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Sudan University of Science and Technology

College of Graduate Studies

Characterization of Thyroid Benign Nodules using Ultrasonography and Scintigraphy

توصيف العقد الحميده للغده الدرقيه بإستخدام التصويربالموجات فوق الصوتيه والنظائر المشعة

A Thesis Submitted for Partial Fulfillment of the Requirement of (M.Sc.)Degree in Medical Diagnostic Ultrasound

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Dedications

With my love and appreciation I dedicate this thesis:

To my father’ssoul

To my mother for her endless support

and always pray for my

To anyone who ever taught me

To my brothers and sisters

To my colleagues and to all people that

I do love and respect

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Firstly praise and thanks are due to***Allah, the lord creator.***

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Abstract

Recently in Sudan there is a noticeable increase of thyroid diseases, which is related to several factors. There are several investigations tools and methods used to assess thyroid disorders; hence the main objective of this study is to characterize thyroid benign nodules using Ultrasonography and Scintigraphy.This is a descriptive cross-sectional study conducted mainly in the Radiation and Isotopes Centre of Khartoum and Nilein Medical Diagnostic Center, Academy Charity Teaching Hospital and Bashair Teaching Hospital, in the period from May 2016 to December 2016. Sample size consisted of 50patients from both genderwere investigated using Toshiba and Alpinion E-CUBE 7ultrasound Machine with high frequency transducer 7.5-10 MHz linear probe and radionuclideTechnetium-^{99m},all patients scan in supine position technique. The results was analyzed using Statistical Package for Social Science (SPSS), the results can be summarized as follow; the incidence of thyroid benign nodules is more common in female 86%, about 76% in married, detected in age between 22 – 70 years, the incidence are less common in young and elder patients, site is more bilateral than the left or right lobe 62%, also show high uptake 74%, distribution of radiotracer is more homogeneous 62%, most nodules outline are regular 60%. When investigated by ultrasound showed 60% heterogeneous texture and other are homogeneous appearance, the echogenicty obtained is 60% isoechoic, 20% hypoechoic and 12% hyperechoic, and the nodule out line showed 90% well define outline and 10% ill defined outline. Beside the study connected the results of nuclear medicine with ultrasound finding. Finally the study recommended that radiation Scintigraphy only dose not accurately but it can give a picture about the nodule and by comparing the sonographic finding we obtain the most real diagnosis, and increased research in this direction, use of ultrasound technology with high facility like Doppler toknow the blood flow indices for more accurate results.

الخلاصه

في الأونه الاخيره حدثت زياده ملحوظه في امراض الغده الدرقيه في السودان ومنها الدرنات الحميده (الاورام الحبيبيه الحميده لل

غده الدرقيه)، وتعزى هذه الزياده لأسباب عديده وتوجد وسائل وطرق متعدده لتشخيص وتقويمالأورام الحبيبه للغده الدرقيه، ولذا كان الهدف الأساسي من قيام هذه الدراسه هو الكشف عن خصائص أمراض الدرنات الحميده (الأورام الحبيبه) للغده الدرقيه بإستخدام التصوير بالموجات فوق الصوتيه والنظائر المشعة والمقارنه بين نتائج الموجات الصوتيه وفحوصات النظائر المشعه. وهذه دراسه وصفيه أجريت بصوره اساسيه في مستشفى الذره الخرطوم بالإضافه لبعض المستشفيات الأخري مثل مركز النيلين للتشخيص الطبي ومستشفي الأكاديميه الخيري ومستشفى بشاير الجامعي في الفتره من مايو 2016 الى ديسمبر 2016،وقد تم جمع البيانات لهذه الدراسه بإجراء الفحوصات على عدد خمسين مريضا من الجنسين ، والجهاز الذي اجريت عليه الدراسه هو جهاز Alpinion E-CUBE 7 وجهازتوشيبا مزودين بمسبار ذي سطح مستوي وتردد يتراوح بين 7- 10 ميغا هيرتز، وجهاز قاما كاميرا سيمينس الالماني وميدسو الهنغاري وتم إجراء المسح بتقنية وضع الإستلقاء. وقدتم التحليل باستخدام نظام برنامج الحزم الإحصائية للعلوم الاجتماعية وأوضحت النتائج أنمعظم المرضى إناث (86%) مقارنة بالذكوروكذلك غالبيتهم من المتزوجين 76% كما أظهرت الدراسه ان معظم الاورام الحميده وُجدت في الاعمار من ما بين 22 و 70 سنه ، وان النسبه منخفضه بين الفئات العمريه الصغيره والكبيره جدا، كما ان اكثر الفئات العمريه تعرضا لأورام الغده الحميده هم من تتراوح اعمارهم ما بين 28 و 37 سنه ووجود العقد الحميده في الفصين الايمن والايسر معآ أكثر من وجودها في احداهما منفردآ 62% كما أوضحت ان 74% من الأورام الحميده للغده تظهر امتصاص عالي جدآ لمادة التكنيشوم المشعه وتوزيع هذه الماده يكون متجانسأ في حوالي 62% وحواف العقد الحميده في الغده معظمها منتظم 60% وعند اجراء فحوصات الموجات فوق الصوتيه لنفس المرضى وجد ان 60% من نسيج العقد غير متجانس و 40% متجانس، و60% منتظمة الحواف والأخرى غير منتظمه، كذلك 60% متساوية الصدى و20% منخفضة الصدى و 12% مرتفعة الصدى، و90% منتظمة الحواف و10% غير منتظمه كما ربطت الدراسه بين فحوصات النظائر المشعه وفحوصات الموجات فوق الصوتيه وقد خلصت الدراسه الى ان فحوصات الطب النووي مهمه جدآ لكنها غير كافيه لوحدها في توصيف هذه الأورام ولكن عند اجراء الفحصين معأ يمكن الحصول على التشخيص الأكثر دقه كما اوصت الدراسه بزيادة البحوث في هذا الاتجاه واستخدام الموجات فوق الصوتية بتقنيه أعلى مثل تقنية الدوبلر لمعرفة مؤشرات تدفق الدم للمساعده في توصيف هذه الاورام والتمييز بينها وبين اورام الغده الخبيثه.

List of Contents

List of Tables

List of Figures

List of Abbreviations

Abbreviation	*Meaning*
BFI	Blood Flow Indices
DIT	Di-iodotyrosine
DNA	deoxyribonucleic acid
FNAB	Fine-needle aspiration biopsy
FT_4F	Free thyroxine fraction
FT_4I	Free thyroxine index
MIT	Monoiodotyrosine
NIS	sodium-iodide symporter
PI	Pulsatility index
PTH	parathyroid hormone
PTU	propylthiouracil
RI	Resistive index
RAIU	Radioactive iodine-123 uptake
T_4	Thyroxin hormone
T_3	Tri-iodo thyronine hormone
Tg	Thyroglobulin
TBG	Thyroxine-binding globulin
TFT	Thyroid function tests
TPO	Thyroid peroxidase
TgAb	Thyroglobulin antibody titer
THBR	Thyroid hormone binding ratio
TRH	Thyroid releasing hormone
TSH	Thyroid-stimulating hormone
TMAb	Thyroid microsomal antibody titer

CHAPTER ONE

INTRODUCTION

Chapter One
Introduction

1-1 Introduction:

The thyroid gland is a crucial gland and is a one of the largest endocrine glands in the body that develops within the third week of gestation. In the embryo, the thyroid begins its initial development at the base of the tongue. It descends down the thyroglossal duct to ultimately rest anterior to the trachea. It is fully functional by the end of the first trimester.1. The thyroid consists of two connected lobes, right and a left lobe. A bridge of tissue, the isthmus, crosses over the midline of the neck anterior to the trachea, providing a link between the two thyroid lobes.The thyroid found in the anterior neck, below the laryngeal prominence (Adam's apple)occasionally, individuals may have a superior extension of the isthmus. This normal variant is termed a pyramidal lobe*(Steven et al. 2009)*.

The thyroid gland controls rate of use of energy sources, protein synthesis, and controls the body's sensitivity to other hormones. It participates in these processes by producing thyroid hormones, the principal ones being thyroxin (T_4) and tri-iodothyronine (T_3), which is more active. These hormones regulate the growth and rate of function of many other systems in the body. T_3 and T_4 are synthesized from iodine and tyrosine. The thyroid also produces calcitonin, which plays an important role in calcium homeostasis*(Boron et al. 2012)*.

Hormonal output from the thyroid is regulated by thyroid-stimulating hormone (TSH) produced by the anterior lobe of pituitarygland which situated in the hypophyseal fossa, at the base of skull below the brain, which itself is controlled by thyroid releasing hormone (TRH) produced by the hypothalamus*(Boron et al. 2012)*.

The thyroid consists of multiple follicles that contain a fluid called colloid. Colloid is composed of proteins and thyroid hormones. As a result of the thyroid-stimulating hormone that was released by the pituitary gland, the thyroid, in turn, releases the hormones contained within its cells by utilizing iodine to manufacture these hormones. Iodine is found in some vegetables, seafood, and within many processed foods that contain iodized salt. Accordingly, the subscripted numbers “3” and “4” found in the thyroid hormones denote the number of iodine atoms contained within each hormone. Thyroxine is the most abundant hormone produced by the thyroid. However, each hormone is vital and they work together to regulate metabolism, growth and development, and the activity of the nervous system. A surplus of these hormones will produce hyperthyroidism and a reduction wills causehypothyroidism*(Boron et al. 2012).*

The thyroid may be affected by some frequent thyroid diseases. Hyperthyroidism occurs when the gland produces excessive amounts of thyroid hormones, the most common cause being Graves' disease an autoimmune disorder. In contrast, hypothyroidism is a state of insufficient thyroid hormone production. Worldwide, the most common cause is iodine deficiency. Thyroid hormones are important for development, and hypothyroidism secondary to iodine deficiency remains the leading cause of preventable intellectual disability. In iodine-sufficient regions, the most common cause of hypothyroidism is Hashimoto's thyroiditis also an autoimmune disease. In addition, the thyroid gland may also develop several types of nodules and cancer*(Longo et al. 2012).*

The thyroid is well suited to ultrasound study because of its superficial location, vascularity, size and echogenicity. In addition, the thyroid has a very high incidence of nodular disease, the vast majority benign. Most structural abnormalities of the thyroid need evaluation and monitoring, but not intervention *(Longo et al. 2012)*. Thus, the thyroid was among the first organs to be well studied by ultrasound. The first reports of thyroid ultrasound appeared in the late 1960s.

Between1965 and 1970 there were seven articles published specific to thyroid ultrasound. In the

last ten years there have been over 1,300 published. `Thyroid ultrasound has undergone a dramatic transformation from the cryptic deflections on an oscilloscope produced in A-mode scanning, to barely recognizable B-mode images, followed by initial low resolution gray scale, and now modern high resolution images. Recent advances in technology, including harmonic imaging, contrast studies, and three- dimensional reconstruction, have furthered the field.

Application of ultrasound for thyroid imaging began in the late 1960s. In July 1967 Fujimoto et al. reported data on 184 patients studied with a B-mode ultrasound "tomogram" utilizing a water bath. The authors reported that no internal echoes were generated by the thyroid in patients with no known thyroid dysfunction and nonpalpable thyroid glands*(O'Malley et al. 2002)*. Radioisotope scanning can be used to determine if a thyroid nodule is functioning, and used technetium (Tc^{99m}), I^{123}, and I^{131}, and though similar information is obtained with similar amounts of radiation exposure, radioiodine is preferred (Shibuyaet al .2003). About 80 to 85% of thyroid nodules are cold, and about 10% of these nodules represent a malignancy. Hot nodules account for 5% of all nodules, and the likelihood of malignancy is less than 1% for these nodules. Taken together, the sensitivity for the diagnosis of thyroid cancer is 89 to 93%, specificity is 5%, and the positive predictive value of malignancy is only 10%. Except for obviating the need to perform an FNAB on a hyperfunctioning nodule in a thyrotoxic patient, the use of radioisotope scanning has been nearly abandoned in the initial workup of a thyroid nodule*(Cases andSurks . 2003)*.

1-2 Justification of the Study:

This study was highlighted on the estimation of the thyroid benign nodules patients. Ultrasonic and Scintigraphy evaluation of the thyroid will help in detecting of these diseases. Also because sonography is a rapid and relatively inexpensive means of assessment with no radiation exposure.

And because of heinous of thyroid problems and its greatest damage in human society, in addition to:-

1- The value of incidence of thyroid diseases, like thyroid nodules and other thyroid’s problems is increase among Sudanese people.

2- Some types of diseases initially start silently without any symptoms or signs.

3- The mortality of thyroid diseases is increased among Sudanese population.

All the previous points motivate the researcher to cast round for the importance of detecting the thyroid nodules using ultrasound and Scintigraphy because aregive a reliable method and gold standard for indicating thyroid nodules.

1-3 Problem of the Study:

Recently in Sudan there is a noticeable increase of thyroid diseases, which is related to several factors. There is several investigation tools and method used to assess thyroidnodules they includes nuclear medicine and ultrasound. Nuclear medicine examination gives the most reliable results but it include administration of radioactive material to the patients, which has a potential risk of radiation as well as the availability of nuclear medicine center is another hinder factor for the practice.

Thereforeultrasound is considered as one of the most reliable optionforthyroid nodules diagnosis; therefore if nuclear medicine result integrated with Ultrasonography result in a way that nuclear medicine result can be predicted using Ultrasonography characteristic this will overcome problems associated with nuclear medicine test for thyroid.

1-4 The Study Objectives:

1-4-1 General Objective:

The general objective of this study is to estimate the Characterization of Thyroid Benign Nodules using Ultrasound and Scintigraphy in order to keep it as standards reference for diagnostic purposes and to relate the ultrasound results to thyroid Scintigraphy.

- **Specific Objective:**
- To assess the thyroid benign nodules using ultrasound and Scintigraphy.

  •To measure the size (width and length) of the thyroidand nodule using ultrasound

  •To find thyroid uptake and blood flow indices

  •To correlate between the thyroid texture, echogenicity and contour using ultrasound and Scintigraphy as well as between thyroid uptake and blood flow indices.

1-5 Overview of the Study: -

The following thesis will be laid out in five chapters:-

Chapter One: is an introduction theoretical framework, shows the definition and basic information about the thyroid gland, and the chapter presents the objectives of the study, statement of the problem and Justification of the Study.

Chapter Two: shows the human thyroid, and will highlight the literature review (anatomy and physiology, pathology, thyroid ultrasound and previous study).

Chapter Three: describe the methodology (material, method) used in this study.

Chapter Four: was included result of presentation of final finding of study and description of figures and will highlight the result of the study.

Chapter Five: included discussion, conclusion for future scope in addition to references and appendices.

And the last parts of this thesis consist of references and appendices.

CHAPTER TWO

Literature review & Previous StudieS

Chapter Two

Literature Review and Previous Studies

2-1-1 Introduction:

Thyroid gland: is gland that makes and stores hormones that help regulate the heart rate, blood pressure, body temperature, and the rate at which food is converted into energy. Thyroid hormones are essential for the function of every cell in the body. They help regulate growth and the rate of chemical reactions (metabolism) in the body. Thyroid hormones also help children grow and develop.

The two most important thyroid hormones are thyroxine (T4) and tri-iodothyronine (T3). Thyroid stimulating hormone (TSH), which is produced by the pituitary gland, acts to stimulate hormone production by the thyroid gland. The thyroid gland also makes the hormone calcitonin, which is involved in calcium metabolism and stimulating bone cells to add calcium to bone*(Boron et al. 2003)*.

2-1-2 Location and Description:

The thyroid gland is located in the lower part of the neck, below the Adam's apple, wrapped around the trachea (windpipe). It has the shape of butterfly and is composed of two cone-like lobes or wings, lobusdexter (right lobe) and lobus sinister (left lobe), connected via the isthmus. Each lobe is about 5 cm long, 3 cm wide and 2 cm thick. The organ is situated on the anterior side of the neck, lying against and around the larynx and trachea, reaching posteriorly the esophagus and carotid sheath. It starts cranially at the oblique line on the thyroid cartilage (just below the laryngeal prominence, or 'Adam's Apple'), and extends inferiorly to approximately the fifth or sixth tracheal ring. It is difficult to demarcate the gland's upper and lower border with vertebral levels because it moves position in relation to these during swallowing*(Lemaire and David 2005)*. There is occasionally (28%-55% of population, mean 44.3%) a third lobe present called the pyramidal lobe of the thyroid gland. It is of conical shape and extends from the upper part of the isthmus, up across the thyroid cartilage to the hyoid bone. The pyramidal lobe is a remnant of the fetal thyroid stalk, or thyroglossal duct. It is occasionally quite detached, or may be divided into two or more parts. The pyramidal lobe is also known as Lalouette'spyramid. *(Kim DW et al. 2013)*

2-1-3 Structure of the thyroid gland:

The thyroid gland is covered by a thin fibrous sheath, the capsula glandulaethyreoideae, composed of an internal and external layer. The external layer is anteriorly continuous with the pretracheal fascia and posterolaterally continuous with the carotid sheath. The gland is covered anteriorly with infrahyoid muscles and laterally with the sternocleidomastoid muscle also known as sternomastoid muscle. On the posterior side, the gland is fixed to the cricoid and tracheal cartilage and cricopharyngeus muscle by a thickening of the fascia to form the posterior suspensory ligament of thyroid gland also known as Berry's ligament. The thyroid gland’s firm attachment to the underlying trachea is the reason behind its movement with swallowing. In variable extent, the pyramidal lobe is present at the most anterior side of the lobe. In this region, the recurrent laryngeal nerve and the inferior thyroid artery pass next to or in the ligament and tubercle*(Fehrenbach and Herring 2012)*.

