CHAPTER ONE

Introduction

1.1. Introduction:

A thyroid nodule is an abnormal growth of cells within the thyroid gland and can be non-cancerous (benign) or cancerous (malignant). The diagnosis for nodule malignancy is currently made via fine needle aspiration cytology (FNAC) biopsy, which draws cytological samples from the nodule using a 25-gauge needle. It is estimated that somewhere between 250,000 and 300,000thyroid FNAC biopsies are performed annually in the United States. However, a large percentage (approximately 70%) of these biopsies turns out to be benign (M. Dighe et al,2008). Thus, considering the increasing number of thyroid nodules being detected and the vast number of benign nodules undergoing FNAC biopsies, the challenge lies in judiciously deciding which nodules should be aspirated.

Several studies have shown the incidence of thyroid nodules ranging from 41% on ultrasonography (US) to at least 50% on pathology (Mortensen et al., 1955; Tan et al., 1997). The higher detection rate has been attributed to technical improvement in conventional US, leading to the detection of clinically silent nodules (Davies et al., 2006). Certain characteristics on conventional US can be helpful in differentiating benign from malignant nodule, including hypo echoic, poorly defined margin, irregular shape, micro calcification, taller than wide (anteroposterior to transverse diameter ratio greater than 1) (Ahn et al., 2010). However, none of the aforementioned characteristics have a high positive predictive value for malignancy, and some characteristics of benign and malignant nodules overlap (Cappelli et al., 2006; Tamsel et al., 2007; Kim et al., 2008). It has been observed that some benign degenerating cystic thyroid nodules have malignancy-mimicking characteristics during follow-ups (Kim et al., 2011). It is difficult to distinguish the degenerating cystic thyroid nodule with hypo echoic, changed morphologically in the natural course, from papillary thyroid carcinoma (PTC) via conventional US.

Ultrasound elastography measures the tissue deformation in response to stress to derive and display tissue stiffness. Recent studies demonstrated the potential of applying ultrasound elastography to the thyroid gland in noninvasively differentiating between malignant and benign thyroid nodules. Rago et al 2007. In a study by Lyshchik et al.2005. The elastic modulus of excised thyroid tissues was shown to correlate with the malignancy of thyroid nodules. They observed that malignant thyroid nodules are 5 times stiffer than normal thyroid tissue while benign nodules are only 1.7 times stiffer than normal tissue. They reported that US elastography could be used for differential diagnosis of thyroid cancer. A. Lyshchik et al 2005.Previous elastography studies employed the freehand external compression. Bae et al.2007, developed a new approach where the carotid artery was used as an in vivo compression source, taking advantage of its inherent periodic pulsation (e.g., expansion of the carotid artery lumen diameter during systole) and its position (adjacent to the thyroid).

Several studies have proved that real time ultrasound elastography has a high accuracy for predicting malignancy in thyroid nodules and cervical lymph nodes (Rago et al., 2007; Asteria et al., 2008; Rubaltelli et al., 2009; Friedrich-Rust et al., 2010; Teng et al., 2012). However previous studies have not specifically focused on changes in degenerating cystic thyroid nodule on elastography.

1.2 Problem of the study:

FNAC is still the most popular method of diagnosing thyroid nodules; it is not expected to be done for all patients. Some patients may be missed, others show insufficient specimen and others have very small nodules that are difficult to be biopsied.

1.3 Objectives of project:

- **General objectives**

1- Thyroid ultrasonography has gained widespread acceptance as a diagnostic tool for the evaluation of thyroid disorders.

2- US are precise to guide minimally invasive procedures, such as fine needle aspiration biopsy (FNAB) or injections.

3- Ultrasound elastography is a promising imaging technique that is useful in the differential diagnosis of thyroid cancer.

- **Specific objectives**

1- To evaluate the elastographic appearances of thyroid nodules.

2- To determine whether ultrasound elastography (USE) may assist in differentiating benign from malignant thyroid nodules.

3- Results in reducing of thyroid biopsies

4- To evaluate the diagnostic utility of conventional US, Doppler and real time ultrasound elastography in differentiating degenerating cystic thyroid nodule with malignancy.

CAPTER TWO

Literature review

2.1 Thyroid Anatomy

The Thyroid gland is a brownish red, highly vascular organ, situated interiorly in the lower part of the neck, at the level of the fifth, sixth and seventh cervical and first thoracic vertebrae (Fig.2-1). It is ensheathed by the pretracheal layer of the deep cervical fascia and consists of right and left lobes connected across the median plane by a narrow region termed ‘isthmuses. (8,15) its weight is somewhat variable. At birth, it is about 1-2 gram, at puberty (10-15 gram) and in adults (15-35 gram). The mean weight is always higher in women and varies in size with menstrual cycle. (Gharib H et al,2004) The lobes are approximately conical in shape, the apex of each ascending and diverging laterally to the level of the oblique line of the thyroid cartilage. The base is on a level with the fourth or fifth tracheal ring. Each lobe is about 5 cm long. Its greatest transverse and anteroposterior dimension being about 3cm and 2cm respectively (fig.2-2).The posteromedial aspect of each lobe is attached to the side of the cricoid cartilage by a ligamentous band called the lateral ligament of the thyroid gland. The lateral or superficial surface is convex. External to the sheath of the pretracheal fascia, this aspect of the gland is closely covered with the sternothyroid and it is the insertion of this muscle into the oblique line on the lamina of the thyroid cartilage which prevents the upper part of the lobe from extending on to the thyrohyoid muscles. More anteriorly, strnohyoid and superior belly of the omohyoid overlap below by the anterior border of the sternocleido mastoid muscle. The medial surface is adapted to the larynx and trachea. At its superior pole, it is in contact with the inferior pharyngeal constrictor and posterior part of the cricothyroid, which intervenes between the gland, and the posterior part of the lamina of the thyroid gland and the side of the cricoid cartilage. The external laryngeal nerve is medial to this part of the gland. Inferiorly, it is related anteriorly to the trachea and the recurrent laryngeal nerve, and posteriorly to the oesophagus. The posterolateral surface is related to the carotid sheath and overlaps the common carotid artery. The anterior border -closely related to the anterior branch of superior thyroid artery is thin and descends obliquely and medially. The posterior border which is blunt and rounded is closely related below to the inferior thyroid artery and an anastomosing branch that connects it to the posterior branch of superior thyroid artery. The para thyroid glands are usually related to the posterior surface of the thyroid gland (fig.2-3). The lower end of the posterior border of the left lobe is closely related to the thoracic duct. (Dr Andrew Potter)(Evered, D., 3,3,425-449)

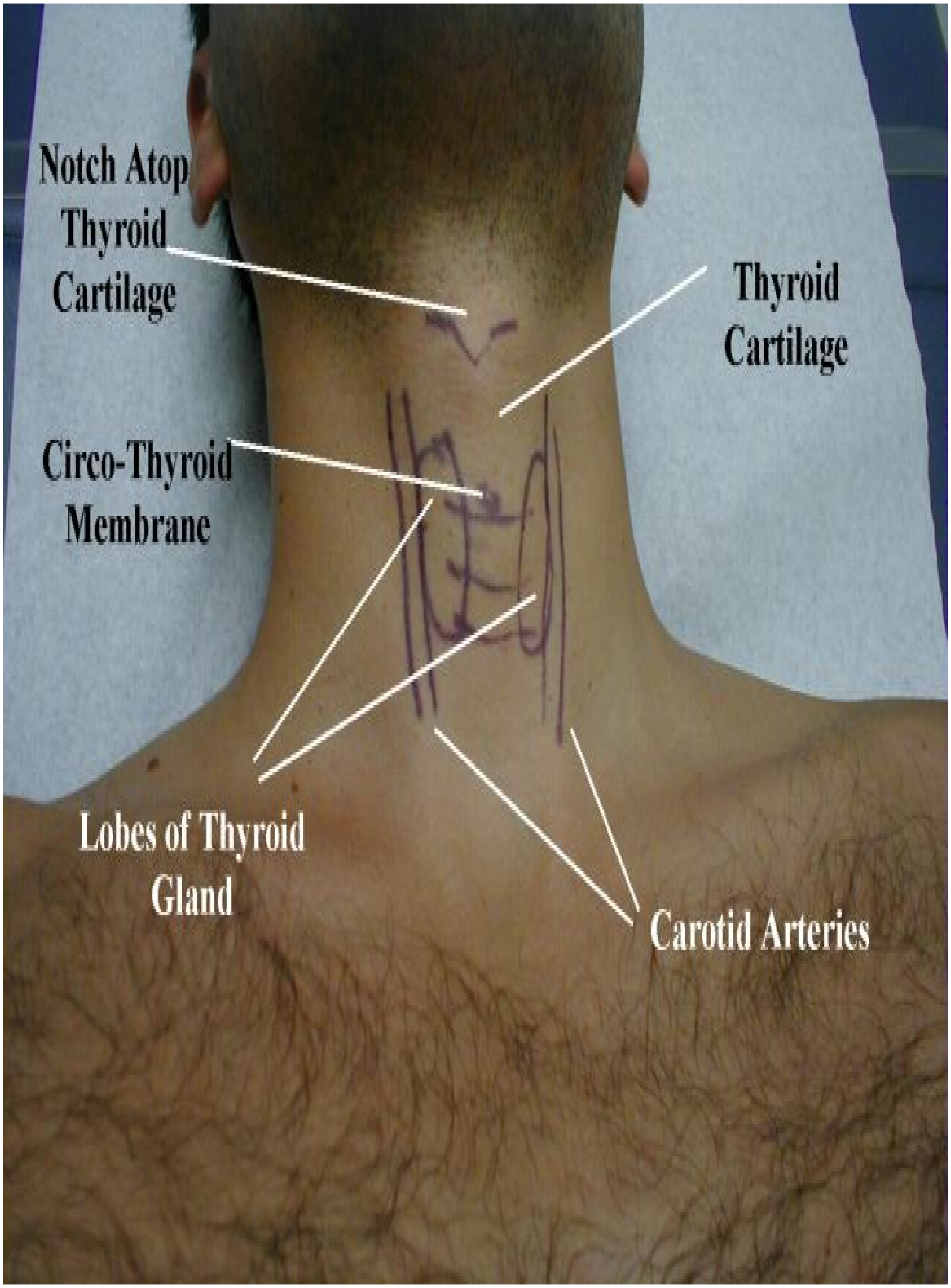


Fig (2-1) shows surface anatomy of thyroid gland , shows thyroid cartilage, lobes of thyroid gland , carotid artteries and circo-thyroid membrane. (Stephen Nussey et al, 2001).

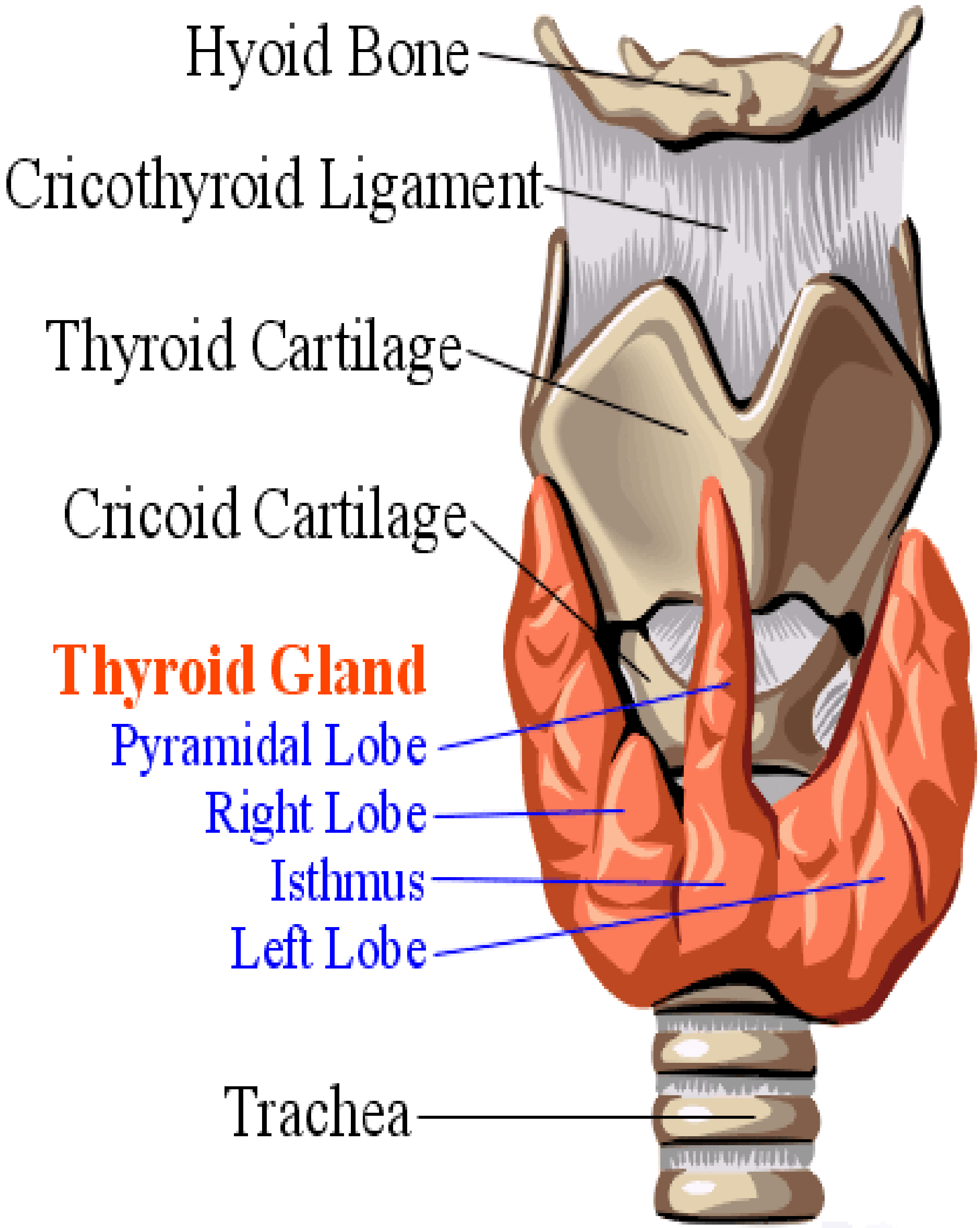


Fig (2-2) the thyroid gland and its relations with hyoid bone , cricothyroid ligment .thyroid cartilage and trachea (Dr Andrew Potter)(Evered, D., 3,3,425-449)

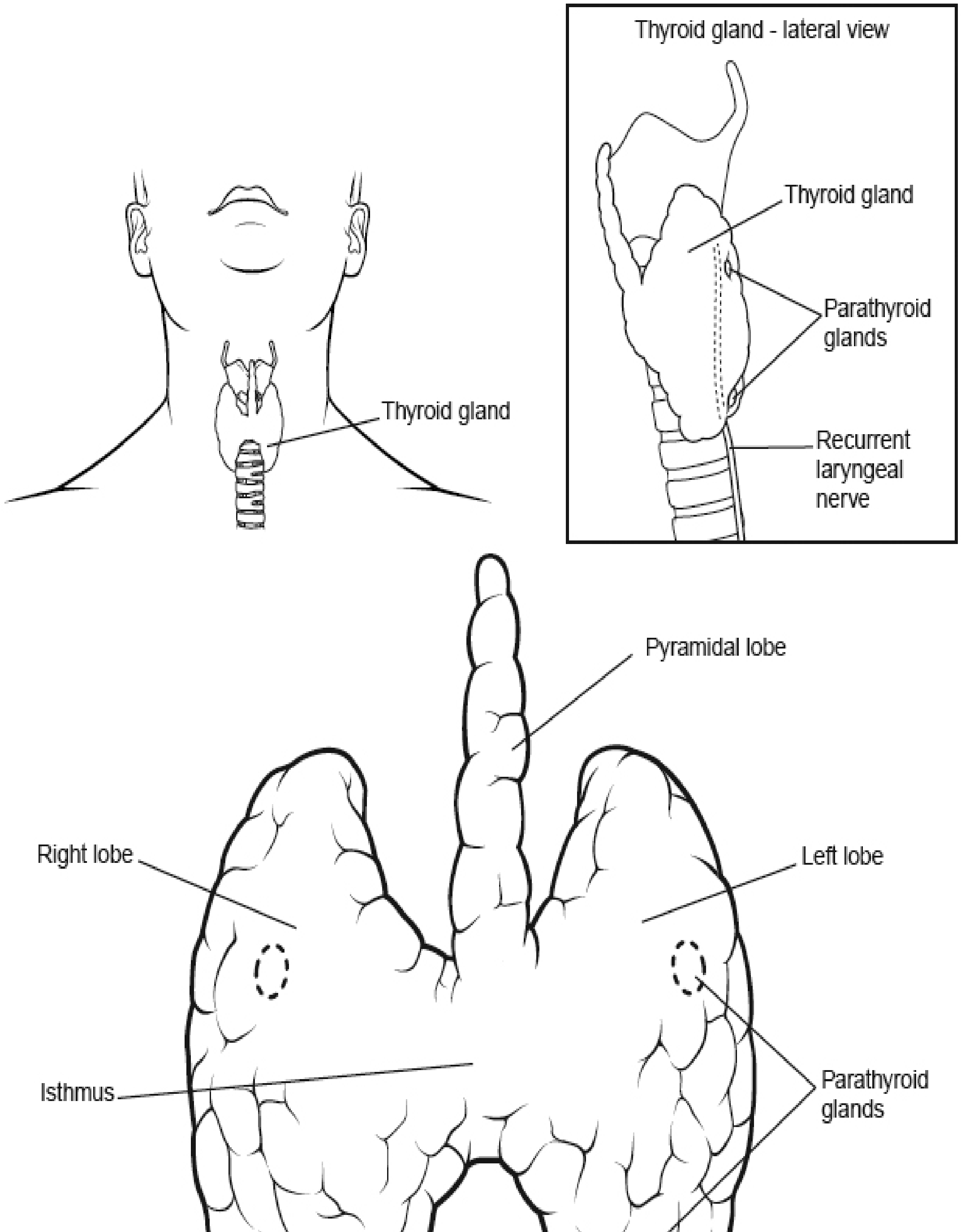


Fig (2-3) A,B,C shows thyroid gland posterior and lateral views.

(Emanuel Rubin et al)

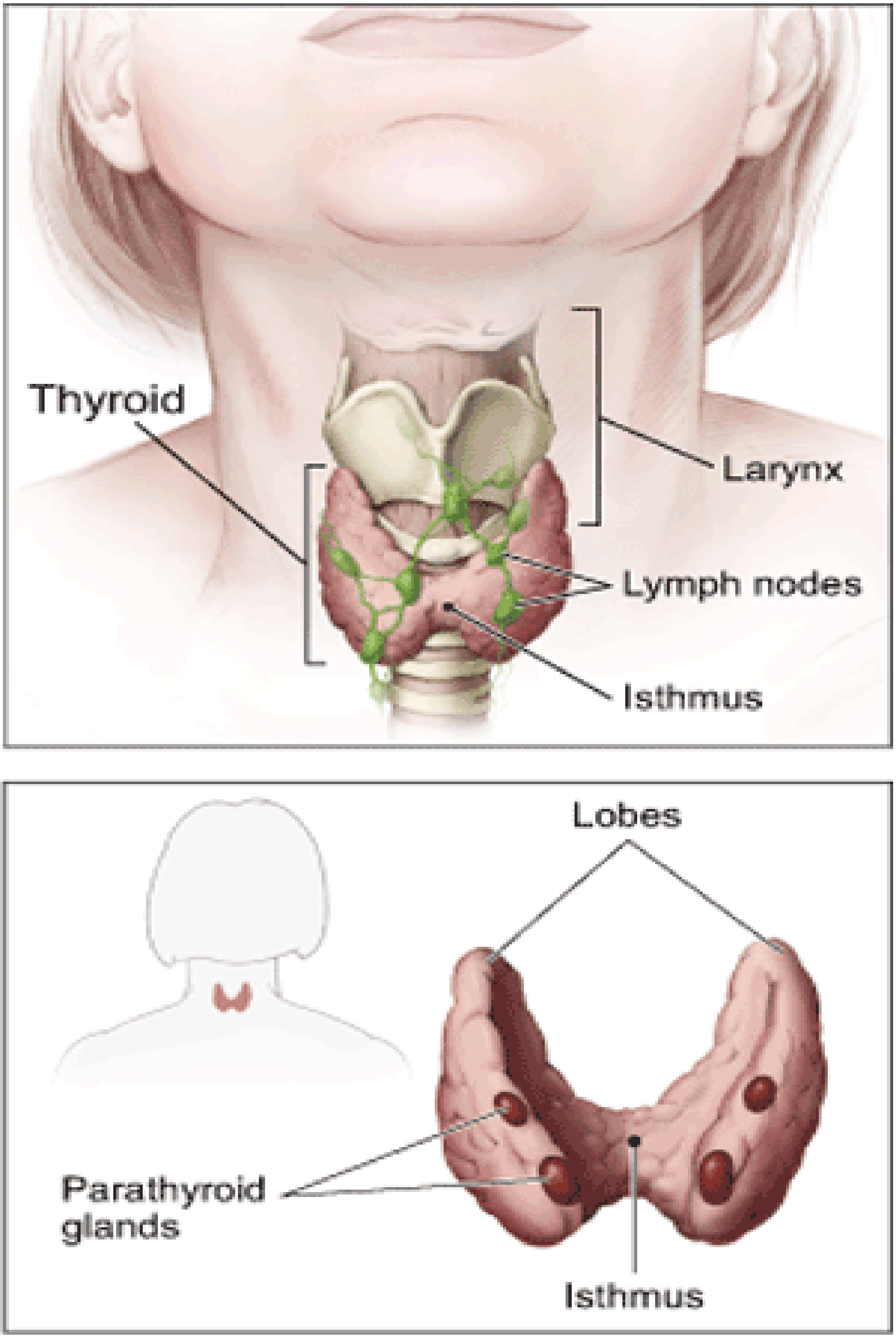


Fig .(2-4) The pictures a , b show the front and back of the thyroid.

(http://www.eyeinstitue.net/subfiles/comocprb/graves.htm ,2008)

The isthmus connects the lower part of the two lobes, and measures about 1.25cms transversely and 0.5 cm vertically and usually extends anterior to the second and third rings of the trachea. Superficially, strenohyoid, anterior jugular vein, fascia and the skin cover it. An anastamotic branch of the two superior thyroid arteries runs along its upper border. A fibrous or fibromascular band sometimes descends from the body of the hyoid bone to the isthmus, when it is muscular; it is termed levator of the thyroid gland. Small detached masses of the thyroid tissue are sometimes present in the vicinity of the lobes or superior to the isthmus, and are called accessory thyroid gland. (Dr Andrew Potter et al)

Fig (2-5) shows the thyroid cartilage surrounding the trachea. The four green shaded areas represent the parathyroid glands, positioned behind the thyroid gland.(http://www.eyeinstitue.net/subfiles/comocprb/graves.htm ,2008)

2.1.1 Blood supply, venous and lymphatic drainage of the thyroid gland

The superior thyroid arteries arise from the external carotid and enter at the upper pole of the gland. The inferior thyroid arteries arise from the subclavian arteries and enter at its lower pole. Sometimes an additional thyroeaidima artery, a branch from the brachio-cephalic trunk or aortic arch ascends upon the front of the trachea. Interlobular veins drain to a plexus on the surface of the gland and on the front of the trachea. From this plexus superior, middle, inferior thyroid veins arise. Superior and middle thyroid veins drain into the external jugular vein, and the inferior thyroid vein drains into the brachio-cephalic vein (fig.2-6) .A wide spread lymphatic network drains to pre and Para tracheal and to internal jugular lymph nodes. They contain colloid material. They end in thoracic duct and right lymphatic duct. Nerves are derived from superior, middle and inferior cervical ganglia. (Dr Andrew Potter et al)

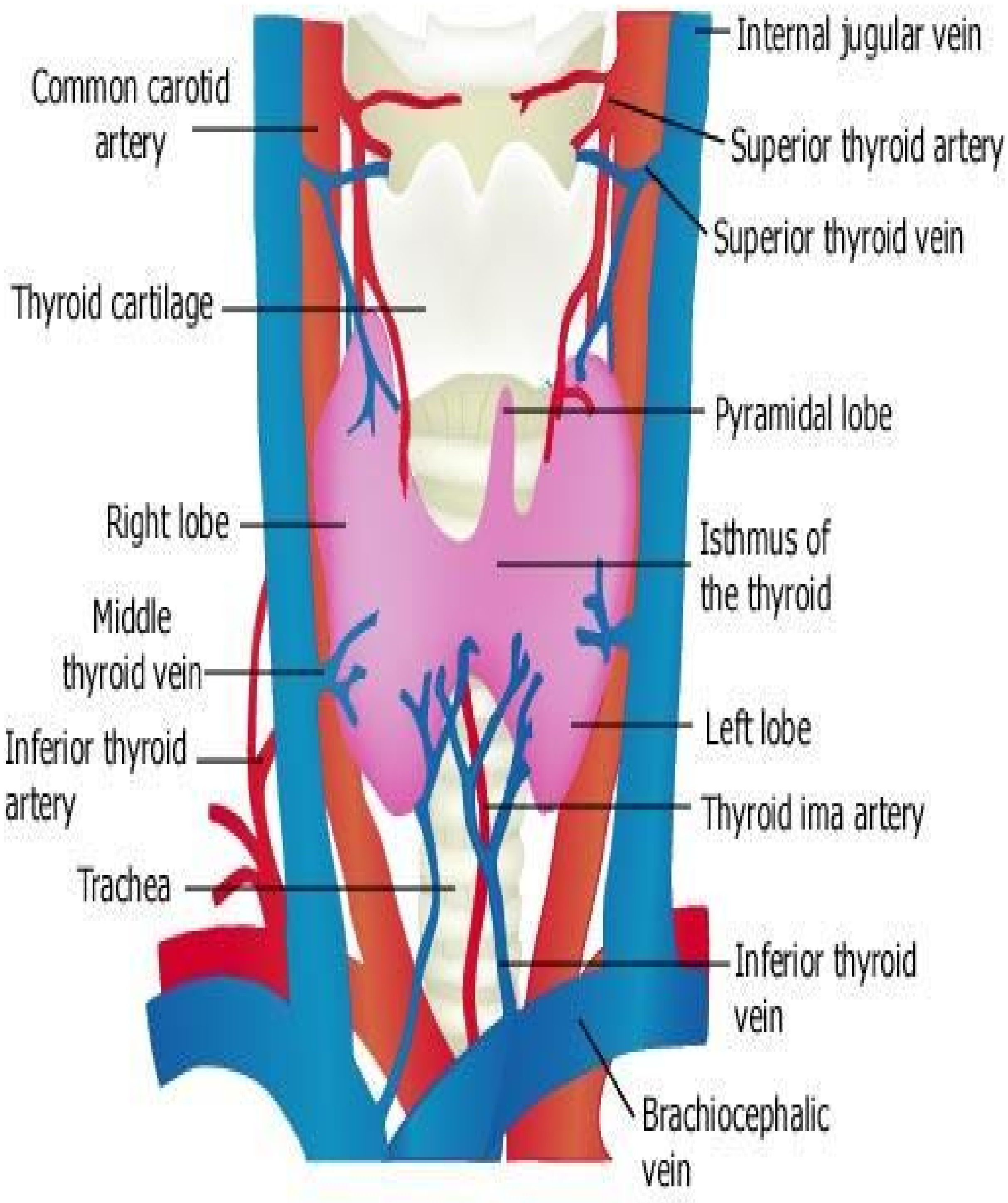


Fig (2-6) Shows blood supply and venous drainage of the thyroid gland which includes common carotid artery, internal jugular vein, superior thyroid artery and superior thyroid vein (Stephen Nussey et al, 2001).

