Chapter One

Introduction

The thyroid is made up of the isthmus which overlying the 2nd and 3rd rings of the trachea, the lateral lobes which each extending from the side of the thyroid cartilage downwards to the 6th tracheal ring and an inconstant pyramidal lobe which projecting upwards from the isthmus, usually on the left side, which represents a remnant of the embryological descent of the thyroid. The thyroid gland is enclosed in the pretracheal fascia, covered by the strap muscles and overlapped by the sternocleidomastoids.On the deep aspect of the thyroid lie the larynx and trachea, with the pharynx and oesophagus behind and the carotid sheath on either side. Two nerves lie in close relationship to the gland; in the groove between the trachea and oesophagus lies the recurrent laryngeal nerve and deep to the upper pole lies the external branch of the superior laryngeal nerve passing to the cricothyroid muscle (Abdallah YMY et al 2014, Adam et al 2005).

SPECT or PET resulting in SPECT/CT and PET/CT respectively. This section will concentrate on study of the effect of thyroid disease in thyroid hrmone concentration and levels by using of planar imaging, SPECT and SPECT/CT methods [AdelsBall on, E.Het al 1997- Ball,et al 1991]. The gamma camera is composed of a collimator, a scintillator crystal usually made of NaI (or CsI), the photomultiplier tubes, the electronic circuits and a computer equipped with the suitable software to depict the nuclear medicine examinations. In planar imaging, the patient, having being delivered with the suitable radiopharmaceutical, is sited under the gamma camera head. The gamma camera head remains stable at a fixed position over the patient for a certain period of time, acquiring counts (disintegrations). These will constitute the radiopharmaceutical distribution image. The counts measured in a specific planar projection originate from the whole thickness of patient (Ball Jet al 1995, Buehler,2001). In SPECT, the gamma camera head rotates around the patient remaining at well-defined angles and acquiring counts for specific periods of time per angle.

In order to obtain the most accurate quantitative data from SPECT images, two issues that have to be resolved are the attenuation correction and the Compton scattering that the photons are undergone until reach and interact with the slice of interest tissues. As an examining organ has certain dimensions, each slice along the axis of the gamma camera has different distance from the detector. Thus, each photon experiences different attenuation. These two phenomena usually lead to distortion of the measured activity concentration (Farr, Ret al 1997, Mazzaferri 1993).

Hyperthyroidism refers to any condition in which the body has too much thyroid hormone or overactive tissue within the thyroid gland, resulting in overproduction and thus an excess of circulating free thyroid hormones: thyroxine (T_4), tri-iodothyronine (T_3), or both. Symptoms may include weight loss, nervousness, irritability, increased perspiration, a racing heart, hand tremors, anxiety, difficulty sleeping, increased bowel movements, fine brittle hair, and muscular weakness especially in the upper arms and thighs. In Graves' disease, a bulging of one or both eyes may occur. A classification of hyperthyroidism causes had been made by William et.al 2005, in which he stated that 95% associated with increased radioiodine uptake in patient with Graves' and Plummer's disease. Many treatment options had been proposed since 1941 and have since evolved to the treatment modality of choice for the majority of adult patients, particularly in the USA. The effectiveness of radioiodine treatment for hyperthyroidism is due to radiation-induced cellular damage resulting from high-energy beta emission, the magnitude of which is directly proportional to the radiation dose received by the thyroid gland (Fred et al, 2006).

This study aimed to discuss the role of thyroid treatment of hyperthyroidism by using of I^{131} radioisotopes in Sudanese population.Nuclear Medicine is the section of science that utilizes the properties of radiopharmaceuticals in order to derive clinical information of the human physiology and biochemistry. The radiopharmaceutical follows its physiological pathway and it is concentrated on specific organs and tissues for short periods of time. Then, the patient is positioned under a nuclear

medicine equipment which can detect the radiation emitted by the human body resulting in images of the biodistribution of the radiopharmaceutical. In Nuclear Medicine, there are two main methods of patient imaging, the imaging with Planar Imaging, Dynamic Imaging or SPECT and the PET. During the last decade, hybrid systems have been developed integrating the CT technique with either. A physical examination and laboratory tests that measure the amount of thyroid hormone (thyroxine, or T4, and triiodothyronine, or T_3) and thyroid-stimulating hormone (TSH) in blood are necessary and thyroid scan and uptake. Measurement of antibodies in the blood that attack the thyroid (antithyroid antibodies) may help in diagnosing the cause of hyperthyroidism (Fred et al 2006).

Therapy for hyperthyroidism is generally safe and effective, but no one treatment is best for all patients with hyperthyroidism, the appropriate choice of treatment will be influenced by age, the type of hyperthyroidism, the severity of hyperthyroidism, other medical conditions that may be affecting health. The three basic approaches to the therapy of primary hyperthyroidism are firstly; antithyroid drugs, such as thiomides, propythiouracil and methimizole, secondly; surgery and thirdly; ^{131}I therapy. Iodine131 regarded as the treatment of choice for hyperthyroidism in patients older than 30 years and in patient of any age in whom hyperthyroidism is accompanied by medical complications or in whom other treatments have failed. Although Antithyroid drugs are frequently used as initial approach to the control of diffuse toxic goiter (Greaves disease); such drugs are generally not used in the treatment of toxic nodules or multinodular goiter. In significant number of patients with Graves' disease, Antithyroid drugs produced intolerable side effects, does not adequately control the disease, or result in patient compliance problem. In these patients and in patients with toxic nodular disease, ^{131}I therapy is of considerable value. Iodine-131therapy is also of considerable value in patients with recurrent hyperthyroidism after previous thyroidectomy when repeat surgery would cause enhanced risks; in children who have experienced toxicity to Anti-thyroid drugs; and in patient refused other therapy (Fred et al., 2006).

1.1. Problem of the study

Thyroid hyper function may be related to many more underlying causes leading to significant change in much system and may lead to many syndromes due to overexpression of thyroid hormone in serum. In significant number of patients with hyperthyroidism, anti-thyroid drug therapy produces intolerable side effects and does not adequately control the disease, or result in patient compliance problem in these patients and in patients with toxic nodular disease. Therefore, I^{131} therapy is of considerable value. $Iodine^{131}$ therapy is also of great value in patient with recurrent hyperthyroidism after previous thyroidectomy.

1.2. Study Objective:

1.2.1. General Objective:

The main objective of this study was to assess radioactive iodine as a treatment of hyperthyroidism, in order to assess the efficiency of the treatment.

1.2.2. Specific Objective:

- To measure thyroid profile and uptake before and after radioactive iodine therapy.
- To evaluate the response of hyperthyroidism to radioactive iodine therapy.
- To find the association between the doses delivered to the patients and thyroid profile and uptake.
- To find the relationship between the thyroid uptake and laboratory thyroid profile (TFT).
- To find the significant difference between TFTs before and after 3, 6, and 9 month of treatment

1.3. Significant of the Study:

The thyroid plays an important role in regulating the body's metabolism and calcium balance so any thyroid functions disturbance affects the body. This study highlighted the assessment of treatment of hyperthyroidism related to its causative factor in which radioactive iodine considered as the first line of treatment in the most of hyperthyroidism patients where the other medical management can lead to lesser response rate and outcome.

