Dissertation

"A STUDY OF MALIGNANT THYROID TUMOURS PRESENTING AS SOLITARY NODULE IN TERTIARY REFERRAL CENTRE"

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CERTIFICATE

This is to certify that, the dissertation entitled **"A STUDY OF MALIGNANT THYROID TUMOURS PRESENTING AS SOLITARY NODULE IN TERTIARY REFERRAL CENTRE"**

Is the bonafide work done by **DR. VENKATACHALAM.V** , during his **M.S. (General Surgery)**course**2016-2019**, done under my supervision and is submitted in partial fulfilment of the requirement for the M.S.(BRANCH-I)- General Surgery of The Tamilnadu Dr.MGR Medical University, May 2019 examination.

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DECLARATION

I, certainly declare that this dissertation titled **"A STUDY OF MALIGNANT THYROID TUMOURS PRESENTING AS SOLITARY NODULE IN TERTIARY REFERRAL CENTRE"** represents a genuine work of mine. The contributions 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, either in India or abroad. This is submitted to The TamilNadu Dr. M.G.R Medical University, Chennai in partial fulfilment of the rules and regulations for the award of Master of Surgery Degree Branch I (General Surgery).

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(POST GRADUATE)

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As I walk down the memory lane I realize with a deep sense of humility that what I have done now would not have materialized, but for certain luminaries, who have enlightened my path to wisdom.

"*Surgery is learnt by apprenticeship and not from textbooks, not even from one profusely illustrated" – Ian Aird.*

While I put these words together, it is my special privilege and great pleasure to record my deep sense of gratitude and indebtness to my revered Professor and Guide **Prof. USHA DORAIRAJAN M.S., FRCS(Ed)** but for whose constant guidance, help and encouragement this research work would not have made possible. The unflinching academic, moral and psychological support will remain ever fresh in my memory for years to come. Words cannot simply express my gratitude to her for imparting to me the surgical skills I have acquired.

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LIST OF ABBREVATIONS

AG Adenomatous goiter
ATC Anaplastic thyroid carcinoma
ECG Electrocardiogram
FNAC Fine needle aspiration cytology
HPE Histopathological examination
MIT Monoiodotyrosine
MNG Multinodular goiter
MTC Medullary thyroid carcinoma
RLN Recurrent laryngeal nerve
SNT Solitary nodule thyroid
T3 Tri-iodotyrosine
T4 Thyroxine
TBG Thyroxine binding globulin
TR Thyroid hormone receptor
USG Ultrasonography
NIFTP Non Invasive Follicular Neoplasm Of Thyroid With Papillary Like Features

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INTRODUCTION

The solitary thyroid nodule has aroused interest of thyroidologist since the time of **Warren H Cole** (1949). Thyroid nodules are very common entities, though varying in incidence in different geographical regions. The prevalence of palpable nodules in general population is 4-7%.

A single nodule in the thyroid is a definite clinical entity with important pathological significance. It is necessary to consider the status of opposite lobe when considering the '**solitariness**' of a nodule. Many pre operative solitary nodules turn out to be multi-nodular during radiological and intra-operative evaluation.

In general a solitary nodule is defined as "a palpable single clinically detected nodule in the thyroid gland that is otherwise normal." Visibility or palpability of opposite thyroid lobe precludes the definition of solitary nodule thyroid.

The usual presentation of a thyroid nodule is an asymptomatic mass that is discovered by either the patient or the clinician. Nodules of at least 0.5cm to 1cm can be usually be detected by palpation. It can be difficult to palpate any nodule in patient with a thick, short neck.

Solitary nodules of thyroid are about **four times** more common in women than in men. Overall incidence of malignancy in solitary thyroid nodule ranges from 10-30%. At present no single investigation will tell the thyroid malignancy with 100% accuracy. Current studies show that the occurrence of thyroid carcinoma is increasing over the years. To differentiate benign thyroid nodule from malignant is very important to **avoid unnecessary extensive surgery and surgery related complications**, such as hypothyroidism, hypocalcaemia, and recurrent laryngeal nerve injury.

The optimal management of thyroid nodule continues to be a source of controversy and the operative intervention recommended by most of surgeons is not always considered divine by some physicians who are advocating either observation or suppression.

Because of possibility of malignancy, some clinicians especially those in surgical subspecialties recommend that all nodules have to be removed. On the other hand endocrinologist recommends Ultrasonogram (USG) and Fine needle Aspiration Cytology (FNAC) performed as initial step of evaluation in order to avoid unnecessary surgery.

AIMS AND OBJECTIVES

1. The purpose of this study is to assess the role of clinical evaluation and investigations in diagnosing malignant thyroid tumours presenting as solitary thyroid nodule.

2. To correlate the pre operative tissue diagnosis of follicular neoplasms in Solitary nodule with intra-operative frozen section and post-operative HPE reports.

3. To identify the type of malignancy arising from Solitary nodule and calculate the incidence of patients requiring completion thyroidectomy.

REVIEW OF LITERATURE

Thyroid nodules are a common entity and their clinical significance has been a point of discussion since **19th century**. Palpable thyroid nodules are encountered in about 8% of the adult population. With the use of imaging techniques, particularly ultrasound, the chance of detection of thyroid nodules has increased many folds. The prevalence of palpable thyroid nodule in South India is about 12.2%. However, the reported incidence of thyroid cancer in general population is low, being only about 1%.

Thyroid cancers occur in approximately 5% of all thyroid nodules independent of their size. The recent data suggest that the incidence of thyroid malignancy is increasing over the years. The occurrence of malignancy is more in solitary thyroid nodules (SNT) compared to multinodular goiter.

The preoperative evaluation of thyroid nodules to distinguish between benign and malignant nodules is very important. It helps to avoid unnecessary extensive surgery and potential surgery related adverse effects, such as hypothyroidism, hypocalcemia, and recurrent laryngeal nerve injury.

The aim of the present study was to evaluate patients with clinically detected SNT for the presence of malignancy, in relation to various factors like age, gender, and ultrasonography (USG) findings like size of the nodule, echogenicity, micro calcification, and presence of lymphadenopathy.

Historical review

Goiters (from the Latin guttur, throat), defined as an enlargement of the thyroid, have been recognized since 2700 B.C. The term thyroid gland (Greek thyreoeides, shield-shaped) is, however, attributed to ***Thomas Wharton***. In 1776, the thyroid was classified as a ductless gland by ***Albrechtvon Haller*** and was thought to have numerous functions ranging from lubrication of the larynx to acting as a reservoir for blood to provide continuous flow to the brain, to beautifying women's necks. Burnt seaweed was considered to be the most effective treatment for goiters.

The first accounts of thyroid surgery for the treatment of goiters were given by ***Roger Frugardi*** in 1170. In response to failure of medical treatment, two setons were inserted at right angles into the goiter and tightened twice daily until the goiter separated. The open wound was treated with caustic powder and left to heal. However, thyroid surgery continued to be hazardous with prohibitive mortality rates (>40%) until the latter half of the nineteenth century, when advances in general anesthesia, antisepsis, and hemostasis enabled surgeons to perform thyroid surgery with significantly reduced mortality and morbidity rates. The most notable thyroid surgeons were ***Emil Theodor Kocher*** (1841– 1917) and ***C.A. Theodor Billroth*** (1829–1894), who performed thousands of operations with increasingly successful results.

However, as more patients survived thyroid operations, new problems and issues became apparent. After total thyroidectomy, patients (particularly children) became myxedematous with cretinous features. Myxedema was first effectively treated in 1891 by ***George Murray*** using a subcutaneous injection of an extract of sheep's thyroid and later, ***Edward Fox*** demonstrated that oral therapy was equally effective. In 1909, Kocher was awarded the Nobel Prize for medicine in recognition "for his works on the physiology, pathology, and surgery of the thyroid gland."[1-2]

EMBRYOLOGY AND ITS SIGNIFICANCE

The thyroid gland appears by the end of the third week as an epithelial thickening of the floor of the pharynx at the level of the first pharyngeal pouch. This, the large median thyroid anlage, may be a diverticulum or a solid bud. Cranial growth of the tongue, together with elongation of the embryo, carries the origin of the thyroid gland far cranial to the gland itself. The site of this origin is the foramen cecum of the adult tongue. In some individuals it is not grossly visible.

The thyroid gland remains connected with the foramen cecum by a minute, solid thyroglossal duct that passes through, or anterior to, the hyoid bone. By the fifth week of gestation, this duct usually becomes fragmented; persistence of any portion is not unusual. In about 50 percent of the population, the duct can be traced distally to the pyramidal lobe of the thyroid gland.

Follicles appear during the second month of gestation and increase through the fourth month. Colloid formation and uptake of iodine begins at about eleventh week. Epithelial structures, the paired lateral anlages, are formed from the ventral portions of the fourth and fifth branchial pouches. This structure, the well-known **ultimobranchial body** (caudal pharyngeal pouch complex), becomes lost in the developing thyroid gland, and its cells become dispersed as the C (calcitonin) cells among the thyroid follicles.

Present evidence suggests that the primary origin of the calcitonin-producing cells of the thyroid gland is the neural crest of the embryo. From the neural crest these cells migrate to the ultimobranchial body, and later become part of the thyroid gland. C cells belong to a group of **neural-crest derivatives known as APUD** (amine precursor uptake and decarboxylation) cells. [3]

ANATOMY

The thyroid gland consists typically of two lobes, a connecting isthmus, and an ascending pyramidal lobe. One lobe, usually the right, may be smaller than the other (7 percent) or may even be completely absent (1.7 percent). The isthmus is absent in about 10 percent of thyroid glands, and the pyramidal lobe is absent in about 50 percent. A minute epithelial tube or fibrous cord, the **thyroglossal duct**, almost always extends between the thyroid gland and the foramen cecum of the tongue. The thyroid gland normally extends

from the level of the 5th cervical vertebra to the body of the 1st thoracic vertebra. It may lie higher (lingual thyroid), but rarely lower.

The normal thyroid gland weighs about 30 g in the adult somewhat more in females than in males. Each lobe is approximately 5 cm in length, 3 cm at its greatest width, and 2-3 cm thick. The isthmus connecting the two lobes is about 1.3 cm in breadth. The lobes have a broad lower portion and a relatively conical apex.

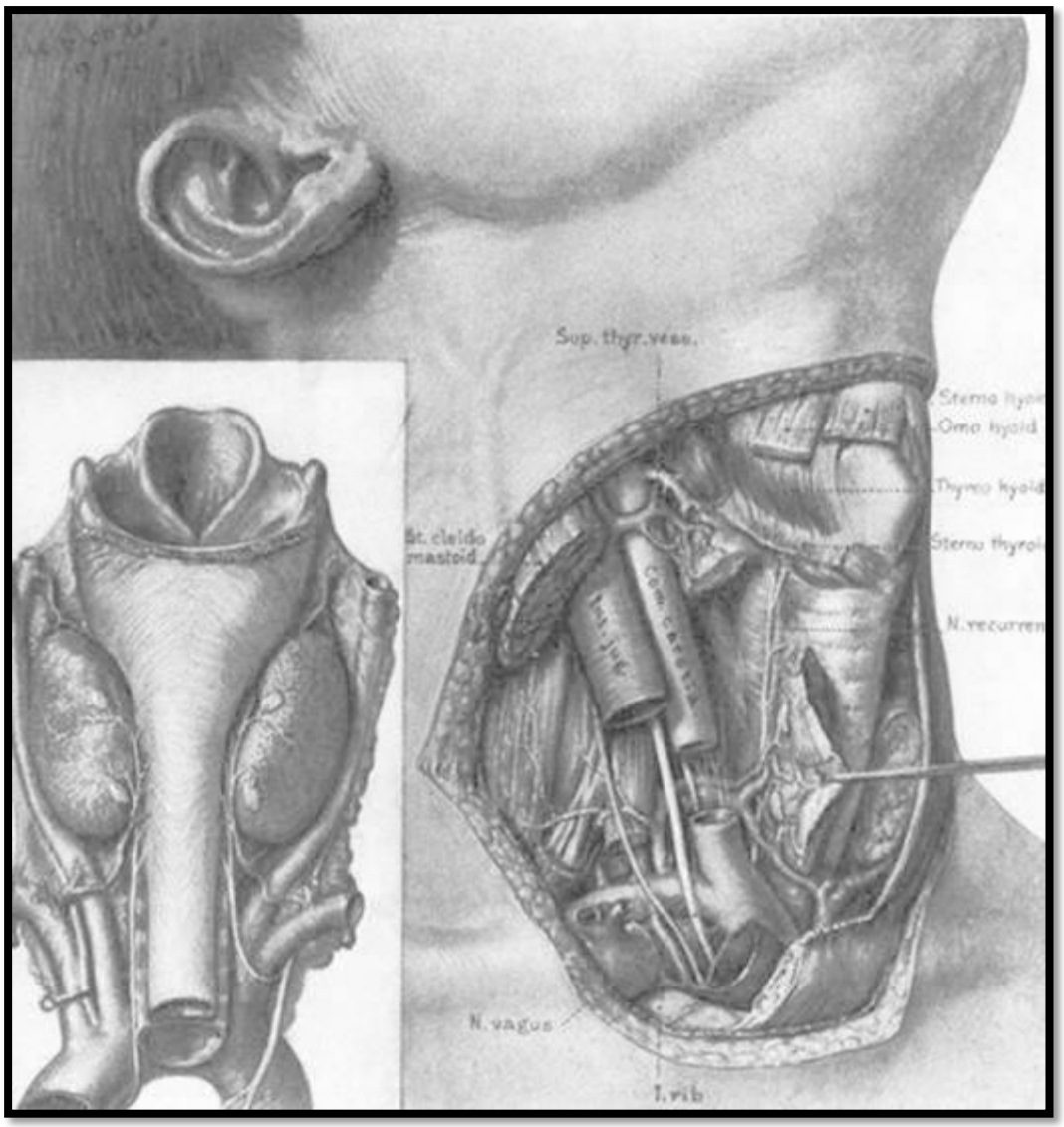


Fig 1 Anatomy of neck in the region of thyroid gland

Capsule of the Thyroid Gland

The thyroid gland has a connective tissue capsule which is continuous with the septa, and which makes up the **stroma** of the organ. This is the true capsule of the thyroid. External to the true capsule is a well developed (to a lesser or greater degree) layer of fascia derived from the pretracheal fascia. This is the false capsule, also called the **perithyroidal sheath or surgical capsule**. Anteriorly and laterally this fascia is well developed; posteriorly it is thin and loose, permitting enlargement of the thyroid gland posteriorly. There is a thickening of the fascia that fixes the back of each lobe to the cricoid cartilage. Such thickenings are the ligaments of Berry. The false capsule, or fascia, is **not removed** with the gland during thyroidectomy.[4]

Amongst the parathyroid glands**, inferior is more constant than the superior.** The superior parathyroid glands normally lie between the true capsule of the thyroid and the fascial false capsule. The inferior parathyroids may be between the true and false capsules, within the thyroid parenchyma, or lying on the outer surface of the fascia. The levator muscle of the thyroid is one or more muscular slips that occasionally connect the hyoid bone with the thyroid gland. These vestigial muscles are inconstant in occurrence, location, and innervation. They have been divided into anterior, lateral, and posterior levators.