2.1.2. Histology of the thyroid gland

The thyroid gland is invested by a thin capsule of connective tissue and it is divided into masses of irregular form and size by extension of connective tissue. The thyroid parenchyma is mainly derived from the endoderm of the thyroglossal duct. Branching, solid, epithelial cords and sheets grow out from the distal end of the duct, and the lumina filled with a yellow, viscid colloid appear within them. (Stephen Nussey et al, 2001)

The thyroid gland has a characteristic histology. Because thyroid cancer originates from this tissue and maintains some of its characteristics, it is important to have a thorough understanding of this aspect of the thyroid gland. The main histological structure is the thyroid follicle (Fig 2-7) consists of a single layer or epithelial cells—the thyroid follicular cells—surrounded by a basement membrane. The follicle is filled with a colloid material that contains thyroglobulin, the precursor macromolecule and storage protein for the thyroid hormones: thyroxine (T4) and triiodothyronine (T3). The size of these follicles varies significantly. Every 20–40 (up to 200) follicles are separated from the rest of the gland by connective tissue septa. Each follicle is consisting of a central core of colloid surrounded by a single layer of epithelial cells and enclosed in a basal lamina. Circulating pituitary thyrotrophin controls the activity of the follicular cells. The follicular cells have a striking ultrastructural and functional polarity. When activated by the pituitary thyroid stimulating hormone (TSH) or nerve terminals, they become in the apically directed process of thyroglobulin synthesis and exocytosis, and decreased TSH pushes them in the basally directed processes of thyroglobulin endocytosis, degradation and liberation of the thyroid hormones T3 and T4 into the blood capillaries. (Stephen Nussey et al, 2001)

Although most authors believe that the thyroid cells are monoclonal in origin, emerging evidence suggests that different parts of the thyroid originate from different precursors, most interestingly with different malignant potential. These could be reflected by those groups of thyroid follicles separated by the connective tissue septa. Blood vessels and supporting connecting tissue are seen in between the follicles, as well as groups of C cells (also called “par follicular cells”) that produce calcitonin. These cells are concentrated in the lower part of the upper third

of the thyroid gland and the reason why many authors consider nodules in that part of the thyroid gland as more suspicious for medullary thyroid cancer. (Cerbone G et al, 1999)

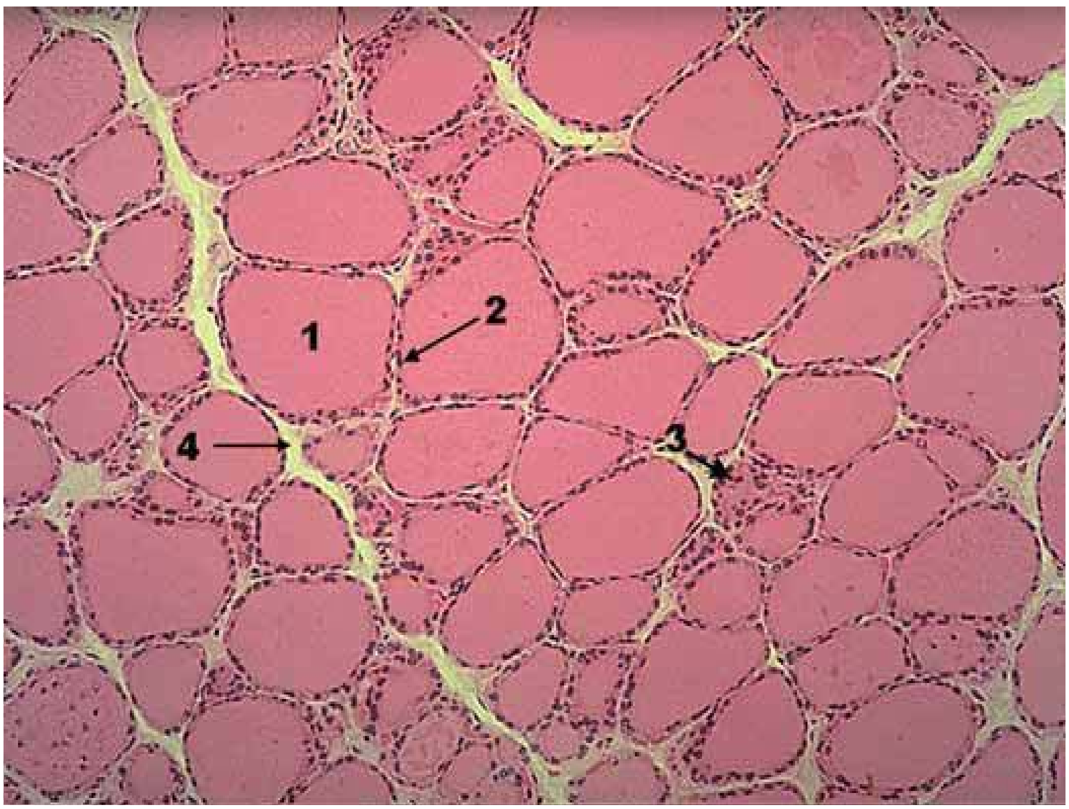


Fig. (2-7) Shows Histology of normal adult thyroid gland: 1, Colloid of a thyroid follicle; 2, follicular cells. Single layer cells forming a follicle; 3, par follicular cells (C cells); 4, connective tissue septum. (Vikas Chaudhary et al , 2014) (Yurong Hong et al)

2.1.3 The Parathyroid Glands

The human body is complex and multi-faceted. Interworking parts spread throughout the body must all function in tandem for optimal health, growth and development. The glands in the body, small organs responsible for the production of hormones, are some of the most important structures within the human body.Of the glands in the human body, the parathyroid glands, are often misunderstood or mislabelled. Because their name sounds similar to the thyroid, many people mistakenly believe that the thyroid and parathyroid glands are one in the same. In fact, the parathyroid has a completely different function to the thyroid.

The parathyroids only share its name with the thyroid because of its close proximity to the thyroid gland Fig. (2-8). In some people, the parathyroid glands are actually housed within the thyroid, but more commonly the parathyroid are located on either side of the neck or even in the upper chest. The parathyroids are responsible for producing hormones that regulate the amount of calcium within the blood and in the bones. Because calcium is important for strong and healthy bones, the parathyroid gland is highly significant. The parathyroid also play a part in the regulation and processing of Vitamin D, an essential vitamin that is absorbed through diet and by exposure to sunlight.

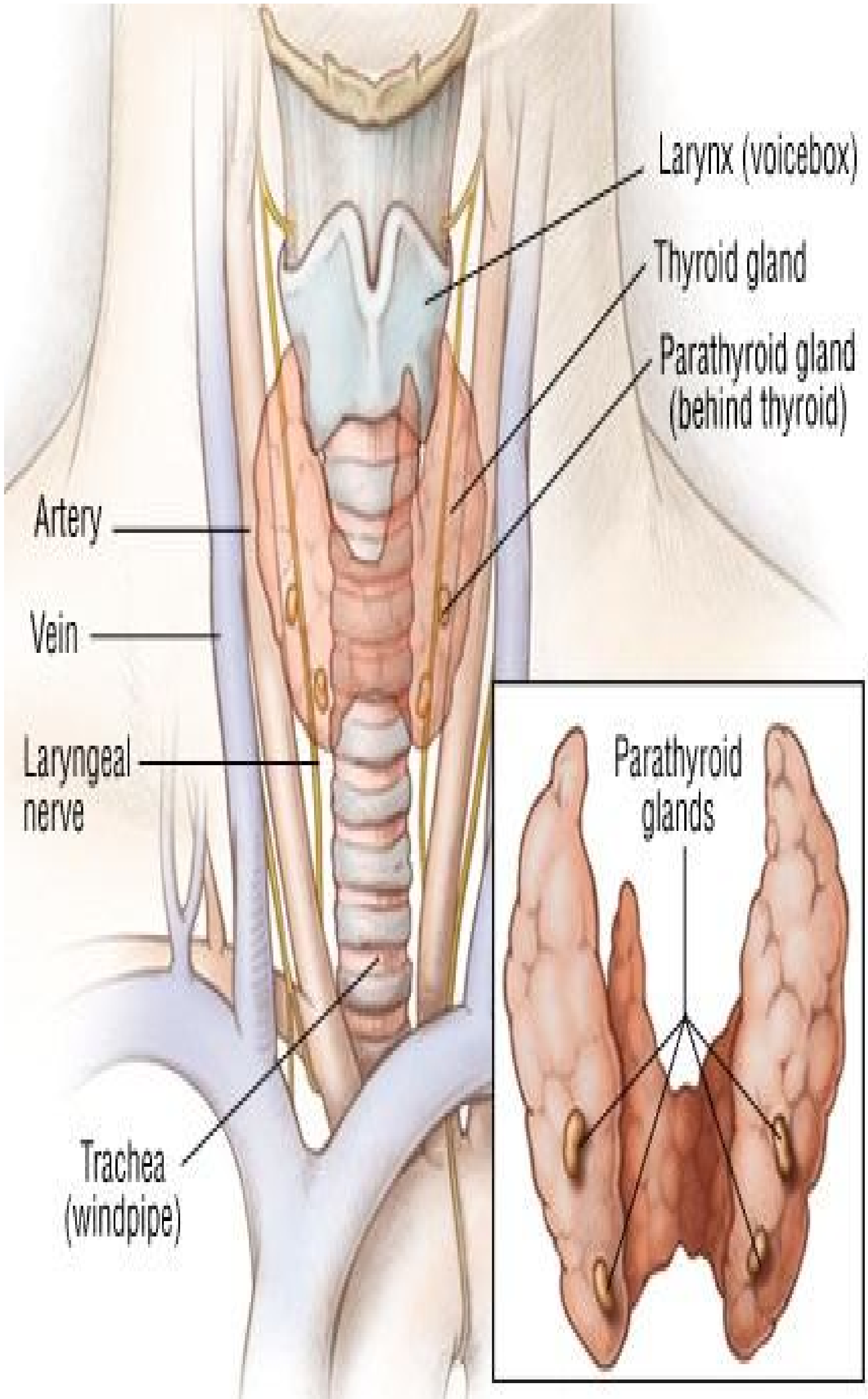


Fig. (2-8) shows Parathyroid glands, commonly the parathyroid are located on either side of the neck or even in the upper chest.
(www.webmd.com/women/thyroid-hormone-tests)

2.2 Physiology of the thyroid gland

The main function of the thyroid gland is to produce T3 and T4 hormones which regulate metabolism, increase protein synthesis and increase oxygen consumption in all cells of the body. T3 and T4 hormones are also important for growth, development, and maturation of peripheral and central nervous system. Thyroid gland also produces a hormone called calcitonin (CT).Hypothalamus releases thyroid releasing factor (TRF) into hypothalamic-pituitary portal blood circulation, which travels to the pituitary gland, which in turn releases the thyroid stimulating hormone (TSH) into the blood. Follicular cells normally synthesize thyroglobulin and secrete it into the follicular lumen. The tyroid peroxidase, found in the apical membrane of the follicular cells, catalyzes iodination of tyrosine residues on thyroglobulin molecule and coupling of iodotyrosyl residues to form T4 and T3, which are still bound to thyroglobulin, making them inactive; they are then stored as colloid. In response to TSH, follicular cells release the thyroglobulin, and secrete now active T4 and T3 into bloodstream. Human body needs 100 mg of iodide per day from diet to synthesize adequate T4; iodide uptake is mediated by human sodium iodide symporter, and then oxidized to iodine by iodide peroxidase, which binds to tyrosine. Most T4 and T3 are reversibly bound to thyroid binding globulin, which maintains their levels within narrow limits. Free T4/T3 enter the cells, bind to nuclear receptors, increase protein synthesis and help catabolism of carbohydrates and fats (basal metabolic rate).Decreased serum T4/T3 stimulates the release of TRF and TSH via negative feedback regulation; elevated levels have opposite effect (fig.2-9). Chronically stimulated (hyperplastic) follicular cells are tall and columnar, may be also papillary. (Ranade AV et al, 2008)

Thyroid Function

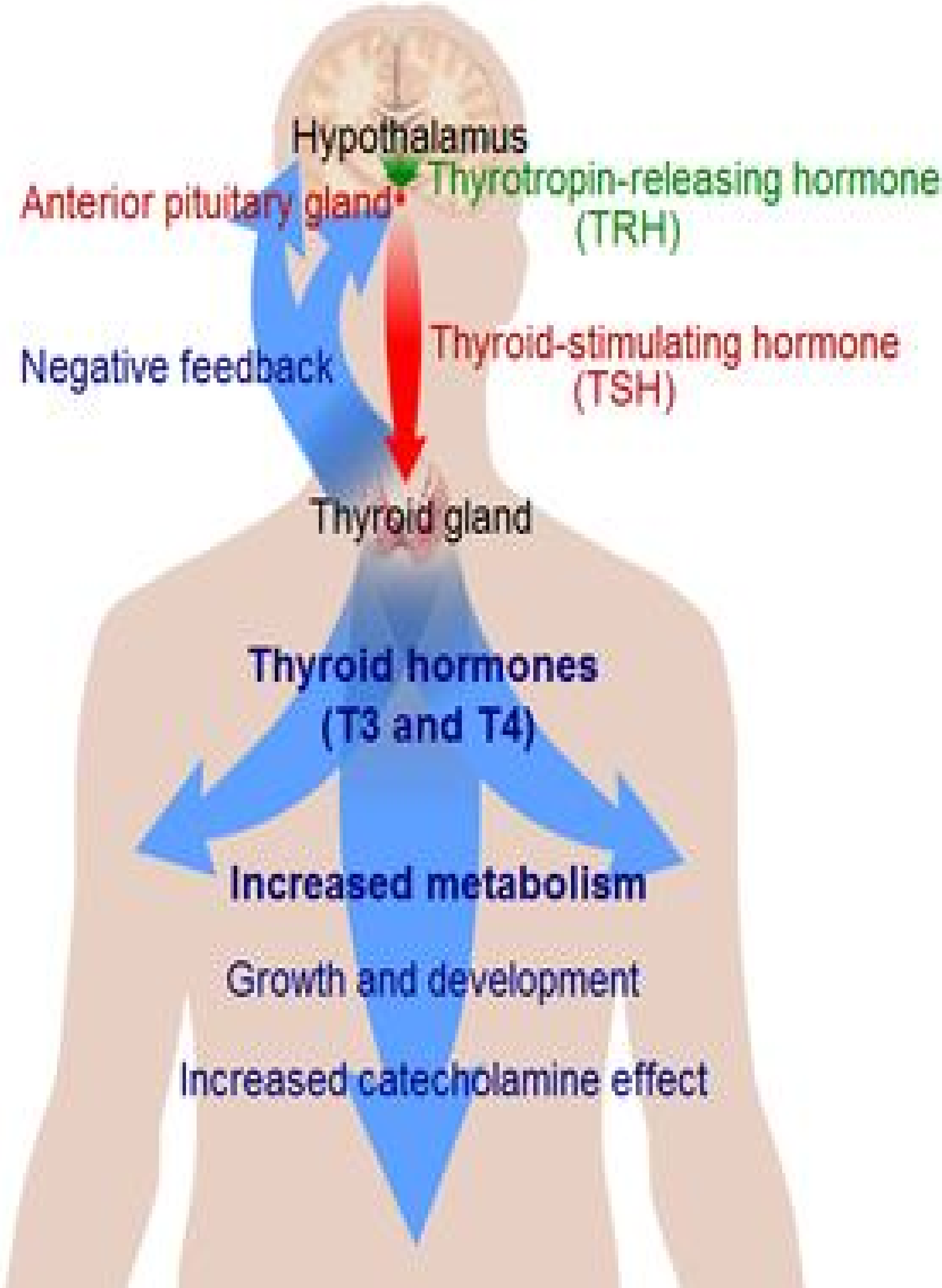


Fig (2- 9) Shows the system of thyroid hormones T_3 and T_4. Also looks function of the thyroid gland is to produce T3 and T4 hormones which regulate metabolism, increase protein synthesis and increase oxygen consumption in all cells of the body. (Ranade AV et al , 2008)

On the other hand, C cells secrete calcitonin, which lowers the serum calcium by promoting bone absorption of calcium and inhibiting bone resorption by osteoclasts. In humans, calcitonin has only a minor role in calcium homeostasis. Major role of calcitonin may be to protect the skeleton during periods of calcium stress, such as growth, pregnancy and lactation. (Ranade AV et al , 2008)

Goitrogens: suppress T4/T3 synthesis by interfering with iodide uptake or other parts of biochemical pathways, causing an increased TSH, which causes goiter (enlargement of thyroid gland). Iodine in large doses is present in vegetables such as cabbage, turnips and cassava. (Ranade AV et al , 2008).The origin and target organs of different thyroid and parathyroid hormones are summarized in table (Gharib H et al, 2004)(Dr Andrew Potter et al).

Table (2-1) shows summary of thyroid gland hormones (Gharib H et al, 2004)

Hormone	Source	Target
Triiodothyronin (T3)	Thyroid gland (follicular cells)	General
Thyroxin (T4)	Thyroid gland (follicular cells)	General
Calcitonin (CT)	Thyroid gland (Parafollicular cells)	Bone tissue
Parathyroid hormone(PTH)	Parathyroid gland	Bone tissue and kidney

2.2.1 Triiodothyronine (T3)

T3 thyroid hormone is normally synthesized and secreted by the thyroid gland in much smaller quantities than thyroxin (T4). Most T3 is derived from peripheral monodeiodination of T4 at the outer ring of the iodothyronine nucleus. (A. Lyshchik et al, 2005) T3 is several times more powerful than T4, which is largely a prohormone, perhaps four or even ten times more active. (Williams PL, Bannister LH, et al, 1995)

2.2.2 Thyroxine (T4)

The major hormone derived from the thyroid gland. Thyroxin is synthesized via the iodination of tyrosines (monoiodotyrosine), and the coupling of iodotyrosines (diiodotyrosine) in the thyroglobulin. Thyroxin is released from thyroglobulin by proteolysis and is secreted into the blood. Up to 80% of the T4 is converted to T3 by peripheral organs such as the liver, kidney and spleen.T3 exerts a broad spectrum of stimulatory effects on the cell metabolism and organ function. (How Your Thyroid Works, 2009)

2.2.3 Calcitonin

Beside thyroid hormones (T3 and T4), the thyroid gland also produces a hormone called calcitonin from the parafollicular C cells. Calcitonin influences the processing of calcium by bone cells. Calcitonin apparently controls calcium content of the blood by increasing bone formation by osteoblasts and inhibiting bone breakdown by osteoclasts. Calcitonin then tends to decrease blood calcium levels and promote conservation of hard bone matrix. Parathyroid hormone, discussed later, is an antagonist to calcitonin, because it has opposite effects. Together, calcitonin and Parathyroid hormone help maintain calcium hormeostasis. (How Your Thyroid Works, 2009).

2.2.4 Parathyroid Hormones:-

A polypeptide hormone secreted by the parathyroid glands which maintains intracellular calcium levels in the body. Parathyroid hormone increases intracellular calcium by promoting the release of calcium from bone, increases the intestinal absorption of calcium, increases the renal tubular reabsorption of calcium and increases the renal excretion of phosphates.(Ranade AV et al, 2008)

2.2.5. Thyroid Hormone Tests

Thyroid hormone tests are blood tests that check how well the thyroid gland is working. The thyroid gland makes hormones that regulate the way the body uses energy.

The thyroid gland is a butterfly-shaped gland that lies in front of your windpipe (trachea), just below your voice box (larynx). The thyroid gland uses iodine from food to make two thyroid hormones: thyroxin (T4) and triodothyronine (T3). The thyroid gland stores these thyroid hormones and releases them as they are needed.

Thyroid hormones are needed for normal development of the brain, especially during the first 3 years of life. Intellectual disability may occur if a baby's thyroid gland does not produce enough thyroid hormone (congenital hypothyroidism). Older children also need thyroid hormones to grow and develop normally, and adults need the hormones to regulate the way the body uses energy (metabolism). The United States Preventive Services Task Force recommends that all newborns be tested for congenital hypothyroidism.

♦ **Thyroid hormone blood tests include:**

- Total thyroxine (T4). Most of the thyroxine (T4) in the blood is attached to a protein called thyroxine-binding globulin. Less than 1% of the T4 is unattached. A total T4 blood test measures both bound and free thyroxine. Free thyroxine affects tissue function in the body, but bound thyroxine does not.

- Free thyroxine (FTI or FT4). Free thyroxine (T4) can be measured directly (FT4) or calculated as the free thyroxine index (FTI). The FTI tells how much free T4 is present compared to bound T4. The FTI can help tell if abnormal amounts of T4 are present because of abnormal amounts of thyroxine-binding globulin.
- Triiodothyronine (T3). Most of the T3 in the blood is attached to thyroxine-binding globulin. Less than 1% of the T3 is unattached. A T3 blood test measures both bound and free triiodothyronine. T3 has a greater effect on the way the body uses energy than T4, even though T3 is normally present in smaller amounts than T4.

♦ **Thyroid hormone tests are done to:**

Find out what is causing an abnormal thyroid-stimulating hormone (TSH) test. For more information, see the topic Thyroid-Stimulating Hormone (TSH). This is the most common reason for thyroid hormone tests.

- Check how well treatment of thyroid disease is working. The total thyroxine (T4), free thyroxine (FT4), and free thyroxine index (FTI) values are often used to keep track of treatment for hyperthyroidism.
- Screen newborns to find out if the thyroid gland function is normal a condition called congenital hypothyroidism can prevent normal growth and development and cause other severe problems, such as intellectual disability, if it is not treated soon after birth.

Many medicines may change the results of this test. Be sure to tell your doctor about all the nonprescription and prescription medicines you take. If you are taking thyroid medicines, tell your doctor when you took your last dose. Your doctor may instruct you to stop taking thyroid medicines temporarily before having this test. (www.webmd.com/women/thyroid-hormone-tests).

2.3. Pathology of the Thyroid Gland

Disorders of the thyroid gland could be classefied into:

- Congenital
- Inflammation
- Functional disorders
- Diffuse and multinodular goiter (MNG).
- Neoplasia

2.3.1. Congenital thyroid lesions

These include:

- agenesis, aplasia and hypoplasia of the thyroid gland.
- Accessory or aberrant gland
- Thyroglossal duct cyst.

Thyroglossal duct cyst is a rare congenital lesion. It may present as a midline neck swelling (fig 2-10). It arises from the partial persistence of the embryonic tract between the thyroid gland and base of the tongue (Dumont, J.E., Ermans et al, 1963).Fig. (2-11)

Fig (2-10) Thyroglossal duct cyst it present as a midline neck swelling (Yurong Hong et al)

Fig. (2-11): ShowsThyroglossal duct cyst (Dumont et al, 1963)

The major significance of thyroglossal cyst is when presented as a mass that must be differentiated from a tumor and, indeed rarely they give rise to a carcinoma. In addition, they sometimes communicate as draining sinuses with either the skin or the base of the tongue (Dumont et al, 1963)

2.3.2. Inflammation of the thyroid gland

Acute and chronic nonspecific thyroiditis may be caused by a variety of viral and bacterial agents that secondarily affect the thyroid (Dumont et al, 1963). Thyroiditis may be acute with enlarged painful gland, subacute (De Quervain's), fibrous (Riedel's) and the most common form auto immune thyroiditis (Hashimoto's disease).

2.3.2.1 Hashimoto's disease:

This is by far the most common thyroiditis. The classic case is characterized by 1- symmetrical, rubbery enlargement of the thyroid gland, 2- mild hypothyroidism, 3-massive infiltration of the thyroid by lymphoid cells admixed with plasma cells and 4- the presence of auto antibodies directed against thyroidal antigens (Tolling SR et al, 2000). Females have the manifest disease 20 times as commonly as males and typically are most vulnerable about the time of menopause. Adult males usually develop a severe form of the disease associated with greater destruction and fibrosis, with a correspondingly more marked hypothyroidism.

Hashimoto's disease has been cited as causing about (40%) of all nontoxic goiters in children and adolescents (Dumont et al, 1963).Patients usually seeks medical attention because of enlargement of the thyroid gland with symptoms of pressure on the trachea or esophagus. Hashimoto's thyroiditis frequently coexists with other disorders of presumed autoimmune origin, including rheumatoid arthritis, Addison's disease, and pernicious anemia, a feature that supports the possible autoimmune origin of this disorder (Dumont et al, 1963).

2.3.2.2. Subacute thyroiditis (De Quervain's disease):

This is a much less common form of specific thyroiditis, probably of viral origin, which manifests itself by painful swelling of the thyroid, often with malaise and other systemic reactions. In contrast to Hashimoto's disease, it is not considered to be an autoimmune disorder (Dumont et al, 1963).

2.3.2.3. Riedel's thyroiditis:

This is an extremely rare disease of unknown etiology in which part or the entire thyroid is replaced by an aggressive fibrosis. This may lead to dysphagia and recurrent laryngeal nerve paralysis. It is often associated with idiopathic fibrosis in the retro peritoneum and mediastinum, suggesting some systemic derangement (Dumont et al, 1963).

2.3.3. Functional thyroid disorders

Alteration of the thyroid gland function includes either excessive secretion of the thyroid hormones (hyperthyroidism), or decrease hormonal secretion (hypothyroidism).

2.3.3.1. Hyperthyroidism:

Hyperthyroidism refers to the state of hyper metabolism and hyperactivity of the cardiovascular and neuromuscular systems induced by abnormally high levels of circulating T_4 and T_3 (Dumont et al, 1963).Causes of hyperthyroidism are shown in table (2.2). The most common cause is Graves' disease (diffuse goiter). Much less frequently, hyperthyroidism is caused by a functioning (toxic) adenoma or an autonomously functioning focus within a multinodular goiter (MNG). Only very rarely carcinoma of the thyroid gland is associated with hyper function. Excess pituitary secretion of TSH has been demonstrated as a cause of hyperthyroidism only in a few extraordinary cases of pituitary tumors (Dumont et al, 1963).Clinical features of hyperthyroidism include elevation of body temperature, heart rate and systolic blood pressure, increased sensitivity to heat, with nearly continuous perspiration, marked irritability and "nervousness," with a fine tremor of the hands, weight loss despite increased appetite, fatigability, and muscle weakness in addition to thyroid opthalmopathy. Sometime, particularly in older patients, there are cardiac arrhythmias. Women develop oligomenorrhea, which may progress to amenorrhea. (Delange et al, 1972).

Table (2-2) shows causes of hyperthyroidism:-

Cause	Hormone concentrations	Goiter
Abnormal thyroid-stimulating immunoglobulin (e.g. Grave's disease)	↑ T_3 and T_4, ↓ TSH	Yes
Secondary to excess hypothalamic or pituitary secretion	↑ T_3 and T_4, ↑ TSH and/or ↑ TRH	Yes
Hypersecreting thyroid tumor	↑ T_3 and T_4, ↓ TSH	No

2.3.3.1.1. Graves' disease:

In 1835 Robert Graves wrote about cases of thyroid disease and proptosis (protrusion) of the eye, and this form of hyperthyroidism was named after him (Cummings CW, et al,1998) Graves' disease is an autoimmune disorder characterized by three features: 1.hyperthyroidism, 2. diffuse enlargement of the thyroid gland, and 3. thyroid opthalmopathy (eye changes) which include; lid retraction, exophthalmos and weakness of eye muscles (ophthalmoplegia) (fig 2-12) (Delange et al, 1972). Females are affected four times as commonly as males. This condition tends to occur in young to middle-age adults and has a marked familial pattern. The cause of Graves' disease is not fully understood, but it seems to involve the interplay between a numbers of factors. Patients with Graves' disease owing to the presence of thyroid-stimulating immunoglobulin’s (TSI) in the blood. These antibodies, acting on the TSH receptor, presumably lead to the stimulation of thyroid acinar cells releasing excessive thyroid hormone into the circulation (Dumont et al, 1963) Graves' disease is established by documenting an increased uptake of radioactive iodine by the thyroid and elevated serum levels of T_4 and T_3 (Delange et al, 1972).

Figure (2- 12): Shows eye manifestations of Graves' disease, thyroid opthalmopathy (eye changes) which include; lid retraction, exophthalmos and weakness of eye muscles (ophthalmoplegia) (Delange et al, 1972)

Fig. (2-13). Shows apathetic face in a female with hypothyroidism. (Dumont et al, 1963)

2.3.3.2. Hypothyroidism:

This term refers to the hypometabolic state caused by deficiency of thyroid hormones. In adults when associated with generalized interstitial edema, it is known as myxedema. Causes include: 1- Hashimoto's disease, 2- iodine deficiency or inborn metabolic errors, 3- hypothalamic TRH or pituitary TSH insufficiency and 4-surgical or chemical ablation of the thyroid in the treatment of Graves' disease (Dumont et al, 1963).congenital hypothyroidism is referred to (Cretinism).table 2-3 shows causes, hormonal changes and thyroid size in cases of hypothyroidism (Dumont et al, 1963)

Table (2-3) shows causes of hypothyroidism:-

Cause	Hormone concentrations	Goiter
Primary failure of thyroid gland	↓T_3 and T_4, ↑ TSH	Yes
Secondary to hypothalamic or pituitary failure	↓T_3 and $T_{4,}$ ↓ TSH and/or ↓ TRH	No
Dietary iodine deficiency	↓T_3 and T_4, ↑ TSH	Yes

2.3.3.2.1. Congenital hypothyroidism (Cretinism):

When severe hypothyroidism is present from birth, the syndrome, termed cretinism, is dramatic and it is twice as frequent in girls as is boys. These children become dwarfed, with ossification epiphyseal fusion and dentition all being markedly delayed. Their tongues are enlarged and their abdomen protuberant. More important, if the condition is not treated promptly, the children suffer irreversible mental retardation. Although the principle cause of cretinism was once maternal iodine deficiency, congenital errors in thyroxin and triiodothyronine synthesis and release are become relatively more important as severe dietary deficiencies of iodine become less common. Serum levels of T_4 and T_3 are low and the serum level TSH is elevated (Dumont et al, 1963).Children in which hypothyroidism is detected early respond well to treatment with thyroid hormone and develop an apparently normal mental capacity. Children who are treated at a large age may be left with irreversible brain damage

2.3.3.2.2. Hypothyroidism in adults (myxedema):

Hypothyroidism in the adult most often occurs as a variant or end-result of Hashimoto's disease. Usually the functional impairment is mild and even asymptomatic. Fully developed myxedema, however, produces a striking clinical picture, characterized by 1- markedly slowed mentality, speech, and movement with apathetic-looking face (Figure 2-10). 2- Deepened voice 3- thick, dry, pale-yellow skin and coarse, spare hair 4- thickened tongue 5- generalized interstitial edema rich in proteins and mucopolysaccharides 6- intolerance to cold and 7- fatigability and weakness Sometimes there is massive pericardial and pleural effusion. The heart may show nonspecific degenerative changes and dilatation without hypertrophy. These patients become hypercholesterolemic and show an acceleration development of atherosclerosis. Severs myxedema tends to occur in an older age group, often in the sixth decade with a female to male ratio of about 5:1. Circulating thyroid auto antibodies are present in about (89 %) of patients whose disease is of recent onset and in (70%) to (80%) of those with long-standing myxedema (Dumont et al, 1963)

2.3.4. Goiter

Goiter means enlarged thyroid gland which may be diffuse or nodular, toxic or non toxic.

2.3.4.1. Nontoxic goiter:

Nontoxic goiter (physiological, endemic, colloid and multinodular goiter) refers to an enlargement of the thyroid that is not associated with functional, inflammatory or neoplastic alterations. Thus, patients with nontoxic goiter are euthyroid (Backdahl M et al, 1987). Nontoxic goiter is far more common in women than in men (8:1). The diffuse form characterizes the early stage of the disease and is frequently presents during adolescence and pregnancy. The thyroid gland is diffusely enlarged, whereas the multinodular type evolves as the disease become more chronic and presents in persons older than 50 years of age. Simple nodular enlargement of the thyroid tends to be familial, thereby suggesting a genetic contribution to the disorder (Dumont et al, 1963).