1.4. Overview of the Study:

The following thesis was laid out into five chapters. Chapter one deals with introduction, problem of the study, objectives, significance and overview of the study. Chapter two highlighted the literature review which includes the theoretical background about anatomy, pathophysiology and treatmentsof hyperthyroidism and NM imaging of thyroid gland also about radioactive iodine therapy in addition to the previous study. Chapter three cares about methodology, Chapter four about results and Chapter Five show the discussions, conclusion and recommendation in addition to the references and appendices.

Chapter Two

Literature Review

2.1. Thyroid Anatomy:

The thyroid gland is situated in the neck in front of the larynx and trachea at the level of the 5th, 6th and 7th cervical and 1st thoracic vertebrae. It resembles a butterfly in shape, consisting of two lobes; one on either side of the thyroid cartilage and upper cartilaginous rings of the trachea (Anne et al 2001).The name of the gland is derived from the Greek word for shield. Because of its embryological development from pharyngeal pouches and descent, ectopic tissue can be found anywhere from the foramen caecum at the base of the tongue to the myocardium. The pyramidal lobe extends towards the hyoid bone and is a remnant of the thyroglossal duct. The normal adult thyroid gland weighs approximately15–20 g. The gland consists of many follicles of varying size lined by epithelium made up of cuboidal and columnar follicular cells, which secrete toward the large lumen of the follicle containing colloid. The thyroid gland is 50–75% colloid by weight (Harold 2006).The gland is enclosed in the pretracheal fascia, covered by the strap muscles and overlapped by the sternocleidomastoids. The anterior jugular veins course over the isthmus. When the thyroid enlarges, the strap muscles stretch and adhere to the gland so that, at operation, they often appear to be thin layers of fascia (Harold 2006).

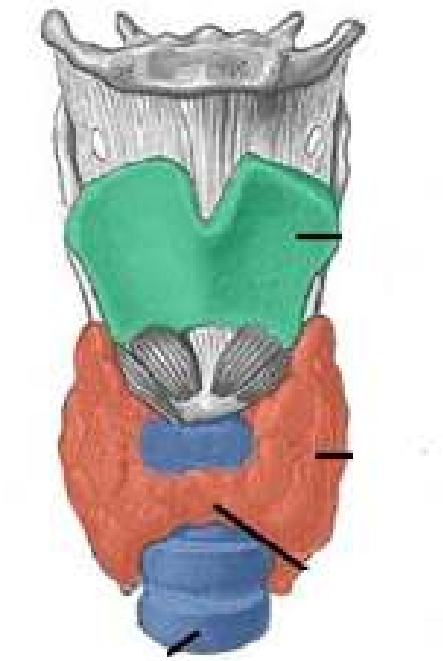

Figure (2.1): showed the anatomy of thyroid gland.
(https://teachmeanatomy.info/neck/viscera/thyroid-gland/).

2.2 Physiology of Thyroid Gland:

The thyroid gland is composed of large numbers of closed follicles (100 to 300 micrometers in diameter) filled with a secretory substance called colloid and lined with cuboidal epithelial cells that secrete into the interior of the follicles. The major constituent of colloid is the large glycoprotein thyroglobulin, which contains the thyroid hormones within its molecule. Once the secretion has entered the follicles, it must be absorbed back through the follicular epithelium into the blood before it can function in the body. The thyroid gland has a blood flow about five times the weight of the gland each minute, which is a blood supply as great as that of any other area of the body, with the possible exception of the adrenal cortex (Cooper 2003).

2.2.1 Thyroid Metabolic Hormones:

The thyroid gland, located immediately below the larynx on each side of and anterior to the trachea, is one of the largest of the endocrine glands, normally weighing 15 to 20 grams in

adults. The thyroid secretes two major hormones, thyroxine and triiodothyronine, commonly called T4 and T3, respectively (Besser et al., 2002).

Both of these hormones profoundly increase the metabolic rate of the body. Complete lack of thyroid secretion usually causes the basal metabolic rate to fall 40 to 50 per cent below normal, and extreme excesses of thyroid secretion can increase the basal metabolic rate to 60 to 100 per cent above normal. Thyroid secretion is controlled primarily by thyroid-stimulating hormone (TSH) secreted by the anterior pituitary gland. The thyroid gland also secretes calcitonin, an important hormone for calcium metabolism (Burger 2004).

About 93 per cent of the metabolically active hormones secreted by the thyroid gland are thyroxine, and 7 per cent tri-iodothyronine. However, almost all the thyroxine is eventually converted to tri-iodothyronine in the tissues, so that both are functionally important. The functions of these two hormones are qualitatively the same, but they differ in rapidity and intensity of action. Tri-iodothyronine is about four times as potent as thyroxine, but it is present in the blood in much smaller quantities and persists for a much shorter time than does thyroxine (Burger 2004).To form normal quantities of thyroxine, about 50 milligrams of ingested iodine in the form of iodides are required each year, or about 1 mg/week. To prevent iodine deficiency, common table salt is iodized with about 1part sodium iodide to every 100,000 parts sodium chloride (Besser et al., 2002).Iodides ingested orally are absorbed from the gastrointestinal tract into the blood in about the same manner as chlorides(Burger 2004). Normally, most of the iodides are rapidly excreted by the kidneys, but only about one fifth are selectively removed from the circulating blood by the cells of the thyroid gland and used for synthesis of the thyroid hormones (Dayan2001).

The first stage in the formation of thyroid hormones is transport of iodides from the blood into the thyroid glandular cells and follicles. The basal membrane of the thyroid cell has the specific

ability to pump the iodide actively to the interior of the cell (Dohan2003). This is called iodide trapping. In a normal gland, the iodide pump concentrates the iodide to about 30 times its concentration in the blood. After oral ingestion, iodine is rapidly reduced to iodide in the upper small intestine. More than 90% of the iodide is systemically absorbed within 60 minutes of oral ingestion. It distributes in the blood as an extracellular ion similar to chloride. Most leaves the extracellular space through thyroid extraction (20%) or urinary excretion (80%).Some is taken up by the salivary glands and gastric mucosa, which secrete into the gastrointestinal tract (James et al., 2006).