VASCULAR SUPPLY

The thyroid gland competes with the adrenal glands for having the greatest blood supply per gram of tissue. One consequence is that haemostasis is a major problem of thyroid surgery, especially in patients with toxic goitre. Two paired arteries, the superior

and inferior thyroid arteries, and an inconstant midline vessel, **THE THYROID IMA ARTERY** supply the thyroid .

Superior Thyroid Artery

The superior thyroid artery arises from the external carotid artery just above, at, or just below the bifurcation of the common carotid artery. It passes downward and anteriorly to reach the superior pole of the thyroid gland. In part of its course, the artery parallels the **external branch of the superior laryngeal nerve** which supplies the cricothyroid muscle and the cricopharyngeus muscle, the lowest voluntary part of the pharyngeal musculature.

There are **six *branches of the superior thyroid artery*** - the infrahyoid, sternocleidomastoid, superior laryngeal, cricothyroid, inferior pharyngeal constrictor, and terminal branches of the artery for the blood supply of the thyroid and parathyroid glands.[5]

Usually there are two branches to the thyroid —the anterior and posterior— but occasionally there may be a third, the so-called **lateral branch.**

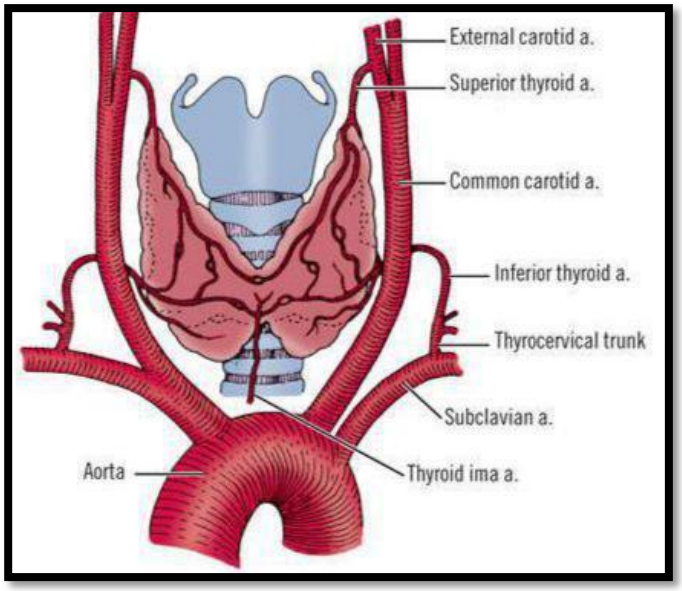


Fig 2. Arterial supply of thyroid gland

At the superior pole, the superior thyroid artery divides into anterior and posterior branches. The anterior branch anastamoses with the contralateral artery; the posterior branch anastamoses with branches of the inferior thyroid artery. From the posterior branch, a small parathyroid artery passes to the superior parathyroid gland. [6]

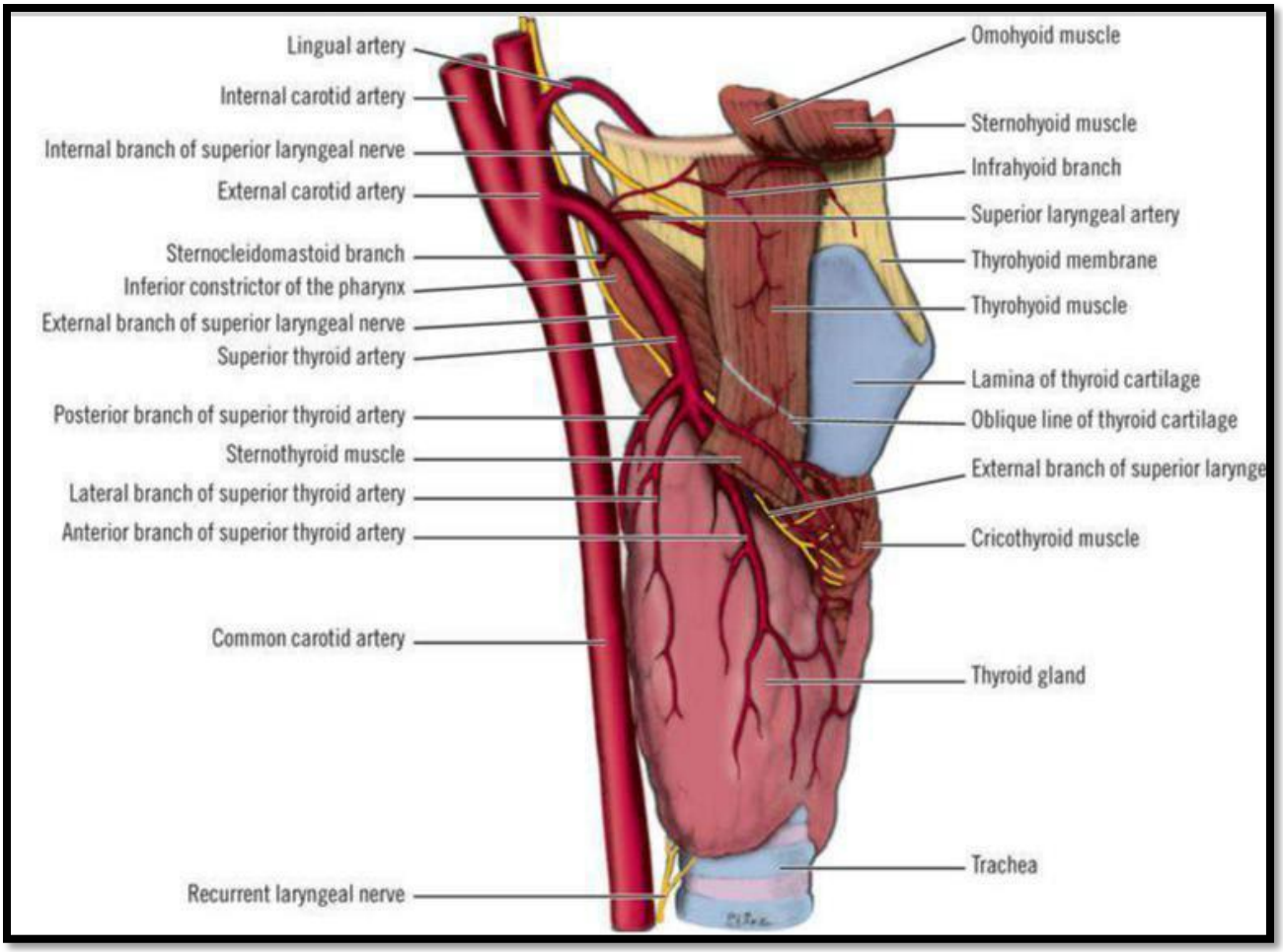


Fig 3 : Branches of superior thyroid artery

Inferior Thyroid Artery

The inferior thyroid artery usually arises from the thyrocervical trunk, but in about 15 percent of individuals it arises directly from the subclavian artery. The inferior thyroid

artery ascends behind the carotid artery and the internal jugular vein, passing medially and posteriorly on the anterior surface of the longus coli muscle. After piercing the prevertebral fascia, 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. The lowest branch sends a twig to the inferior parathyroid gland and supplies the lower pole of the thyroid gland. The upper branch supplies the posterior surface of the gland, usually anastamosing with a descending branch of the superior thyroid artery. On the right, the inferior thyroid artery is absent in about 2 percent of individuals. On the left, it is absent in about 5 percent. The artery is occasionally double.[7]

Thyroid Ima Artery

The thyroid ima 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, according to Montgomery. It may be as large as an inferior thyroid artery or it may be a mere twig. **Its position anterior to the trachea makes it important in tracheostomy.**

Veins

Veins of the thyroid 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.

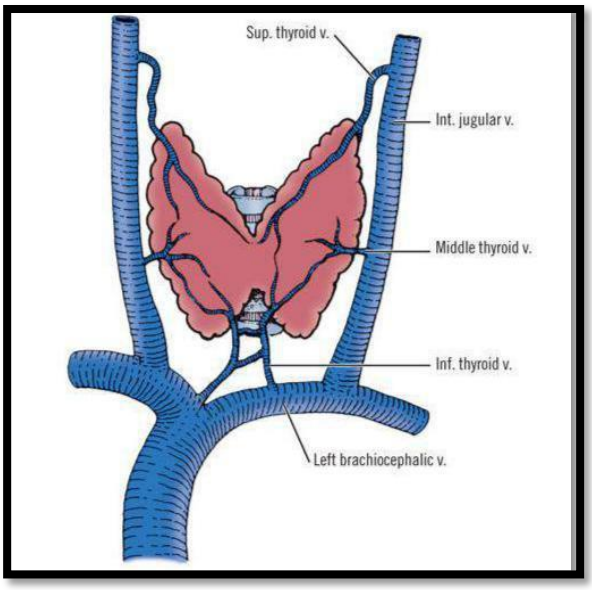


Fig 4. Venous drainage of thyroid gland

Superior Thyroid Vein

The superior thyroid vein accompanies the superior thyroid artery. Emerging from the superior pole of the thyroid, the vein passes superiorly and laterally across the omohyoid muscle and the common carotid artery to enter the **internal jugular vein** alone or with the common facial vein.

Middle Thyroid Vein

The middle thyroid vein arises on the lateral surface of the gland at about two-thirds of its anteroposterior extent. No artery accompanies it. It crosses the common carotid artery to open into the internal jugular vein. This vein may be absent or, occasionally, double. The extra vein is inferior to the normal one; it has been called the ***"fourth" thyroid vein.*** The importance of these middle thyroid veins is in their vulnerability during thyroidectomy.[8]

Inferior Thyroid Vein

The inferior thyroid vein is the **largest and most variable** of the thyroid veins; the right and left sides are usually asymmetric. The right vein leaves the lower border of the thyroid gland, passes anterior to the brachiocephalic artery, and enters the right brachiocephalic vein. The left vein crosses the trachea to enter the left brachiocephalic vein. Rarely, the right vein crosses the trachea to enter the left brachiocephalic vein, sometimes forming a common trunk with the left vein. ***This common trunk is called the thyroid ima vein.*** [9]

LYMPHATICS

Several broad patterns of lymphatic drainage of the thyroid gland have been proposed. Each conceptualization is based on the same facts; each is correct. We will follow that of ***Hollinshead***. Patterns of Drainage:-

Median Superior Drainage

Three to six vessels arise from the superior margin of the isthmus and from the medial margins of the lateral lobes. These vessels pass upward in front of the larynx to end in the digastric lymph nodes. Some vessels may enter 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 by a vessel passing from the Delphian nodes downward over the front of the thyroid. It has been suggested that there is a connection between the lymphatic drainage of the superior thyroid artery and the orbit by

way of the jugular chain of cervical lymph nodes. In neither the orbit nor the eye itself can lymphatic vessels be demonstrated.

Median Inferior Drainage

Several lymph vessels drain the lower part of the isthmus and the lower medial portions of the lateral lobes. They follow the inferior thyroid veins to end in the pretracheal and brachiocephalic nodes.[10]

Right and Left Lateral Drainage

Lymphatic trunks arise from the lateral border of each lobe. Superiorly they pass upward with the superior thyroid artery and vein. Inferiorly they follow the inferior thyroid artery.. Between these two groups, some vessels pass laterally, anteriorly, or posteriorly to the carotid sheath to reach the lymph nodes of the internal jugular chain. Occasionally,such vessels drain into the right subclavian vein, jugular vein, or thoracic duct without passing through a lymph node.