In MNG, the gland is asymmetrically enlarged and shows numerous nodules of variable sizes. Some nodules may be seen filled with colloid material; others may show hemorrhage, cystic changes or calcification.

Clinical features: patients with nontoxic goiter are typically asymptomatic and come to medical attention because of a mass in the neck. Large goiters may cause dysphagia or inspiratory stridor by compressing the esophagus or trachea (Dumont et al, 1963). Pressure from the goiter on the neck veins leads to venous congestion of the head and face. Hoarseness of voice may results from compression of the recurrent laryngeal nerve. Importantly, blood concentrations of T_4 and T_3, and usually of TSH as well, are normal.Nontoxic goiter is most commonly treated with the administration of thyroid hormone to reduce TSH levels and, thus, stimulation to thyroid growth, radioactive iodine therapy is indicated . Although surgery is ordinarily contraindicated, it may become necessary if local obstructive symptoms become troublesome. Many patients with nontoxic goiter eventually develop hyperthyroidism in which the term toxic multinodular goiter is applied (Delange et al, 1972).

2.3.4.2. Endemic goiter

The term endemic goiter is a descriptive diagnosis and reserved for a disorder characterized by enlargement of the thyroid gland in a significantly large fraction of a population group, and is generally considered to be due to insufficient iodine in the daily diet. Since nontoxic goiter also exists when there is abundant iodine in the diet, the distinction between endemic and non endemic goiter is necessarily arbitrary. Endemic goiter may be said to exist in a population when more than 5% of the preadolescent (at 6-12) school-age children have enlarged thyroid glands, detected by palpation. (Gaitan et al, 1980)

However, the evaluation of the prevalence of goiter based on palpation has been questioned because the reproducibility of assessment by palpation is low, especially with the size estimation of smaller glands, particularly in children (Dumont et al, 1995).Therefore, the method of choice is now US which is reproducible with a maximum deviation of 10 %. Normative values for thyroid volume measured by ultrasonography as a function of age, sex and body surface area have been proposed by Delange et al, 1994.

2.3.4.3. Toxic nodular goiter

All long standing diffuse endemic goiter may eventually convert to multinodular toxic goiter. The nodules become autonomus.Pathologic and sonographic features are the same as non toxic form, but the patient suffers from thyrotoxicosis due to increased serum levels of T3 &T4 hormones.

2.3.4.4. Toxic adenoma

Toxic adenoma is a solitary, hyper functioning, follicular neoplasm and otherwise normal thyroid. They commonly occur in young adults, but may affect any age group. The lesion presents clinically as a solitary, discrete mass, usually up to 4 cm in diameter. Hyper functioning toxic adenoma eventually suppresses the remainder of the thyroid, which then atrophies. Most patients do not suffer symptoms of hyperthyroidism until the adenoma has grown to a diameter of approximately 3 cm. because the normal thyroid tissue is suppressed; toxic adenoma is effectively treated with radiolabeled iodine. Large nodules may be excised surgically (Dumont et al, 1963).

2.3.5. Thyroid neoplasm

Thyroid neoplasm's are:

1- Primary tumors

- Epithelial
- Malignant lymphoma
- Mesenchymal tumors

2- Metastatic tumors

Epithelial thyroid neoplasms are classified according to the cell of origin into:

- Tumors arising from the follicular cells
  - Benign (follicular adenoma)
  - Malignant (papillary, follicular or anaplastic carcinoma)
- Tumors arising from the C-cell
  - Medullary carcinomas.

Metastatic deposits reach the thyroid gland from malignant tumors of the breast, lungs, kidneys and colon. (Gene J et al, 2001)

2.3.5.1. Follicular adenoma

It is a benign, encapsulated tumor showing evidence of follicular differentiation. It is a common thyroid tumor predominantly seen in young to middle age women. It presents as a painless, solitary thyroid nodule of viable size. The thyroid gland shows normal function. (Gene J et al, 2001)

2.3.5.2. Thyroid carcinoma:

Thyroid cancer is infrequent and causes only about (0.5%) of all cancer deaths. Women are affected more often than men in a ratio of 2:1. The peak incidence is between the ages of 40 and 60 years. (Backdahl M et al, 1987).

Thyroid cancers are classified on the basis of their cells of origin. The human thyroid gland contains follicular cells, parafollicular (C cells) and connective tissue cells. Tumors arising from the follicular cells are sub classified into papillary, follicular and anaplastic carcinoma on the basis of their histologic pattern. The parafollicular cells give rise to the medullary carcinoma. Connective tissue tumors within the thyroid are very rare (Dumont et al, 1963).

2.3.5.3. Papillary carcinoma:

These are the most common form of the thyroid cancer (60-70%). Females below 40 year of age are most commonly affected (Dumont et al, 1963). Usually these tumors become evident as palpable nodules within the thyroid, which if untreated, eventually, extend via the lymphatic to the regional lymph nodes but not metastasize via the bloodstream. Others may remain undiscovered until removal of a lymph node bearing a metastatic deposit calls attention to the possibility of an occult primary lesion. (Dumont et al, 1963) These tumors may be solitary or multicenteric, solid or cystic, and of variable sizes. (Gene J et al, 2001).

Surgical resection and removal of involved nodes is almost always curative, particularly in younger patients with pure papillary pattern. Even the less favorable mixed papillary and follicular pattern has an (80 to 90 %) 20-years survival rate (Dumont et al, 1963).(Fig.2-14)

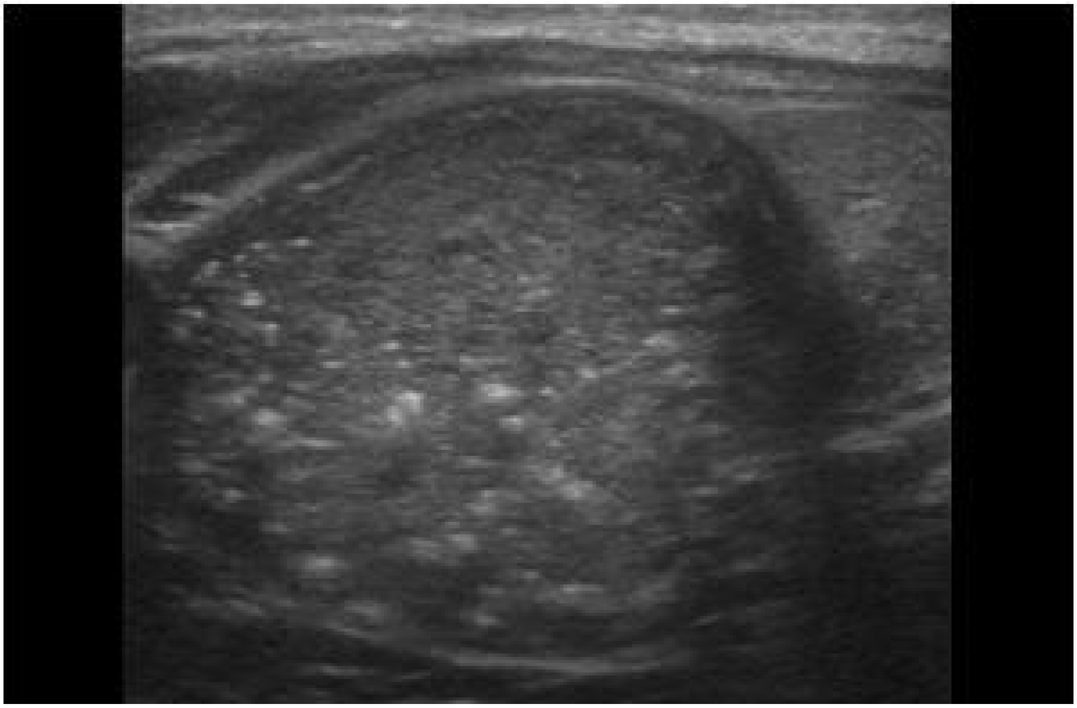


Fig.(2-14) Shows B-mode ultrasound of papillary carcinoma with microcalcification (Horlocker TT et al, 1985)

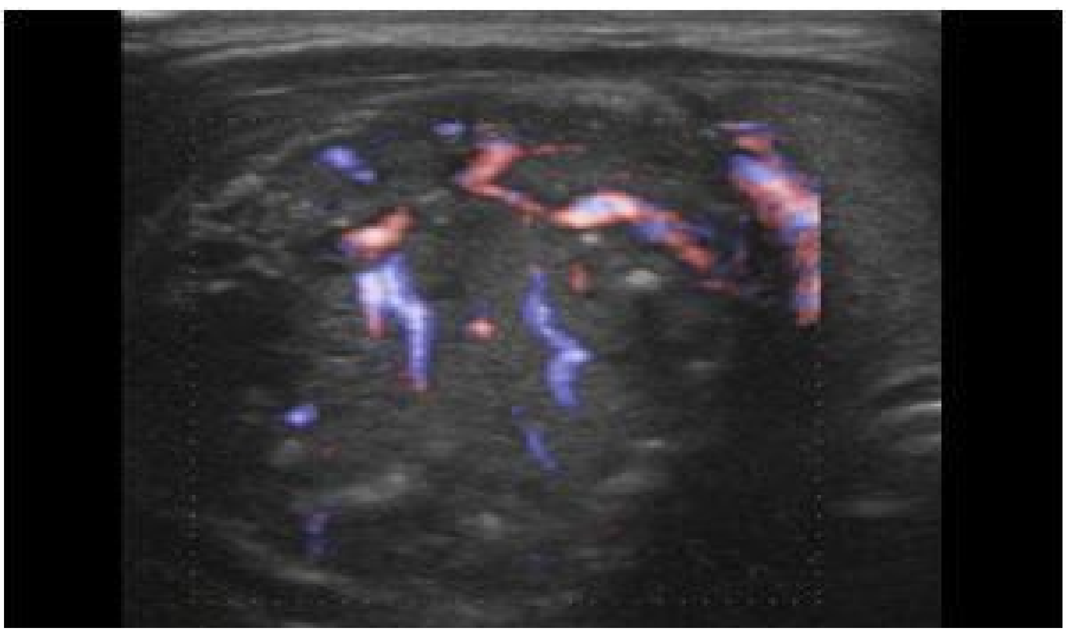


Fig (2-15) Shows papillary carcinoma with microcalcification (Horlocker TT et al, 1985).

2.3.5.4 Follicular carcinoma:

This pattern constitutes about (20%) of thyroid cancers. They are characterized by the formation of more or less well-developed acini or follicles. By their adherence to surrounding structures, these tumors produce pressure symptoms, such as dyspnea and dysphagia. Involvement of the recurrent laryngeal nerves leads to hoarseness and cough. In addition to local spread, most tumors eventually metastasize to the lungs, bones and other distant sites. Lymphatic spread to local nodes may occur but is not common. The 5-year survival rate is about (60%) overall (Dumont et al, 1963)

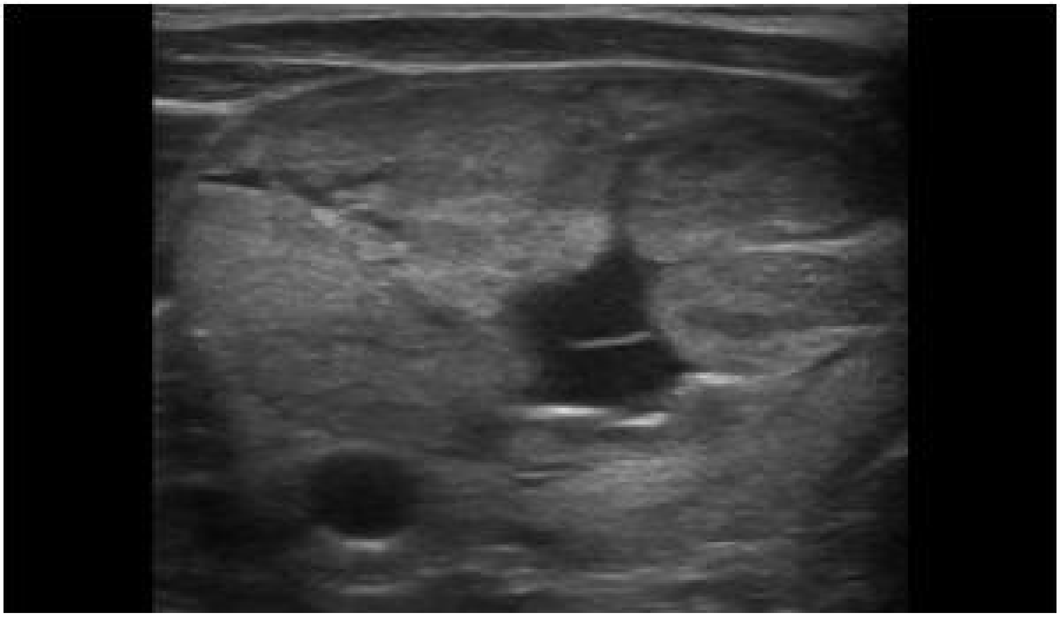


Fig.(2-16) Shows ultrasound of Follicular carcinoma (Horlocker TT et al, 1985)

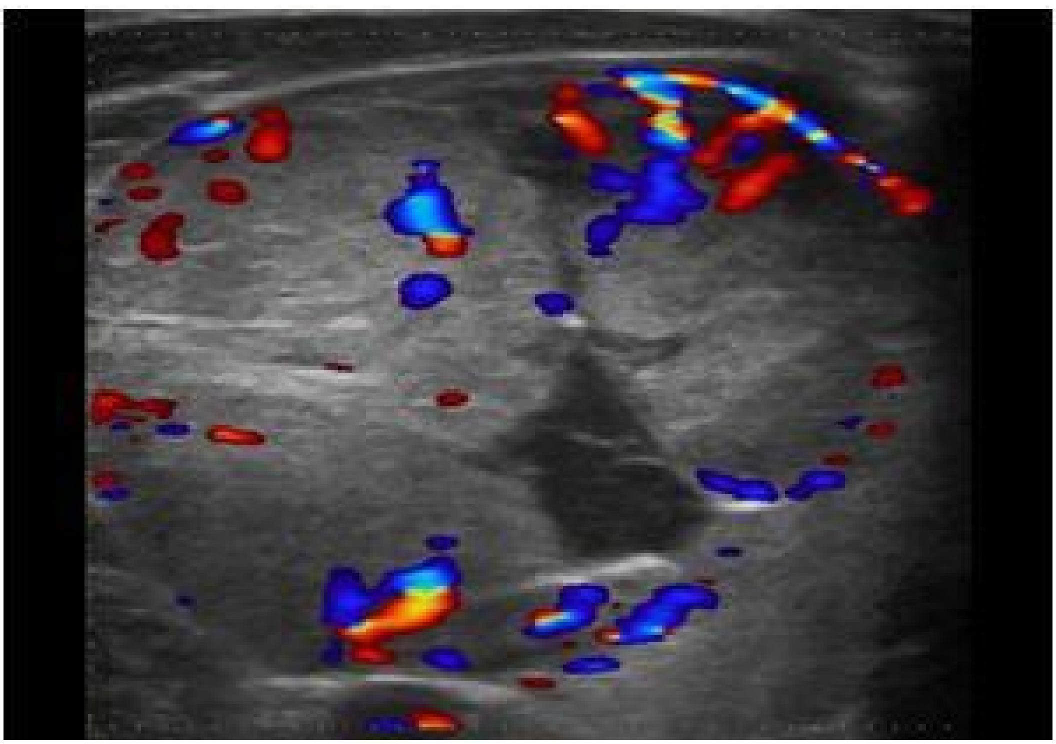


Fig (2-17) Shows Doppler ultrasound of folliculr crcinoma (Horlocker TT et al, 1985)

2.3.5.5. Anaplastic (undifferentiated) carcinoma:

This is a highly malignant tumor that always causes death within 2 years. It affects older individuals, commonly between the ages of 60 and 80 years. Less than 5% of thyroid carcinomas fall into this category these tumors are usually large, firm, necrotic mass that replaces the entire gland. Rapid advance in size, extension beyond the thyroid and widespread metastases, all occurring within 1 year, are characteristic of this aggressive neoplasm (Dumont et al, 1963).

2.3.5.6 Medullary carcinoma:

Relatively uncommon, medullary carcinomas have received considerable attention due to several unusual features: 1) 10 % to 15% medullary carcinomas are encountered in well-defined genetic syndrome that transmitted by autosomal dominant inheritance. These syndromes, characterized by the concurrence of tumors in several endocrine glands called multiple endocrine neoplasia MEN. 2) The cells, which give rise to the tumor, are a part of the Amine Precursor Uptake and Decarboxylation APUD system, they produce excessive amounts of calcitonin and less commonly adrenocorticotropin ACTH, prostaglandins, and serotonin. 3) Histological the neoplasm is characterized by the presence of an amyloid that seem to be produced by the tumor cells (Dumont et al, 1963). It usually affects middle-aged adults, with unilateral involvement of the gland, with or without cervical lymph nodes metastasis. (Gene J et al, 2001). Fig.(2-16)

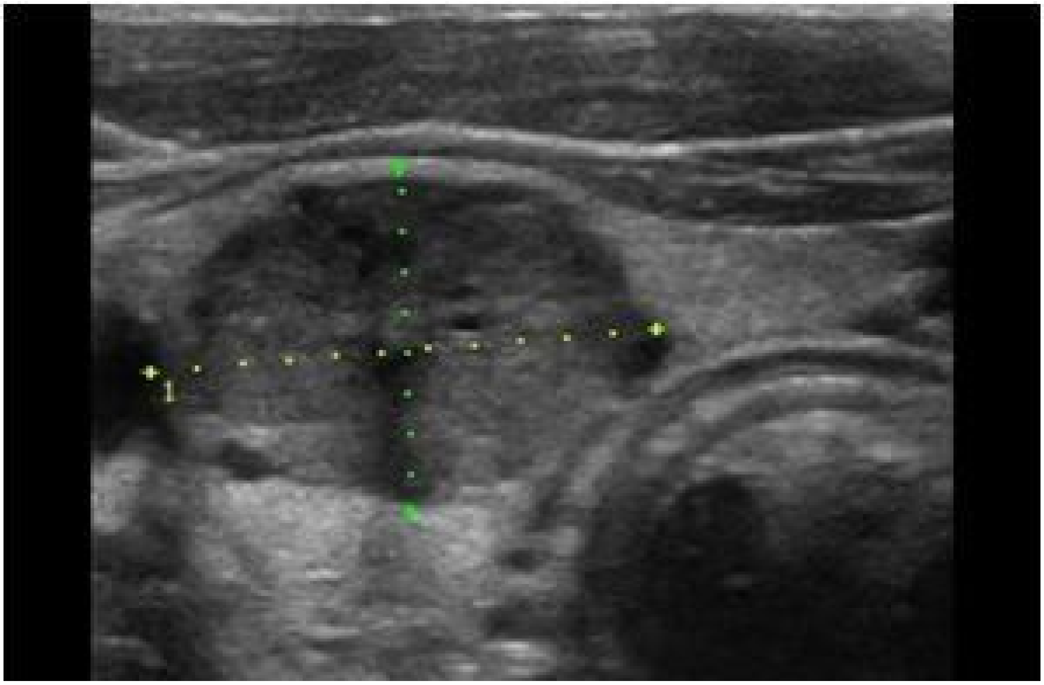


Fig.(2-18) Shows ultrasound of Medullary carcinoma. (Horlocker TT et al, 1985)

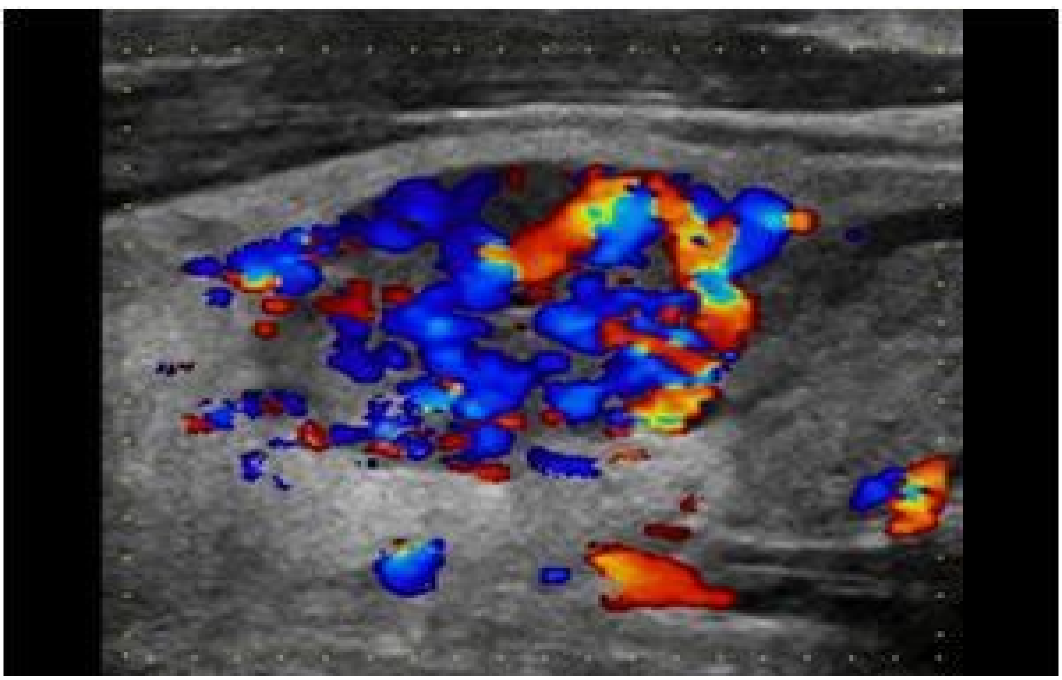


Fig (2-19)Shows Doppler of Medullary carcinoma(Horlocker TT et al, 1985).

2.3.6. Differential diagnosis of solitary thyroid nodules: (79).

- Papillary carcinoma
- Follicular carcinoma
- Medullary carcinoma
- Follicular adenoma
- Hyperplastic (dominant) nodule
- Metastatic neoplasm
- Colloid nodule
- Thyroid cyst
- Part of Hashimoto's disease.

2.4. Ultrasound in general.

Ultrasound was first introduced for examination of small parts by Howry in 1955.The thyroid ultrasound in A and a B mode were described in 1966-1967 (Fujimoto Y. et al., 1967) and has been widely practiced since 1970s. An ultrasound examination is now one of the routine radiological methods for diagnosing thyroid disease. This method is based on the ability of tissues with different acoustic to reflect ultrasound waves. Modern ultrasound equipments are fast enough to supply real-time scanning (fig.2-20). It permits visualization of an organ, motion and assessment of some organ functionality .Ultrasonography can be easily applied as a screening modality to detect people with an increased risk of thyroid pathology (Parshyn V.S.et al., 1999). There are many advantages of ultrasound screening as shown below, but one disadvantage is its low diagnostic accuracy. Negative results do not guarantee the absence of the disease, whereas on other side positive results may not be considered as fully-reliable evidence of pathology. Patient with abnormal thyroid are subject to further qualified ultrasound examinations using the entire available modes including color and power Doppler studies.

Fig (2-20) Fig. Shows Ultrasound equipment u/s machine with ultrasound transducer used is Broadband Linear Array Transducer 12 to 5 MHz extended operating frequency range. (Philips medical system)

2.4.1. US. Technique

The patient is examined in a supine position with the neck mildly hyperextended. The thyroid gland should be examined with a high-frequency linear array transducer ranging from 7.5 to 10 MHz. Blood flow can be studied using Duplex sonography, in which gray scale 2D sonography is combined with pulsed Doppler. The thyroid gland should be imaged entirely in both the transverse and longitudinal planes. Both sides of the neck should be examined for the presence of enlarged nodes, particularly in patients known to have a suspicious thyroid nodule. Detailed analysis of any thyroid abnormality is done. The relation of the thyroid gland to the neighboring structures is also assessed.

2.4.2. Advantages of ultrasound examination of the thyroid gland:

- Efficient, fast, and relatively simple.
- Noninvasive and painless.
- No need for special patient preparation.
- No contraindications.
- Harmless and safe for children, pregnant women, and nursing mothers, patients with severs concomitant pathology.
- Multiple examinations are possible.
- US is efficient regardless of patient medications including thyroid blocking agents.
- Easy differentiation of cystic from solid lesions.
- Can detect nodules as small as 2-3mm.
- Multiple additional ultrasound modalities for differential diagnosis such as Doppler modes, 3D reconstruction, elastography, etc are available.
- Digital visual data is easy archived and transferred for efficient follow up and distant consultations.

- US is precise to guide minimally invasive procedures, such as fine needle aspiration biopsy (FNAB) or injections

2.4.3. Indications of thyroid ultrasound

The most common indications of thyroid ultrasound are:-

♦ Patients complaints are suspicious of thyroid pathology e.g. dyspnea, cough, irritability, Palpitation, heat intolerance…etc.

♦ Palpable masses in the anterior part of the neck.

♦ Thyroid pathology detected by other diagnostic techniques.

♦ Cardio vascular pathology, especially arrhythmia.

♦ Diseases of anatomically related organs such as larynx, pharynx and trachea.

♦ monitoring the treatment efficiency of thyroid disease.

♦ Postoperative follow up.

2.4.4. Ultrasound appearance of normal thyroid gland:

Anatomical structures of the anterior part of the neck are depicted rather well with standard gray scale US. The thyroid gland is slightly more echo-dense than the adjacent structures because of its iodine content. It has a homogenous ground glass appearance. Each lobe has a smooth globular-shaped contour and is no more than 3 - 4 centimeters in height, 1 - 1.5 cm in width, and 1 centimeter in depth (fig. 2-21). Ultrasound allows volumetric analysis of the thyroid lobes. Each lobe can be considered as a separate sphere whose volume is given by $v = (\pi/6 \times \text{height} \times \text{Width} \times \text{depth})$. The average volume has been estimated at between 12 and 40 cm3.

The isthmus is identified, anterior to the trachea as a uniform structure that is approximately 0.5 cm in height and 2 - 3 mm in depth. The pyramidal lobe is not seen unless it is significantly enlarged. In females, the upper pole of each thyroid lobe may be seen at the level of the thyroid cartilage, and is seen lower in males. The surrounding muscles are of lower echogenicity than the thyroid gland and the tissue planes between muscles are usually identifiable. The air-filled trachea does not transmit the ultrasound and only the anterior portion of the cartilaginous ring is represented by dense, bright echoes. The carotid arteries are echo-free unless they are calcified. The jugular veins are usually in a collapsed condition and distend with Valsalva maneuver (fig.2-21). Blood vessels on the surface and within the thyroid gland are seen as 1-2 mm echo-free zones. The vascular nature of all of these echoless areas can be demonstrated by color Doppler imaging to differentiate them from cystic structures. Lymph nodes may be observed and nerves are generally not seen. The parathyroid glands are observed only when they are enlarged and are less dense ultrasonically than thyroid tissue because of the absence of iodine. The esophagus may be demonstrated posterior to the medial part of the left thyroid lobe, especially if it is distended by a sip of water (Hirumatsu Y et al, 1999).

Fig. (2-21) Thyroid measurements on transverse (A) an Longitudinal (B) scans.

