomy (ipsilateral total lobectomy with isthmusectomy) versus bilateral resection (including total thyroidectomy and bilateral subtotal or near total thyroidectomy). They were able to demonstrate that, after 20 years, the rates for local recurrence and nodal metastasis were 14% and 19% after thyroid lobectomy and only 2% and 6% after bilateral resection, respectively [48].

Twenty percent to ninety percent of patients diagnosed with PTC have involved cervical lymph nodes at the time of diagnosis. In addition to thyroidectomy, a routine

ipsilateral central compartment (level VI) lymph node dissection may be considered. This remains a controversial topic; however, there is some evidence to support its role in reducing the risk for nodal recurrence and improving survival [49–51].

A preoperative ultrasound of the lateral neck (levels II–V) should be performed to determine if there are any pathological nodes present, and if so, these should undergo FNAB. If there is biopsy-proven metastatic disease in the lateral neck, a selective lymph node dissection is required.

Follicular thyroid cancers (FTCs) are classified as minimally or widely invasive. This diagnosis can only be made histogically. Minimally invasive FTC, the more common type, is where there is only slight tumor invasion into or through the capsule with or without vascular invasion. The presence of vascular invasion increases the risk for metastatic disease, and in tumors with this finding, if the patient has had only a thyroid lobectomy, a completion thyroidectomy is warranted [18]. Otherwise, for minimally invasive FTC (of only the capsule), thyroid lobectomy may be adequate. Widely invasive FTC should undergo total thyroidectomy without lymph node dissection because these tumors tend to spread hematogenously, as compared with PTCs, which metastasize through the lymphatics.

Following total thyroidectomy in patients with PTC and FTC, ^{131}I ablation should be undertaken to destroy residual thyroid tissue, decrease the risk for locoregional recurrence, and facilitate long-term surveillance with whole-body iodine scans and stimulated thyroglobulin measurements [52]. This has been shown to have the greatest benefits in patients with tumors >15 mm or those with residual disease after surgery.

For patients with low-risk disease (unifocal PTC <10 mm with no extrathyroidal extension or lymph node metastasis), the benefit is more controversial, and the recommendation is to give smaller amounts of ^{131}I [52]. Retrospective studies have demonstrated superior outcomes in patients with high-risk disease with TSH suppression to <0.1 mU/l, with maintenance of TSH at or slightly below the lower limit of normal (0.1–0.5 mU/l) being appropriate for low-risk patients [15].

MTCs should be treated with total thyroidectomy and level VI node dissection. As per PTC, if the lateral neck lymph nodes are positive on FNAB, a level II–V lymphadenectomy should be performed. Because these tumors are not iodine avid, surgery is the mainstay of treatment.

Anaplastic thyroid cancers are aggressive tumors with an extremely poor prognosis. Surgery is rarely possible because of the extent of the local disease. Radiotherapy and chemotherapy are the main modalities of treatment [14].

Indeterminate

Nodules with this cytological diagnosis require surgical excision, usually with thyroid lobectomy. If a "follicular neoplasm" was the preoperative diagnosis, definitive histological confirmation of whether this is an adenoma or a carcinoma (based on the presence or absence of capsular invasion) is necessary. If the nodule is confirmed as a follicular carcinoma on paraffin section, then a completion thyroidectomy is performed if it is the widely invasive type or has vascular invasion. This is usually done in the first or second week following the initial surgery. An FNAB result of "suspicious for malignancy," particularly if it is papillary, allows the use of an

intraoperative frozen section diagnosis for decision making [53, 54]. If the pathologist is confident of a diagnosis of papillary carcinoma on frozen section, the patient should proceed to a total thyroidectomy and possibly ipsilateral level VI lymph node dissection. This has the advantage of having a definitive operation performed immediately.

Nondiagnostic

Cysts that recur and nodules that are >4 cm or are repeatedly nondiagnostic on FNAB should be considered for surgical excision. Any nodule that has suspicious features on ultrasound that returns a nondiagnostic FNAB should be strongly considered for excisional biopsy, particularly in patients with a family history of thyroid malignancies or who have had radiation exposure as a child.

There are three main thyroid operations:

1. Thyroid lobectomy
2. . Total or Near-total thyroidectomy
3. Completion thyroidectomy

1. Thyroid lobectomy

This operation involves removing the half of the thyroid gland that has the nodule. It is sometimes called a "diagnostic lobectomy " because the preoperative diagnosis may be uncertain and part of the reason for the operation is to make a diagnosis of cancer or no cancer. These patients may have had a FNA biopsy result that is non-diagnostic, suspicious for malignancy, or shows a follicular or Hurthle cell Neoplasm.

A diagnostic lobectomy may or may not involve a frozen section. A frozen section is biopsy of the nodule that is taken during the operation while the patient is still under anesthesia. The pathologist will examine one or two slices of the thyroid nodule under the microscope and try to make a diagnosis. If definite cancer is found on the frozen section, then the patient would likely have a total thyroidectomy. It is important to note that frozen section is not 100% accurate. Since the pathologist is looking at only one or two slices of the nodule, there is a good chance that there may be evidence of cancer, just not in the slices that are examined. More often than not, the pathologist cannot make the diagnosis of follicular or Hurthle cell cancer on frozen section and it is necessary to wait for the final pathology (permanent sections that require special processing and allow for the entire specimen to be reviewed). The final pathology usually is ready about 5-7 business days after the surgery. If the cancer is not found on the frozen section, but found on the final pathology, then a second surgery may be needed to remove the rest of the thyroid gland (completion thyroidectomy). Ultimately, whether or not to send a frozen section will depend on the experience and expertise of the surgeon.)

All patients that have one half of the thyroid gland removed will need to have their thyroid levels checked sometime after surgery. Depending on these levels, some patients may need thyroid hormone replacement and some patients will not.

2. Total or Near-total thyroidectomy

This operation involves removing all or nearly all of the thyroid gland. It may be done for benign thyroid conditions that affect both thyroid lobes, such as large goiter or Graves disease, or it may be done for cancer. A near-total thyroidectomy means that

the surgeon decided to leave a very small amount of benign thyroid tissue behind. Thyroid tissue may be intentionally left behind in areas around important structures, such as the nerves that control the voice, swallowing, and breathing, or the parathyroid glands. All patients who undergo a total or near-total thyroidectomy will need to be on life-long thyroid hormone replacement after surgery.

3. Completion thyroidectomy

A completion thyroidectomy involves removing the remaining thyroid tissue after a patient has had a previous partial thyroid resection (i.e. lobectomy). It may be done years later or it may be done soon after a lobectomy (as early as the next week). The reasons for completion thyroidectomy are the same as for a lobectomy or total thyroidectomy. All patients who undergo a completion thyroidectomy will need to be on life-long thyroid hormone replacement after surgery

CONCLUSION

Thyroid nodules are common, and with the increasing use of ultrasound unrelated problems are detected with greater frequency. The aim of management is to identify which nodules warrant further investigation to exclude the presence of malignancy. Although a thorough history and clinical examination are indispensable, FNAB is essential to decision making and is able to provide highly accurate information that will ultimately determine the management of a nodule. This study is to find bio chemical markers predicting malignancy..correlation of TSH and TG with malignancy will be explored in this study.

Thyroid Stimulating Hormone (TSH)

TSH is a peptide hormone produced by the anterior pituitary. Specifically, it is composed of 2 chains: 1 alpha, and 1 beta chain and has a molecular mass of approximately 28,000 Da. This also holds true for other glycoprotein hormones made by the anterior pituitary, including luteinizing hormone (LH), follicle-stimulating hormone (FSH), and human chorionic gonadotropin (HCG).

This is important because TSH has the same alpha subunit as LH, FSH, and HCG. However, TSH has a different beta chain than LH, FSH, and HCG that confers biological specificity. Since TSH, LH, FSH, and HCG all have the alpha subunit, they all have the cyclic adenine monophosphate (cAMP) second messenger system. TSH also activates the IP3 signaling cascade.