Posterior Drainage

Posterior lymphatic vessels arise from the inferomedial surfaces of the lateral lobes to drain into nodes along the recurrent laryngeal nerve. Occasionally, a posterior ascending trunk from the upper part of the lobe reaches the retropharyngeal nodes.[11]

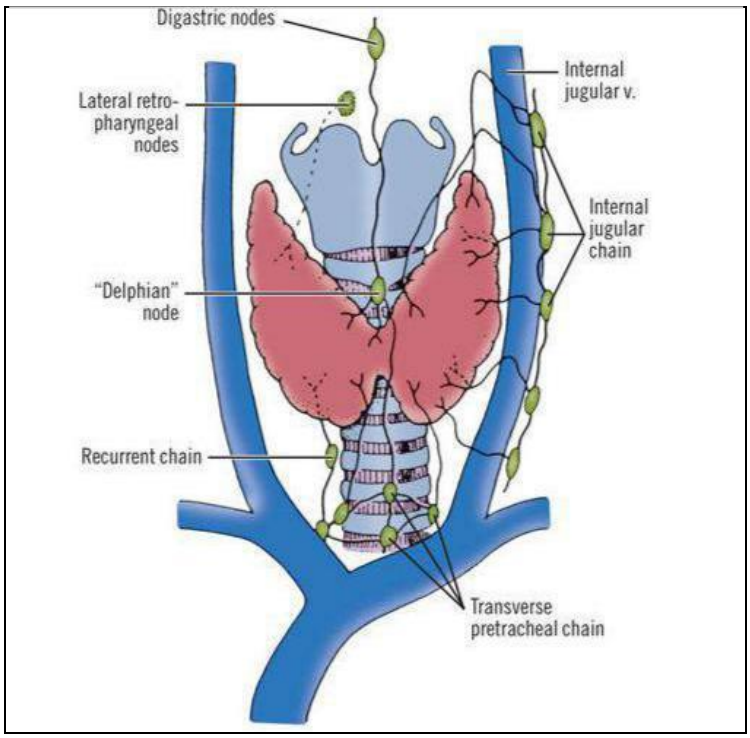


Fig 5.Lymphatic drainage of the thyroid gland

Metastatic Spread

A representation of lymph node regions of importance for management of thyroid carcinoma and Lymph node groups at the highest risk for regional metastasis from differentiated thyroid carcinoma are shown below.

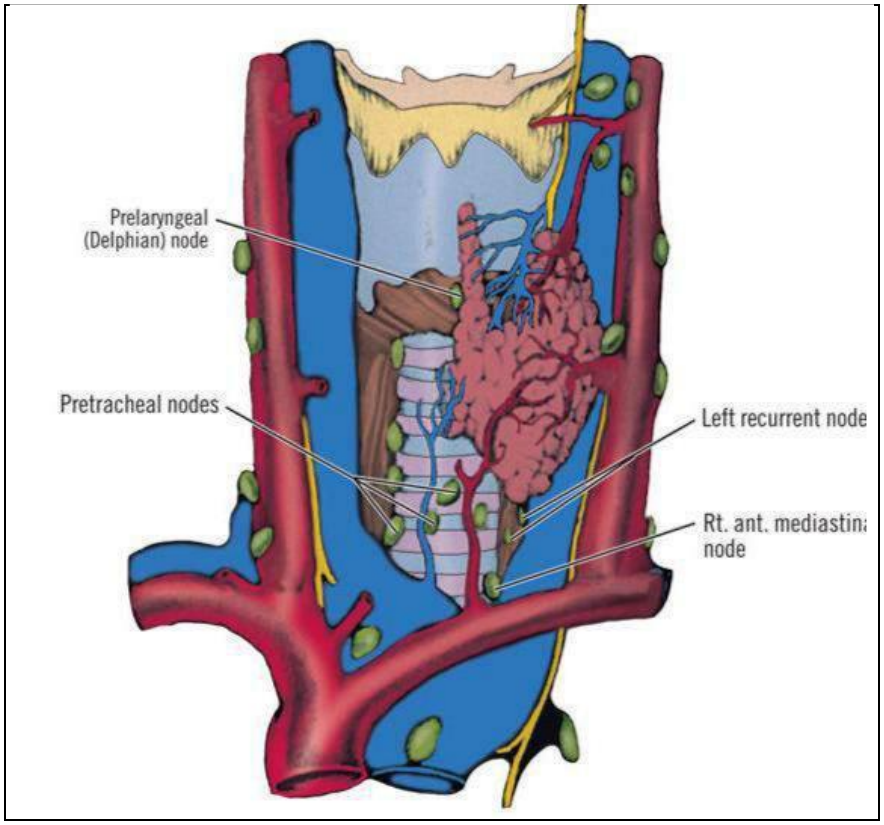


Fig 6. LN regions of importance for thyroid carcinoma

HISTOLOGY

The thyroid gland is surrounded by the thyroid capsule, which is a thin layer of connective tissue. From the capsule, several septa extend within the thyroid parenchyma,which is subdivided into several lobules. Epithelial cells (cuboidal or squamous) form the thyroid follicles; they are separated by thin connective stroma which is rich in both lymphatic and blood vessels. Small bundles of nerves are present. There is a colloidal gelatinous collection in the centre of the follicle. **Each follicle has two types of cells: follicular and parafollicular, or C cells.**

According to **Ross and Reith**, the follicular cells are responsible for the following actions: synthesis of thyroglobulin, iodination, storage of thyroglobulin, resorption of

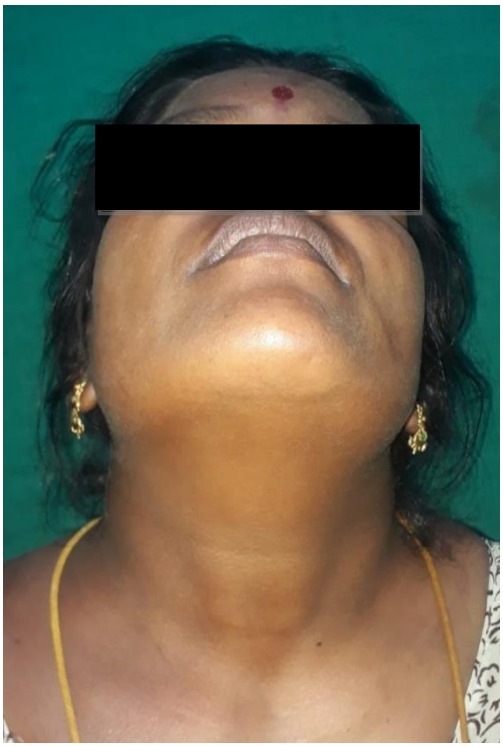
thyroglobulin, hydrolysis of thyroglobulin, and release of thyroid hormone into the blood and lymphatics.

The parafollicular, or C cells, can be found in the connective stroma between the follicles or in the follicular epithelium. Characteristically, they contain several secretory granules.[16]

SOLITARY NODULE OF THYROID

Thyroid nodule refers to a distinct lesion within the thyroid gland that is palpably or radiologically distinct from the surrounding thyroid parenchyma. Benign causes of thyroid nodule include the colloid nodule and the classical multinodular goiter. Occasionally, nodularity is noticed in patients with Hashimoto's thyroiditis and graves' disease. Malignant causes of nodules include thyroid cancer, lymphoma as well as metastasis to the thyroid gland. Therefore, it is recommended that all **thyroid nodules >1 cm** in size should undergo evaluation. This includes both palpable and nonpalpable nodules, detected by imaging.

"**Solitary thyroid nodules**" are defined clinically as a localized thyroid enlargement with an apparently normal adjacent gland. According to literature, STN has a higher risk of malignancy than multiple nodules. Because of this reason, surgeons tend to treat them with high degree of suspicion and plan treatment in a systematic manner. Clinically, STNs are common, being present in up to 50% of the elderly population. The majority of STNs are malignant.Preliminary investigation should include careful history and thorough clinical examination and thyroid function tests.



EPIDEMIOLOGY AND INCIDENCE

Disorder of thyroid including the ‘Solitary nodule’ occur worldwide, palpable thyroid nodule in Euthyroid individual is common in clinical practice occurring up to 4% of general population, their incidence increase with age. Autopsy finding disclose even a higher incidence, most series reports an incidence of 5-10. However, clinical interest in the nodule is disproportionate to actual biological significance since majority will be related to multinodular goiter.

In contrast, however, a true solitary thyroid nodule, accounting for up to approximately 25% of clinically detectable solitary thyroid nodule is important both clinically and pathologically since although most of the case turn out be benign, 10-30% will harbour malignant neoplasm. The incidence of malignancy in solitary nodule who undergo surgery is **increasing chiefly due to improved selection of patients for surgery.**

SEX INCIDENCE:

Thyroid disorders are preponderantly **confined to females** in the ratio of 6:1 and this is due to variations of thyroid hormone demand during female reproductive function, physiological events such as puberty, pregnancy, lactation. Incidence of solitary nodule is also higher in females. But incidence of Malignancy in solitary nodule is **more in men (26%) compared to female (9%)**

AGE INCIDENCE:

Thyroid nodules occur at all ages, the reported age range from 15-69 years with maximum incidence in **30-40 years**. Solitary nodule is rare in children; the incidence of carcinoma in such a nodule under 25 years of age is about 50% and 75% in patient under 15years.[33]

INCIDENCE OF MALIGNANCY IN SOLITARY NODULE OF THYROID:

Though commonest cause of solitary nodule is not carcinoma, a significant proportion is carcinomatous. In general between 10-20% of solitary nodule removed surgically is malignant. Solitary nodule found in thyroid of patient less than 20 years and greater than 60 years carries far greater risk of being malignant. Solitary nodule of thyroid can arise from diverse causes. The common causes of solitary thyroid nodules are **adenomatous goiter, neoplasm and chronic thyroiditis.**

The aetiology of the nodule depends upon the population under study, sex , age of patient and prior history of exposure to ionizing radiation. In practice, a clinical diagnosis of solitary thyroid nodule is, in fact, a dominant nodule of multinodular goiter is 50% of cases, as shown on subsequent investigations any **dominant nodule** within a multinodular goiter should be essentially treated as solitary thyroid nodule, as they have incidence of malignancy of around 10%.[17]

Papillary thyroid cancer (PTC) is by far the **most common** (80% to 85%) compared to 10% to 15% follicular and 3% to 5% HCC. In the different subtypes of thyroid carcinoma, prognosis mirrors incidence in that PTC, which is the most common thyroid malignancy, also carries an excellent prognosis in most patients, whereas ATC is far less common and carries a dismal prognosis[32]

AETIOLOGICAL FACTORS

AETIOLOGY OF THYROID NEOPLASMS:

A) RADIATION: The relationship between ionizing radiation and development of benign adenomas and malignant tumors is well known. Thyroid exposure to radiation can occur in two ways [18]

- External sources
- Internal source.

External exposure can be because of medically administered external beam radiation or environmental exposure previously related to nuclear weapons attack or weapons testing and more recently nuclear power plant accidents.

Internal injection of isotopes of iodine which is concentrated in the thyroid gland can come from the ingestion of the isotopes and from the fallout of nuclear weapons, explosion or power plant accidents.

The carcinogenic radiation is by 2 mechanisms

1. Cellular injury with altered cell division and replication of nucleic acids.

2. The injured cells produce less thyroid hormone leading to TSH stimulation.

Low dose radiation for Tinea capitis (6-5 cGy), thymic enlargement (100 to400 cGy), enlarged tonsils and adenoids (750Egy) Acne vulgaris (200 to 1500 cGy) are best known etiological factor. The risk increases linearly from 6.5 to 2000 cGy, beyond which the incidence decline as radiation causes destruction of thyroid tissues. The risk is maximum 20 to 30years after exposure. Approximately 30% of exposed children develop thyroid nodules and of these estimated 30% are malignant.[19]

B) INGESTION OF RADIOISOTOPES AND MALIGNANCY:

The most common exposure is due $\mathbf{I^{131}}$ administered for diagnostic thyroid scans. A typical scan exposes the thyroid to approximately 50 rads of external beam radiation. Studies have shown that is only a small increase in the of incidence of malignancies of thyroid after exposure to this dose.

A more dangerous type of ingestion of radioisotopes comes from exposure to nuclear fallout contrary to medically administered I^{131} and short lived radio - isotopes such as I^{129} and $I^{131-135}$. Vast majority of patients developing post radiation malignancy have papillary histology.[20]

C) DIET

There is an increased incidence of

- follicular cancer in **iodine deficient**/endemic goiterous areas
- papillary carcinoma in iodine rich regions.

D) SEX:

Factors such as parity, early menopause, contraceptive use and late age at first birth in female population have been reported to have increased risk of thyroid carcinoma but the data been inconsistent. The thyroid nodule is more likely to be cancerous in men than in men than in women and in young (under 20 years) and older (over 60 years) patients rather than others.

E) GENETIC PREDISPOSITION:

There is no clear familial syndrome or genetic disease associated with non-medullary thyroid carcinoma.[21] Loose associations with familial polyposis of colon including **Gardner's syndrome, Cowden's syndrome, melanomas, testicular and bladder cancer have been reported**. This contrasts with medullary thyroid carcinoma, which has a variety of genetic syndromes now being defined at molecular levels. The familial medullary carcinoma syndrome is transmitted as an **autosomal dominant** trait and thus 50% of the offspring would be expected to have this disease.

CLASSIFICATION OF ADENOMAS

Adenomas can be classified into Follicular adenoma and its variants papillary adenoma and atypical adenoma.

A) Follicular adenoma:

Almost all thyroid adenoma show follicle formation to a varying degree; follicle adenoma are usually but may contain a variable amount of colloid; It is unknown whether follicular adenomas show transition over time. The most important clinically relevant fact about follicular adenomas is that many of these tumors cannot be reliably distinguished from follicular carcinoma on clinical, isotopic, USG or FNAC only reliable method of making distinction by careful histological for evidence of capsular or angio invasion.

Macroscopically:

Degenerative changes such as cyst formation and haemorrhage are common. It has a well demarcated capsule; it goes in favour of adenoma.[22]

Microscopically:

Follicular adenomas show constant of follicles. Tumor is surrounded by fibrous capsule, that often contains wide vascular spaces. The tumour cells from large and small follicles which confine to the inner margin of the capsule. According to the size of follicles and the degree of follicle formation, follicular adenomas are further classified as

1. Colloid adenoma [macrofollicular adenoma]

2. Simple adenoma [normofollicular adenoma]

3. Fetal adenoma [microfollicular adenoma]

4. Hurthle cell adenoma [follicular adenoma of oxyphilic cell type]

5. Embryonal adenoma (trabecular adenoma)

6. Follicular adenoma of clear cell type a typical adenoma

8. Atypical follicular of clear cell type.

9. Toxic adenoma (Hyper-functioning adenoma)

B) PAPILLARY ADENOMA:

Papillary adenoma is a very rare neoplasm composed of benign papillae with fibrous stroma but without capsular invasion. This tumor is often cystic and is sometimes referred to as **papillary cystadenoma**. This tumor should not be confused with an encapsulated papillary carcinoma. About 5% of papillary carcinoma are encapsulated without gross evidence of invasion. Diagnosis of benign papillary adenoma should be made only if nuclei have slight pleomorphism and an extensive search fail to demonstrate invasion of capsule, blood vessels of adjacent parenchyma. Some pathologists consider all papillary tumors as malignant, and it may be difficult to exclude invasion, some others refer this as follicular adenoma with papillary hyperplasia structures which prompt confusion.