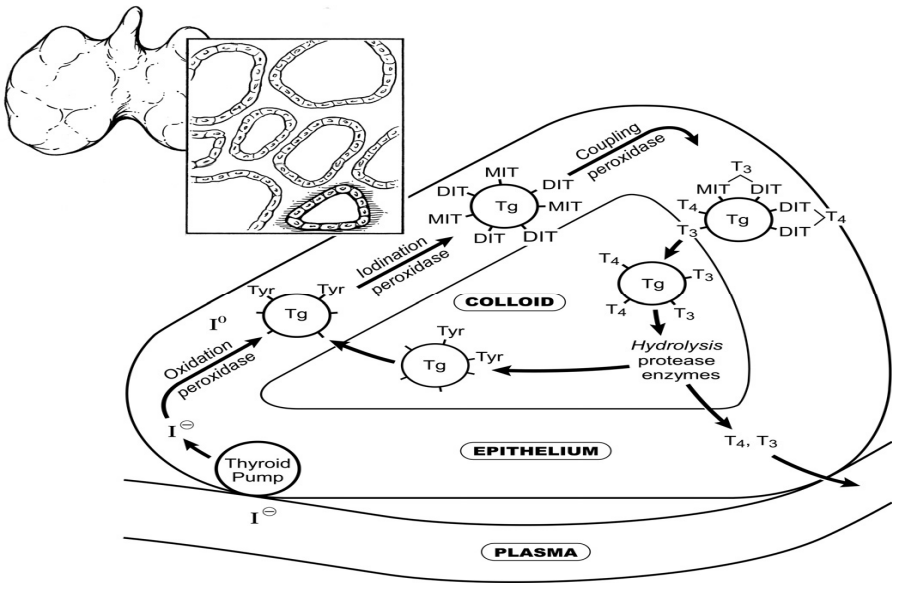

Figure (2-2): showed Iodine metabolism.

2.2.2 Iodide Trapping and Organification:

The thyroid follicular cell traps iodide by means of a high energy sodium iodide "thyroid pump" that concentrates iodine intra cellularly at 25–500 times the plasma concentration. Trapping can be blocked competitively by monovalentanions (e.g., perchlorate). In the normal thyroid, organification promptly follows trapping (see Fig. 2). The iodide is oxidized by thyroid peroxidase at the follicular cell colloid interface to neutral iodine, which binds to tyrosine residues on thyroglobulin. Thesemono- and di-iodinated tyrosines (MIT, DIT) couple to form

T3 and T4, which are stored in the colloid filled follicular lumen. Organification can be blocked by drugs such as propylthiouracil and methimazole(James et al., 2006).

2.2.3. Thyroid Hormone Storage and Release:

Thyroid stimulating hormone (TSH) initiates iodide uptake and organification, as well as release of thyroid hormone through hydrolysis of thyroglobulin. Thyroglobulindoes not normally enter the bloodstream except duringdisease states (e.g., thyroiditis or thyroid cancer). The normal thyroid gland contains a 1-month supply of hormone, thus drugs blocking hormone synthesis (e.g., propylthiouracil) do not become fully effective in controlling hyperthyroidism until intrathyroidal stores are depleted (James et al., 2006), *Thyroid-Pituitary Feedback:* The thyroid-pituitary feedback mechanism is very sensitive to circulating serum thyroid hormone levels and is the dominant method of adjusting TSH secretion. When serum thyroid hormone levels are increased, the serum TSH is suppressed; when serum thyroid hormone levels are low, serum TSH increases. The major hormone released by the thyroid is T4, which is transported to peripheral tissues by thyroid-binding proteins and converted to the more metabolically active T3at peripheral tissue site of action (James et al., 2006).

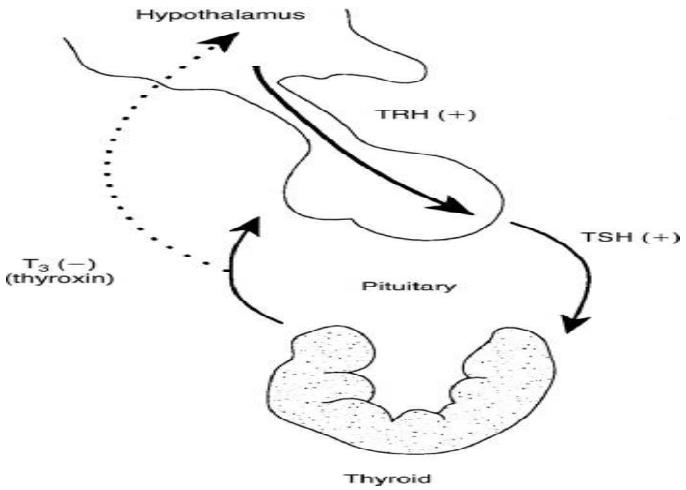

Figure (2-3): showed Thyroid-pituitary feedback loop.

2.3. Thyroid pathology:

2.3.1. Hyperthyroidism:

Most effects of hyperthyroidism are obvious from the preceding discussion of the various physiologic effects of thyroid hormone. However, some specific effects should be mentioned in connection especially with the development, diagnosis, and treatment of hyperthyroidism (Silva2003).

2.3.1.1 Causes of hyperthyroidism:

Hyperthyroidism occasionally results from a localized adenoma (a tumor) that develops in the thyroid tissue and secretes large quantities of thyroid hormone. This is different from the more usual type of hyperthyroidism, in that it usually is not associated with evidence of any autoimmune disease. An interesting effect of the adenoma is that as long as it continues to secrete large quantities of thyroid hormone, secretory function in the remainder of the thyroid gland is almost totally inhibited because the thyroid hormone from the adenoma depresses the production of TSH by the pituitary gland (Tomeret al., 2003).

2.3.1.2 Symptoms of Hyperthyroidism:

The symptoms of hyperthyroidism are obvious from the preceding discussion of the physiology of the thyroid hormones: a high state of excitability, intolerance to heat, increased sweating, mild to extreme weight loss (sometimes as much as 100 pounds), varying degrees of diarrhea, (BesserGM 2002) muscle weakness, (Burger AG, 2003) nervousness or other psychic disorders, (Cooper DS, 2003) extreme fatigue but inability to sleep, and tremor of the hands(Stassi et al., 2002)

2.3.1.2 Diagnostic Tests for Hyperthyroidism:

For the usual case of hyperthyroidism, the most accurate diagnostic test is direct measurement of the concentration of "free" thyroxine (and sometimes triiodothyronine) in the plasma, using appropriate radioimmunoassay procedures. Other tests that are sometimes used are as follows: The basal metabolic rate is usually increased to +30 to +60 in severe hyperthyroidism; the concentration of TSH in the plasma is measured by radioimmunoassay. In the usual type of thyrotoxicosis, anterior pituitary secretion of TSH is so completely suppressed by the large amounts of circulating thyroxine and triiodothyronine that there is almost no plasma TSH (Larsen et al., 2003).

2.3.1.3 Treatment of the hyperplastic thyroid gland with radioactive iodine:

80 to 90 per cent of an injected dose of iodide is absorbed by the hyperplastic, toxic thyroid gland within1 day after injection. If this injected iodine is radioactive, it can destroy most of the secretory cells of the thyroid gland. Usually 5 mill curies of radioactive iodine are given to the patient, whose condition is reassessed several weeks later. If the patient is still hyperthyroid, additional doses are administered until normal thyroid status is reached (Silva2003).

Table (2-1): Clinical Frequency of Various Causes for Hyperthyroidism.