The cAMP second messenger system entails adenine monophosphate (AMP) conversion to cAMP, and the IP3 second messenger system involves calcium release from the sarcoplasmic reticulum. The cAMP and IP3/Ca2+ then leads to downstream physiological effects. There is a diurnal variation in TSH secretion with highest values between midnight and 4:00 am and lowest values in the late afternoon.

The hypothalamic-pituitary axis regulates TSH release. The hypothalamus secretes the thyroid releasing hormone (TRH), which stimulates thyrotrophs in the anterior pituitary to secrete TSH. TSH is released by the anterior pituitary and stimulates the thyroid follicular cells to release thyroxine, or T4 (80%) and triiodothyronine, or T3

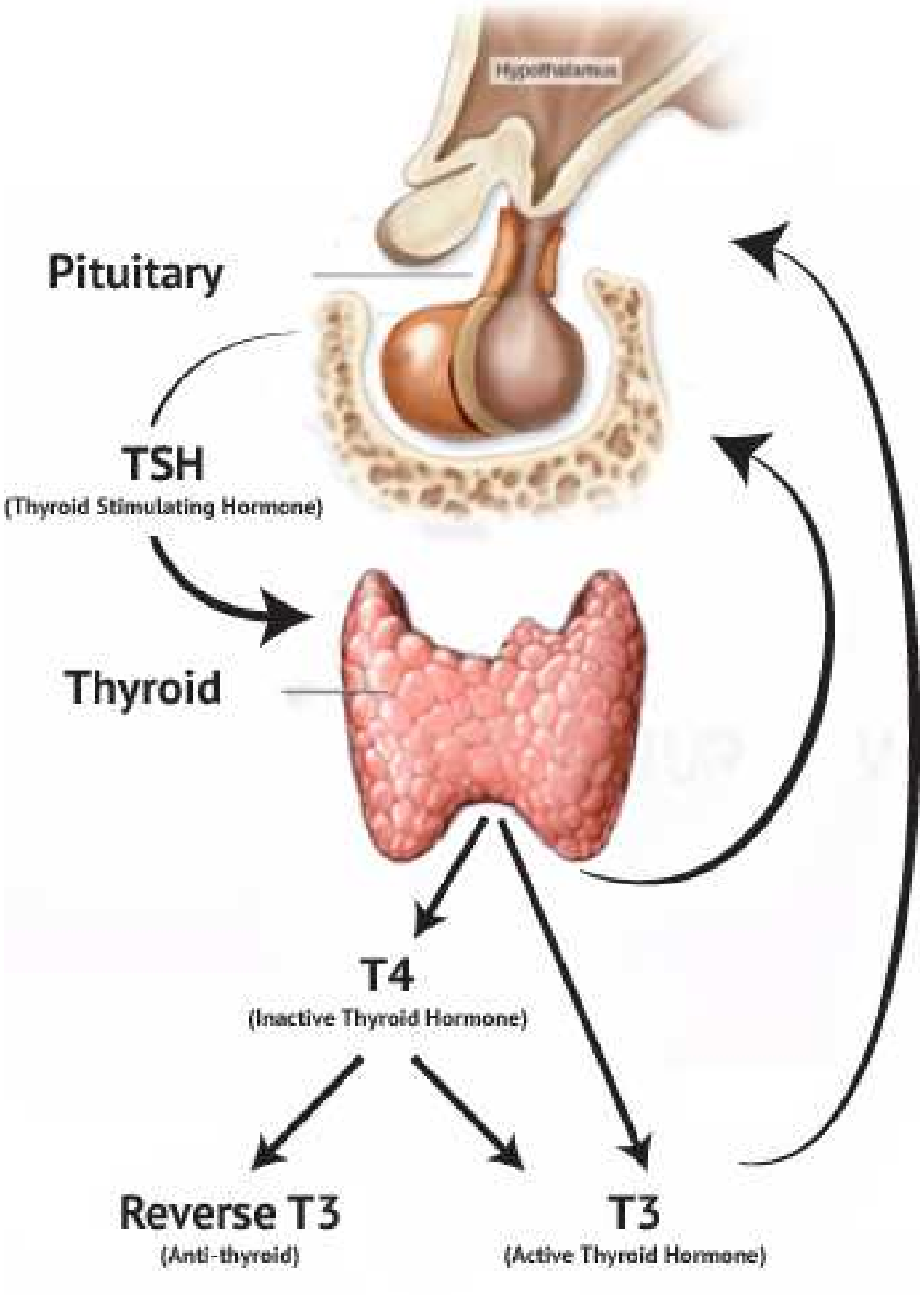
(20%). When T4 is released into circulation, it can be converted to T3 through the process of deiodination.

T4 and T3 can then exert negative feedback on TSH levels, with high levels of T3/T4 decreasing TSH and low levels of T3/T4 increasing TSH levels from the anterior pituitary. T3 is the predominant inhibitor of TSH secretion. Because TSH secretion is so sensitive to minor changes in serum-free T4 through this negative feedback loop, abnormal TSH levels are detected earlier than those of free T4 in hypothyroidism and hyperthyroidism.

There is a log-linear relationship between T3/T4 and TSH with minor changes in TH results in major changes in TSH.TSH binds and activates the TSH receptor (TSHR), which is a G-protein coupled receptor (GPCR) on the basolateral surface of thyroid follicle cells.

TSHR is coupled to both Gs and Gq G-proteins, activating both the cAMP pathway (via Gsa) and the phosphoinositol/calcium (IP/Ca2+; via Gq) second messenger signaling cascades.

The Gs pathway activates iodide uptake, thyroid hormone secretion, and gland growth and differentiation. The Gq pathway is rate-limiting for hormone synthesis by stimulating iodide organification. A gain in function mutation of the TSH receptor can result in hyperthyroidism, while the loss in function mutations can result in hypothyroidism.


Hypothalamus
Pituitary
TSH
(Thyroid Stimulating Hormone)
Thyroid
T4
(Inactive Thyroid Hormone)
Reverse T3
(Anti-thyroid)
T3
(Active Thyroid Hormone)

THYROGLOBULIN

THYROGLOBULIN (Tg), the precursor of thyroid hormones, is synthesized by thyrocytes and secreted into the lumen of thyroid follicles, where it is stored as the major component of colloid. At the cell-colloid interface, posttransitional modifications of Tg occur, which are characterized by coupling of tyrosyl residues with iodide, leading to the formation of thyroid hormone residues within the Tg molecule.