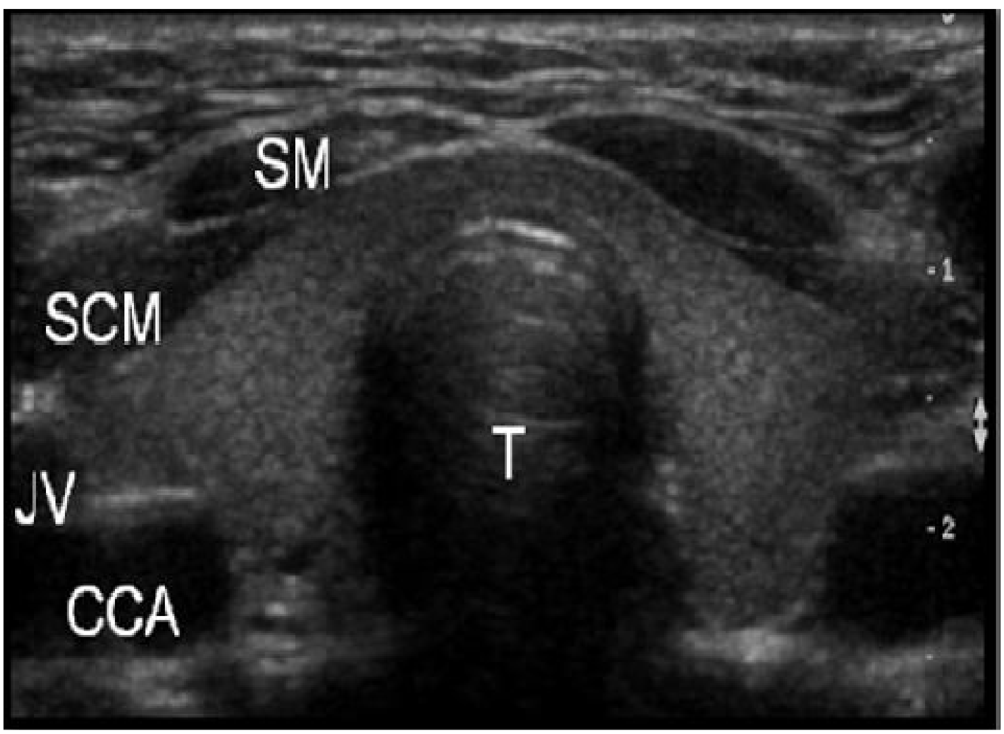
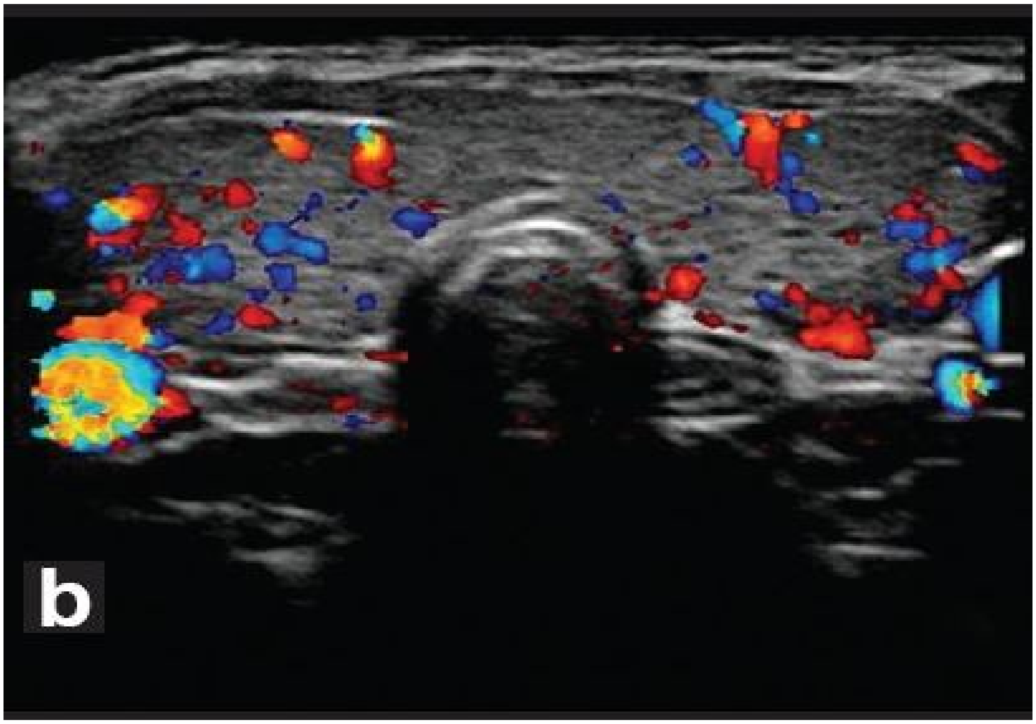


Figure (2-22) shows normal thyroid gland and surrounding structures on transverse scans. A. RL: right lobe. LL: left lobe. I: isthmus. E: esophagus. B. T: trachea. SM: strap muscles. SCM: sterno-cleido-mastoid muscle. JV: jugular vein. CCA: common carotid artery.

2.5. Doppler Ultrasound

The Doppler shift is a change in frequency that occurs when sound (or light) is emitted from, or bounced off of, a moving object. When a moving target reflects a sound the frequency of the reflected sound wave is altered. The frequency is shifted up by an approaching target and shifted down by a receding target. The amount the frequency is shifted is proportional to the velocity of the moving object. Because the Doppler shift was originally described for energy in the visible light spectrum, an upward Doppler shift is referred to as a blue shift, (a shift to a higher visible light frequency) and a downward Doppler shift is referred to as a red shift. Ultrasound utilization of the Doppler shift falls into three main categories; a) analysis of the Doppler frequency spectrum which allows for calculation of velocity, and is used in vascular studies, b) color-flow Doppler and c) power Doppler .In thyroid ultrasound, Doppler imaging is used predominantly to assess the vascularity of tissues (figure 2-21) . The leading use is to help determine the likelihood of a thyroid nodule being malignant. However, other applications of Doppler imaging include assessing the etiology or subtype of thyrotoxicosis, clarifying images and helping to assess the etiology of hyperthyroidism. Analysis of the Doppler spectrum allows for determination of flow velocity and calculation of resistance to flow. By analyzing the waveform, the peak systolic velocity and diastolic velocity can be calculated. Resistive index and pulsatility index can be derived from these measurements. While these values are typically used in studies of peripheral vascular disease, the peak flow velocity and resistive index are occasionally used in reporting the degree of vascularity of thyroid tissue. For most thyroid imaging, color-flow Doppler and power Doppler are used. In color-flow Doppler a unique color (or brightness) is assigned to an individual frequency. Typically a greater frequency shift (corresponding to a higher velocity) is assigned a brighter color. Analysis of the color-flow image gives a graphic illustration of the direction and speed of blood flow within soft tissue (fig2-23). In contrast, power Doppler considers all frequency shifts to be equivalent, integrating the total amount of motion detected. The assigned color represents the total amount of flow present, independent of the velocity (fig. 2-24). Color-flow Doppler provides information regarding both direction and velocity, and is more useful in vascular studies. In contrast, power Doppler does not provide information regarding velocity. However, it has increased sensitivity for the detection of low degrees of flow, has less noise interference, and is less dependent on the angle of incidence between the ultrasound waves and the moving object. Power Doppler is generally the preferred imaging technique for assessing the vascularity of thyroid tissue (Martin HE et al, 1930).



(Fig. (2-23) shows normal vascularity of the thyroid gland

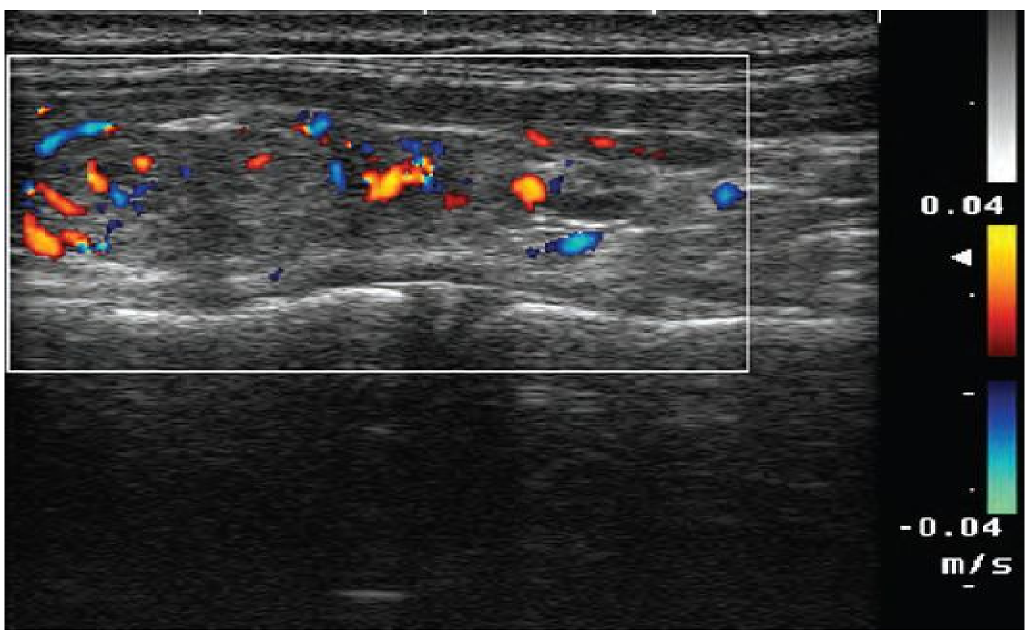


Fig.a (2-24). Color Doppler. Typically a greater frequency shift (corresponding to a higher velocity) is assigned a brighter color.

2.6. Ultrasound Elastography

Elastography is a newly developed dynamic technique that uses ultrasound to provide an estimation of tissue stiffness by measuring the degree of distortion under the application of an external force. It analyzes tissue stiffness based on deformation that takes place when the structures are exposed to external dosed compression and visually depicts the data obtained. Elastography has been applied to estimate tissue stiffness (as in case of fibrosis) and to differentiate malignant from benign lesions. Elastography is a unique modality, which permits the visualization of organ and tissues based on elasticity features (elasticity and stiffness). The technology is available in modern ultrasound equipments. (Blum M et al, 1977).

The use of elastography in the diagnosis of thyroid pathology began comparatively late. The diagnostic value of elastography in early differential diagnosis of thyroid lesions are still being discussed (Lyshchik A.etal, 2005, Rago T. et al.2007, Sencha A.N. et al, 2009). However, preliminary result revealed a correlation between lesion stiffness evaluated by means of elastography and the type of the pathology on the data of FNAB and histological examination of surgically resected specimen.(Blum M et al, 1977)

2.6.1. Elastography Technique:-

i. Elastography is conducted in real time or in the mode of data post-processing depending on scanner. The thyroid tissues are exposed to an external compression with an ultrasound probe. (Blum M et al, 1977) The ultrasound probe is positioned perpendicular to the organ or the lesion. Compression time varies from 2 to 5 seconds. Periodic compression is performed to obtain several images with minor artifacts. The time expense is usually 1 to 5 minutes. The overall time for thyroid ultrasound with elastography, does not exceed the conventional 10-20 minutes (Blum M et al, 1977). There are several elastography techniques that utilize external compression e.g.

ii. (Sonoline Elegra, Siemens, 2012), strain images are built by measuring the local displacement induced by a compressive force applied to the tissue surface. Fields displacements are estimated by using a correlation technique that tracks the echo delays in segmented waveforms recorded before and after the quasi-static compression is displayed as an image called elastogram on which the hard areas appear dark and the soft areas appear bright. Biomechanical tests on samples of excised tumors and normal thyroid gland tissue are performed to validate the results of thyroid strain imaging and elastic modulus using special equation is calculated. The values, expressed in kilopascals (kPA,) for normal thyroid gland tissue.

iii. Another method used in clinical practice (Hitachi Medical Systems), 2011 acquires two ultrasonic images, before and after tissue compression by the probe, and tracks tissue displacement by assessing imaging beam propagation. Dedicated software provides an accurate measurement of tissue distortion. The ultrasound elastogram is displayed over the B-mode image in a color scale that ranges from red, for components with greatest elastic strain (softest components) to blue, for those with no strain (hardest components).

iv. The latest method, shear-elastography mode (Aixplorer, Supersonic), year2012 simultaneously uses ultrasound waves and shear waves to better characterize and quantify tissue stiffness. Shear wave velocity is directly related to the quantifiable measurement of tissue elasticity. The scanner can generate, capture and quantify the velocity of a shear wave by acquiring data much faster than conventional ultrasound technology. A quantitative color coded map displaying local tissue elasticity for a large image region is produced in real-time. An easy-to-read color scale indicates tissue elasticity in kilopascals, displayed usually in the range of 0-200 kPa. It is worth to note that color encoded elastography images are different in Hitachi and Aixplorer brands. In Hitachi, hard tissue is blue, while it is the opposite in Aixplorer (shear wave), where soft tissue is blue. (Wiest PW et al, 1998).

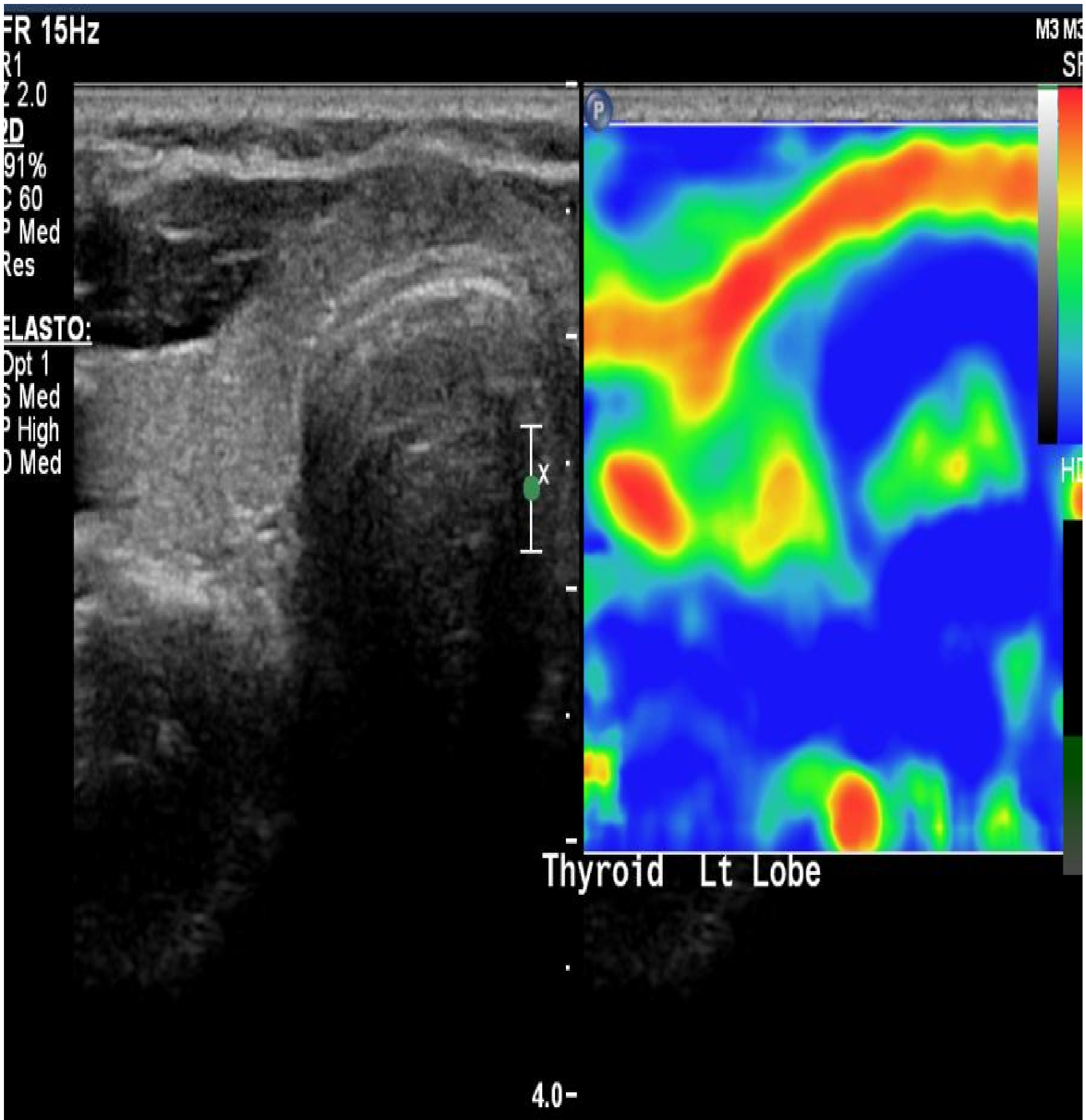


Fig (2- 25) shows real-time elastogrophy for Normal thyroid gland, read color scale indicates tissue elasticity

2.7 Equipmensts For FNAB

The basic equipment needed to perform FNAB is simple and relatively inexpensive (64 66.67). The following items are essential (Fig 2-26):

FNA biopsy equipment is simple and inexpensive. It 4-inch gauze pads, 10-mL plastic syringes, 25-gauge×includes an alcohol wipe, 4 1 1/2-inch stiff, noncutting, bevel-edged needles, glass slides, alcohol bottles, and a pistol-grip mechanical syringe holder.

A syringe holder or syringe pistol—most commonly used is the Cameco syringe pistol (Belpro Medical, Anjou, Quebec). The pencil-grip syringe holder is another syringe-holding device (developed by Tao and Tao Technology, Incorporated, Camano Island, WA). Disposable 10-mL plastic syringes Disposable 25- or 27-gauge needles, 1 1/2 inches long Glass slides, with 1 end frosted on 1 side, 1.0 mm thin (Gold Seal, Erie Scientific Company, Portsmouth, NH) (Backdahl M et al, 1987) .The operator stands on the side of the patient opposite that of the thyroid nodule. Current Occupational Safety and Health Administration regulations require the use of gloves because of concern about blood-borne diseases. D, with a quick motion, the needle passes through the skin and enters the nodule. Immediate mild suction follows. As soon as aspirate appears, suction is released and the needle is withdrawn (Gharib H et al, 1997). The technique For FNA is illustrated in fig (2-26).

(Fig. 2-26) shows Equipments for FNA

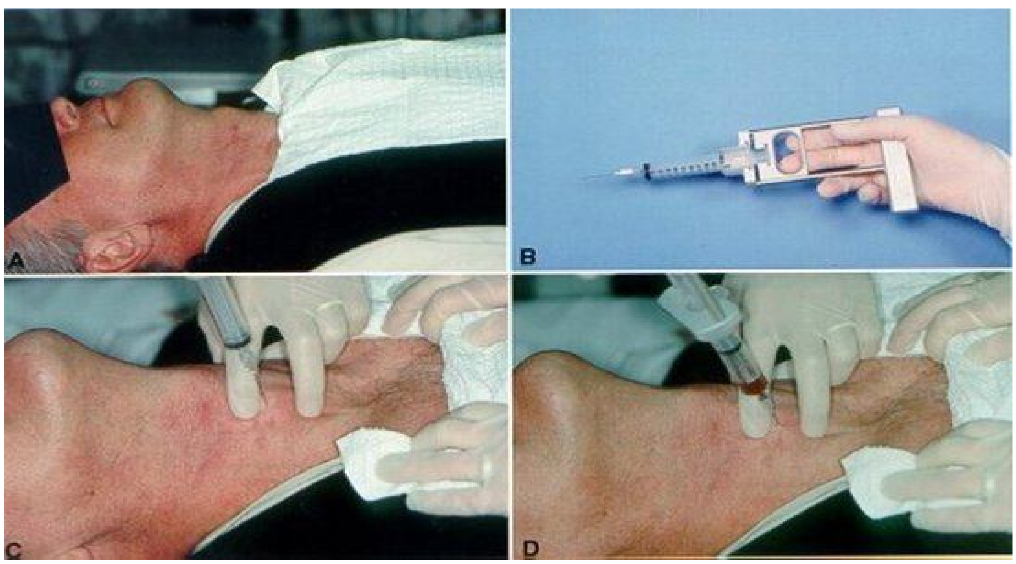


Figure (2-27) A, Position of patient during FNA. Supine position and a pillow under the patient’s shoulder allow hyperextension of the neck and maximal exposure. B, Syringe is placed in syringe holder. C, Nodule is identified and stabilized with operator’s “nonaspirating” hand.

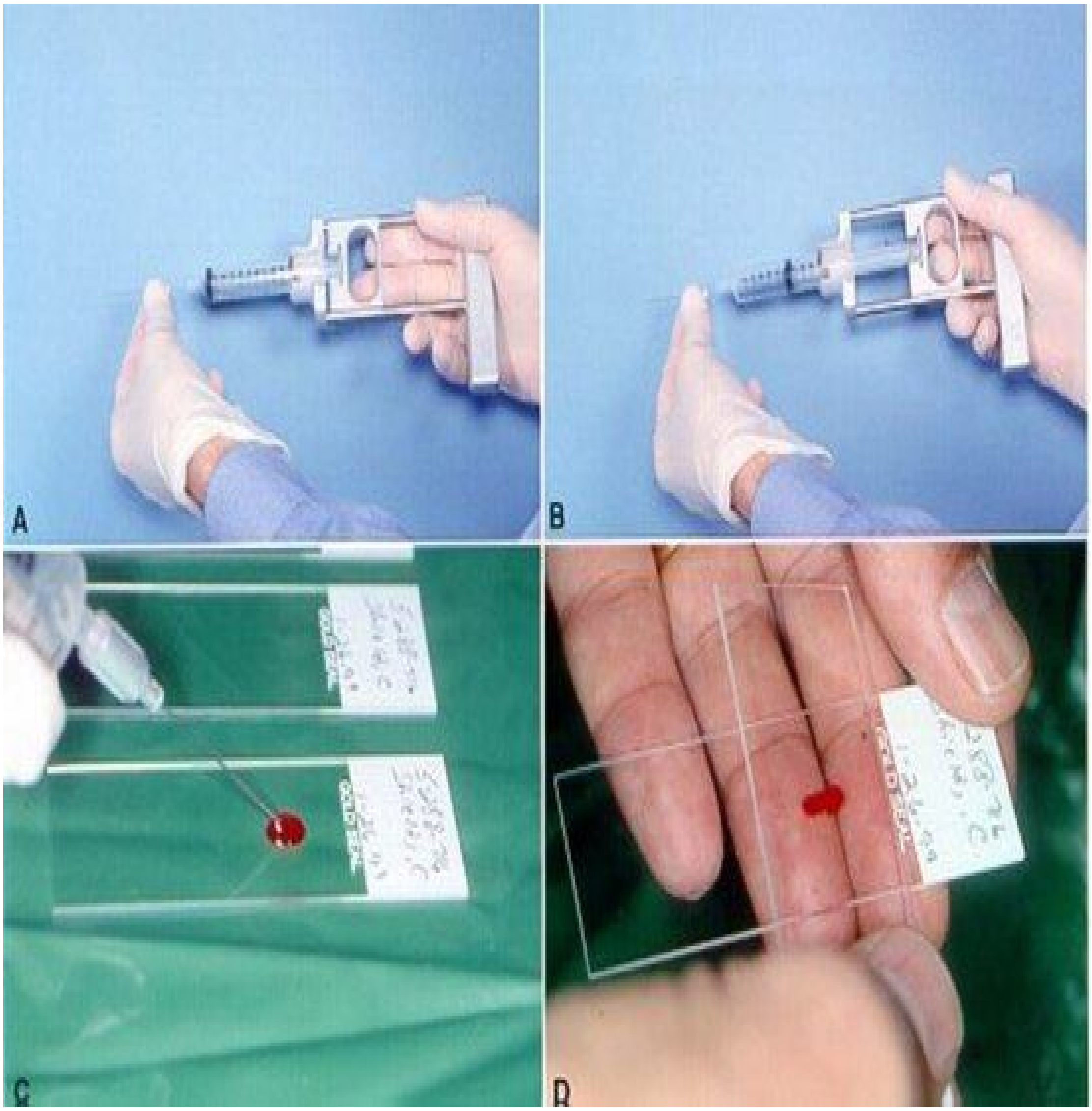


Figure (2-28) Shows the needle is removed quickly from the syringe. B, Five milliliters of air is aspirated into the syringe, and the needle is placed back on the syringe. C, with the needle bevel facing down, 1 drop of aspirated material is expelled onto each of several glass slides. Slides are labeled and placed on the table before aspiration, ready for use. D, with a second slide, smears are prepared in a manner similar to that for blood smears. Slides are then immediately wet-fixed by placing them in an alcohol bottle. (Singer PA et al, 1996)

2.7.1 Complications of FNAB:-

Thyroid FNA biopsy is safe. No serious complications such as tumor seeding, nerve damage, tissue trauma, or vascular injury have been reported needle puncture causes slight pain and some skin discoloration at the aspiration site(s). However, even a minor hematoma is uncommon. Patient use of anticoagulants or salicylates does not preclude FNA biopsy. Needle track implantation of thyroid carcinoma is extremely rare; it has been poorly documented and is not considered a real problem by most experts (www.@ThyroidClinic , 2013). Post aspiration hemorrhage within a cystic lesion can occur.

CHAPTER THREE

Materials and Methods

3.1. Type of study

This is a prospective hospital-based study. We test the sensitivity and specificity of elatography in detection of malignant thyroid nodules, and compare its results with those of US &Doppler. Both results were correlated to the FNAC results as a gold standard technique.

3.2. Study area

This study was done in King Abdulaziz University Hospital (KAUH), Diagnostic Radiology Department, Jeddah, KSA.

3.3 Duration of the study

From 2011 to 2014.

3.4. Population of the Study

This study included 300 patients presented for US of the thyroid gland after obtaining verbal consents. They were classified into two groups;

(Group (A).170 patients suffering from thyroid disease were randomly selected and subjected to real time US, Doppler and elastography. In cases of thyroid nodules, FNAC was performed and the results of elastography were correlated with those of Cytology.

Control Group. Patients with thyroid diseases were subjected to only US &Doppler examinations with no elastography. FNAC was done for 170 cases of thyroid nodules, and its results were correlated to those of US& Doppler.

In all 300 patients, (30 male, 270 female). Therefore, 206 patients with benign nodules were excluded and 94 with malignant nodules.

3.5. Thyroid US scanning protocol

Ultrasound examination was done by an expert sonographer and radiologist using high-frequency linear array transducer (5 to 12 MHz) with spatial digital iU22 Philips compounded B-mode, color Doppler US (CDUS) and real time elastography on the Aixplorer MultiWave Ultrasound System. Fig. (3-28) and Fig. (3-29).The elasticity measurements and ratios between nodules and adjacent parenchyma were calculated. Thyroid nodules were classified into benign or malignant based on and elastography results which were correlated to histopathology results after FNAB. The subjects were examined in supine position, with pillow placed under their shoulders to hyperextend the neck. US gel was applied over the thyroid area. The transducer was directly placed on the skin over the thyroid gland and images of each lobe were obtained in transverse and longitudinal planes. The craniocaudal and the sagittal dimensions of both lobes were measured on the longitudinal image. The transverse dimension was measured on the transverse image. Examination of the isthmus was also done.

♦ SCANNING TECHNIQUE

- We begin with a survey scan in transverse down the midline to assess for tracheal deviation and obvious pathology.
- We tilt the patients head slightly to the contra lateral side and scan down in transverse.
- We rotate into longitudinal and scan from medial to lateral.
- We repeat this for the other side with the head tilted the other way.
- With the patients head/neck straight, we scan the isthmus in longitudinal and transverse.
- We scan down each side of the neck in transverse for alternative pathology.

♦ BASIC HARD COPY IMAGING

A thyroid series were include the following minimum images:

- Transverse images of the gland from superior to inferior.
- Longitudinal images of the gland with a length measurement.
- Measure the glands volume: Normal=7-11cc/lobe
  (or at least the maximum length, thickness and width)
- Isthmus, trans and long with a maximum AP diameter.
- Left neck.
- Right neck.
- Assess the paracervical lymph nodes, carotid artery and jugular vein.
- Document the normal anatomy. Any pathology found in 2 planes, including measurements and any vascularity.

♦The Thyroid Examination

The examination should be performed with the neck in hyperextension. The right and left lobes of the thyroid gland should be imaged in the longitudinal and transverse planes. Recorded images of the thyroid should include transverse images of the superior, mid, and inferior portions of the right and left thyroid lobes; longitudinal images of the medial, mid, and lateral portions of both lobes; and at least a transverse image of the isthmus. The size of each thyroid lobe should be recorded in 3 dimensions, anteroposterior, transverse, and longitudinal. The thickness (anteroposterior measurement) of the isthmus on the transverse view should be recorded. A color or power Doppler examination can be used to supplement the grayscale evaluation of either diffuse or focal abnormalities of the thyroid. It is often necessary to extend imaging to include the soft tissue above the isthmus (eg, to evaluate a possible pyramidal lobe of the thyroid), congenital abnormalities such as a thyroglossal duct cyst, or if any superior palpable abnormality is noted. The examination should also include a brief evaluation of the lateral neck compartments. Thyroid abnormalities should be imaged in a way that allows for reporting and documentation of the following:

1. The location, size, number, and character of significant abnormalities, including measurements of nodules and focal abnormalities in 3 dimensions;
2. The localized or diffuse nature of any thyroid abnormality, including assessment of overall gland vascularity.
3. The sonographic features of any thyroid abnormality with respect to echogenicity, composition (degree of cystic change), margins (smooth or irregular), presence and type of calcification (if present), and other relevant sonographic patterns.
4. The presence and size of any abnormal lymph node in the lateral compartment of the neck .In patients who have undergone complete or partial thyroidectomy, the thyroid bed should in transverse and longitudinal planes. Any masses or cysts should be measured and reported. Additionally, the lateral neck should be evaluated of thyroid abnormalities or other masses of the neck or for other interventional procedures.

3.5.1 The Cervical Lymph Node Evaluation

A high-resolution ultrasound examination of the neck is used for the staging of patients with thyroid cancer and other head and neck cancers and in the surveillance of patients after treatment of such cancers.23–29 In these patients, the size and location of abnormal lymph nodes should be documented. Suspicious features such as calcification, cystic areas, absence of a cencentralhilum, round shape, and abnormal blood flow should be documented. The location of an abnormal lymph node should be described according to the image-based nodal classification system developed by Som et al,30 which corresponds to the clinical nodal classification system developed by the American Joint Committee on Cancer and the American

Academy of Otolaryngology–Head and Neck Surgery, or in a fashion that allows the referring clinician to convert the location of abnormal nodes to that system.