Clinical Frequency of Various Causes for Thyrotoxicosis (Hyperthyroidism)	
Graves' disease	70%
Thyroiditis	20%
Toxic multinodular goiter	5%
Toxic adenoma	5%
Others	<1%

2.4Thyroid scintigraphy and Radioactive Iodine uptake:

2.4.1 Thyroid Scintigraphy:

The thyroid scan depicts the entire gland in a single image and permits direct correlation of physical findings with abnormalities in the image. The combination of gamma camera and pinhole collimator offers the flexibility of obtaining multiple-view high-resolution images of the thyroid. Pinhole collimator magnification provides image resolution superior to parallel-hole collimators in the range of 5mm, compared to 1–2 cm with a parallel-hole collimator (James et al 2006).

Thyroid Examination, the thyroid gland should be routinely examined by palpation at the time of imaging in order to estimate the size of the gland and to confirm the presence and location of nodules. A radioactive marker source (122-keV Cobalt-57 or Tc-99m) can then be placed over the palpated nodule for anatomical and functional correlation (James et al 2006).

Methodology: Procedure Radioiodine is administered orally. The usual I-123 thyroid scintigraphy dose is 200–300 μCi. The scan is usually acquired at 2–6 hours after administration but may be acquired at the time of the 24-hour%RAIU. The higher count rate obtainable at 2–6 hours allows for shorter imaging time and better image quality. The low count rate at 24 hours requires longer acquisition time which increases the likelihood of patient movement. With Tc-99m Pertechnetate, 3–5 mCi is administered intravenously and imaging begins 20–30 minutes after injection. For both radiopharmaceuticals, a standard or large field-of-view gamma camera is used, equipped with a pinhole collimator that has an interchangeable lead pinhole insert of 3- to 6-mm in internal diameter placed in its distal aspect. Smaller diameter inserts provide higher resolution but lower sensitivity. A 15–20% photo-peak window is set at 159 keV forI-123 and at 140 keV for Tc-99m. Imaging protocols for thyroid imaging for the two radiopharmaceuticals

are similar and described in more detail in Boxes 5-6 and 5-7.the patient is positioned supine with the neck hyper extended so that the plane of the thyroid gland is parallel to the crystal face of the camera. The thyroid gland should fill approximately two-thirds of the field of view. This is achieved with a 6–8 cm distance from the collimator to the surface of the neck. Magnification increases as the pinhole collimator approaches the neck (James et al., 2006).

On one image, a radioactive marker (Tc-99m orCobalt-57) or computer cursor is placed at the sterna notch and on the right. A 4- to5-cm line source marker or two point sources 4–5 cm apart may be placed on the neck just lateral to the thyroid lobes and parallel to their long axis to estimate the size of the thyroid and nodules. Because of the three-dimensional nature of the gland and pinhole collimator distortion, this is an approximate measurement and does not obviate physical exam size estimation (James et al 2006).

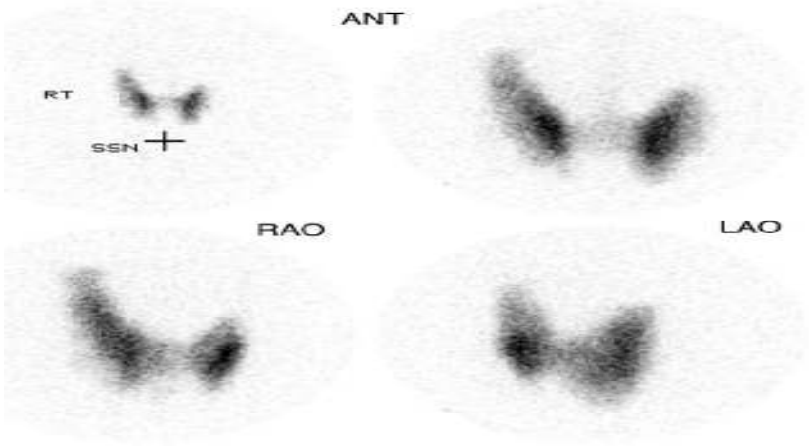

Figure (2-4): Normal I-123 thyroid scan

Images are routinely obtained in the anterior, right anterior oblique (RAO), and left anterior oblique (LAO) views. Each image is obtained for 100,000counts. It is preferable for the patient to remain in one position while the camera and collimator are moved to the different projections, thus making images more reproducible between patients and resulting in less image distortion and patient motion (James et al 2006).

Additional images with a radioactive marker may be indicated to determine whether a palpable nodule takes up the radiopharmaceutical (i.e., a hot or cold nodule). Special care should be taken to avoid the parallax effect of pinhole collimator. The parallax effect results in a change in the relationship between a near and distant object when viewed from different angles. With a pinhole collimator, this can result in misregistration of the relationship between the nodule and the marker or, in the case of a suspected substernal goiter, the suprasternal notch marker and the thyroid. The effect can be minimized in several ways. One method is to obtain an image with the collimator at an increased distance from the thyroid, decreasing the effect of magnification and distortion. A second method is to place the marker region of interest in the center of the field-of-view. Finally, a parallel whole collimator might be used for the marker image (James et al 2006).

2.4.2 Clinical Indications for Thyroid Scintigraphy:

Thyroid scans have been used diagnostically for decades for the evaluation of various types of thyroid disease. They are requested less today than in the past because of the availability of other thyroid imaging modalities and the aggressive use of diagnostic percutaneous aspiration biopsy of thyroid nodules. Because of the thyroid scan's functional nature, scintigraphy still provides valuable clinical information for many patients (James et al 2006).

2.4.3 Normal Thyroid Scintigraphy: Thyroid scans should always be correlated with physical examination of the thyroid gland and interpreted with knowledge of the patient's thyroid function studies and other imaging studies (James et al 2006).

The normal thyroid has a butterfly shape with lateral lobes extending along each side of the thyroid cartilage. The lateral lobes are connected by an isthmus that crosses the trachea anteriorly below the level of the cricoid cartilage. However, the appearance of the gland is quite variable from patient to patient. The right lobe is often larger than the left. The lateral lobes

measure 4–5 cm from superior to inferior poles and are 1.5–2 cm wide. The pyramidal lobe ascends from the isthmus or adjacent part of either lobe (more often the left lobe) to the hyoid bone. The normal gland has homogeneous and uniform distribution of radiotracer throughout. Some increased intensity may be seen in the middle or medial aspects of the lateral lobes, owing to the thickness of the gland in this location. The amount of activity in the isthmus varies greatly, with little or no activity in some patients and prominent activity in others. In normal adults, the thin pyramidal lobe is usually not seen. The salivary glands are routinely seen on Tc-99m Pertechnetate imaging at 20 minutes' post injection. However, they are not usually seen on I-123 scans imaged at 4 hours because the radiopharmaceutical has cleared. Higher generalized background is seen on Tc-99m Pertechnetate compared to I-123 imaging. Esophageal activity can be problematic with either agent. It is frequently not in the midline, being displaced by the trachea and cervical spine when the neck is hyper extended in the imaging position. It is more often seen just to the left of midline and can usually be confirmed by having the patient swallow water to clear the esophagus, followed by repeat imaging (James et al., 2006).