C) ATYPICAL ADENOMA:

These are occasionally encountered, described as ground of tumor which display unusual microscopic features such as cellular hyper-chromasia, bizarre nuclei from squammous islands and spindle cell growth pattern. This comprises about 2-3%. ***Hazard*** establised that atypical adenoma have histologic architecture of carcinoma but have a benign behavior, he emphasized the importance of invasiveness and stated that encapsulated tumour without evidence of capsular or blood vessel invasion were benign.

Gross:

These are solid and have fleshy appearence and completely defined by capsule. They lack the gelatinous or semi translucent character of usual adenoma. They are firm to hard.

Microscopy:

They are cellular with compactly arranged cells than other adenomas. *Hazard* sub-classified them as; [25]

Follicular type - clearly packed follicles.

Solid type - cells in sheets or columns

Alveolar type - Organised but solid.

Focal atypical type - In diffuse cellular mass.

MALIGNANT NEOPLASMS OF THYROID :

DUNHILL CLASSIFICATION of malignant neoplasm of thyroid:

a) *Well differentiated thyroid carcinoma*

i) Papillary carcinoma

ii) Follicular carcinoma

b) *Poorly differentiated thyroid carcinoma;*

i) Hurthle cell carcinoma.

ii) Variants of papillary carcinoma:

Tall cell variant.

Insular variant.

Columnar variant.

c) *Medullary carcinoma.*

d) Undifferentiated (Anaplastic) carcinoma

e) Others (rare)

- Lymphoma

- Squamous cell carcinoma.[26]

- Sarcoma

- Metastatic tumors.

I) PAPILLARY CARCINOMA OF THE THYROID:

Papillary CA is the **most common thyroid** CA in both children and adults with incidence of 62%. It frequently presents in 4th and 5th decades with male to female ratio of 1:3. Incidence of papillary carcinoma is common in young adults due to child hood exposure to radiation. There is convincing evidence for an increase in incidence in incidence of papillary carcinoma in Hashimoto's thyroiditis.

Multicentricity of primary tumour is the most important feature. It spreads via intraglandular lymphatic within the thyroid gland and then to the subcapsular and pericapsular lymphnodes. In one large series, the disease was localized to the thyroid gland in 67% of cases, thyroid and Lymph nodes in 13%, and lymphnode alone in 20%. Minimal or occult / microcarcinoma tumors are defined as tumours of 1cm or less in size. They are non-palpable and usually incidental finding at operative, histologic or autopsy examination. Occult papillary thyroid cancer is present in 2 to 36% of thyroid glands removed at autopsy. Papillary carcinoma is associated with **excellent prognosis** (10 years survival rate is 95%).[27]

GROSS:

Papillary CA is usually non encapsulated hard, white, sclerotic tumour with an irregular margin. Some are well encapsulated and resemble follicular adenoma. Macroscopic papillae or cyst formation may be present. On occasion, the carcinoma diffusely infiltrates the gland. At other times the carcinoma may be so small as to be discovered only incidentally in a microscope section from thyroid removed for an unrelated

lesion. Multicentricity is present in 20-60% of cases depending on exclusiveness of sampling.

MICRO:

Histologic diagnosis is made on the basis of papillary architecture or characteristic nuclear features. True papillae have fibrovascular core and are generally lined by single row of overlapping nuclei. The nuclei have been designated as ground glass nuclei, optically clear nuclei or **orphan-annie nuclei**. They are best appreciated on formalin fixed permanent sections. They are not seen on alcohol fixed fine needle aspirate smears and are occasionally and very focally seen on frozen section. Occasional sharply delineated intra nuclear cytoplasmic inclusions are seen in about half of papillary CA. They are more easily appreciated on touch imprints and fine needle aspirated smears than on formalin fixed sections.

Recently, there is increasing attention to grooved nucleus resulting from deep in folding of nuclear membrane along axis of nucleus. Like all other nuclear features, it is not 100% specific for papillary CA. **Psammoma bodies**-calcific areas that are laminated, (quite specific for papillary carcinoma)are seen in less than half of papillary CA and are rarely present in other thyroid lesions. They are believed to represent remains of dead papillae. Diagnosis of papillary CA is not based on single criteria but on **constellation of findings**, in particular, **papillary projecting** into open spaces as well as clear nuclei with **prominent nuclear groove and psammoma bodies**. It is increasingly recognized that carcinoma partially or completely composed of follicles but having nuclear features characteristics of papillary carcinoma behave biologically as papillary carcinoma. They usually have favourable prognosis and a propensity for lymph node metastasis than haematogenous

dissemination as follicular carcinoma do. These carcinoma are now diagnosed as papillary carcinoma, and those with exclusive or near-exclusive follicular component are designated follicular variants of papillary carcinoma. Majority of papillary carcinoma have some follicular component. Sub types of papillary carcinoma worthy of special mention include –

Insular variant is a poorly differentiated tumor composed of solid clusters or nests of cells often containing microfollicles and has prognosis intermediate between typical anaplastic carcinoma and differentiated carcinoma .

Encapsulated papillary carcinoma are surrounded by thick or thin fibrous capsule and comprise 4- 14% of papillary carcinoma. They have much better prognosis than those with infiltrating margins.recently these are refered to as **Non Invasive Follicular Neoplasm With Papillary Like Features (NIFTP).**

The tall cell variant of papillary carcinoma is characterized by elongated tall cells with basally oriented nuclei. These have worse prognosis than usual papillary carcinoma, with higher incidence of extra thyroidal invasion, recurrence, distant metastasis and death. The diffuse sclerosing variant of papillary carcinoma is also more aggressive. It diffusely involves one or both lobes and is associated with extensive sclerosis, numerous bodies, a focally solid pattern, and a lymphocytic infiltrate. Lymph node metastasis is present in most cases and pulmonary metastasis often occurs.

Cervical lymph node metastases are present in 37-54% of patients with papillary carcinoma. Indeed lymph node metastases are found more frequently with small tumors probably as a reflection of patient presentation, lymph node involvement may overshadow the primary especially if it is microscopic size. Lymph node involved may be totally

replaced by thyroid tissue, a circumstance which was earlier designated as replaced aberrant thyroid.[47] Nodal metastasis are more frequent in young. There is no difference in survival between patient regional nodes are uncommon and occur in 12-14% of papillary Carcinoma. Metastases are usually to lung, mediastinum and less often to bone, brain. Reported mortality varies from 2 -11 %. The most important factors associated with poor outcome are patient age over 50 yrs at diagnosis, extra thyroidal extension, tumor size greater than 1.5cm, angioinvasion, male sex and possibly DNA aneuploidy. Relative proportion of papillary and follicular components, presence of Squamous metaplasia, psomomma bodies and fibrosis do not correlate with prognosis.

II) FOLLICULAR CARCINOMA:

It is the next most common thyroid carcinoma comprising 20-25%, incidence is less in iodine sufficient areas. They occur more commonly in women (F:M= 2.6:1), most often in middle aged or older individual. They tend to behave more aggressively than papillary carcinoma and have a lower survival rate. While lymph node metastasis are unusual, a significant number of patients initially present with or subsequently develop distant metastasis.

Gross:

Follicular carcinomas are solid, fleshy tumors that unlike papillary carcinoma are rarely occult, larger tumor may have focal haemorrhage or necrosis.

Micro:

Follicular carcinomas have a range of pattern similar to those found in follicular adenomas. They may be solid with little actual follicle formation, form trabeculae or cords

or have micro follicles. The architectural pattern has no pleomorphic and usually do not show a marked increase in mitotic activity, multicentricity is much less common than papillary carcinoma. Follicular carcinomas have been divided into:

- Encapsulated or minimally invasive carcinoma

- Widely invasive carcinoma[48]

Minimally invasive carcinomas are grossly and microscopically encapsulated and thus follicular adenoma. Grossly they are **not as colloid rich** as adenomatous nodules and some follicular adenomas. They are distinguished from follicular adenomas by presence of microscopic **capsular or blood vessel** invasion. It is generally agreed that cytologic atypia and increased mitotic activity in an encapsulated follicular neoplasm should not be used as basis for diagnosis of carcinoma in absence of capsular or vascular invasion. Capsular or blood vessel invasion is usually focal, and many sections are needed to be examined before this is demonstrated.

Widely invasive carcinomas include non-encapsulated carcinoma and encapsulated carcinoma with marked vascular and thyroid invasion, which may be microscopically apparent.

Definition of capsular invasion varies among authors. ***Kahn and Perzin*** **defined capsular invasion as presence of tumor in capsule beyond the main tumor mass**. ***Evans*** defined it as tumor nests within capsule. While tumor nests within capsule might represent invasion, it could also represent entrapment within capsule of adenoma. Therefore, growth of tumor cells into capsule roughly perpendicular to main tumor mass is necessary to diagnose as capsular invasion.

The definition of blood vessel invasion also varies among authors. It is generally agreed that vessels should be in the capsule or outside the capsule rather than in the tumor itself, that the vessels should be of venous caliber and tumor thrombus should he attached to vessel wall or covered by endothelium. The prognosis of patient with encapsulated minimally invasive carcinoma is much better than for those with widely invasive carcinoma. It is found that metastasis developed in 2-3% and 25% of patient with minimally and widely invasive carcinoma respectively and cumulative death rate at 10 years was 3% and 32% respectively. Other unfavourable prognostic factors include age >50 years at diagnosis, size more than 4 cm extra thyroidal invasion and to less extent histologic differentiation. Presence of metastasis at time of diagnosis appears to be most un-favorable risk factor.

Unlike papillary carcinoma, regional lymph node metastasis are unusual and distant metastasis are much more common usually to be bone, lungs via hematogenous route. Metastasis and recurrence may be cytologically bland, even resembling normal thyroid, and may be histologically diagnosable as malignant only because of their location.

HURTHLE CELL CARCINOMA:

Hurthle cell carcinoma accounts for 3% of all thyroid malignancies is a subtype of follicular carcinoma that closely resembles follicular carcinoma. This occurs in older persons usually 60-70years of age. The tumor contains an abundance of oxyphilic cells or oncocytes. They differ from follicular carcinoma in that they are more often multifocal and

bilateral (approximately 30%),usually do not take up RAI are more likely to metastasize to local nodes (25%) and distant sites and are associated with high, mortality rate.

Gross:

The tumors are characteristically solid and well vascularized. Most are well encapsulated throughout, invasive tumors tend to grow into the parenchyma in a multinodular fashion than can be very deceptive in that it can be misinterpreted as nodular hyperplasia.

Micro:

The pattern of growth may be follicular, trabecular or papillary. The former is most common. The follicles when large are separated by long and thin fibrovascular septa that stimulate papillae when cut tangentially[50]

c) MEDULLARY CARCINOMA;

Medullary carcinoma accounts for 5% to 10% of thyroid malignancies. The malignancy involves the para follicular cells or c cells derived from neural crest cells. This can occur in sporadic cases as a part of MEN type 2A or 2B. Sporadic cases are more common in women while familial cases are autosomal dominant and affect both sexes equally. In sporadic cases, the lesion usually within one lobe where as men involves upper halves of both lobes.

Medullary thyroid tumors secrete not only calcitonin and carcino-embryonic antigen (CEA) but also calcitonin gene related peptide (CGRP), histaminadases, prostaglandins E2 and F2a and serotonin. The calcitonin excess is not associated with hypocalcemia. The presence of both a mass and an elevated calcitonin level is diagnostic of medullary

carcinoma. Calcitonin is more sensitive tumor marker but CEA is a better predictor of prognosis. Screening for pheochromocytoma with 24 hour urinary catecholamines is mandatory in any patient whose thyroid mass is suspected as being medullary thyroid carcinoma.

Medullary carcinoma invades locally and gives rise to metastasis in cervical and mediastinal lymph nodes(50%) and also in distant organs (15-25%) particularly in lung, liver and skeletal system.

Gross:

The tumour is solid, firm and non-encapsulated but relatively well circumscribed and has a grey to yellowish cut surface.

Micro:

The classic presentation is represented by a solid proliferation of round to polygonal cells of granular amphophilic cytoplasm and medium sized nucleus, separated by a highly vascular stroma, hyalinized collagen and amyloid. The nuclei resemble those of neuroendocrine tumours in other areas of body. They are usually round and stippled "**pepper and salt**" chromatin.[51]

There are several historical variants which include

a. Enacapsulated - better prognosis.

b. Follicullar.

c. Papillary.

d. Small cell- worst prognosis.

e. Giant cell.

f. Clear cell.

g. Melanontic .

h. Oncocytic.

i. Squamous.

j. Amphicrine.

k. Paraganglioma like

Age <40yrs, female sex, association with MEN 2a, uniform cytology, abundant amyloid and tumor confined to the thyroid are pointers to favourable outcome, while association with MEN 2b, necrosis with in tumor and high mitotic activity are adverse features.