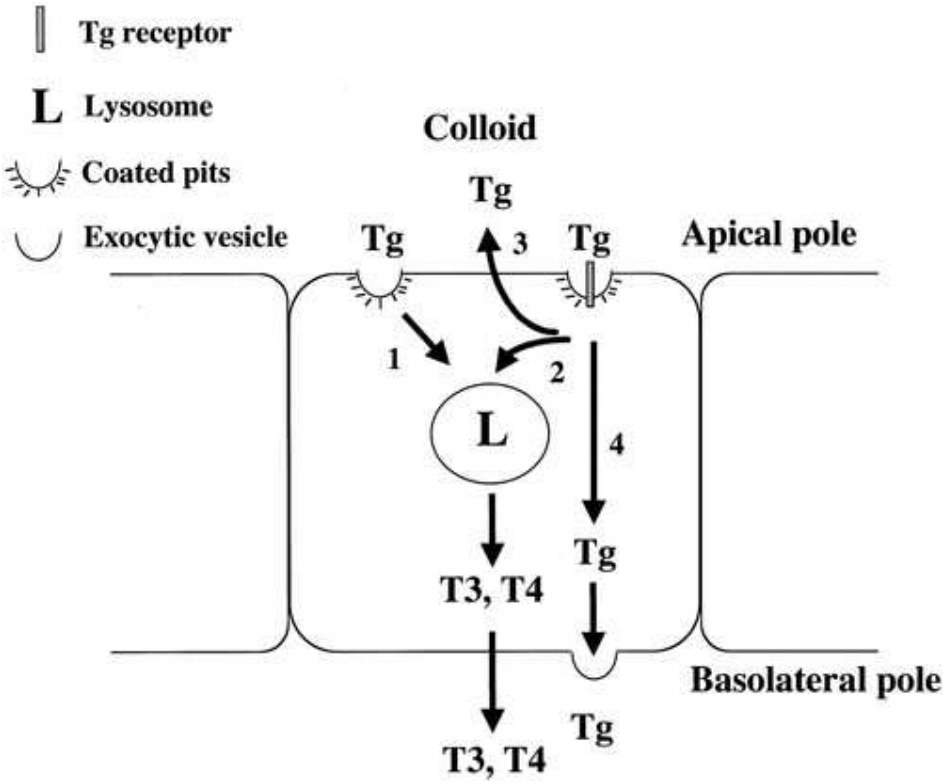
Hormone release generally requires uptake of Tg from the colloid by thyrocytes and proteolytic cleavage along the lysosomal pathway. However, thyroxine (T4), but not triodothyronine (T3), can also be released to some extent by extracellular proteolysis of Tg within the colloid, at the apical surface of thyrocytes (8, 28). Furthermore, some Tg molecules that reach the circulation can be degraded peripherally after uptake by macrophages, especially Kupffer cells (7, 9). However, the contribution of this mechanism to the total pool of circulating thyroid hormones is probably minimal.

It is obvious that the process of internalization and degradation of Tg by thyrocytes must be strictly regulated to provide appropriate amounts of thyroid hormones and to avoid excessive hormone release. A major problem stems from the extremely high concentration of Tg within the colloid, which can reach up to 800 mg/ml. Even though much of the Tg is insoluble and, therefore, not readily available for uptake, the concentration of soluble Tg available to thyrocytes is probably also relatively high.

If effective mechanisms of Tg internalization (whether receptor-mediated or fluid-phase uptake) were to deliver hormone-rich forms of Tg to lysosomes unchecked, excessive hormone release would ensue.

Indeed, the problem of avoiding excessive hormone release may be of greater importance than the often discussed issue of how to avoid the wasteful process of internalizing and degrading immature forms of Tg that are poor in hormone residues. Figure1 illustrates the principal intracellular pathways that Tg follows after micropinocytosis.

In the present review, we consider mechanisms that are known or have been postulated to promote and control Tg endocytosis by thyroid cells and hormone release, under physiological and pathological conditions, with particular emphasis on the role of Tg receptors. To introduce the subject, we review the general features of structure, synthesis, and secretion of Tg.



Schematic representation of the principal intracellular pathways of thyroglobulin (Tg) after endocytosis by thyroid epithelial cells. 1: Tg is internalized by fluid-phase nonspecific micropinocytosis and transported to lysosomes, where it is degraded with release of thyroid hormones [triodothyronine (T3) and thyroxine (T4)]. 2: Tg is internalized by an unidentified low-affinity receptor and possibly transported to lysosomes.3: Tg is internalized by a receptor (possibly the asialoglycoprotein receptor) and recycled back into the colloid.4: Tg is internalized by megalin (gp330) and transported by transcytosis at the basolateral surface of thyroid cells, where it is released by exocytosis into the bloodstream. This process reduces the extent of thyroid hormone release because Tg escapes the lysosomal pathway.

REFERENCES

Serum TSH levels as a predictor of malignancy in thyroid nodules: A prospective study **Lenara Golbert et al**

This study prospectively evaluated the usefulness of serum TSH levels as a predictor of malignancy in thyroid nodules.

Analyses using TSH levels as a categorical variable, defined by ROC curve analysis, showed that the risk of malignancy was approximately 3-fold higher in patients with TSH levels ≥2.26 μU/mL than in patients with lower TSH levels (P = 0.00).

Higher serum TSH levels are associated with an increased risk of thyroid cancer in patients with thyroid nodules. Using TSH levels as an adjunctive diagnostic test for stratifying the risk of malignancy associated with a thyroid nodule may help on defining the best therapeutic approaches.

Preoperative serum thyroglobulin as a useful predictive marker to differentiate follicular thyroid cancer from benign nodules in indeterminate nodules.

Eun kyung lee et al

This study retrospectively evaluated to find useful and simple predictive tools to differentiate malignant thyroid nodules from indeterminate nodules. With a cut-off value of 187.5 ng/mL Tg, sensitivity and specificity were 54.8% and 90.1%, respectively (AUC 0.748, $P < 0.001$).

In the case of nodule size > 1.7 cm, elevated serum Tg predicts the risk of malignancy; especially Tg > 70 ng/mL (odds ratio 3.245, 95% confidence interval 1.115-9.450, $P = 0.038$). Preoperative Tg levels had very high specificity in predicting thyroid cancer in case of suspicious follicular neoplasm.

Therefore, Tg levels may be a useful marker for differentiating thyroid cancer from benign thyroid nodules in the cytological diagnosis of indeterminate nodules.

Rinaldi s et al

Thyroid stimulating hormone, thyroglobulin and thyroid hormones and risk of differentiated thyroid carcinoma

Increased levels of thyroglobulin (Tg) and thyroid-stimulating hormone (TSH) are associated with differentiated thyroid carcinoma (TC) risk, but strong epidemiological evidence is lacking.

. Levels of total and free (f) thyroxine (T4) and triiodo-thyronine (T3), TSH, Tg, and anti-Tg antibodies (TgAb) were measured by commercially available immunoassays. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed using conditional logistic regression. All statistical tests were two-sided. TC risk was positively associated with Tg (OR for the highest vs lowest quartile = 9.15; 95% CI = 5.28 to 15.90; P < .001) and

negatively associated with TSH level (OR = 0.56; 95% CI = 0.38 to 0.81; P = .001). Odds ratios were not modified by adjustment for weight and height and were consistent across sexes, age groups, and countries. The association with Tg was stronger in follicular than papillary TC.

The odds ratio for TgAb-positivity was 1.50 (95% CI = 1.05 to 2.15; P = .03). Among case patients, TSH level was stable over time, whereas Tg level was higher in proximity to TC diagnosis.

Jon hrafnkelsson et al

Serum thyroglobulin as a risk factor for thyroid carcinoma final study material consisted of 59 cases of papillary and follicular carcinomas. These cases were compared with 164 controls, matched for sex, age and time of sample taking.

The most interesting finding was that concentrations of thyroglobulin in serum were abnormally elevated in cases compared with controls, equal to or above 30 mg:L, with odds ratio 7.0 (CI 3.1?15.7). This elevation of serum thyroglobulin occurred in 44%of the carcinoma cases.

Sensitivity was around 50 for measurements taken up to 15 years prior to diagnosis, but 21 when the interval was over 15 years. Specificity was 89. No differences were found between cases and controls in values for thyroid-stimulating hormone and thyroxin.

MATERIALS AND METHODS:

Study Design:

This is hospital based cross sectional Study.

Study Sample:

With confidence interval of -95%

Power of the study -80

Ratio of benign to malignant cases - 3:1

Proportion of increased Tsh in malignant nodules -70

Proportion of increased Tsh in benign nodules -20

A total of 49 will be enrolled in the study from Tertiary Care Centre, after meeting inclusion and exclusion criteria.

Present study is a cross sectional study carried out with a sample size of 49 patients. This is a cross sectional study of patients presenting with complaints of thyroid swelling presenting to the Departments of General Surgery in KMCH.

Methodology

All patients presenting with the solitary thyroid nodules in the age group 18 to 70 years who are willing to participate in the study were explained about the study in detail and after obtaining consent from them they were included in the study.