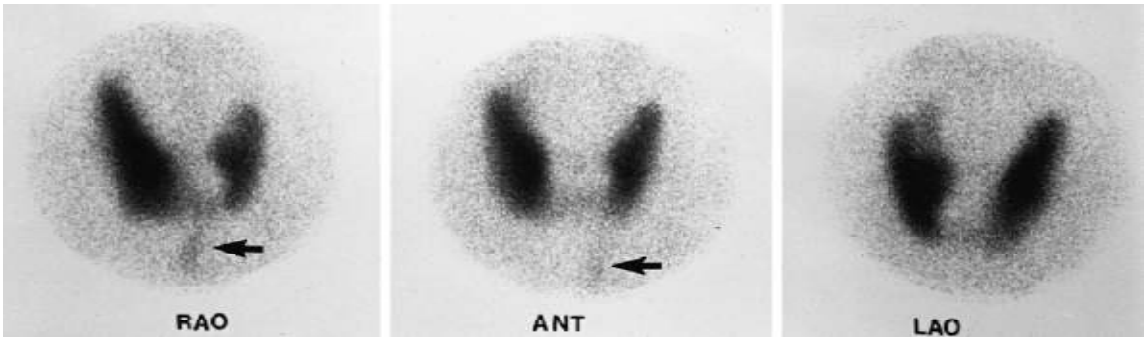

Figure (2-5): Anterior (ANT) and right and left anterior oblique (RAO, LAO) views obtained with Tc-99m Pertechnetate. Note the esophageal activity below the thyroid to the left of midline (arrows*).*

2.4.3 ***Abnormal Thyroid Scintigraphy:*** A systematic interpretation of the thyroid scintigram requires assessment of thyroid size and configuration and the identification of focal abnormalities. These include hot and cold nodules and extra-thyroidal activity in the neck or

mediastinum. The thyroid scan allows for correlation of palpable abnormalities with scintigraphic findings. This is frequently critical in assigning significance to a palpable abnormality. Radionuclide markers can aid in confirming that the palpated nodule correlates with the scintigraphic finding. Gland size can be estimated using the thyroid scan but this has limitations due to the scan's two-dimensional nature and the magnification and distortion caused by pinhole collimation. However, image appearance and surface radio-markers provide some indication of size. Enlargement seen on the scan is often accompanied by a change from a relatively concave to a convex appearance of the lobes. (James et al., 2006).

2.4.3.1*Thyroid nodule:* Thyroid nodules are quite common; they occur more often in women than men. The incidence of both benign and malignant nodules increases with age. Determining whether a nodule is benign or malignant is a common clinical problem. A nodule presenting in a young person, a male, or with recent nodule growth increases concern for malignancy. The presence of multiple nodules decreases the likelihood of malignancy. A nodule in a patient with Graves' disease requires evaluation (James et al., 2006).

2.4.3.1.1Cold Nodule: Greater than 85–90% of thyroid nodules are cold (hypo-functional) on thyroid Scintigraphy, that is, they have decreased uptake compared to adjacent thyroid tissue. Many have benign etiologies, such as simple cysts, colloid nodules, thyroiditis, hemorrhage, necrosis, and infiltrative disorders such as amyloid or hemochromatosis. However, a significant subgroup of patients with cold nodules has malignancy as the etiology. The incidence of thyroid carcinoma in a single cold nodule is reported to be as high as 40% in surgical series but as low as 5% in general medical series. Overall, the incidence of cancer in a cold thyroid nodule is generally considered to be approximately 15–20%.With multinodular goiters, the incidence of malignancy in cold nodules is lower, less than 5%. Enlarging nodules or "dominant "nodules

(i.e., those that are distinctly larger than the other nodules in a multinodular goiter) require further evaluation because of relatively increased risk (James et al., 2006).

2.4.3.1.2 ***Hot and Warm Nodules:*** Radioiodine uptake within a nodule denotes function. A functioning nodule is very unlikely to be malignant. Less than 1% of hot nodules harbor malignancy. The term hot nodule should be reserved for those that not only have high uptake in the nodule scintigraphically, but also have suppression of extra-nodular tissue If extra-nodular tissue is not suppressed, it should be referred to as a warm nodule (James et al., 2006). Hot nodules are caused by toxic adenomatous nodules. Warm nodules may be caused by autonomous hyper-functioning adenomas. However, they are not toxic, that is, they are not producing enough thyroid hormone to cause thyrotoxicosis and thus TSH is not suppressed. A warm nodule may also be due to nonautonomous hyperplastic tissue or even normal functioning tissue surrounded by poorly functioning thyroid. Differentiation can be made by administration of thyroid hormone (thyroid suppression test). Autonomous nodules cannot be suppressed. However, the suppression test is rarely needed in current practice. Large hot nodules greater than 2.5–3.0 cm usually produce overt hyperthyroidism. Some patients with smaller nodules have subclinical hyperthyroidism, which can be confirmed by a suppressed serum TSH but normal T4. In the past, a small autonomous nodule might be followed clinically because some stabilize, whereas others regress or undergo involution. Increasingly, nodules are treated at an early stage because of the low incidence of regression and increased awareness of adverse consequences associated with subclinical hyperthyroidism (e.g., bone mineral loss).

2.4.3.1.3 Indeterminate Nodule: When a palpable or sonographically detected nodule greater than a centimeter in size cannot be differentiated by thyroid scan as hot or cold compared to surrounding normal thyroid, it is referred to as an indeterminate nodule. A cold nodule arising from the posterior aspect of the gland may have normal glandular activity superimposed over

the nodule, making it appear to have normal uptake. For management purposes, an indeterminate nodule has the same significance as a cold nodule. The possibility of an indeterminate nodule highlights the need for close correlation between physical and scintigraphic findings Discordant Nodule Discordance in appearance between radioiodine and Tc-99m Pertechnetate scans is seen in a small minority of patients. A nodule may appear hot on Pertechnetate imaging but cold on radioiodine imaging because Tc-99m Pertechnetate is trapped but not organified (James et al., 2006).

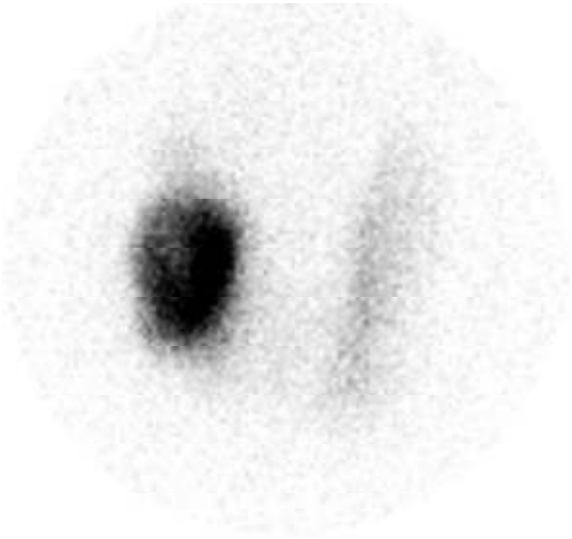

Figure (2-6): Toxic (hot) thyroid nodules.

