STUDY OF THYROID SWELLINGS IN TERTIARY CARE CENTRE

By

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DISSERTATION

Submitted to

THE TAMIL NADU DR.M.G.R MEDICAL UNIVERSITY

In partial fulfillment of the requirement for the award of the degree of

M.S General Surgery

Branch I

May 2020

CERTIFICATE

This is to certify dissertation entitled "**STUDY OF THYROID SWELLINGS IN TERTIARY CENTRE**" is a bonafide record of the work done by **Dr. John B Jacob** during the period 2017-2020. This has been submitted in the partial fulfillment of the award of MS degree in General Surgery [Branch I] by the Tamil Nadu Dr. MGR Medical University, Chennai.

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1.INTRODUCTION

Thyroid swellings are not rare and incidence is about 3-4% of adult population [1]. Thyroid is not palpable normally. Swellings in thyroid may be solitary nodule, multiple nodules in single lobe or diffuse swelling. It can be toxic or non toxic. Non toxic can be endemic or sporadic. Endemic is one which more than 10% of population shows thyroid enlargement [2].

Thyroid diseases are one of the commonest endocrine disorders worldwide. Incidence of thyroid disorders are increasing due to excessive use of goitrogens and changing food habits. Thyroid diseases are easy to diagnose, have easy access to medical treatment and swellings are easily visible to the treating doctor.

The prevalence of goiter is different according to the geographical region, age and sex[3]. In India, it is estimated that 42 million people are affected by thyroid diseases[4] and coastal states like Goa, Gujarat, Kerala and hilly areas like Himalayan regions are endemic for thyroid lesions[5]. Study done by R. Mansoor(2010)[6] of 139 cases, maximum fell between 16 and 40 years of age. Colloid goiter was most common among thyroid swelling followed by colloid goiter with cystic degeneration[7]. Thyroid swellings are predominantly present in females of ratio 5:1. Women often develop thyroid enlargement during puberty, pregnancy, lactation and the menopause due to variation of thyroid hormones. Risk for malignancy is more in isolated than diffuse, solid swellings and men more than women.

Thyroid swelling whether diffuse or solitary has to be evaluated to rule out neoplasm. USG, FNAC, TFT are the investigations done to determine who needs surgery or can be managed conservatively. FNAC has excellent patient compliance and is readily repeated[8]. Some malignancies are difficult to be diagnosed by cytology alone, like follicular carcinoma, papillary carcinoma [9]. So the ultimate test for diagnosis is by HPE of excised thyroid gland.

Population of Kulashekaram comes from mixed topography. People are from hilly and immigrants from coastal areas of Kerala. It is a Panchayat under Kanyakumari district. So the food habits also vary. Hence there will be variation in thyroid swellings in this area. More over there is a change in prevalence of goiter in hilly areas. Hence this study is conducted to find out the prevalence of various thyroid swellings in this population.

2. AIMS AND OBJECTIVES

Aim: To conduct study on thyroid swellings in tertiary care hospital

Objective: To find prevalence of each swelling in the population

3.HISTORICAL PERSPECTIVE

Thyroid is derived from word “thyros” which in Greek means shield [10]. Name thyroid was coined by Thomas Wharton in 1645 [11] owing to its close proximity to thyroid cartilage. Anatomy of gland was described by 16th and 17th century. Pathological enlargement of thyroid or goiter was first described in 19th century [12].Thyroid surgeries were associated with higher mortalities. Then later on two scientists Theodor Billroth and Emil Theodor Kocher, through development of reformed techniques proved safety and efficacy of thyroidectomy. In 1909, Kocher received a noble peace prize for his developments in understanding of thyroid physiology[12].

FNAC was first developed in Sweden in 1950 [13]. In 1983 Frable used FNAC for diagnosis of thyroid swellings[14].

4.REVIEW OF LITERATURE

Critical research as resulted in endemic goiter being reported from all over country and not just from Himalayan regions, Researchers from New Delhi had shown that this link to iodine deficiency led to decompensated hypothyroidism in many cases [15]. This led to landmark studies which showed that iodine deficiency was associated with hypothyroidism in neonates setting the scene for the now legendary salt iodization programmes supported by the government of India.

In the post iodinization phase what happens to prevalence of goiter. This was answered in an elegantly conducted study [16]. About 24,672 children from all over India were studied for the following characteristics: goiter prevalence, urinary iodine and thiocyanate excretion, functional status of the thyroid as well as serological and cytopathological markers for thyroid autoimmunity. About 23% of subjects had a goiter. A significantly higher level of median urinary thiocyanate excretion was noted in goitrous subjects when compared with controls. Authors suggested that despite iodinization prevalence as not declined.

The prevalence of thyroid swelling ranges from 4% to 10% in the general adult population and from 0.2% to 1.2% in children. Thyroid nodules are very common occurring in 4% of the population aged between 30 and 60.[17]

Kageswar Rout [18] found that colloid goiter was most common among thyroid swelling followed by colloid goiter with cystic degeneration.

4.1 Development

Thyroid gland appears as an epithelial proliferation of endodermal origin in the floor of pharynx between tuberculum impar and the copula called foramen caecum around 3rd week of gestation. Then it descends in front of pharyngeal gut as bilobed diverticulum. During descend it remains connected to the tongue by narrow canal called thyroglossal duct which later disappears [19].

With further descend it reaches final position in front of trachea by 7th week. At this time it acquires a small isthmus and two lateral lobes. First follicles with colloid appear by end of 8th week and functioning of thyroid gland starts by 11thweek [20].

Parafollicular cells are derived from ultimobrachial body of 4th pharyngeal pouch. They are the only component of adult gland which is not endodermal in origin [12]

Due to abnormal descend aberrant thyroid tissue may be found anywhere along path like base of tongue, just behind foramen caecum and can have same diseases as the gland itself [19].

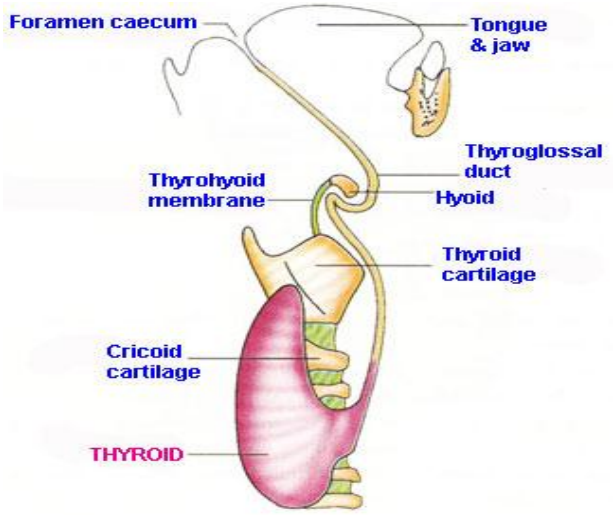


Figure 1 Development of thyroid

4.2.Anatomy

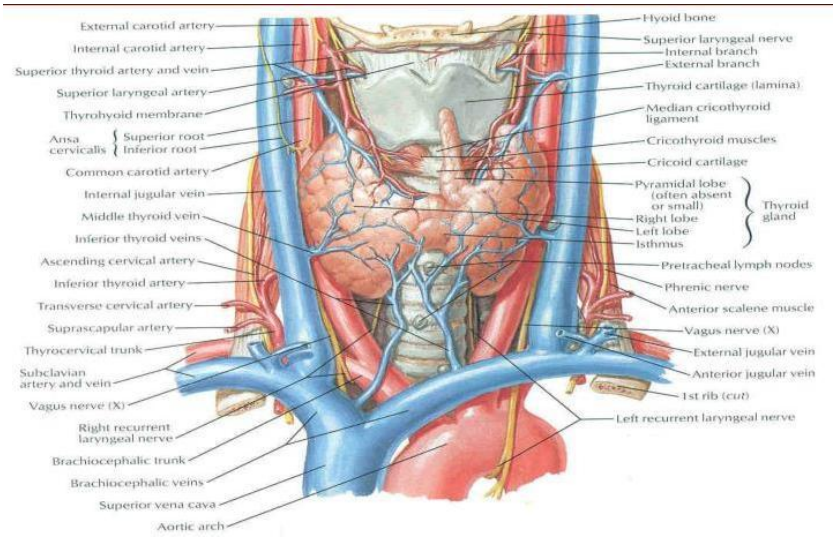
Adult thyroid gland is a brownish red, butterfly shaped gland placed anteriorly in lower neck at level of C5 to T1 vertebrae[21]. It encircles approximately 75% of junction of larynx and trachea and weighs about 20 to 25g[12].

It has 2 lobes and 1 isthmus. Lobes are conical. Upper part of each lobe is at the level of oblique line of thyroid cartilage laminae. Base is at the level of 4^{th} or 5^{th} tracheal rings. Each lobe is 5x3x2cm in dimension. Isthmus is about 1.25x1.25cm (transverse x vertical) and is present anterior to 2^{nd} or 3^{rd} tracheal ring[21].

Pyramidal lobe if present ascends from isthmus or adjacent lobe (Left>Right) to hyoid bone. A fibromuscular band, levator of thyroid, glandular thyroidea sometimes descends from body of thyroid to isthmus or pyramidal lobe [21].

It has a fibrous capsule which sends septae deep to gland. Outside capsule it is ensheathed by pretracheal layer of deep cervical fascia (accounts for mobility on swallowing). Posteromedially the capsule and fascia condenses and connects thyroid to cricoids cartilage forming berry ligament [22]. It is covered by fascia and strap muscles and more laterally it is tucked underneath diverging anterior borders of sternocleidomastoid muscles [23].Thyroid is highly vascular and supplied by two sets of arteries. Superior thyroid artery, a branch of external carotid artery, descends along lateral border of thyrohyoid muscle and ends by dividing into anterior and posterior branches. Inferior thyroid artery, a branch of thyro-cervical trunck from first part of subclavian, ascends along medial edge of anterior scalene muscles, passes posterior to carotid sheath, and ends at inferior lobe by dividing into ascending and inferior branch. Sometimes (1-4%) a branch from brachiocephalic trunk or arch of aorta, thyroidea ima ascends on anterior surface of trachea and supply the isthmus or

replace inferior thyroid artery. Superior and middle thyroid veins drain into internal jugular vein. Inferior thyroid vein drains into brachioephalic veins[24].



Anatomy of thyroid anterior view

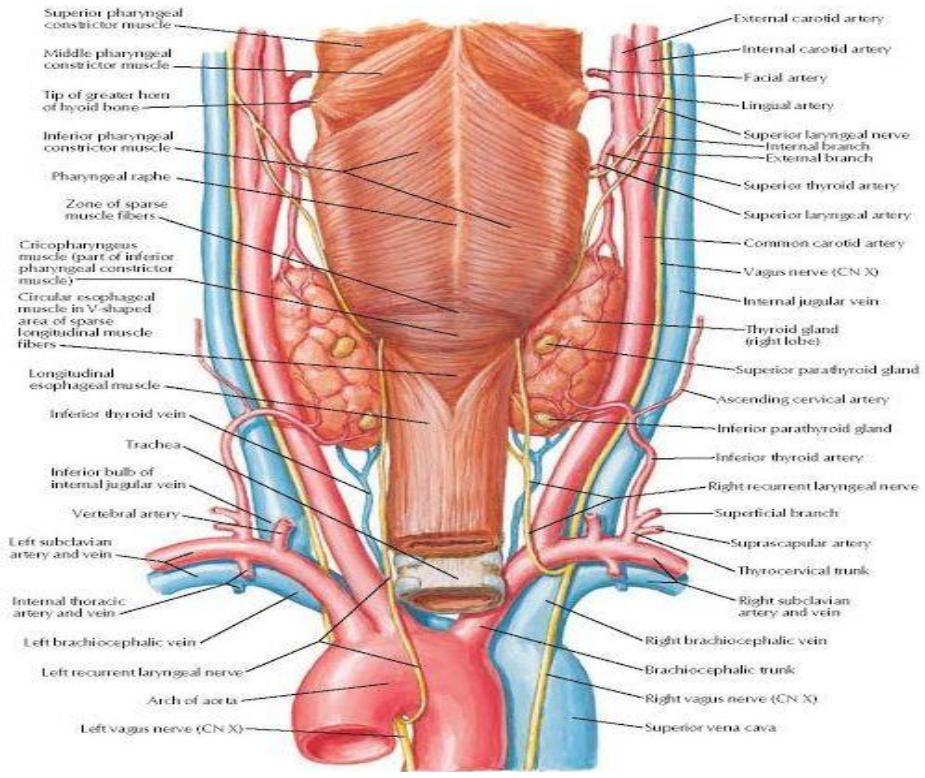


Figure 2.2 Anatomy of thyroid posterior view

Superior laryngeal nerve descends towards superior pole of thyroid and medial to carotid sheath. At level of cornua of hyoid 2 to 3 cm from superior

pole of thyroid it divides onto external and internal branches. Internal branch supplies sensory innervations to larynx cranial to vocal cord. External branch travels along lateral surface of inferior constrictor and descend anteriorly and medially along superior thyroid artery. Within 1cm from entrance of superior thyroid artery to gland it takes a medial course and supplies cricothyroid muscle[12].

The left recurrent laryngeal nerve arises from vagus, crosses aortic arch, loops around ligamentum arteriosum and ascends within tracheoesophageal groove. Right nerve arises from vagus after crossing with right subclavian artery and pass posterior to the artery before ascending in neck. It has high incidence of variations. It may be non recurrent branch, and may pass anterior, posterior or pass between branches of inferior thyroid artery and terminate by entering larynx posterior to cricothyroid.

Lymphatic drainage to tracheal plexus, prelaryngeal nodes, pretracheal, paratracheal nodes and deep cervical lymph nodes. Sometimes drain to brachiocephalic and thoracic duct[12].

4.3.Histology

Each lobe has 30-40 follicles (functional unit) having average diameter of 200μm. Follicles are surrounded by connective tissue stroma having capillaries, lymphatics and sympathetic nerve fibres[21].They are lined by follicular cells whose shape changes with activity. They have well developed Golgi apparatus, lysosomes, granular endoplasmic reticulum and numerous microvilli in luminal border. Follicular cells with abundant acidophilic cytoplasm are called Hurthle cells/Askanazy cells/oxyphilic cells/oncocytes. This granularity is due to accumulation of mitochondria. The activity of follicular cells varies with age, highest in prenatal group and lowest in adults[25].

Intraluminal colloid is pale staining with scalloped borders when active and densely eosinophilic in inactive ones. Birefringent calcium oxalate crystals found intraluminally is the distinguishing factor from parathyroid tissue at time of frozen section. They represent functional inactivity on those follicles. Collections of small follicles protruding into the lumen of large follicles are seen in active secreting glands known as Sanderson polsters. They are much prominent in hyperplastic conditions [25].When inactive colloid is abundant, cells are flat, follicles are large. When active follicles are small, cells are cuboid or columnar and, area where colloid is absorbed into thyrocytes are visible as reabsorption lacunae[26].

Other major epithelial component is the parafollicular or C cells. Though they are called parafollicular, they can sometimes have intrafollicular position. They are largely restricted to the middle and upper thirds of lateral lobes along their central axes. They are members of APUD system of neuroendocrine cells[21]. Their number varies according to age; numerous in infancy and old age than in adults. In old age they may form nodular aggregates[25].

Solid cell nests (rests) represent remnant of ultimo brachial body. Measuring about 0.1mm and can be detected in almost 90% of neonatal thyroid glands. They are composed of polygonal or oval cells with occational clear cells with occational glandular lumina having mucinous secretion giving combined solid and cystic appearance. Some C cells may also be there in these cell nests[25].

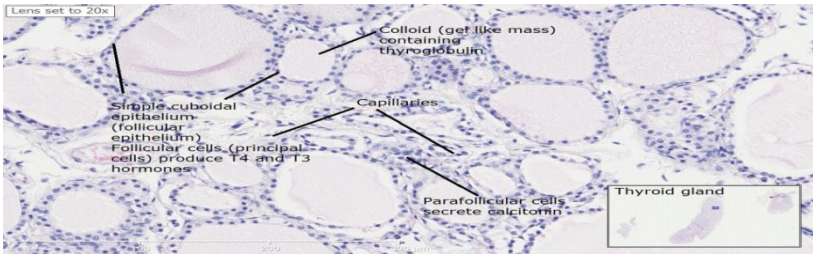


Figure 3 Histology of thyroid

4.4.Physiology

Thyroid function is regulated by variations in circulating level of TSH from anterior pituitary. TSH secretion is regulated by TRH from hypothalamus. TSH secretion is inhibited in negative feedback manner by free T_4 and T_3.

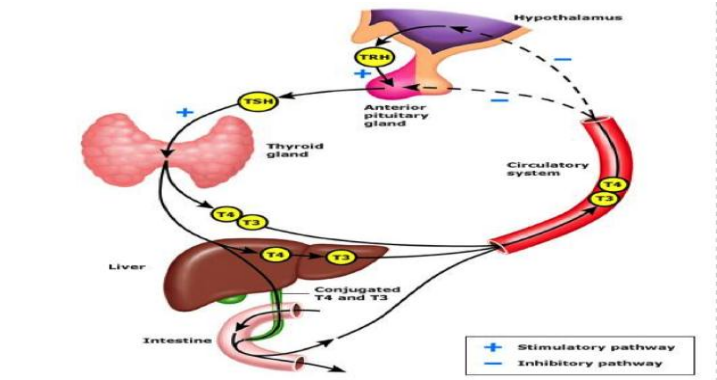


Figure 4.1 Physiology of thyroid

Thyrocyte or thyroid follicular cell has apical (luminal) membrane, basolateral membrane (facing capillaries and stroma) and tight junctions in lateral sides (facing adjacent cell). Apical membrane has Cl^-/I^- exchanger or pendrin and membrane bound enzyme thyroid peroxidase. Basolateral membrane has TSHR, Na^+/I^- symport and Na^+/K^+ ATPase. Thyrocyte nuclei also produce mRNA and by translation in ribosomes, thyroglobulin is produced. This thyroglobulin will be glycosylated in endoplasmic reticulum, packed into vesicles in golgi apparatus and secreted into colloid by exocytosis of vesicles. Thyroglobulin has 123 tyrosine residues among which only 4-8 are normally incorporated in thyroid hormones.

TSHR are GPC Receptor. It is coupled to G_s protein. When TSH binds TSHR, a G protein signal cascade is activated. This leads to increased intracellular cAMP and protein kinases levels. They activate all functional aspects of thyrocyte.

Action of TSH:

- Induces NIS expression
- Increase NIS in basolateral membranes

Functions of thyrocytes are:

- Collect and transport iodine
- Synthesize thyroglobulin and secrete it to colloid
- Fix iodide to thyroglobulin
- Remove thyroid hormones from thyroglobulin and secrete to circulation

Iodine transport: Iodide from interstitium enter thyrocytes through NIS by active transport utilizing energy from ATPase. This iodide is transported to colloid across apical membrane by pendrin.

Oxidalion: Iodide undergoes oxidation with the help of thyroid peroxidase into reactive iodine species. Thyroglobulin is secreted into colloid by endocytosis. With help of peroxidase enzyme, iodine species are added to tyrosine residue to form MIT or DIT.

Coupling: With help of thyroid peroxidase MIT and DIT couple among themselves to form T3, T4and RT3.

- MIT + DIT = T_3
- DIT + DIT = T_4
- DIT + MIT = RT_3

Secretion: When needed thyroglobulin is internalised into cell by endocytosis and undergo lysosomal degradation. Now by hydrolysis of peptide bonds, T_3

and T_4 are separated from thyroglobulin. They are discharged into cytosol and to the capillaries.

Human thyroid secretes about 80µg of T_4, 4µg of T_3 and 2µg of RT_3 daily. MIT and DIT are deiodinated by microsomal iodotyrosine deiodinase and iodine, tyrosine are recovered. Iodide recovered is reutilized for iodination and is about twice that formed from NIS [26].

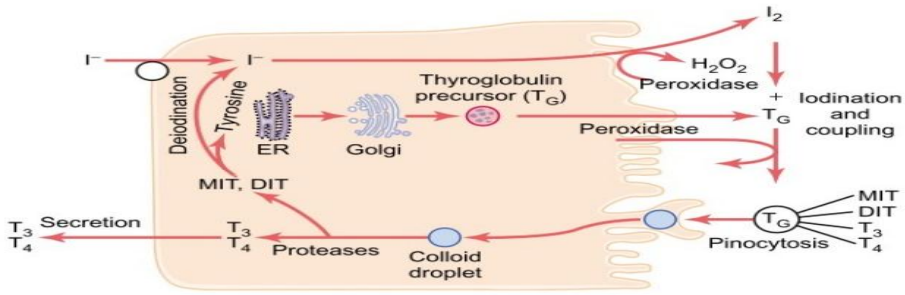


Figure 4.2 Physiology of thyroid

4.5.Pathogenesis of nodule [27]

Thyroid nodule genesis is due to amplification of thyroid heterogeneity due to genetic and epigenetic processes. They can be classified into

1. Hyperplastic
2. Neoplastic
3. Colloid
4. Cystic
5. Thyroiditic

*Hyperplastic:*Apart from TSH several paracrine and autocrine factors are responsible for thyroxine production. They are TSHR, cAMP and protein kinases. When there is point mutation of TSHR or Gs protein, there will be cAMP overproduction leading to overgrowth and hyperfunction.

Neoplastic: Several oncogenes have been identified. They are TRK, RET, ras, c-MET, p53. Tumour initiates by RET or ras and then becomes undifferentiated when p53 mutation occurs.

Colloid: This is due to flattening of epithelium and dilatation of follicles having thyroglobulin. This is due to defective reabsorbtion of thyroglobulin.

Cystic: 15-40% of nodules are partly or entirely cystic. Most are pseudocysts which follow necrosis and colliquation. This is due to imbalance between growth and angiogenesis. Recently VEGF/VPF has been found as the main substance.