Between the two layers of the capsule and on the posterior side of the lobes, there are on each side two parathyroid glands .The thyroid isthmus is variable in presence and size, can change shape and size, and can encompass the pyramidal lobe (lobus or processuspyramidalis*(Fehrenbach and Herring 2012)*. The thyroid is one of the larger endocrine glands, weighing 2-3 grams in neonates and 18-60 grams in adults, and is increased in pregnancy*(Williams and Wilkins 2004)*.

In a healthy person the gland is not visible yet can be palpated as a soft mass. Examination of the thyroid gland includes the search for abnormal masses and the assessment of overall thyroid size*(Williams and Wilkins 2004)*.

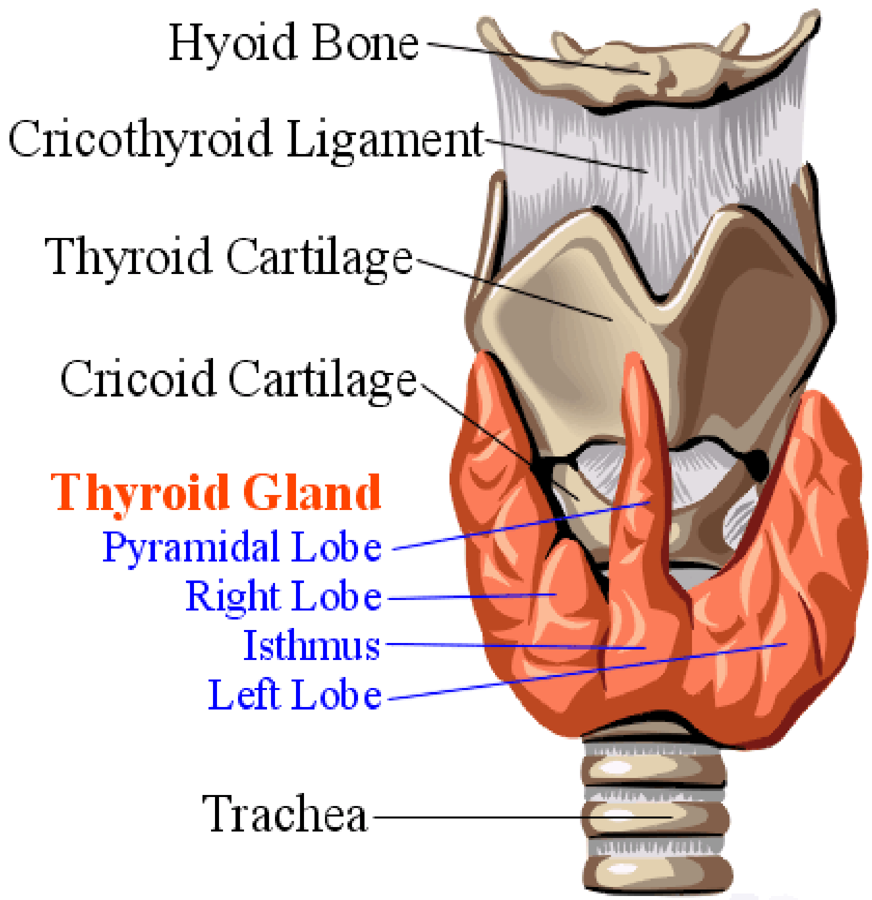


Figure (2-1): anatomy of thyroid gland

2-1-4Blood supply:

The thyroid is supplied with arterial blood from the superior thyroid artery, a branch of the external carotid artery, and the inferior thyroid artery, a branch of the thyrocervical trunk, and sometimes by the thyroid ima artery, branching directly from the subclavian artery. The venous blood is drained via superior thyroid veins, draining in the internal jugular vein, and via inferior thyroid veins, draining via the plexus thyreoideusimpar in the left brachiocephalic vein*(Fish et al. 2008)*.

2-1-5Lymph drainage:

Lymphatic drainage passes frequently the lateral deep cervical lymph nodes and the pre- and paratracheal lymph nodes. The gland is supplied by parasympathetic nerve input from the superior laryngeal nerve and the recurrent laryngeal nerve*(Fish et al. 2008)*.

2-1-6Nerve supply:

The nerve supply to the thyroid gland is derived from the superior, middle and inferior cervical sympathetic ganglia. These nerve fibers are vasomotor, causing

constriction of the blood vessels*(Yalçin and Ozan 2006)*.

2-1-7 Vagus nerve and the thyroid gland

The relationship of the thyroid gland and the two vagus nerve branches, the recurrent laryngeal nerve and the external branch of the superior laryngeal nerve, is of major surgical significance because damage to these nerves leads to disability in phonation or to difficulty breathing. The right recurrent laryngeal nerve arises from the vagus nerve, loops around the subclavian artery, and ascends behind the right lobe of the thyroid. It enters the larynx and innervates its intrinsic muscles, which produce the voice and close the laryngeal opening*(Yalçin and Ozan 2006)*.

2-1-8Development of the thyroid gland:

In the embryo, at 3–4 weeks of gestation, the thyroid gland appears as an epithelial proliferation in the floor of the pharynx at the base of the tongue between the tuberculumimpar and the copula linguae at a point later indicated by the foramen cecum. The thyroid then descends in front of the pharyngeal gut as a bilobed diverticulum through the thyroglossal duct. Over the next few weeks, it migrates to the base of the neck, passing anterior to the hyoid bone. During migration, the thyroid remains connected to the tongue by a narrow canal, the thyroglossal duct*(Zoeller 2003)*.

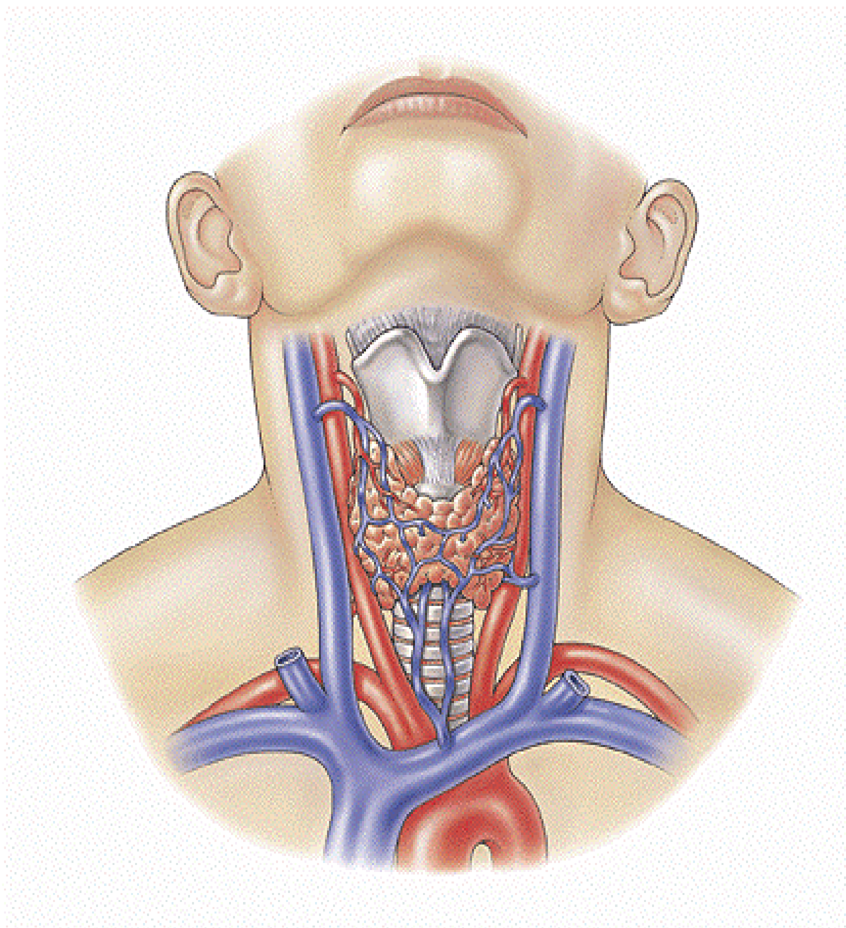


Figure (2-2):blood supply of thyroid gland

2-1-9 Histology:

At the microscopic level, there are three primary features of the thyroid Follicles, first discovered by Geoffary Websterson in 1664

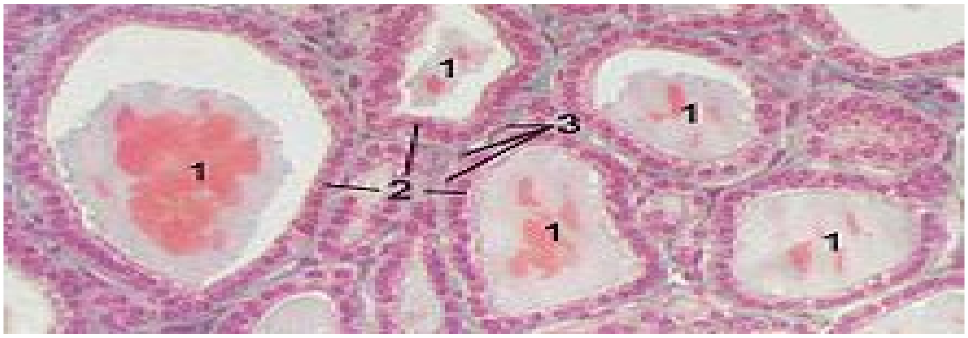


Figure (2-3): Section of a thyroid gland under the microscope. 1 follicles, 2 follicular cells, 3 endothelial cells

The thyroid is composed of spherical follicles that selectively absorb iodine (as iodide ions, I^-) from the blood for production of thyroid hormones, and also for storage of iodine in thyroglobulin. Twenty-five percent of the body's iodide ions are in the thyroid gland. Inside the follicles, in a region called the follicular lumen, colloid serves as a reservoir of materials for thyroid hormone production and, to a lesser extent, acts as a reservoir for the hormones themselves. Colloid is rich in a protein called thyroglobulin.Follicular cellsthe follicles are surrounded by a single layer of follicular cells, which secrete T_3 and T_4. When the gland is not secreting T_3 and T_4 (inactive), the epithelial cells range from low columnar to cuboidal cells. When active, the epithelial cells become tall columnar cells*(Fawcett et al. 2002)*

Parafollicular cellsScattered among follicular cells and in spaces between the spherical follicles are another type of thyroid cell, parafollicular cells (also called "C cells"), which secrete calcitonin*(Fawcett et al. 2002)*.

2-1-10 Physiology of the Thyroid gland:

The primary function of the thyroid is production of the hormones T_3, T_4 and calcitonin. Up to 80% of the T_4 is converted to T_3 by organs such as the liver, kidney and spleen. T_3 is several times more powerful than T_4, which is largely a prohormone, perhaps four or even ten times more active.*(Nussey and Whitehead 2001)*

2-1-11 Iodide sequestration:

Iodidet the ionized form of iodineis essential for proper thyroid function. Iodide is taken up by follicular cells through the sodium-iodide symporter (NIS) present on the basolateral membrane, which transports two sodium cations and one iodide ion into the cell. It works against the iodide concentration gradient and uses energy of sodium gradient (maintained by the sodium-potassium pump) and therefore acts by secondary active transport. Thus, NIS helps to maintain a 20- to 40-fold difference in iodide concentration across the membrane.This iodide is transported to the follicular space through the apical membrane of the follicular cell with the help of the iodide-chloride antiporterpendrin. This iodide is then oxidized to iodine and attached to thyroglobulin by the enzyme thyroid peroxidase to form the precursors of thyroid hormones*(Boron et al. 2012)*.

2-1-12 T_3 and T_4 production and action:

Synthesis of the thyroid hormones, as seen on an individual thyroid follicular cell (fig 2-3); Thyroglobulin is synthesized in the rough endoplasmic reticulum and follows the secretory pathway to enter the colloid in the lumen of the thyroid follicle by exocytosis. Meanwhile, a sodium-iodide (Na/I) symporter pumps iodide (I^-) actively into the cell, which previously has crossed the endothelium by largely unknown mechanisms.This iodide enters the follicular lumen from the cytoplasm by the transporter pendrin, in a purportedly passive manner. In the colloid, iodide (I^-) is oxidized to iodine (I^0) by an enzyme called thyroid peroxidase. Iodine (I^0) is very reactive and iodinates the thyroglobulin at tyrosyl residues in its protein chain (in total containing approximately 120 tyrosyl residues). In *conjugation*, adjacent tyrosyl residues are paired together. The entire complex re-enters the follicular cell by endocytosis. Proteolysis by various proteases liberates thyroxine and triiodothyronine molecules, which enters the blood by largely unknown mechanisms. (*Boron WF* et al.*2003)*

Thyroxine (T_4) is synthesised by the follicular cells from the tyrosine residues of the protein called thyroglobulin (Tg). It has 123 tyrosine residues, but only 4-6 are active. Iodine is captured with the "iodine trap" by the hydrogen peroxide generated by the enzyme thyroid peroxidase (TPO) and linked to the 3' and 5' sites of the benzene ring of the tyrosine residues on Tg sequentially on tyrosine residue forming monoiodotyrosine (MIT) and then diiodotyrosine (DIT) (iodination). Two DIT can couple (coupling) to form T_4 hormone attached to thyroglobulin releasing one alanine. Upon stimulation by the thyroid-stimulating hormone (TSH), the follicular cells reabsorb Tg and cleave the iodinated tyrosines from Tg in lysosomes, forming free T_4, DIT, MIT, T_3 and traces of RT_3 (in T_3 and RT_3 has three iodine atom while T_4 has four), and releasing T_3 and T_4 into the blood. Deiodinase releases the sequestred iodine from MIT and DIT. Deiodinase enzymes convert T_4 to T_3 and $RT_{3,}$which is a major source of both RT_3 (95%) and T_3 (87%) in peripheral tissues Thyroid hormone secreted from the gland is about 80-90% T_4 and about 10-20% T_3*(Stephen el al. 2001)*.

Cells of the developing brain are a major target for the thyroid hormones T_3 and T_4. Thyroid hormones play a particularly crucial role in brain maturation during fetal development. A transport protein that seems to be important for T_4 transport across the blood–brain barrier (OATP1C1) has been identified. A second transport protein (MCT8) is important for T_3 transport across brain cell membranes *(Jansen et al 2005)*.

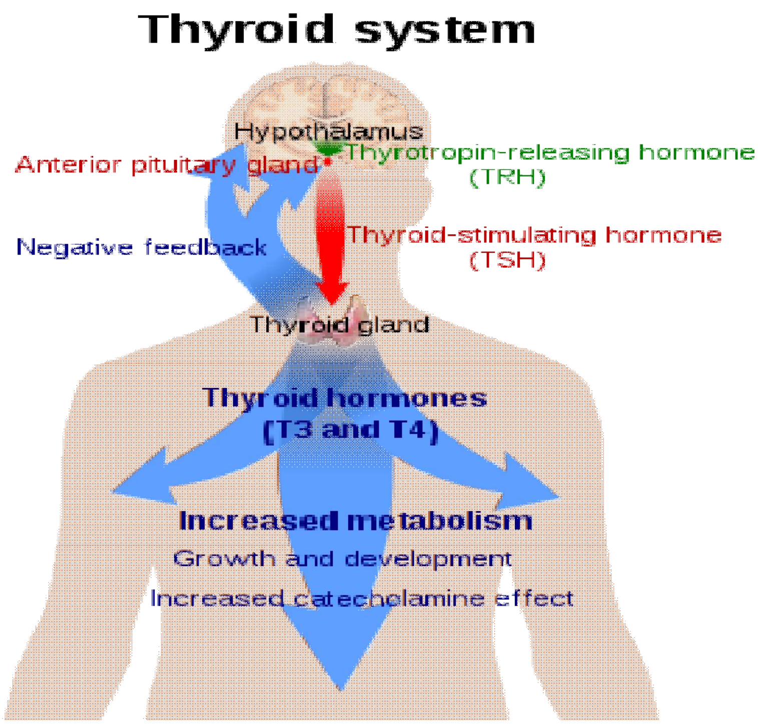
Non-genomic actions of T_4 are those that are not initiated by liganding of the hormone to intranuclear thyroid receptor. These may begin at the plasma membrane or within cytoplasm. Plasma membrane-initiated actions begin at a receptor on the integrin alphaV beta3 that activates ERK1/2. This binding culminates in local membrane actions on ion transport systems such as the Na^+/H^+ exchanger or complex cellular events including cell proliferation. These integrins are concentrated on cells of the vasculature and on some types of tumor cells, which in part explains the proangiogenic effects of iodothyronines and proliferative actions of thyroid hormone on some cancers including gliomas. T_4 also acts on the mitochondrial genome via imported isoforms of nuclear thyroid receptors to affect several mitochondrial transcription factors. Regulation of actin polymerization by T_4 is critical to cell migration in neurons and glial cells and is important to brain development. T_3 can activate phosphatidylinositol 3-kinase by a mechanism that may be cytoplasmic in origin or may begin at integrin alpha V beta3. In the blood, T_4 and T_3 are partially bound to thyroxine-binding globulin (TBG), transthyretin, and albumin. Only a very small fraction of the circulating hormone is free (unbound) - T_4 0.03% and T_3 0.3%. Only the free fraction has hormonal activity. As with the steroid hormones and retinoic acid, thyroid hormones cross the cell membrane and bind to intracellular receptors (α_1, α_2, β_1 and β_2), which act alone, in pairs or together with the retinoid X-receptor as transcription factors to modulate DNA transcription *(Bowen, R. (2000).*

2-1-13 T_3 and T_4 regulation:

The production of thyroxine and triiodothyronine is primarily regulated by thyroid-stimulating hormone (TSH), released by the anterior pituitary. The thyroid,and thyrotropes in the anterior pituitary, form a negative feedback loop: TSH production is suppressed when the free T_4 levels are high. The negative feedback occurs on both the hypothalamus and the pituitary, but it is of particular importance at the level of the pituitary The TSH production itself is modulated by thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus. This is secreted at an increased rate in situations such as cold exposure (to stimulate thermogenesis) which is prominent in case of infants. TSH production is blunted by dopamine and somatostatin which act as local regulators at the level of the pituitary, in response to rising levels of glucocorticoids and sex hormones (estrogen and testosterone), and excessively high blood iodide concentration.An additional hormone produced by the thyroid contributes to the regulation of blood calcium levels. Parafollicular cells produce calcitonin in response to hypercalcemia. Calcitonin stimulates movement of calcium into bone, in opposition to the effects of parathyroid hormone (PTH). However, calcitonin seems far less essential than PTH, as calcium metabolism remains clinically normal after removal of the thyroid (thyroidectomy), but not the parathyroids*(Biancoet al. 2002)*.