2.4.3.2 Goiter: The term *goiter* refers to thyroid gland enlargement, but it is often qualified to indicate the cause of the enlargement (e.g., toxic nodular goiter, colloid goiter, or diffuse toxic goiter [Graves' disease]).

2.4.3.2.1 Graves' disease vs. Multinodular Toxic Goiter: In a patient with newly diagnosed thyrotoxicosis, the physical exam can usually differentiate the diffuse goiter of Graves' disease from a multinodular toxic gland. The thyroid scintigram can help make the distinction. Toxic nodular goiter has the characteristic scintigraphic pattern of increased uptake that corresponds to palpable nodules and suppression of extranodular thyroid tissue. This contrasts with the diffuse

homogenous increased uptake of Graves' disease (12).The pyramidal lobe, a paramedic structure arising superiorly from the isthmus (right or left lobe), is also usually well visualized with Graves' disease (James et al., 2006).

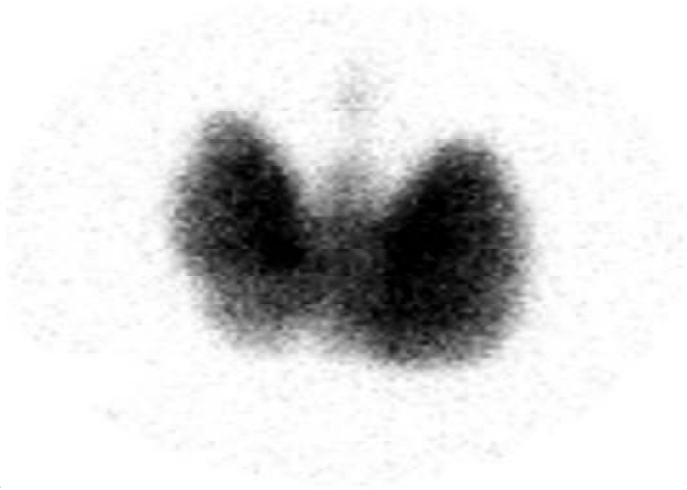

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Figure (2-7): Graves' disease. Large goiter Note the pyramidal lobe.

2.4.3.3 Ectopic Thyroid Tissue: The thyroglossal duct runs from the foramen caecum at the base of the tongue to the thyroid. If it fails to migrate from its anlage, lingual or upper cervical thyroid tissue can present in the neonate or child as a midline mass with or without obstructive symptoms and often accompanied by hypothyroidism. Ectopic thyroid tissue may also be mediastinal (substernal goiter) or even pelvic/ovarian (struma ovarii). Scintigraphy: The typical appearance of a lingual thyroid is a focal or nodular accumulation at the base of the tongue and absence of tracer uptake in the expected cervical location. However, lingual thyroids usually function poorly. Lateral thyroid rests are also often hypofunctional.

However, rests can function, hyperfunction, or be involved with adenocarcinoma of the thyroid. Functioning ectopic thyroid tissue should be considered metastatic until proven otherwise (James et al., 2006).

2.4.3.4 Subacute thyroiditis: This entity is discussed in the section Thyrotoxicosis. With hyperthyroidism, the scan shows only suppression. During recovery phases, the appearance of the thyroid is variable and depends upon the severity and distribution of the disease. The scintigram may show inhomogeneity of uptake, regional areas of hypofunction, or even focal hypofunction (James et al., 2006).

2.4.3.5 Chronic Thyroiditis (Hashimoto's Thyroiditis): Scintigraphic findings are highly variable. Diffuse enlargement is usual, although the scan may be normal early in the process. Uptake may be inhomogeneous throughout the gland or there may be focal cold areas without a palpable nodule. The pyramidal lobe is often seen in Hashimoto's disease (James et al., *2006).*

2.4.3.6 Acute Thyroiditis: Suppurative bacterial infection is the usual cause for this rare condition. The thyroid is typically enlarged and tender. Focal abscesses will appear as cold regions scintigraphically. *Reidel's struma* is an uncommon form of thyroiditis where all or part of the gland is replaced by fibrous tissue. No uptake is seen in the region of fibrous tissue (James et al., 2006).

2.4.3.6 Thyroid Cancer: Whole body thyroid cancer scintigraphy has long been used for well-differentiated papillary and follicular thyroid cancer. It is often performed post-thyroidectomy prior to radioiodine I-131 therapy and for evaluating response therapy. The most common sites of metastasis are locally in the lymph nodes of the neck, lung, mediastinum, and bones. Medullary carcinomas and anaplastic carcinomas do not concentrate radioiodine and are not detected with conventional thyroid scintigraphy.

Whole body thyroid cancer scanning requires patient preparation. The traditional approach is to withdraw hormone replacement therapy for 4–6 weeks so that patients may achieve a maximal endogenous thyroid stimulating hormone (TSH) response (>30 U/ml). To minimize symptoms of hypothyroidism, patients are sometimes switched to short-acting triiodothyronine (T3), which

is discontinued 2 weeks prior to the scan. Imaging with I-131 is typically performed 48 hours after I-131 diagnostic dose administration (James et al., 2006).

More lesions are demonstrated in this time than at 24 hours due to background clearance and the higher target- to-background ratio. Serum thyroglobulin levels are also measured during maximum TSH stimulation (a sensitive tumor marker). For I-123, whole body imaging is acquired at 24 hours. Post thyroidectomy, it is not uncommon to have high intensity uptake in the thyroid bed (star artifact), which may preclude good visualization of the neck or mediastinum. The artifact is caused by septal penetration of high-energy photons through the collimator. A pinhole collimator that has no septa can better resolve the high intensity uptake in the neck. In the postoperative state, uptake in the neck may be due to residual normal thyroid or to thyroid cancer. The scan cannot make the distinction. Activity outside the thyroid bed is very likely metastatic (James et al., 2006).

2.4.4 Thyroid Radiopharmaceuticals:

Radioiodine: Because radioiodine is selectively trapped and organified by the thyroid and incorporated into thyroid hormone, radioactive iodine is an ideal physiological radiotracer, providing clinically important physiological information regarding thyroid function. I-123 and I-131 are the two radiopharmaceuticals used clinically. Because of the rapid absorption, prompt uptake, and organification of iodine, radioactivity is detectable in the thyroid gland within minutes and normally reaches the thyroid follicular lumen by 20–30 minutes. A progressive increase in thyroid uptake normally occurs over 24 hours. The time delay between radioiodine ingestion and imaging (e.g., 2–6 hours for routine I-123thyroid imaging and 1–3 days for I-131) is dictated more by the desire for background clearance and a high target to-background ratio than by slow gland uptake. Radioiodine is also taken up in the salivary glands, stomach, and to a lesser extent, choroid plexus. It is not concentrated in these organs. The kidneys and gastrointestinal tract serve as the excretory route (James et al., 2006).