Thyroiditic: It could be due to:

- Lymphocyte thyroiditis nodule growing in a hyperplastic or normal gland
- Lymphocyte thyroiditis in a nodule with other nodular diseases of thyroid like lymphoma, papillary thyroid cancer

4.6.Various swellings in thyroid [(1)]

Simple Goitre

Diffuse hyperplastic

- Physiological
- Endemic

Multinodular goitre

Toxic

*Diffuse:*Graves' disease

Multinodular

Toxic adenoma

Solitary nodule

Retrosternal Goiter

Neoplastic

Benign

- Follicular adenoma
- Hyalinizing trabecular adenoma

Malignant

- Differentiated
  - Papillary adenocarcinoma
  - Follicular adenocarcinoma
- Medullary Carcinoma
- Poorly differentiated
- Undifferentiated
- Miscellaneous
  - Lymphoma
  - Squamous cell
  - Metastatic tumour

Inflammatory

Autoimmune:

- Hashimoto's thyroiditis
- Lymphocytic thyroiditis

Granulomalous: De Quervain's thyroiditis

Fibrosing: Riedel's thyroiditis

Infective

- Acute
- Chronic

Other

4.6.1. Simple Goiter

Any enlargement of thyroid gland is known as goiter. They are usually due to hyperplastic changes in follicles[28]. Simple goiter means enlargement in euthyroid state. They can be:

Physiological*:* Goitre can occur physiologically due to some physiological changes in our body. They are:

1. *Pregnancy*: β-HCG causes stimulation of thyroid gland during first trimester due to structural similarity with TSH receptor [29]. This results in decrease in serum TSH in first trimester. Levels of thyroglobulin are increased due to estrogen stimulation (prolongs half life). Also there is increased clearance of iodide by kidney foetal absorbtion and placental metabolism [30]. This results in goiter.

2. *Puberty*: Puberty occurs by maturation of hypothalamo-pituitary-gonadal axis. This is due to increased need for energy[31]. This adaptation is also helped by prepubertal surge of TSH between 9-9.5yrs followed by increase in circulating hormones and increased peripheral conversion. With ongoing puberty surge, levels of hormones comes to normal. This transient surge in TSH results in goiter.

Multinodular: Due to active stimulation there will be hyperplasia and there will be uniform iodine uptake and lobules have active follicles. Later due to fluctuation in stimulation there will be disorganized growth and results in areas of active and inactive lobules. Active lobules become vascular, hyperplastic till haemorrhage occurs forming a central rim of necrosis and peripheral active cells. Necrotic lobules coalesce to form nodules. Active follicles are present in intermodal tissue [1]. It can be sporadic or endemic.

1. *Endemic:* This refers to enlargement of thyroid gland in significant portion of a region or population. It may be 5% or more of children between 6 and 12yrs of age having thyroid enlargement [28]. Usually due to dietary iodine deficiency.

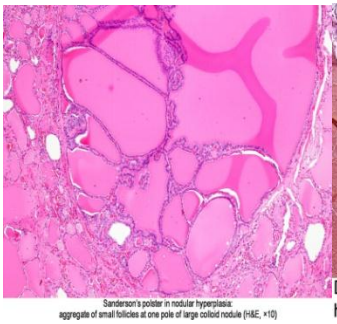
2. *Sporadic:* It can be due to iodine deficiency or excess ingestion of goitrogens, medications, dyshormonogenesis and mutation of TSH receptor gene[28].

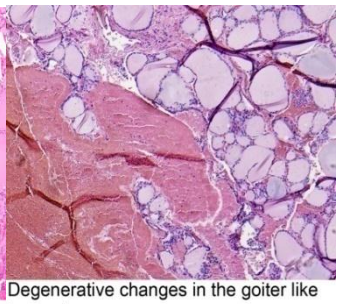
There will be mild to moderate thyroid enlargement. Most have evident nodules grossly. Enlargement may be symmetric or asymmetric.

FNAC: Mixture of colloid and benign follicular cells arranged in monolayer sheets evenly. Macrophages with haemosiderin are also seen.

Sectioned surface may be nodular, heterogenic with colloid, haemorrhages, fibrosis, cystic degeneration or calcification.

Microscopically follicles have colloid with flattened or cuboidal or columnar epithelium. There may be Sanderson's polster which is aggregate of small nodules in one pole of nodule. There may be features of degeneration like haemorrhage, foamy histiocytes and giant cell formation [28].





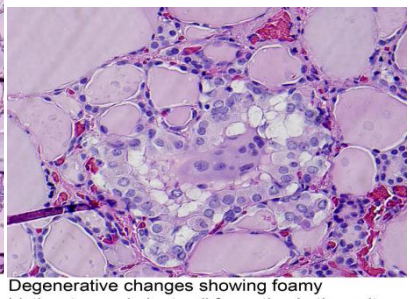


Figure 5.1 Sanderson's polster **Figure 5.2 Haemorrhage** **Figure 5.3 Foamy histiocytes and giant cell**

4.6.2 Toxic goiter

It means goiter with toxic features (hyperthyroidism). It can be:

Diffuse toxic goiter (Grave's disease): It is also known as Base dow disease. It is common in young adult females. It is due to IgG antibodies against TSH receptor. Patient can present with muscle weakness, weight loss, irritability, tachycardia, goiter, increased apetite and exophthalmos in 25-50%. Patient can have atrial fibrillation in acute state and myxedema or thyroid acropachy (periosteal new bone formation) in late stage. There is a variant called T3 predomint Grave's. Incidental carcinomas (1-9%) usually papillary are associated with it [28].

Eye signs[32]:

- *Van Graefe sign:* Upper eyelid lags behind as [atient looks down

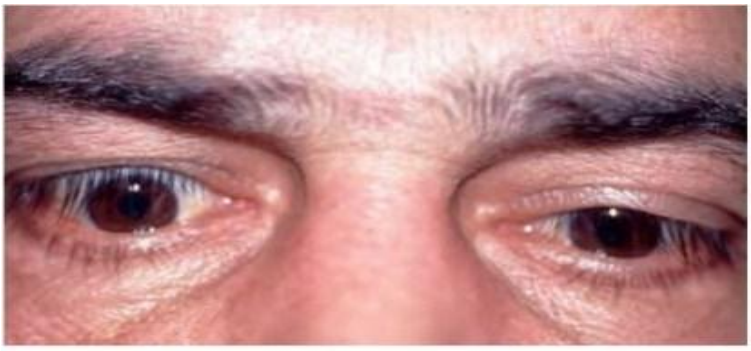


Figure 6,1 Right side Von Greefe sign

- *Joffroy' sign:* No wrinkling of forehead when patient looks up with face inclined down.

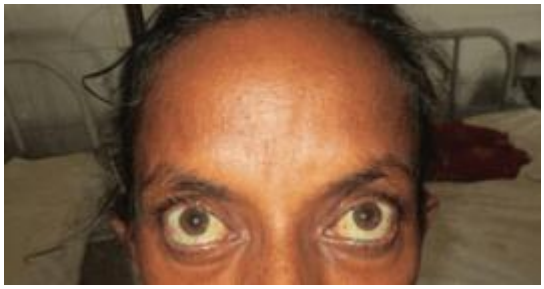


Figure 6.2 Joffroy sign

- *Stellwag sign:* Staring look and infrequent blinking with wide palpebral fissures.

Figure 6.3 Stellwag sign

- *Moebius sign:* Failure to converge eyeballs.

Figure 6.4 Moebius sign

- *Dalrymple sign:* Upper sclera is visible due to retraction of upper eyelid.

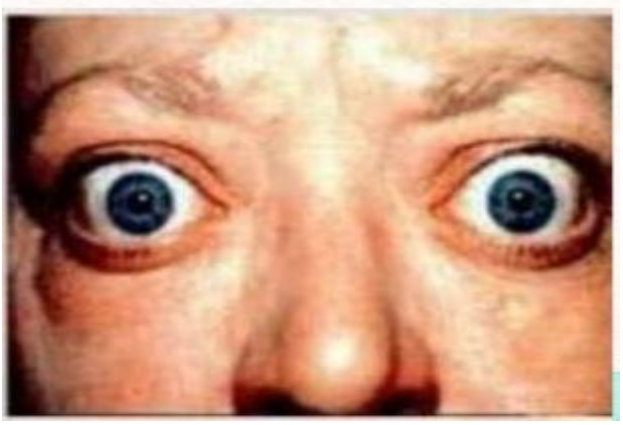


Figure 6.5 Dalrymple sign

- *Opthalmoplegia*

Investigations show raised T3 and T4, RAI uptake increased when TSH is less than 0.1. Grossly there is diffuse enlargement of gland. It will be red and succulent. Cut section shows gray or red surface depending on the vascularity. In long standing cases it will be friable. Microscopically there will be hyperplastic follicles with prominent papillary fold sometimes extending to muscle layer. Lining epithelium will be columnar with clear cytoplasm with fat and glycogen. There will be variable amount of oxyphilic cells. Colloid is pale and vacuolated with scalloping. Stroma has lymphoid tissue with germinal centre formation. Lymphoid cell usually will be T-cell. Mild fibrosis will be noted in long standing cases [(28)].

Treatment includes antithyroid drugs like propylthiouracil, ablation with RAI, subtotal thyroidectomy after giving beta blockers. 5g remnant of thyroid tissue on each side ensures euthyroid state. Greater the lymphocytic infiltration and oxyphilic cells, more the chance for myxedema in post operative period [(28)].

Toxic nodular Goitre: It is a complication of MNG. It is also known as Plummer disease. In this, one or more collections of follicular cells secrete excessive amount of thyroid hormone. They are grossly comparable to non toxic goiter. Microscopically some may show hyperfunction, and scant watery colloid with peripheral scalloping. Diagnosis depends on clinical and laboratory findings of hyperthyroidism [(28)].

Toxic adenoma:It is an overactive nodule, may be part of generalized nodularity or true toxic adenoma. It is not due to TSH-RAb. TSH secretion will be suppressed by high levels of thyroid hormones. The normal surrounding tissue itself will be suppressed. Microscopically there will be hyperplasia of acini, and are lined by columnar epithelium. Acini are usually empty or may contain vacuolated colloid with characteristic scalloped pattern near the thyrocytes[(1)].

4.6.3 Solitary Nodule of thyroid[(12)]

A discrete and radiologically definable lesion within thyroid is called solitary nodule thyroid. Many are not palpable and not all palpable lesions can be solitary. Although they are common only some require intervention. Frequency of nodules increases with age. 5% are malignant. They are more common in women. Indications for resection are: 1)compression 2)hyperfunction 3)malignancy or suspicious.Compression symptoms include dysphagia, dyspnea, chocking, pain and foreign body sensation.

Risk factors for malignancy include:

1. Male
2. Adult <30yrs and >60yrs of age
3. Radiation exposure
4. Family history of malignancy
5. Vocal cord palsy
6. Lymphadenopathy
7. Rapid enlargement
8. Size more than 1.5cm
9. Solid nodule

Malignancy features in ultrasonogram[28]:

1. Microcalcifications
2. Taller than wide
3. Rim calcifications
4. Extrathyroidal extension
5. Irregular margins
6. Increasesd vascularity
7. Hypoechogenicity

Pattern	USG	Risk	Consider biopsy
High suspicious	Solid hypoechoic with or without cystic component and having one or more of malignant features	>70-90%	>1cm
Intermediate suspicion	Solid hypoechoic with or without cystic component and no features of malignancy	10-20	>1cm
Low suspicion	Iso or hyperechoic solid or partially cystic with eccentric solid areas and no features of malignancy	5-10	>1.5cm
Very low	Spongiform or partially cystic without any of above mentioned features	<3	>2cm
Benign	Purely cystic	<1	No biopsy

Table 1: Risk stratification for carcinoma in SNT[(28)]

If FNAC is nondiagnostic [(28)]:

Solid nodule:

1. Young, large nodule with atypia – Surgical exicion
2. Elderly with same features
    - No anaesthetic risk – Surgical exicion
    - Co morbidities – Repeat FNAC and closely observe

Cystic:

1. Ultrasound shows partly solid nodule with microcalcifications – Repeat US guided FNAC or Surgery
2. With cystic lymph node enlargement(paratracheal) – Surgery and frozen section
3. Lateral neck lymph node mimicking branchial cyst – Aspirate fluid and check thyroglobulin levels :
    - Raised – Cystic papillary carcinoma
    - Normal – cancer not excluded.

4.6.4 Retrosternal Goiter [28]:

According to Lahey and Swinton any thyroid gland having greatest diameter of intrathoracic mass, well below thoracic inlet are called retrosternal goiter. Incidence is about 0.02-0.5%. They can grow considerably before causing symptoms. They can impinge on trachea causing narrowing of tracheal lumen, deviation of trachea, impinge on esophagus causing dysphagia, and impinge on greater vessels causing venous engorgement. Most common compressive symptom is dyspnea.

Classification:

Higgins:

1. Intrathoracic : four fifth of thyroid in thorax
2. Sub sternal : Part or all of gland extend below sternum
3. Subclavicular : Part or all of gland extend below clavicle

Cohen and Cho:

1. Grade 1 : upto 25% of gland in chest
2. Grade 2 : 26%-50% of gland in chest
3. Grade 3 : 51%-70% of gland in chest
4. Grade 4 : more than 75% of gland in chest

If patient is asymptomatic and moderate compression on radiology then observation with FNAC of dominant nodule is required.

If patient is symptomatic rule out other causes for dysphagia or dyspnoea by CT chest, ECHO. If other causes are ruled out then subtotal or near total thyroidectomy is needed if anesthetic risks are low. If co morbidities exist then radioactive iodine is used which will shrink gland and reduce symptoms.

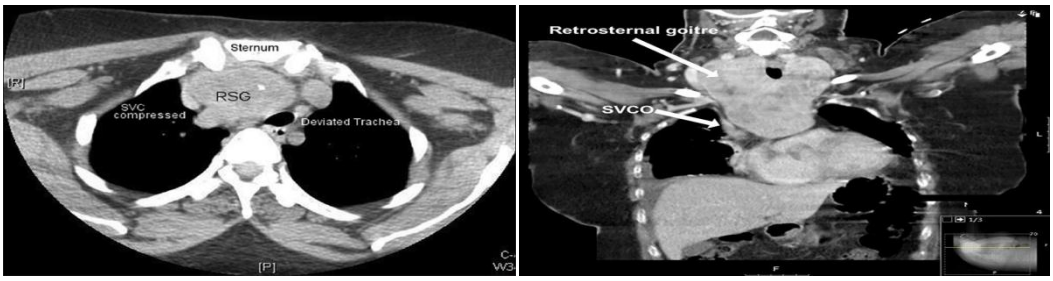


Figure 7.1 Retrosternal goitre Figure 7.2 Retrosternal goitre

4.6.5 Neoplasia[25]

It can be benign or malignant.

Benign: They are of two types. They are:

1. *Follicular adenoma:* It is a benign encapsulated tumour having follicular cell differentiation and lacks extra thyroidal invasion or nuclear features of papillary family of neoplasm. It is the most common thyroid neoplasm. Many have high levels of thyroglobulin but rarely

have symptoms of hyperthyroidism. Rest of gland shows intraluminal calcium oxalate crystals showing signs of hypofunction.

They are commonly solitary and have thin complete capsule. Surrounding areas show signs of compression.

There are various patterns: simple (normofollicular), colloid (macrofollicular), fetal (microfollicular) and embryonal(solid). As a rule, larger the nodule less likely it can be follicular adenoma. Usually mitosis is absent. Secondary degenerative changes like haemorrhage, edema, fibrosis, calcification, bone formation and cystic degeneration are present commonly in large tumours. Vessels in periphery show prominent wall thickening referred to as muscular cushions. They may exhibit papillary or pseudopapillary structures when they are labelled as papillary adenoma[(25)].

There are various histological variants. They are:

- Hurthle cell adenoma
- Atypical adenoma-pronounced cellular proliferation and less regular cytoarchitectural patterns but no invasion.
- Adenoma with bizarre nuclei-huge hyperchromatic nuclei in clusters without any features of malignancy.
- Clear cell-signet ring, mucin producing, lipid rich type
- Adenolipoma-adipose metaplasia
- Adenochondroma-cartilagenous metaplasia
- Spindle cell adenoma-resemble meningioma
- Black adenoma-deposition of cytoplasmic black pigment following minocycline therapy.

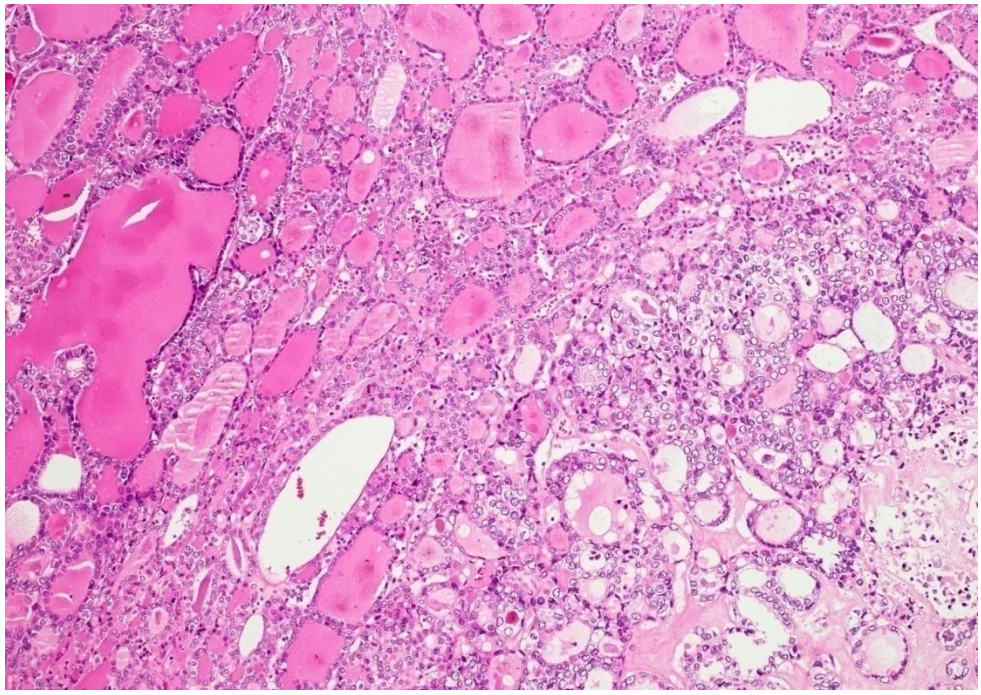


Figure 7 FollicularAdenoma

2. *Hyalinizing trabecular adenoma:* It is a term given by Carney to a type of follicular adenoma having prominent trabecular arrangement and hyaline appearance in both tumour cells and in stroma. Latter present in both cytoplasm of tumour cells due to accumulation of intermediate filaments and in extracellular space due to heavy deposition of hyalinised collagen fibres and basement membrane material. It is now considered as a microscopic incidental finding in nodular hyperplasia and in neoplasms showing capsular or vascular invasion. They are positive for thyroglobulin and TIF-1 in half cases and focal or inconstant reactivity for neuroendocrine markers. They also have peculiar cell membrane and cytoplasmic immunoreactivity for some monoclonal antibodies [(25)].

Malignant: Thyroid cancers are effectively curable. Most have a favourable prognosis. Mean survival rate after 10 years is 90% and almost 100% in young patients with non metastatic disease. Mean mortality rate is about 1.5% for females and about 1.4% for males. It is more common in women.

Five year survival rates by stage of diagnosis [33]:

- All stages: 96.7%
- Local: 99.7%
- Regional: 96.9%
- Distant: 56%

Many genetic mutations are associated with thyroid cancer. Most extensively studied are:

- RET/PTC: It is a receptor tyrosine kinase. Usually 3' portion of RET is fused with 5' portion of partner gene. They result in activation of RET proto-oncogene and are in 43% of papillary thyroid cancers. Two types are common RET/PTC1 and RET/PTC3. They are associated with radiation exposure and result in increased growth rate. Usually seen in classical papillary thyroid malignancies. They are also present in follicular adenomas and other benign thyroid pathology.

- BRAF: They result in activation of BRAF kinase and are associated with papillary thyroid cancers and poorly differentiated thyroid malignancies. Main mutations are BRAF V600E and BRAF K601E. It is activated by point mutation, small inframe insertions and deletions. V600E is associated with classical and tall cell variant. K601E is associated with follicular variant of papillary thyroid cancer. BRAF also may activated by fusion of BRAF to AKAP9 seen in 11% of cases. It is associated with old age, lymph node metastasis, distant metastasis, and persistent disease. Coexistent BRAF and RET are present in 13% of papillary cancer thyroid especially in advanced stages. Mathur *et al* found out that the increased incidence of papillary carcinoma is due to BRAF mutation [34].

- RAS: They are G proteins that function in MAPK and PI3K pathways. Mutations in 4 RAS genes HRAS, KRASA, KRASB and NRAS results in conformational change to active form and cause downstream growth effects. They are mainly seen in follicular adenomas and follicular variant of papillary thyroid malignancies. They have the worst outcomes.

- PAX8/PPRAG: It is a fusion gene as a result of t(2;3)(q13;p25) chromosome translocation. PAX8 is a paired domain transcription factor and PPARG is a nuclear hormone receptor. Its activation results in overexpression of PPRAG and results in loss of inhibition of cell proliferation and apoptosis and there by uncontrolled growth. It is common and present in 50% of follicular adenomas and 35% of follicular carcinomas.

- NTRK: Rearrangement in NTRK genes are present in 5% of papillary cancers. They are members of neutrophilic receptor kinase pathway and on fusion, they activate MAPK signalling pathway. TPM3, TPR, TFG are fusion partners of NTRK1. ETV6 is fusion partner for NTRK3.

- PI3K/AKT: Abnormal signalling of this pathway may be due to activation of promoters or due to mutation of PIK3CA and AKT1 or due to inactivation of PTEN (inhibitor). PIK3CA, a catalytic subunit of PI3K, is activated by mutation sin exon 9 and 20.

- P53: It is common in undifferentiated thyroid cancers.

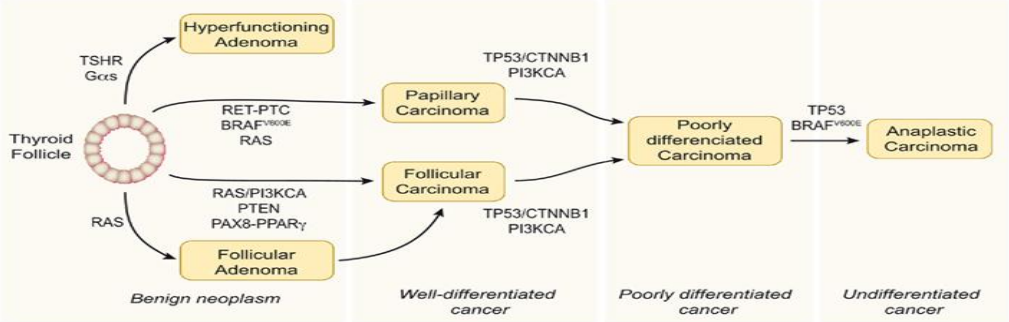


Figure 8 Genetics in thyroid malignancies

1) *Papillary carcinoma:* It is the most common thyroid malignancy. It is about 90% of thyroid malignancies in children. Incidence is more in females than males. It can occur in any age group. Mean age at diagnosis is 40 years. Increased incidence in Hashimoto and radiation exposure.