Patients were evaluated clinically with detailed history including personal history, family history of malignancies, exposure to radiation were collected, physical examination of the thyroid swelling including consistency, fixity were recorded,detailed eamintion of the neck nodes were done, ultrasonography of neck, biochemical tests like thyroid profile (serum TSH, T3 and T4), TSH (0.4-5.0mIU/L), T3 (100-200ng/dl), T4 (4.5-11.5mg/dl), thyroglobulin, and FNAC of the thyroid nodule.

Other investigations like contrast enhanced CT scan of the neck etc are left to the discretion of the clinician treating the patient. Based on the results of the FNAC a treatment plan is arrived and those who are undergoing surgery are further evaluated for fitness of surgery. A decision of hemi vs total thyroidectomy is made based primarily on the FNAC report and secondarily on the presenting clinical scenario.

The nodules where the preoperative FNAC was inconclusive (either suspicious or indeterminate) will be sent for frozen section at the time of surgery. All the specimen will be sent for Histopathological examination (HPE).

A detailed note of the clinical size of the nodule/ (as measured clinical and by ultrasound), presence of voice change, age and sex of the patient, results of the FNAC, and final histopathology along with biochemical information such as preoperative thyroglobulin, and serum TSH will be made on Microsoft Excel spread sheet and factors will be analyzed. The further treatment and follow up of the patient will be decided as per the protocol of the departments based on the final histopathology.

Inclusion criteria

All patients presenting with thyroid nodules aged between 18-70 years willing to participate in the study.

Exclusion criteria

.Patients presenting with multi nodular goitre

• Patients with poorly differentiated cytology, lymphoma or metastasis from elsewhere.

• Patients with FNAC or biopsy proven lymph node metastases, extra thyroidal invasion, and previous thyroid surgeries or recurrence.

• Patients who have undergone part of the treatment elsewhere.

• Patients with diffuse enlargement of the thyroid gland, primary and secondary thyrotoxicosis.

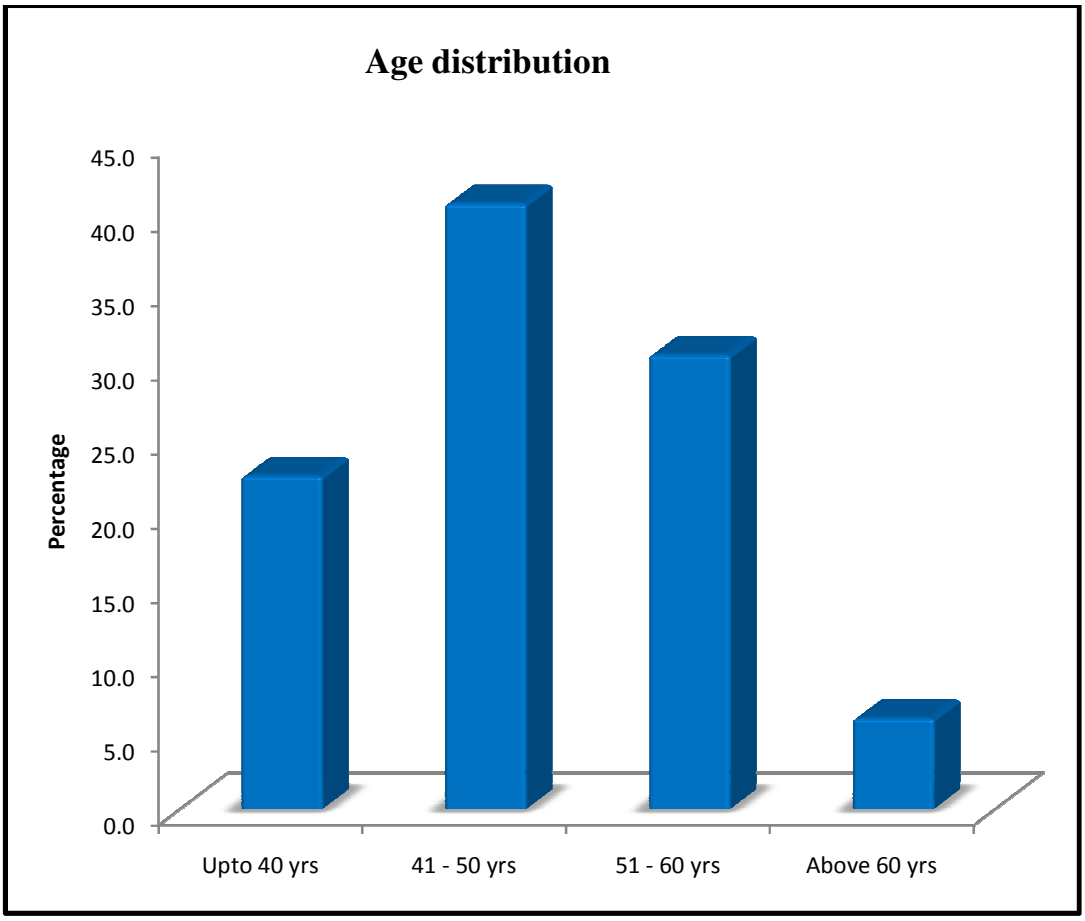
• Patients with frank clinical hypothyroidism.

STATISTICAL ANALYSIS

Patients are grouped into benign or malignant group according to final diagnosis. The collected data were analysed with IBM.SPSS statistics software 23.0 Version.To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference between the bivariate samples in Independent groups the Unpaired sample t-test was used. In the above statistical tool the probability value .05 is considered as significant level**.**

AGE DISTRIBUTION

	Frequency	Percent
Upto 40 yrs	11	22.4
41 - 50 yrs	20	40.8
51 - 60 yrs	15	30.6
Above 60 yrs	3	6.1
Total	49	100.0



In this study total of 49 memebers are enrolled

The age distribution are as above

11 memebers of the study was below 40 years contributing to 22.4%

20 memebers of the study fall between 40-50 yrs contributing to 40.8%

15 members of the study fall between 50-60 yrs amounting to 30.6%

Above 60 years was 3 in number and is 6.1% of the total study population

Majority of the study population falls in 40 to 60 years of age cumulative of 35 in number which amounts to 70% of the study population

Age as a baseline character of the study doesn't have correlation to the malignanacy