D) ANAPLASTIC CARCINOMA:

Anaplastic thyroid carcinoma represent less than 1% of all thyroid malignancies. This occurs in 7^{th} or 8^{th} decade. It is most aggressive from with dysphagia, cervical tenderness and painful neck mass. Superior venacava syndrome can also be part of presentation regional lymph nodes are frequently enlarged. Distant metastases to lungs and bones are not uncommon

Gross:

The tumour is bulky, locally invasive, with a firm, whitish appearance with extensive intrathyroidal extension.[52]

Micro:

These carcinomas are poorly differentiated with varying combinations ofgiant cells, spindle cells, squamous cells and fibrosis. Mitotic figures are abundant as are necrosis and vascular invasion.

LYMPHOMAS:

Lymphomas account for less than 1% of thyroid malignancies and most are of the non-B-cell type.

SECONDARIES IN THYROID:

can occur from

- RENAL CELL CARCINOMA

- MALIGNANT MELANOMA

- BRONCHOGENIC CARCINOMA;

- BREAST CARCINOMA

These are rare very in thyroid.

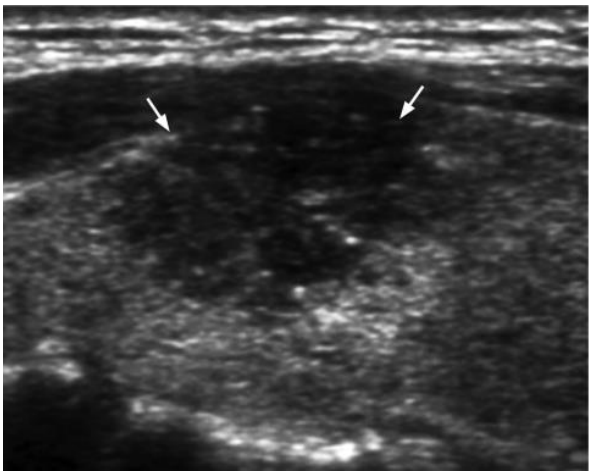
USG FEATURES OF MALIGNANCY

The vast majority of thyroid nodules are benign, and the role of a radiologist in assessment of the thyroid gland is to differentiate a malignant thyroid nodule from the more commonly seen benign ones. It is therefore important to evaluate the sonographic features of thyroid nodules as these aids in their characterization.[33]

Ultrasonography is the most cost-effective imaging procedure, and is highly sensitive in **assessing nodule size and number**. There are a few USG patterns which suggest malignancy like irregular shape, ill-defined borders, hypoechogenicity, solid texture, heterogeneous internal echoes, micro calcification, absence of a halo, an anteroposterior to transverse diameter ratio (A/T) >1, infiltration into regional structures, and suspicious regional lymph nodes.

Echogenicity

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%)

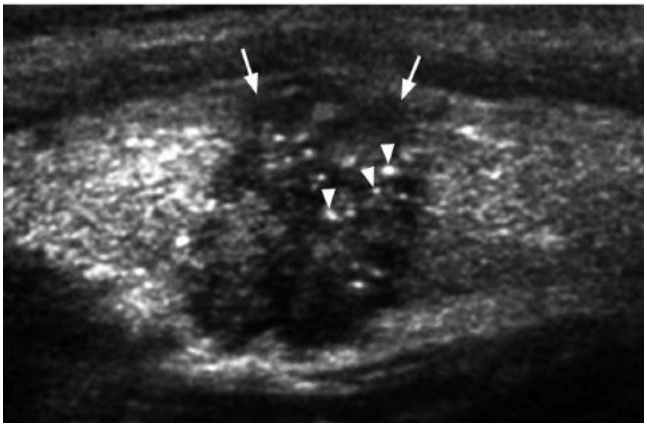


Margins

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

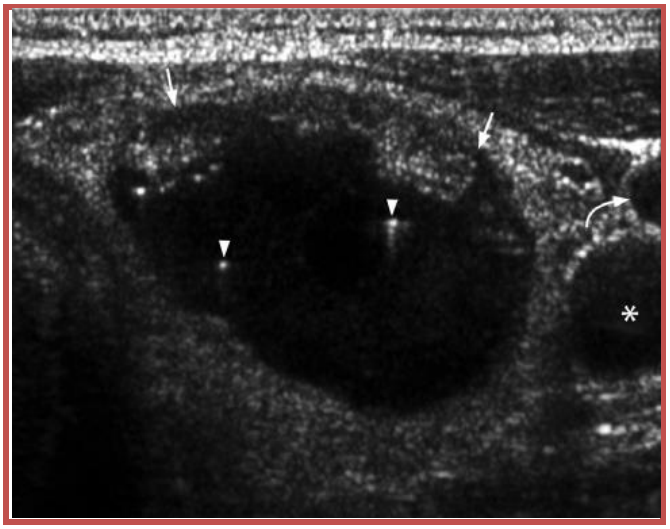
Calcification

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.



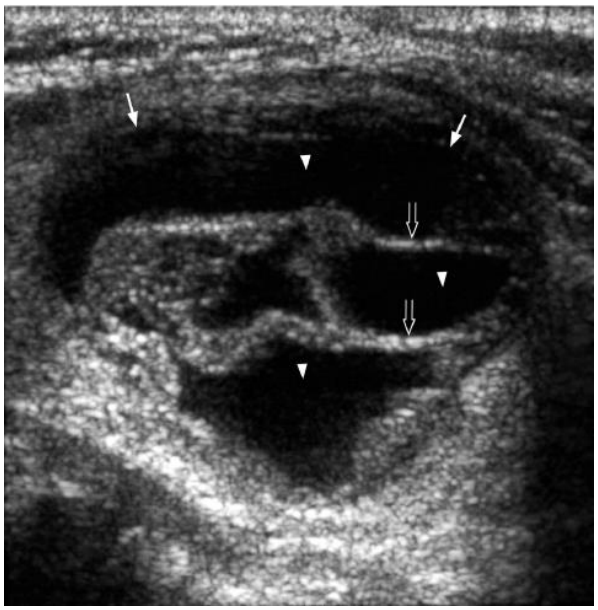
Comet tail sign

The presence of a comet tail sign in a thyroid nodule indicates the presence of colloid within a benign colloid nodule and is a strong predictor of benignity.

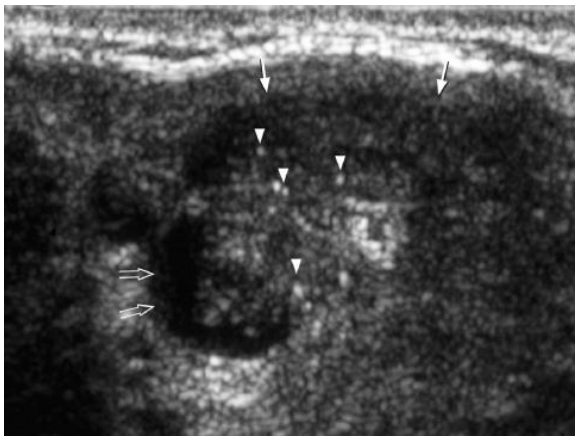


Solid/cystic

It is generally believed that thyroid nodules with large cystic components are usually benign nodules that have undergone cystic degeneration or haemorrhage. However, papillary carcinoma occasionally demonstrates a cystic component and may mimic a benign nodule, though the presence of punctate calcification within the solid component helps in its identification.



SOLID NODULE IN USG



CYSTIC NODULE IN USG IN PTC PATIENT.

FINE NEEDLE ASPIRATION CYTOLOGY (FNAC)

This is the investigation of choice for evaluation of thyroid nodules. An aspirate is considered "adequate" if it contains a minimum of six grouping of well preserved thyroid epithelial cells consisting of at least 10 cells per group [34]. This diagnostic procedure appears to be 90-95% accurate in experienced hands. False positivity and false negativity of FNAC is 4%.

Sometimes FNAC is inconclusive. The causes for inconclusive FNAC are:

• Cystic lesion – cells along the margin of cyst.

• Small nodule

• Fibrotic reaction

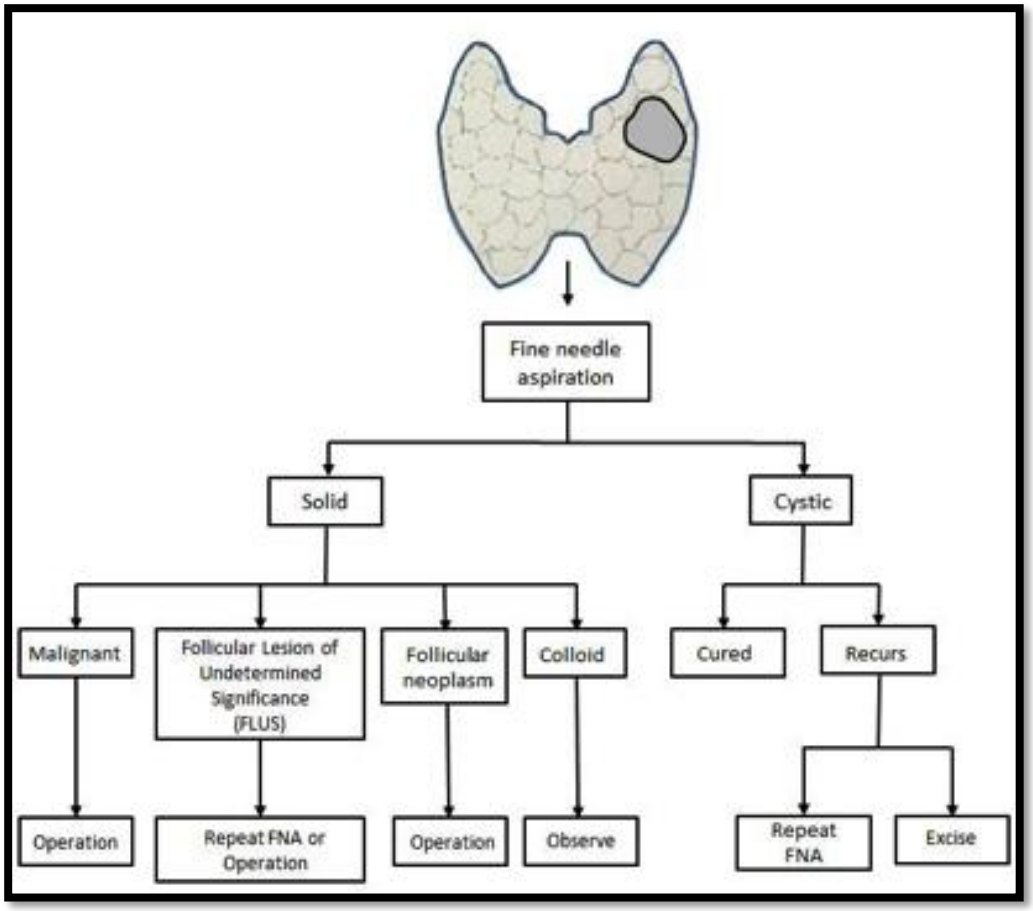
• Doubtful report

• Cannot assess malignant capsular invasion in neoplasm.

So in these cases we have to go for repeat FNAC from the largest nodule under ultrasound guidance. If still doubt persists than excisional biopsy should be done.

Bethesda Cytology Category	Ancillary Testing		PPV	NPV	Recommendation
III (AUS/FLUS)	GEC	suspicious	38%		Diagnostic lobectomy
		benign	5%		Active surveillance
	7-gene MT	positive	88%		Oncologic thyroidectomy
		negative	6%		Active surveillance or diagnostic lobectomy
IV (FN/FL)	GEC	suspicious	37%		Diagnostic lobectomy
		benign	6%		Active surveillance
	7-gene MT	positive	87%		Oncologic thyroidectomy
		negative	14%		Diagnostic lobectomy
	ThyroSeq 2.0 panel	positive	87%		Oncologic thyroidectomy
		negative	5%		Observation
V (SMC)	GEC	suspicious	76%		Oncologic thyroidectomy
		benign	15%		Diagnostic lobectomy
	7-Gene MT	positive	95%		Oncologic thyroidectomy
		negative	28%		Diagnostic lobectomy

AUS, atypia of uncertain significance; FLUS, follicular lesion of undetermined significance; FN, follicular neoplasm/suspicious for follicular neoplasm; GEC, gene expression classifier; 7-gene MT, 7-gene molecular panel; NPV, negative predictive value; PPV, positive predictive value; SMC, suspicious for malignant cells. Data extracted from Ferris RL, et al. *Thyroid*. 2015 May 18. [Epub ahead of print]



MANAGEMENT OF THYROID TUMOURS

STAGING AND PROGNOSTICATION: [35]

Primary Tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Tumor ≤2 cm or less in greatest dimension limited to the thyroid

- T1a Tumor ≤1 cm in greatest dimension limited to the thyroid
- T1b Tumor >1 cm but ≤2 cm in greatest dimension limited to the thyroid

T2 Tumor >2 cm but ≤4 cm in greatest dimension limited to the thyroid

T3 Tumor >4 cm limited to the thyroid, or gross extrathyroidal extension invading only strap muscles

- T3a Tumor >4 cm limited to the thyroid
- T3b Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid, or omohyoid muscles) from a tumor of any size

T4 Includes gross extrathyroidal extension

- T4a Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve from a tumor of any size
- T4b Gross extrathyroidal extension invading prevertebral fascia or encasing the carotid artery or mediastinal vessels from a tumor of any size

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No evidence of locoregional lymph node metastasis

N0a One or more cytologically or histologically confirmed benign lymph nodes

N0b No radiologic or clinical evidence of locoregional lymph node metastasis

N1 Metastasis to regional nodes

- N1a Metastasis to level VI or VII (pretracheal, paratracheal, or prelaryngeal/Delphian, or upper mediastinal) lymph nodes. This can be unilateral or bilateral disease
- N1b Metastasis to unilateral, bilateral, or contralateral lateral neck lymph nodes (levels I, II, III, IV, or V) or retropharyngeal lymph nodes

Distant Metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

HISTOPATHOLOGIC TYPE[35]

- Papillary carcinoma
- Papillary microcarcinoma
- Follicular variant
- Solid variant
- Hurthle cell variant
- Follicular carcinoma
- Encapsulated noninvasive
- Minimally invasive
- Widely Invasive
- Hurthle cell carcinoma
- Poorly differentiated carcinoma (used for insular carcinoma as a subtype of poorly differentiated)
- Anaplastic carcinoma

Prognostic Scoring Strategies

Several staging and clinical prognostic scoring strategies use patient age older than 40 years as a major feature to identify cancer mortality risk from differentiated thyroid carcinoma.These strategies include the **EORTC, TNM 8th edition, AMES (Age, Metastases, Extent, and Size), and AGES (Age, tumor Grade, Extent, and Size).** All of these strategies effectively distinguish between patients at low and high risk.