Grossly size varies from microscopic to huge. Most are solid, whitish, firm, and clearly invasive. Some have complete capsule.

Microscopically they have true papillae which may be complex, branching and randomly oriented with central fibrovascular core and single or stratified lining of cuboidal cells, some having hoebnail features. Papillae are associated with follicles. Follicles are usually irregularly shaped, often tubular and branching. Stroma may be oedematous, may contain hyaline, or lymphocytes, foamy macrophages, haemosiderin or adipose tissue. Nuclear features are:

- Ground glass nuclei (Orphan Annie nucleus) with thickened nucleolus to one side.

- Nuclear pseudo-inclusions- They are invagination of cytoplasm and are sharply outlined round vacuoles. They are positive for β-catenin and type IV collagen.

- Nuclear grooves-They like, pseudoinclusions, are the morphologic expression of infoldings of redundant nuclear membrane. They occur in oval or spindle nuclei.

- Nuclear microfilaments- due to accumulation of fine thread like fibrils.

Mitoses are rarely seen. Most show extensive fibrosis ranging from sclerohyaline to highly cellular. Stroma has extensive elastic tissue.

Psammoma bodies are seen in majority of cases. They are located in stalk, in stroma or between tumour cells. They are clinching features in papillary carcinoma. They are basophilic structures having concentric laminations which stain with mucin, calcium and iron. They appear to arise from necrosis of tumour cells. Osteopontin from macrophages is the source for their development.

There are areas of solid or trabecular pattern and foci of metaplasia. This means it is poorly differentiated. Sometimes it has spindle cell component showing metaplastic change. Blood vessel invasion seen in some cases.

Histological variants:

- Papillary microcarcinoma-These are papillary carcinoma measuring less than 1cm. Most have stellate pattern and formerly known as occult sclerosing carcinoma or nonencapsulated sclerosing tumour. Others show partial or near total encapsulation. Mutational profile same as bigger counterpart. It is a common incidental finding. It is common in males than females. Associated with cervical metastasis.

- Encapsulated variant-Papillary carcinoma totally covered with capsule. It is also associated with metastasis but less incidence of distant metastasis. They are hot on thyroid scan and characterized by pale, vacuolated colloid. Cells tend to be columnar with basal normochromatic nuclei.

- Follicular variant-This composed almost entirely of follicles. Diagnosis based on typical nuclei of papillary cancer. High incidence of nodal metastasis. They are of different types:

  - Solid variant-Common in children. Develops when proliferation exceeds secretion. Has solid nests of round shape viewed as follicles. Nuclear features are same as papillary carcinoma. This is the distinguishing feature from poorly differentiated carcinoma.

  - Macrofollicular variant-There is secretary activity more than proliferation.

  - Diffuse variant-Both lobes are involved by tumour growth.

  - Encapsulated follicular variant-Most common type. It is a neoplasm surrounded by capsule and have features of papillary carcinoma. Also known as Lindsay tumour. May or may not have vascular invasion.

- Diffuse sclerosing variant-It is characterized by diffuse involvement of both lobes, dense sclerosis, abundant psammoma bodies, solid foci, squamous metaplasia, lymphocytic infiltration, and lymph vessel permeation. Lung and brain metastasis are common.

- Oncocytic variant-It has nuclear features of papillary carcinoma and has abundant granular oxyphilic cytoplasm. Pattern may be papillary or follicular, encapsulated or invasive. May have lymphocytic stroma.

- Tall cell and columnar cell-It is a type of papillary carcinoma with single layer of tall cells and abundant acidophilic cytoplasm. May have extensive lymphocytic infiltration of stroma. This has high incidence in old age more often than conventional form and is said to be more aggressive. It has strongest association with V600E BRAF mutation. In columnar cell there will be prominent stratification and clear cytoplasm.

Mitotic figures may be seen. It lacks typical nuclear features of papillary carcinoma.

- Cribriform morular variant-It is characterized by cribriform pattern of growth and morular formation. Nuclear clearing can be seen.

- Papillary carcinoma with exuberant nodular fasciitis like stroma-In this there is prominence of stromal reaction of tumourwhich obscures neoplastic epithelial component.

Extrathyroidal extension into soft tissues of neck seen in 25% of cases. Cervical lymph node involvement is very common. Blood borne metastasis are less frequent than other thyroid cancers. Most common site is lung(identifiable by only ^{131}I scintiscan), bones, pancreas and breast.

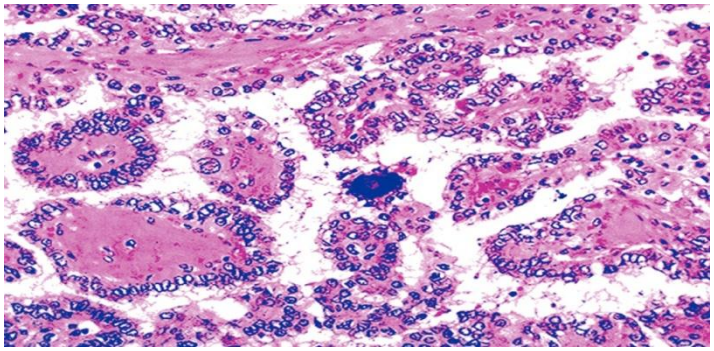


Figure 9.1 Papillary cancer conventional form

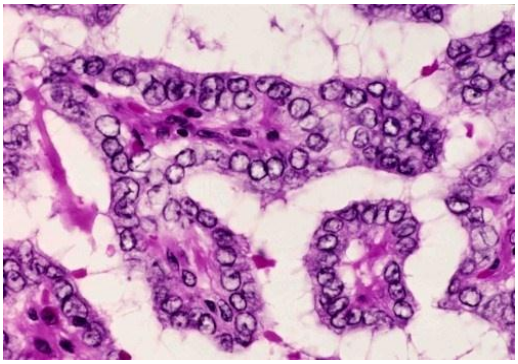


Figure 9.2 Orphan annie nuclei

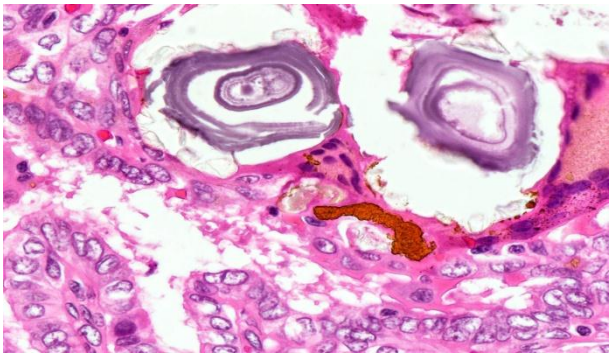


Figure 9.3 Psammoma bodies

2) *Follicular carcinoma:* It is a rare neoplasm than papillary and has same predeliction in females as that of papillary. The main feature is invasion. Mitotic activity and nuclear atypia may be lacking. There are no psammoma bodies and metaplasia is rare.

There are many subtypes. They are:

- Minimally invasive-It is a grossly encapsulated tumour with solid and fleshy cut surface. It is thought to be malignant transformation from adenoma. There may be tumour cells in vessel covered by endothelium. There will be capsular invasion.

- Widely invasive follicular-It is high risk counterpart of minimally invasive type. Has widespread infiltration of vessel. Lacks encapsulation.

- Hurthle cell-Has oxyphilic cells and occurs mainly in older patients. They have increased mitochondria and eosinophilic cytoplasm. Have increased chance of local recurrence.

They are almost always solitary and occult. Metastasis is usually blood borne. Most common sites are lungs, bone, kidney and skin. They have pulsatile bony metastasis. They have high affirmity to radioiodine and may be seen as normal tissue.

Tumours showing definite capsular invasion and no nuclear changes, are termed as follicular carcinoma.

Tumours with questionable invasion and without nuclear changes are termed follicular tumour of uncertain malignant potential.

Tumours with questionable invasion and questionable nuclear changes are termed well differentiated tumour of uncertain malignant potential.

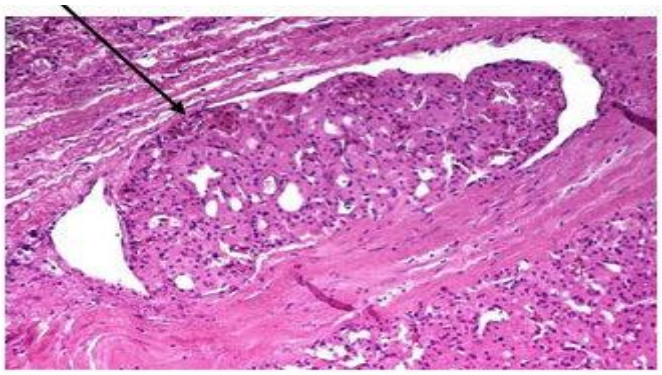


Figure 10.1 Follicular carcinoma with vascular invasion

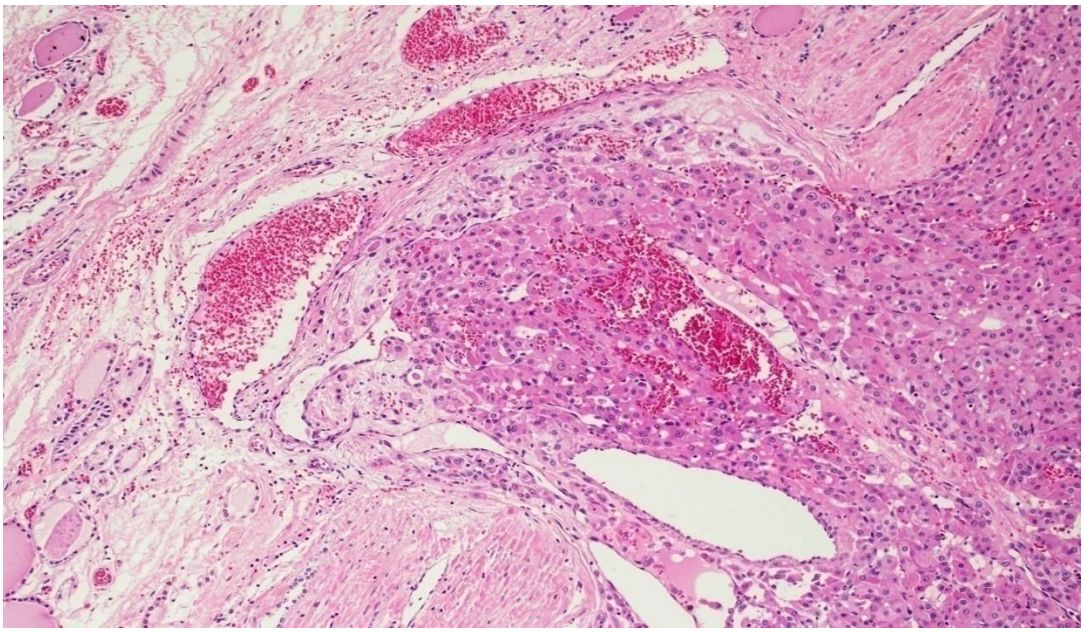


Figure 10.2 Hurthle cell variant

- ✓ Prognosis- For prognosis of well differentiated cancers certain scoring systems are involved. They are:
  - AGES: Age, Grade, Extent of disease, Size
  - AMES: Age, Metastasis, Extent of disease, Size
  - MACIS: Metastasis, Age at presentation, Completeness of surgical resection, Invasion, Size (modification of AGES)[20]
  - TNM: Tumour Node Metastasis
  - DAMES: DNA analysis, Age, Metastasis, Extent, Size

Table 2: Poor Prognostic risk classification for well differentiated thyroid cancer (AMES or AGES)

	Low Risk	**High Risk**
Age	<40 years	>40 years
Sex	Female	Male
Extent	No local extention, intrathyroidal or capsular invasion	Capsular invasion, extrathyroidal extension
Metastasis	None	Regional or distant
Size	<2cm	>4cm
Grade	Well differentiated	Poorly differentiated

3) *Medullary carcinoma:* Cancer arising from C cells of thyroid gland, also described as solid carcinoma. Grossly it is solid, firm and nonencapsulated but well circumscribed. When largest diameter is less than 1cm it is termed microcarcinoma. Most are located in midportion of upper half of gland. Microscopically it hasround to polygonal cells of granular amphophilic cytoplasm and medium sized nucleus with vascular stroma with collagen, amyloid. Calcification is common. There are many variants:

    - Inflammatory type
    - Anaplastic
    - Hurthle cell
    - Mucinous
    - Small cell type
    - Melanin producing
    - Carcinoid like
    - Pseudopapillary
    - Glandular
    - Paraganglionoma like
    - Trabecular

FNAC shows eccentric nuclei, neuroendochromatin like chromatin, inconspicuous nucleoli, amyloid and multinucleated cells.

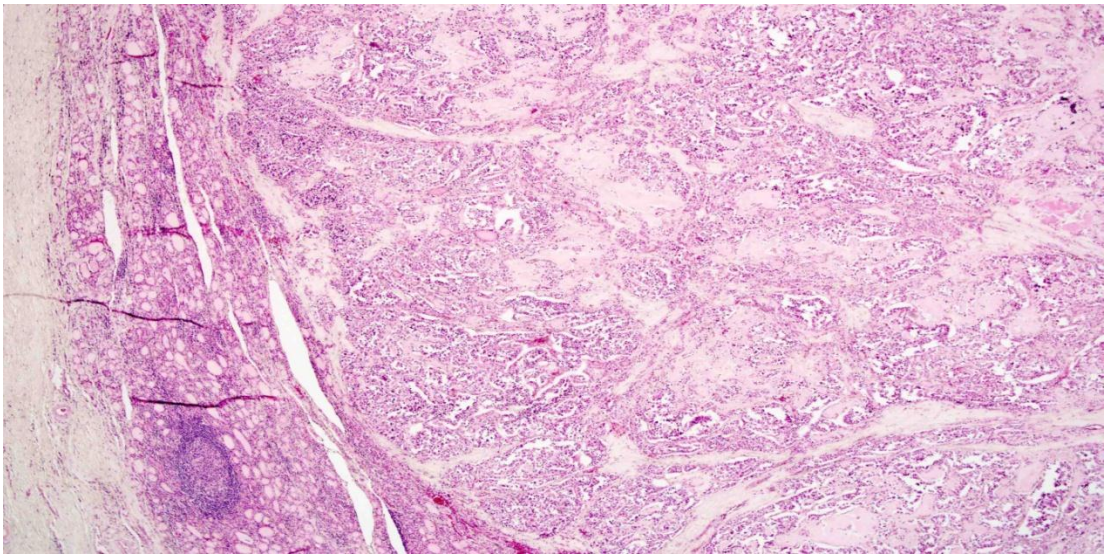


Figure 11.1 Medullary carcinoma

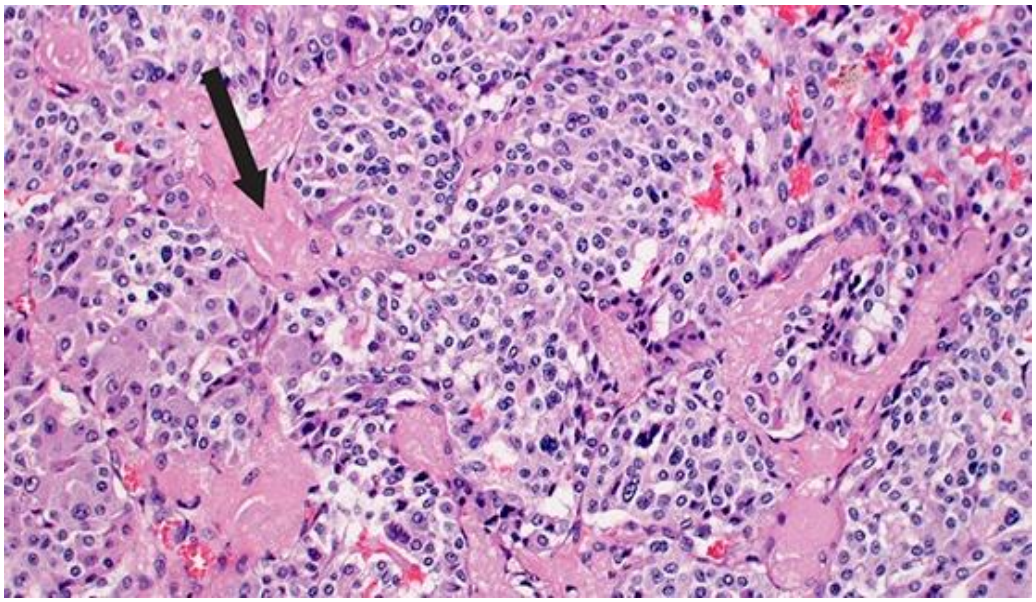


Figure 11.2 Amyloid

There are two types clinically. They are:

- Sporadic: It is about 80% of cases and mean age at presentation is 45 years. It is always solitary. It might be accompanied by diarrhea or Cushing syndrome.

- Hereditary: Occurs in younger age group (mean age of 35). It is often multiole and bilateral. It is almost always accompanied by C-cell hyperplasia. It is autosomal dominant in inheritance.

- It occurs in one of the three conditions:

  - MEN2a
  - MEN2b
  - Isolated(Familial Medullary thyroid Carcinoma)

In patients with MEN medullary cancer might be the first presentation. Gene involved is RET in chromosome 10q11.2. C-cell hyperplasia (Figure 11.3) is the clinching feature in familial disease. It is usually located in central part of lateral lobes. Might be diffuse or nodular and at least 6 cells per follicle should be present to be called C-cell hyperplasia. They have raised levels of calcitonin, CEA and chromogranin A. It invades locally and gives metastases to cervical, mediastinal, lung, liver and bones.

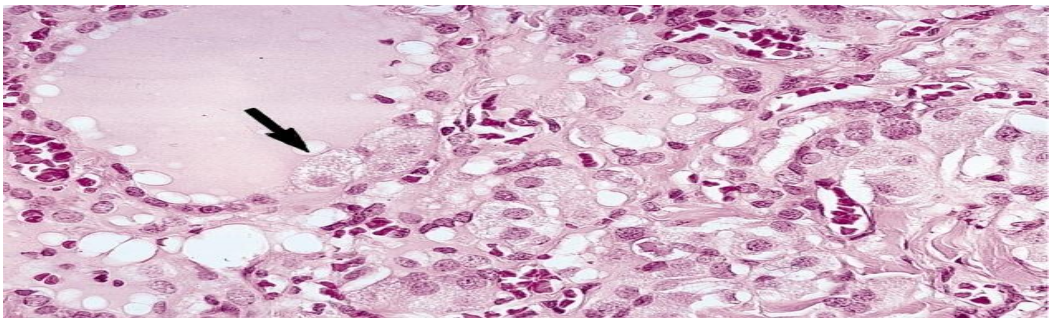


Figure 11.3 Medullary carcinoma

Table 3 Types of MEN

Syndrome	**Features**
MEN 1(Wermer Syndrome)	Pituitary adenoma Parathyroid hyperplasia Pancreatic tumours(Zollinger-Ellison, Prolactinoma, Acromegaly)
MEN 2a(Sipple Syndrome)	Parathyroid hyperplasia Medullary carcinoma thyroid Pheochromocytoma
MEN 2b(Multiple mucosal neuroma Syndrome)	Mucosal neuromas Marfanoid body habitus Medullary carcinoma thyroid Pheochromocytoma Intestinal neuroganglionomas

4) *Poorly differentialed carcinoma:* This comes in between well differentiated and poorly differentiated. Also known as insular carcinoma. Usually occur in older age group when compared to well differentiated tumours. It is grossly invasive.

   Microscopically there is nesting pattern of growth with solid to microfollicular arrangement, having variable mitotic activity and having fresh tumour necrosis giving a peritheliomatous pattern. There is focal reactivity for neuroendocrine markers.

In FNAC there is high cellularity with necrotic background having low grade atypia, nests trabeculae and microfollicles.

They can concentrate radioiodine and hence it is used for therapeutic and diagnostic purpose. They have high degree of nodal and blood borne metastasis.

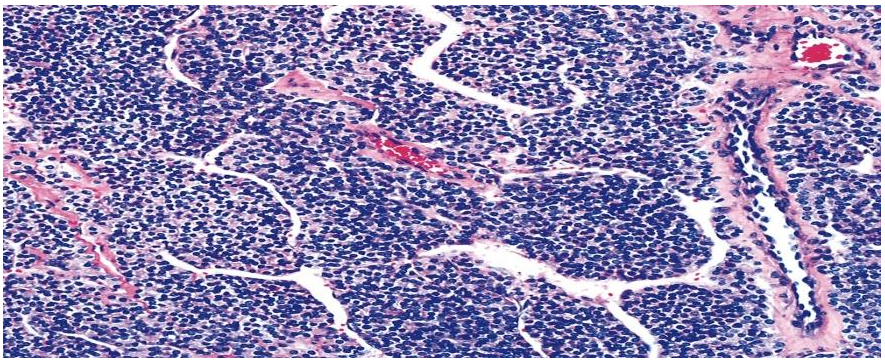


Figure 12 Poorly differentiated thyroid carcinoma

5) *Undifferentialed thyroid carcinoma:* Usually present in elderly, as rapidly growing mass with hoarseness. Also known as anaplastic carcinoma. Extra thyroidal extension is very common. Grossly there is necrotic and haemorrhagic solid mass replacing much of gland.

Microscopically two types exist. They are

- Squamoid-It has clear cut foci of keratinization. Sometimes has lymphoepithelium but not related to Epstein Barr virus.

- Sarcomatoid-It has two patterns namely spindle and giant cell. They may show variety of soft tissue sarcomas. Osteoclast like multinucleated giant cells may be present. A variant of spindle type called paucicellular variant shows extensive fibrosis and hyalinization.

Nodal metastasis are common. Mortality rate is 95% and mean survival rate is about 6 months and cause of death is usually due to involvement of vital structures on neck.