AGE DISTRIBUTION IN MALIGNANACY

AGE	FREQUENCY	DISTRIBUTION
UPTO 40	1	14.3
40-50	3	42.8
50-60	2	28.6
ABOVE 60	1	14.3
TOTAL	7	100

Out of 7 malignant patients

1 belongs to age group below 40

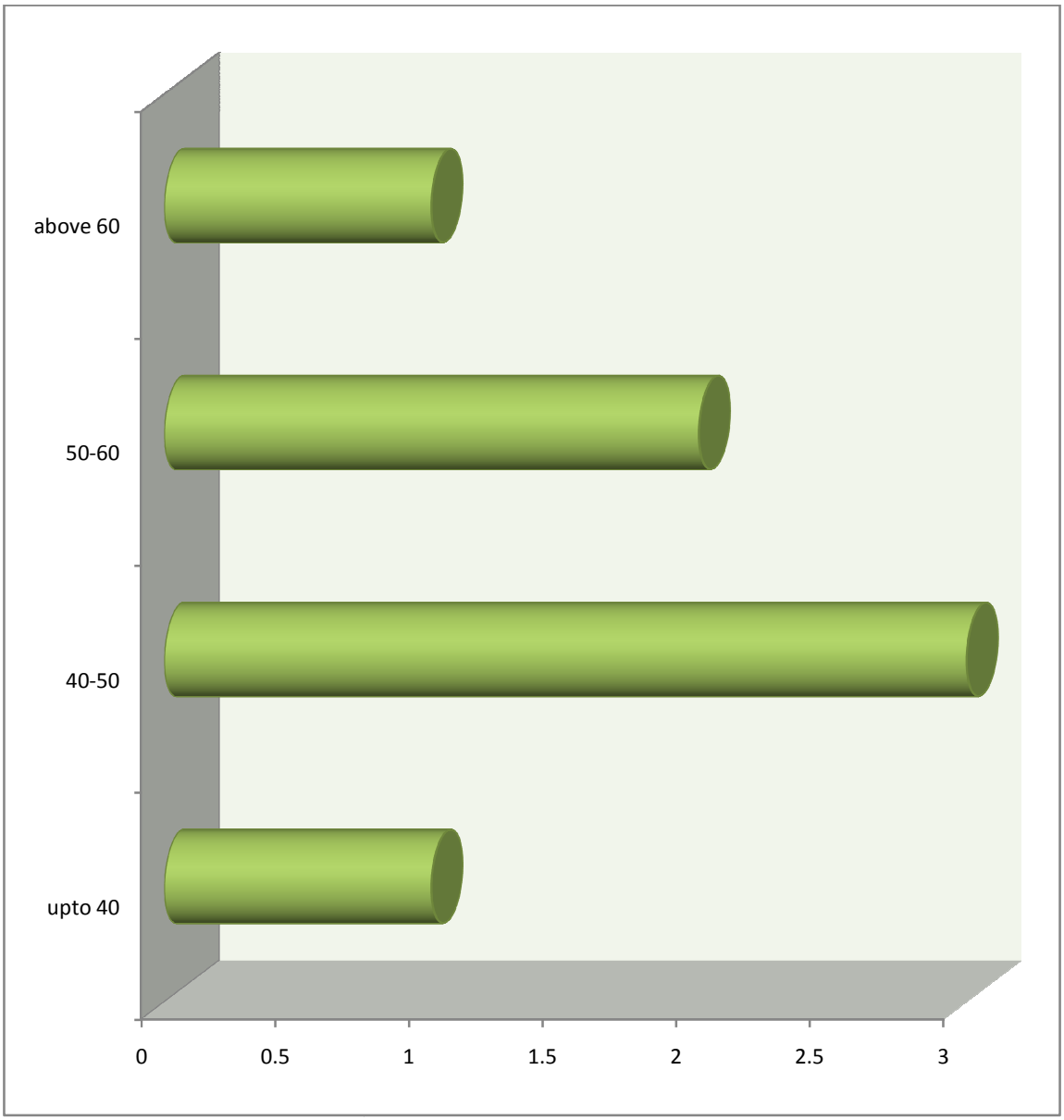
3 belongs to age group 40-50

2 belongs to age group 50-60

1 is in age group above 60

Majority falls in age of 40-60 amounting to 70%

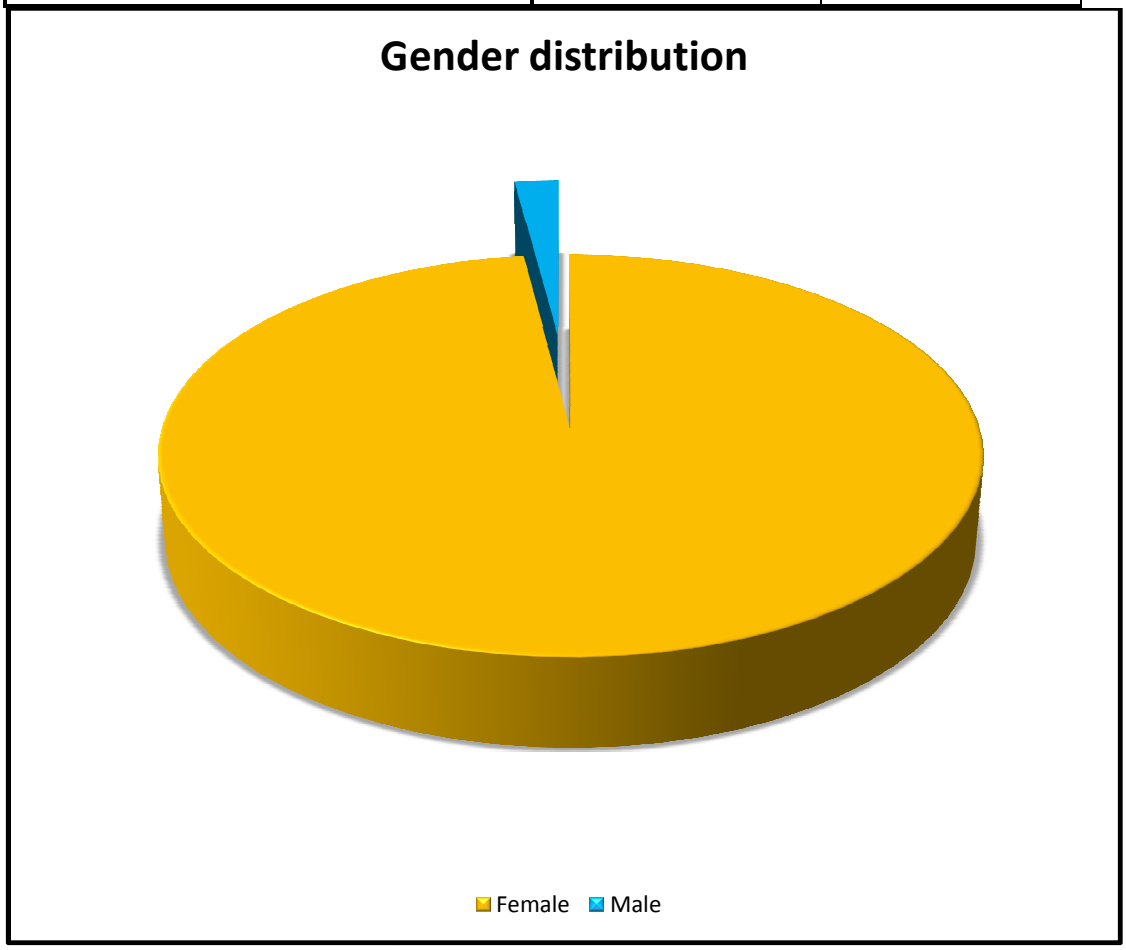
AGE DISTRIBUTION IN MALIGNANACY



SEX DISTRIBUTION

SEX

	Frequency	Percent
Female	48	98.0
Male	1	2.0
Total	49	100.0



Out of total 49 members enrolled in the study the sex distribution are as follows

Female sex is 48 in frequency which is 98 percent of the study population

Male sex is 1 in frequency which is 2 percent of total population

In similar studies the female is male ratio is 7:1

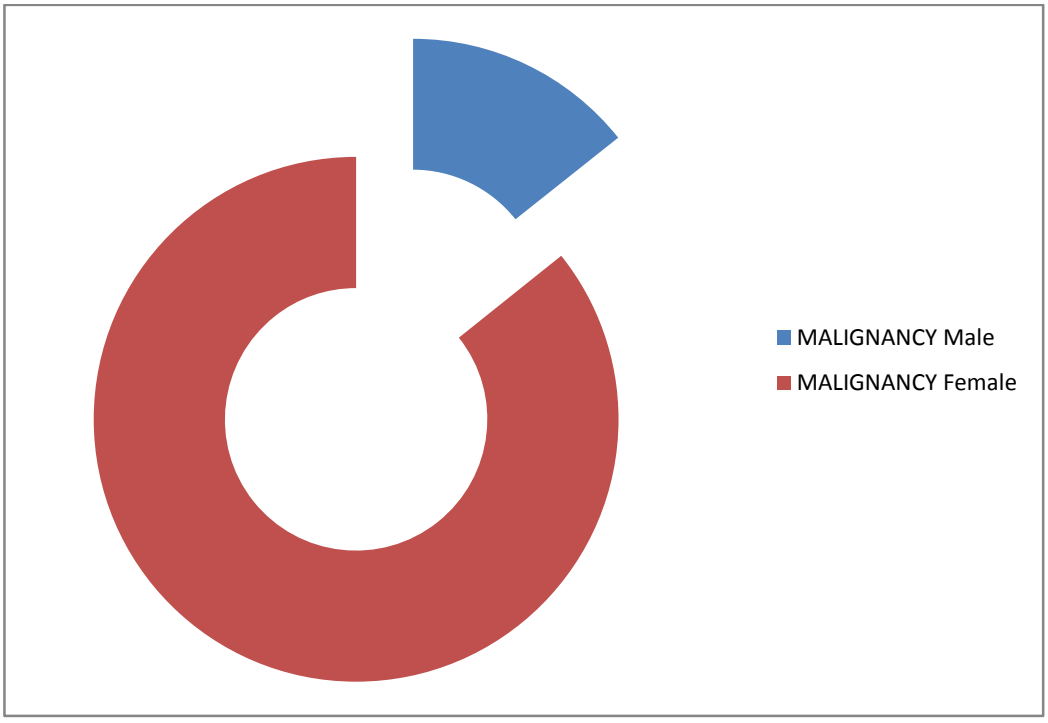
Whereas in our study it is around 50:1

The study population is small and this might be factor increased frequency of female sex in our study