With incrementally worsening MACIS (Metastasis, Age, Completeness of resection, Invasion, and Size) scores of less than 6, 6 to 6.99, 7 to 7.99, and 8+, however, the 20-year survival rates were 99%, 89%, 56%, and 24%, respectively.

Unfortunately, a study that classified 269 patients with papillary carcinoma according to 5 different prognostic paradigms found that some patients in the lowest-risk group from each approach died of cancer. This is particularly true of classification schemes that simply categorize patients dichotomously as low or high risk. The AJCC TNM staging approach, which is perhaps the most widely used indicator of prognosis, classifies tumors in all patients younger than 55 years as stage I or stage II, even those with distant metastases. **Although it predicts cancer mortality reasonably well, TNM staging was not established as a predictor of recurrence** and therefore does not accurately forecast the recurrences that often occur in patients who developed thyroid carcinoma when they were young. Two studies have shown the poor predictive value of most staging approaches for thyroid carcinoma, including the TNM system.

A **three-tiered staging system**—low, intermediate, high—that uses clinicopathologic features to risk stratify with regard to the risk of recurrence has been suggested and validated. This staging system effectively risk stratifies patients with regard to the risk of recurrence, risk of persistent disease after initial therapy, risk of having persistent structural disease, likelihood of achieving remission in response to initial therapy, and likelihood of being in remission at final follow-up. In another approach, emphasis has been placed on evaluation of response to therapy using a dynamic risk assessment approach in which the initial risk estimates are modified during follow-up as additional data are

accumulated. This allows ongoing re-assessment of risk and allows the management paradigm to be better tailored to realistic estimates of risk that may change substantially over time.[35]

IPSILATERAL LOBECTOMY VERSUS TOTAL THYROIDECTOMY

The appropriate extent of thyroid resection—ipsilateral lobectomy versus total thyroidectomy—is very controversial for lower-risk papillary carcinoma, which is reflected in the NCCN **category 2B** recommendations for these procedures. In most clinical settings, decisions about the extent of thyroidectomy should be individualized and done in consultation with the patient. This debate reflects the limitations of prognostic scoring and the morbidity often associated with total thyroidectomy performed outside of major cancer centers.

Most NCCN Panel Members recommend total thyroidectomy for patients with biopsy-proven papillary carcinoma who have large-volume pathologic N1 metastases (>5 involved nodes with metastases >2 mm in largest dimension) because this procedure is associated with improved disease-free survival. Some centers report that patients treated by lobectomy alone have a 5% to 10% recurrence rate in the opposite thyroid lobe. After lobectomy, these patients also have an overall long-term recurrence rate of more than 30% (vs. 1% after total thyroidectomy and ^{131}I therapy) and the highest frequency (11%) of subsequent pulmonary metastases. However, in properly selected patients treated with lobectomy alone, recurrence rates may be as low as 4%.Higher recurrence rates are also observed with cervical lymph node

metastases and multicentric tumors, providing some additional justification for total thyroidectomy.[35]

COMPLICATIONS OF THYROIDECTOMY

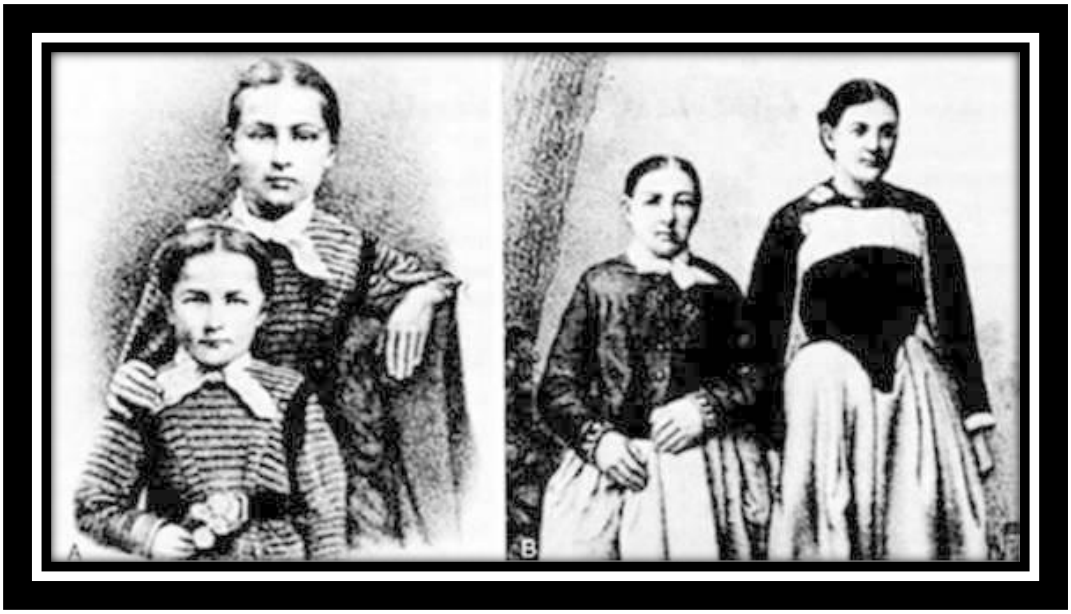


Fig 7 Dramatic case of Maria Richsel, the first patient with postoperative myxedema to have come to Kocher's attention. A , The child and her younger sister before the operation. B , Changes 9 years after the operation.

By 1920, advances in thyroid surgery had reached the point that **Halsted** referred to this operation as a "**feat which today can be accomplished by any competent operator without danger of mishap**". Unfortunately, decades later, complications still occur. In the best of hands, however, thyroid surgery can be performed today with a mortality that varies little from the risk of general anesthesia alone, as well as with low morbidity. To obtain such enviable results, however, surgeons must have a thorough understanding of the pathophysiology of thyroid disorders; be versed in the preoperative and postoperative care

of patients; have a clear knowledge of the anatomy of the neck region; and, finally, use an unhurried, careful, and meticulous operative technique.[36]

Five major complications are associated with thyroid surgery: 1) thyroid storm, 2) wound hemorrhage, 3) wound infection, 4) recurrent laryngeal nerve injury, and 5) hypoparathyroidism.

Thyroid storm reflects an exacerbation of a thyrotoxic state; it is seen most often in Graves' disease, but it occurs less commonly in patients with toxic adenoma or toxic multinodular goiter.

Wound hemorrhage with hematoma is an uncommon complication reported in 0.3% to 1.0% of patients in most large series. However, it is a well-recognized and potentially lethal complication. A small hematoma deep to the strap muscles can compress the trachea and cause respiratory distress. A small suction drain placed in the wound is not usually adequate for decompression, especially if bleeding occurs from an arterial vessel. Swelling of the neck and bulging of the wound can be quickly followed by respiratory impairment.

Injuries to the recurrent laryngeal nerve occur in 1% to 2% of thyroid operations when performed by experienced neck surgeons and at a higher prevalence when thyroidectomy is done by a less experienced surgeon. They occur more commonly when thyroidectomy is performed for malignant disease, especially if a total thyroidectomy is done. Sometimes the nerve is purposely sacrificed if it runs into an aggressive thyroid cancer. Nerve injuries can be unilateral or bilateral and temporary or permanent, and they can be deliberate or accidental. Loss of function can be caused by transection, ligation, clamping, traction, or handling of the nerve. Tumor invasion can also involve the nerve. Occasionally, vocal cord

impairment occurs as a result of pressure from the balloon of an endotracheal tube on the recurrent nerve as it enters the larynx. In unilateral recurrent nerve injuries, the voice becomes husky because the vocal cords do not approximate one another. Shortness of breath and aspiration of liquids sometimes occur as well.

Most nerve injuries are temporary and vocal cord function returns within several months; it certainly returns within 9 to 12 months if it is to return at all. If no function returns by that time, the voice can be improved by operative means. The choice is insertion of a piece of Silastic to move the paralyzed cord to the midline; this procedure is called a laryngoplasty. Early in the course of management of a patient with hoarseness or aspiration, the affected vocal cord can be injected with various substances to move it to the midline and to alleviate or improve these symptoms.

Bilateral recurrent laryngeal nerve damage is much more serious, because both vocal cords may assume a medial or paramedian position and cause airway obstruction and difficulty with respiratory toilet. Most often, tracheostomy is required. In the authors' experience, permanent injuries to the recurrent laryngeal nerve are best avoided by identifying and carefully tracing the path of the recurrent nerve. Accidental transection occurs most often at the level of the upper two tracheal rings, where the nerve closely approximates the thyroid lobe in the area of Berry's ligament. If recognized, many believe that the transected nerve should be reapproximated by microsurgical techniques, although this is controversial. A number of procedures to later reinnervate the laryngeal muscles have been performed with improvement of the voice in unilateral nerve injuries, but with only limited success when a bilateral nerve injury has occurred (65).

Injury to the external branch of the superior laryngeal nerve may occur when the upper pole vessels are divided (Fig. 6) if the nerve is not visualized (9). This injury results in impairment of function of the ipsilateral cricothyroid muscle, a fine tuner of the vocal cord. This injury causes an inability to forcefully project one's voice or to sing high notes because of loss of function of the cricothyroid muscle. Often, this disability improves during the first few months after surgery.

Postoperative hypoparathyroidism can be temporary or permanent. The incidence of permanent hypoparathyroidism has been reported to be as high as 20% when total thyroidectomy and radical neck dissection are performed, and as low as 0.9% for subtotal thyroidectomy. Other excellent neck surgeons have reported a lower incidence of permanent hypoparathyroidism, even about one percent following total thyroidectomy (66). Postoperative hypoparathyroidism is rarely the result of inadvertent removal of all of the parathyroid glands but is more commonly caused by disruption of their delicate blood supply. Devascularization can be minimized during thyroid lobectomy by dissecting close to the thyroid capsule, by carefully ligating the branches of the inferior thyroid artery on the thyroid capsule distal to their supply of the parathyroid glands (rather than ligating the inferior thyroid artery as a single trunk), and by treating the parathyroids with great care. If a parathyroid gland is recognized to be ischemic or nonviable during surgery, it can be autotransplanted often after identification by frozen section. The gland is minced into 1 to 2 mm cubes and placed into a pocket(s) in the sternocleidomastoid muscle.

Postoperative hypoparathyroidism results in hypocalcemia and hyperphosphatemia; it is manifested by circumoral numbness, tingling of the fingers and toes, and intense anxiety occurring soon after surgery. Chvostek's sign appears early, and carpopedal spasm

can occur. Symptoms develop in most patients when the serum calcium level is less than 7.5 to 8 mg/dL. Parathyroid hormone is low or absent in most cases of permanent hyopoparathyroidism.

Patients who have had a thyroid lobectomy rarely develop significant hypocalcemia postoperatively since two contralateral parathyroid glands are left intact. Many of these patients may be discharged on the day of operation if they are otherwise satisfactory. However, patients who have had a total or near total thyroidectomy for cancer or for Graves' disease are at greater risk of a low calcium and are generally observed in the hospital postoperatively. We have found the one hour postoperative PTH level to be equivalent to the parathyroid hormone level drawn the following morning. A value of 15 pg/ml or greater at one hour is very reassuring and is rarely associated with symptomatic postoperative hypocalcemia or with permanent hypoparathyroidism. A central lymph node dissection makes transient hypocalcemia more likely.[36]

MATERIALS AND METHODS

Study Centre

Institute of General Surgery, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai

Duration of Study

May 2017 to October 2018

Study Design

Prospective study (Observational)

Sample Size

50 {n = Z2 1-α/2 P(1-P) /e2 P=3% e= 5% Z=1.96}

Inclusion Criteria

- All patients presenting with a Solitary nodule discovered by a doctor on routine neck palpation or by the patients during self-examination were enrolled into the study.
- Solitary thyroid nodule patients who are clinically and biochemically euthyroid are alone included in the study

Exclusion criteria

- Patients with multinodular goitre / diffuse goitre and those who are hyperthyroid are excluded from the study.
- Patients not consenting for the Research study were also excluded.
- Pregnant women
- Age < 18 or >80 years

Ethics Clearance

Obtained

Methodology

Fifty consecutive patients who fit the inclusion criteria will be studied and the following data collected

- Age, sex of the patient
- Side of SNT
- Size of the nodule
- Pre operative duration of the nodule
- Sonogram findings of the nodule
- FNAC diagnosis of the nodule

- Intra-operative frozen section report
- Post op HPE report

In most of the patients, the plan of surgery was decided beforehand. If it was a STN, diagnosed clinically as well as ultrasonographically, hemi-thyroidectomy of the involved side was done and the specimen was sent either for frozen section or for routine histopathological examination (HPE). In the event of a malignant frozen section report, completion thyroidectomy was done in the same sitting, whereas in inconclusive frozen section, we preferred to wait till the final histopathology report. The decision for other procedures like total thyroidectomy, total thyroidectomy with central neck dissection, total thyroidectomy with selective neck dissection, total thyroidectomy with modified radical neck dissection was based on the clinical, radiological, FNAC and histopathology findings.