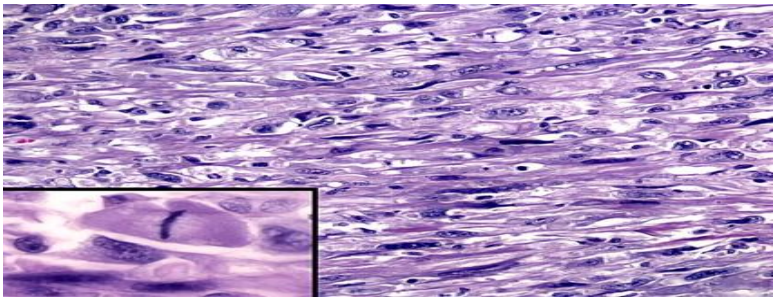


Figure 13 Anaplastic carcinoma

6) *Lymphoma thyroid:* Usually seen in adult females. Enlargement of gland is rapid and can lead to compressive symptoms. Tumour is seen as cold nodule in thyroid scan. Grossly appears as solid white surface with fish flesh appearance. Histologically it is of two types. They are:

- Diffuse B cell-Most common type. In this sclerosis is prominent. Many show focal plasmacytoid features. Some show signet ring cells. They belong to MALT type category of B-cell lymphomas. Diagnostic finding is the presence of packing of follicular cells by lymphoid cells.

- True follicular-They are very rare. Most have lymphoepithelial lesions. Mostly associated with extrathyroidal disease.

Most lymphomas arise in a sitting of systemic disease like Hashimotos. So most patients have serum anti thyroid levels high. Tumour may be local or spread to soft tissues by local spread or involve lymph nodes. Prognosis better for focal disease.

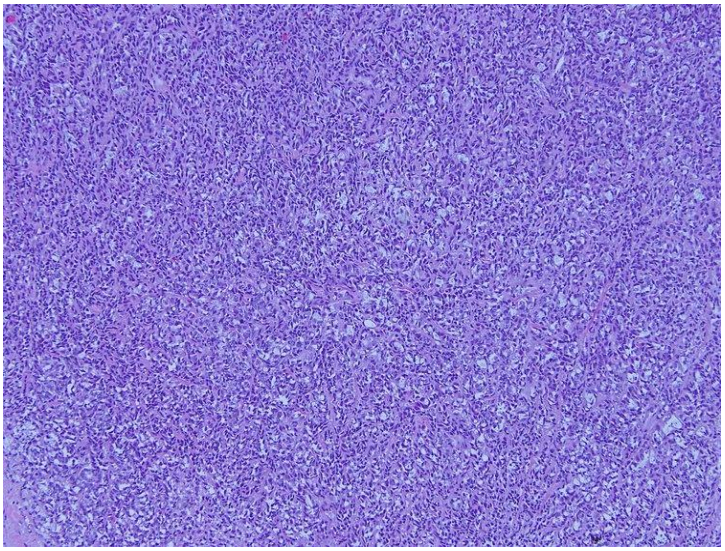


Figure 14 Lymphoma thyroid

7) *Squamous cell:* They occur due to persistent thyroglossal duct or structures from branchial pouch or in Hashimotos thyroiditis. Pure squamous cell carcinoma are extremely rare. Some are often seen with leukocytosis and hypercalcemia. Many a times they develop from papillary carcinoma(tall cell variant). There are many histological variants. They are:

- Mucoepidermoid-They are low grade thyroid neoplasm combining squamous change with mucin production.

- Sclerosing with eosinophilia-Arise from gland with Hashimotos often of fibrous type. In this there are squamous cells with pleomorphism or infiltrate dense fibrohyaline stroma. There is infiltration of eosinphils which concentrate around tumour cells. There is lymph node metastasis.

- Mucinous-Lacks squamous cell component but have varying degrees of differentiation.

- CASTLE-Also known as carcinoma showing thymus like differentiation. It is an ectopic thymic carcinoma.

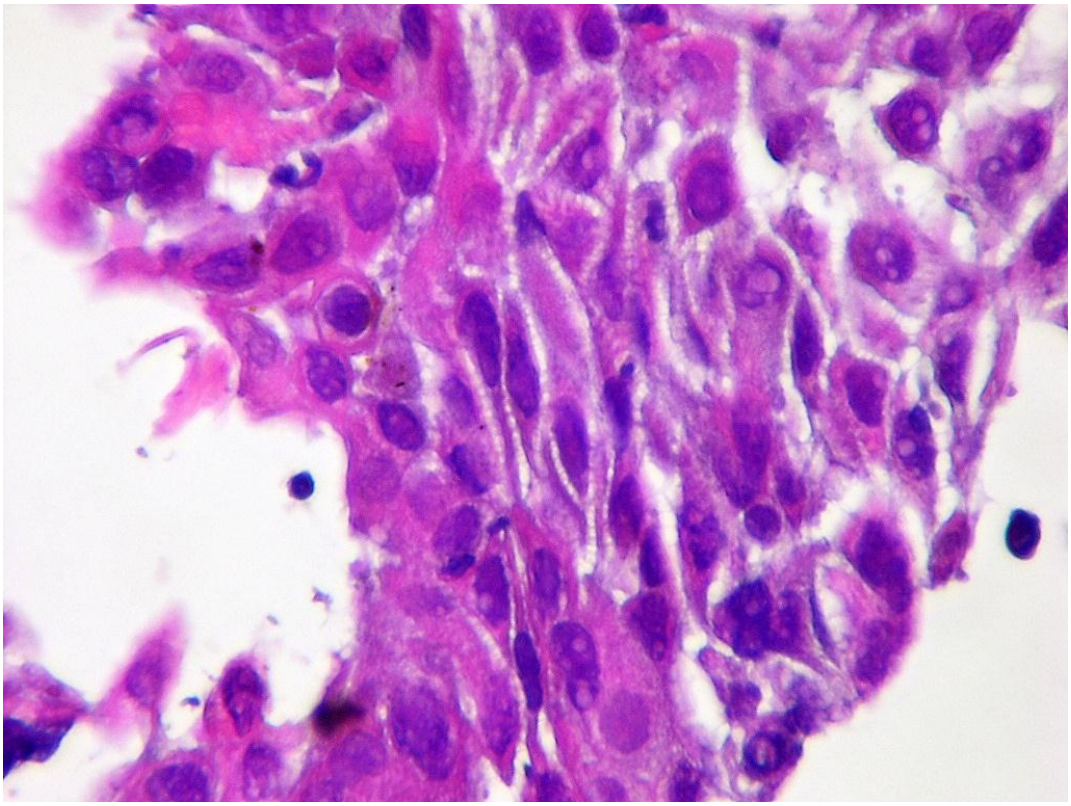


Figure 15 Squamous cell carcinoma thyroid

8) Metastalic carcinoma: Usually occur in local spread of cancer from pharynx, larynx, trachea or esophagus and also from adjacent cervical lymph nodes. Most are squamous cell type. Most common sites of primary are skin (melanoma), breast, kidney, and lung. They can be solitary or diffuse.

4.6.6 Inflammatory[25]

I. *Autoimmune*: In this condition there is production of autoantibodies against TSH and TRH, due to specific defect in suppressor T lymphocytes, that alter thyroid function. Also there is role in aberrant HLA-DR antigen expression. Due to this, there will be immune mediated insult which leads to diffuse or nodular hyperactivity and to exhaustion atrophy which manifest as diffuse oxyphilia of follicular epithelium. They are of two types:

- Hashimoto thyroiditis-It is also known as struma lymphomatosa. It predominantly occurs in women over 40years of age. Sometimes has compressive symptoms. First, patient has symptoms of hyperthyroidism followed by hypothyroidism. Sometimes it can be seen in association with lymphocytic inflammation of other organs like lymphocytic adrenalitis(Schmidt syndrome) and lymphocytic interstitial pneumonitis.

Grossly there is diffuse and symmetrical enlargement of gland or at times focal enlargement also seen. Consistency is firm and there are no extrathyroidal extension. No necrosis or calcification seen.

Microscopically there is lymphocytic infiltration of stroma and oxyphilic change of follicular epithelium. Lymphocytes are mainly T lymphocytes and are mainly present in and around follicles with prominent germional centres. Sometimes plasma cells, histiocytes, eosinophils and scattered multinucleated giant cells can be seen. Follicles are atrophic and may show persistent regenerative hyperplasia and lined by Hurthle cells. Sqamous nests and duct like structures also seen.

Two histological variants exist:

- Fibrous-It comprises about 12% of cases and is more extensive. It is of dense hyaline type and not extending beyond capsule.

- Nodular-More common type.

Complications include malignant lymphoma, leukemia, papillary carcinoma, medullary carcinoma and Hurthle cell neoplasm.

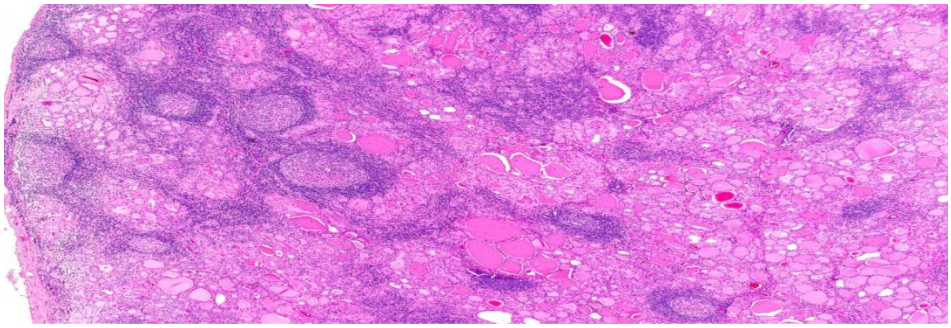


Figure 16 Hashimoto thyroiditis

- Lymphocytic thyroiditis-More common in children. Also referred to as juvenile form of autoimmune thyroiditis. They usually present as asymptomatic goiter of short duration. Radioactive iodine uptake is low. Grossly there is diffuse enlargement of gland with solid white nodular surface. Microscopically there are lymphocytic nodules with germinal centres in interstitium. Some follicles may show atrophy or oncocytic changes.

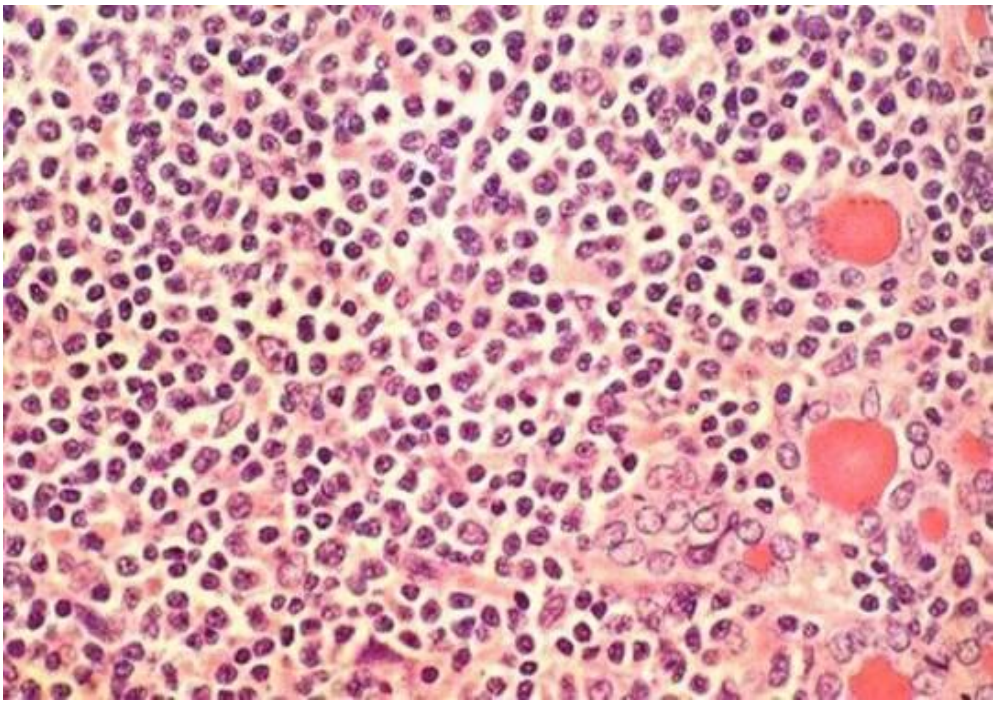


Figure 17.1 Lymphocytic thyroiditis

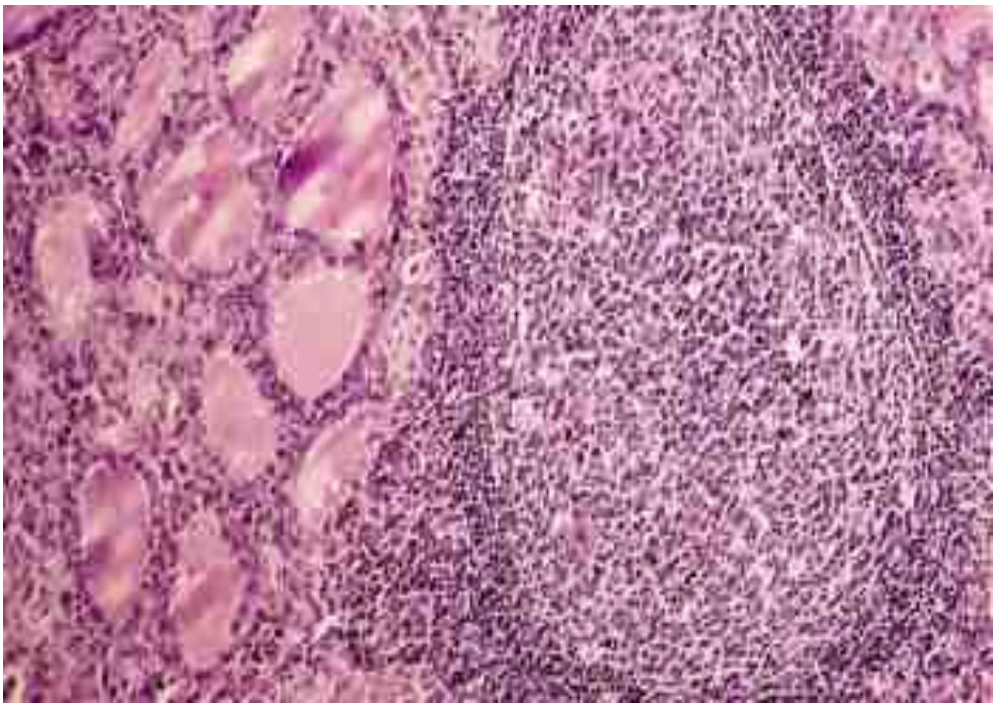


Figure 17.2 Lymphocytic thyroiditis

II. *Reidel's thyroiditis:* It is also known as Reidel struma, fibrous thyroiditis and invasive thyroidits. It is extremely rare and affects elderly people. It is more common in females. It may present as ill-defined enlargement of thyroid with dyspnea. It is extremely firm and binds to soft tissue of neck. It is not followed by acute inflammatory process. There is regional lymph node enlargement. Grossly it appears as stony hard mass and cuts with resistance. On cutting there are areas of complete obliteration of architecture.

Microscopically there is extensive hyalinization of gland. Muscles are infiltrated. Giant cells are absent. Inflammation is of mononuclear type especially lymohicytes and plasma cells. Eosinophils also present. Medium sized veins encased by fibrosis shows inflammation which is pathognomonic.

It may be associated with other disorders like inflammatory fibrosclerosis, retroperitoneal fibrosis, sclerosisng cholangitis or inflammatory pseudotumour of orbit.

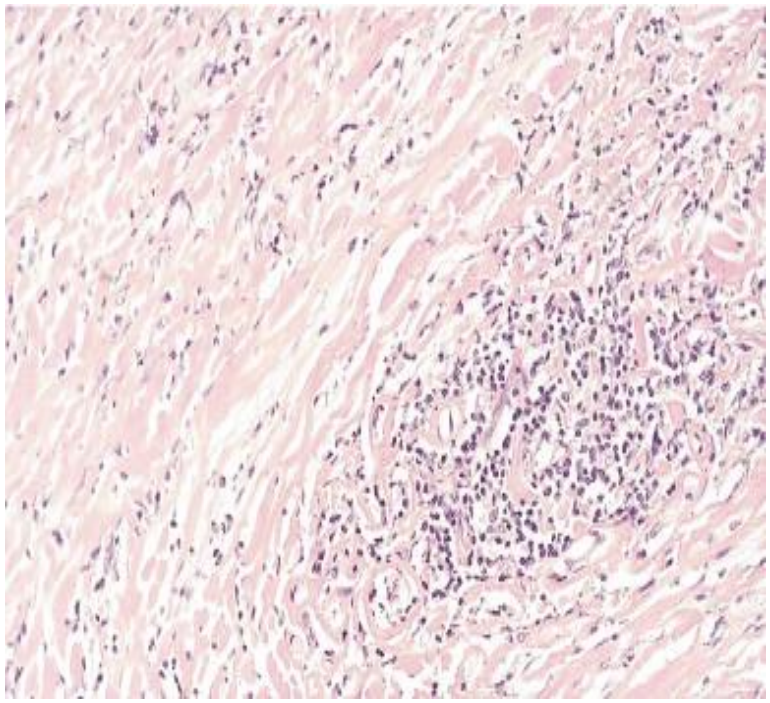


Figure 18 Reidel thyroiditis

III. *De Quervain thyroiditis:* Also known as sub acute thyroidits. Etiology unknown. Viral etiology is been suggested. Occurs in middle aged woman and presents with sore throat, painful deglutition and marked tenderness on palpation with fever and malaise. Then pressure symptoms develop. As there is often asymmetric involvement of gland it may be confused with carcinoma. It is also associated with HLA-B35 haplotype.

Grossly it has diffuser involvemet. Areas are firm with little or no infiltration.

Microscopically there are giant cells seen around follicles. Thereare no caesiating necrosis. Areas of fibrosis also seen.

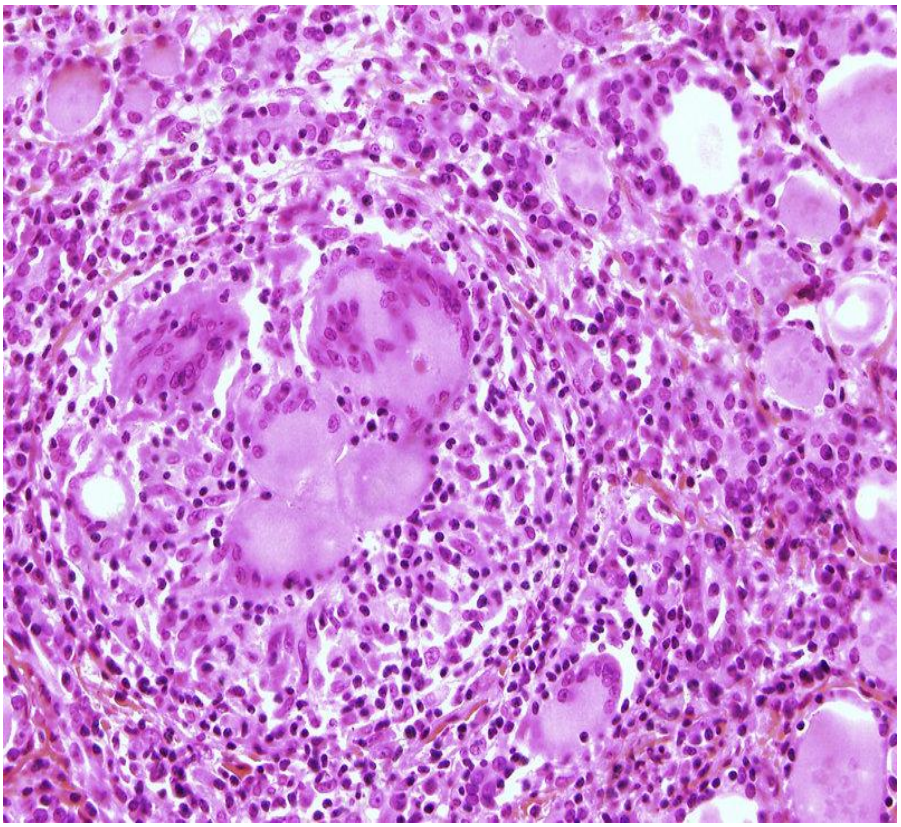


Figure 19 Quervain thyroiditis

4.6.7Infective[25]

It may be acute or chronic.

a. *Acute:* It may be associated with upper respiratory tract infection like pharyngitis or tonsillitis, sepsis or major trauma to neck with open wound. It is common in malnourished infant or bed ridden elderly and immunocompromised. Organisms involved are *Streptococcus haemolyticus, Staphylococcus aureus, Pneumococcus, Candida, Pneumocystis*. Viral infection is not common. Several cases of cytomegalovirus infection in AIDS patients reported. There will be neutrophilic infiltration and tissue necrosis. Non suppurative and suppurative forms are there. Most of suppurative forms are due to presence of piriform sinus fistula from ultimobranchial body confirmed by barium meal.

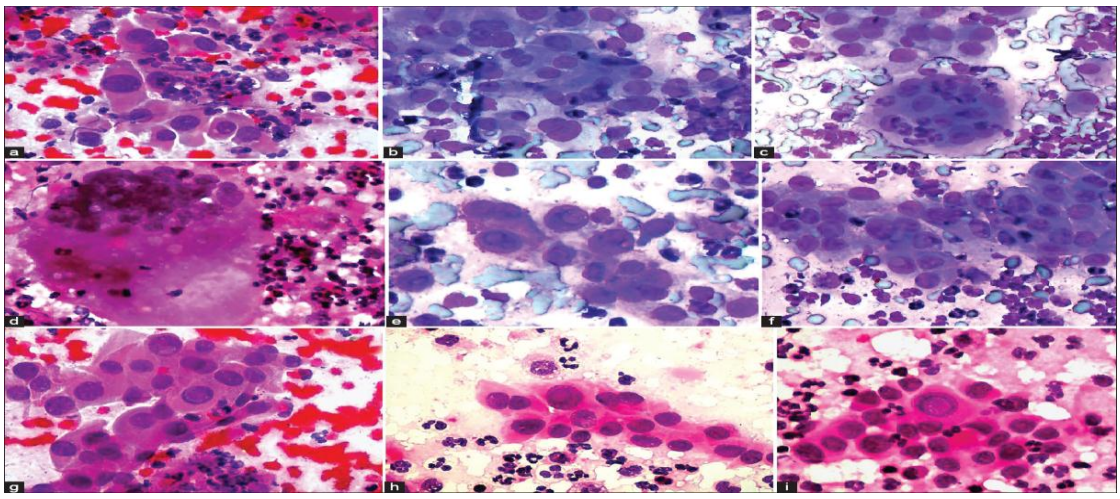


Figure 20 Acute thyroiditis

b. *Chronic thyroiditis:* It can be due to tuberculosis or syphilis.