In sub group of malignant population

6 members are female and 1 is male

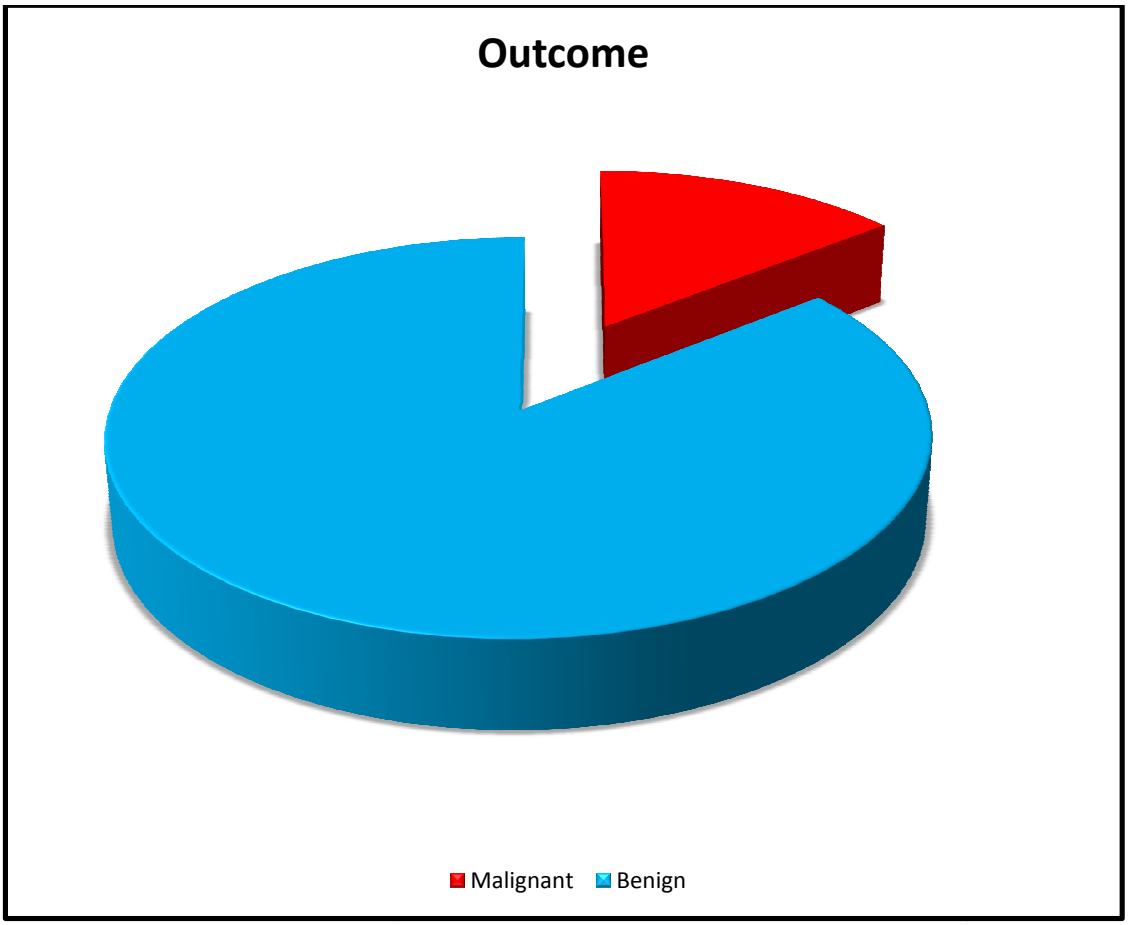
The ratio 6:1 in malignanat population is comparable to other studies



RESULTS AND OBSERVATIONS

Outcome

	Frequency	Percent
Malignant	7	14.3
Benign	42	85.7
Total	49	100.0



Outcome of Malignanacy:

Our study population is classified into Benign and Malignant

Out of 49 people enrolled in the study 7 were diagnosed with malignancy by histopathological examination

Out of 7 malignant lesions 6 were found to be papillary carcinoma and 1 was follicular carcinoma of thyroid.

42 were diagnosed with benign lesions by histopathological examination

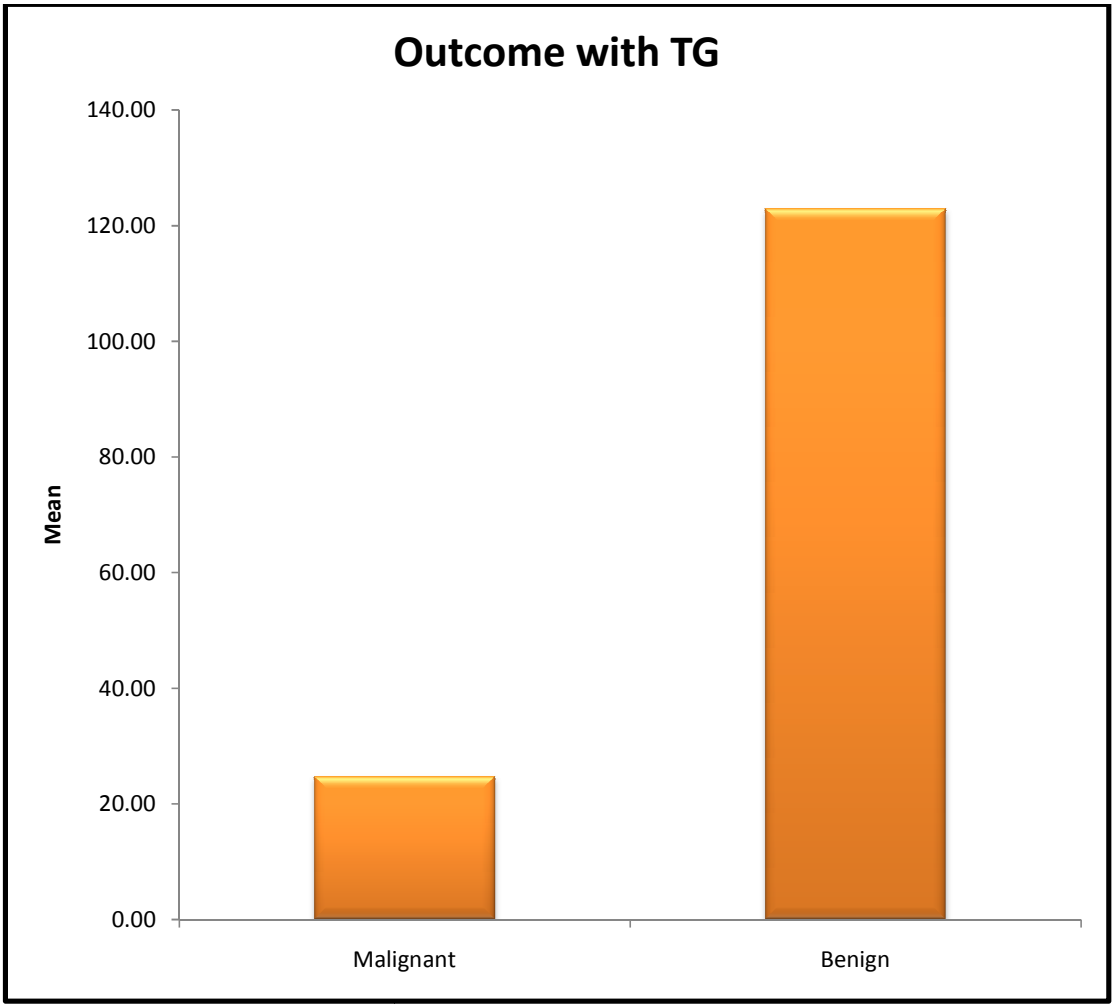
The malignant lesions amounts to 14.3 percent of total study population which is within the limit of expected percentage of malignancy 5-15%