Stastical Analysis

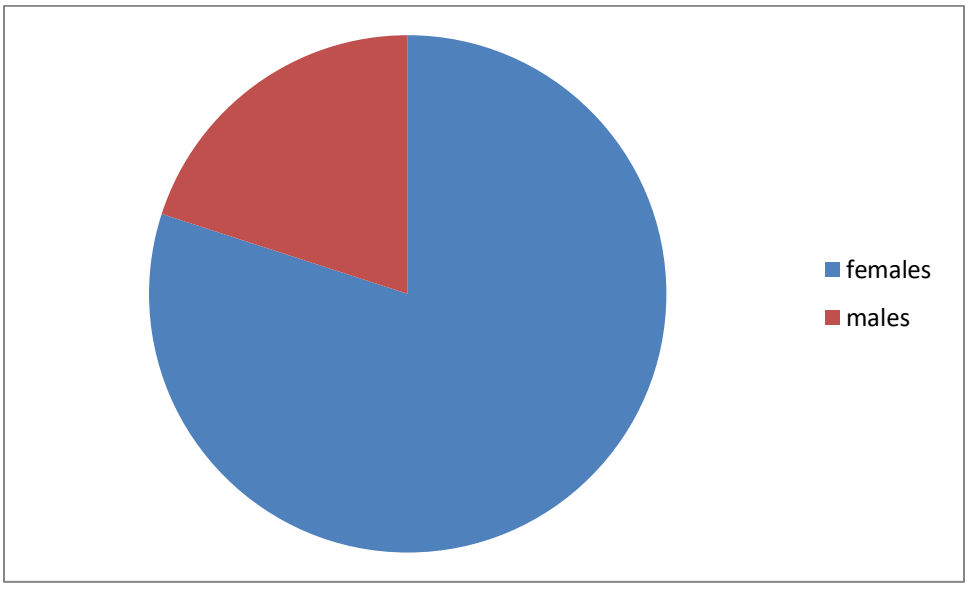
All the collected data were tabulated on MS Excel sheet .All the above collected data will be analysed and conclusions will be derived through statistical analysis using Mann-Whitney U test for continuous variables and Chi-square test for categorical variables.

RESULTS

The study was conducted in Institute of general surgery, RGGGH between May 2017-October 2018. The total study population was 50 who met the criteria for inclusion in the study.

AGE AND SEX DISTRIBUTION

MALES	FEMALES
10	40

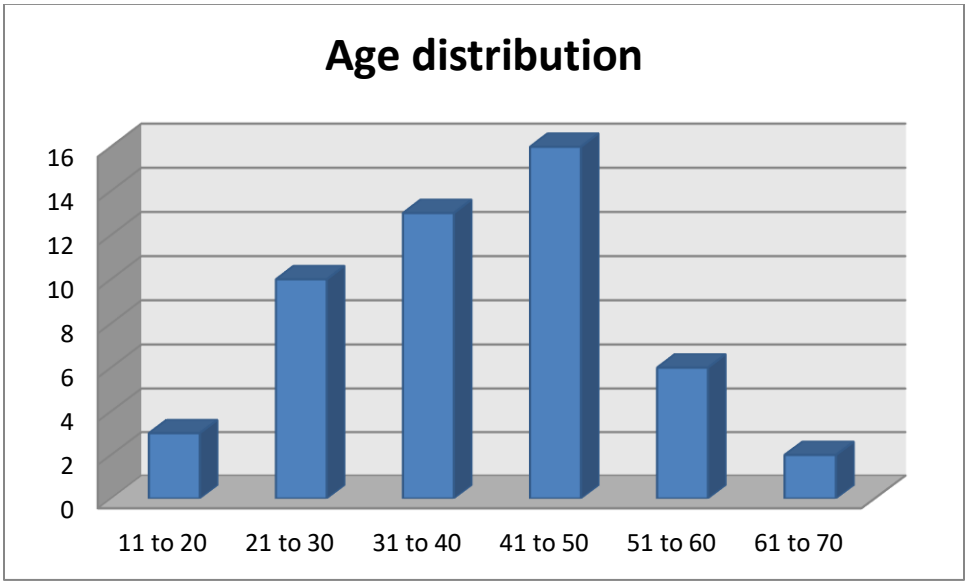


- The number of females (40) outnumbered the males (10) in this study population with a female to male ratio of 4:1

Age distribution:

AGE (years)	NO OF PATIENTS	PERCENTAGE
11 to 20	3	6
21 to 30	10	20
31 to 40	13	26
41 to 50	16	32
51 to 60	6	12
61 to 70	2	4

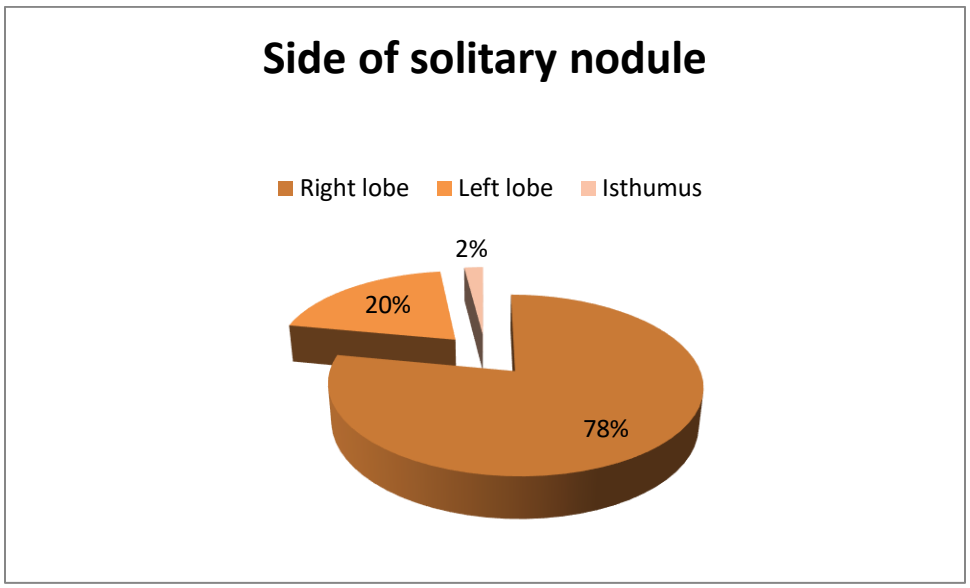
- The mean age group of the study population was **38.73 years** with majority of the incidence between **3rd and 4th** decade of life.



SIDE AND SITE OF LESION

Right lobe	Left lobe	Isthmus
78	20	02

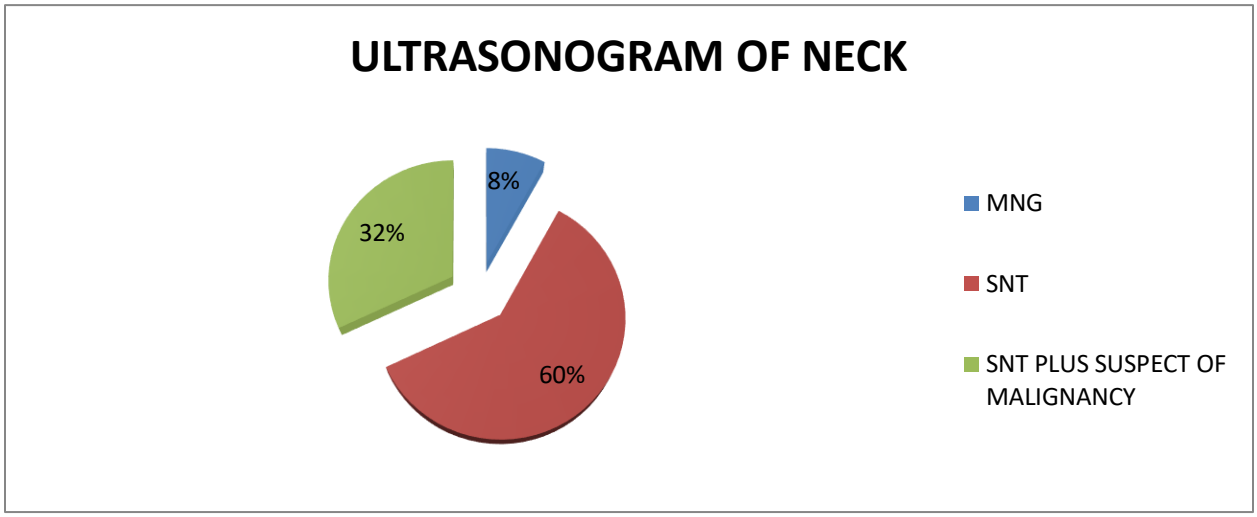
SNT was more common on the **right side** 78% (39) compared to left side 20% (11) and 2% involved the isthmus.



USG and Solitary Nodule

USG FEATURES	NO OF PATIENTS
MNG	4
SNT	30
SNT PLUS SUSPECT OF MALIGNANCY	16

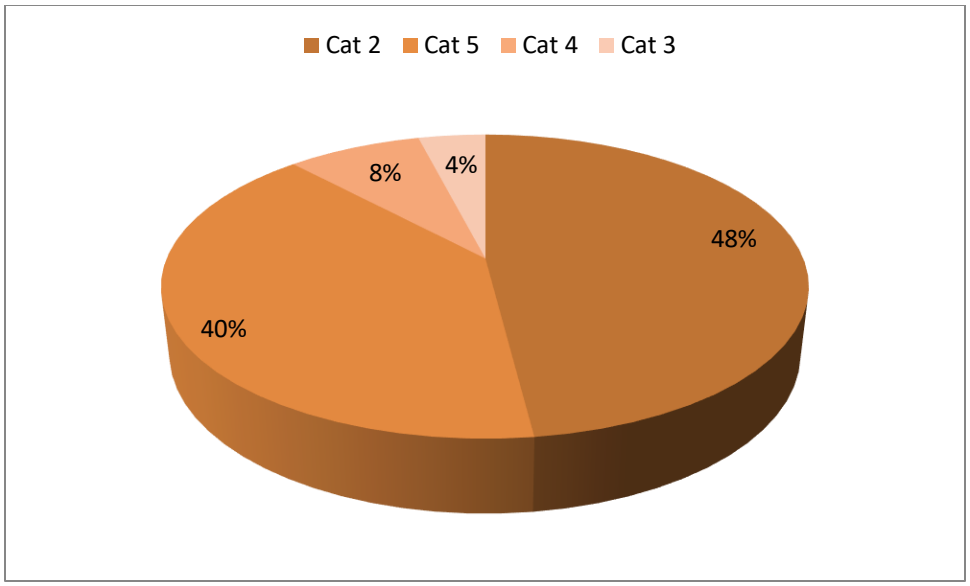
- USG features suspicious of malignancy were present in 16 out of 50 patients sent for Ultrasonogram neck which represents **32% of cases**.



FNAC RESULTS

CATEGORY	**NO OF PATIENTS**
Cat 2	24
Cat 5	20
Cat 4	04
Cat 3	02

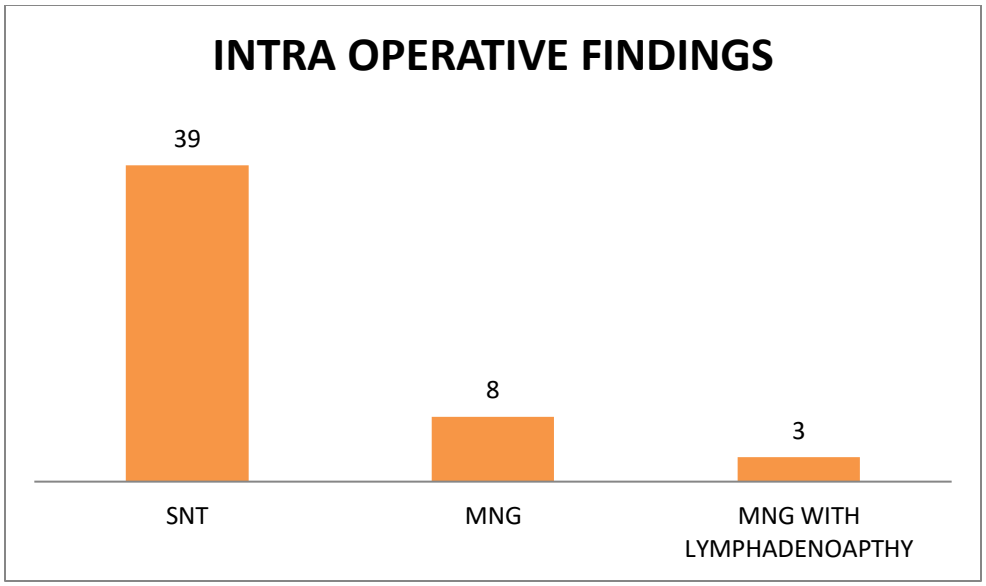
FNAC reported as category 2 in 24 percent of the patients and category 5 in 20 patients and 4 were reported as category 4 and 02 of them were reported as category 3.



INTRA OP CORRELATION

INTRA OP FINDING	**NO OF PATIENTS**
SNT	39
MNG	8
MNG WITH LYMPHADENOAPTHY	3

39 patients were intraoperatively having SNT, 08 MNG AND 03 patients had MNG with LYMPHADENOPATHY.