- Tuberculosis-Usually occurs in disseminated TB and has tubercle in gland. Also occurs in cervical lymph nodes or larynx TB. (Figure 21)

- Syphilis-Usually occur in tertiary syphilis. May present as diffuse cirrhosis of gland without tumour formation or with tumour formation. Grossly looks like adenoma of thyroid. Microscopically shows irregular interstitial proliferation and giant cells with arteritis. There will be extensive fibrosis.

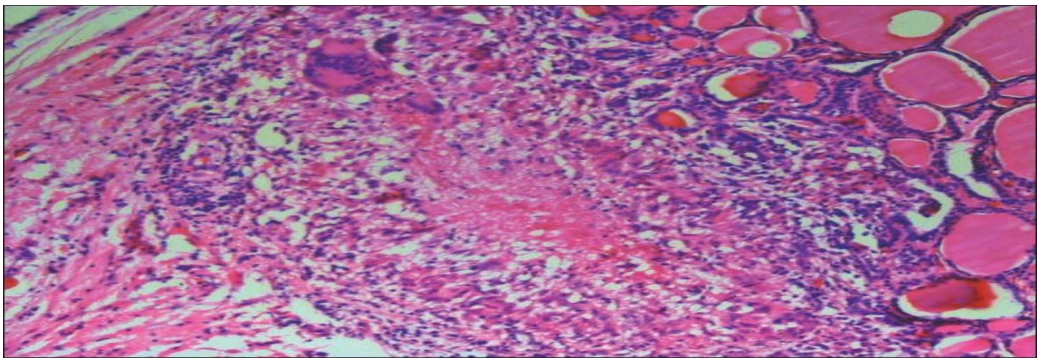


Figure 21 Tuberculosis thyroiditis

4.6.8 Others[25]

a) Palpalion thyroiditis: It is relatively common but insignificant and inconspicious process. Occurs due to minor trauma to thyroid gland or due to vigorous palpation of gland. Microscopically there are collections of histiocytes, lymphocytes and giant cells in lumen of scattered follicles or perifollicualr region.

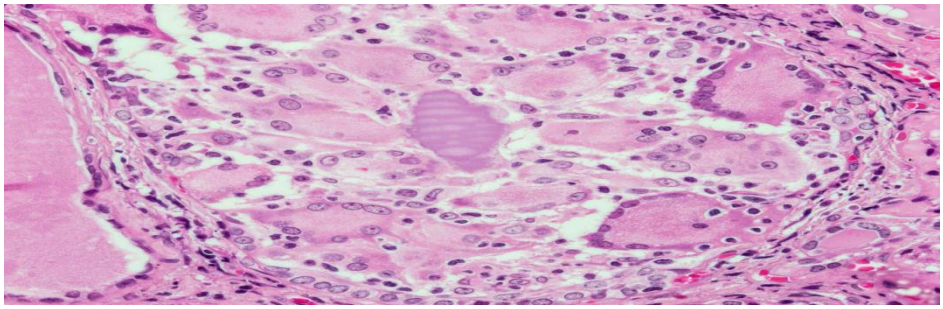


Figure 22 Palpation thyroiditis

b) *Sarcoidosis:* It may occur in form of interstitial noncaseating granulomas. It occurs usually in immunocompromised patients. Sometimes present as mass(Figure 23).

c) *Mycoses:* It usually occurs in immunocompromised patients. There will be necrosis and acute inflammation.

d) *Post operalive necrotizing granulomas*

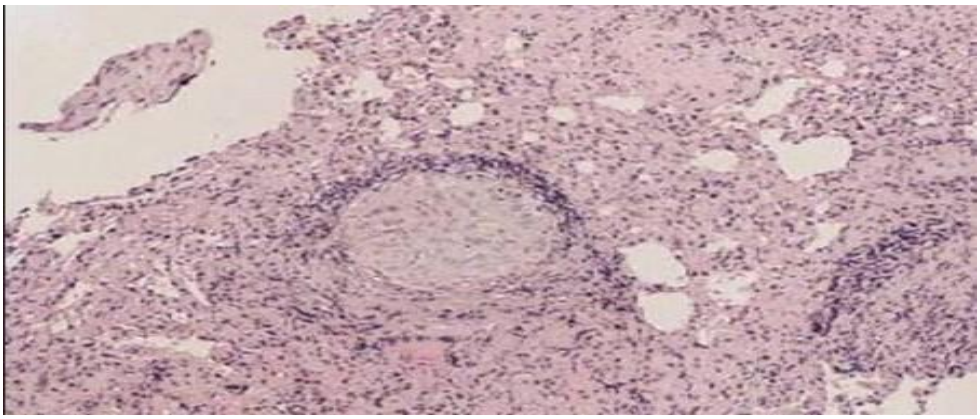


Figure 23 Sarcoidosis thyroid

4.7. Approach to thyroid swelling

4.7.1 History[32]

Usually present as swelling in neck (Figure 24) either diffuse or unilateral. Majority of cases are seen in females. Patients with thyrotoxicosis might be working in stress. Primary toxic goiter may have features of psychosis.

One should know onset, duration, rate of growth and whether painful or not. Ask for symptoms of thyrotoxicosis like palpitation, tremors, preference to cold or protruding of eyes, symptoms of cardiac failure, irritability, insomnia, weak muscles. Also symptoms of hypothyroidism have to be noted like loss of apetite, constipation, weight gain, tiredness, loss of hair, menstrual abnormality.

Ask for pressure symptoms like stridor, hoarseness of voice, dyspnea, dysphagia and snoring. Diet and drugs has relation to thyroid disorders. Ask for intake of goitrogens. Some thyroid diseases run in families. That should also be noted.

History about metastasis like bone pain, dyspnea have to be asked. This is because while presenting, about 10-15% of patients will have distant metastasis.

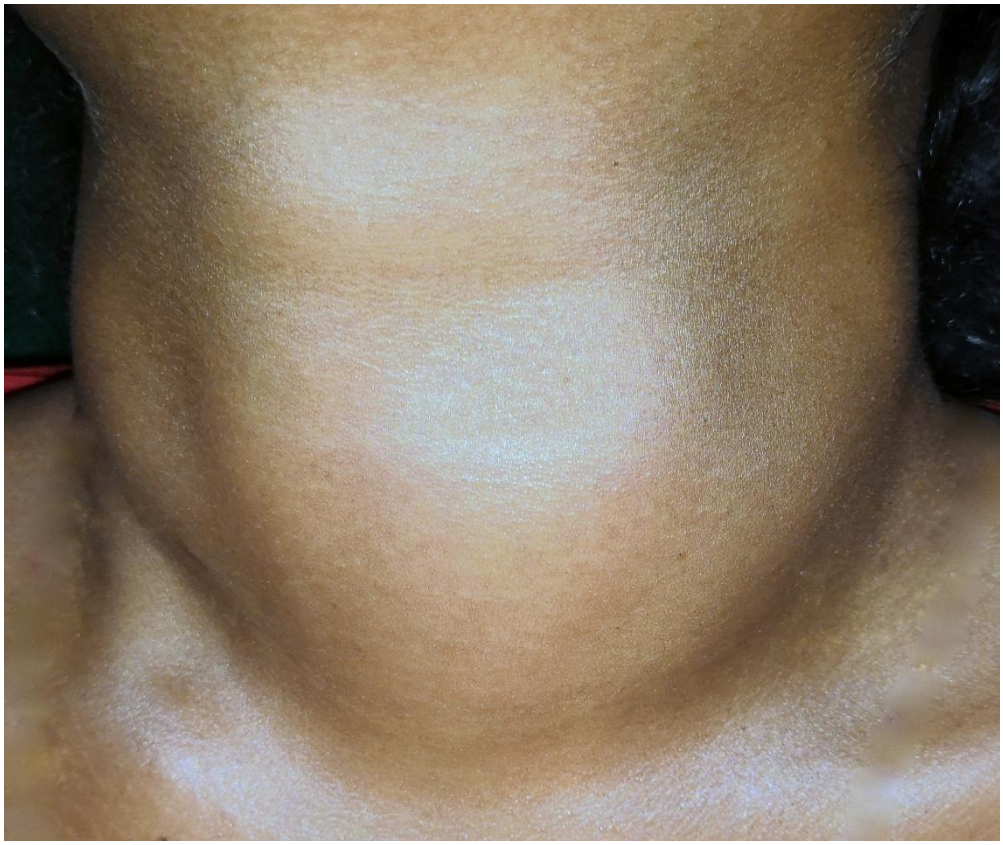


Figure 24 Diffuse swelling of neck in goiter

4.7.2 Physical Examination[32]

General survey: Look for signs of toxicity like tremors, palpitation, pedal edema, moist skin, tachycardia, arrhythmia, built and nourishment.

Local examinalion: Thyroid gland is seen only when it is enlarged. For inspection of thyroid gland some methods are there. They are:

- Pizillo's method-Patient's hands are placed behind head and patient is asked to push his/her head back against clasped hands on occiput. This will make thyroid more evident.

- Ask patient to swallow. Thyroid swelling moves up with deglutition.

In retrosternal goiter owing to pressure in great viens there will be dilatation of subcutaneous veins over anterior part of thorax. Ask patient to lift

arms above head and maintain that position for a while. If there is retrosternal extension there will be obstruction of great veins and there will be congestion of face and distress (Pemberton sign).

For palpation of thyroid gland methods are available. They are:

- Lahey's method- Examiner stands in front and to palpate left lobe, gland is pushed to left from right side by left hand of examiner. *Vice versa* for right lobe.
- Crile's method-Place thumb on the gland while patient swallows.

While palpation check whether you are able to get below swelling, to see for retrosternal extension. Also check for mobility, whether localized, whether whole thyroid gland is enlarged or focal swelling. Palpate trachea to see whether there is deviation. Check for pulsation of carotid as it may be engulfed by malignant thyroid swelling. Check for cervical lymph nodes.

Percussion: Percuss over manubrium sterni to exclude retrosternal goiter.

Auscultaion: Systolic bruit may be heard over thyroid in case of primary toxic goiter due to increased vascularity.

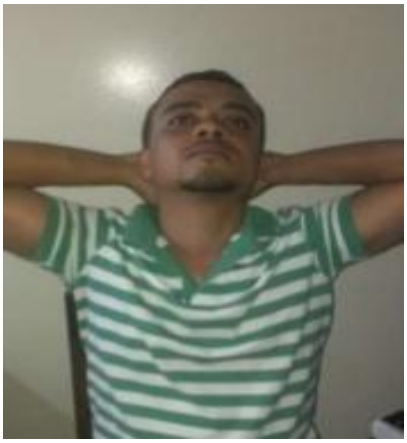


Figure 25.1 Pizzillo's method

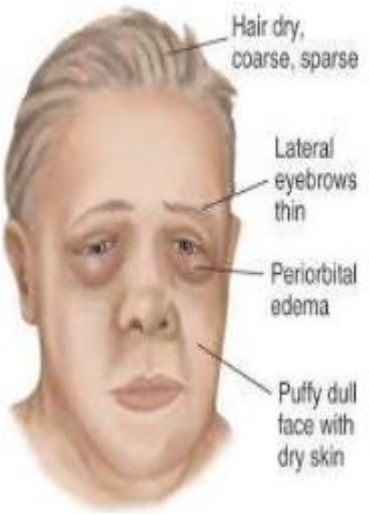


Figure 25.4 Physical examination

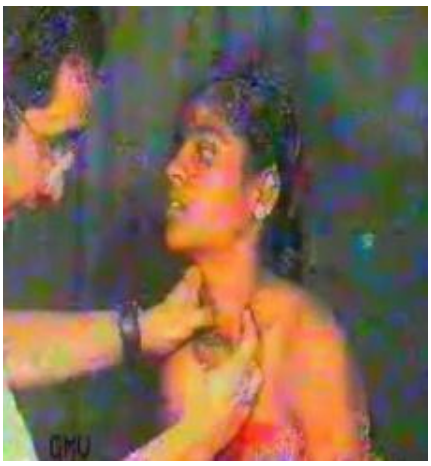


Figure 25.2 Lahey's method

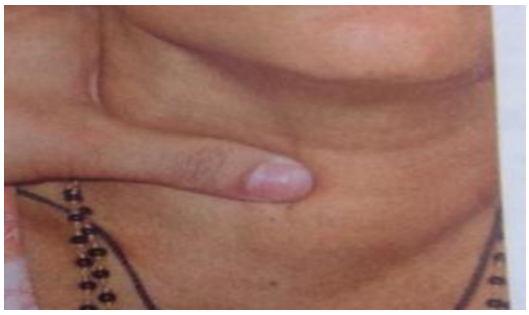
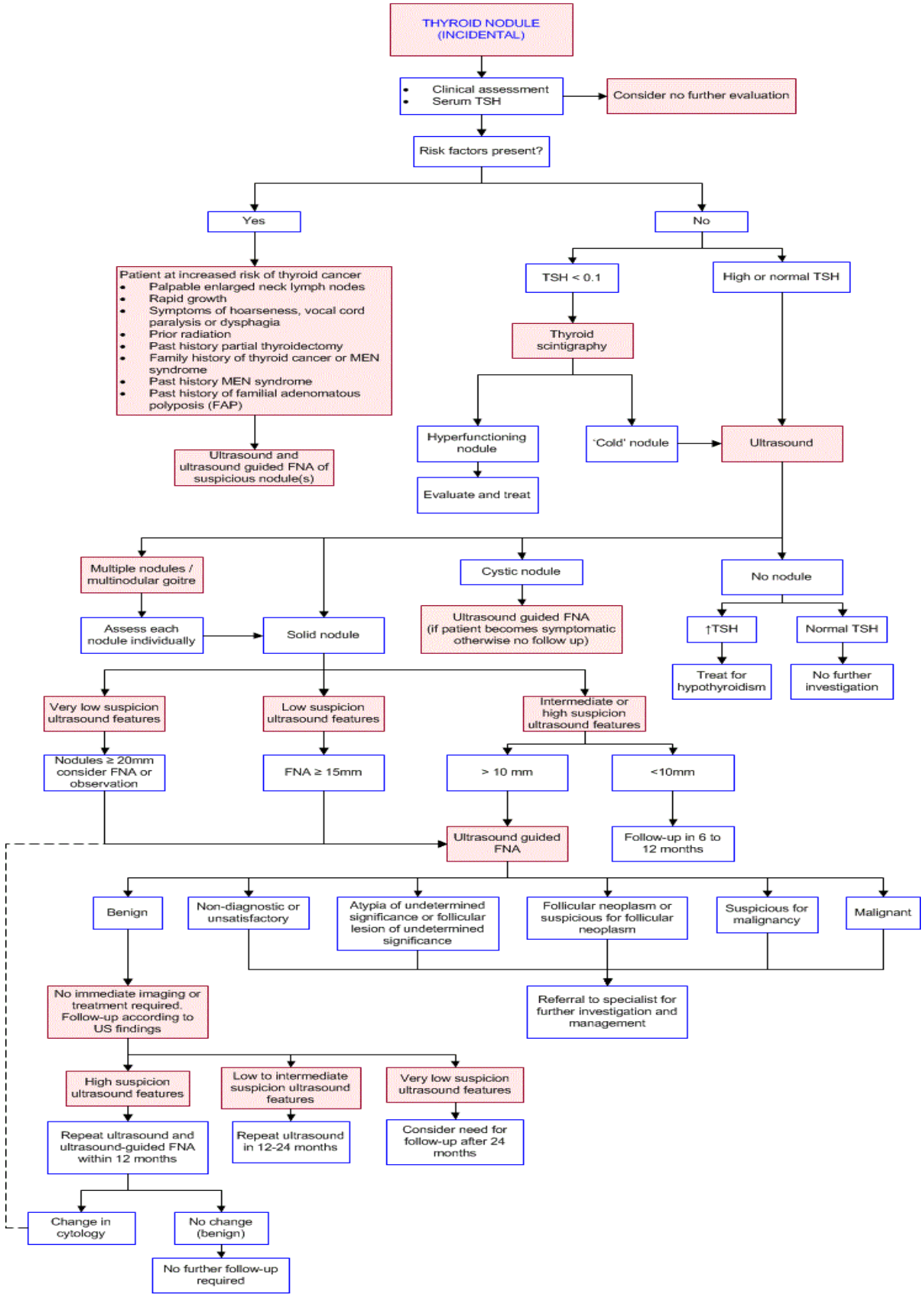


Figure 25.3 Crile's method

4.8 Algorithm for thyroid nodule



4.9 Thyroid function test[32]

There are some tests to access function of thyroid gland. If function is in excess, it is hyperthyroidism and if it is low it is hypothyroidism. Components of TFT are:

A. Serum thyroxin(T4): It is present in plasma mainly in bound form. It is bound to thyroglobulin and to prealbumin. IT is slow acting, 4-14days. Normal range is 3.0-7.5μg/dl.

B. Serum tri-iodothyronine(T3): Detected by only radioimmunoassay. It is effective in selective T3 toxicity. It is quick acting, in few hours. Normal range is 0.89-2.44nmol/L

C. Free T3: It is considered to be the single best test available at present. Normal range is 3.5-8μmol/L.

D. FreeT4: Normal range is 10-30nmol/L

E. TSH: Measured by immunoassay. Raised in hypothyroidism and vice versa in hyperthyroidism. It is an important investigation following radioiodine therapy and sub total thyroidectomy. Normal level is 0.3-3.3mU/L.

F. Calcitonin: Produced by parafollicular cells. Normal value is <8.5pg/ml for men and <5pg/ml for woman.

G. Thyroid autoantibodies: Antibodies against TPO and thyroglobulin are estimated for autoimmune diseases. Levels >25IU/ml for TPO and titres >1:100 for antithyroglobulin are significant. For Grave's disease TSH-RAB estimation is useful.

TSH	T3	T4	State
Normal	Normal	Normal	Euthyroid
Low	High	High	Primary Hyperthyroidism
High	Normal	Normal	Subclinical Hypothyroidism
High	Low	Low/Normal	Hypothyroidism
Low	Normal	Normal	Subclinical Hyperthyroidism
Low	Low/Normal	Low/Normal	Secondary Hyperthyroidism
Low/Undetectable	High	Low/Normal	T3 toxicity
Undetectable	High/Normal	High	Suppressive T4 therapy

Table 4 TFT in different thyroid pathology

4.10 Thyroid imaging

Imaging of thyroid plays an important role in evaluation of thyroid swelling. Ultrasound plays primary role in evaluating thyroid pathology. Other cross sectional modalities include CT and MRI. For functional evaluation nuclear scintigraphy is done.

- *Ultrasound*[(28)]: It is imaging tool of choice for accessing thyroid disorder. It gives accurate assessment of gland size and parenchymal echogeneity. Indications for USG include:

- Palpable neck mass
- Incidental thyroid abnormality by other imaging studies.
- Screening tool for high risk patients for malignancy
- Evaluating nodal metastasis
- Screening surgical bed for post thyroidectomy patients.
- Find other nodules in palpable solitary nodule
- Type of thyroid nodule-cystic, solid or mixed
- For FNAC guidance
- Long term follow up of benign thyroid pathology

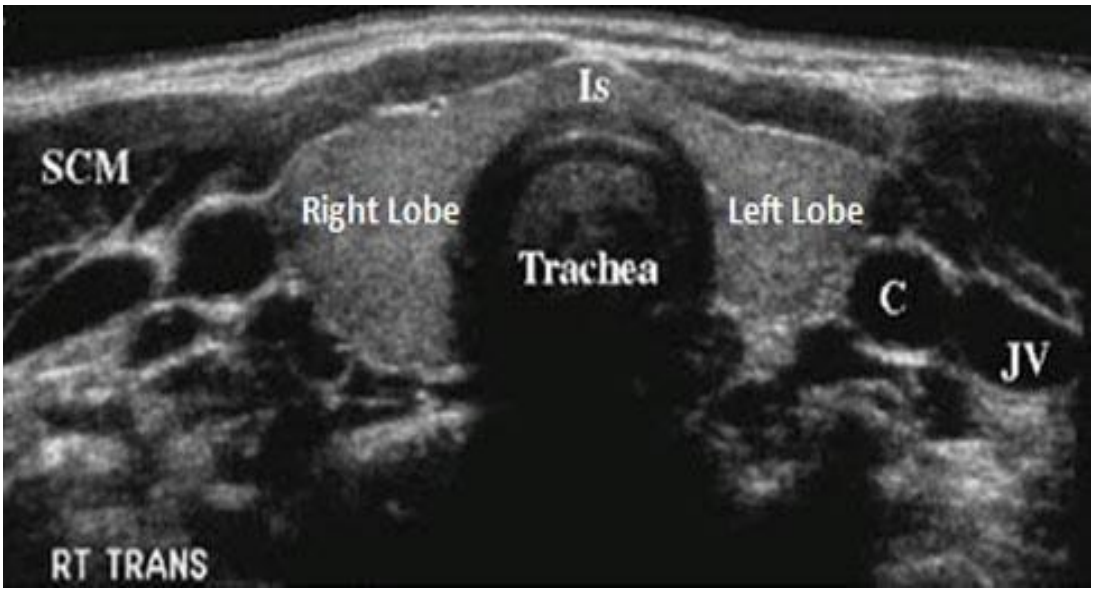


Figure 26 Thyroid in USG. SCM-sternocleidomastoid, IS-isthmus, C-commojn carotid, JV-jugular vein

Table 5 EU-TIRADS for thyroid

Category	Features	Malignancy
1: Normal	No nodules	None
2: Benign	Pure cyst, entirely spongiform	≈0
3: low risk	Ovoid, smooth iso/hyperechoic, No features of high suspicion	2-4
4: intermediate risk	Ovoid, smooth, mildly hypoechoic, No features of high suspicion	6-17
5: high risk	At least one of the features of high suspicion: ➢ Irregular shape ➢ Irregular margin ➢ Microcalcification ➢ Marked hypoechogenicity and solid	26-87

EU-TIRADS-European Thyroid Imaging and Data System

- *CT/MRI* [(28)]: They have limited ability to evaluate thyroid pathology. They are mainly used for staging of thyroid cancers. Also important for accessing retrosternal extension and assessing lymph node metastasis.