2-1-14 Physiological action of T_3 and T_4:

T_3 of particular physiological importance produced mainly in tissue after deiodination. It has calorigenic, cardiovascular, neural and other metabolic actions.It increases oxygen consumption of all tissues except brain, uterus, testis (though it is important for normal fertility) lymph node, spleen, and its source, anterior pituitary, mainly by its action on sodium potassium pump and fat metabolism.It is helps in conversion of carotene into vitamin A in hepatic cells, therefore, hypothyroidism may lead to high levels of carotene in the blood, resulting in yellowish tint of only skin (and not the mucous membrane, like sclera).It increases growth and results in positive nitrogen usage. (Protein anabolism).But high levels result in protein catabolism. Produced potassium due to catabolism appears in urine.Decreased level of thyroid hormone result in retention of hyaluronic acid and chondroitin sulfuric acid in the skin, which results in water retention (due to polyolic nature and myxedema).It also has significance in proper mentation. Increased levels results in irritability. Decreased levels results in poor mentation and increased protein level in CSF. It has significance in proper development of cochlea, and hypothyroidism may lead to low IQ and deaf mutism.Many cardiovascular effects are reported. Increased peripheral resistance, increased rate and force of heart beat occur by effects of circulatory T_3 .It increases carbohydrate absorption.It is also reported to decrease cholesterol levels*(Biancoet al. 2002)*.



Figure(2-4): The system of the thyroid hormonesT_3 and T_4

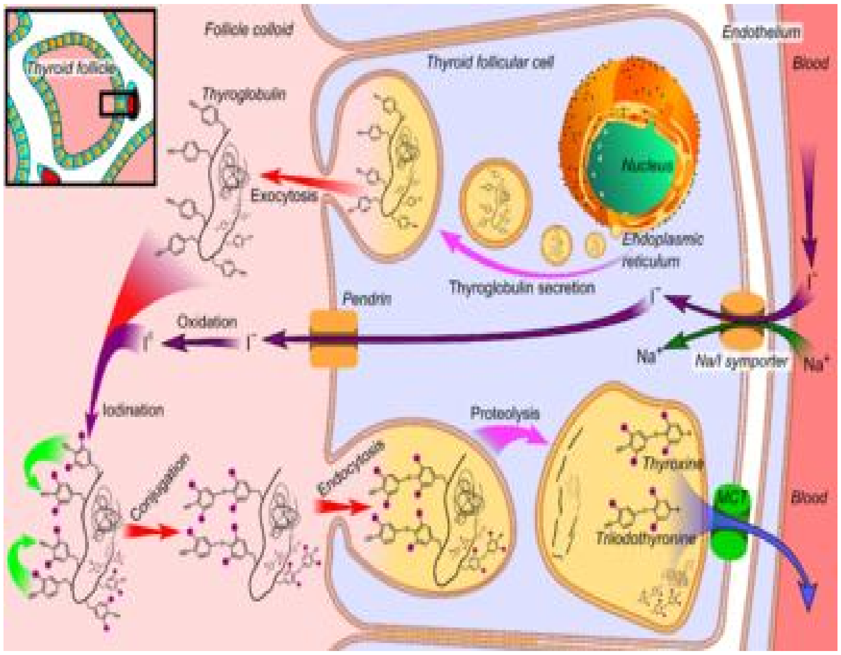


Figure (2-5): Synthesis of the thyroid hormones

2-1-15Pathology of thyroid gland:

2-1-16 Hyperthyroidism:

Hyperthyroidism, or overactive thyroid, is defined as an overproduction of the thyroid hormones T_3 and T_4. This condition is most commonly caused by the development of Graves' disease, an autoimmune disease in which anomalous antibodies stimulate the thyroid to secrete excessive quantities of thyroid hormones. The disease can progress to the formation of a toxic goiter as a result of thyroid growth in response to a lack of negative feedback mechanisms. It presents with symptoms such as a thyroid goiter, protruding eyes (exopthalmos), palpitations, excess sweating, diarrhea, weight loss, muscle weakness and unusual sensitivity to heat. The appetite is often increased.Beta blockers are used to decrease symptoms of hyperthyroidism such as increased heart rate, tremors, anxiety and heart palpitations, and anti-thyroid drugs are used to decrease the production of thyroid hormones, in particular, in the case of Graves' disease. These medications take several months to take full effect and have side-effects such as skin rash or a drop in white blood cell count, which decreases the ability of the body to fight off infections. These drugs involve frequent dosing (often one pill every 8 hours) and often require frequent doctor visits and blood tests to monitor the treatment, and may sometimes lose effectiveness over time. Due to the side-effects and inconvenience of such drug regimens, some patients choose to undergo radioactive iodine-131 treatment. Radioactive iodine is administered in order to destroy a portion of or the entire thyroid gland, since the radioactive iodine is selectively taken up by the gland and gradually destroys the cells of the gland. Alternatively, the gland may be partially or entirely removed surgically, though iodine treatment is usually preferred since the surgery is invasive and carries a risk of damage to the parathyroid glands or the nerves controlling the vocal cords. If the entire thyroid gland is removed, hypothyroidism results *(Semin Nucl et al. 1995)*

2-1-17 Hypothyroidism:

Hypothyroidism is the underproduction of the thyroid hormones T_3 and T_4.Hypothyroid disorders may occur as a result of

- Congenital thyroid abnormalities (Thyroid deficiency at birth. See congenital hypothyroidism),
- autoimmune disorders such as Hashimoto's thyroiditis,
- iodine deficiency (more likely in poorer countries) or
- the removal of the thyroid following surgery to treat severe hyperthyroidism and/or thyroid cancertypical symptoms are abnormal weight gain, tiredness, baldness, cold intolerance, and bradycardia. Hypothyroidism is treated with hormone replacement therapy, such as levothyroxine, which is typically required for the rest of the patient's life. Thyroid hormone treatment is given under the care of a physician and may take a few weeks to become effective.Negative feedback mechanisms result in growth of the thyroid gland when thyroid hormones are being produced in sufficiently low quantities, as a means of increasing the thyroid output; however, where hypothyroidism is caused by iodine insufficiency, the thyroid is unable to produce T_3 and T_4 and as a result, the thyroid may continue to grow to form a non-toxic goiter. It is termed non-toxic as it does not produce toxic quantities of thyroid hormones, despite its size*(Kim JH, et al. 2003)*.

2-1-18 Thyroiditis:

There are two types of thyroiditis where initially hyperthyroidism presents which is followed by a period of hypothyroidism; (the overproduction of T_3 and T_4 followed by the underproduction of T_3 and T_4). These are Hashimoto's thyroiditis and postpartum thyroiditis.Hashimoto's thyroiditis or Hashimoto's Disease is an autoimmune disorder whereby the body's own immune system reacts with the thyroid tissues in an attempt to destroy it. At the beginning, the gland may be overactive, and then becomes underactive as the gland is damaged resulting in too little thyroid hormone production or hypothyroidism. Some patients may experience "swings" in hormone levels that can progress rapidly from hyper-to-hypothyroid (sometimes mistaken as severe mood swings, or even being bipolar, before the proper clinical diagnosis is made). Some patients may experience these "swings" over a longer period of time, over days or weeks or even months. Hashimoto's is more common in females than males, usually appearing after the age of 30, and tends to run in families, meaning it can be seen as a genetic disease. Also more common in individuals with Hashimoto's thyroiditis are type 1 diabetes and celiac disease.[31]Postpartum thyroiditis occurs in some females following the birth of a child. After delivery, the gland becomes inflamed and the condition initially presents with overactivity of the gland followed by underactivity. In some cases, the gland may recover with time and resume its functions. In others it may not. The etiology is not always known, but can sometimes be attributed to autoimmunity, such as Hashimoto's thyroiditis or Graves' disease.There are other disorders that cause inflammation of the thyroid, and these include subacute thyroiditis, acute thyroiditis, silent thyroiditis and Riedel's thyroiditis*("Thyroiditis." www.thyroid.org American Thyroid Association- 2005)*.

2-1-19 Cancers: In most cases, thyroid cancer presents as a painless mass in the neck. It is very unusual for thyroid cancers to present with symptoms, unless they have been neglected. One may be able to feel a hard nodule in the neck. Diagnosis is made using a needle biopsy and various radiological studies *(Danese et al. 1998)*.

2-1-20 Non-cancerous nodules(Thyroid nodule) : Many individuals may find the presence of thyroid nodules on the gland. The majority of these thyroid nodules are benign (non cancerous), and their presence does not necessarily indicate disease. Most thyroid nodules do not cause any symptoms, and most are discovered on an incidental examination. Often there can be many nodules, which is termed a multinodular goiter. Doctors usually perform a needle aspiration biopsy of the thyroid to determine the status of the nodules. If the nodule is found to be non-cancerous, no other treatment is required. If the nodule is suspicious then surgery is recommended*(Danese et al. 1998)*.

2-1-21 Congenital disorders: Apersistent thyroglossal duct is the most common clinically significant congenital disorder of the thyroid gland. A persistent sinus tract may remain as a vestigial remnant of the tubular development of the thyroid gland. Parts of this tube may be obliterated, leaving small segments to form thyroglossal cysts. These occur at any age and might not become evident until adult life. Mucinous, clear secretions may collect within these cysts to form either spherical masses or fusiform swellings, rarely larger than 2 to 3 cm in diameter. These are present in the midline of the neck anterior to the trachea. Segments of the duct and cysts that occur high in the neck are lined by stratified squamous epithelium, which is essentially identical to that covering the posterior portion of the tongue in the region of the foramen cecum. The disorders that occur in the lower neck more proximal to the thyroid gland are lined by epithelium resembling the thyroidal acinar epithelium.

Characteristically, next to the lining epithelium, there is an intense lymphocytic infiltrate. Superimposed infection may convert these lesions into abscess cavities, and rarely, give rise to cancersanother disorder is that of thyroid dysgenesis which can result in various presentations of one or more ectopicaccessory *thyroid glands*. These can be asymptomatic*(Merck and Dohme 2010)*.

2-1-22 other disorders

- Limited research shows that seasonal allergies may trigger episodes of hypo- or hyperthyroidism.
- Some rapid-cycling versions of bipolar disorder seem to have a complex relationship with thyroid dysfunction; however the specifics of the relationship are poorly understood*(Hidaka et al 1993)*.

2-1-23 Significance of iodine and endemic goiter: In areas of the world where iodine is lacking in the diet, the thyroid gland can become considerably enlarged, a condition called endemic goiter. Pregnant women on a diet that is severely deficient of iodine can give birth to infants with thyroid hormone deficiency (congenital hypothyroidism), manifesting in problems of physical growth and development as well as brain development (acondition referred to as endemic cretinism). In many developed countries, newborns are routinely tested for congenital hypothyroidism as part of newborn screening. Children with congenital hypothyroidism are treated supplementary with levothyroxine, which facilitates normal growth and development*(Venturi and Sebastiano 2011)*.Thyroxine is critical to the regulation of metabolism and growth throughout the animal kingdom. Among amphibians, for example, administering a thyroid-blocking agent such as propylthiouracil (PTU) can prevent tadpoles from metamorphosing into frogs; in contrast, administering thyroxine will trigger metamorphosis. In amphibian metamorphosis, thyroxine and iodine also exert a well-studied experimental model of apoptosis on the cells of gills, tail, and fins of tadpoles. Iodine, via iodolipids, has favored the evolution of terrestrial animal species and has likely played a crucial role in the evolution of the human brain. Iodine (and T4) trigger the amphibian metamorphosis that transforms the vegetarian aquatic tadpole into a carnivorous terrestrial adult frog, with better neurological, visuospatial, olfactory and cognitive abilities for hunting, as seen in other predatory animals. A similar phenomenon happens in the neotenic amphibian salamanders, which, without introducing iodine, don't transform into terrestrial adults, and live and reproduce in the larval form of aquatic axolotl. Because the thyroid concentrates iodine, it also concentrates the various radioactive isotopes of iodine produced by nuclear fission. In the event of large accidental releases of such material into the environment, the uptake of radioactive iodine isotopes by the thyroid can, in theory, be blocked by saturating the uptake mechanism with a large surplus of non-radioactive iodine, taken in the form of potassium iodide tablets. One consequence of the Chernobyl disaster was an increase in thyroid cancers in children in the years following the accident*(Venturi and Sebastiano 2014)*.The use of iodised salt is an efficient way to add iodine to the diet. It has eliminated endemic cretinism in most developed countries, and some governments have made the iodination of flour, cooking oil, and salt mandatory. Potassium iodide and sodium iodide are typically used forms of supplemental iodine.As with most substances, either too much or too little can cause problems. Recent studies on some populations are showing that excess iodine intake could cause an increased prevalence of autoimmune thyroid disease, resulting in permanent hypothyroidism*(Patrick L 2008)*.

2-1-24 Previous Studies:

In the department of Radiology, University of North Carolina at Chapel Hill, Julia, et al. (2005) carried out a work; to determine the sonographic findings of nodule hyperplasia of the thyroid, to compare these with reported findings associated with malignancy and to assess inter observer reliability. Seventy thyroid nodules were scanned, and then the biopsies of the nodules were performed under sonographic guidance with fine needle cytologic analysis; in all cases images were reviewed by 2 experienced radiologists without knowledge of clinical outcome. Findings reported associated with malignancy were specifically assessed. Interobserver agreement between the expert and secondary readers for each finding was calculated by the µ or weighted µ statistic and 2 nodules in a population of 63 male and 7 female in the patients. The mean benign nodule size was; 2.9 cm 60% were solid; 45% hypoechoic; 59% were microlobulated or macrolobulated; 47% had central vascularity; 24% and 82% were elliptical in shape and good agreement for the presence and location of vascularity (µ = 0.75) and the amount of cystic components (µ= 0.62; all $P< 0.01$). The study found that the sixty nine percent of benign nodules had at least 1 finding reported previously as associated with malignancy. TheInterobserver reliability of the sonographic findings was good to very good for 3 of the 5 finding assessed.Liebeskind et al.(2005) studied patients with thyroid disorders for surgery is a difficult task. The traditional approaches of radionuclide and ultrasonography have been shown to be good specific in diagnosis of thyroid benign nodules or thyroid malignancy. To compare the useful nesses of thyroid disorders Scintigraphy, thyroid ultrasonography differential diagnosis of thyroid, when reviewed the records of 183 patients who underwent thyroidectomy for thyroid nodules. Thyroid carcinoma was diagnosed in 36 patients (19.7 %). In this retrospective study, the incidence of thyroid carcinoma with cold nodules on thyroid Scintigraphy was 16 % which was similar to the incidence of thyroid carcinoma with hyperfunctioning nodules (22.2%). Sonographic characteristics were analyzed in 60 patients including 54 benign and 5 malignant nodules. Six items were examined; presence of halo and irregular margin. But the difference in benign and malignant nodules was not significant *(Liebeskind et al. 2005).*

The false negative rate was 9.8% (4l/41), false positive rate was 14.4% (1/7), sensitivity to detect malignancy was 60%, specificity to exclude malignancy was 97.4%, and diagnosis accuracy to diagnose malignancy was 89.6%, We found that fine needle aspiration biopsy was useful to differential diagnosis of thyroid nodules, while thyroid Scintigraphy and thyroid ultrasonography were not.

Hyperthyroidism in people over 50 years of age in Senegal, study of 31 cases observed a 14 years period Ersoy, et al. (1998), the study through common in elderly, with poor and masked symptomatology, benign nodules has never been studied in people older than 50 years of age in African countries. The study was done for 300 cases of hyperthyroidism it analyzed the frequency of Scintigraphy characteristics, etiology and etiologic factors, and treatment. The results found that the frequency of benign nodules in this population was 10%. Housewives were more numerous, with 20 cases observed in the 31 patients. The main group (13/13)was of rural origin*(Jeffery et al. 1998).*

Signs that predominantly led to consultation were weight loss (23/31), cervical tumor (17/31), and palpitations (12/31). Three major organs were associated with the thyrotoxic syndrome: weight loss (29 cases), tachycardia (27/31), and the existence of tremors in the extremities (22/31). Hormone assays showed that thyroxin (T4) was about 265 +/- 74 nmol/L and triiodothyronine (T3) about 6 +/- 2 nmol/L, at immunoradiometric assay; thyroid-stimulating hormone (TSH) was about 0.17 +/- 0.23 muIU/ ml. Eye protrusion predominated in the nonthyrotoxic syndrome, with 25 cases in the 31 patients. Etiologic forms of the disease were composed of 25 Grave's disease, with 22 typical cases. Etiologic factors were various, however without any case of neoplasia. Cardiac complications included two cases of atrial fibrillation. No iatrogenic form of the disease was observed. Mean initial carbimazole dosage was about 34 +/- 8 mg/d. of the 23 patients, 15 had a favorable outcome*(Jeffery et al. 1998)*

In this series, the high number of housewives and the patient's rural origin were less characteristic of hyperthyroidism than the Greave's disease etiology. This might be due to the young age of this African population.