Fig (3-29) Shows protocol of thyroid Scan plane transverse
(www.webmd.com/women/thyroid-hormone-tests)

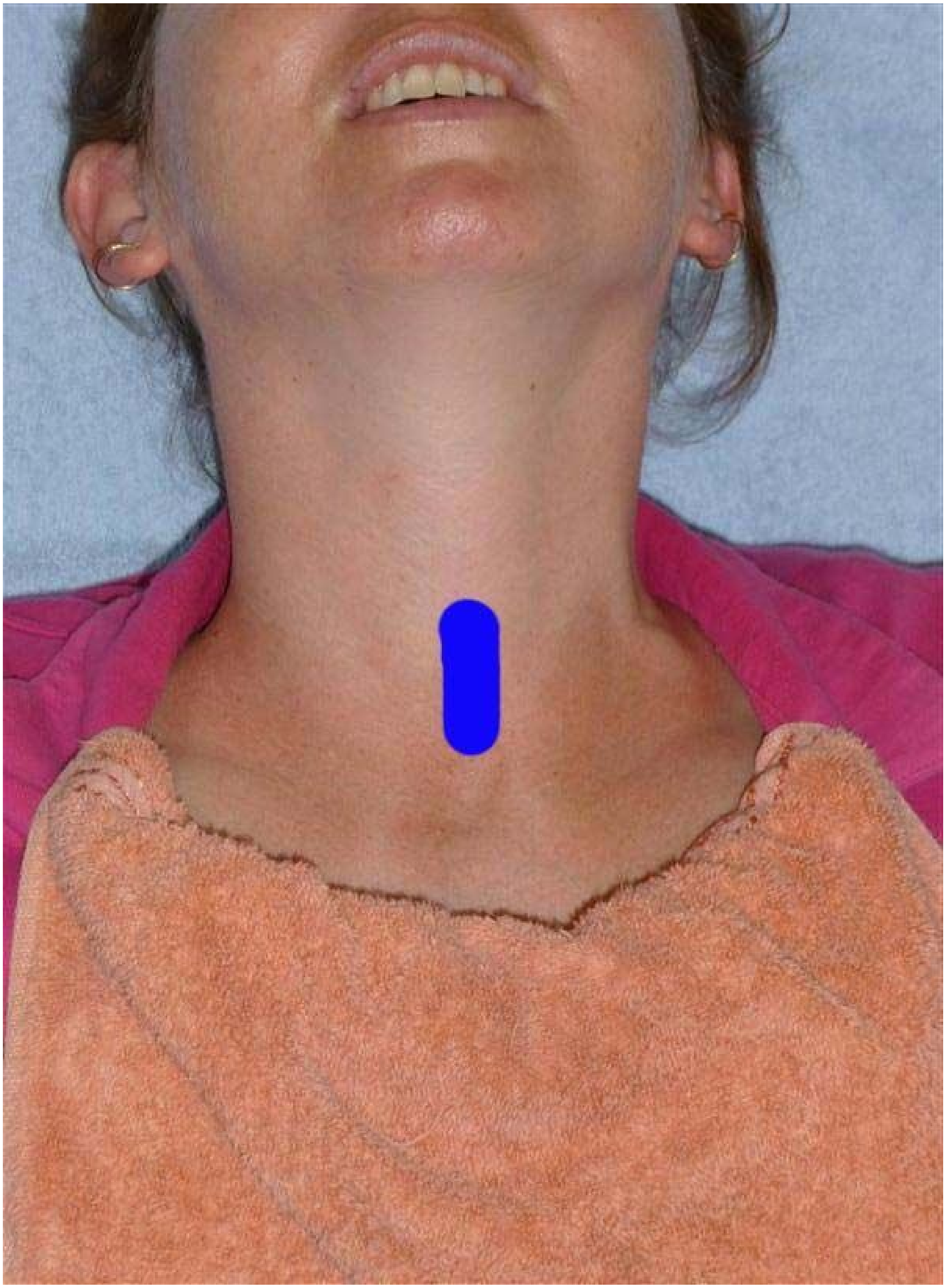


Fig (3-30) Shows protocol of Isthmus scans plane-longitudinal view
(www.webmd.com/women/thyroid-hormone-tests)

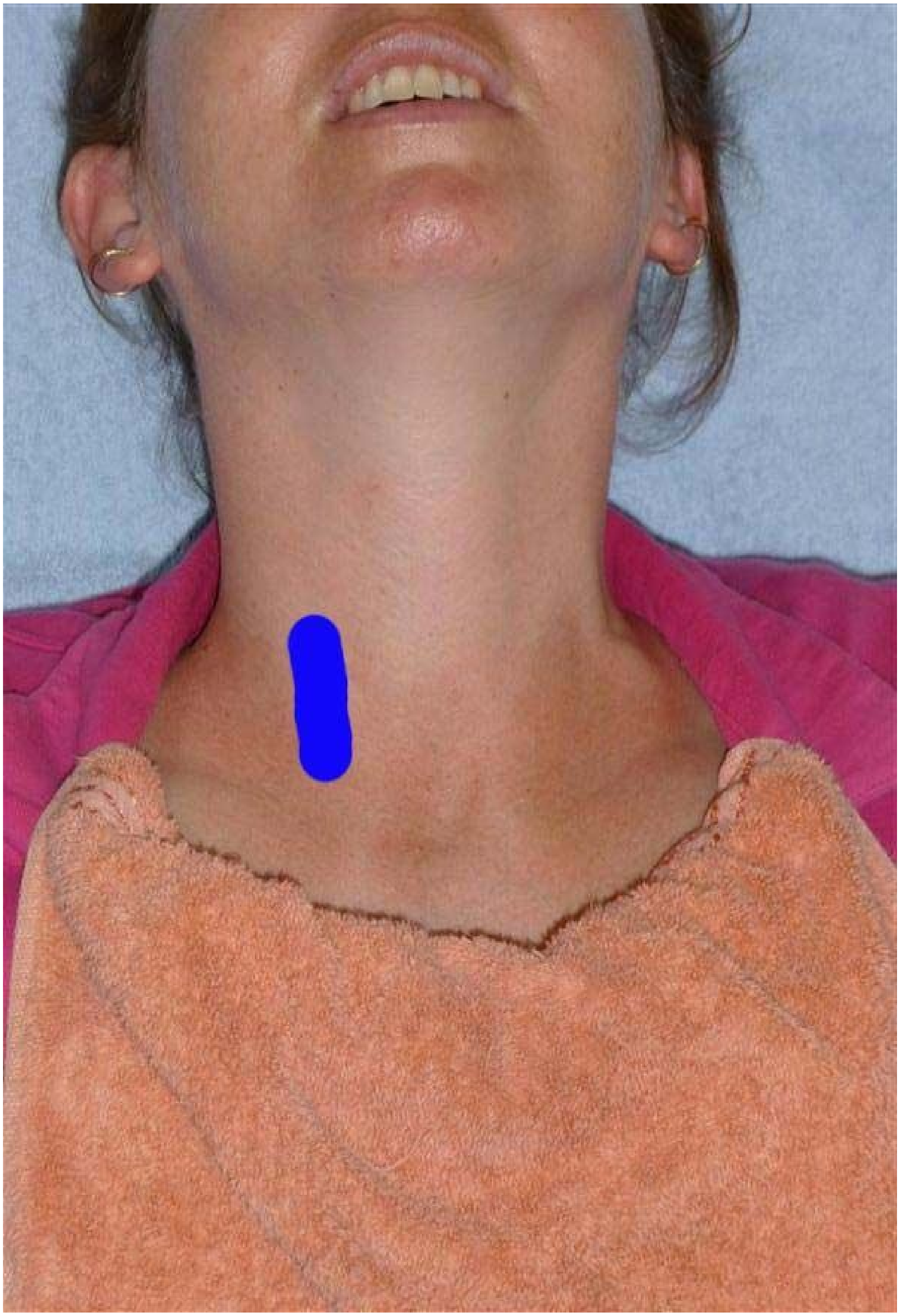


Fig (3-31) Shows protocol Scan plane for longitudinal view Right lobe
(www.webmd.com/women/thyroid-hormone-tests)

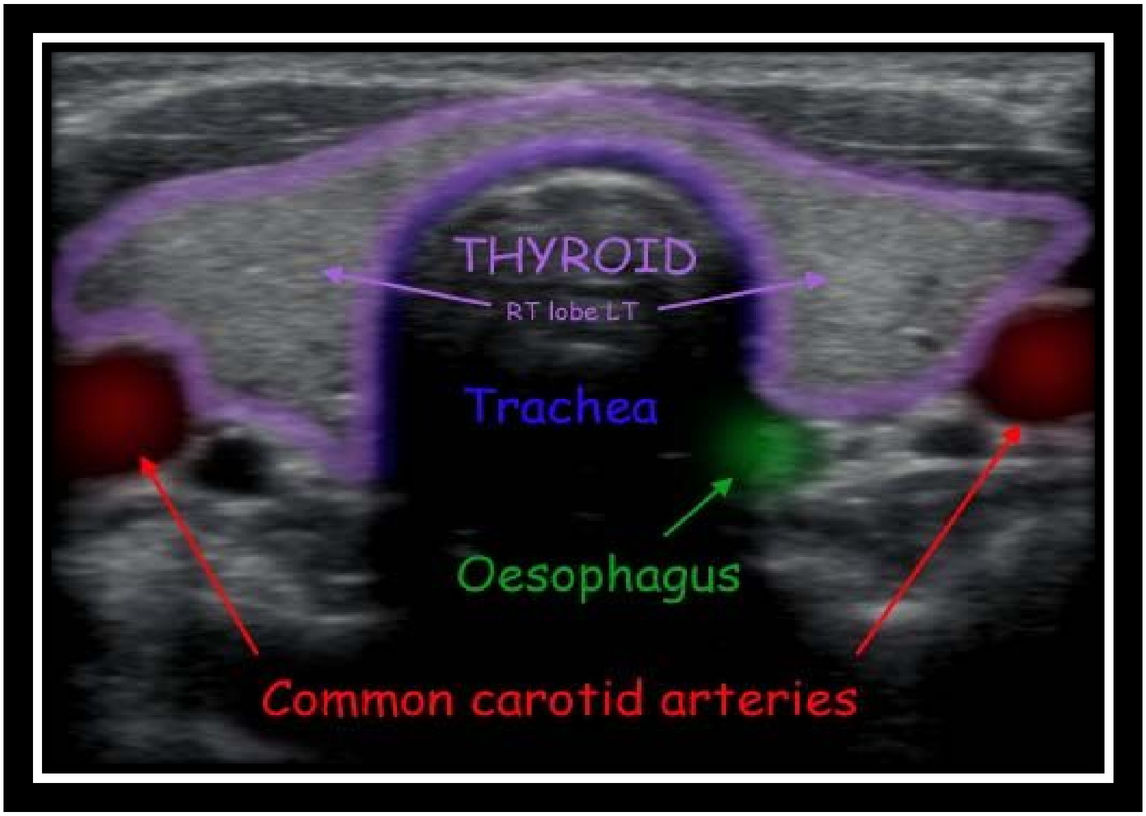


Fig (3-32) Shows ultrasound image transverse view of a normal thyroid

(www.webmd.com/women/thyroid-hormone-tests)

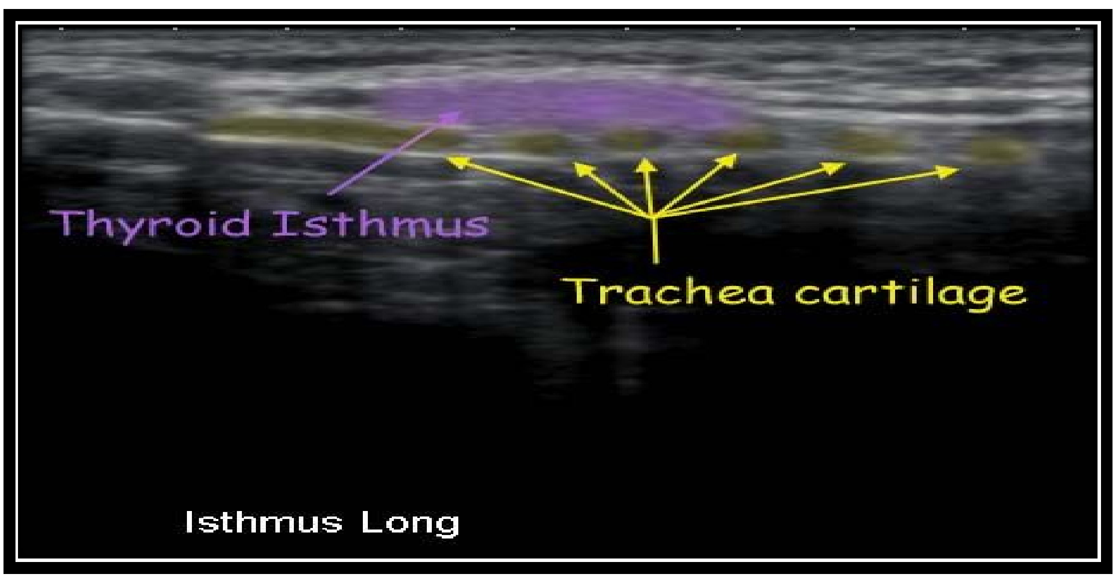


Fig (3-33) Shows ultrasound image of the isthmus should be less than 10mm

. It can be almost imperceptibly thin. (www.webmd.com/women/thyroid-hormone-tests)

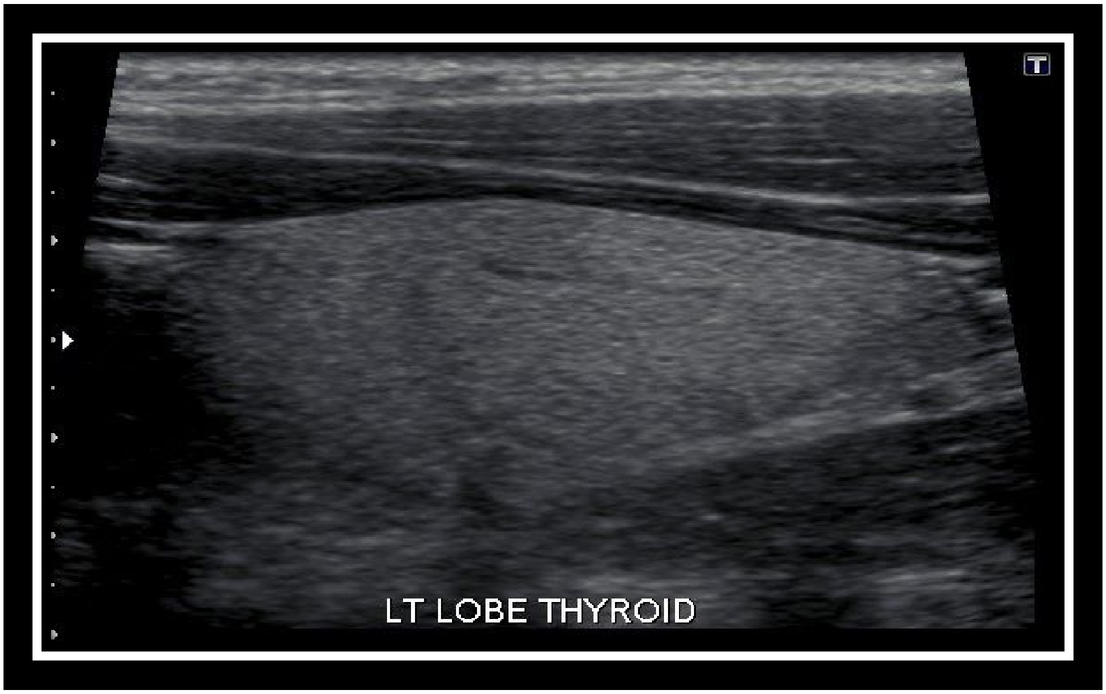


Fig. (3-34)Shows Normal Thyroid Lobe - longitudinal view of left lobe (www.webmd.com/women/thyroid-hormone-tests)

Fig. (3-35) Shows position of ultrasound probe for right thyroid lobe

(www.webmd.com/women/thyroid-hormone-tests)

Fig. (3-36) Shows Thyroid US scanning protocol.

3.6 Ultrasound.

Ultrasound was first introduced for examination of small parts by Howry in 1955.The thyroid ultrasound in A and a B mode were described in 1966-1967 (Fujimoto Y. et al., 1967) and has been widely practiced since 1970s. An ultrasound examination is now one of the routine radiological methods for diagnosing thyroid disease. This method is based on the ability of tissues with different acoustic to reflect ultrasound waves. Modern ultrasound equipments are fast enough to supply real-time scanning .It permits visualization of an organ, motion and assessment of some organ functionality (Blum M et al, 1977)

3.6.1. Doppler ultrasound.

For most thyroid imaging, color-flow Doppler and power Doppler are used. In color-flow Doppler a unique color (or brightness) is assigned to an individual frequency. Typically a greater frequency shift (corresponding to a higher velocity) is assigned a brighter color. Analysis of the color-flow image gives a graphic illustration of the direction and speed of blood flow within soft tissue .In contrast, power Doppler considers all frequency shifts to be equivalent, integrating the total amount of motion detected. The assigned color represents the total amount of flow present, independent of the velocity .Color-flow Doppler provides information regarding both direction and velocity, and is more useful in vascular studies. In contrast, power Doppler does not provide information regarding velocity. However, it has increased sensitivity for the detection of low degrees of flow, has less noise interference, and is less dependent on the angle of incidence between the ultrasound waves and the moving object. Power Doppler is generally the preferred imaging technique for assessing the vascularity of thyroid tissue (Martin HE et al, 1930).

3.6.2. Real time ultrasound elastography

Real time ultrasound elastography was performed after the conventional US examination with the same real-time equipment and the same probe. In brief, the probe was placed on the anterior neck. The gentle freehand compression was applied using the probe along the beam axis. To keep the strain distributed evenly, compression was applied with 1 to 2 mm thickness and two to three times per second. The elastogram was displayed over the B-mode image in a color scale that ranged from red, indicating components with greatest elastic strain, to blue, indicating components with no strain. Meanwhile, green indicated moderate strain. The region of interest for the real time ultrasound elastography was selected including the nodule and sufficient surrounding normal thyroid parenchyma. Nodule was evaluated with the probe orientated in both transverse and longitudinal planes. To minimize the inter- and intraobserver variability, the freehand compression was standardized by elastic column displayed on a numeric scale to maintain a stable intermediate level optimal for evaluation (Bhatia et al., 2011). Elasticity was classified in four different patterns as described previously: pattern I: the nodule displays homogeneously in green; pattern II: nodule displays predominantly in green as well as sporadic parts in blue; pattern III: nodule displays predominantly in blue as well as sporadic parts in green, or green displays in the periphery; pattern IV: the nodule displays completely in blue (Rubaltelli et al., 2009). Fig (3-37)

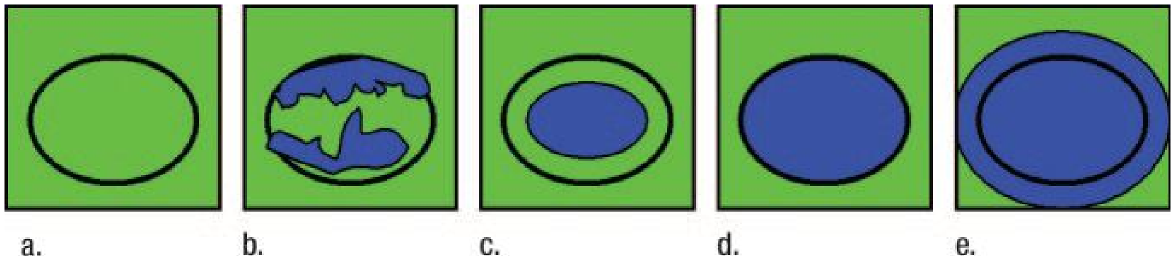


Figure (3-37). Shows Images present general appearance of lesions for elasticity scores of (a) 1, (b) 2, (c) 3, (d) 4, and (e) 5. Black circle indicates outline of hypo echoic lesion (ie, border between lesion and surrounding thyroid tissue) on B-mode images.

Fig. (3.38) Shows u/s machine with ultrasound transducer used is Broadband Linear Array Transducer 12 to 5 MHz extended operating frequency range. (Philips medical system).

3.6.3. UG-FNA Procedure

The procedure was performed by the same sonographer. Immediate specimen adequacy evaluation was not provided. UG-FNA was performed with a 23-gauge needles attached syringe. Freehand biopsy and capillary action technique was used. With the nonparallel solution, the needle was inserted adjacent to the side of the midpoint of the transducer and angled minimally back toward the transducer with the degree of angulations varying. Once within the nodule, the needle tip was moved back and forth.

3.7. Image interpretation:

U.S Doppler and Elastography findings were interpreted by an expert radiologist at King Abdulaziz university hospital.

3.8 Data analysis:

Demographic patients data including their age, sex and complain associated with detailed US, Doppler and elastography findings of the thyroid lesions were collected and correlated with histopathologic results of cases subjected to FNAB. All these data were statistically analyzed using SPSS program. Data results in number and percentage were described. The P value was considered to be significant if it was <0.05.

CHAPTER FOUR

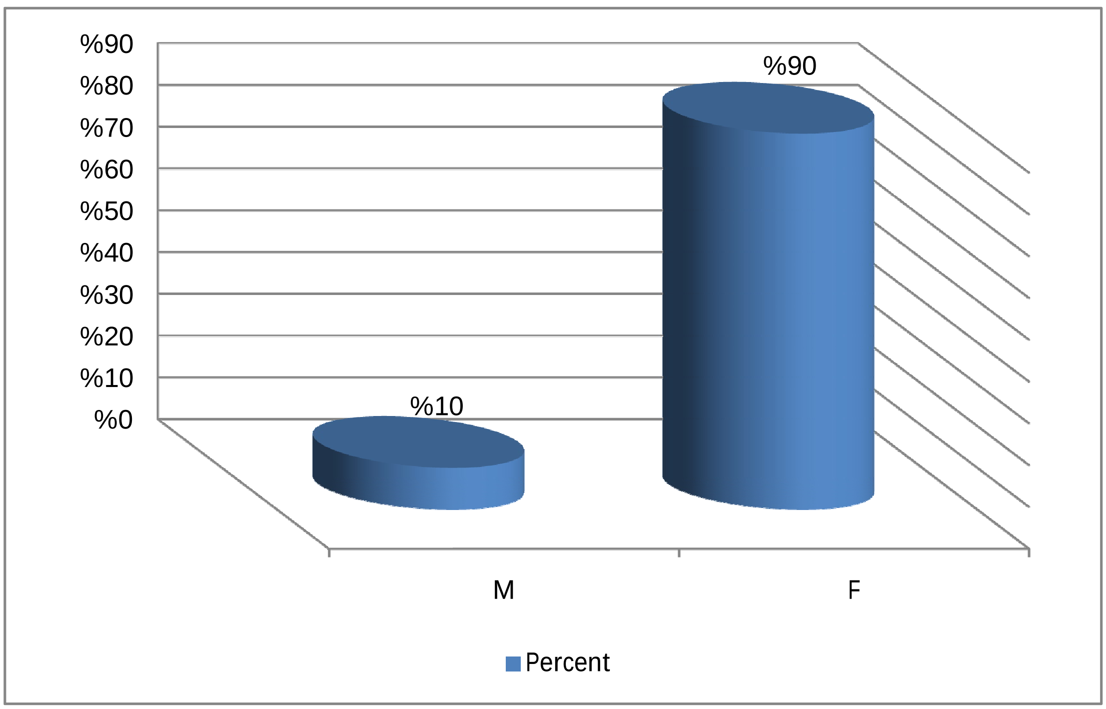
Results analysis

4.1. Gender Distribution:

Table (4.1) this study included 300 patients who referred radiology department, ultrasound section. The majority of patients studied were females 270 (90%), while males present the percent of 30 (10%).

Table (4-1): Shows gender distribution of 300 patients.

Gender	Frequency	Percent
Male	30	10%
Female	270	90%
Total	**300**	**100%**



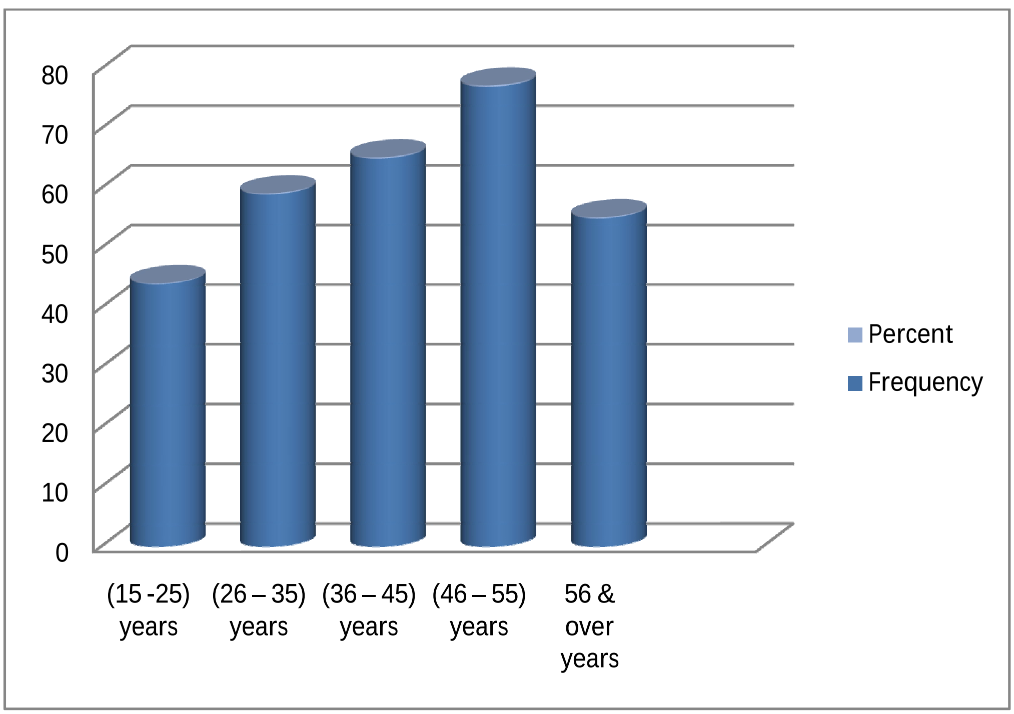
Graph (4.1): Shows gender distribution of 300 patient

4.2. Age distribution

Table (4-2).The average age of the patients studied was 44.9 years. The peak incidence was among the age between 45-55 years of age presenting the percent of (25.7%) of the total patients (300).

Table (4-2): Age group distribution of 300 patients.

Age	**Frequency**	**Percent**
(15 -25) years	44	14.7%
(26 – 35) years	59	19.7%
(36 – 45) years	65	21.7%
(46 – 55) years	77	25.7%
56 & over years	55	18.3%
Total	300	100%



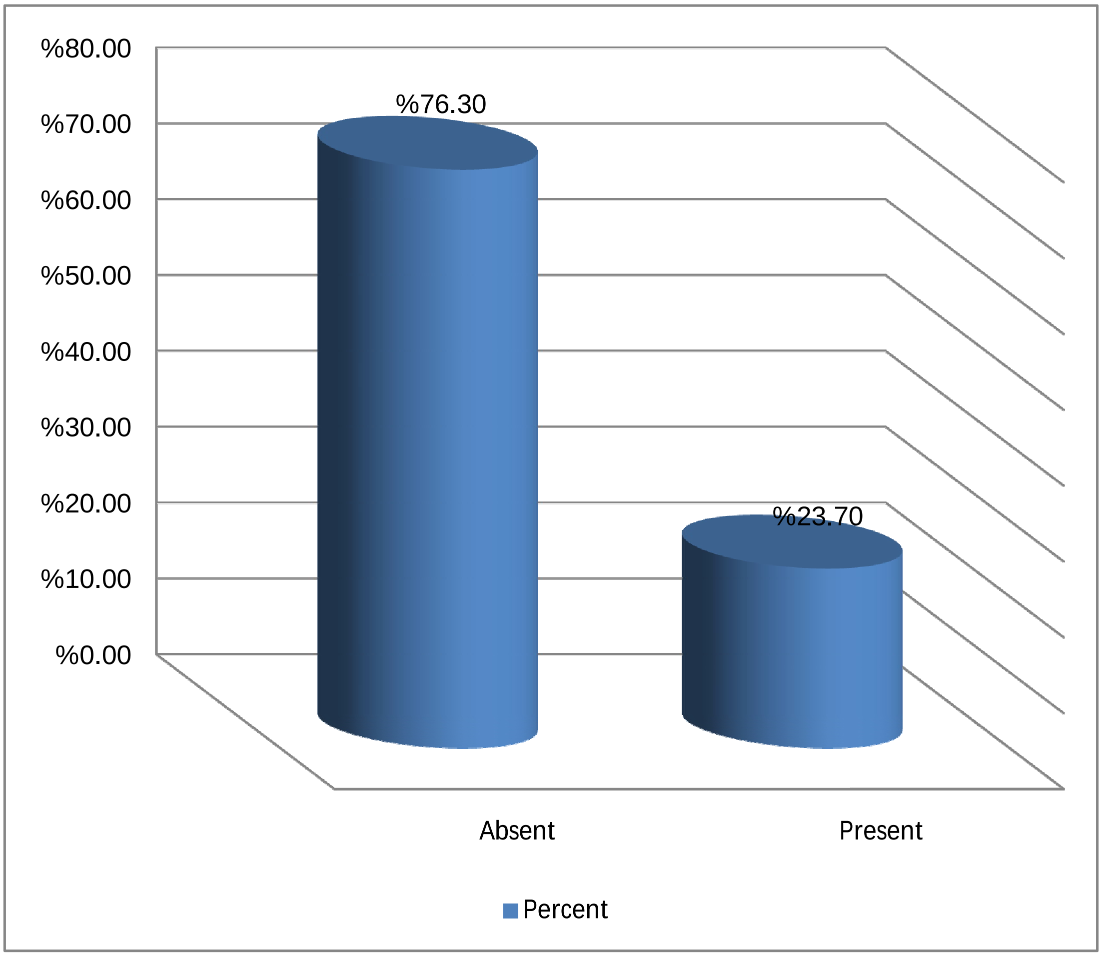
Graph (4-2): Age group distribution of 300 patients.