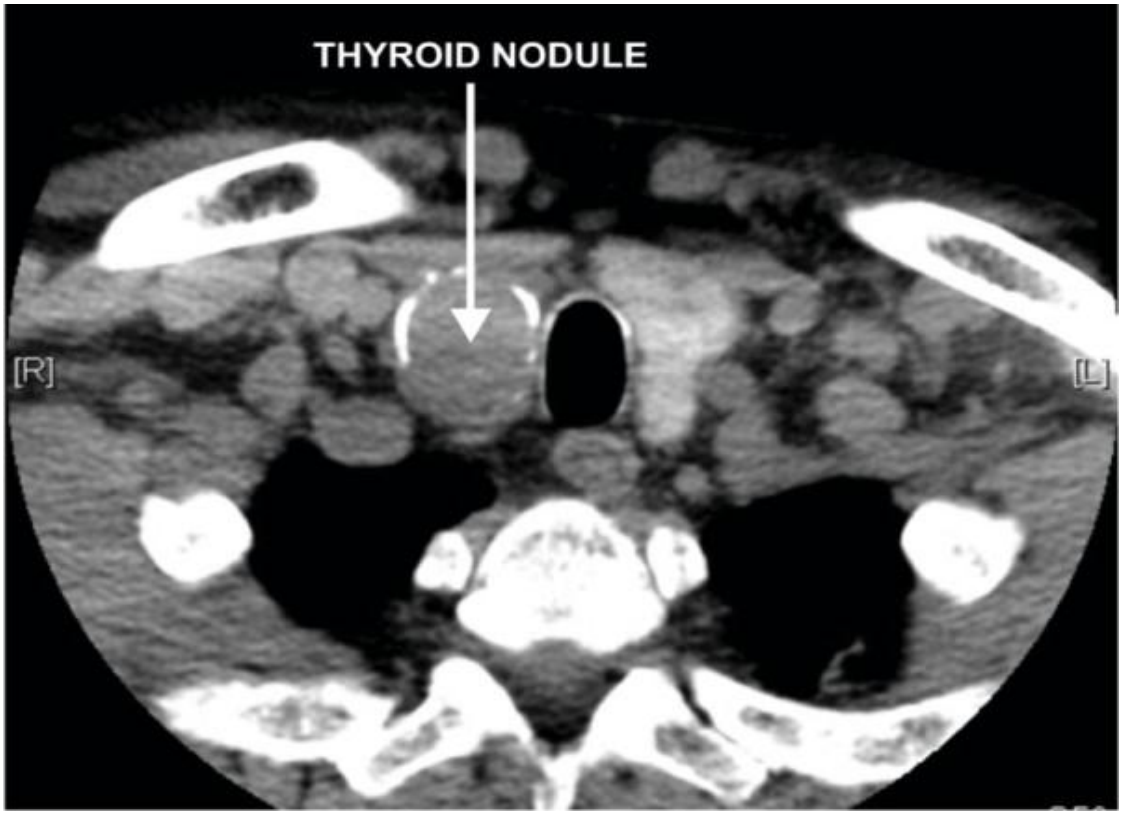


Figure 27 CT thyroid showing partially calcified complex dominant nodule in lower pole of thyroid

- *Nuclear scintigraphy*[(28)]: It is used to assess function of thyroid gland and physiological state. Isotopes used are technetium-99m (Tc-99m) pertechnetate and iodine 123(I-123). Former is trapped whereas latter is processed and organified. Advantage over Tc-99m is that it can be used when nodule is warm in Tc-99m. If cold in I-123 then FNAC is suggested. I-123 is also used for localizing ectopic tissue. Uptake is measured at 4 and 24 hours. At 4 hours it is normally about 5-15% and at 24 hours it is about 8-35%. Since iodine plays an important role, less iodine diet is advised 7-14 days prior to procedure.

This investigation is based on hormone production of gland. More the hormone produced, more will be the uptake of iodine. So if a nodule is hot in scan, it means it produces excess hormone when compared to rest of the gland. If a nodule is cold then it means it is non functional. If a nodule is warm then it means it has normal function compared to rest of the gland. Cold nodule is 16-

20% malignant, hot nodule in Tc-99m is <5% and in I-123 is <1% malignant and warm nodule is<5% malignant.

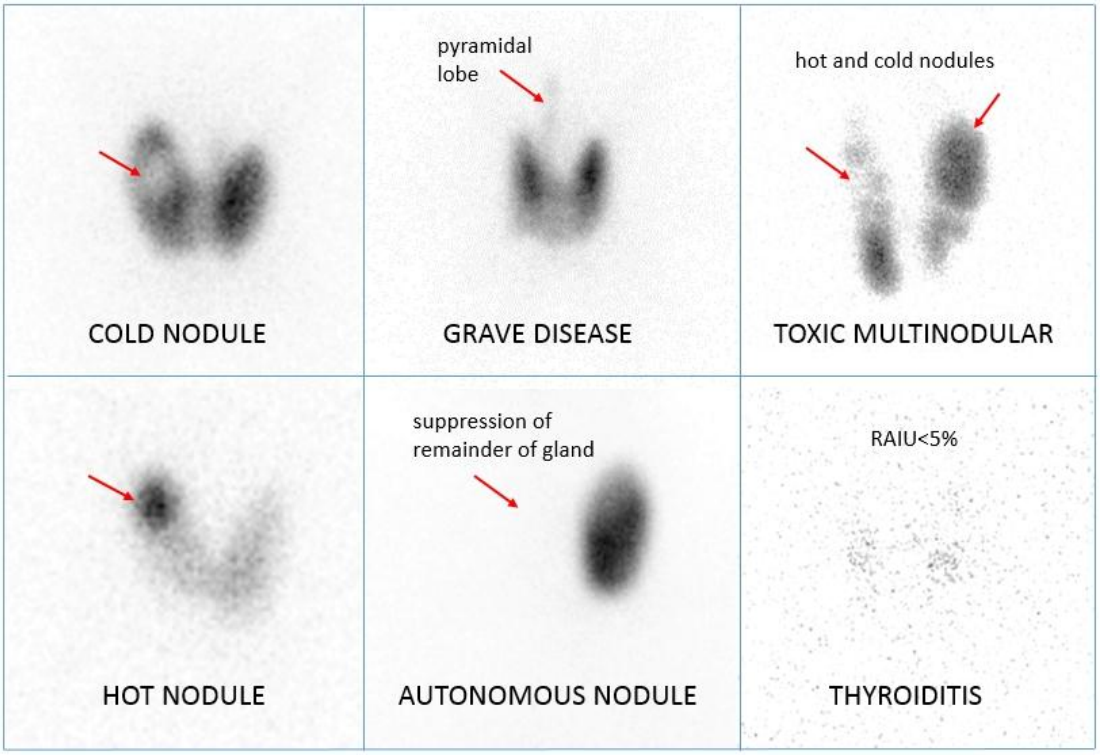


Figure 28 Radio uptake scan of thyroid

4.11 FNAC

It is the investigation of choice in evident thyroid swelling. Has good patient compliance and is simple and quick to perform. It can be easily repeated. It can be done with or without USG guidance [(1)]. It is usually the first investigation to be done while managing a case of thyroid swelling [(35) (36)].

Accuracy is more in lesions between 1cm and 4 cm. Patients with inadequate specimen should repeat or undergo thyroidectomy for further management[(37)]. It is safe, inexpensive and reliable in evaluation of nodules in childhood [(38)].

Interpretation is by THY diagnostic category system.

Table 6 FNAC Classification in thyroid [(1)]

Category	Description
Thy1	Non-diagnostic. Repeat immediately
Thy1c	Non-diagnostic cystic
Thy2	Non-neoplastic. Repeat in 3-6months. Again benign and not high risk wait and watch
Thy3	Follicular. Remove and sent for histopathological examination.(Malignancy 5-30%)
Thy4	Suspicious of malignancy(75-80%). Needs immediate thyroid exploration
Thy5	Malignant(97-99%).

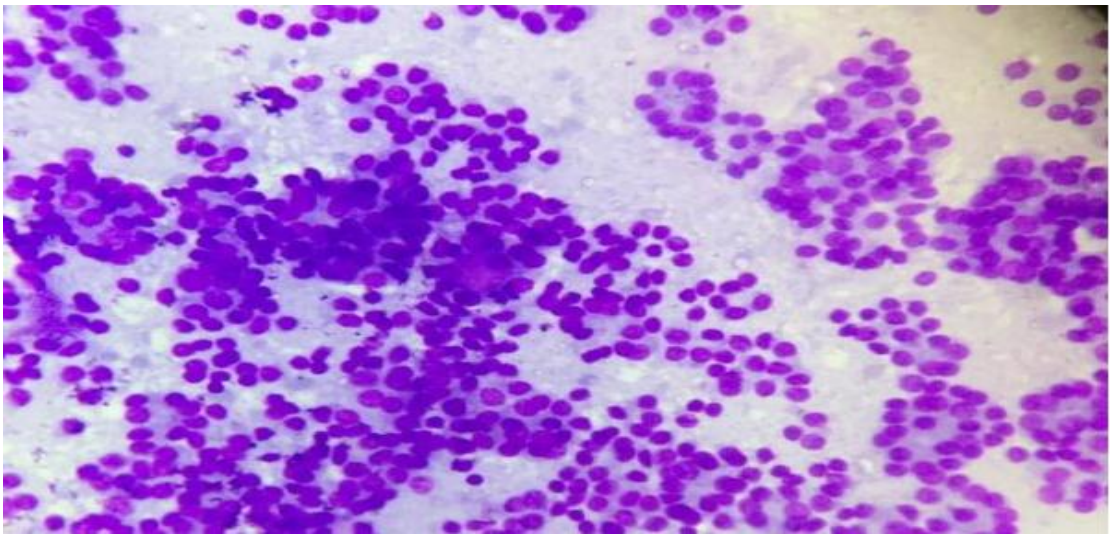


Figure 29 FNAC thyroid

4.13 TNM classification of differentiated thyroid tumours[20]

Table 7 TNM classification of differentiated thyroid tumours

Primary tumour (T)	
Tx	Primary cannot be assessed
T0	No evidence of primary tumour
T1	Tumour ≤ 2cm in diameter, limited to thyroid
T2	Tumour > 2cm but < 4cm limited to thyroid
T3	Tumour > 4cm limited to thyroid or any size with minimal extrathyroid extension
T4a	Any size with extension beyond capsule to invade subcutaneous tissue, larynx, esophagus, trachea or recurrent laryngeal nerve or intrathyroidal muscles
T4b	Tumour invading prevertebral fascia or encasing carotid artery or mediastinal vessels or extrathyroidal anaplastic cancer
Regional Lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes
N1a	Metastasis to level VI(pretracheal, paratracheal, prelaryngeal)
N1b	Metastasis to unilateral, bilateral or contralateral cervical or superior mediastinal lymph nodes
Metastasis	
Mx	Distant metastasis cannot be assessed
M1	Distant metastasis

4.14 Staging of differentiated thyroid tumours[20]

Table 8 Staging of differentiated thyroid tumours

I	T1N0M0
II	T2N0M0
III	T1-T3N1aM0 T3N0M0
IVa	T1-4aN1bM0 T4aN0-1aM0
IVb	T4bN0-1bM0
IVc	T0-4bN0-1bM1

4.15 Treatment

Patients who have high risk tumours or bi-lateral tumours should undergo total thyroidectomy. Enlarged ipsilateral central neck nodes if present should be removed by neck dissection. Prophylactic neck dissection is not necessary.

Advantages of total thyroidectomy:

- Enables use of RAI to detect and treat residual thyroid tissue
- Makes serum TG more sensitive
- Eliminates contralateral occult cancers
- Reduces recurrence
- Decreases progression to undifferentiated cancer

- Reduces need for reoperation

Advantages of lobectomy:

- Less complication rate
- Tumour multicentricity is of little prognostic significance
- Patient who underwent lesser procedure still have good prognosis
- Recurrence is rare and treatable by surgery

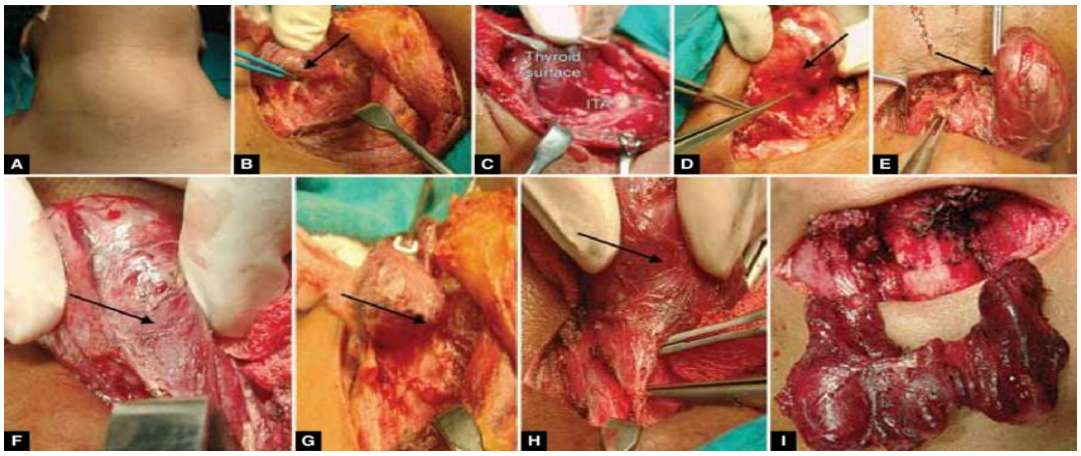


Figure 30 Steps of thyroidectomy A to I: Steps of PBC parathyroid-sparing thyroidectomy. Block arrows indicate plane of PCB dissection: (A) clinical photograph of goiter, (B) plane of dissection lower pole, (C) showing ITA and surface dissection is on surface of thyroid, (D) posteromedial dissection using pinch, burn and cut, (E) showing parathyroid, (F) one pole completely mobilized, (G) recurrent laryngeal nerve, (H) attachment at ligament of berry and (I) excised thyroid displaced

4.16 Post operative management of differentiated cancer

Thyroid hormone: TSH suppression help reduce recurrence. Thyroid hormone has to be supplemented to keep TSH at level of 0.1μU/L.

Thyroglobulin measurement: Levels should be < 2ng/ml when taking T4 and <5ng/ml when hypothyroid. Any value >2ng/ml after surgery is suggestive of metastasis or residual tissue. Levels have to be checked at 6 month interval, then 1year interval if clinically free. In high risk patients in addition USG neck or CT or MRI neck is advisable.

Radioiodine therapy: Post operative radioiodine, according to researchers suggestreduction in recurrences and improves survival even in low risk patients. Also metastasis can be treated by I-131 therapy. For this thyroxine is discontinued 6 weeks before scanning with I-131. To prevent hypothyroidism he/she should be on oral T3. Also low iodine diet is advisable. Maximum dose that can be given at a time is 200mCi with maximum of 1000-1500mCI per day. If scans are negative but still Tg levels remain elevated, then USG/MRI/FDG-PET scan is advisable.

External beam radiotherapy: It is occasionally used to control unresectable or locally invasive disease and to treat metastasis.

5. MATERIALS AND METHODS

This study is based on reports of biopsy and FNAC by Department of pathology, Sree Mookambika Institute of Medical Sciences, Kulasekharam and case record of patients coming to OPD and admitted in surgical wards in this hospital.

FNAC was performed by 22 or 23 guage needle with 10ml syringe. The nodule is fixed with finger and needle is rapidly directed through skin to nodule. Six samples of aspirated are collected and mounted on slides and dipped in alcohol fixative. Then it is stained with Papnicolou or Haematoxylin-Eosin stain.

Comparison between USG thyroid, FNAC thyroid and Histopathology report were done and statistical data was obtained.

- Study design

  It is a descriptive cross sectional study

- Study setting

  Department of General Surgery, Sree Mookambika Institute of Medical Sciences, Kulasekharam

  Department of Pathology, Sree Mookambika Institute of Medical Sciences, Kulasekharam

- Study subjects

  Patients presenting to OPD in general surgery in Sree Mookambika Institute of Medical Sciences with thyroid swelling.

- Study period

  18 months

- Inclusion Criteria

  - Cases of thyroid swellings from Sree Mookambika Institute of Medical Sciences
  - Patients above age of 18

- Exclusion Criteria

  - Patients having other head and neck swellings
  - Patients below 18 years of age
  - Patients not giving consent

- Number of groups

  1 group involved

- Whether placebo used **:**

  No

- Whether drug used **:**

  No

- Whether study is intradepartmental or extradepartmental ?

  Yes. Department of Pathology

- Any extra materials/ finance required/ obtained to carry out the study:

  Yes

- If yes, write in detail about the source of the finance:

  Self-funding

- Procedure in detail:

Data is collected at time of consultation in OPD as well as admission in hospital bydirect interview of patient using structured questionaire along with clinicalexamination.

Patient is subjected to USG thyroid, FNAC and Exision biopsy. Biopsy reports are collected at time of review. Cross sectional analysis of histopathological reports are done.

Thyroidectomy : Patient in supine position. Parts painted and draped. Kocher's incision made. Incision deepened. Deep fascia dissected. Strap muscles separated. Vessels identified and ligated. Nerve identified in both sides. Thyroid gland exiced in toto. Haemostasis achieved. Incision sutured in layers.

- Software :
  - Microsoft Excel and Microsoft Word for data entry.
  - Analysis by SPSS software.
- Statistical tests used :
  - Descriptive statistics
  - Sensitivity and specificity
- Sample size:

  Size: 65

  Scientific Basis for sample size used in the study

  Sample Size(n) = $z_\alpha^2 4pq/d^2$

  Where z_α^2 = error(taken as 1.96)

  p = prevalence(of occult carcinoma) = 60%

q = 100-p = 40%

d = precision(taken as 20% of p) = 12

n = (1.96x1.96x60x40)/(12x12)

= 64.026 ≈ 65

6. RESULTS

6.1Age

The distribution of age in the study population ranges from 20 to 76 years.

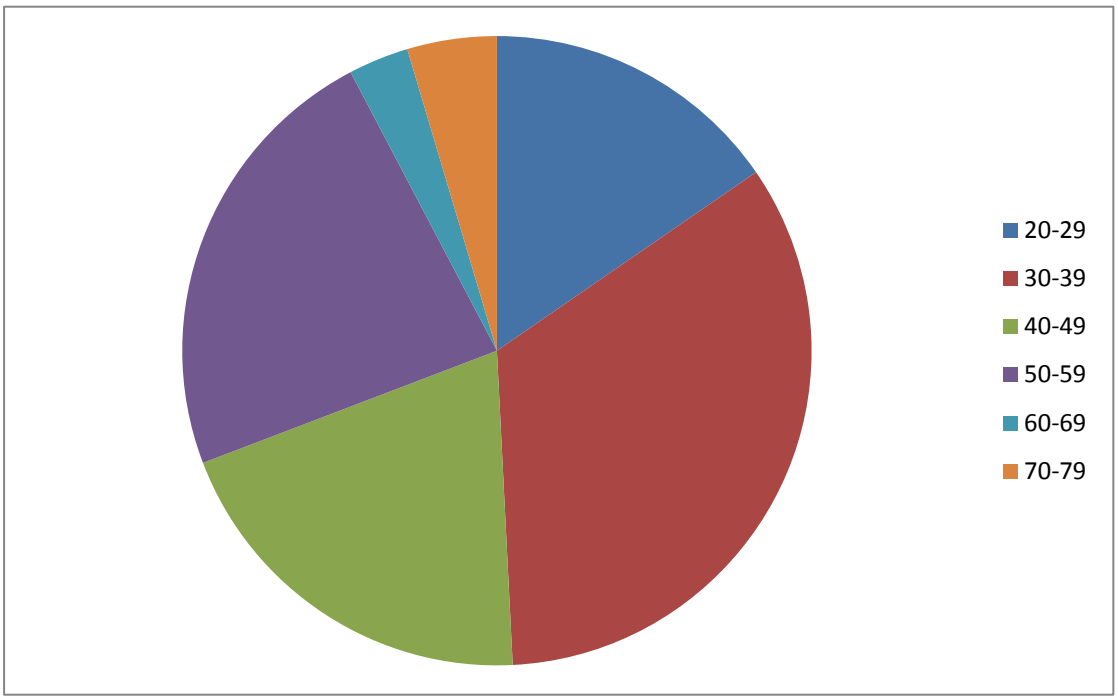
6.2 Distribution according to age of participants

Age characteristics (Years)	Value (N=65)
Mean	42.34
Standard deviation	12.452
Minimum	20
Maximum	76

6.3Distribution according to age group of participants

Age group	**Frequency**	**Percentage**
20-29	10	15.4
30-39	22	33.8
40-49	13	20
50-59	15	23.1
60-69	2	3.1
70-79	3	4.6
Total	65	100

6.4 Distribution of age group in the study population

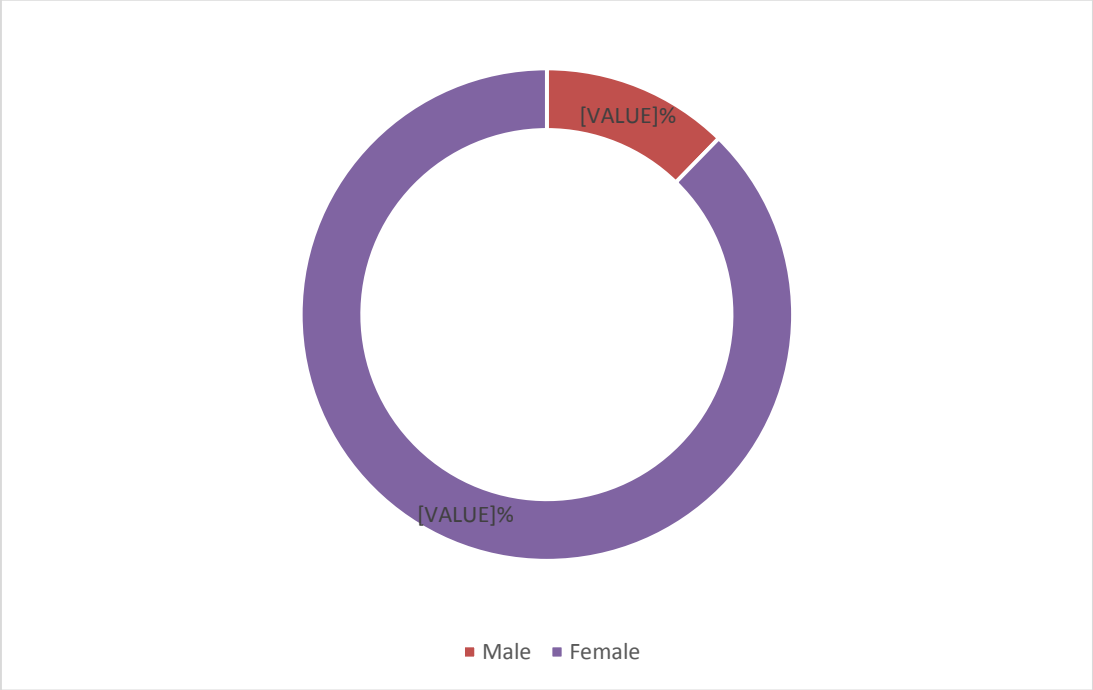


6.5 Gender

Majority of the study population were females (87.7%).