In Sudan Dr. Mohamed M. Omer Yousef (2010),carried out a work; todiagnosis evaluation of ultrasound, nuclear medicine and biopsy findings of goiter in Sudanese patients, a thesis submitted in fulfillment of the requirement of doctor of philosophy (PhD) degree in nuclear medicine by the current study aimed to evaluate the thyroid volume and its related hormones using ultrasound and radio-immuno Assay (RIA) in health Sudanese adults, evaluate the incidence of thyroid goiter Sudanese patients in Khartoum to assess the value of Scintigraphy, ultrasound, and biopsy in the detection of nodules quantify and to evaluate both patient and staff doses by direct thermoluminescent dosimetry (TLD) during thyroid scan procedure.

CHAPTER THREE

Material & Methods

Chapter Three
Material and Methods

3-1 Material:

- All thyroid U/S scans were performed by the same operator, who used high resolution unit with 7.5 MHz broadband linear probe
- U/S system (Philips HDI 4000) Gel (KONIX –turkuaz)
- Probe (linear C5-2-40R),7.5 MHz
- Gamma Camera (mediso SPECT nucline).
- Hungarian Gamma Camera.
- Siemens Gamma Camera.
- Collimators
- Hot Lab tools.
- Syringe 20 ml.
- Syringe shield.
- Radionuclide $Tc99^m$.
- Radiopharmaceutical.
- Dose calibrator
- Equipments used:

  -SPECT mediso, single positron emission computed tomography.

  -Single Head Gamma Camera, mediso.

  -Ultrasound MachineToshibaand Alpinion E-CUBE 7

2-3 Methods:

3-2-1 Study design:

Analytical study; where the data will be collected prospectively.

3-2-2 Population of study:

The study carried out in adult’s patients attending the Department of Nuclear Medicine department of RICK, Nilein Medical Diagnostic Center, Academy Charity Teaching Hospitaland Bashair Teaching Hospital suffering from thyroid benign nodules, from both gender. This study will be conducted in the period from May 2016 to December 2016

3-2-3 Criteria of the study:

.Inclusion criteria:

The study was including all patients with benign thyroid nodules.

.Exclusion criteria:

-Any patient with suspected thyroid malignant nodules will be excluded from this study, as well as those of physiological goiter.

-Nodules size that is less than 1cm in diameter because it is not demonstrated or detected by gamma camera

3-2-4 Sample size and type:

This study will be consisted of 50 patients using convenient sample method.

3-2-5 Method of collection:

All thyroid patients recruited for scan selected for this study andthe data were collect on master data sheet from the diagnostic stations which was include all parameters need for evaluations.

3-2-6 Variables of the study:

This study will be collected using the following variables: patient’s age, sex, weight, height, body mass index, gamma camera results (thyroid uptake, nodule site, distribution of radiotracer and outline), and ultrasound results (size of thyroid and nodule, texture, echogenicity, outline, blood flow indices)

3-2-7 Data Analysis:

All collected data from the reports of ultrasound & nuclear medicine images put in sheets and then analyzed by statistics programmer which use for entry and analysis, and the computer provide details information.

.Statistical analysis:

All data were presented as mean±SD values. Data were analyzed by correlation analysis with the use of the SPSS (Inc., Chicago, Illinois version 21.0). A value of $P<0.05$ was considered significant.

3-2-8 Ethical Issue:

- Permission of nuclear medicine department has been granted.
- No patient data will be published.
- Permission of ultrasound department has been granted.
- Permission of statistic department has been granted.

CHAPTER FOUR

THE RESULTS

Chapter Four
The Results

This chapter highlights the results of characterization of thyroid benign nodules using ultrasound and thyroid scan, and the following tables and figures demonstrate the result of data which collected from the patientsand statically relationship between the study variable.

Table (4 -1): Shows the frequency distribution of thyroid nodule according to the gender.

Gender	Frequency
Male	7
Female	43
Total	50

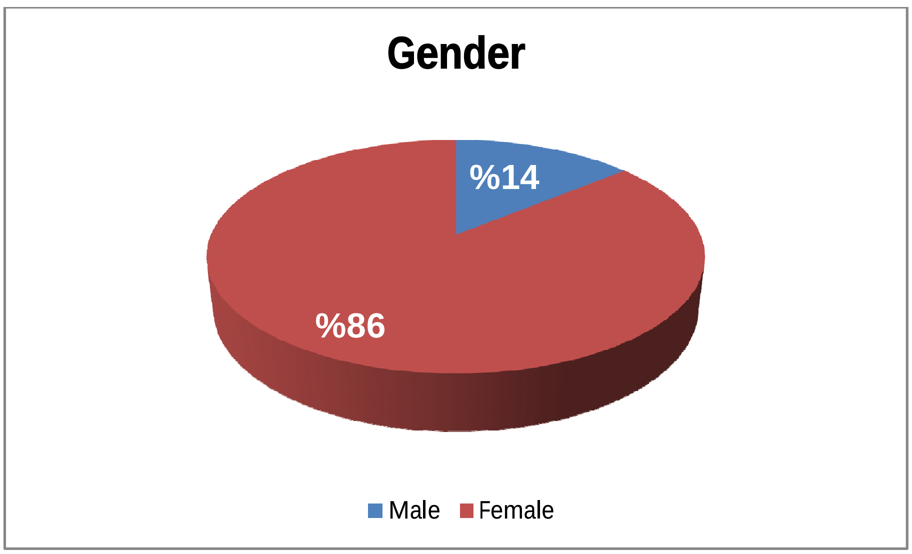


Figure (4 -1): Shows the percentage distribution of thyroid nodule according to the gender.

Table (4-2): Shows the frequency distribution of thyroid nodule with Marital Status:

Marital Status	Frequency
Married	38
Single	12
Total	50

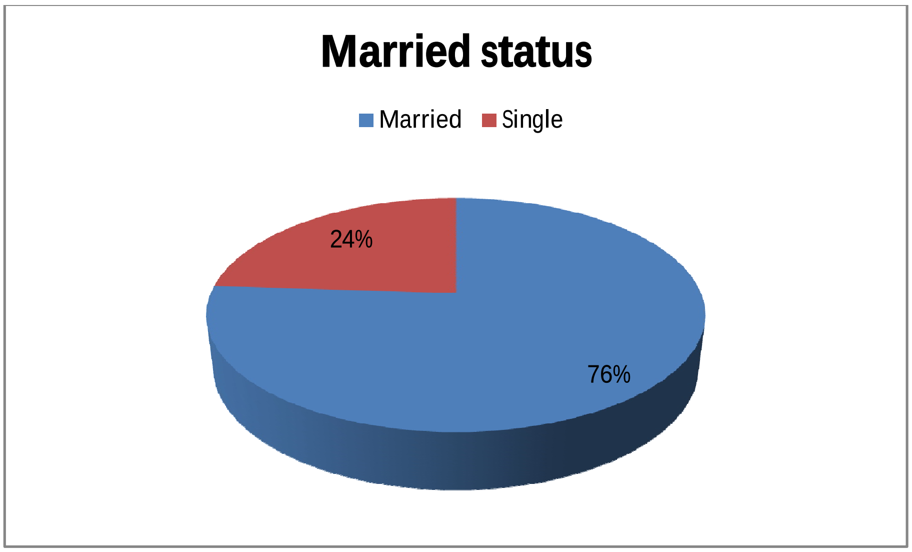


Figure (4-2): Shows the frequency distribution of with Marital Status:

Table (4-3): Show the frequency distribution of thyroid nodule according to nodule site:

Nodule Site	Frequency
Lt lobe	14
Rt lobe	5
Bilateral	31
Total	50

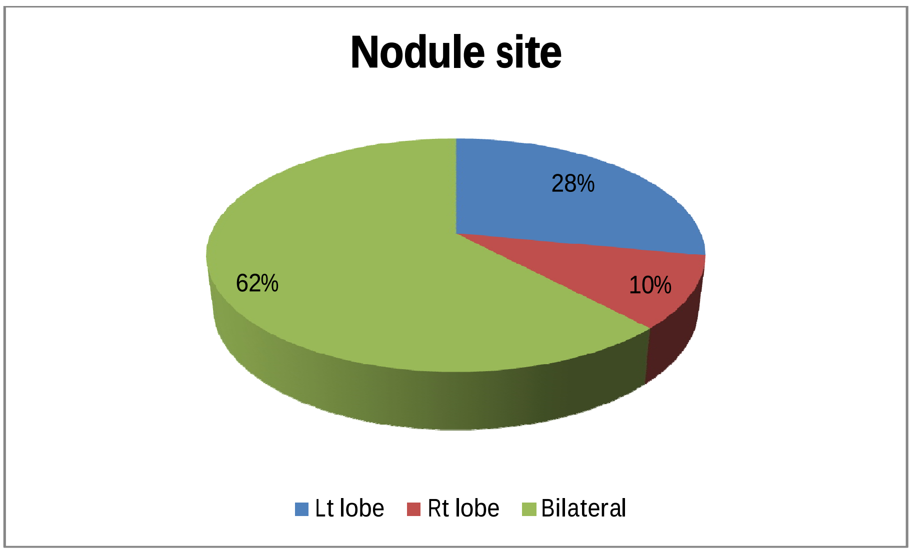


Figure (4-3): Show the frequency distribution of thyroid nodule according to nodule site:

Table (4-4): Show the frequency distribution of thyroid uptake in Nuclear Medicine Imaging:

Thyroid uptake	Frequency
Normal	5
High	37
Low	8
Total	50

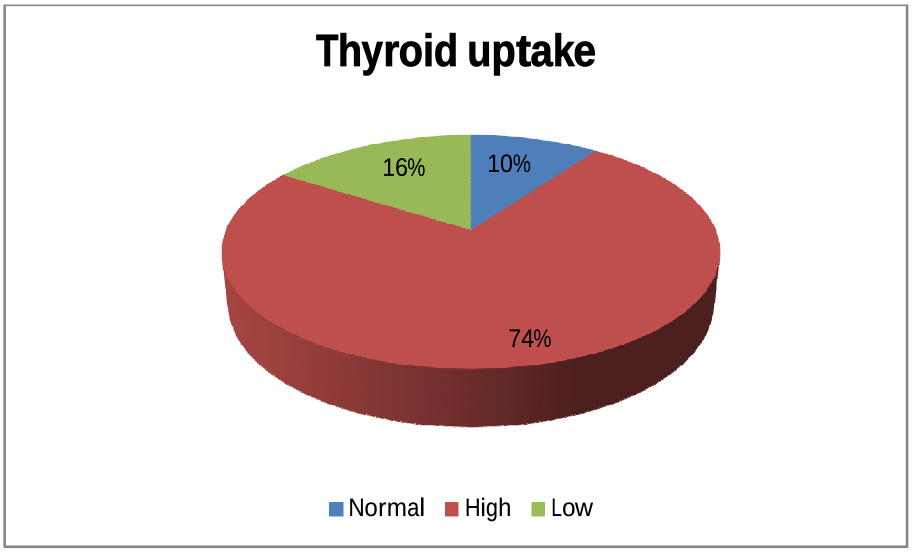


Figure (4-4): Show the frequency distribution of thyroid uptake in Nuclear Medicine Imaging:

Table (4-5): Shows the frequency distribution of Radiotracer(Tc-^{99m}) of thyroid gland in Nuclear Medicine Imaging:

Distribution of Radiotracer	Frequency
Hemogenous	31
Inhomogeneous	19
Total	50

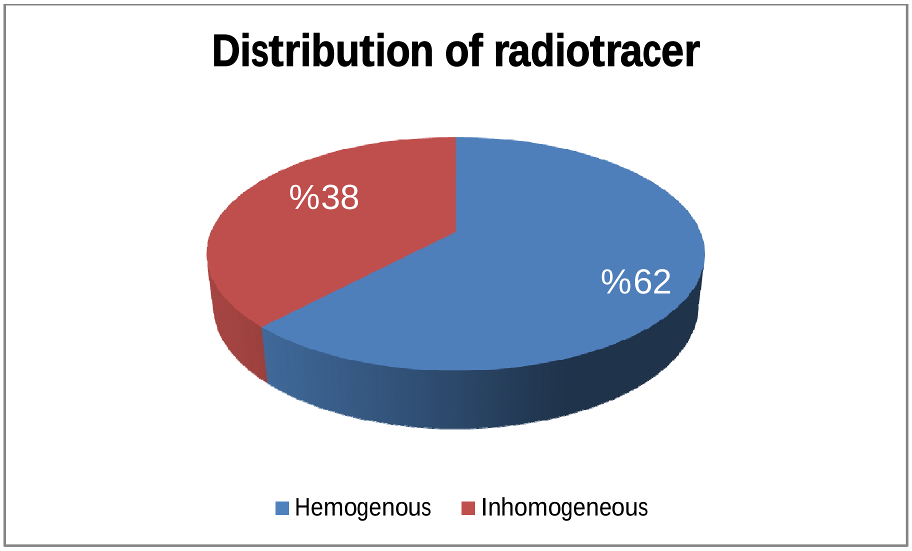


Figure (4-5): Shows the frequency distribution of Radiotracer(Tc-^{99m}) of thyroid gland in Nuclear Medicine Imaging:

Table (4-6): Shows the frequency distribution of thyroid gland outline in Nuclear Medicine Imaging:

Outline	Frequency
Regular	30
Irregular	20
Total	50

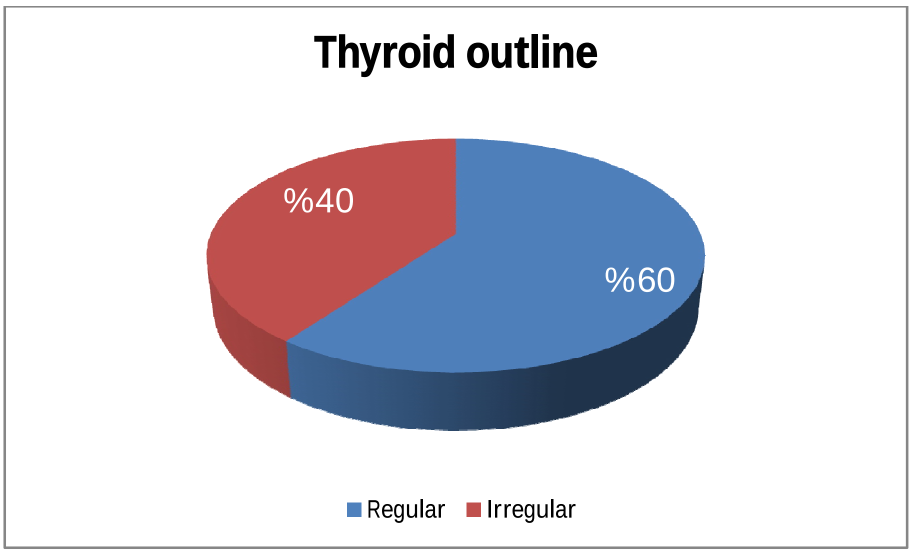


Figure (4-6): Shows the frequency distribution of thyroid gland outline in Nuclear Medicine Imaging:

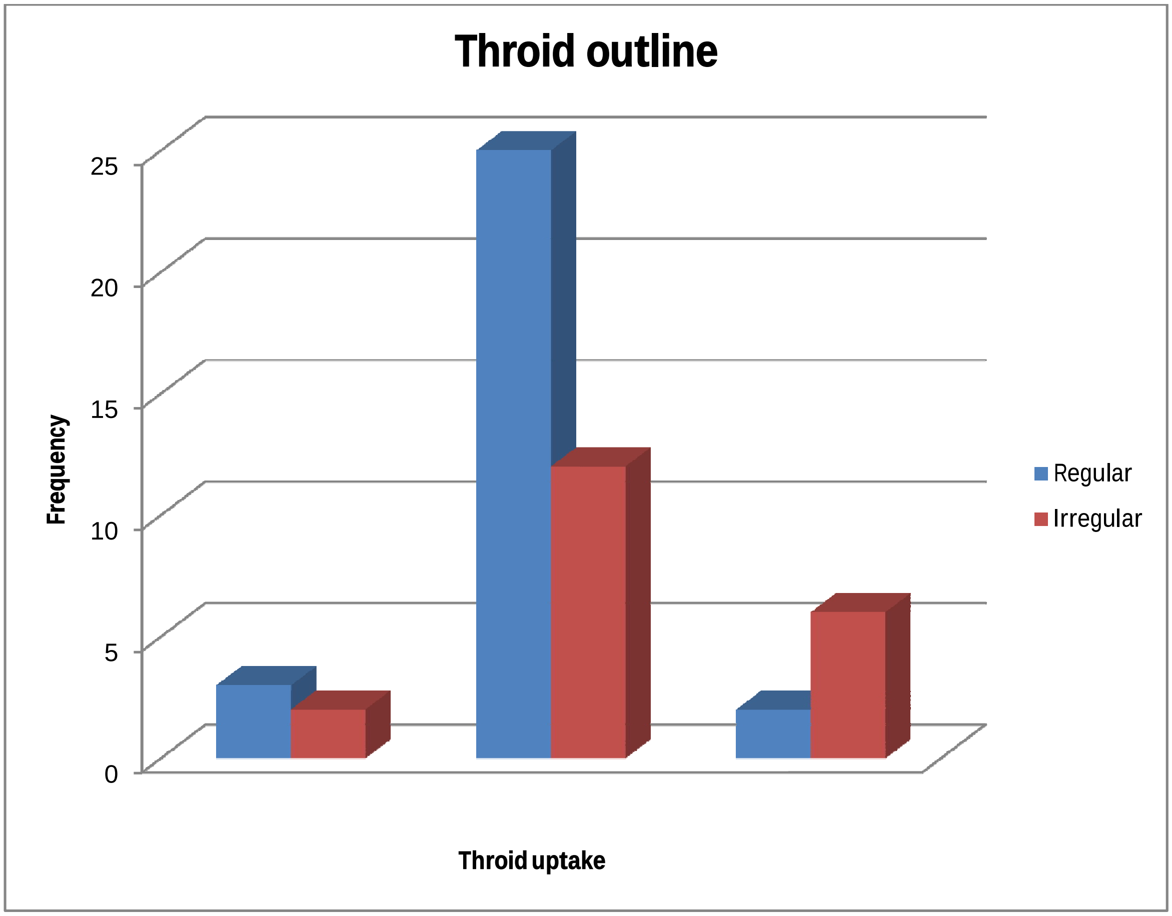


Figure (4-7): Shows the relationship between thyroid gland uptake and thyroid outline in Nuclear Medicine Imaging:

Table (4-7): Show the frequency distribution of thyroid nodule according to the texture in ultrasound Imaging:

Texture	Frequency
Hetrogneous	30
Homogeneous	20
Total	50

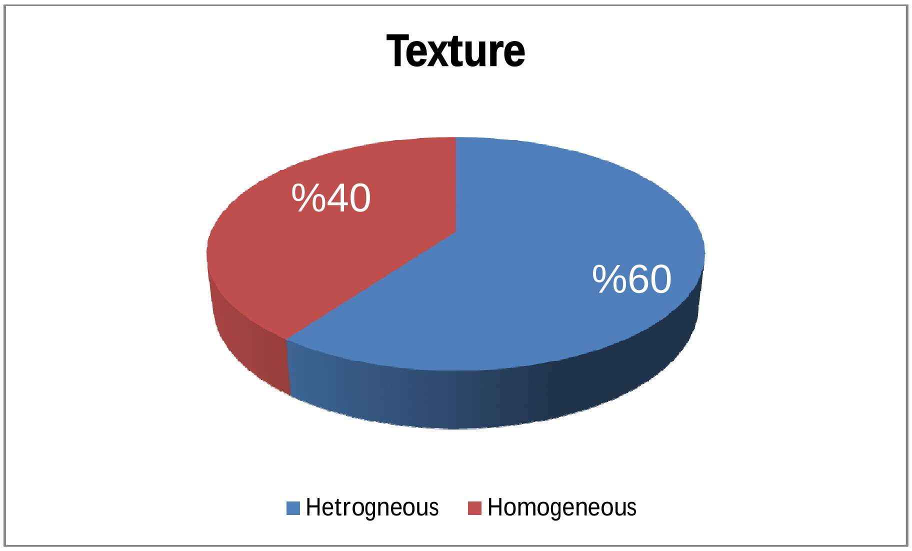


Figure (4-8): Show the frequency distribution of thyroid nodule according to the texture in ultrasound Imaging:

Table (4-8): Shows the frequency distribution of thyroid nodule according to theEchogenicity in ultrasound Imaging:

Echogenicity	Frequency
Hypoechoic	10
Hyperecohic	6
Isoechoic	34
Total	50

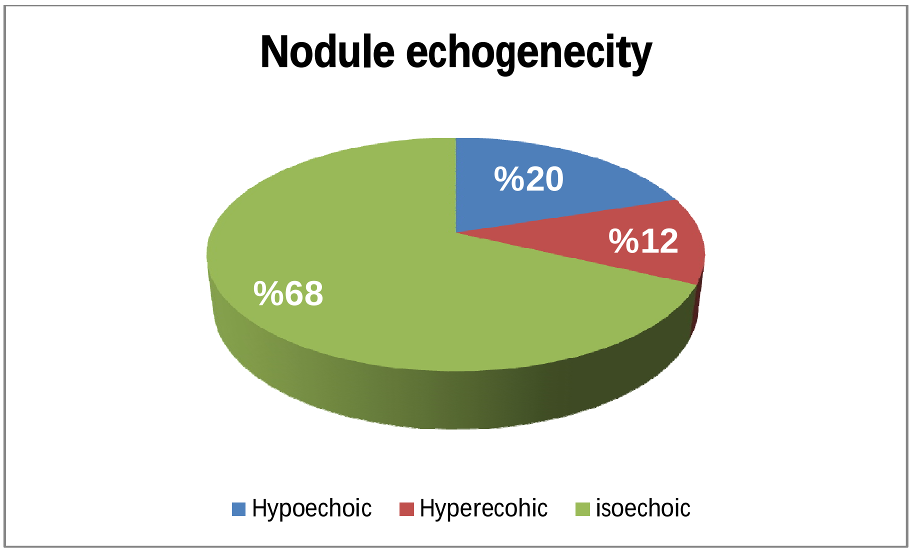


Figure (4-9): Shows the frequency distribution of thyroid nodule according to theechogenicity in ultrasound Imaging:

Table (4-9): Shows the frequency distribution of thyroid nodule according to theoutline in ultrasound Imaging:

Outline	Frequency
Well define	45
ill define	5
Total	50

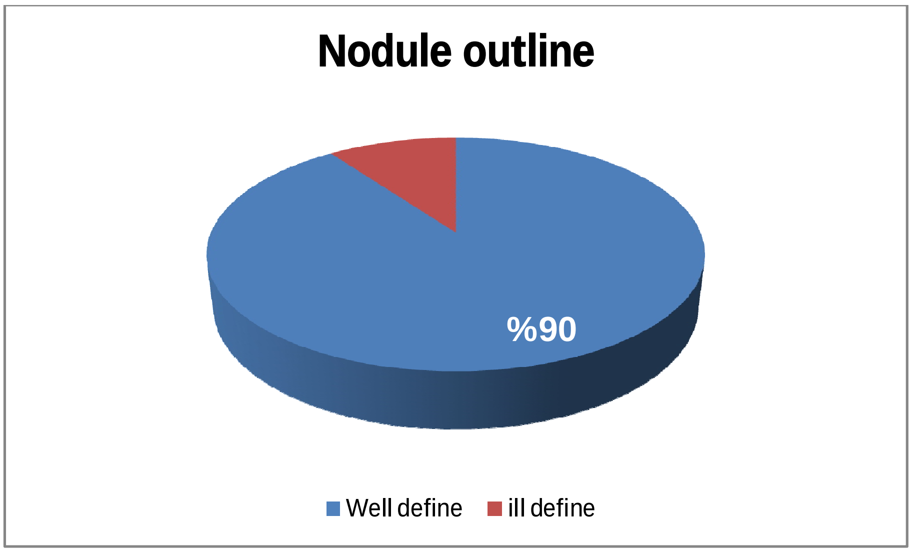


Figure (4-10): Shows the frequency distribution of thyroid nodule according to theoutline in ultrasound Imaging:

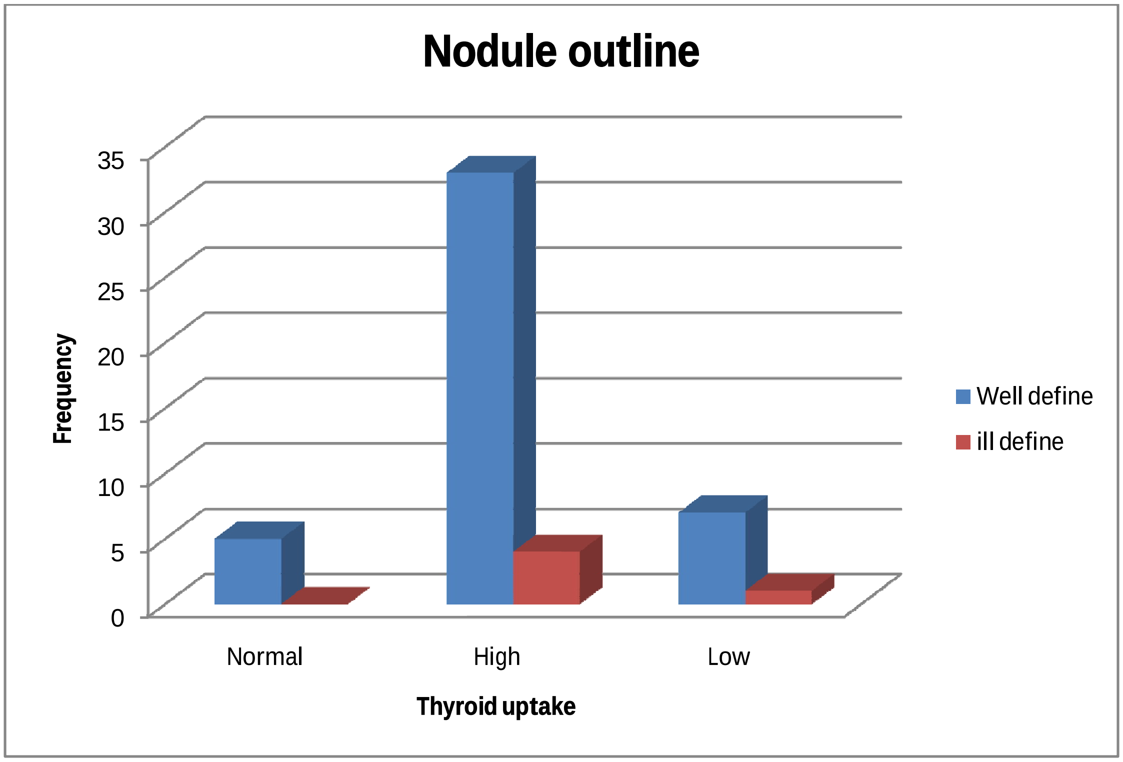


Figure (4-11): Shows the relationship between the thyroid uptake in Nuclear Medicine Imaging and outline in ultrasound Imaging:

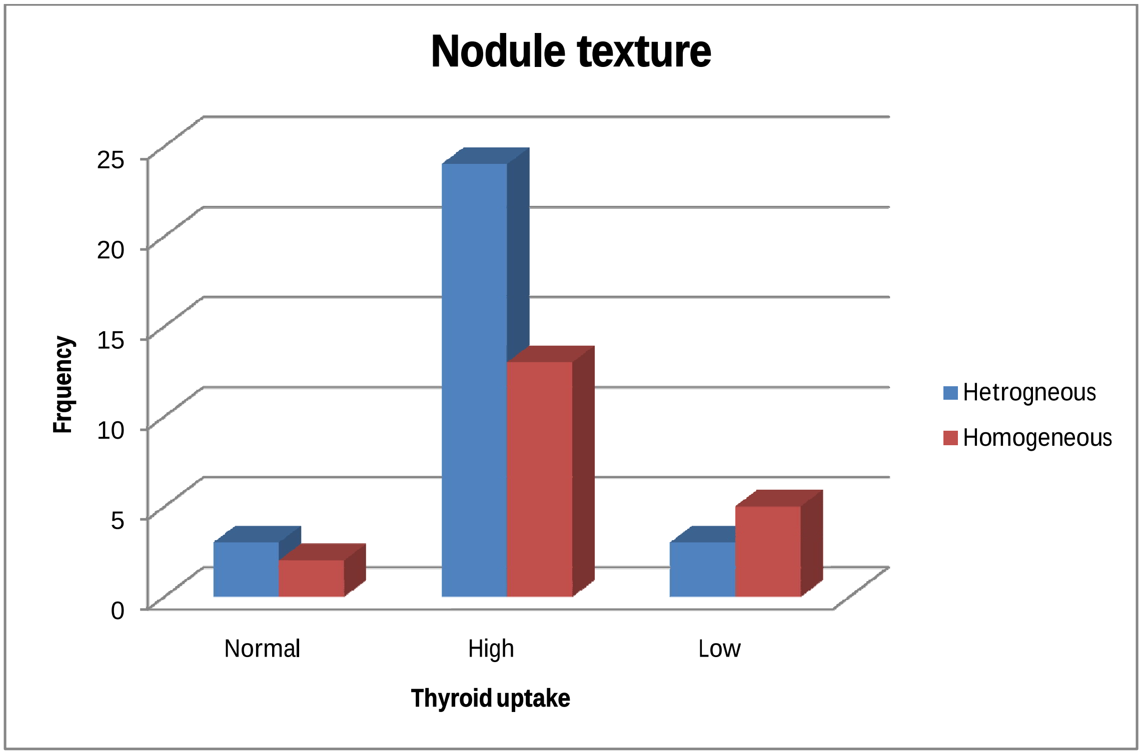


Figure (4-12): Shows the relationship between the thyroid uptake in Nuclear Medicine Imaging and nodule texture in ultrasound Imaging:

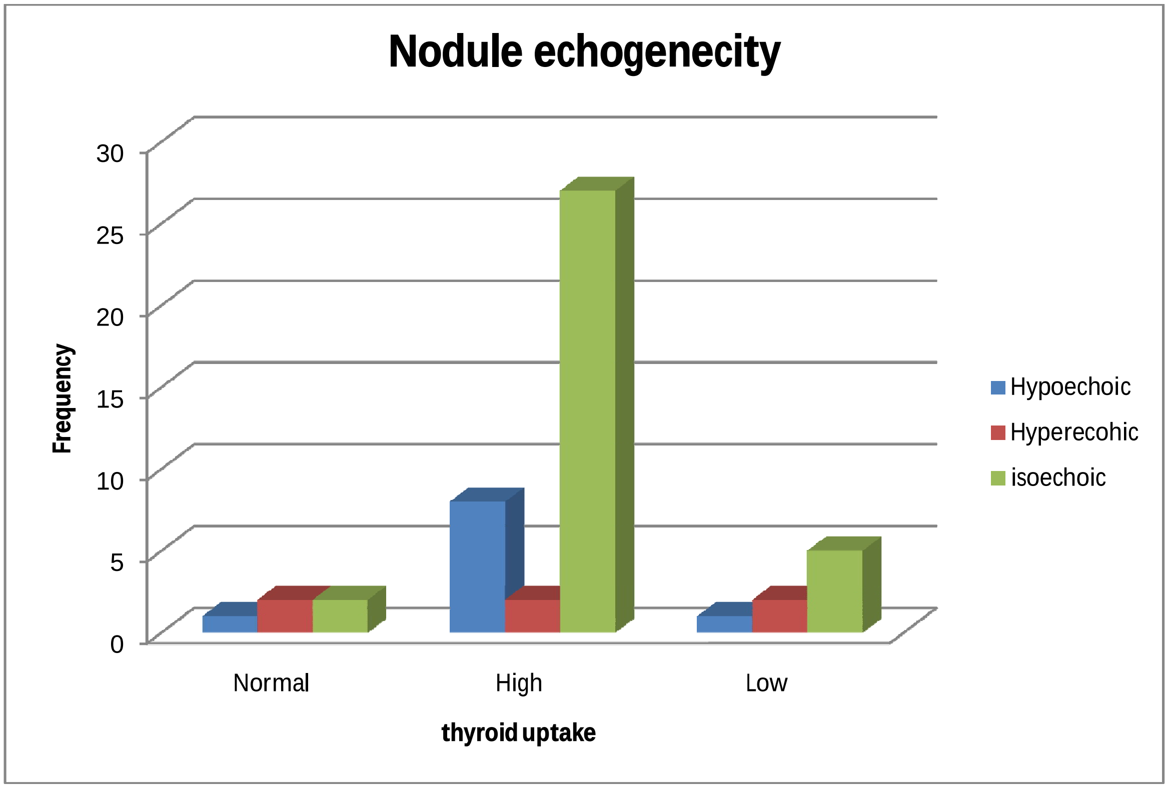


Figure (4-13): Shows the relationship between the thyroid uptake in Nuclear Medicine Imaging and echogenicity in ultrasound Imaging:

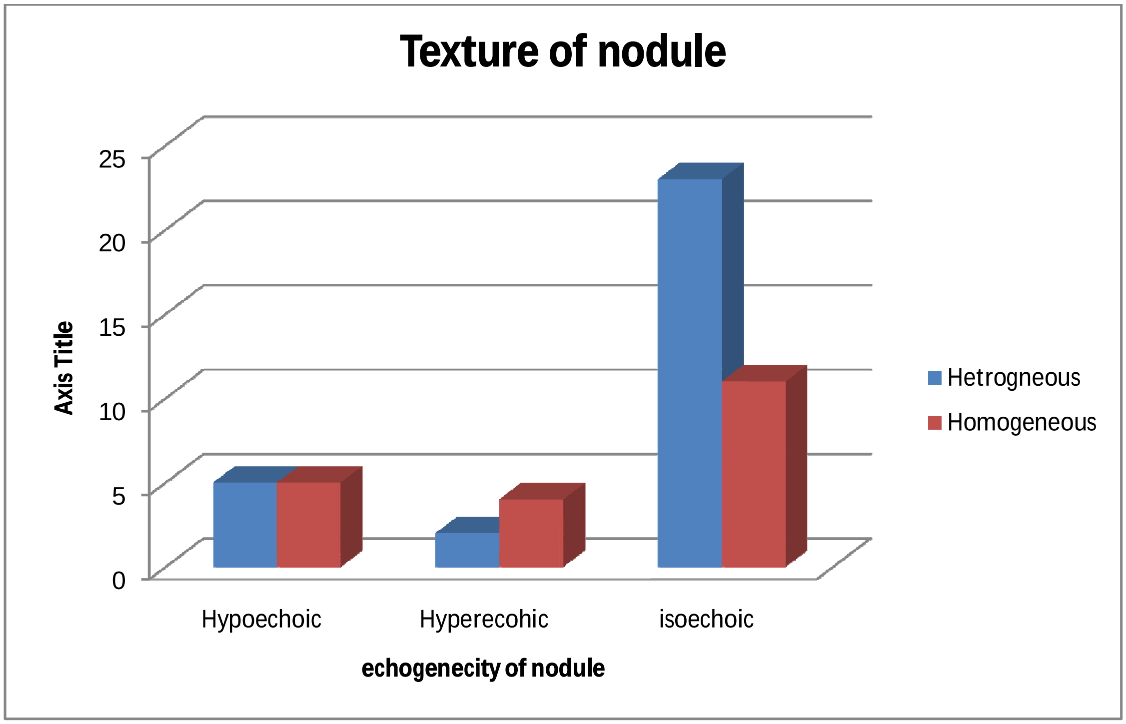


Figure (4-14): Shows the relationship between nodule echogenicity and texture in ultrasound Imaging:

Table (4-10): Shows the mean value of uptake types:

	Normal uptake	High uptake	Low uptake
Age (year)	47.6±14.9	36.8±13.9	45.4±13.5
Weight (Kg)	71.6±10.2	64.2±8.6	65.6±6.5
Height (m)	1.6±0.1	1.7±0.1	1.6±0.1
BMI (Kg/m^2)	26.4±3.8	23.9±+3.4	24.7±2.9
Thyroid volume (cm3)	11.0±8.4	10.8±7.2	8.7±5.7
Nodules volume (cm3)	2.4±1.2	2.6±1.0	2.7±1.1
RI	0.41±0.2	0.59±0.1	0.30±0.1
PI	0.74±0.2	0.85±0.2	0.81±0.9
PSV	1.0±0.0	1.2±0.6	1.8±0.9

Table (4-11): Shows the Thyroid volume andNodule volume, betweengroups and within groups:

ANOVA (thyroid uptake 'normal, high and low'**)**					
		Sum of Squares	Mean Square	F	Sig.
Thyroid volume	Between Groups	28.026	14.013	.273	.763
	Within Groups	2416.237	51.409		
	Total	2444.262			
Nodule volume	Between Groups	.231	.116	.115	.892
	Within Groups	47.369	1.008		
	Total	47.600			

Table (4-12): Shows the Resistive Index and Pulsatility Index, between groups and within groups:

ANOVA (thyroid Uptake 'normal, high and low'**)**					
		Sum of Squares	Mean Square	F	Significant
RI	Between Groups	.606	.303	14.973	**.000**
	Within Groups	.951	.020		
	Total	1.556			
PI	Between Groups	.052	.026	.173	.841
	Within Groups	7.015	.149		
	Total	7.067			
PSV	Between Groups	2.656	1.328	3.713	**.032**
	Within Groups	16.812	.358		
	Total	19.469			

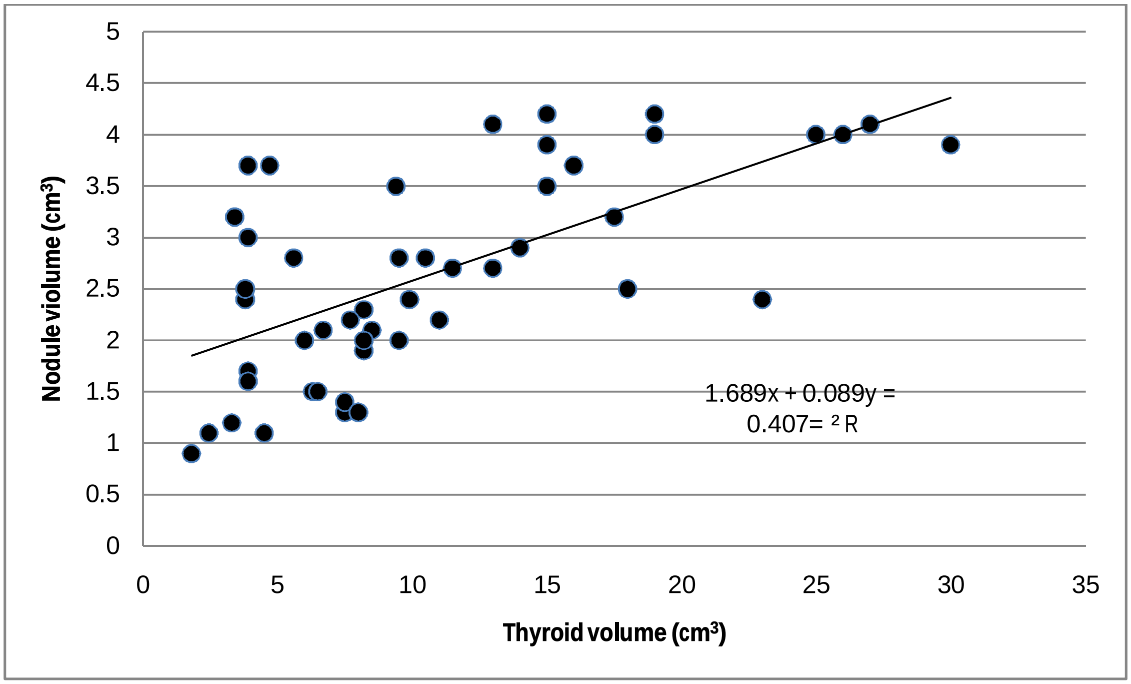


Figure (4-15):correlation between nodule volume and thyroid volume, the scatter plots indicate that thyroid nodule volume increases by the rate of 0.89cm^3 foreach cm^3 of thyroid volume

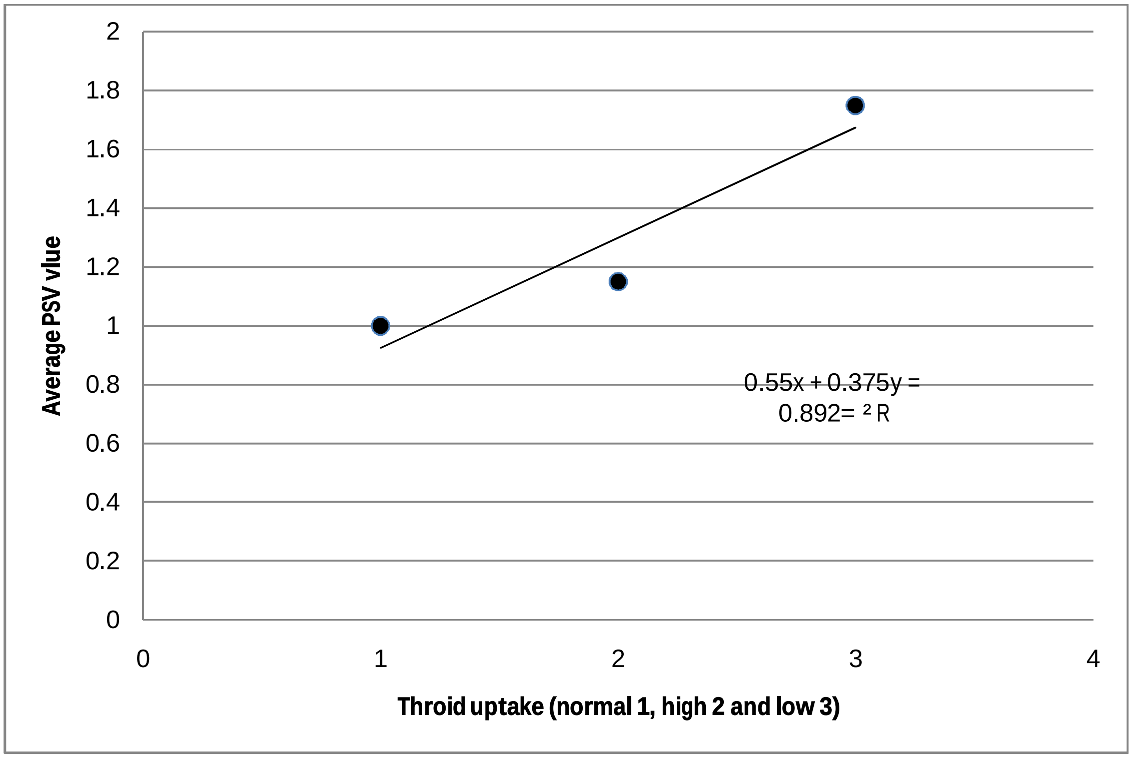


Figure (4-16): the regression line indicate the relation between thyroid uptake and blood flow indices, a linear fashion where the highest values recorded for low uptake; PSV increase by 0.37 per status, where the status will be 1, 2, 3 andfor normal, high and low respectively, $PSV = 0.37\times status+0.55$.

CHAPTER FIVE

Discussion, conclusion & RECOMMENDATIONS

Chapter Five
Discussion, Conclusion& Recommendations

5-1 Discussion:

The Thyroid scan by Nuclear Medicine (thyroid Scintigraphy) and thyroid ultrasound scan are screening and potential reduce the risk of mortality in thyroid disorders like thyroid nodules whose prognosis has improved minimally during the last decades.

The data of this study included 50 patients 86% of them were female 78% of them were married (Table and Figures 4-1 and 4-2), all patients were suffer from thyroid nodules; 62% of the patient had bilateral nodules while 28% on the Left lobe and 10% on the Right one (Table and Figure 4-3); this results indicates that thyroid problem mostly associated with female as well as mostly nodules found bilaterally in more than 2/3 of the patient.The present study in comparing with the study. Conducted in Sudan University 2010 by Dr. Mohammed M. OmerYousef I agree with him.

Using nuclear medicine examination the result showed that 74% of the patient had a high thyroid uptake, with only 10% showed normal uptake while the rest showed low uptake (Table and Figure 4-4); this result demonstrate that thyroid nodules mostly associated with high uptake; which means nodules represent hot spot, while for low uptake generally the nodule consumed the whole thyroid or the whole thyroid were enlarge, and sometime with the presence of nodule still the activity of thyroid might be normal. As well radiotracer showed homogenous distribution in 62% of the cases and the rest were heterogeneous appearances (Table and Figure 4-5) which comparing these with reported findingsin the department of Radiology, University of North Carolina at Chapel Hill, Julia, et al, (2005) the results is resemblance. On the other hand ultrasound showed that thyroid outline was regular in 60% of the cases; which means nodules were not affect the shape or texture of thyroid approximately in 2/3 of the patient, while texture showed 60% heterogeneity of thyroid, which means nodules affected the homogeneity of the thyroid surface (Table and Figure 4-6 and 4-7).

Concerning the nodules 68% of the nodules showed iso-echoic appearance, with 90% well define outline, which represent resemblance of benign features (Figure and Table 4-8 and 4-9). From texture point of view the homogenous and heterogeneous nodules both associate with high thyroid uptake (Figure 4-10), Also nodules with well outline showed high uptake. Current study observed in people over 50 years of age in Senegal, study of 31 cases observed a 14 years period Ersoy, et al. (1998), the study through common in elderly, with poor and masked symptomatology, nodule has never been studied in people older than 50 years of age in African countries. The study was done for 300 cases of nodule it analyzed the frequency of Scintigraphy characteristics

The result of this study showed that there were no significant differences in thyroid volume or nodule volume for thyroid with high, low or normal uptake using ANOVA test at $p = 0.05$, which means the activity of the thyroid represented by thyroid uptake does not affect the volume. But in case of blood flow indices which is represented by PI, RI and PSV using ANOVA test for the same groups of thyroid uptakes significance effect were scored by RI and PSV, which means follow of blood affected by the function as normal behavior.

This study also showed that there is a correlation between the thyroid nodule volume and thyroid volume, where thyroid nodule volume increases by the rate of 0.089cm^{3}for each cm^3 of thyroid volume, where *thyroid nodules = 0.089× thyroid volume + 1.7,* as well PSV increase as the uptake goes from, normal, high to low in a linear fashion where the highest values recorded for low uptake; PSV increase by 0.37 per status, where the status will be 1, 2 and 3 for normal, high and low respectively,

$PSV = 0.37 \times status + 0.55$. Similarstudies done by Liebeskind et al (2005) studied patients with thyroid disorders for surgery is a difficult task. The traditional approaches of radionuclide and ultrasonography have been shown to be good specific in diagnosis of thyroid benign nodules or thyroid malignancy. To compare the useful nesses of thyroid disorders Scintigraphy, thyroid ultrasonography differential diagnosis of thyroid, we reviewed the records of 183 patients who underwent thyroidectomy for thyroid nodules. Thyroid carcinoma was diagnosed in 36 patients

5-2 Conclusion

The thyroid nodule diseases were widely spread among Sudanese peopleand common entities; therefore evaluation and best diagnosis of this disease it's curial, the modalities of diagnosis were deferent but the Ultrasonography and thyroid Scintigraphy play an important role in this diagnosis, hence the main objective of this study is to evaluate and to knowcharacterization of thyroid benign nodules using Ultrasonography and Radiation Scintigraphy to compare between ultrasound finding and thyroid scan by nuclear medicine examinations.The majority of thyroid nodules are benign, but they warrant surgical excision when they are large enough to be symptomatic or if there is concern for malignancy. Ultrasound is the primary study by which the thyroid gland is imaged. Nodules one centimeter or larger or sonographically suspicious sub centimeter warrant cytologic analysis through fine-needle aspiration biopsy (FNAB) to determine the risk of malignancy.Out of the results enumeration for this study have been investigated by ultrasound and radionuclide Technetium-^{99m} pertechnetate(Tc^{99m})to assessment of characterization thyroid benign nodules by this modalitiesand the final conclusion could be summarized as following;All patients scan with supine position technique, among the sample the study reveals that the incidence of thyroid benign nodules is more common in female (85%), and showed that 70% of thyroid benign nodules detected in age between 28 – 57 years and the incidence are less common in the young and elder patients.The data analysis by statistical methods that include the linear association and line plots as well as chart.The study also showed significant correlation between the thyroid nodule volume and thyroid volume.

Finally the usefulness of Ultrasonography and thyroid Scintigraphy as an index for the detectionand differentiation of thyroid benign nodules is beyond doubt.

Recommendations:

Finally we recommended by the following scientific points for their importance: •Thyroid scan by ultrasound or nuclear medicine is useful because its serve as: method of thyroid disorders detection, monitor of patient's response to treatment, and as method of recurrencedetection. • Full patient history should be taken before starting U/S scan. • Ultrasound is operator dependable so, the operator should get the utmost level of training.

•High resolution ultrasound equipments with multiple capabilities must be used to make the right diagnosis. •Thehospitals should be equipped with Doppler Ultrasound machines. •The government must award a lot of care for nuclear medicines center and construct more centers, especially there is of a few centers if compare with populationnumbers.

•Combination of ultrasonography, thyroid Scintigraphy and other modalities (biopsy, ultrasound guided, fine needle aspiration) if needed, make the most reliable results. • Researchers are recommended to go ahead for such studies, to use the obtained data for all the Sudan to construct a data base for thyroid nodules and all thyroid disorders. •***Eventually"prevention is better than cure,"***take balanced diet and foodstuff which rich with iodine likevegetables and seafood,use of iodized saltby adding iodine to the diet. It has eliminated endemic cretinism in most developed countriesand some governments have made the iodination of flour, cooking oil, and salt mandatory.

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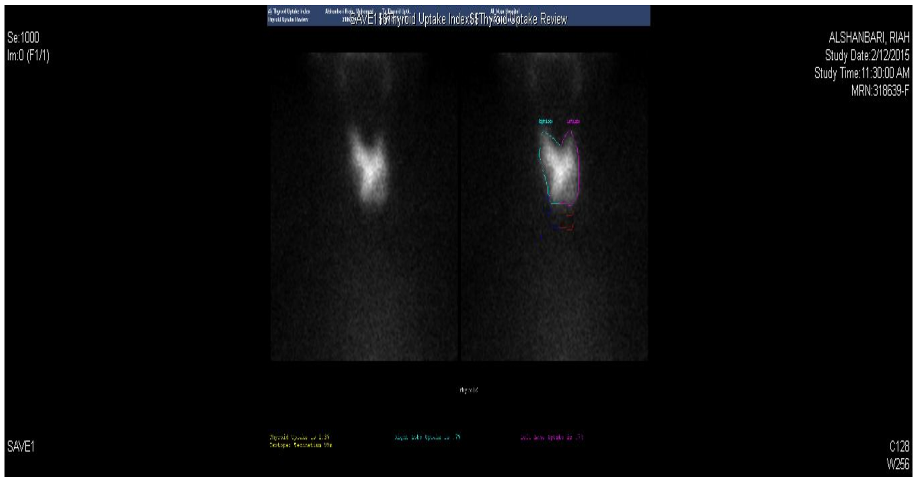
Appendices

Appendix (1)

Nuclear medicine and ultrasound images from the sample of the study

Case # (1)



THYROID IMAGING:

TC^{99m}Pertechentate Thyroid scan and uptake

Clinical data: 42 years old female patient with thyrotoxicosis with nodules.

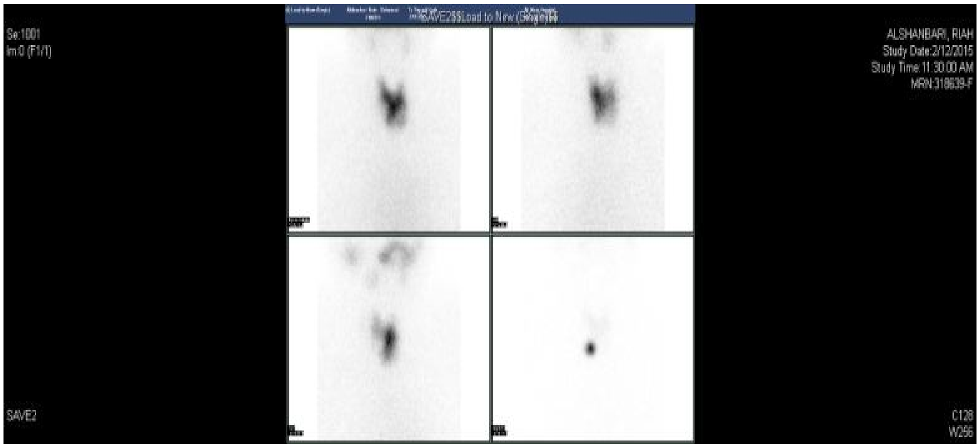
Indication of the study: Verifying the nature of the nodules.