4.3 Ultrasound Characteristics features for the identification of malignant thyroid nodules.

4.3.1 Hypoechogenicity in thyroid gland.

Table (4-3) shows presence of a hypoechogenicity pattern of ultrasound features in 300 patients with thyroid nodules

Hypo-echoic	**Frequency**	**Percent**
Absent	229	76.3%
Present	71	23.7%
Total	**300**	**100**

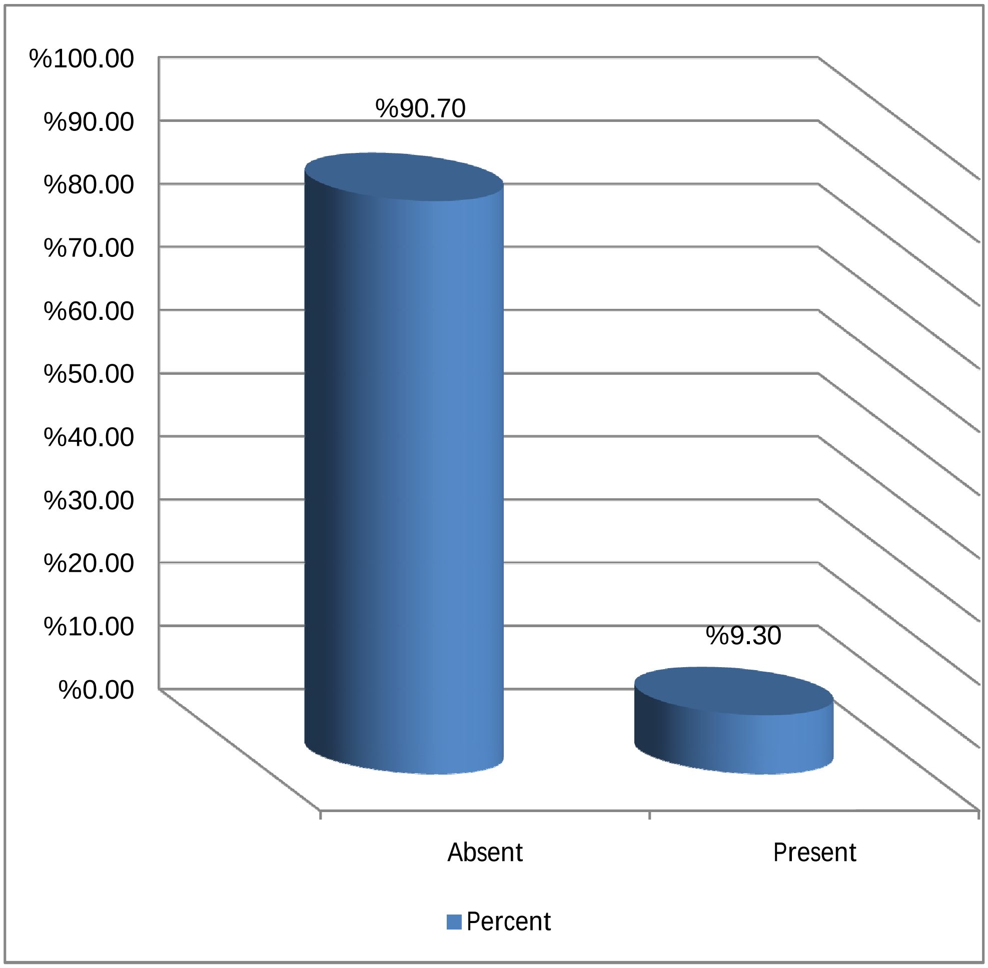


Graph (4-3) shows presence of a hypoechogenicity pattern of ultrasound features in 300 patients with thyroid nodules.

4.3.2 Halo Sign in thyroid nodule.

Table (4-4) shows presence of a halo sign pattern of ultrasound features in 300 patients with thyroid nodules

Halo sign	Frequency	Percent
Absent	272	90.7%
Present	28	9.3%
Total	300	100

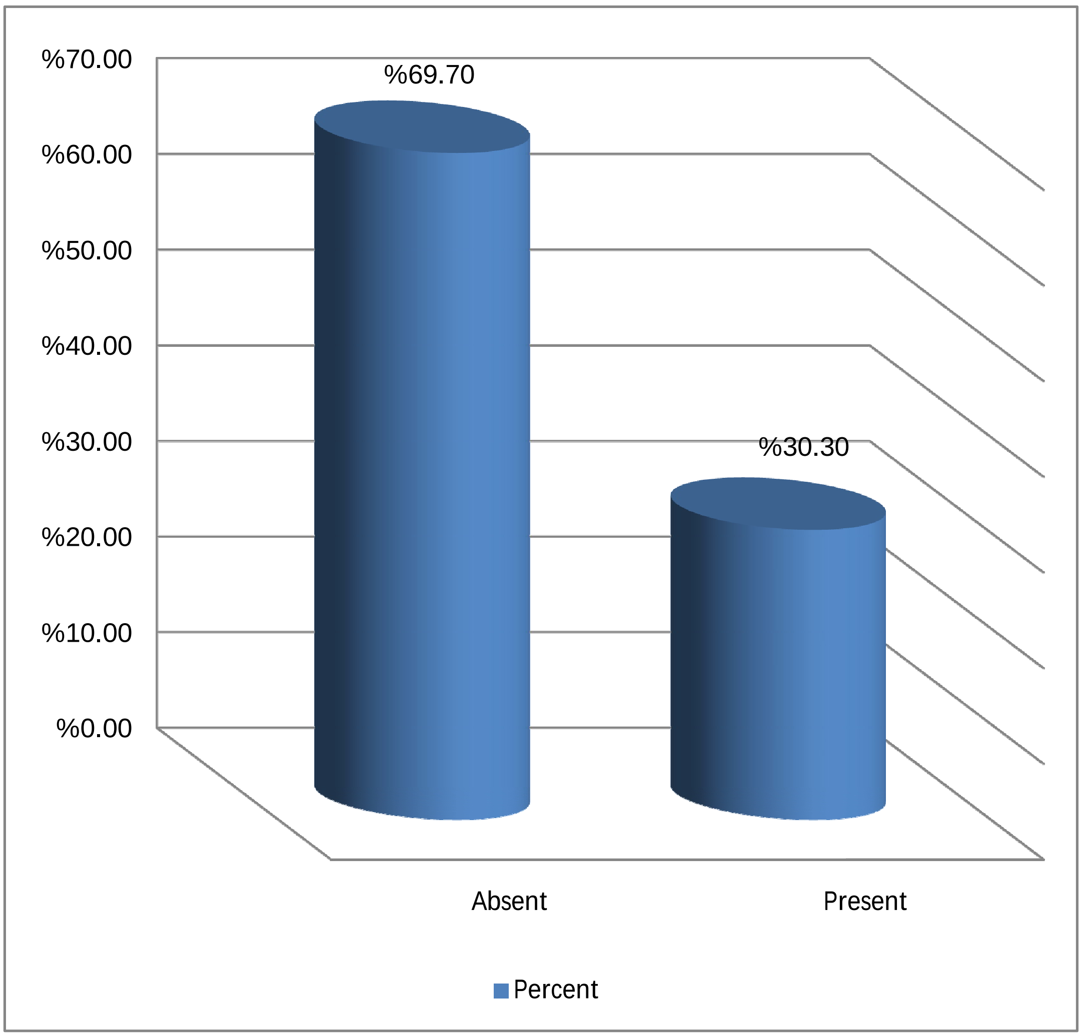


Graph (4-4) shows presence of a halo sign pattern of ultrasound features in 300 patients with thyroid nodules.

4.3.3 Intra-nodular Vascularity.

Table (4-5) shows presence of intra-nodular pattern of ultrasound features in 300 patients with thyroid nodules.

vascularity	Frequency	Percent
Absent	209	69.7%
Present	91	30.3%
Total	**300**	**100%**

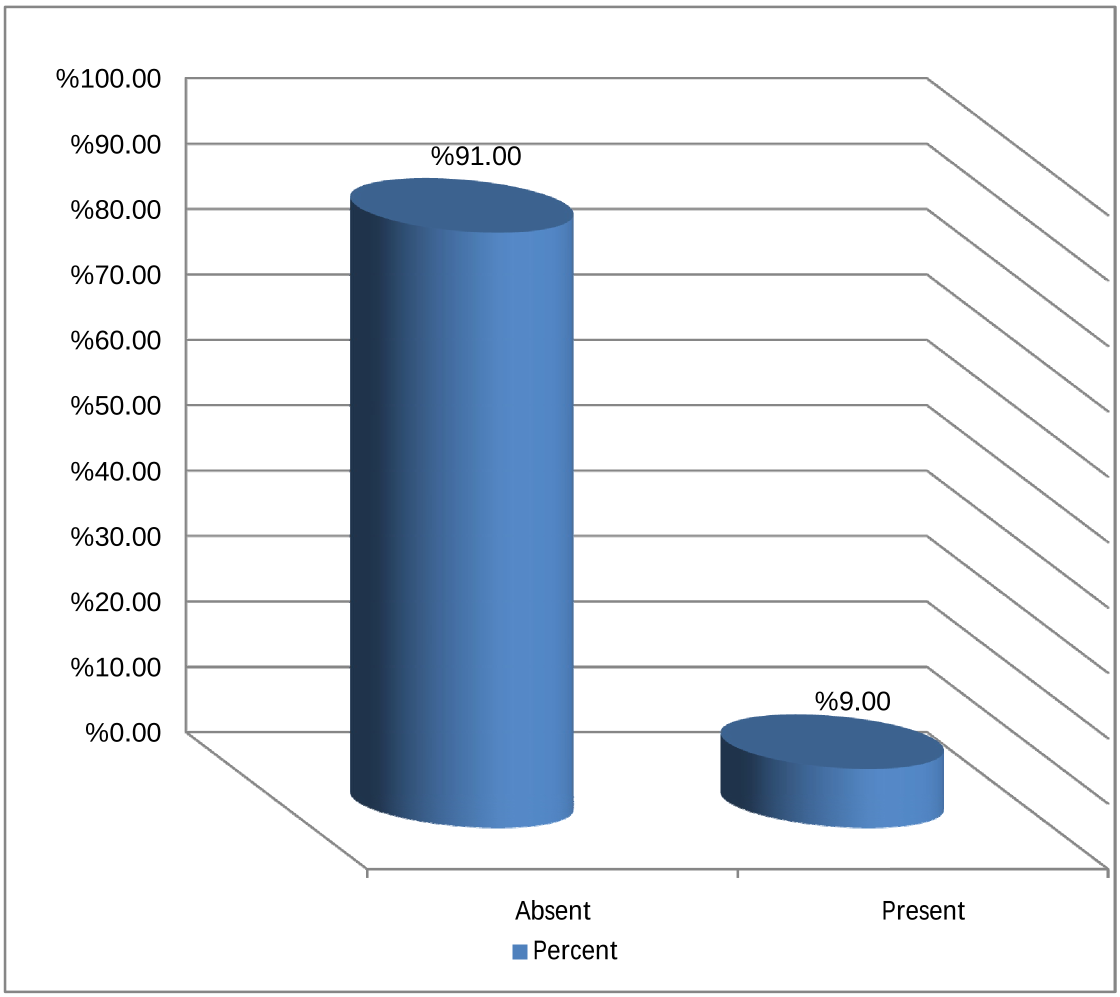


Graph (4-5) shows presence of intra-nodular pattern of ultrasound features in 300 patients with thyroid nodules.

4.3.4 Micro calcification

Table (4-6) shows presence of micro calcification pattern of ultrasound features in 300 patients with thyroid nodules

Micro-calcification	Frequency	Percent
Absent	273	91.0%
Present	27	9.0%
Total	**300**	**100%**

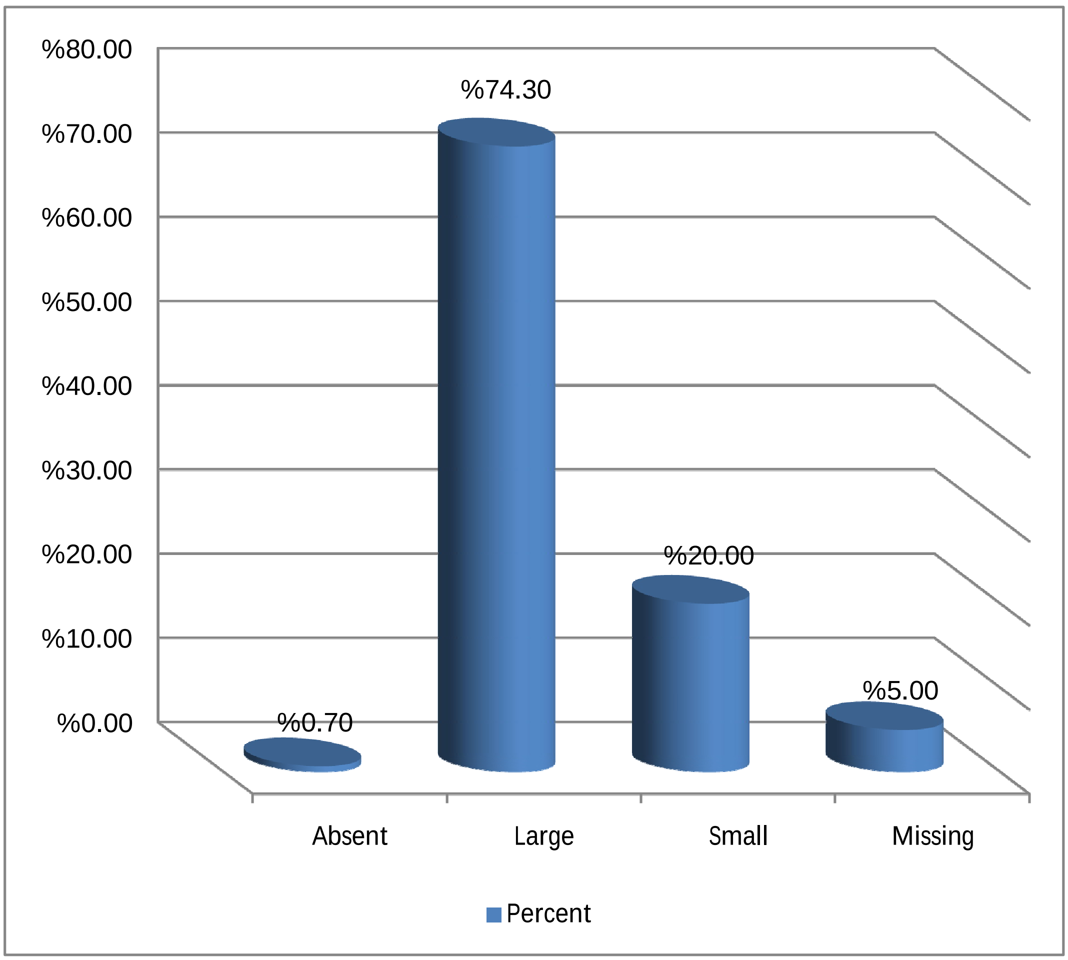


Graph (4-6) shows presence of micro calcification pattern of ultrasound features in 300 patients with thyroid nodules

4.3.5 Antero-posterior/Transverse > 1

Table (4-7) shows presence of nodule sizes pattern of ultrasound features in 300 patients with thyroid nodules

A/T >1	Frequency	Percent
Absent	2	0.7%
Large	223	74.3%
Small	60	20.0%
Missing	15	5.0%
Total	**300**	**100%**

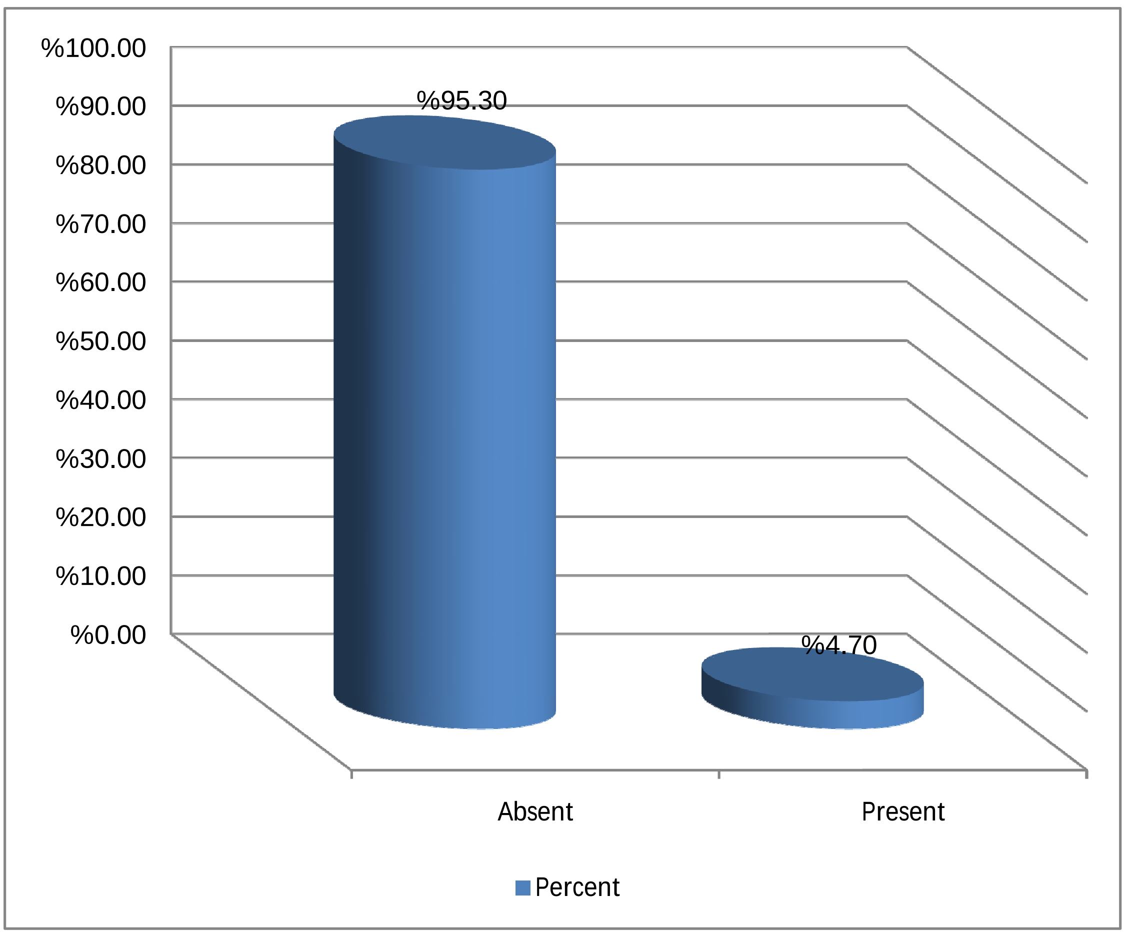


Graph (4-7) shows presence of nodule sizes pattern of ultrasound features in 300 patients with thyroid nodules.

4.3.6 Irregular blurred margin.

Table (4-8) shows presence blurred margin pattern of ultrasound features in 300 patients with thyroid nodules

Blurred margin	Frequency	Percent
Absent	286	95.3%
Present	14	4.7%
Total	**300**	**100%**

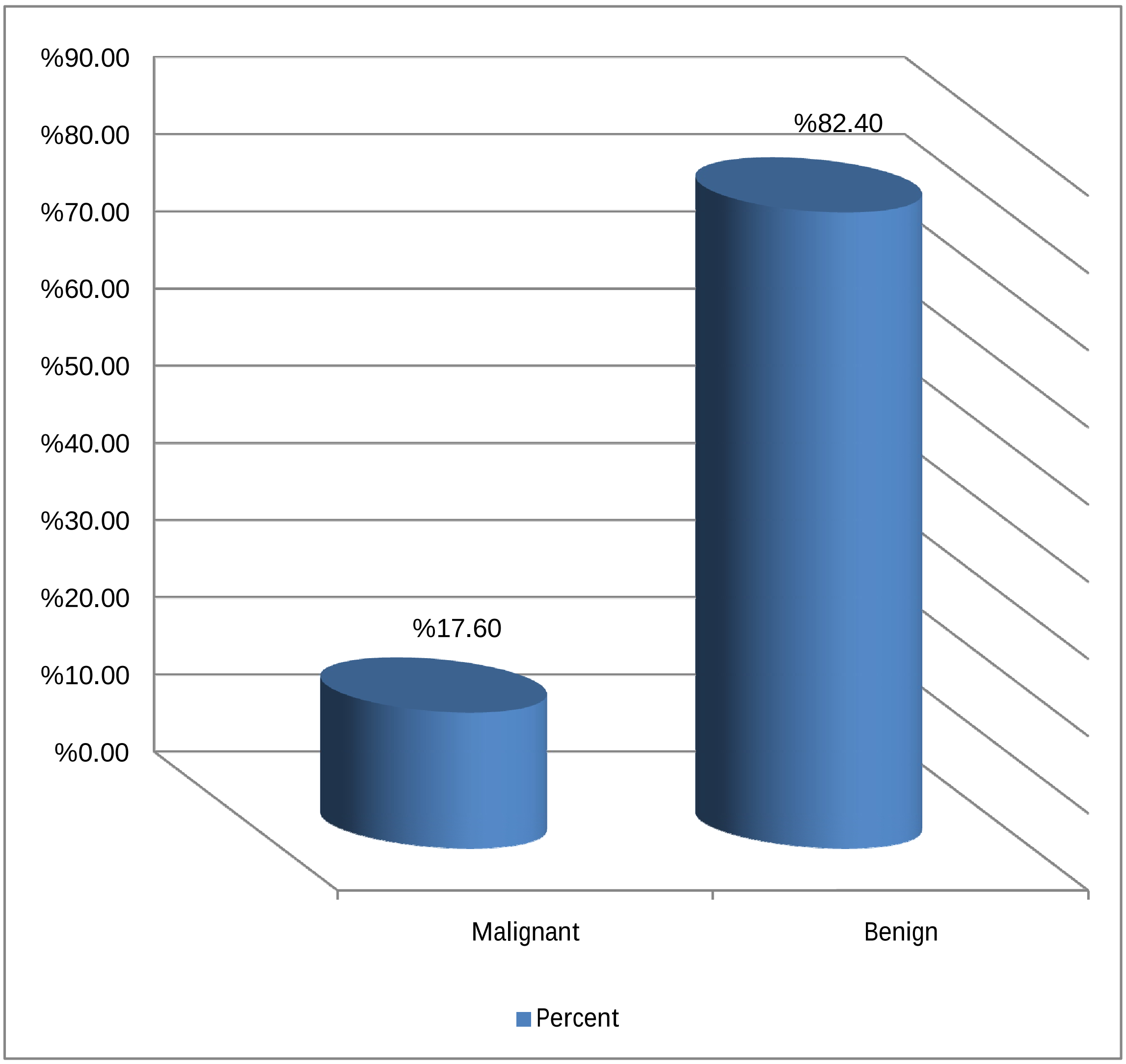


Graph (4-8) shows presence of blurred margin pattern of ultrasound features in 300 patients with thyroid nodules.

4.4 Ultrasound Result

Table (4-9) Shows ultrasound result

US Result	Frequency	Percent
Malignant	30	17.6 %
Benign	140	82.4 %
Total	**170**	**100%**

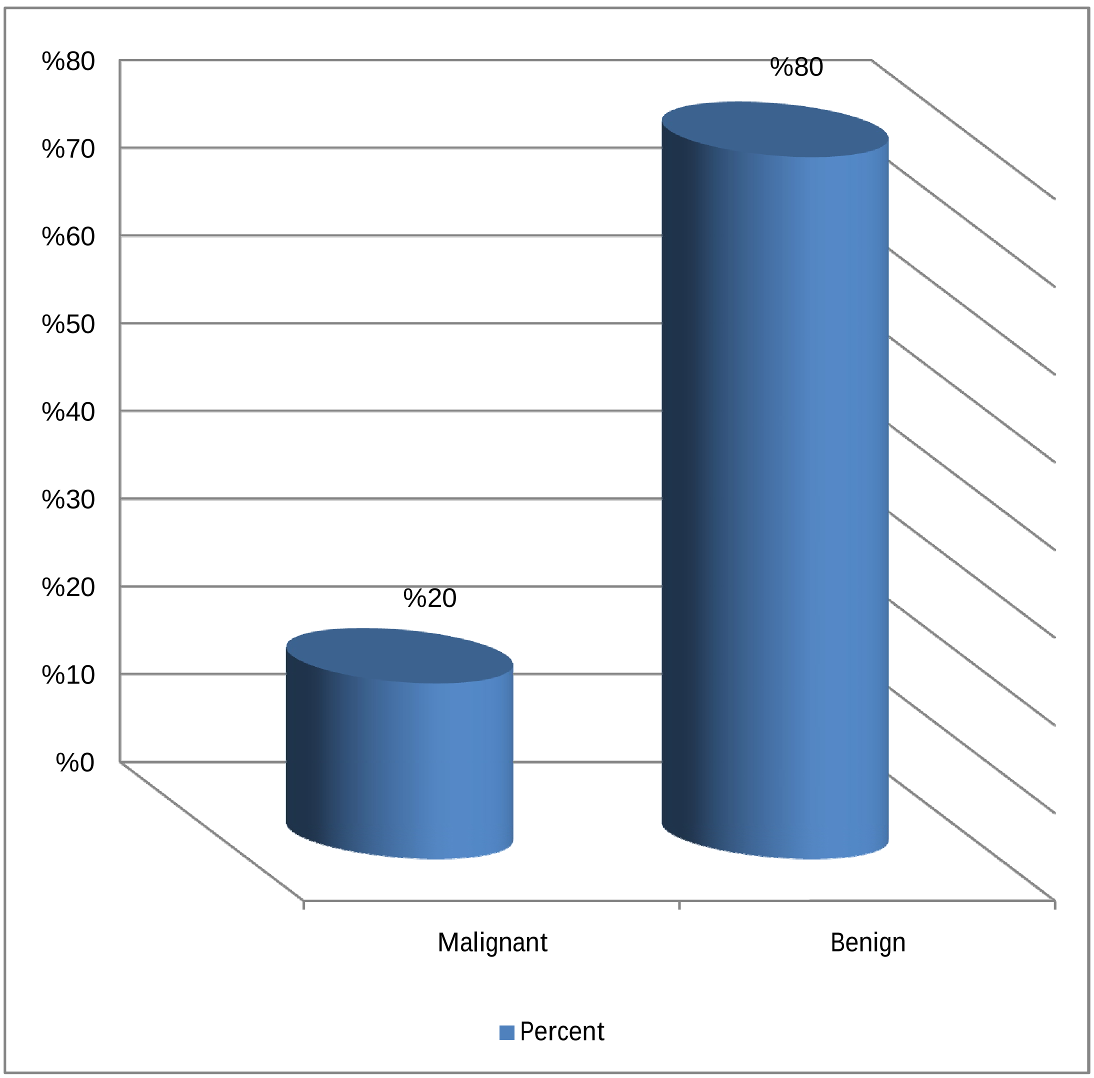


Graph (4-9) Shows ultrasound result.

4.5 Elastography result.

Table (4-10) shows elastography result.

Elasto. Result	Frequency	Percent
Malignant	34	20 %
Benign	136	80 %
Total	**170**	**100%**

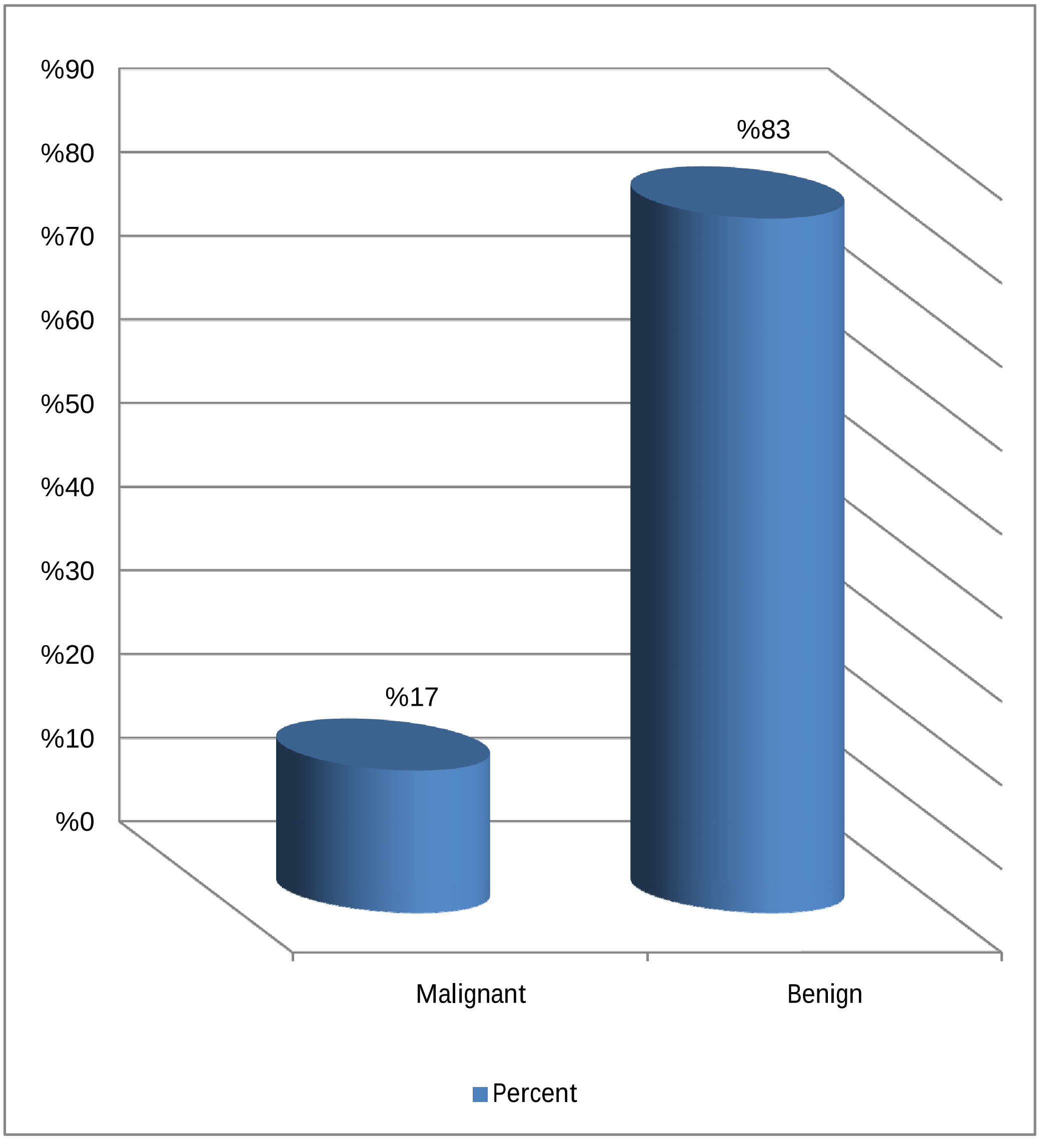


Graph (4-10) shows elastography result

4.6 Fine Needle Aspiration cytology

Table (4-11) Fine Needle Aspiration cytology

Fine Needle Aspiration	Frequency	Percent
Malignant	29	17 %
Benign	141	83 %
Total	**170**	**100%**



Graph (4-11) Fine Needle Aspiration cytology

4.7. Ultrasound Result * Fine Needle Aspiration Cross tabulation

Table (4-12) Shows Ultrasound Result * Fine Needle Aspiration Cross tabulation.