Iodine I-131: Physics: The physical half-life of I-131 is 8 days. It undergoes beta minus decay and emits a principle primary gamma photon of 364 keV. The 364-keVgamma photons are not optimal for modern-day gamma cameras. Camera count detection sensitivity for I-131 is poor; approximately half of the photons penetrate the typical three-eighths-inch crystal and thus are not detected. Septal penetration of the collimator by the high-energy emissions results in image degradation. High energy beta particles are also emitted, the principle one being 0.606 MeV (James et al., 2006).

Dosimetry, The high-energy beta emissions and long physical half-life of I-131 result in relatively high radiation to the patient, particularly to the thyroid (approximately 1 rad/μCi). This high radiation absorbed dose severely limits the dose that can be administered, further impacting on image quality (James et al., 2006).

Iodine I-123: Physics I-123 decays by electron capture with a half-life of 13.2 hours. The principal gamma emission is a 159 keV photon which is well-suited for gamma cameras. There are a small percentage of higher energy emissions (2.4% 440–625 keV) and 0.15% (625–784 keV).There are no particulate emissions (James et al., 2006).

Dosimetry, Methods used for I-123 production in the United States today result in long-lived radionuclide impurities. In the past, I^{123} was contaminated with I-124and I-125. The maximal levels of identified impurities are Te-121 (0.05%) and I-125 (0.06%). The thyroid receives 1.5–2.6 rads (15–25% RAIU) from a 200 μCi dose of I^{123}.The considerably lower radiation dosimetry of I-123 compared to I^{131} allows administration of 200–400 μCi of I-123 for routine thyroid scanning compared to 50 μCi of I-131. This higher administered dose results inconsiderably better image quality (James et al., 2006).

Tc-99m Pertechnetate: Because of Tc-99m pertechnetate's low cost and ready availability from molybdenum-99/Tc-99m generator systems, it has long served as an alternative to radioiodine

for thyroid scintigraphy. Physics: The 140-keV photopeak of Tc-99m is ideal for use with the gamma camera. It has a short 6-hour half-life and no particulate emissions (James et al., 2006). Pharmacokinetics: In contrast to the oral administration of radioiodine, Tc-99m Pertechnetate is administered intravenously. Tc-99m is trapped by the thyroid in an identical manner as iodide, but it is not organified nor incorporated into thyroid hormone. Because it is not organified, it is not retained in the thyroid. Thus, thyroid imaging is performed at peak uptake 20–30 minutes after injection.

Dosimetry: The lack of particulate emissions and the short half-life of 6 hour's results in relatively low radiation dosimetry to the thyroid. Thus, the allowable administered activity of Tc-99m Pertechnetate (3–5 mCi) is considerably higher than I-123 for routine thyroid scans. The large photon flux provides high quality images (James et al., 2006).

Table (2-1): Physical Characteristic of Thyroid Radiopharmaceuticals

	Tc-99m	**I-123**	**I-131**
Mode of decay	Isometric transition	Electron capture	Beta minus
Physical half-life(t1⁄2)	6 hr	13.2 hr	8.1 days
Photon energy	140 keV	159 keV	364 keV
Abundance	89%	83.4%	81%
Beta emissions			606 keV

Table (2-2): Dosimetry of Thyroid Radiopharmaceuticals

	Tc-99m **(rads/5 mCi, cGY/18MBq)5**	**I-123** **(rads/200 µCi,) cGy/7.5 MBq)**	**I-131** **(rads/50 µCi, cGy/3.7 MBq)**
THYROID	0.600	1.5 to 2.6*	39.000 to 65.000
BLADDER WALL	0.430	0.070	0.150
STOMACH	0.250	0.050	0.085
SMALL INTESTINE	0.550	0.030	0.003
RED MARROW	0.100	0.060	0.007
TESTIS	0.050	0.027	0.006
OVARIES	0.150	0.072	0.009
TOTAL BODY	0.070	0.009	0.035

***Lower estimate assumes a 15% RAIU and higher estimate assumes a 25% RAIU, both at time of calibration.**

2.4.4 Methodology for thyroid uptake:

The role of thyroid uptake has evolved to confirming a diagnosis of hyperthyroidism or hypothyroidism, to calculating I131 dose before therapy of hyperthyroidism (Paul et al., 2004). Thyroid iodine uptake is, in fact non-specific as measure of thyroid function, because the value is influenced by total iodine uptake. The 24 hour uptake is greater than normal in areas of dietary iodine deficiency, and its low when patient have increase dietary iodine, take supplement or medication containing iodine or have recently undergone studies using x-ray

contrast material (Paul E et al.,2004). Any 24-hour thyroid uptake values in excess of %25 represent greater iodine uptake than is usually encountered in normal population, in hyperthyroidism patients values of 35% to 95% are typically observed. Occasionally a patient present with rapid elevation of serum T3 and T4 and appropriate suppression of TSH but is found to have very low iodine uptake so-called subacute thyroiditis, which is not appropriate to treat these patients with radioactive iodine. (Paul E et al., 2004).

The thyroid uptake probe contains a 1 to 2-inch sodium iodide crystal with open face collimation. The thyroid uptake test is billable as stand-alone procedure or in combination with thyroid scan, the most frequently physician request a thyroid uptake and scan, this is typically performed using 4.0 mci of Tc-99m pertechnetate for imaging followed by 5 mci of I131 given orally with patient return the next day for the 24-hour thyroid iodine uptake. (Paul E et al.,2004)

Radioiodine Percent Uptake: Both I-131 and I-123 can be used for calculation of the %RAIU or the percent of the administered radioactive iodine taken up by the thyroid. Clinical indications for uptake determinations are few, but important. Indications: The most common clinical indication for a %RAIU study is to aid in the differential diagnosis of newly diagnosed thyrotoxicosis. In most cases, the referring physician seeks to differentiate Graves' disease, the most common cause for thyrotoxicosis, from other causes (e.g., thyroiditis, the second most common cause). Therapy of Graves' disease is quite different than that for other causes. The %RAIU is elevated in Graves' disease, but suppressed or decreased in most other causes of thyrotoxicosis with diffuse goiter, such as thyroiditis (James et al., 2006).

Methodology: Medications that might interfere with thyroid uptake should be discontinued for an appropriate length of time. Patients should have nothing by mouth for 4 hours prior to the study to assure good radioiodine absorption. I-123 and I-131 are usually administered in capsule

form rather than liquid. The unit-dosed capsule formulation minimizes airborne exposure of radioiodine to technologists and is convenient for handling (James et al., 2006).