Gender	Frequency	Percentage
Female	57	87.7
Male	8	12.3
Total	65	100

6.6 Distribution of gender in the study population

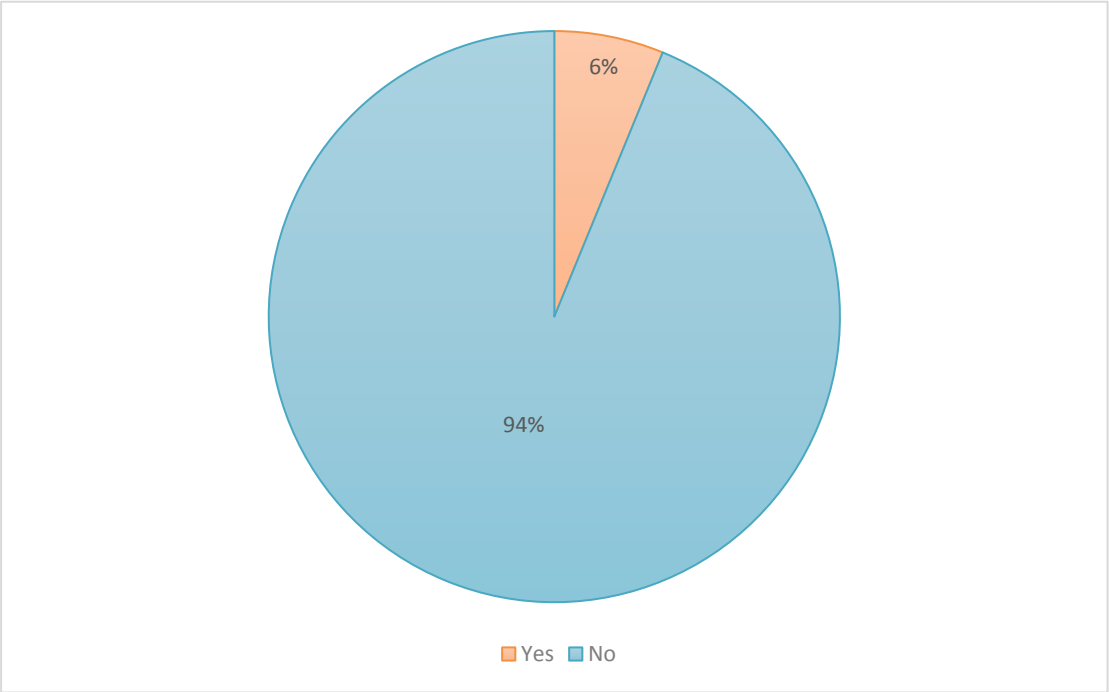


6.7 DM

Only 6.2% of the study population have diabetes.

DM	Frequency	Percentage
No	61	93.8
Yes	4	6.2
Total	65	100

6.8 Distribution of diabetes in the study population

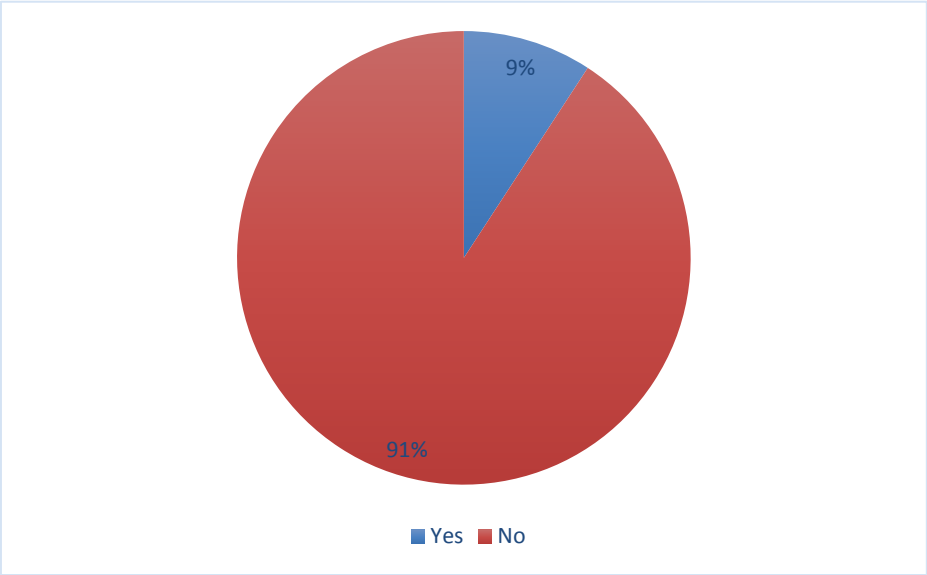


6.9 HTN

9.2% of the study population have hypertension.

HTN	Frequency	Percentage
No	59	90.8
Yes	6	9.2
Total	65	100

6.10 Distribution of hypertension in the study population



6.11USG

USG	Frequency	Percentage
DG	5	7.8
MNG	42	64.6
MNG WITH NODULE	1	1.5
SNT	16	24.6
THYTOIDITIS	1	1.5
Total	65	100

6.12 FNAC

FNAC	Frequency	Percentage
COLLOID GOITRE	38	63.3
Cyst	1	1.5
Follicular neoplasm	15	23
HASHIMOTO	5	7.7
LT	6	9.2
Total	65	100

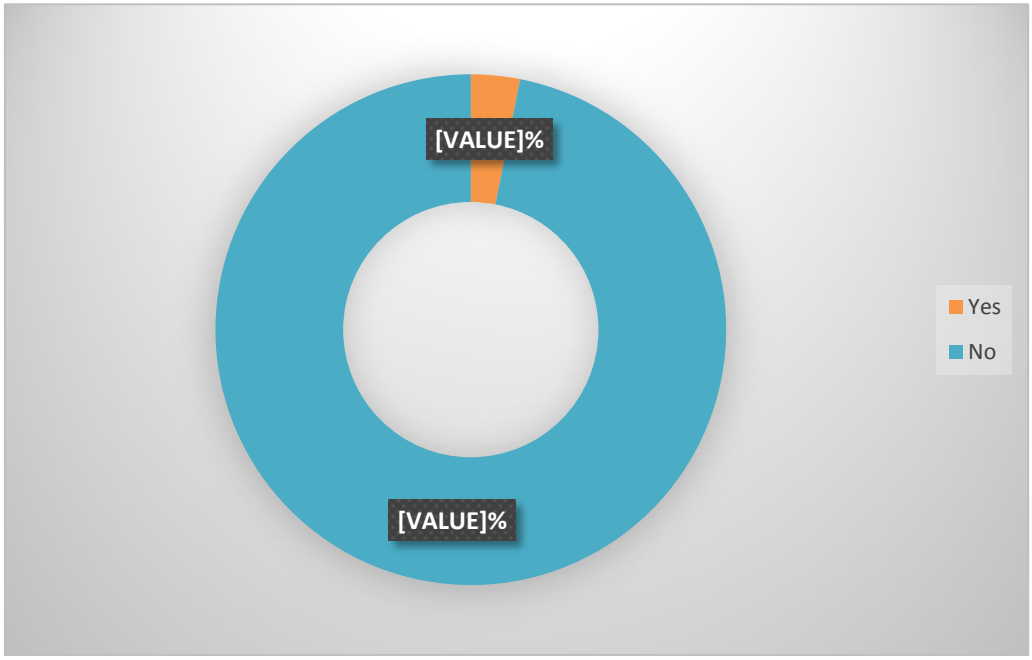
6.13 HPE

HPE	Frequency	Percentage
Adenoma with LT	1	1.5
FOLLICULAR CA	3	4.6
Hashimotos	8	12.3
Hashimotos with micro papillary	1	1.5
Hashimotos with PAPILLARY CA	1	1.5
LT	2	3.1
Medullary Carcinoma Thyroid	1	1.5
Nodular Colloid Goitre	36	55.3
Nodular Colloid Goitre with micropapillary Ca	1	1.5
PAPILLARY CA	11	16.9
Total	65	100

6.14 Micro Malignancy

Micro malignancy	Frequency	Percentage
No	63	96.9
Yes	2	3.1
Total	65	100

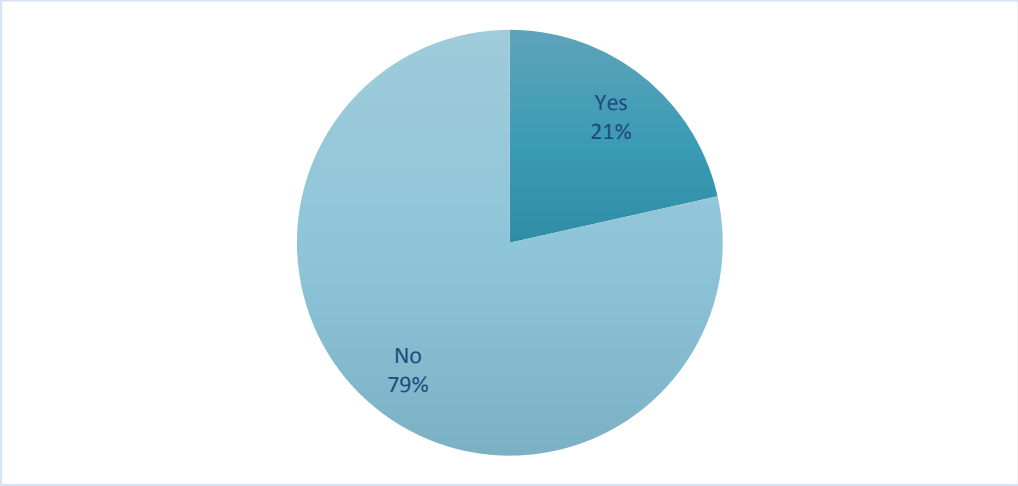
6.15 Distribution of micro malignancy in the study population



6.16 SNT

SNT	Frequency	Percentage
No	51	78.5
Yes	14	21.5
Total	65	100

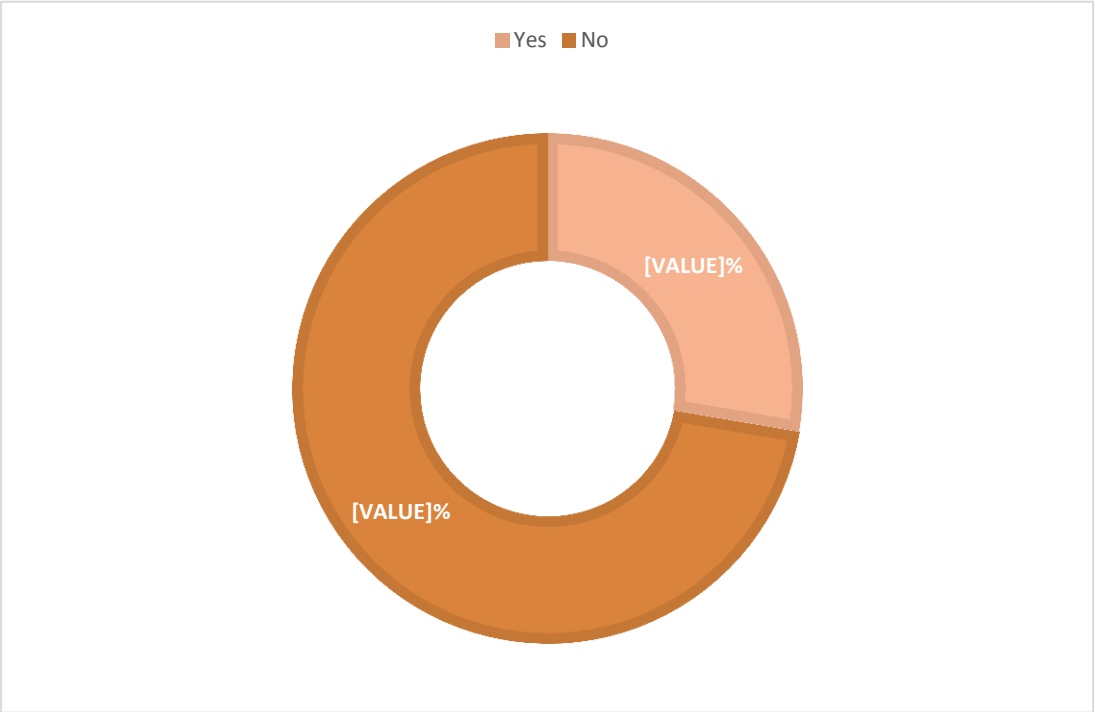
6.17 Distribution of SNT in the study population



6.18 Malignancy

Malignancy	Frequency	Percentage
No	47	72.3
Yes	18	27.7
Total	65	100

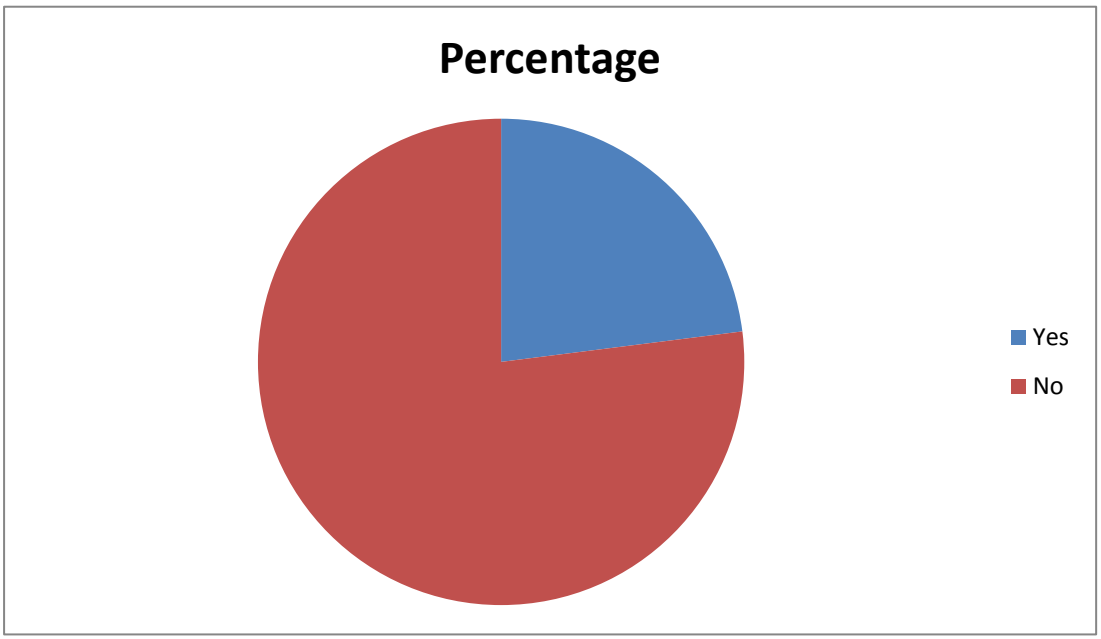
6.19 Distribution of malignancy in the study population



6.20 FNAC Neoplasia

FNAC Neoplasia	Frequency	Percentage
No	50	77
Yes	15	23
Total	65	100

6.21 Distribution of FNAC neoplasia in the study population



6.22 Relationship between SNT and malignancy

In this study it is found that SNT have statistically significant association with malignancy ($p<0.05$).

6.23 Association between SNT and malignancy

SNT	Malignancy		Total
	Yes N (%)	No N (%)	
Yes	11 (61.1)	3 (6.4)	14
No	7 (38.9)	44 (93.6)	51
Total	18	47	65

$p=0.001^{*}$

6.24 Relationship between FNAC Neoplasia and malignancy

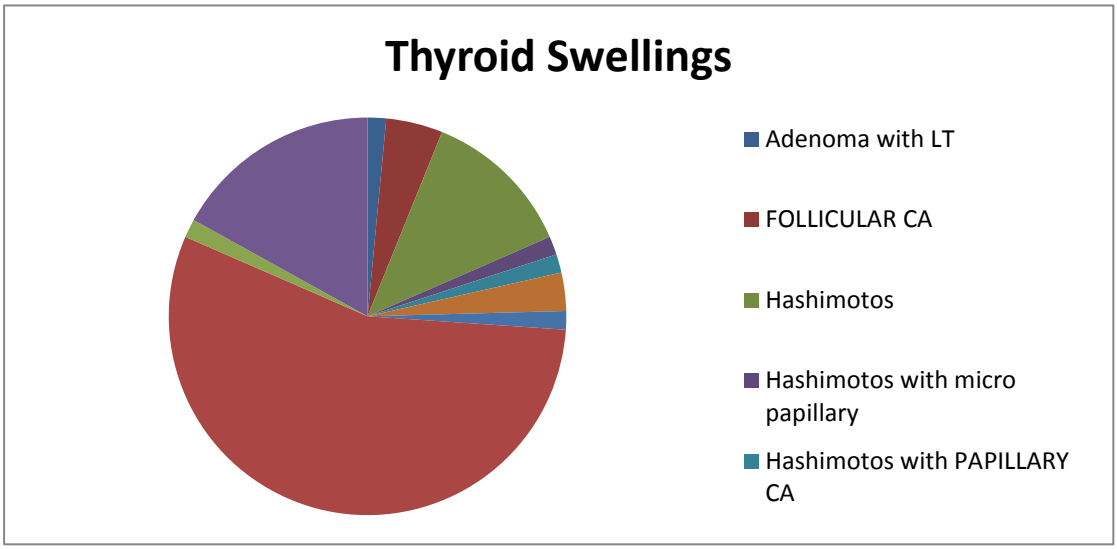
In this study it is found that FNAC Neoplasia have statistically significant association with malignancy ($p<0.05$).

6.25 Association between FNAC Neoplasia and malignancy

FNAC Neoplasia	**Malignancy**		**Total**
	Yes **N (%)**	**No** **N (%)**	
Yes	9 (50)	2 (4.3)	11
No	9 (50)	45 (95.7)	54
Total	18	47	65

$p=0.001^{*}$

6.26 Distribution of thyroid swellings



6.27 Sensitivity, Specificity and Accuracy in FNAC

Total (n)=65

True positive (TP) =12

False positive (FP)=3

True negative (TN)=48

False negative (FN)=2

Sensitivity= (TP x 100)/ (TP+FN) =85.71%

Specificity = (TN x 100)/ (TN+FP) =94.11%

Positive predictive value= (TP x 100)/ (TP+FP) =80%

Negative predictive value = (TN x 100)/ (TN+FN) =96%

Percentage of False negative = (FN x 100)/ (FN+TP) =14.28%

Percentage of False positive = (FP x 100)/ (FP+TN) =5.88%

$$\text{Accuracy} = \frac{(TP+TN)}{(TP+TN+FP+FN)} \times 100 = 92.30\%$$

7. DISCUSSION

Thyroid is a butterfly shaped organ in front of neck. Thyroid is the second endocrine organ to produce systemic disease. Its pathology can be systemic or localized.

Thyroid produces several hormones for calcium homeostasis and for metabolism and maturation of human body. Its production varies due to endogenous and exogenous causes. It could be due to neoplasia, dyshormonogenesis, infection or inflammation. Thyroid diseases can occur in any age group.

Thyroid is in close relation to parathyroid glands which are important for calcium metabolism. It is also related to nerves needed for muscles of pharynx. So while during thyroid surgery they are at risk of damage.

The aim of this study was to find prevalence of various thyroid swellings in the population of Kulashekaram attending our hospital. Sample size consisted of those patients attending surgery OPD of our institution and more than 18 years of age.

To find prevalence of thyroid swellings, patients underwent FNAC, USG neck, was admitted, underwent relevant investigations, total thyroidectomy was done and thyroid was subjected to histopatholgocal examination. Then results were compared.

The youngest patient of this study was 20 years of age and oldest was of 70 years of age with diagnosis nodular colloid goiter.

In a study done by Aravindan *et al* [39] in 2007 and Sengupta *et al* [40] in 2011, mean age for thyroid diseases were 47 and 35.39 respectively. In my study the mean age for study population was 42.

There is a wide variation regarding sex ratio in various studies. Sengupta *et al* in 2011 reported a ratio of 3.8:1[40], while in present study, female to male ratio is 7.125:1.

An incidence of 51.1% and 60% of colloid goiter was observed by Huque *et al* [41] in 2012 and Sushel *et al* [42] in 2009 respectively. The same was found to be 56.8% by histopathological examination, 64% by USG and 63% by FNAC as per the current study.

All patients after thyroidectomy were started on suppressive dose of eltroxin and came for regular follow up. Of all the patients diagnosed to have carcinoma only 1 underwent total thyroidectomy with lymph node dissection. They were sent for radiouptake study and came for regular follow up.

The percentage of false negative for malignancy by FNAC is found to be 14%. This proves that FNAC does not change our plan for total thyroidectomy, even for benign lesion proven by FNAC as, second surgery is very difficult and is disastrous.

The incidence of malignancy in SNT in the current study is 61.1%. As per statistical data there is definitely an association between SNT and malignancy. Also Yao *et al* (2011) has found that thyroid cancers are common in woman, but they present in later stage and with bad prognosis when present in men. Rahbari *et al* (2010) has found that poorly differentiated cancers have equal preponderance to both men and woman.

Less than 10% of population in the study, with thyroid disease, were found to have diabetes and hypertension.

Incidence of malignancy of 9.1% and 11% was reported by Halbhavi *et al* [43] in 2018 and Rout *et al* [44] in 2011 respectively while a high rate of 27.7% was observed in the present study.

Most of population came under age group of 30-39 years. In a study by Raniwala *et al* (2017) [45] the mean age group for thyroid diseases comes under age group 21-40years followed by 40-60years. Sushel *et al* (2009) suggested age as an important indicator for thyroid malignancies.

In US the most common cause of hypothyroidism is hashimoto thyroiditis [46]. It is more common in women than men [47]. In UK it is about 0.8% [48]. Some studies have shown that there is association with thyroid cancer [49] [50]

Hypothyroidism can present in multiple ways. One of the rare ways of presentation is acute kidney injury due to decreased flow and GFR[51] [52]. It is reversible. It can also exacerbate CKD [53]. It can also present as paralytic ileus. Tone of muscle takes time to be change to normal and is usually fatal. [54]. It is due to autonomic neuropathy [55].