US Result			Fine Needle Aspiration		Total
			Malignant	Benign	
Malignant		Count	21	30	51
		% within Fine Needle Aspiration	**72.4%**	21.3%	30 %
	Benign	Count	8	111	119
		% within Fine Needle Aspiration	27.6%	**78.7%**	70 %
Total		Count	29	141	170
		% within Fine Needle Aspiration	100.0%	100.0%	100.0 %

Table (4- 13) Predictivity of combinations of thyroid ultrasound patterns in patients with thyroid nodules, that resulted in benign lesions (B) or malignant (M) on fine needle aspiration cytology.

		F.N.A Result		Sensitivity	Specificity	PPV%	NPV%	PV
		M	B					
U.S. Result	M	21	30	72.4%	78.7			
	B	8	111					

4.8. Elasto. Result * Fine Needle Aspiration Cross tabulation.

Table (4-14) Elasto. Result * Fine Needle Aspiration Cross tabulation.

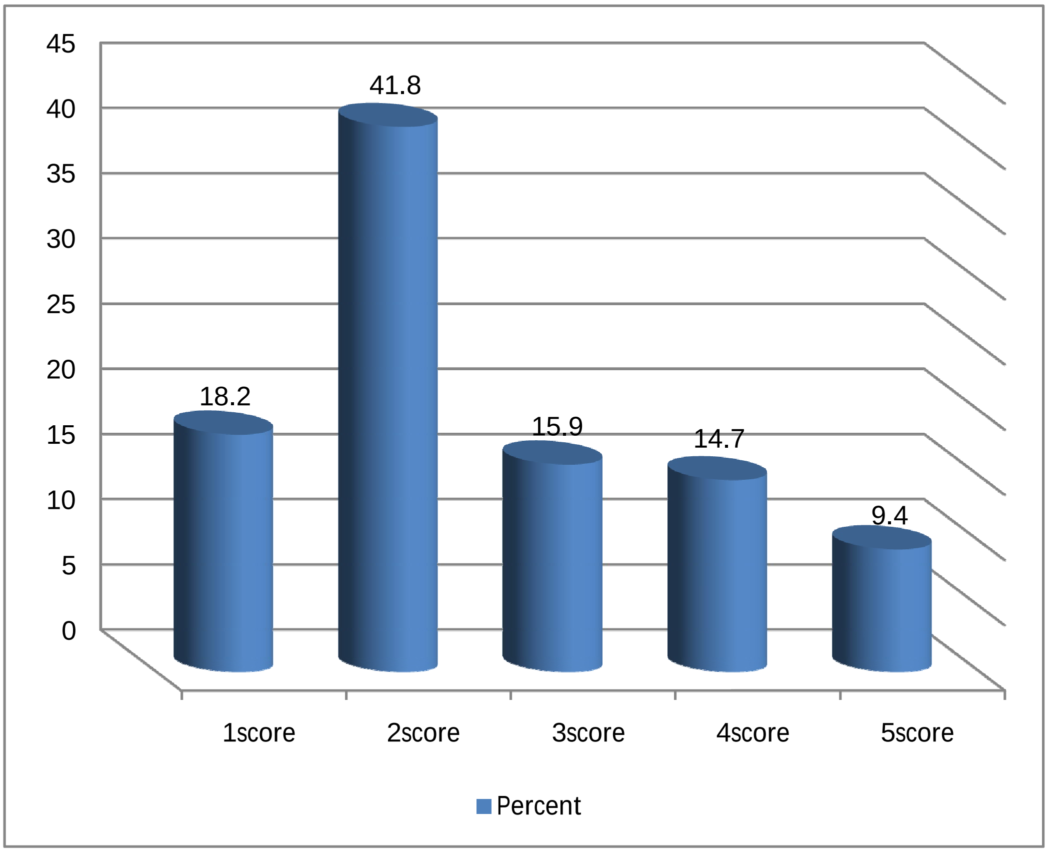
			Fine Needle Aspiration		Total
			Malignant	Benign	
Elasto. Result	Malignt	Count	27	13	40
		% within Fine Needle Aspiration	**93.1%**	9.3%	23.5 %
	Benign	Count	2	128	130
		% within Fine Needle Aspiration	6.9 %	**90.7%**	76.5 %
Total		Count	29	141	170
		% within Fine Needle Aspiration	100.0%	100.0%	100.0%

Table (4- 15) Predictivity of combinations of thyroid elastography patterns in patients with thyroid nodules, that resulted in benign lesions (B) or malignant (M) on fine needle aspiration cytology.

Elastography Result	F.N.A.C Result		Sensitivity	Specificity	PPV%	NPV%	PV
	M	B					
M	30	12	93.8	90.3			
B	2	112					

Table (4.16): Evaluation of elastography scores in characteristics of thyroid diseases in170 patients.

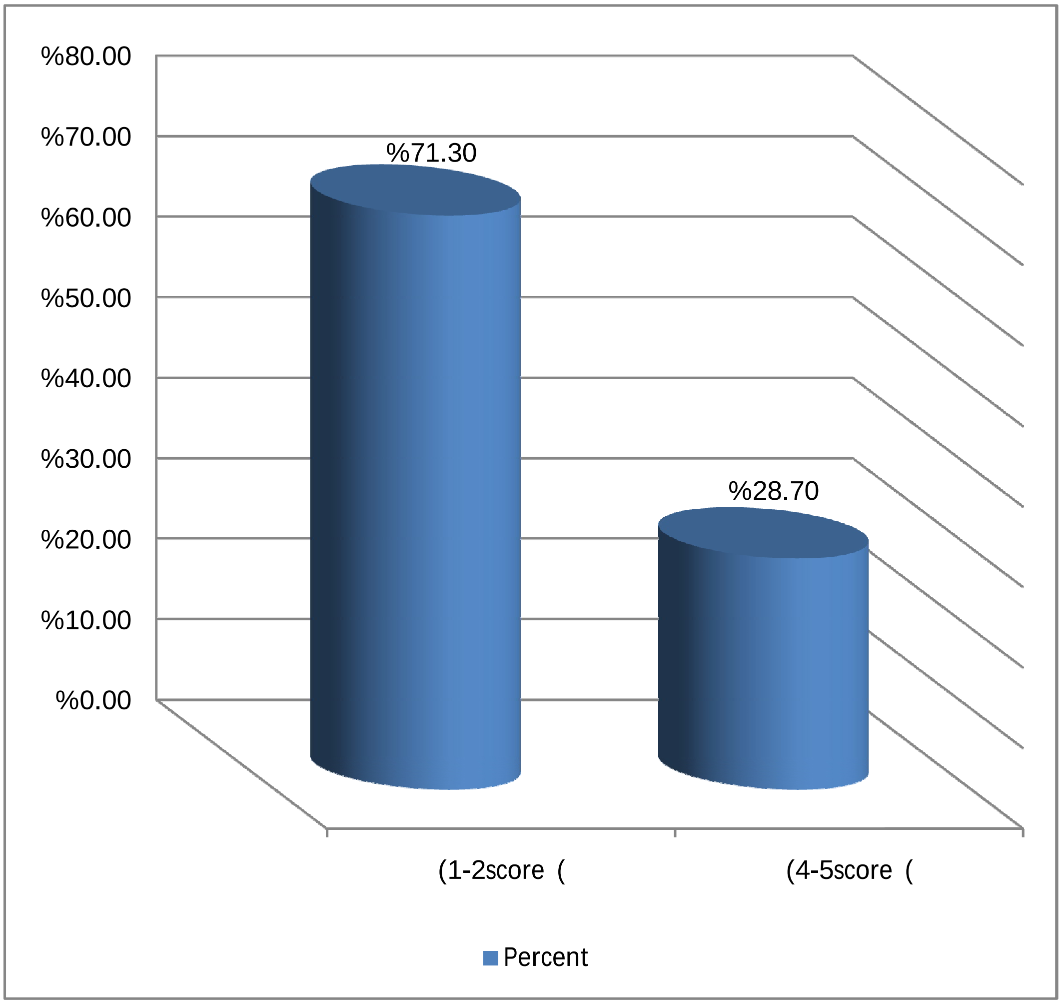
Elasto - score	**Frequency**	**Percent**
score 1	31	18.2
score 2	71	41.8
score 3	27	15.9
score 4	25	14.7
score 5	16	9.4
Total	**170**	**100%**



Graph (4.16): Evaluation of elastography scores in characteristics of thyroid diseases in300 patients.

Table (4-17) Elasticity Scores in Thyroid Nodules in 170 patients with fine needle aspiration biopsy

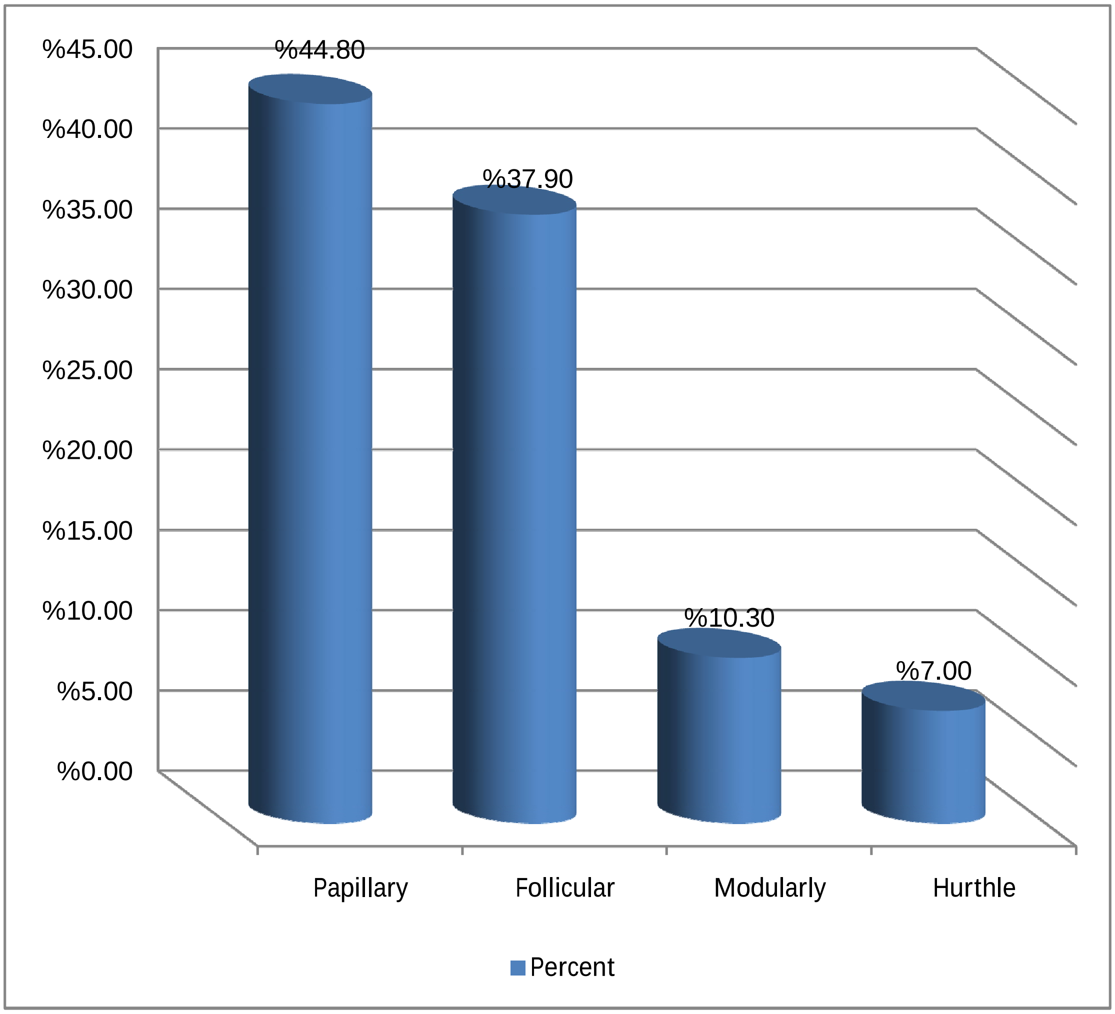
Score	Frequency	Percent
score (1-2)	102	71.3%
score (4-5)	41	28.7%
Total	**143**	**100%**



Graph (4-17) Elasticity Scores in Thyroid Nodules in 170 patients with fine needle aspiration biopsy.

Table (4.18) Demonstrate types of carcinomas in 29 patients with malignant nodules of the 170 patients enrolled in the study.

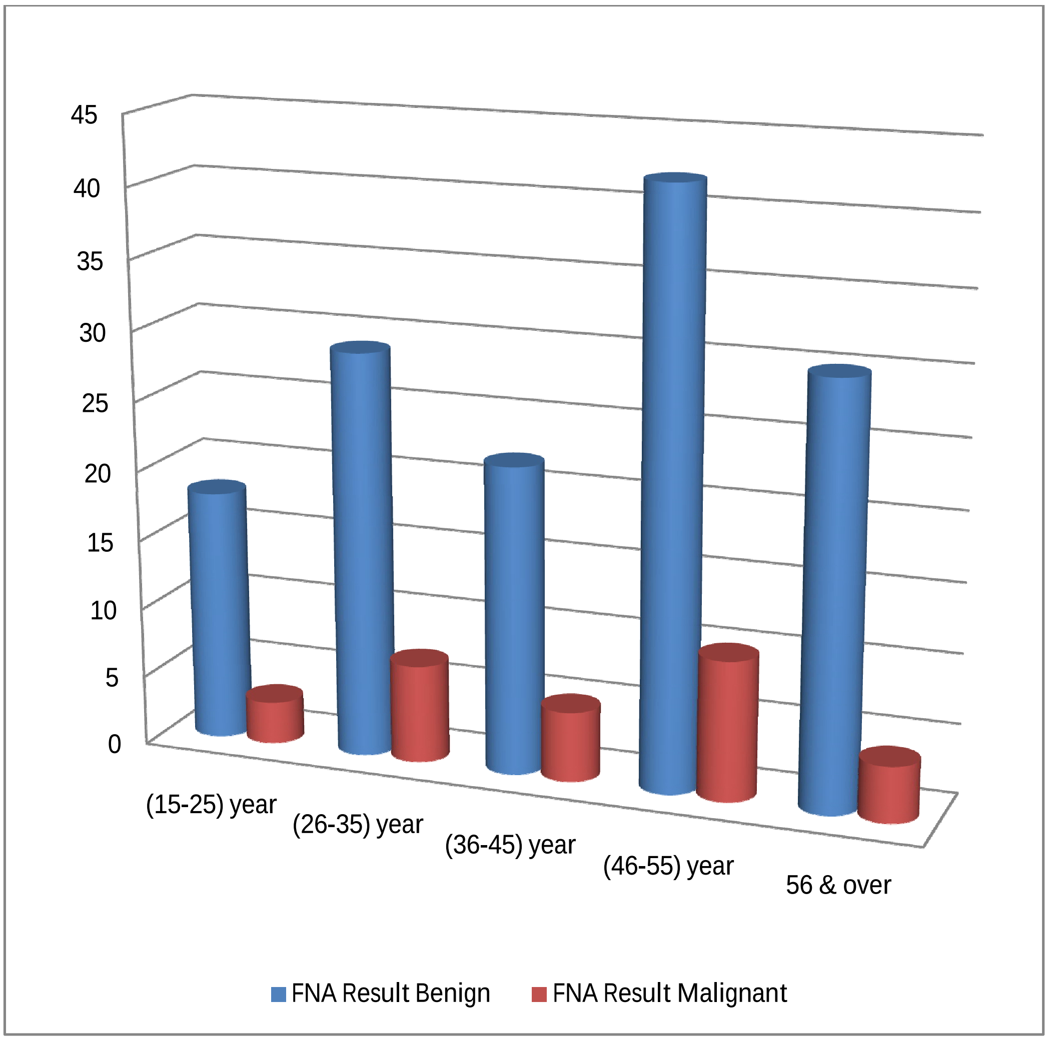
Tybe of malignant	**Frequency**	**Percent**
Papillary	13	44.8%
Follicular	11	37.9%
Modularly	3	10.3%
Hurthle	2	7.0%
Total	**29**	**100%**



Graph (4.18) Demonstrate types of carcinomas in 29 patients with malignant nodules of the 170 patients enrolled in the study.

Table (4- 19).The relationship between the malignant nodules and age group

	Count	FNA Result	
		Benign	Malignant
age	(15-25) year	18	3
	(26-35) year	29	7
	(36-45) year	22	5
	(46-55) year	42	10
	56 & over	30	4
	Total	141	29



Graph (4-19). The relationship between the malignant nodules and age group

Table (4-20) Predictivity of thyroid ultrasound features for the identification of malignant thyroid nodules.

Feature	Benign, (n = 141)	Malignant (n = 29)	Sensitivity %	Specificity %
Hypoechogenicity	Present 19 Absent 122	19 10	65	87
Halo Sign	Present 17 Absent 124	0 29	0	89
microcalcifications	Present 7 Absent 134	8 21	28	95
Intranodular blood flow	Present 27 Absent 114	17 12	59	81
A/T ≥1 cm	Present 33 Absent 108	24 5	83	23
Blurred margins	Present 2 Absent 139	3 26	10	98

4.9. Ultrasound features result * F.N.A.C cross tabulation

Table (4-21) Shows Ultrasound features result * F.N.A.C cross tabulation (hypoechogenicity)

			Fine Needle Aspiration		Total
			Malignant	Benign	
Hypo-ehoic	Present	Count	18	19	37
		% within Fine Needle Aspiration	62.1%	13.5%	22 %
	Absent	Count	11	122	133
		% within Fine Needle Aspiration	37.9%	86.5%	78 %
Total		Count	29	141	170
		% within Fine Needle Aspiration	100.0%	100.0%	100.0%

Table (4-22) Shows Ultrasound features result * F.N.A.C cross tabulation (Halo and sign vascularity)

			Fine Needle Aspiration		Total
			Malignant	Benign	
Halo sign	Present	Count	0	17	17
		% within Fine Needle Aspiration	0.0%	12.1%	9.5%
	Absent	Count	29	124	153
		% within Fine Needle Aspiration	100.0%	87.9%	90.5%
Total		Count	29	141	170
		% within Fine Needle Aspiration	100.0%	100.0%	100.0%

			Fine Needle Aspiration		Total
			Malignant	Benign	
vascularity	Present	Count	17	32	49
		% within Fine Needle Aspiration	58.6%	22.7%	30.5%
	Absent	Count	12	109	121
		% within Fine Needle Aspiration	41.4%	77.3%	69.5%
Total		Count	29	141	170
		% within Fine Needle Aspiration	100.0%	100.0%	100.0%

Table (4-23) Shows Ultrasound features result * F.N.A.C cross tabulation (Micro-calcification)

			Fine Needle Aspiration		Total
			Malignant	Benign	
Micro-calcification	Present	Count	8	8	16
		% within Fine Needle Aspiration	27.6%	5.7%.	9.0%
	Absent	Count	21	133	154
		% within Fine Needle Aspiration	72.4%	94.3%.	91.0%
Total		Count	29	141	170
		% within Fine Needle Aspiration	100.0%	100.0%	100.0%

Table (4-24) Shows Ultrasound features result * F.N.A.C cross tabulation (A/T >1)

			Fine Needle Aspiration		Total
			Malignant	Benign	
A/T >1	Large	Count	24	108	132
		% within Fine Needle Aspiration	**82.8%**	**76.6%**	79.0%
	Small	Count	5	33	38
		% within Fine Needle Aspiration	**17.2%**	**23.4%**	21.0%
Total		Count	29	141	170
		% within Fine Needle Aspiration	100.0%	100.0%	100.0%

Table (4-25) Shows Ultrasound features result * F.N.A.C cross tabulation (blurred margin)

			Fine Needle Aspiration		Total
			Malignant	Benign	
blurred margin	Present	Count	3	4	7
		% within Fine Needle Aspiration	**10.3%**	2.8%	4.5%
	Absent	Count	26	137	163
		% within Fine Needle Aspiration	**89.7%**	**97.2%**	95.5%
Total		Count	29	141	170
		% within Fine Needle Aspiration	100.0%	100.0%	100.0%

Table (4-26) Shows Elasto. Result * Fine Needle Aspiration Cross tabulation.

Elasto. Result * Fine Needle Aspiration Cross tabulation.

Elasto Score				Fine Needle Aspiration		Total
				Malignant	Benign	
1	Elasto. Result	Benign	Count	1	13	14
			% within Fine Needle Aspiration	100.0%	**100.0%**	100.0%
	Total		Count	1	13	14
			% within Fine Needle Aspiration	100.0%	100.0%	100.0%
2	Elasto. Result	Benign	Count		34	34
			% within Fine Needle Aspiration		**100.0%**	100.0%
	Total		Count		34	34
			% within Fine Needle Aspiration		100.0%	100.0%
3	Elasto. Result	Malignant	Count	2	1	3
			% within Fine Needle Aspiration	**100.0%**	10.0%	25.0%
		Benign	Count	0	9	9
			% within Fine Needle Aspiration	0.0%	**90.0%**	75.0%
	Total		Count	2	10	12
			% within Fine Needle Aspiration	100.0%	100.0%	100.0%
4	Elasto. Result	Malignat	Count	7	4	11
			% within Fine Needle Aspiration	**100.0%**	100.0%	100.0%
	Total		Count	7	4	11
			% within Fine Needle Aspiration	100.0%	100.0%	100.0%
5	Elasto. Result	Malignat	Count	6	1	7
			% within Fine Needle Aspiration	**100.0%**	100.0%	100.0%
	Total		Count	6	1	7
			% within Fine Needle Aspiration	100.0%	100.0%	100.0%

CHAPTER FIVE

Discussion, Conclusion and Recommendations

Discussion

The aims of our prospective study were to evaluate the elastographic appearances of thyroid nodules and to determine whether ultrasound elastography (USE) may assist in differentiating benign from malignant thyroid nodules and results in reducing of thyroid biopsies.

The sample of this study consisted of 300 patients all had U/S scan and 200 patients had U/S, real time ultrasound elastography and FNAC examination.

The majority of the sample study were females; 270 patients with percentage of (90%), while males were 30 with percentage of (10%).Females to Males ratio was approx (9:1), and from 29 patients had malignant nodules there were 22 female had malignant nodules with percentage of (75.9%) and 7 male (24.1%), with females: males ratio of (3:1) , and this is true since Elgizouli et al [(45)] reported that thyroid malignancy in female in reproductive age group i.e. less than 40 years of age (60 %),with a female : male ratio of (10:1) .

Omeran and Ahmed [(60)] those assessed carcinoma of the thyroid in Khartoum, their study included 112 patient with thyroid malignancy seen at (RICK), Khartoum during the period from (1982-1989), the females: males ratio approx was (3:1), with a high incidence of malignancy between the ages 40-70 years old.

Also the study of Safi Allah et al [(130)] reported ratio of (9:1) between females: males. So this study showed the high ratio of attack with thyroid nodules between females: males as in most of the previous studies.

This study showed that the mean age was 45.5 years the result agree with previous studies of Safi-Allah et al. ([130]) whom done their study on 300 cases and the reported mean age in their study was 45.5 years.

There are many US criteria for differentiating benign from malignant thyroid nodules. Such differentiation is important for selecting patients for further FNAB in cases with suspicious of malignancy, or to avoid unnecessary biopsy for those with benign criteria. It has been found in literature that no single criteria is sure of malignancy, and combination of the known criteria of malignancy gives higher sensitivity and specificity than depending on single individual one [13,5,27]. There are multiple US features that are highly suggestive of malignancy in a thyroid nodule including presence of calcifications, hypoechogenicity, irregular margins, absence of a halo sign, predominantly solid composition, and intranodule abnormal vascularity. However, the sensitivities, specificities, and negative and positive predictive values for these criteria are extremely variable from study to study, and no US feature has both a high sensitivity and a high positive predictive value for thyroid malignancy [5]. It has been shown that the possibility of cancer in a thyroid nodule has been shown to be the same regardless of the size of the nodule [17, 8, 19,22].The nodule size and multiplicity have not been shown to affect the likelihood of malignancy [8, 17, 12,].

In our study, the sensitivity and specificity of hypoechogenicity to malignancy was 65% and 87% respectively. Out of the 29 cases with hypo echoic nodules, 19 of them proved to be malignant by FNAB. These results are matching with the results of some authors [8, 17, 12, 29], where they found that marked hypoechogenicity has been a characteristic that is suggestive of malignancy. Studying the margin of a nodule is an important part of the examination. A hypo echoic or anechoic rim encircling a nodule, known as the halo sign is highly predictive of benignity [8, 17, 12, and 29].

However, this sign may be absent in more than 50% of benign nodules and present in up to 20% of malignant nodules [11].In our study, all nodules that show halo sign on US are proved to be benign on FNAB. Halo sign is not a criteria of any malignant nodule in our study population. Blurred margin is an indicator to malignant lesions that invade the surrounding tissues. In the current study, blurred margin is a strong indicator of malignancy with 98% specificity. The presence of calcification within the nodule raises the probability of malignancy. Microcalcifications and macrocalifications in a solid nodule are associated with an approximately threefold and twofold increase in cancer risk respectively, as compared with predominantly solid nodules without calcifications [19]. The sensitivity and specificity of microclcification detected by US as a predictor to malignancy is 28% and 95% respectively. Supporting our results are those of [8], where the specificity of microcalcification to papillary carcinoma is 95% with a relatively low sensitivity 29%. In another study of [19], although microcalcifications carry low sensitivity 26.1%–59.1%, they show the highest positive predictive value (41.8%–94.2%) for malignancy. A shape that is taller than wide is highly suggestive of malignancy [8, 17, 12, 29]. In the current study, the ratio of the nodular height to width of > 1 is found in 55 malignant and only 10 benign nodules. Color Doppler US has also been evaluated as a diagnostic tool for

Predicting thyroid malignancy, where peripheral nodular flow is suggestive of a benign nodule, while flow predominantlyin the central portion of the nodule is suggestive of malignancy. The results of these studies are controversial, with some reporting that Doppler US is helpful in differentiating benign from malignant lesions [8, 20] and others reporting that it did not improve diagnostic accuracy of thyroid nodules [21, 25]. In one study [29] central flow was seen in a higher percentage of malignant nodules than benign nodules

(42% vs 14%). However, like other US features, color Doppler US cannot be used to diagnose or exclude malignancy with a high degree of confidence; rather, the color Doppler US finding of predominantly internal or central blood flow appears to increase the chance that a nodule is malignant [5].out of the 20 cases showing intranodular abnormal vasculature, 11 are malignant and 9 are benign on FNAB. intranodular abnormal blood vessels carry a 59% sensitivity and 81% specificity for malignancy.Putting the whole previous criteria together increases the likelihood of malignancy with confidence. Combining the hypoechogenicity, absent halo sign, intranodularmicrocalcification, increased height than width and presence of intranodule vascularity increase the sensitivity and specificity of US for malignant lesions to 59% and 81% respectively. As mentioned by some authors [8, 18], the combination of features improves the positive predictive value of US to some extent. In conclusion, US is the modality of choice in evaluation of thyroid nodules. No single criteria are sure of malignancy, however, combination of some criteria- in particular- hypoechogenicity, microclcification and intranodular vascularity increases the likelihood of malignancy that warrants biopsy.

The aims of our prospective study were to evaluate the elastographic appearances of thyroid nodules and to de- termine whether ultrasound elastography (USE) may assist in differentiating benign from malignant thyroid nodules and results in reducing of thyroid biopsies.

In our study, tissue stiffness on ultrasound elastography was scored from 1 (greatest elastic strain) to 5 (no strain) based on subjective analysis of the elastogram image. The scoring was classified to differentiate benign and malignant lesions and is based on color pattern with elastography image. Score 1, and 2 included nodules with high elasticity, score 3 was maintained as an intermediate score; and scores 4 and 5 included nodules with low elasticity. Using this score classification, the predictivity of US elastography was highly rewarding. Scores 4 and 5 were associated with malignancy with sensitivity of 87%, specificity of 90%, a PPV of 68%, and an NPV of 90%. This study confirmed by recent study of Rago et al. [37],

In our study ultrasound elastography (USE) had a sensitivity of 93.7%, a specificity of 92%, a positive predictive value of 72%, a negative predictive value of 98.0%, and an accuracy of 90.1% in the prediction of malignancy. Our results are very close to the findings reported by previous studies [36, 44], showing RTE sensitivity of 92% and specificity of 93.7% (considering Elastography Score 1 and 2 as benign and Elastography Score 4 and 5 as malignant).

In the May 2008 issue of the journal thyroid a group of Italian researchers described their experiences using elastography for the differential diagnosis of thyroid cancer. Sixty-seven patients who had a total of 86 thyroid nodules were examined with gray scale sonography, power Doppler imaging and elastography. Elastography data was scored based on four levels of tissue stiffness (class 1 being soft; class 2 and 3 indicating nodules with an intermediate degree of stiffness and class 4 for stiff lesions).The final diagnosis was determined with cytology. Of the 86 nodules evaluated 17 were malignant and 69 were benign. The sensitivity of elastography for detection of thyroid cancer was 94.1%, the specificity was 81% and the accuracy was 83.7%.