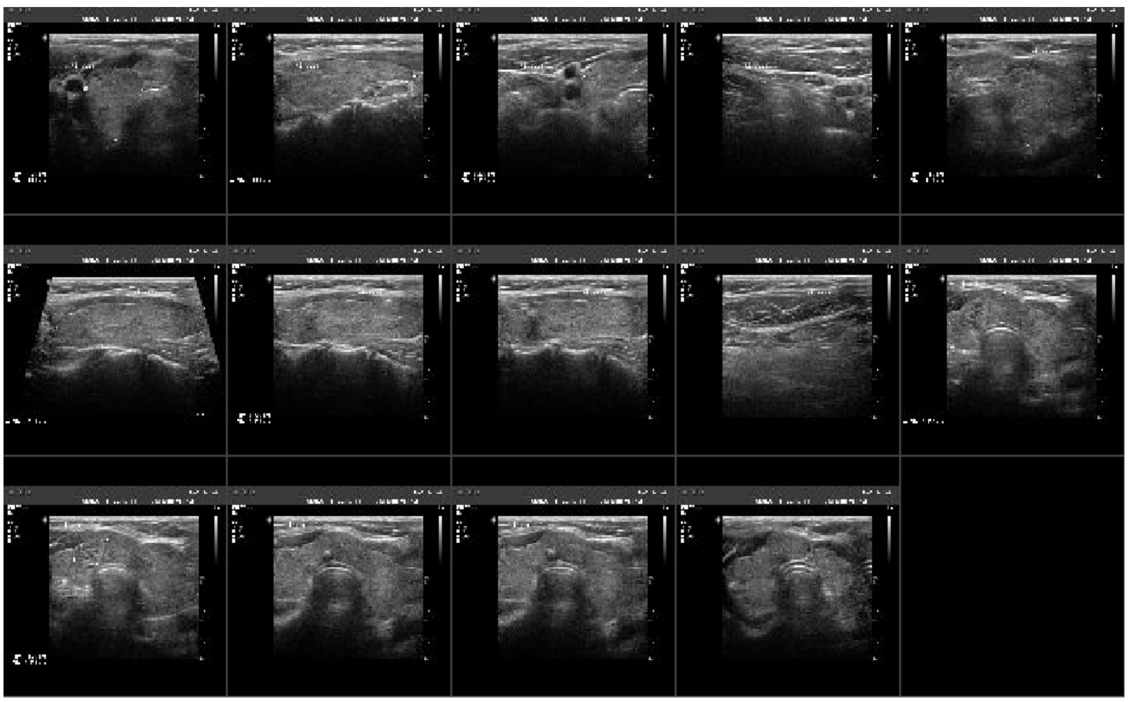
Technique:

Static image to the anterior neck was acquired following administration of 5 mCiTc 99^{m}pertechnitate with calculation of thyroid uptake.

Finding:

Heterogonous radiotracer uptake is portrayed all over the gland" Thyroid Uptake: 1.3 % (the normal uptake 0.5 -4%).

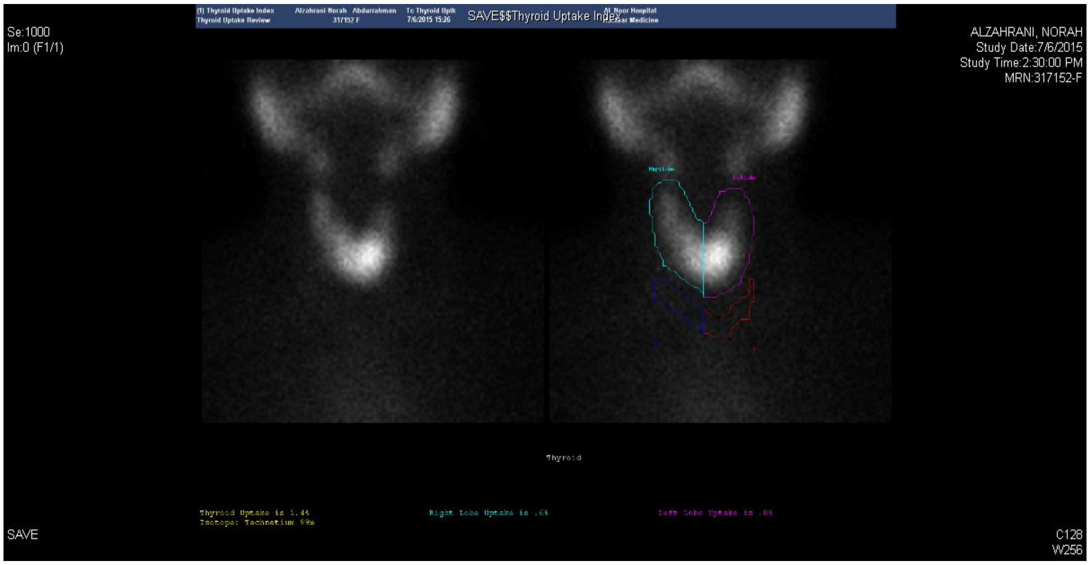




U.S.THYROID

- Both lobes & isthmus: asymmetrically enlarged, heterogenous echopattern with calcification.
- Both lobes show small well defined, hyperechoic nodules,
- Few enlarged Lt cervical LN with intact hilum

Case #(2)



THYROID IMAGING :

Tc^{99m} Pertechnitate Thyroid Scan and Uptake

Clinical Data: 43 years old female patient with low TSH.

Indication of the study: thyroid scan and uptake

Technique:

Static image to the anterior neck was acquired following administration of 5 mCiTc ^{99m} pertechnitate with calculation of thyroid uptake

Finding:

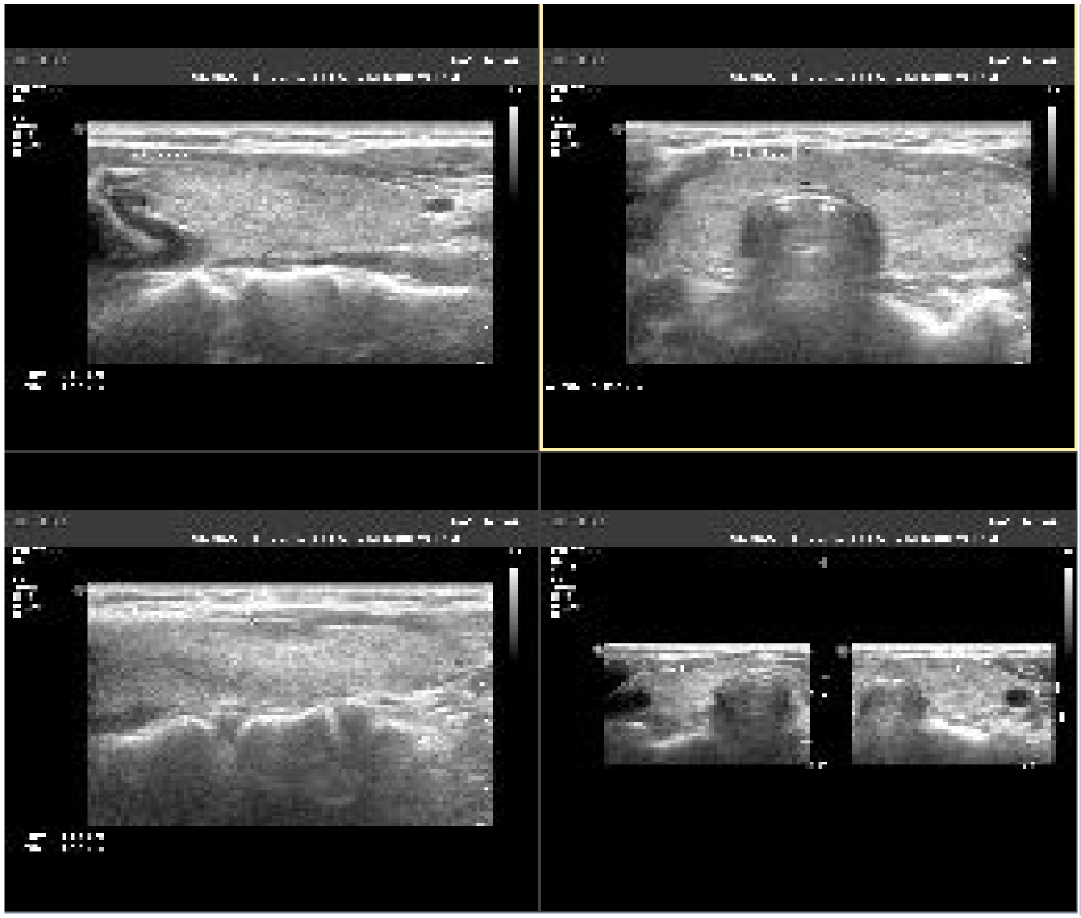
Enlarged thyroid gland with no evidence of reterosternal extension.

Focal area of increase radiotracer uptake is noted in the lower part of left thyroid lobe with normal rest of the gland,.

Thyroid Uptake: 1.4% (N 0.5 -4%).

Impression:

Warm lower left thyroid lobe nodule for U/S correlation.

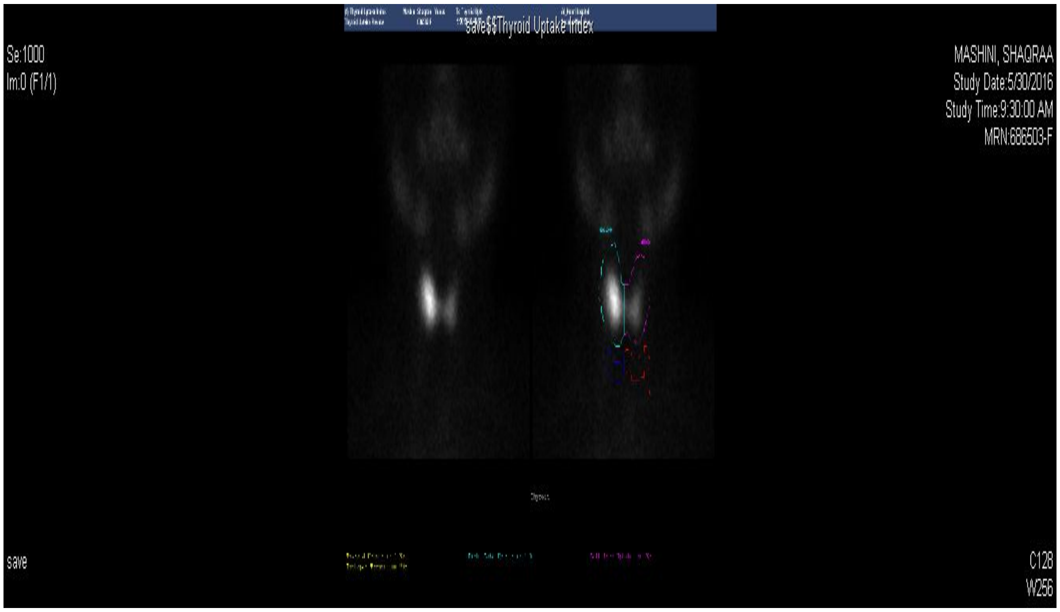


U.S. THYROID:

Findings:

- Both thyroid lobes & isthmus are slightly bulky with diffuse heterogenous texture. No definite solid or cystic nodules.

Case #(3)



THYROID IMAGING:

Tc^{99m} Pertechnitate Thyroid Scan and Uptake

Clinical history: 37 year old female with history of ? hyperthyroidism.

Indication of the study: Thyroid scan and uptake.

Technique:

Static image to the anterior neck was acquired following administration of 5 mCi Tc^{99m} pertechnitate with calculation of thyroid uptake.

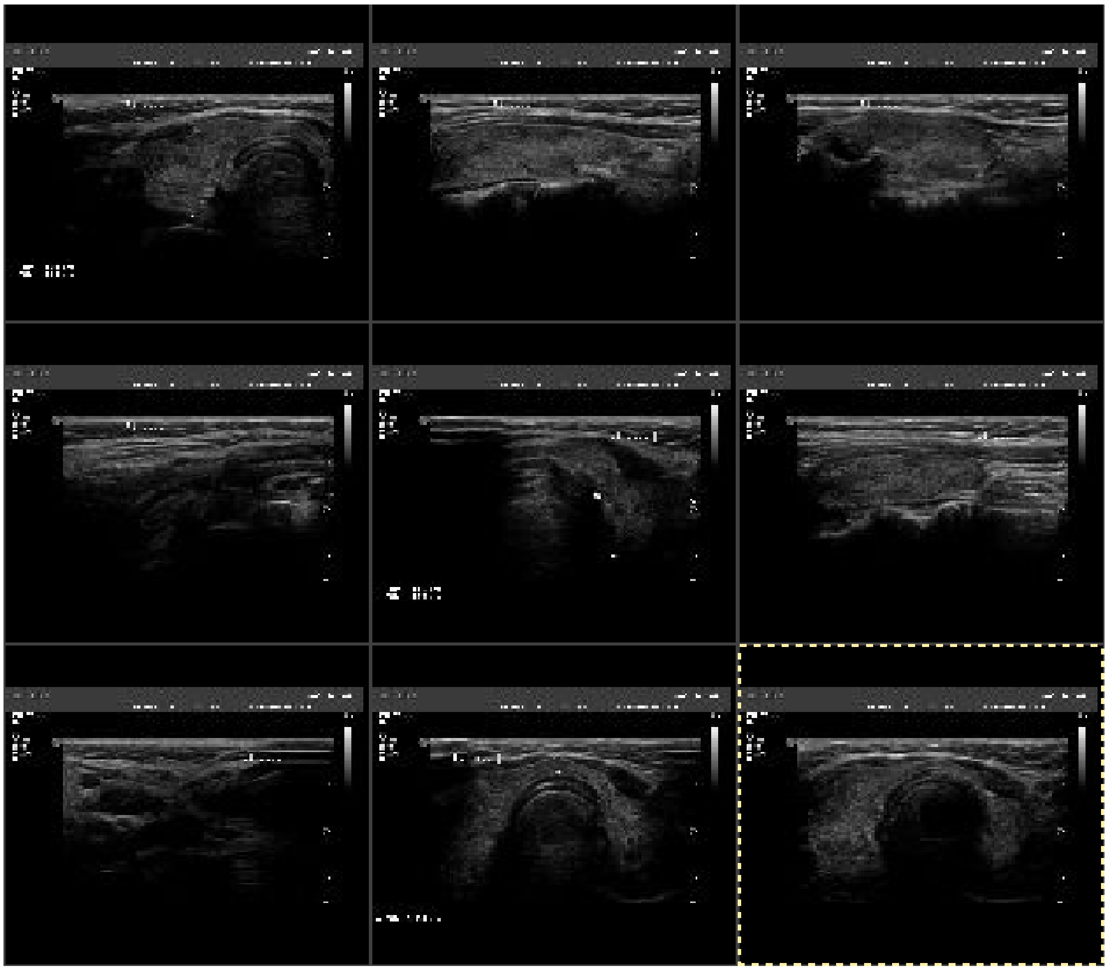
Finding:

Focal area of increase tracer uptake is noted in the right thyroid thyroid lobe, while the rest of thyroid gland shows reduced tracer uptake.

Thyroid Uptake: 1.3% (N 0.5% - 4%).

Impression:

Warm nodule in the right thyroid lobe with reduced left lobe uptake with normal over all thyroid uptake value for U/S correlation.



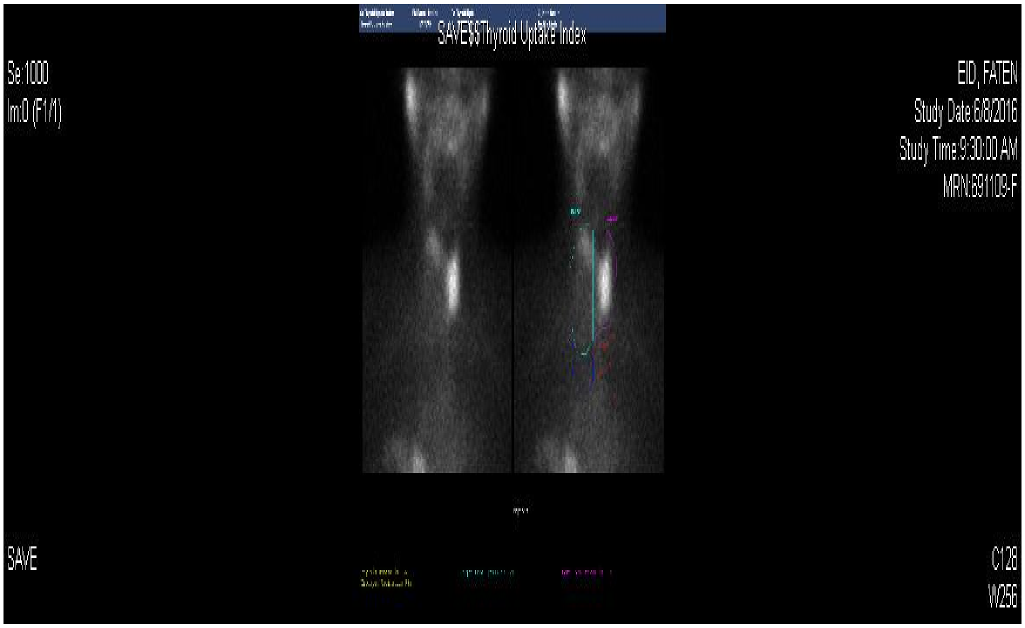
U.S. THYROID of 17-MAY-2016:

- Average sized both thyroid lobes with diffuse heterogeneous parenchyma.
- No significant enlarged cervical LNS.
- No retrosternal extension.
- Normal great vessels of the neck.

CONCLUSION:

- Findings are impressive of thyroiditis.

Case #(4)



THYROID IMAGING:

Tc^{99m} pertechenitate Thyroid Scan and Uptake

Clinical data: 38 years old female patient with follicular neoplasm.

Indication of the study: thyroid scan and uptake.