Thyroid hormones have influence on brain development [56-61]. Patients with depression can have subclinical hypothyroidism [62]. Genes regulated by thyroid hormones are known to encode myelin and neuroendorphins for intracellular signalling[63]. Thyroid hormones are known to cause migration, myelination, synaptogenesis and dendritic branching[64-66]. Thyroid hormones are needed for cognitive and emotional functions. So they can lead to dementia and depression[67].

Thyroidectomy is one of the most common surgeries done worldwide[68]. Main reason is to prevent respiratory passage compression and to detect early haemorrhage [69][70]. Some suggest use of drains only for hypervascular and complicated thyroid diseases [71-73]. In uncomplicated thyroid surgeries like lobectomy, drain can be omitted as it reduces hospital stay and chance of infection [74].

Complications in total thyroidectomy occur due to its relation to vital nearby structures. Reducing complications require careful dissection [75-80].

Several methods are there for identifying recurrent laryngeal nerve. They are nerve stimulation, intramuscular electodes and visualization by laryngoscopy [(81)]. But gold standard is direct visualization [(82)]. Use of toludine dye makes artery and nerve easily visible and can be dissected out easily[(83)].

Prevalence of thyroid nodules by palpation is about 4% [(84)]. While majority are benign, some sonological features raises the suspicion of malignancy [(85)]. By radioactive scintigraphy using I-123 or tc-99m, usually cold nodules are suggestive of malignancy. Usually hot nodules are hyperfunction nodules and usually not suggestive of malignancy [(86)].In 2009 Sundariya *et al* found a case of follicular carcinoma in setting of hyperfunctional nodule in radioactive scan [(87)]. In 2012 study by Pazaitao *et al* found relation between hyperfunctional nodules and cancer [(88)].

Medullary carcinoma thyroid occurs by mutation of proto oncogene. Ion familial type experts have suggested prophylactic total thyroidectomy as treatment at 5-10 years of age. Newer development suggests emergence of drugs targeting molecular pathway of developing medullary carcinoma, like tyrosine kinase which have better response [(89)].

Jan Komorowski *et al* in 2013 found that there is an association between impaired Vitamin D3 levels and development of thyroid cancer in Poland. Also there was an association between levels of Vitamin D3 and stage of disease. More the level more advanced the stage of disease was[(90)].

Grzegorz *et al* (2013) suggested a new treatment modality for thyroid diseases when standard treatment measures fail. It is by selective embolization of feeding vessels for thyroid. It reduces symptoms and morbidity in life. It had no significant decrease in activity of parathyroid glands. Also it can be used preoperatively to reduce size of a huge goitre and reduce complications [(91)].

COX-1 expression has been attributed to several thyroid malignancies especially medullary cancer. It helps in synthesis of thromboxane A2 and

prostacyclins [92][93]. COX-2 inhibits apoptosis and induces proliferation of cells and helps in metastasis and infiltration[94][95]. It was also found that use of COX-2 inbitors slows neovascularization[96]. Lee *et al* in 2008 proved presence of significant expression of COX-2 in thyroiditis, benign and malignant thyroid disorders and not in normal thyroid tissue [97]. Also Speech *et al* in 2002 found that there is no evidence of increased expression of COX-2 in malignant thyroid diseases than in benign and inflammatory diseases[98]. Also high expression of COX-2 and low expression of KAI-1/CD8 is associated with more aggressive tumour [99].

Increased TPO activity is a hallmark of thyroid differentiation and is observed in pathological diseases of thyroid[100]. It has also been noted that TPO activity is less in thyroid malignancies when compared to benign and normal functional tissue[101]. Study by De Micco *et al* in 1991 observed that anti TPO antibodies are present in approximately 3% of thyroid malignancies[102]. Pulcarno *et al* in 2007 suggested that TPO expression means there is less chance for aggressive behavior of tumour and metastasis[103]. Romei *et al* reported that BRAF mutated tumours like papillary thyroid cancers have low TPO expression[104]. Even though TPO has a relation to pathology it cannot be used a diagnostic marker, but only prognostic marker to see for recurrence or residual tissue[105] [106].

Hyalinizing trabecular tumours are rare thyroid tumours which comprise about 0.44-1.3% of all thyroid tumours[107]. Mostly present in 21-80years of age[108] [109]. There is a close relation between multinodular goiter, radiation, familial polyposis and lymphocytic thyroiditis[110]. Due to the uncertainity in the tumour many a times it has been overtreated by total thyroidectomy instead of lobectomy alone[111]. Hirokawa *et al* in 1995 has found that Ki-67 can be used as a tool for diagnosis of this tumour[112]. Also they have found that it is a separate entity and not a type of papillary carcinoma[113]. But its non reactiveness does not exclude the tumour[114] [115].

Calcitonin is found to be a good marker for both diagnosis and follow up of a case of medullary carcinoma thyroid[116-122]. Accuracy of FNAC is also less in papillary carcinoma thyroid[123-128]. Some studies have proved that calcitonin measurement in even washings from fine needle aspirate is satisfactory[129-132]. Elisai *et al* in 2004 suggested that the calcitonin has higher sensitivity when compared to fine needle aspiration [133].

Both diabetes and hypothyroidism are diseases requiring prolonged life long follow up with slightly increased risk for complications in former [134] [135]. Hypothyroidism also contributes to hypertriglyceridemia and adds to cardiovascular risk [136]. Recent studies have shown that prevelance of hypothyroisdism is high in diabetis patients and risk of microvascular complications increases if both are present together [137]. Hypothyroidism is present in 11% of population [138]. Also TPO antibiody is present in 9.5% of population [139]. There is conflicting evidence from Norway which suggest comparable prevalence of hypothyroidism in diabetics and non diabetics [140].

FNAC has always proved to be a reliable, safe and rapid test for diagnosis of thyroid swellings. Its sensitivity for thyroid swellings ranges from 80-98% and specificity is from 58-100% [141-146]. A sensitivity of 85.7% and specificity of 94.11% as observed in the present study is in consensus with the previous studies.

8. CONCLUSION

- There is gender preponderance in thyroid swellings to female (87.7%).
- Most common swelling in thyroid in the population under study was nodular goiter (55.3%).
- There is an association between SNT and FNAC of swellings showing neoplasia to malignancy [p was 0.001 in both cases].
- Most common malignancy in study population was papillary carcinoma thyroid.
- Majority of patients with thyroid swelling were in age group 30-39years.
- Mean age of patients with thyroid swellings was 42years.
- Sensitivity of FNAC for identifying malignancy was 85.71% and that of specificity was 94.11%.

9. SUMMARY

Thyroid diseases are one of the most common endocrine disorders worldwide second only to diabetes. Thyroidectomy is one of the most common endocrine surgeries done worldwide. Thyroid diseases could be due to increase production or decreased production of hormone which will be manifested differently. Swelling in thyroid could be due to dyshormonogenesis, neoplastic, infective or inflammatory.

Even though there are devastating complications and high mortality in earlier days for total thyroidectomy which gave nightmares to patients with thyroid swellings, with latest advances and technology the complications and mortality have drastically come down. Also latest advances have helped us to identify cancers in thyroid in earlier stage before they even produce symptoms.

The present study consisted of 65 patients coming to surgery OPD of Sree Mookambika Institute of Medical Sciences with thyroid swellings. They were made to undergo FNAC, USG thyroid to get a probable diagnosis. Then they were admitted and after doing relevant investigations and getting proper consent they underwent total thyroidectomy and specimen was sent for HPE examination.

Data was collected from patients using a proforma and with help of pathology department relevant information were collected. Data was entered in an excel sheet and was analysed. Descriptive analysis of the data was done. Sensitivity and specificity of FNAC was also derived from the data collected. Analysis was done using Statistical Package for Social Sciences (SPSS v20). Variables studied were gender, age, HPE in population, SNT, Malignancy in population, USG and FNAC data of swellings.

From the present study it was found that females were more commonly affected with thyroid disorders than men. Age also had some relation. Most common age group involved was 30-39years. Most common swelling in

population was nodular goiter. Most common malignancy encountered was papillary carcinoma thyroid. It was also found that there is an association between SNT and swellings with neoplasia in FNAC with malignancy [p=0.001]. It was also found that there is no relation between diabetes or hypertension on thyroid diseases in population. It was found that even if swelling was found to be benign by USG, FNAC and clinically HPE showed malignancy (3.1%) which strengthens the aspect that any swelling in thyroid should undergo total thyroidectomy and not lobectomy or any conservative measures.

Limitations of the current study was that patients below 20 years of age were not considered. Thyroid swelling can occur in children which are also endemic goiter and dyshormonogenic goiter. This could not be added to my study population which might vary my result. Government has brought forward many measures to reduce endemic goiter by iodination of table salt and other measures. This has drastically reduced the prevalence of endemic goiter to some extent.

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ABBREVIATIONS

AKAP9	:	A Kinase Anchoring Protein 9
AKT	:	stock A strain K Transforming
APUD	:	Amine Precursor Uptake and Decarboxylation
ATP	:	Adenosine Triphosphate
cAMP	:	Cyclic adenosine monophosphate
Cl^-	:	Chloride
DG	:	Diffuse Goiter
DIT	:	Di iodotyrosine
FNAC	:	Fine Needle Aspiration Cytology
GPCR	:	G-protein coupled receptor
HCG	:	Human Chorionic Gonadotropin
HPE	:	Histopathological Examination
I^-	:	Iodide
K^+	:	Pottassium
LT	:	Lymphocytic thyroiditis
MAPK	:	Mitogen Activated Protein Kinase
MEN	:	Multiple Endocrine Neoplasia
MET	:	Mesenchymal to epithelial transition
MIT	:	Mono iodotyrosine
MNG	:	Multi nodular goiter
mRNA	:	Messenger Ribonucleic Acid
Na^+	:	Sodium
NIS	:	Sodium Iodide Symport
NTRK	:	Neurotropic Tyrosine Receptor Kinase

PAX	:	Paired Box
PI3K	:	Phosphatidinyl inositol 3 kinase
Pi3KCA	:	Phosphatidinyl inositol 3 kinase catalytic alpha polypeptide
PPAR	:	Peroxisome Proliferator Activated Receptor
PTEN	:	Phosphatase and Tensin homologue
RAb	:	Receptor Antibody
RAI	:	Radioactive iodine
RAS	:	Rat Sarcoma
RET	:	Rearranged during transfection
SNT	:	Solitary Nodule Thyroid
T_3	:	Triiodotyrosine
T_4	:	Tetraiodotyrosine
TFT	:	Thyroid Function Test
Tg	:	Thyroglobulin
TPO	:	Thyroxine peroxidase
TRH	:	Thyrotropin Releasing Hormone
TRK	:	Tropomyosin Receptor Kinase
TSH	:	Thyroid Stimulating Hormone (Thyrotropin)
TSHR	:	Thyrotropin receptor
USG	:	Ultra sonogram
VEGF	:	Vascular Endothelial Growth Factor
VPF	:	Vascular Permeability Factor

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES

Department of GENERAL SURGERY

Kulashekaram, Kanyakumari District, Tamil Nadu, India

CASE RECORD FORM

Name :Age in years :

Address & Phone no :

Sex : **Male ☐** **Female ☐**

Occupation :

DOA : **DOS :** **DOD :**

Family history of thyroid malignancy

Family history of other malignancy

History of radiation therapy

History of prior thyroid surgery

DM **HTN**

Personal history : **Smoking** **Alcohol** **Diet**

CLINICAL EXAMINATION

Vitals – BP : **Pulse rate**

Pallor **Icterus** **Cervical Lymphadenopathy**

Intrathoracic Extension

INVESTIGATION

Blood HB :

TC :

DC :

ESR :

Thyroid Function Test

- T_3
- T_4

- TSH

USG

FNAC

TREATMENT

HPR

CONSENT FORM

PART 1 OF 2

INFORMATION FOR PARTICIPANTS OF THE STUDY

We welcome you and thank you for your keen interest in participating in this research project. Before you participate in this study, it is important for you to understand why this research is being carried out. This form will provide you all the relevant details of this research. It will explain the nature, the purpose, the benefits, the risks, the discomfort, the precautions and the information about how this project will be carried out. It is important that you can read and understand the contents of the form carefully. This form may contain certain scientific terms and hence, if you have any doubts or if you want more information, you are to ask the study personnel or the contact person mentioned below before you give your consent and also at any time during the entire course of the project.

1. Name of the Principal Investigator : Dr John B Jacob
Postgraduate-M.S General Surgery
SMIMS, Kulaseharam
Mob No: 8289881408
Email ID: johnykuttan376@gmail.com

2. Name of the Guide : Dr. Balajee
Professor
Department of General Surgery
SMIMS, Kulasekharam

3. Institute: Details with Address : Sree Mookambika Institute of Medical Sciences,
Kulasekharam,
Kanyakumari District-629161,
Tamil Nadu

4. Title of the study : Study of thyroid swellings in tertiary care centre

5. Background Information:

Thyroid swellings can occur in any age group and vary with population. In some areas thyroid swellings are common where as in some other areas it is very rare. It is common in females. Though malignancy can occur in both genders, it is more common in old males. From this study we can get an idea about prevalence of thyroid swellings and distribution in various age groups.

6. Aims and Objectives:

The objectives of the present study are:

- To conduct study on thyroid swellings in tertiary care hospital
- To find the prevalence of each swelling in the population.

7. Scientific justification of the study:

Population of Kulasekaram come from mixed topography. People are from hilly and immigrants from costal areas of Kerala. It is a Panchayat under Kanyakumari district. So the food habits also vary. Hence there will be variation in thyroid swellings in this area. More over there is a change in prevalence of goiter in hilly areas. Hence this study is conducted to find out the prevalence of various thyroid swellings in this population.

8. Procedure of the study:

Data is collected at time of consultation in OPD as well as admission in hospital by direct interview of patient using structured questionnaire along with clinical examination.
Patient is subjected to USG thyroid, FNAC and Exision biopsy. Biopsy reports are collected at time of review. Cross sectional analysis of histopathological reports are done and proportion of each types of thyroid swellings analysed.

Thyroidectomy : Patient in supine position. Parts painted and draped. Kocher's incision made. Incision deepened. Deep fascia dissected. Strap muscles separated. Vessels identified and ligated. Nerve identified in both sides. Thyroid gland exiced in toto. Haemostasis achieved. Incision sutured in layers

9. Expected risk of the participants:
Yes

Complications of Thyroidectomy : Haemorrhage, Infection, Hypothyroidism, Hypocalcemia, Hoarseness of voice and Airway obstruction.

Comlications form Anaesthesia : Mouth or throat pain, hoarseness of voice, Injury to mouth or throat, vocal chord injuries, awareness under anaesthesia, Injury to blood vessels, vomiting, aspiration Pneumonia

10. Expected benefits of the research for the participants:
Reduce operation stress for the patient and reduce morbidity and mortality

11. Maintenance of confidentiality:
All data collected for the study will be kept confidentially. No personal details will be revealed.
12. Agreement of compensation to the participants: NA

13. Anticipated prorated payment, if any, to the participants of the study: Nil

14. Can I withdraw from study at any time during the study period: Yes

15. If there is any new finding/information, would I be informed: Yes

16. Expected duration of the participant's participation in the study: One time.

17. Any other pertinent information: No

18. Whom do I contact for further information:

Dr John B Jacob.-Post Graduate
Department of General Surgery
Sree Mookambika Institute of Medical Sciences,
Kulasekharam629161
Mobile Number: 8289881408
e-mail :johnykuttan376@gmail.com

Place:

Date:

Signature of Principal Investigator **Signature of the Participant**

CONSENT FORM

PART 2 OF 2

PARTICIPANTS CONSENT FORM

The details of the study have been explained to me in writing and details have been fully explained to me. I am aware that the results of the study may not be directly beneficial to me but will help in the advancement of medical sciences. I confirm that I have understood the study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reasons, without the medical care that normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have given details of the study. I fully consent to participate in the study titled "Study of thyroid swellings in tertiary care centre "

Serial no/Reference no:

Name of the participant:

Address of the Participant:

Contact number of the Participant:

Signature/Thumb impression of the participant

Witness

1.

2.

Date:

Place:

SlNo	Name	Age	Sex	IP No	DM	HTN	USG	FNAC	HPE	Micro Malignancy	SNT	HPE Malignancy	FNAC Malignancy
1	Rubathy Loordh	48	F	1807227	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
2	Sobha	29	F	1807463	N	N	SNT	Follicular neoplasm	Nodular Colloid Goitre	N	Y	N	Y
3	Pushpam	50	F	1808268	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
4	Shamala Kumari	52	F	1810167	N	Y	MNG	Follicular neoplasm	Nodular Colloid Goitre	N	N	N	Y
5	Sheeba	31	F	1810759	N	N	SNT	Follicular neoplasm	PAPILLARY CA	N	Y	Y	Y
6	Sudha	40	F	1811802	N	N	SNT	Follicular neoplasm	Medullary Carcinoma Thyroid	N	Y	Y	Y
7	Chithra	31	F	1811759	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
8	Sreeja	26	F	1724798	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
9	Mary	54	F	1726173	N	Y	MNG	Cyst	Nodular Colloid Goitre	N	N	N	N
10	Thanka Lakshmi	50	F	1726164	N	Y	SNT	Follicular neoplasm	FOLLICULAR CA	N	Y	Y	Y
11	Santha	55	F	1726870	N	N	SNT	Follicular neoplasm	PAPILLARY CA	N	Y	Y	Y
12	Suja	39	F	1727482	Y	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
13	Mary Geetha	22	F	1727871	N	N	MNG	LT	Hashimotos	N	N	N	N
14	Sahaya Sheeja	20	F	1730385	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
15	Arul Mary	48	F	1730705	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
16	Lalitha	46	F	1731150	N	Y	DG	LT	LT	N	N	N	N
17	Lekshmi	51	F	1731822	N	N	SNT	COLLOID GOITRE	Nodular Colloid Goitre	N	Y	N	N
18	Usha	49	F	1733105	Y	N	MNG	HASHIMOTO	Nodular Colloid Goitre	N	N	N	N
19	Rajakumari	43	F	1803108	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
20	Christy	48	F	1804639	N	N	THYTOIDITIS	HASHIMOTO	Hashimotos	N	N	N	N
21	Mary Stella	37	F	1813831	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
22	Sindhukala	39	F	1816766	N	N	DIFFUSE GOITRE	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
23	Muthu laksmi	37	F	1816980	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
24	VanithA	35	F	1815239	N	N	MNG	COLLOID GOITRE	Hashimotos	N	N	N	N
25	Chellakili	49	F	1812421	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
26	Uchimakali	32	F	1814531	N	N	MNG WITH NODULE	COLLOID GOITRE	Nodular colloid Goitre	N	N	N	N
27	Pakiyanathan	54	M	1809940	N	N	SNT	Follicular neoplasm	FOLLICULAR CA	N	Y	Y	Y

SlNo	Name	Age	Sex	IP No	DM	HTN	USG	FNAC	HPE	Micro Malignancy	SNT	HPE Malignancy	FNAC Malignancy
28	Vasanthi	39	F	1813040	N	N	SNT	Follicular neoplasm	FOLLICULAR CA	N	Y	Y	Y
29	Rajakumari	43	F	1802048	N	N	MNG	LT	LT	N	N	N	N
30	Gomathiammal	61	F	1803221	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
31	Jancy Rani	50	F	1803389	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
32	Parvathavardhini	45	F	1906557	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
33	Malathi	33	F	1902724	N	N	MNG	HASHIMOTO	Hashimotos	N	N	N	N
34	Chellathai	57	F	1902437	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
35	Anitha	38	F	1902151	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
36	Valsala Kumari	38	F	1902809	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
37	Sree Kumari	68	F	1902844	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
38	Padmavathi	70	F	1902990	N	N	MNG	LT	Hashimotos with micro papillary	Y	N	Y	N
39	Devi	37	F	1814319	N	N	SNT	HASHIMOTO	Hashimotos	N	Y	N	N
40	Fathima Nisha	36	F	1902112	N	N	MNG	COLLOID GOITRE	PAPILLARY CA	N	N	Y	N
41	Meena	46	F	1902071	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
42	Rani	34	F	1902292	N	N	MNG	Follicular neoplasm	PAPILLARY CA	N	N	Y	Y
43	Uma Lakshmi	27	F	1901959	N	N	MNG	COLLOID GOITRE	PAPILLARY CA	N	N	Y	N
44	Pakiyanathan	54	M	1809940	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
45	Venu Gopalan Nair	70	M	1902814	N	N	DG	Follicular neoplasm	PAPILLARY CA	N	N	Y	Y
46	Kulavendran	55	M	1903238	N	N	SNT	COLLOID GOITRE	PAPILLARY CA	N	Y	Y	N
47	Sanku Krishnan	34	M	1729211	N	N	SNT	COLLOID GOITRE	Nodular Colloid Goitre with micropapillary Ca	Y	Y	Y	N
48	Sobiya	33	F	1902345	N	N	MNG	Follicular neoplasm	PAPILLARY CA	N	N	Y	Y
49	Elaya Perumal	76	M	1903296	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
50	Magdalene Celia	30	F	1903855	N	N	SNT	Follicular neoplasm	PAPILLARY CA	N	Y	Y	Y
51	Anitha	35	F	1894033	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
52	Pushpam	52	F	1832058	N	N	DG	HASHIMOTO	Hashimotos	N	N	N	N
53	Sreeja	35	F	1902456	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
54	Suji	35	F	1945637	N	N	MNG	COLLOID GOITRE	Hashimotos	N	N	N	N
55	Pattu Sheeba	28	F	1902346	N	N	SNT	Follicular neoplasim	PAPILLARY CA	N	Y	Y	Y

SlNo	Name	Age	Sex	IP No	DM	HTN	USG	FNAC	HPE	Micro Malignancy	SNT	HPE Malignancy	FNAC Malignancy
56	Shobana	50	F	1894092	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
57	Ponkala	47	F	1902834	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
58	Girija	40	F	1829388	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
59	Vignesh	22	M	1890747	N	N	SNT	Follicular neoplasm	PAPILLARY CA	N	Y	Y	Y
60	Seetha	26	F	1892748	N	N	DG	LT	Hashimotos	N	N	N	N
61	Naina Beevi	26	F	1902764	N	N	SNT	LT	Hashimotos with PAPILLARY CA	N	N	Y	N
62	Pushkaran	53	M	1892612	Y	Y	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
63	Vimala	27	F	1872187	N	N	SNT	Follicular neoplasm	Adenoma with LT	N	N	N	Y
64	Jerin	33	F	1902865	N	N	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N
65	Rosamma	54	F	1906789	Y	Y	MNG	COLLOID GOITRE	Nodular Colloid Goitre	N	N	N	N