The benign lesions were 85.7% of the total study population

Comparison of Outcome with TG by Unpaired t-test

Outcome		N	Mean	S.D	t-value	P-value
TG(ng/ml)	Malignant	7	24.77	7.63	3.184	0.0005 **
	Benign	42	122.92	74.79		

** Highly Significant at P < 0.01 level



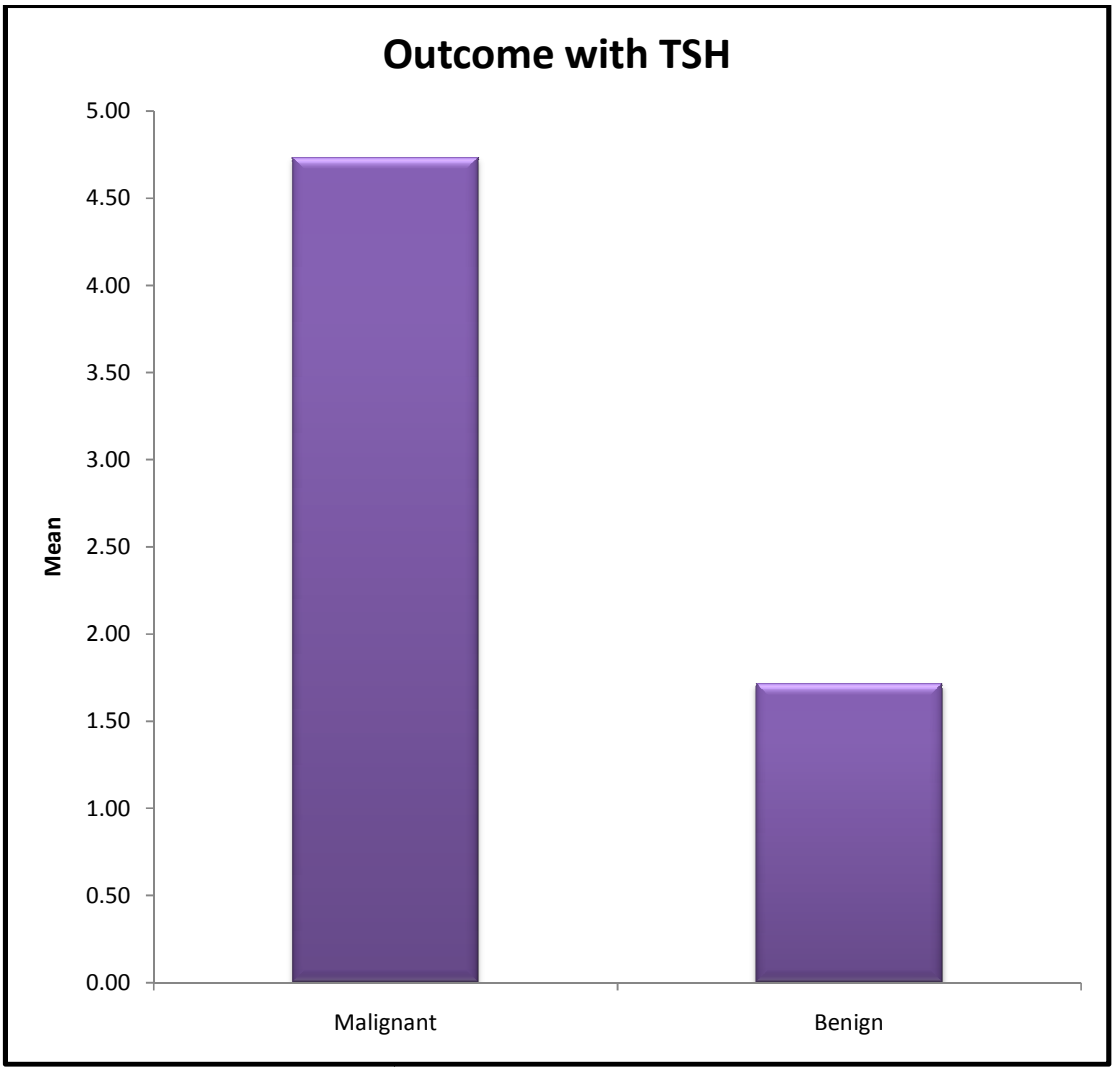
Mean thyroglobulin levels were found to be 24.77 in malignant group

Mean thyroglobulin level of 122.92 is found in benign group

Comparison of Outcome with TSH by Unpaired t-test

Outcome		N	Mean	S.D	t-value	P-value
TSH (µIU/ml)	Malignant	7	4.73	0.90	9.928	0.0005 **
	Benign	42	1.72	0.67		

** Highly Significant at P < 0.01 level



TSH level were found to be with mean value of 4.73 in malignant lesion group

TSH level of benign group were with mean value of 1.72

Thus higher mean value of TSH is found in malignant group

DISCUSSION:

It is of utmost importance to determine which patients with solitary thyroid nodule would benefit from surgery. History., Details regarding the nodule, such as time of onset ,change in size, and associated symptoms such as pain, dysphagia , dyspnea, or choking, should be elicited. Pain is an unusual symptom and, when present, should raise suspicion for intrathyroidal hemorrhage in a benign nodule, thyroiditis, or malignancy.

Patients with MTC may complain of a dull, aching sensation. A history of hoarseness is worrisome, as it may be secondary to malignant involvement of the RLNs. Most importantly, patients should be questioned regarding risk factors for malignancy, such as exposure to ionizing radiation and family history of thyroid and other malignancies associated with thyroid cancer.

Usually clinical and radiological parameters were used in predicting malignancy in thyroid nodules,adding biochemical parameters to these might increase the power of prediction. Baseline charcters like age , sex found not to have correlation with malignancy

THYROID STIMULATING HORMONE

TSH is a major thyroid cell growth factor, while TSH signaling pathway activation may be required for the expression of other growth factors, receptors, and proto-oncogenes[62–64]. Accordingly, TSH suppression is an important therapeutic tool of clinical thyroid cancer management[65,67]. In the last years, several studies have addressed the role of TSH as a predictor of thyroid nodule malignancy but the results are still open to discussion. Here, we have demonstrated that patients with

higher TSH levels have increased risk for malignancy. Remarkable, as TSH quartiles increased, the likelihood of malignancy rose

TSH measurement should be part of the initial workup in every patient with a thyroid nodule and be used as a guide for further management A normal or high TSH level should raise concerns for possible malignant potential of a nodule, whereas a low TSH is an indicator of benignity in most cases.

Therefore, the next step in the evaluation of a patient with a low TSH would be an iodine-123 (123-I) or pertechnetate scintigraphy scan, to explore the possibility of an autonomously functioning nodule. Hyperfunctioning thyroid nodules are almost always benign and generally do not require further cytologic investigation, but a nonfunctioning or "cold" nodule in a patient with low TSH may indicate malignant potential.