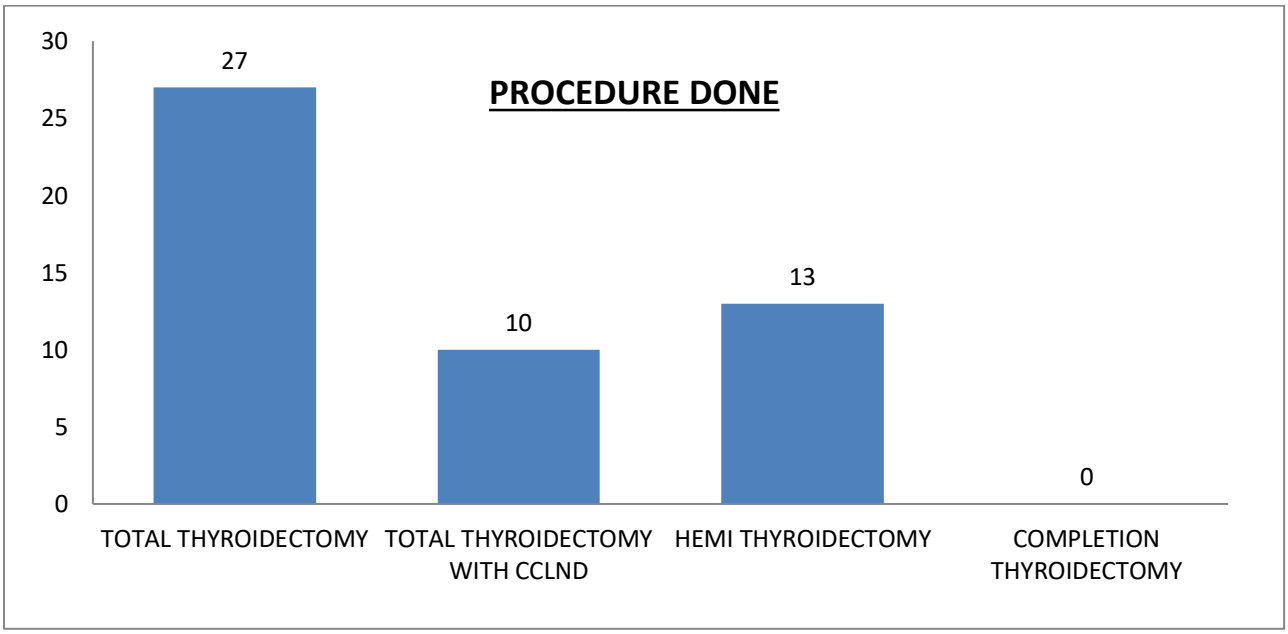


PROCEDURE

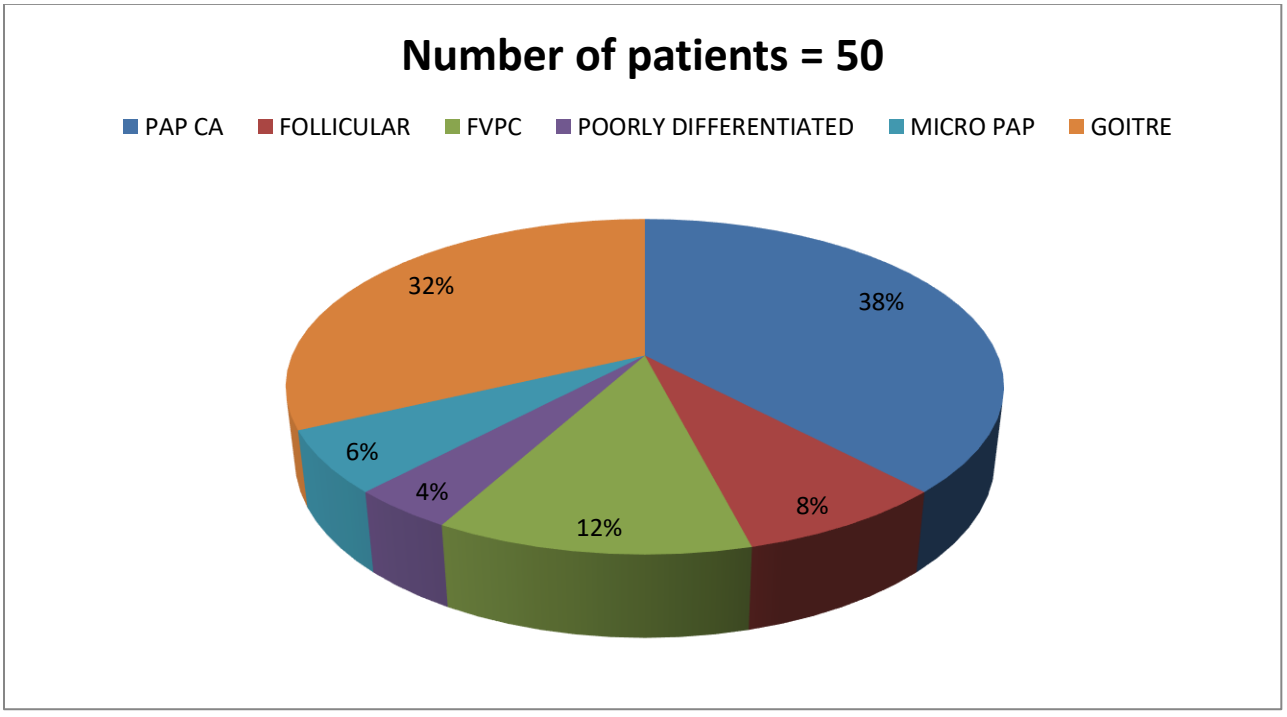
PROCEDURE	**NO OF PATIENTS**
TOTAL THYROIDECTOMY	27
TOTAL THYROIDECTOMY WITH CCLND	10
HEMI THYROIDECTOMY	13
COMPLETION THYROIDECTOMY	0

- 37 patients underwent total thyroidectomy and 13 people underwent hemi-thyroidectomy.
- Out of 13 people who underwent hemi-thyroidectomy, there was no incidence of pathological positivity for malignancy during initial frozen section reporting and final HPE analysis.

- Out of 37 patients who had undergone total thyroidectomy, 10 people underwent CCLND as well as a part of surgical therapy for suspected lesions preoperatively.



HPE results:



TYPE OF LESION	NO OF PATIENTS	PERCENTAGE
PAP CA	19	38
FOLLICULAR	4	8
FVPC	6	12
POORLY DIFFERENTIATED	2	4
MICRO PAP	3	6
GOITRE	16	32

By thorough HPE examination, we inferred that 68% of lesions were malignant and of which 38% of them were Papillary CA, 12% Follicular variant of papillary carcinoma (FVPC) and Follicular carcinoma was 8%.Anaplastic carcinoma accounted for 4% and micro papillary carcinoma was 6%.

FNAC VS HPE correlation

HPE	FNAC	HPE conformation
benign	Benign	16
malignant	Benign	4
malignant	Malignant	17
intermediate	Intermediate	3
benign	Malignant	10

Preoperative FNAC had a **sensitivity** of 80.9% predicting malignancy in 17 patients which correlated with post op HPE reports and **specificity** was 61%

USG vs HPE correlation

USG	**HPE**	**NO of patients**
benign	Benign	10
malignant	Malignant	18
benign	Malignant	14
malignant	Benign	8

USG had a **sensitivity of 56% and specificity of 55%** in this study when used alone to predict features of malignancy in USG.

USG / HPE	Benign	Malignant
Benign	10	14
Malignant	08	18

USG and FNAC vs HPE

The sensitivity was close to 97% and specificity was around 95% when both USG and FNAC were used to predict incidence of malignancy in patients with SNT.

DISCUSSION

This study was a prospective observational study that included 50 patients with Solitary nodule in thyroid gland. Thyroid nodules are very common in the general population and prevalence increases with age, particularly in women. Incidence of SNT was significantly higher in females compared to males (4:1)(p=0.001) as in Haugen BR, Alexander EK, Bible KC, et al. American thyroid association management guidelines study done in the year 2015 [28]

The mean age of patients with malignancy in SNT is 38.73 years with range from 15-70 years. Peak incidence was observed in fourth decade. These results are comparable with other studies. Nagori et al, Ananthakrishnan et al have similar results with mean age of 41 years and 38.2 years respectively. Both have peak incidence in fourth decade of life[30, 31]

Thyroid nodules may be discovered by palpation during a physical exam in 3% to 7% of patients. [29] Nodules may also be found incidentally on imaging studies such as neck ultrasounds, computed tomography (CT) scans performed for unrelated reasons. Risk of malignancy is the same in nodules discovered by palpation and those discovered incidentally.

USG identified the lesions of malignancy suspicion in 16 patients which accounted for 32% of the study population which confirmed to be the same in 13 patients in post op HPE analysis which accounts for an accuracy rate of 82%. [33]

FNAC study of SNT revealed malignancy in 21 patients of which 17 had final biopsy also confirming the same. Preoperative FNAC had a **sensitivity** of 80.9% predicting

malignancy in 17 patients which correlated with post op HPE reports and **specificity** was 61%. This is with accordance to the study of Akash et al.[34]

Combing the Utility of USG and FNAC the sensitivity rose up to 97% and specificity was around 95%. The incidence if malignancy in SNT was around 78% and in MNG it was around 22% in post op HPE reports.. These results are comparable with other studies. Nagori et al evaluated 100 cases of SNT among them 89 cases were benign and 11 cases were malignant with incidence of 11%.[29]

Papillary carcinoma was the most common malignancy in the study with 55.7% incidence closely followed by Follicular variant in 35% of patients. This is similar to the study conducted by Castro et al [32] and These results are comparable with other studies. Among 503 cases studied by Annathakrishnan et al[30] group, 94.8% was attributed to differentiated carcinoma of thyroid and among DTC papillary carcinoma constitutes 62.3%; 32.5% attributed to follicular carcinoma of thyroid. Medullary carcinoma of thyroid constitutes 5.2%.

Size of the nodule has no relation with the malignancy in our study which was also reported by Tai *et al.* A study by Kamran *et al.* opined that the risk of follicular carcinomas and other rare thyroid malignancies increases as nodules enlarge. However, no such association with size was seen in our cases.[30,36]

CONCLUSION

Since the finding of a thyroid nodule is a common clinical problem and the proportion of such nodules that prove to be malignant is small, investigations are of immense help to corroborate with the clinical and morphological findings. Fine needle aspiration and biopsy has been shown to establish a correct diagnosis in a substantial number of cases before resorting to surgery. Examination of tissue by frozen section during surgery is often unhelpful and its use is debatable. We hereby conclude that clinically detected solitary nodules should be treated with high degree of suspicion and patients should be evaluated further with USG and FNAC. However, further management should be on individual basis, depending on the results.

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PROFORMA

Name: IP Number: Age/Sex:

HOPI

Duration of swelling:

Presenting complaints other than swelling:

Past treatment history and its duration:

Family history:

Examination of neck:

Side of the swelling

Site of the swelling

Any other co existent swellings

Thyroid Function Test:

TSH Free T3 Free T4

Ultrasonogram findings:

Pre op Tissue diagnosis:

Intra Operative Frozen section:

Type of surgery done:

Post Operative HPE:

INFORMATION SHEET

- **TITLE**: "**A STUDY OF MALIGNANT THYROID TUMOURS PRESENTING AS SOLITARY NODULE IN TERTIARY REFERRAL CENTRE"**

Name of Investigator: Dr.V.VENKATACHALAM.

Name of Participant:

Purpose of Research: To determine incidence of malignant positive cells in solitary thyroid nodules.

Study Design: Prospective Observational Study

Study Procedures: Patient will be subjected to routine investigations, XRAY Neck, FNAC, Vocal cord Examination , USG, TFT,complete hemogram, operative procedure as indicated, post operative HPEand the data analysed.

Possible Risks: No risks to the patient

Possible benefits

To patient : A better understanding of their problem so has to devise a plan of management which suits their needs.

To doctor & to other people: If this study gives positive results, it can help determine the role of USG and FNAC in the treatment of patients with SOLITARY NODULE OF THYROID. This will help in providing better and complete treatment to other patients in future.

Confidentiality of the information obtained from you: 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

Can you decide to stop participating in the study: Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time

How will your decision to not participate in the study affect you: Your decision will not result in any loss of benefits to which you are otherwise entitled.

Signature of Investigator Signature of Participant

Date :

Place :

PATIENT CONSENT FORM

Study Detail : **"A STUDY OF MALIGNANT THYROID TUMOURS PRESENTING AS SOLITARY NODULE IN TERTIARY REFERRAL CENTRE"**

Study Centre : Rajiv Gandhi Government General Hospital, Chennai.

Patient's Name :

Patient's Age :

Patient may check (☑) these boxes

In Patient Number :

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 Ethics 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 and to undergo treatment ❑

Signature/thumb impression

Patient's Name and Address

CERTIFICATE – II

This is to certify that this dissertation work titled "**A STUDY OF MALIGNANT THYROID TUMOURS PRESENTING AS SOLITARY NODULE IN TERTIARY REFERRAL CENTRE"** of the candidate **Dr. V. VENKATACHALAM** with registration Number **221611018** for the award of **M.S degree** in the BRANCH -1 of **General Surgery**. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **7%** percentage of plagiarism in the dissertation.

Guide & Supervisor sign with Seal.

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To

Dr.V.Venkatachalam
I Year Post Graduate in M.S.General Surgery
Institute of General Surgery
Madras Medical College
Chennai 600 003

Dear Dr.V.Venkatachalam,

The Institutional Ethics Committee has considered your request and approved your study titled "**A STUDY OF MALIGNANT THYROID TUMOURS PRESENTING AS SOLITARY NODULE IN A TERTIARY REFERAL CENTRE " - NO.25062017**

The following members of Ethics Committee were present in the meeting hold on **06.06.2017** conducted at Madras Medical College, Chennai 3

1. Prof.Dr.C.Rajendran, MD.,	:Chairperson
2. Prof.R.Narayana Babu,MD.,DCH., MMC,Ch-3	: Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4. Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
5.Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC	: Member
6.Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai	: Member
7.Prof. Susila, Director, Inst. of Pharmacology,MMC,Ch-3	: Member
8.Prof.K.Ramadevi,MD., Director, Inst. of Bio-Chemistry,MMC,Ch-3	: Member
9.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
10.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist
11.Tmt.J.Rajalakshmi, JAO,MMC, Ch-3	: Lay Person

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.

21/6/17

Member Secretary – Ethics Committee

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