The authors concluded that elastography combined with other ultrasound imaging modes can help identify thyroid nodules that are likely to be malignant. So as our result agree with them.

Most studies show an incidence of malignancy of 2% - 5% in nodules selected for biopsy, and the incidence of malignancy is much lower in all unselected nodules [38].

Inter mediate score; and scores 4 and 5 included nodules with low elasticity. Using this score classification, the predictivity of US elastography was highly rewarding. Scores 4 and 5 were associated with malignancy with sensitivity of 87%, specificity of 90%, a PPV of 68%, and an NPV of 90%. Much more rewarding were the negative predictive values of the pattern of high elasticity scores 1, and 2 to exclude malignancy. In the current study, reported that scores of 1 or 2 were found in 47 cases, all benign lesions diagnosis at cytology. This means that nodules with high elasticity, which represent the largest proportion of nodules with indeterminate cytology, have no probability to bear malignancy (according to our study result. The low number of false-negative results at USE, together with the low progression rate of differentiated thyroid cancer, would allow most patients to be placed in follow-up without significant costs in terms of prognosis. A score 3 (intermediate score) was found in 12 cases with two cases of carcinomas, and 10 cases benign lesions. In score 3 according to our result, all patients with score 3 must be sent to fine needle aspiration cytology (FNAC) for confirmation. Thus, by combining the scores 1, 2, 3, 4, and 5, ultrasound elastography (USE) had a sensitivity of 93.7%, a specificity of 92%, a positive predictive value of 72%, a negative predictive value of 98.0%, and an accuracy of 90.1% in the prediction of malignancy. Our results are very close to the findings reported by previous studies [36, 44], showing RTE sensitivity of 92% and specificity of 93.7% (considering Elastography Score 1 and 2 as benign and Elastography Score 4 and 5 as malignant).

In summary, we found that USE is an easy, non-invasive and rapid technique that can be used routinely in thyroid US scans to select cases for FNAB, and decrease the number of unnecessary biopsies, and consequently decrease its hazards and costs. Cases that show score 1 or 2 are not in need for further investigation, and only fol- low up should be recommended. Cases with score 4 or 5 are considered to be highly malignant and other US criteria of malignancy should be looked for to support the diagnosis e.g. pattern of vascularity and cervical lymph nodes infiltration. FNAB should be recommended in all cases of score 3 where malignancy can't be excluded using USE criteria only.

In the current study, all the 200 nodules selected for biopsy by the real-time ultrasound, the cytology results showed the incidence of malignancy was (15%). This study shows much higher prevalence of malignancy compared with previous reports. Malignant nodules were significantly smaller in diameter than benign (1.91.0 vs. 2.7 1.7 cm), in apparent disagreement with previous studies reporting a higher prevalence of cancer in nodules larger than 4 cm [43, 44]. However, by analyzing the possible relationship between size and cancer in a large series of nodules with indeterminate or suspected cytology, the lowest likelihood of malignancy was observed in lesions of 2.5 cm, the risk increasing either in smaller (53% per centimeter decrease in size) or in larger nodules (39% per centimeter increase in size) [42]. Moreover, a higher prevalence of cancer in nodules with smaller size has been recently described (26% of tumors smaller than 1 cm) [44].

In our study, ultrasound elastograms predicted malignancy with 87.5% sensitivity and 90% specificity,70% positive predictive value and 96.5% negative predictive in nodules that had a greatest diameter of 1 cm or more. 14 nodules of 16 of the total nodules proven by the FNA had a greatest diameter of 1cm or more (1.1 - 2.0 cm). The remaining 2 nodules were less than 1 cm in size. This results match with the previous report mentioned above.

Our study limitations. First, although the ultrasound exams, ultrasound guided fine needle aspiration and elastography had been done by more than three radiologists, reflecting the expected difference between readers definitely exists in clinical practice. There was no significant differences (almost the same) between the examiners in their reading results for ultrasound examinations. But elastography results comparatively showed slight differences between the examiners, this may be because the elastography is an operator dependant tech- nique and the fact that there were different radiologists who involved in this study to obtain the elastography images. This type of elastography procedure which is depending on personal color scale to be replaced by the other elastography techniques appear more independent operator and quantitative analysis of nodule stiffness to improve the real time elastography such as shear wave elastography.

Our study supported by previous studies reported that Different methods have been proposed for the quantita- tive analysis of elastographic images, such as off-line processing of strain images by strain index [17,18], carotid artery pulsation [45,46], and shear wave elastography [43]. These techniques appear more operators inde- pendent and reproducible; although most of them are currently limited in clinical practice (too time consuming for the calculation of nodule stiffness and weak utility in case of multinodular goiter). Recently, however, shear wave elastography has shown a valuable PPV (92.3%) in the presurgical diagnosis of malignant lesions in a large series of unselected thyroid nodules, also in case of mul- tinodular goiter [43].

Second, the previous study reported that, the major limitation of FNA cytology is that 10% to 15% of specimens are no diagnostic [7].

Our study percentage of nodule specimens with insufficient or inadequate for diagnosis at US-FNAC was 22%. This percentage is higher than the percentage of inadequate cytology having previously reported above. These insufficient specimens were excluded could affect the result of elastography by reducing the number of nodules enrolled in the study, because FNA was used as a reference standard.

Conclusion

Ultrasound elastography is a promising imaging technique that is useful in the differential diagnosis of thyroid cancer. Further improvements in the technique and the diagnostic criteria are necessary for this examination to provide a useful contribution to diagnosis.

The use of ultrasound elastography would lead to low thyroid biopsies because of the high elasticity of being strongly associated with a benign cytology. There will be a need for additional studies on large population with thyroid nodules to determine if it has adequate technical sensitivity and predictive value in order to avoid the need for a biopsy. (USE) had a sensitivity of 93.7%, a specificity of 92%, a positive predictive value of 72 %, a negative predictive value of 98.0%, and an accuracy of 90.1% in the prediction of malignancy.

Recommendations

♦ Larger prospective studies are needed to confirm our results and establish the diagnostic accuracy of this technique.

♦ We recommend to utilize the real time ultrasound elastography (RTE) as the protocol with the combination of the conventional ultrasound so as to reduce the thyroid biopsies.

♦ Although RTE still remains a promising non-invasive procedure for discriminating malignant from benign lesions and it is an operator-dependent procedure, therefore sonographers and sonologists should be well trained to improve the results.

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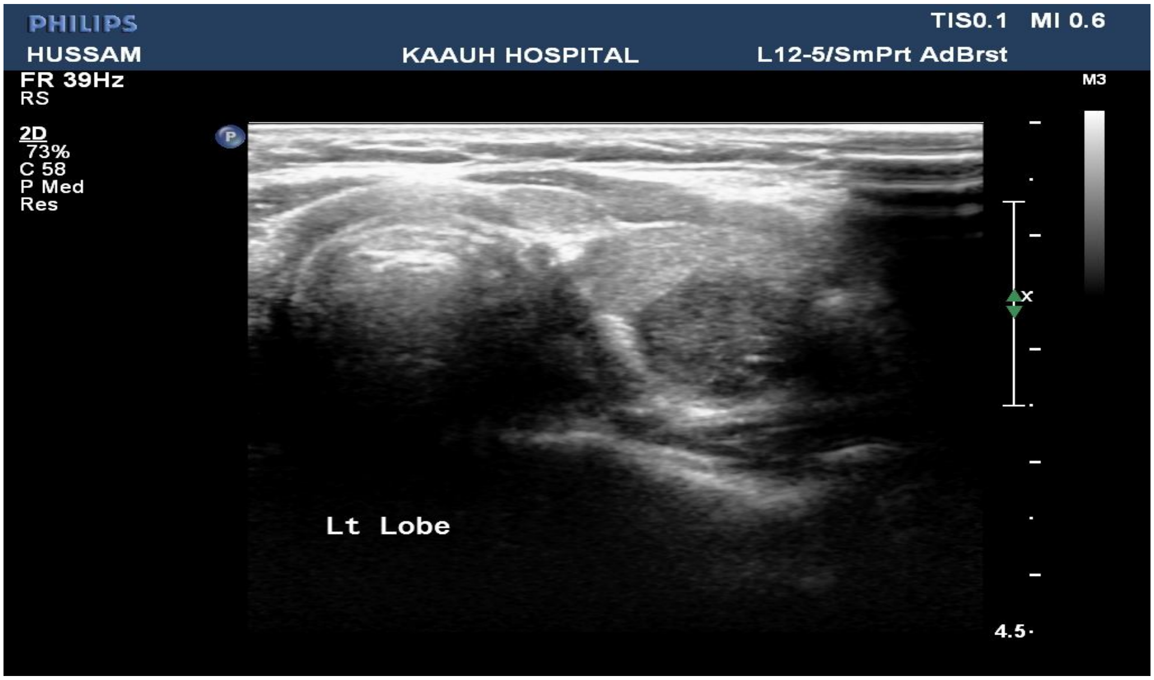
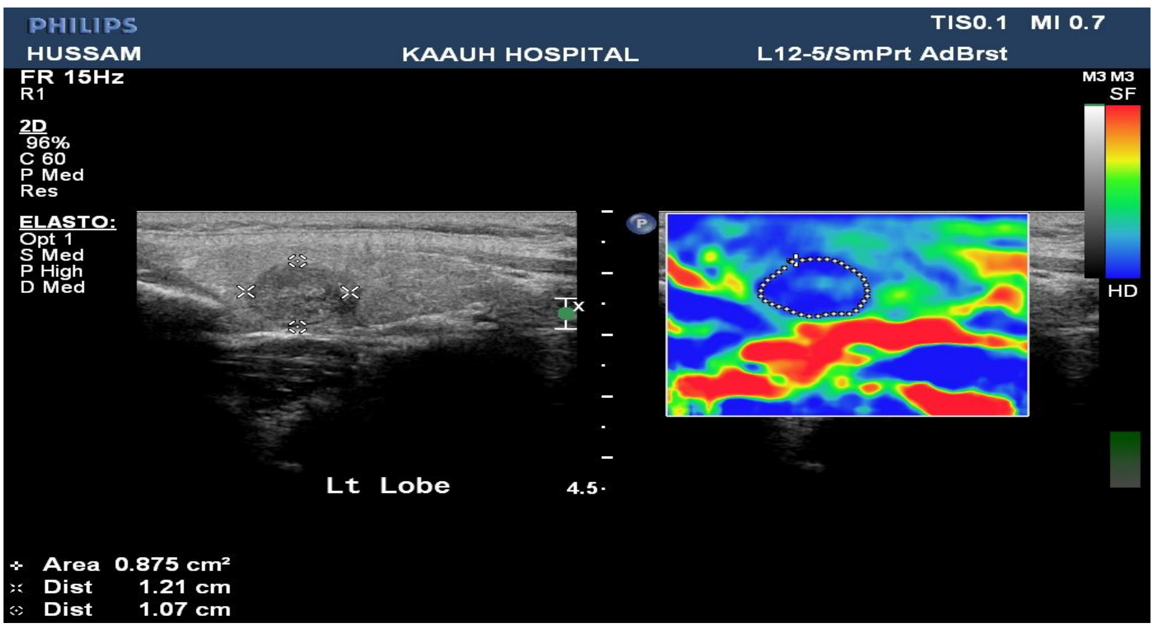
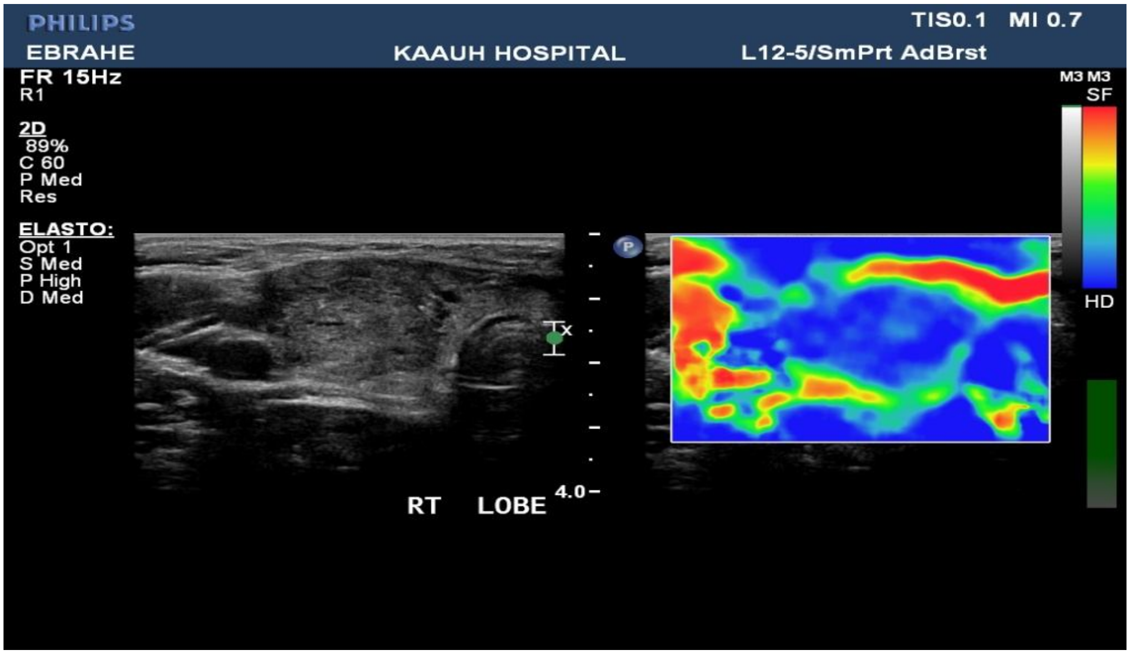


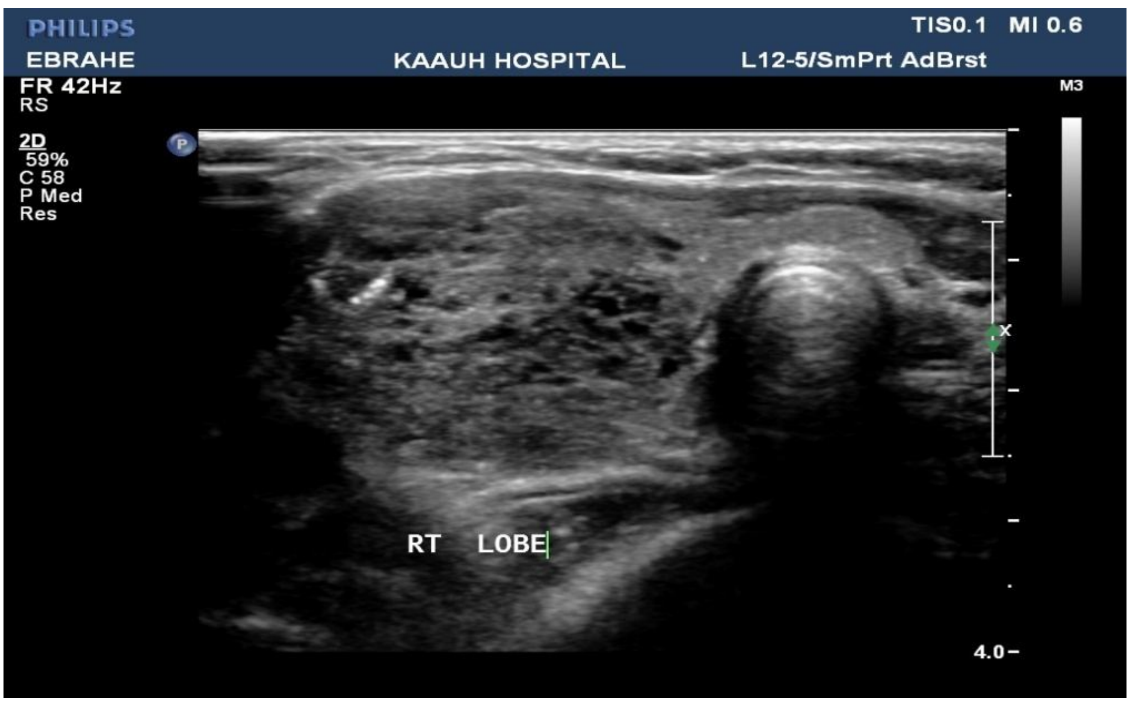
Conventional ultrasound for 31 yrs old female with papillary carcinoma confirmed by FNA cytology.



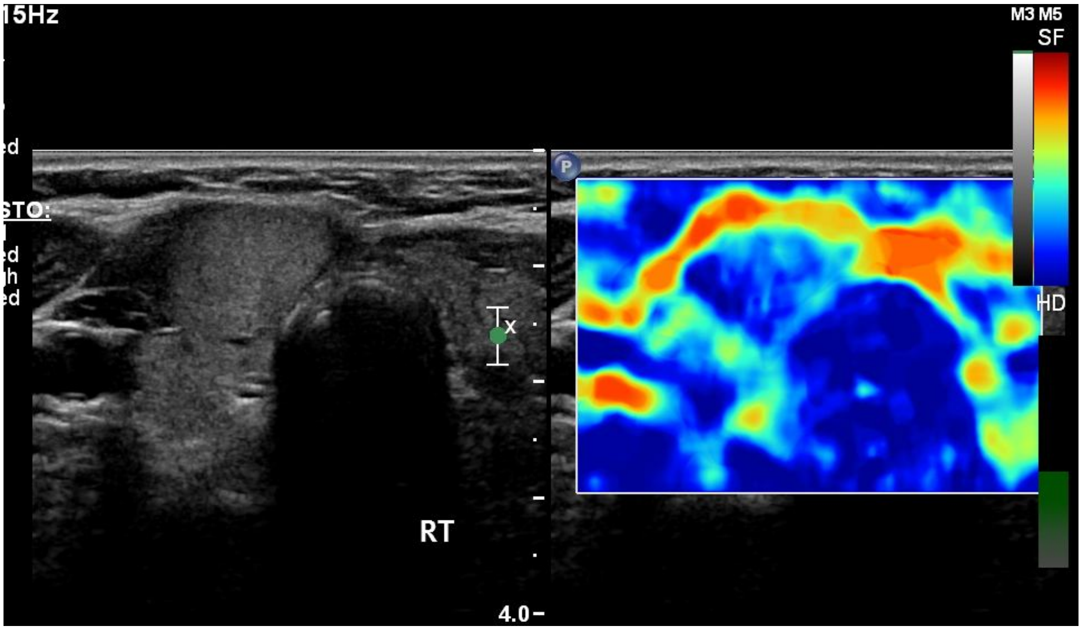
Real time ultrasound for 31 yrs old female with papillary carcinoma confirmed by FNA cytology.



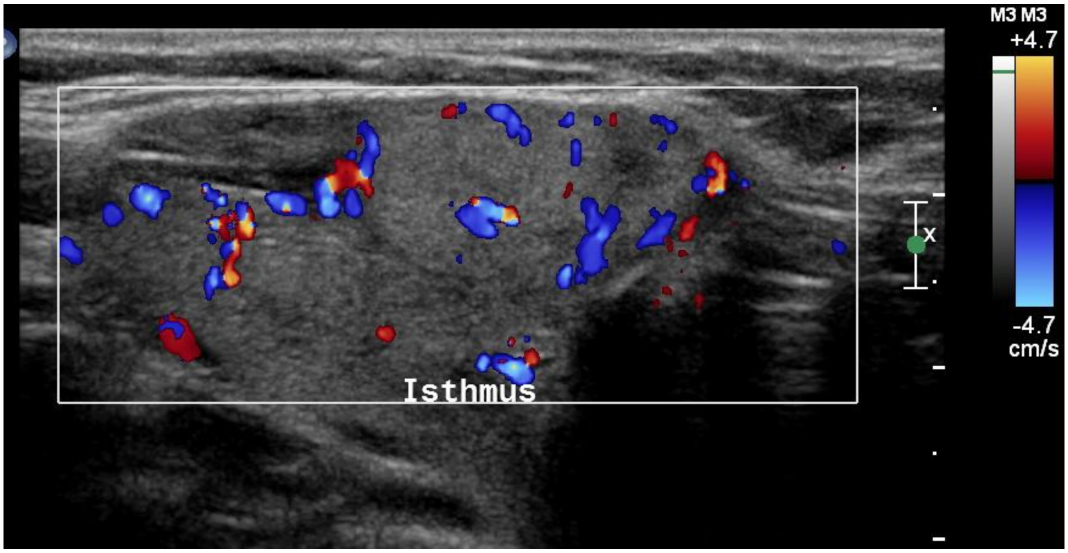
Real time ultrasound for 19 yrs old male with medullary carcinoma Confirmed by FNA cytology.



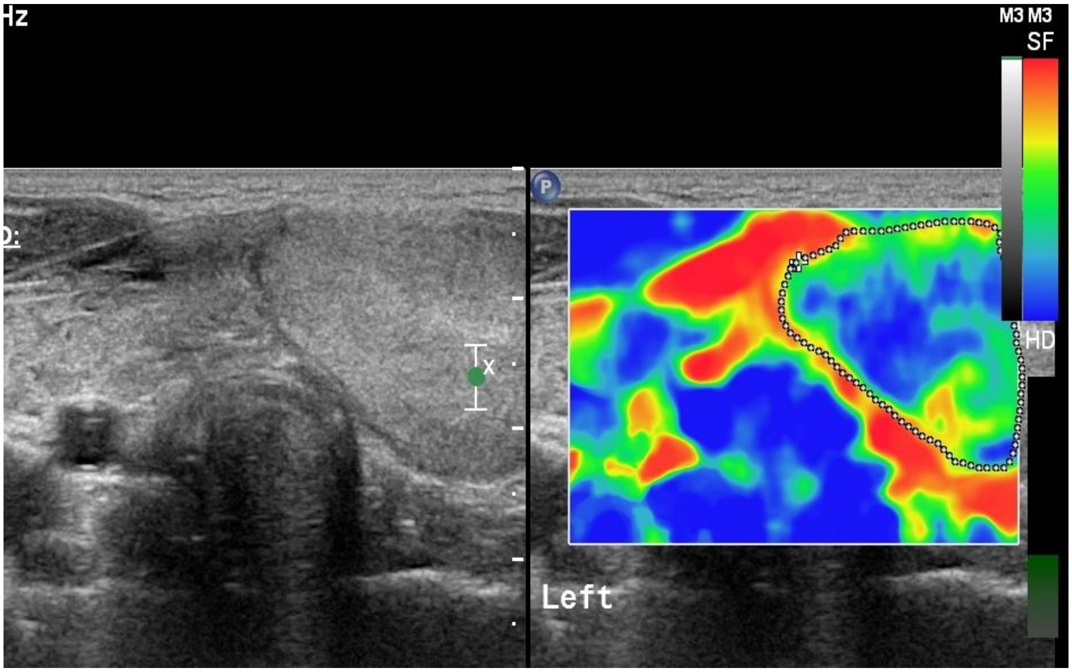
Conventional ultrasound for 19 yrs old male, with medullary carcinoma confirmed by FNA cytology.



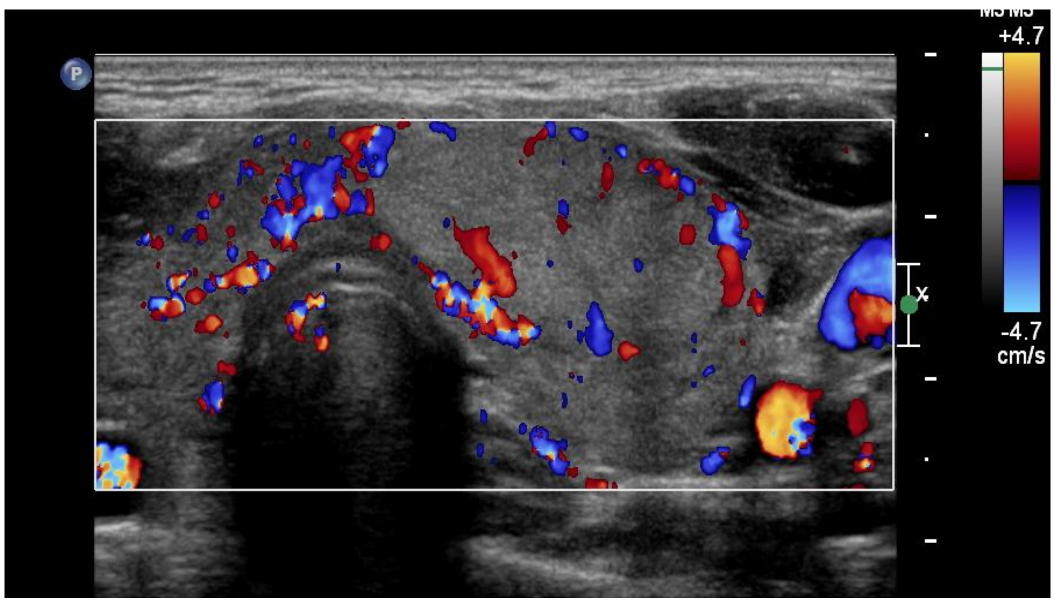
Real time ultrasound for 55 yrs old female with medullary carcinoma confirmed by FNA cytology.



Conventional US for 55 yrs old female with medullary carcinoma confirmed by FNA cytology.

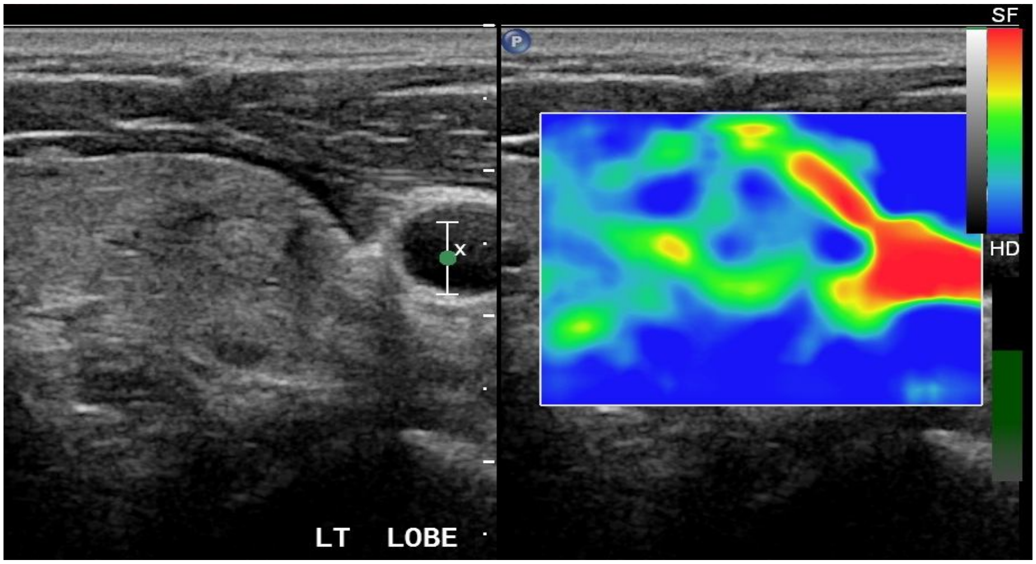


Real time ultrasound for 33 yrs old female, with follicular neoplasm confirmed by FNA cytology.

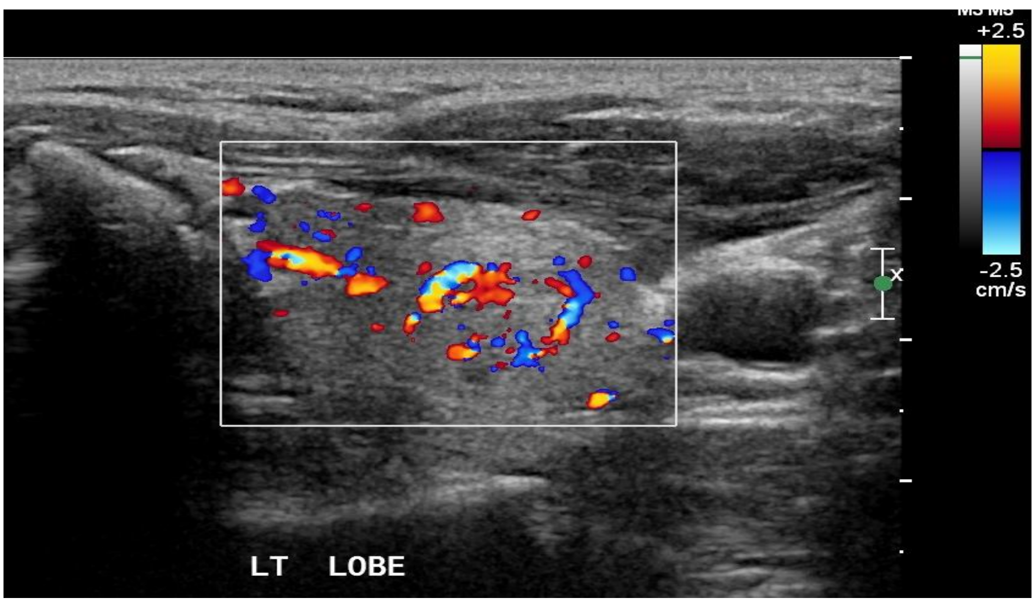


Conventional US for 33 yrs old female, with follicular neoplasm

confirmed by FNA cytology.



Real time ultrasound for 44 yrs old female with papillary carcinoma confirmed by FNA cytology.



Conventional US for 44 yrs old female with papillary carcinoma confirmed by FNA cytology.

DATA COLLECTION SHEET

Serial No.	PT. NO.	AGE	SEX	U.S. Characteristics						US Result	F.N.A Result	Elasto score	Elasto. Result
				Hypo-ehoic	Halo SIGN	Micro-calcificatin	vascularity	A/T >1Cm	blurred margin				