Recent studies have investigated the relationship between serum TSH concentration and thyroid cancer. TSH was found to be an independent predictor of malignancy in thyroid nodules. The risk of malignancy rises in parallel with serum TSH, even within the normal range, and higher TSH levels were found to be associated with advanced-stage thyroid cancer.[2]

Mean TSH level were found to be 4.73 in malignant lesion group whereas mean TSH level of benign group was 1.72.Uunpaired sample t-test is used .In the above statistical tool the probability value .05 is considered as significant **.**p value is found to be <.0005 which is statistically significant and proves higher values of TSH is associated with malignancy. Higher the values of TSH greater the risk of malignancy.

Despite the consistent association between higher TSH levels and malignant nodules shown in most series, including this one, an optimal TSH cutoff value for predicting the risk of cancer has not been yet identified. Indeed, the lack of previous studies validating nomograms or equations intended to determine an optimal TSH cutoff value has limited the use of serum TSH levels as a malignancy predictor. Future studies with larger sample size and setting a cutoff point for predicting malignancy may provider a stronger value in using TSH as a malignancy predictor.

THYROGLOBULIN

Thyroglobulin level was found to be with mean 24.77 in malignant group &

Mean level of 122.92 is found in benign group. Thus thyroglobulin was higher in benign rather than malignant group .Thus in general thyroglobulin is of no value in predictor of malignancy in solitary thyroid nodule. In malignant group follicular carcinoma found to have higher level . future studies with larger population of follicular carcinoma could throw us light about association of follicular carcinoma and thyroglobulin.

Usually Thyroglobulin level falls to less than 2 post thyroidectomy. Any raise in thyroglobulin level is either due to recurrence of the disease or remanant of the disease.follow of patients with thyroglobulin was not studied. Future study with followup of thyroglobulin level with preop level will serve as establishing thyroglobulin as follow up marker of the disease

Serum Tg levels can be elevated in most proliferative thyroid diseases and are known to be an insensitive and nonspecific test for thyroid cancer. Routine measurement of serum Tg levels for initial evaluation of thyroid nodules is not recommended . Sands et al. reported that a combination of indeterminate cytology and preoperative Tg $\geq$ 75 ng/mL increased diagnostic efficacy compared to indeterminate cytology alone and suggested that elevated preoperative Tg levels may be predictive of well-differentiated thyroid However, Suh et al. concluded that Tg has poor accuracy for predicting malignancy in follicular or Hurthle cell neoplasms.

CONCLUSION

From this study we have observed that higher serum TSH levels are associated with an increased risk of thyroid cancer in patients with thyroid nodules. The use of TSH as an adjunctive diagnostic test for stratifying the risk of malignancy associated with thyroid nodules have value to decision-making on diagnostic approaches.

Thyroglobulin does not found to have any correlation with malignancy . But once proven malignant, thyroglobulin can be used as prognostic marker in follow up of cases, finding remanant thyroid tissue post thyroidectomy and relapse of the disease.

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PROFORMA

Name: Age/sex:

Address: IPNO:

Date of admission :

Date of surgery :

Date of discharge :

Presenting History
Duration and side of swelling

Past and personal history

Co-morbid illness :
a.Diabetes mellitus
b.Hypertension
c.past h/o malignancy

Past surgical / drug history
Prior Therapy
1.Chemotheraphy
2.Radiotheraphy

General examination :

Height (cm): Weight(kg): BMI: Pulse:
BP:

Local examination :
Swelling (size, site, consistency)
Lymphnodes (location, number & fixity)

Investigations:

- Hb
- Tc
- Dc-P/L/M
- RBS
- USG neck

- Thyroglobulin
- Free T3 ,T4 , TSH
- FNAC
- HISTOPATHOLOGY OF SPECIMEN

Course and Events in Hospital :

Surgery performed
Number of Lymph Nodes Removed

MASTER CHART

S.NO	AGE	SEX	IP.NO	TG(ng/ml)	TSH (µIU/ml)	MALIGNANCY (Y/N)
1	45	F	38672	200	1.8	BENIGN
2	50	F	31567	45.2	2	BENIGN
3	68	F	32717	52.3	2.6	BENIGN
4	63	F	33678	210.2	0.8	BENIGN
5	56	F	32190	27.8	4.2	MALIGNANT
6	48	F	34125	118	1.8	BENIGN
7	42	F	35102	221.3	1.9	BENIGN
8	38	F	39684	88	1.3	BENIGN
9	41	F	36172	117	2.6	BENIGN
10	39	F	36154	225.6	2.2	BENIGN
11	52	F	32401	93.1	1.8	BENIGN
12	25	F	40123	68.7	1.9	BENIGN
13	51	F	41132	55.2	1.6	BENIGN
14	62	F	42108	21.1	5.4	MALIGNANT
15	39	F	42246	111.2	1.9	BENIGN
16	45	F	44192	90.5	2.3	BENIGN
17	50	F	41534	62.1	1.1	BENIGN
18	56	F	49001	208.3	3.8	MALIGNANT
19	44	F	48923	74.5	2.2	BENIGN
20	28	F	48942	82.1	1.4	BENIGN
21	41	F	47236	111.8	1.8	BENIGN
22	38	F	43622	67	0.9	BENIGN
23	47	F	47634	47.2	1.1	BENIGN
24	55	F	46102	51.2	1.4	BENIGN
25	52	F	47111	211	2.2	BENIGN

26	60	F	48241	32.8	2.2	BENIGN
27	48	M	42356	22.3	5.6	MALIGNANT
28	51	F	41906	56.1	0.8	BENIGN
29	49	F	41164	44.7	0.7	BENIGN
30	33	F	41277	79	2.7	BENIGN
31	54	F	41244	38.1	1.3	BENIGN
32	43	F	44241	67.5	1.6	BENIGN
33	44	F	46277	15.8	5.2	MALIGNANT
34	41	F	41090	63.2	1.1	BENIGN
35	45	F	44523	211	2.6	BENIGN
36	48	F	42644	307	1.2	BENIGN
37	58	F	41133	108.5	2.3	BENIGN
38	53	F	41876	242.5	2.2	BENIGN
39	57	F	46420	251	2.1	BENIGN
40	42	F	44372	23.4	4.8	MALIGNANT
41	47	F	43476	93.2	2.2	BENIGN
42	36	F	44223	207.5	0.7	BENIGN
43	38	F	45378	76.7	0.9	BENIGN
44	57	F	47093	108.9	1.2	BENIGN
45	56	F	43704	114.6	0.9	BENIGN
46	53	F	39887	190	2.2	BENIGN
47	50	F	45899	116.1	1.1	BENIGN
48	39	F	44690	38.2	3.2	MALIGNANT
49	35	F	47512	265.5	1.4	BENIGN

சுயஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு: சீரம் தைரொக்ளோபுலின் மற்றும் தைராய்டு தூண்டுதல் ஹார்மோன் புற்றுநோயுடன் தொடர்பு

இடம்: பொது **அறுவை சிகிச்சை துறை**

அரசு கீழ்பாக்கம் மருத்துவ கல்லூரி மருத்துவமனை

சென்னை

பங்குபெறுபவரின் பெயர் :

பங்குபெறுபவரின் வயது : **பங்குபெறுபவரின் எண் :**

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. நான் இவ்வாய்வில் தன்னிச்சையாக பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த சட்டசிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகிக்கொள்ளல்லாம் என்றும் அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும்போதும் இந்த ஆய்வில்பங்கு பெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக்கொள்ள மறுக்க மாட்டேன்.

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் ஆய்வாளரின் கையொப்பம்

இடம் :

தேதி :

PATIENT CONSENT FORM

Study detail : **"A CROSS SECTIONAL STUDY ON PREDICTORS OF MALIGNANCY IN SOLITARY THYROID NODULE-at a Tertiary Care Hospital in Chennai."**

Study centre : KILPAUK MEDICAL COLLEGE, CHENNAI
Patients Name :
Patients Age :
Identification Number :

Patient may check (✓) these boxes

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

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, 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 this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well-being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ☐

Signature/thumb impression:

Patients Name and Address: place date

Signature of investigator :

Study investigator's Name : place date