Technique:

" Static image to the anterior neck was acquired 20 minutes following administration of 5 mCiTc ^{99m} pertechnitate with calculation of thyroid uptake

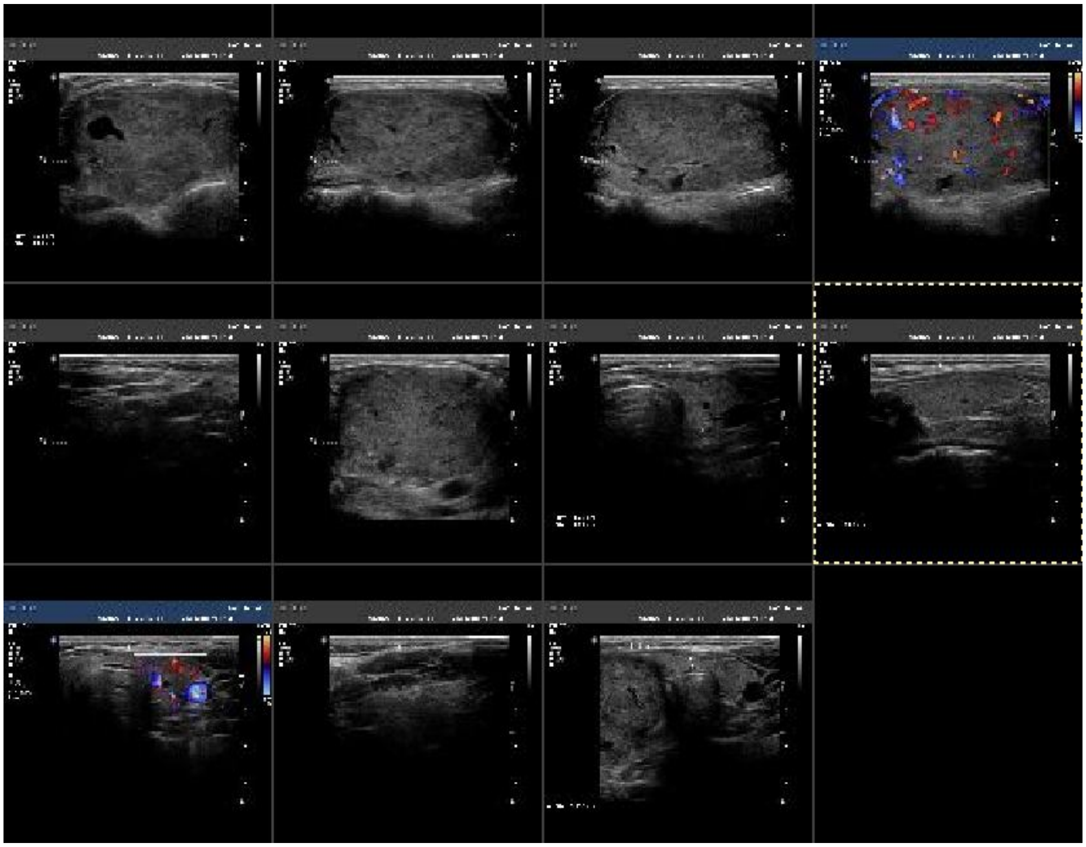
Finding:

Photon deficit area is noted in the lower part of right thyroid lobe while the rest of the gland shows rather uniform tracer uptake.

Thyroid uptake 0.6% (N0.5%-4%).

Impression:

Solitary thyroid cold nodule in the lower part of the right thyroid lobe for U/S correlation.



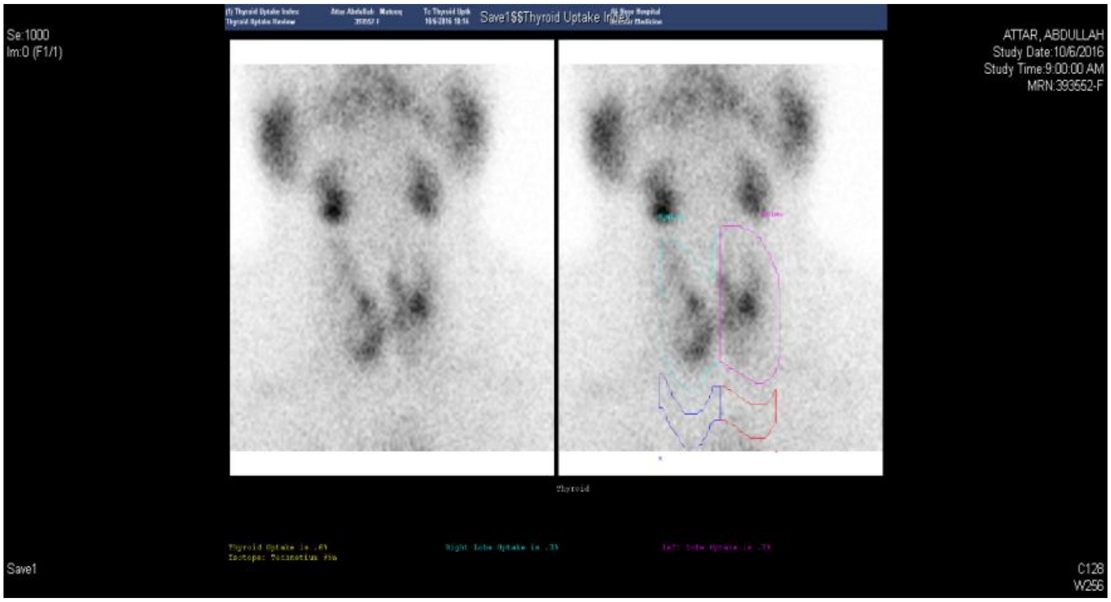
U.S. THYROID :

- Enlarged right lobe occupied by large well defined isoechoic nodule with cystic degeneration, it shows peripheral vascularity.
- Average size left lobe, heterogeneous echopattern shows small hypo echoic nodule with peripheral vascularity.
- No retrosternal extension.
- No significant cervical LN enlargement.

CONCLUSION:

- Enlarged Right thyroid gland with nodule. and small Lt lobe nodule

Case #(5)



THYROID IMAGING:

Tc^{99m} Pertechnitate Thyroid Scan and Uptake

Clinical data: 54 years old male patient with thyroid nodule .

Indication of the study:" Thyroid scan and uptake

Technique:

Static image to the anterior neck was acquired 20 minutes following administration of 5 mCiTc ^{99m} pertechnitate with calculation of thyroid uptake.

Finding:

Heterogonous radiotracer uptake is noted althrough the gland with dominant Thyroid Uptake: 0.6 % (N 0.5% - 4%).

Impression:

Scintigraphic features are of MNG with dominant right upper lobe cold nodule for U/S

U.S. THYROID:

Enlarged thyroid gland,both lobes withheterogenous nodular echo texture appearance ,(? nodular GOITER).

Multiple enlarged LN. seen RT & LT.

Appendix (2)

Data master sheet:-

General Information								N. M. results			Ultrasound Results							
No	Age (yrs)	Sex	W. (kg)	H. (m)	BMI	M.S	N.S	uptak	DRI	Out.	th. Z (cm^3)	N.Z (cm^3)	tex.	ech	out.	Blood flow indices		
																RI	PI	PSV
1	45	2	59	1.58	23.6	1	3	3	1	1	6.3	1.5	2	2	1	0.2	0.4	2
2	50	2	65	1.60	22.5	2	3	1	1	1	7.5	1.3	2	2	1	0.6	1	1
3	43	2	62	1.65	22.8	1	3	2	1	1	8.2	2.3	2	1	1	0.71	1.1	1
4	66	2	61	1.63	23.0	1	3	2	1	1	9.4	3.5	2	1	1	0.6	0.9	1
5	43	2	50	1.59	19.8	1	3	2	2	1	3.4	3.2	2	3	1	0.5	0.9	1
6	55	2	75	1.61	28.9	1	2	3	2	2	3.9	3.7	2	3	1	0.3	0.5	1
7	67	2	69	1.68	24.4	1	2	2	2	1	25	4	1	3	1	0.72	0.95	1
8	48	2	65	1.72	22.0	2	1	2	2	1	27	4.1	1	3	1	0.68	0.7	1
9	23	1	63	1.62	24.0	1	1	2	1	2	19	4.2	2	3	1	0.5	0.9	1
10	40	2	50	1.60	19.5	1	1	2	1	2	11.5	2.7	1	3	1	0.5	0.76	1
11	37	2	65	1.90	18.0	1	3	2	1	2	8.5	2.1	1	3	2	0.6	1.1	1
12	38	1	65	1.68	23.0	1	3	3	1	2	15	4.2	2	3		0.2	0.5	1
13	29	2	57	1.58	22.8	1	3	3	1	1	3.9	1.7	2	3	1	0.3	0.5	1
14	37	2	62	1.69	21.7	1	1	3	2	2	3.8	2.4	2	2	1	0.4	0.6	3
15	54	2	65	1.70	22.5	2	1	3	2	2	7.5	1.4	1	1	1	0.4	0.5	1
16	27	2	59	1.60	23.0	1	3	2	1	1	8.2	1.9	1	3	1	0.4	0.6	0.6
17	20	2	60	1.58	24.0	1	2	2	1	1	6.5	1.5	1	3	1	0.6	0.5	1
18	22	2	55	1.62	21.0	2	1	2	1	1	7.7	2.2	1	3	1	0.5	0.6	1
19	41	2	60	1.52	26.0	1	3	1	1	1	9.9	2.4	1	3	1	0.4	0.6	1
20	60	1	75	1.70	26.0	1	1	2	1	2	30	3.9	2	1	2	0.5	0.7	1
21	19	2	48	1.50	21.3	2	3	2	1	1	8.2	2	1	1	1	0.4	0.6	3
22	23	2	60	1.65	22.0	1	1	2	1	1	3.8	2.5	2	3	1	0.72	1.1	1
23	22	2	55	1.61	21.2	1	1	2	1	1	5.6	2.8	1	3	1	0.5	0.7	1
24	30	2	65	1.63	24.5	1	3	2	1	1	3.9	1.6	2	3	1	0.6	0.8	1
25	52	2	79	1.70	27.3	2	1	2	1	2	6.7	2.1	1	3	2	0.5	0.7	1
26	25	2	63	1.64	23.4	1	3	2	1	2	4.7	3.7	1	1	1	0.5	0.7	1
27	50	1	85	1.62	32.4	1	3	1	1	2	26	4	1	1	1	0.5	0.7	1
28	51	2	59	1.60	23.0	2	3	2	1	1	15	3.5	1	3	1	o.75	1.1	3
29	70	2	60	1.65	22.0	1	3	2	1	1	11	2.2	1	2	1	0.75	0.6	1
30	44	2	55	1.61	21.2	1	3	2	1	2	6	2	1	3	1	0.75	1.2	1
31	35	2	63	1.64	23.4	1	1	2	2	2	17.5	3.2	1	3	1	0.05	0.7	1
32	42	2	85	1.62	32.4	2	1	2	2	1	2.44	1.1	2	1	1	0.73	0.9	3
33	32	2	72	1.60	28.1	2	3	2	2	1	3.9	1.6	2	3	1	0.7	0.7	1
34	41	1	72	1.75	33.5	1	1	2	2	1	23	2.4	1	3	1	0.75	1.2	1
35	69	2	69	1.70	23.9	1	3	1	1	1	8	1.3	1	2	1	0.05	0.7	1

36	39	2	53	1.57	21.5	1	3	2	1	1	18	2.5	1	3	1	0.5	0.7	1
37	25	2	61	1.65	22.4	1	3	2	2	1	13	4.1	1	3	1	0.6	0.8	1
38	32	2	58	1.60	22.7	1	1	2	2	1	4.5	1.1	2	3	1	0.72	0.92	1
39	33	2	70	1.69	24.5	1	3	2	2	1	1.8	0.9	2	1	2	0.7	1.2	1
40	30	1	66	1.65	24.2	1	3	2	1	1	9.5	2	1	3	1	0.5	0.7	1
41	20	2	68	1.63	25.6	2	3	2	1	1	9.5	2.8	1	3	1	0.5	0.7	1
42	50	2	65	1.90	18.0	1	3	2	1	2	16	3.7	1	3	1	0.6	0.7	1
43	35	2	74	1.60	28.9	1	2	3	2	2	10.5	2.8	1	3	1	0.4	0.5	3
44	33	2	73	1.70	25.3	1	3	2	2	1	14	2.9	1	1	1	0.66	0.95	1
45	21	2	70	1.69	24.5	2	3	2	1	1	13	2.7	1	3	1	0.7	1.2	1
46	28	1	79	1.70	27.3	1	3	1	2	2	3.4	3.2	2	3	1	0.5	0.7	1
47	29	2	81	1.63	29.8	1	3	2	2	2	3.9	3	2	3	1	0.5	0.9	1
48	30	2	74	1.60	28.9	1	3	2	2	2	3.3	1.2	2	2	1	0.72	0.8	1
49	38	2	65	1.60	25.4	1	3	2	1	2	15	3.9	1	3	1	0.7	1	1
50	70	2	68	1.62	25.9	2	2	3	2	2	19	4	1	3	1	0.2	0 .3	2

Keywords (codes):-

Sex		Marital Status (M.S)	
Male	**Female**	**Married**	**Single**
1	2	1	2

Thyroid uptake (uptak)		
Normal	**High**	**Low**
1	2	3

Distribution of radiotracer (DRT)	
Homogeneous	**Inhomogeneous**
1	2

Thyroid outline (out)	
Regular	**Irregular**
1	2

Nodule texture (tex)	
Hetrogneous	**Homogeneous**
1	2

Nodule echogenicty (echo)		
Hypoechoic	Hyperecohic	isoechoic
1	2	3

Nodule outline (out)	
Well define	**ill define**
1	2

Blood Flow Indices (*V*= Vascularity)		
Peripheral	**Central**	**Avascular**
1	2	3

Nodule Site		
Left lobe	Right lobe	Bilateral
1	2	3

Thyroid function tests (TFT)

Test	Abbreviation	Normal ranges
Serum thyrotropin /thyroid-stimulating hormone	TSH	0.5–6.0 µU/ml
Free thyroxine	FT_4	7–18 ng/l = 0.7–1.8 ng/dl
Serum triiodothyronine	T_3	0.8–1.8 µg/l = 80–180 ng/dl
Radioactive iodine-123 uptake	RAIU	10–30%
Radioiodine scan (gamma camera)	N/A	N/A - thyroid contrasted images
Free thyroxine fraction	FT_4F	0.03–0.005%
Serum thyroxine	T_4	46–120 µg/l = 4.6–12.0 µg/dl
Thyroid hormone binding ratio	THBR	0.9–1.1
Free thyroxine index	FT_4I	4–11
Free triiodothyronine l	FT_3	230–619 pg/d
Free T3 Index	FT3I	80–180
Thyroxine-binding globulin	TBG	12–20 ug/dl T4 +1.8 µg
TRH stimulation test	Peak TSH	9–30 µIU/ml at 20–30 min.
Serum thyroglobulin l	Tg	0-30 ng/m
Thyroid microsomal antibody titer	TMAb	Varies with method
Thyroglobulin antibody titer	TgAb	Varies with method

- µU/ml = mU/l, microunit per milliliter
- ng/dl, nanograms per deciliter
- µg, micrograms
- pg/d, picograms per day
- µIU/ml = mIU/l, micro-international unit per mil

Effects of some drugs on Tests of Thyroid function

Cause	**Druge**	**Effect**
Inhibit TSH secretion	Dopamine, L-dopa, Glucocorticoids, Somatostatin	$\downarrow T_4$; $\downarrow T_3$; $\downarrow$TSH
Inhibit thyroid hormone synthesis or release	Iodine, Lithium	$\downarrow T_4$; $\downarrow T_3$; $\uparrow$TSH
Inhibit conversion of T_4 to T_3	Amiodarone, Glucocorticoids, Propranolol, Propylthiouracil, Radiographic contrast agents	$\downarrow T_3$; $\uparrow rT_3$; $\downarrow$, $\leftrightarrow$, $\uparrow T_4$ and fT_4; $\leftrightarrow$, $\uparrow$TSH
Inhibit binding of T_4/T_3 to serum proteins	Salicylates, Phenytoin, Carbamazepine, Furosemide, Nonsteroidal anti-inflammatory agents, Heparin (in vitro effect)	$\downarrow T_4$; $\downarrow T_3$; $\downarrow fT_4E$, $\leftrightarrow$, $\uparrow fT_4$; $\leftrightarrow$TSH
Stimulate metabolism of iodothyronines	Phenobarbital, Phenytoin, Carbamazepine, Rifampicin	$\downarrow T_4$; $\downarrow fT_4$; $\leftrightarrow$TSH
Inhibit absorption of ingested T_4	Aluminium hydroxide, Ferrous sulfate, Cholestyramine, Colestipol, Iron sucralfate, Soybean preparations, Kayexalate	$\downarrow T_4$; $\downarrow fT_4$; $\uparrow$TSH
Increase in concentration of T_4-binding proteins	Estrogen, Clofibrate, Opiates (heroin, methadone), 5-Fluorouracil, Perphenzazine	$\uparrow T_4$; $\uparrow T_3$; $\leftrightarrow fT_4$; $\leftrightarrow$TSH
Decrease in concentration of T4-binding proteins	Androgens, Glucocorticoids	$\downarrow T_4$; $\downarrow T_3$; $\leftrightarrow fT_4$; $\leftrightarrow$TSH

$\downarrow$: reduced serum concentration; $\uparrow$: increased serum concentration; $\leftrightarrow$: non change; TSH: Thyroid-stimulating hormone; T_3: Total tri-iodothyronine; T_4: Total thyroxine; fT_4: Free thyroxine; fT_3: Free tri-iodothyronine; rT_3: Reverse tri-iodothyron