When a scan is not needed, 5–10 μCi I-131 or 50–100μCi I-123 is adequate for an uptake because of the probe's high detection sensitivity compared to a gamma camera. When a scan is indicated, both can be performed using the scan dose of I-123 (200 300 μCi). The standard %RAIU uptake is acquired at 24 hours. In some clinics, a 2–6 hours' uptake is also routinely performed. A non-imaging gamma scintillation probe detector is used for radioiodine thyroid uptake studies. It has a 2-cmthick × 2-cm diameter sodium iodine crystal with an open cone-shaped single-hole lead collimator coupled to a photomultiplier tube and electronics. Room background activity is determined. The radioiodine capsule is placed in a Lucite neck phantom and activity counted with the probe detector placed at a standardized distance of 30cm. The capsule is administered to the patient. The probe is placed 30cm from the anterior surface of the patient's neck, such that the entire gland can be detected by the probe but most extra thyroidal activity is not. The patient's neck (background) is counted. At the uptake times (2–6 hours and/or 24 hours), counts are obtained for the neck and the patient's thigh (background). The percent radioiodine uptake is calculated according to this formula:

$$\textbf{\%RAIU} = \frac{\text{Neck counts/min (background corrected)} \times 100}{\text{Administered dose capsule counts}}$$

In the past, a standard reference capsule similar in activity to the administered capsule was counted initially and at the uptake intervals. The purpose of the standard was to correct for decay. A dose-to-standard ratio was determined to correct for the difference in standard and administered dose. In present-day uptake probe-computer systems, decay is automatically corrected (James et al., 2006).

Tc-99m Pertechnetate Uptake: The advantages of using Tc-99m Pertechnetate as an alternative to radioiodine to calculate an uptake includes its favorable radiation dosimetry, a particular consideration for children, and that the study can be completed within 30 minutes with uptake results available soon thereafter. The disadvantages of the Tc-99mpertechnetate uptake include a less well-defined normal range, the standard practice of calculating the therapy dose based on the radioiodine uptake, and the lack of software for this calculation on some newer camera computer systems (James et al., 2006).

Methodology: A scintillation probe is not used for a Tc-99m uptake because of the high neck and body background. This is a gamma camera technique for calculating the percent uptake, similar to that used for thyroid cancer scans. Before and after inject if theTc-99m Pertechnetate, the syringe is imaged with the gamma camera (preinjection counts minus postinjection residual counts = administered counts). Twenty minutes after injection, the thyroid scan is acquired on computer. Regions of interest are drawn on computer for the thyroid, thyroid background, and the syringes. Areas of interest are normalized for pixel size and thyroid and syringe counts are normalized for time of acquisition (James et al., 2006).

The percent uptake is calculated*:*

$$\textbf{Tc-99m Pertechnetate \% uptake} = \frac{\textit{Thyroid counts} - \textit{Background counts}}{\textit{Injected counts} - \textit{R counts}} \times 100$$

Normal Tc-99m uptake ranges from 0.3–4.5%. Accuracy is less than with the %RAIU. A simple qualitative approach has been used to estimate uptake by obtaining images with the salivary glands in the same field-of-view as the thyroid. In the euthyroid patient, relative uptake in the salivary and thyroid glands is similar. With hyperthyroidism, thyroid uptake is considerably greater than salivary gland uptake (James et al., 2006).

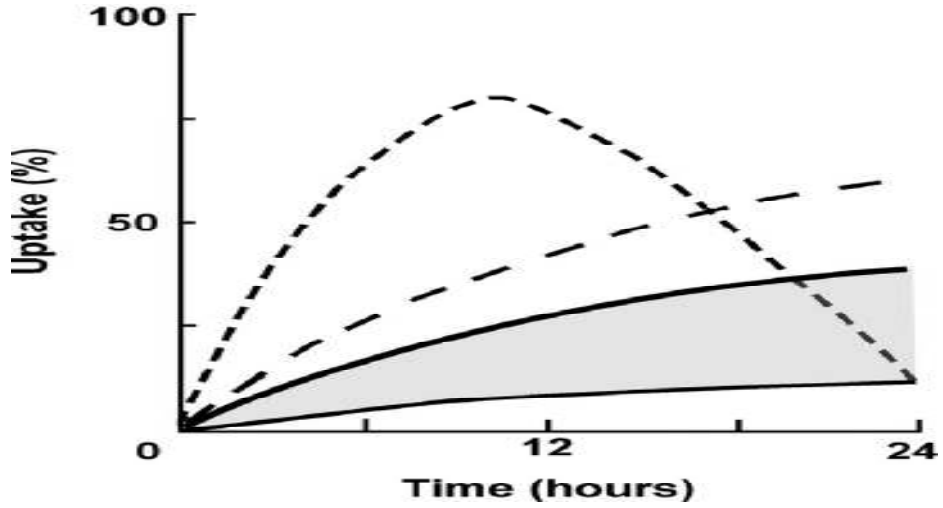

Figure (2-8): Thyroid radioiodine uptake. Radioiodine uptake normally increases progressively over 24 hours (gray area) and is between 10 and 30% at 24 hours. Atypical Graves' hyperthyroid patient is noted by the broken line above the normal range with24-hour uptakes ranging from 50–80%.

2.4.5 Special Considerations and Precautions:

Food and Medications Containing Iodine*:* Stable iodine contained in foods and medications can interfere with radionuclide thyroid studies. Expansion of the iodine pool due to ingestion or parenteral administration of iodine containing agents results in a reduced percent radioiodine uptake (%RAIU) by the thyroid. Increasing amounts of iodine in the normal diet over the years has resulted in a lower normal value for the %RAIU. Suppression of uptake by exogenous iodine may preclude successful imaging or accurate uptake measurements.

As little as 1 mg of stable iodine can cause marked reduction of uptake and 10 mg can effectively block the gland (98% reduction). Radiographic contrast media are a common source of iodine that interferes with radioiodine thyroid studies. A food and drug history should be obtained from all patients prior to undergoing thyroid imaging and uptake studies. Chronic renal failure impairs iodide clearance, expands the iodide pool, and thus lowers the %RAIU. Hypothyroidism slows clearance of radioactive iodine from the body; hyperthyroidism increases the clearance rate (James et al., 2006).

Pregnancy: The fetal thyroid concentrates radioiodine after 10–12 weeks of gestation. Radioiodine crosses the placenta and significant exposure of the fetal thyroid can occur after therapeutic doses to the mother, resulting in fetal hypothyroidism and even cretinism (James et al., 2006).

Nursing Mother: Radioiodine is excreted in human breast milk. Because of its long half-life, nursing should be discontinued after diagnostic or therapeutic studies with I-131.With I-123, it has generally been recommended that breastfeeding may resume after 2–3 days. With Tc-99m Pertechnetate, nursing can be resumed after 24 hours (James et al., 2006).

Patient Information: Thyroid studies must always be interpreted in light of the patient's clinical history, thyroid physical examination, and, importantly, with knowledge of the patient's serum thyroid function studies (James et al., 2006).

2.5. Radionuclide therapy:

2.5.1 Principles of Therapy:

Radionuclide therapy with unsealed sources has several underlying principles, which apply most to all forms of treatment. Where a treatment using a radionuclide is envisioned, it ideally represents a radioisotope–drug combination that is specifically suited for a disease in an individual patient. To begin with, the physical characteristics of the radioisotopes must be considered. Critical characteristics include type and range of emissions, half-life, and chemical characteristics. Most therapy agents utilize b-particle emissions for their ability to penetrate tissues. This deposition of energy in tissue by b emitters results in cellular damage. Among the b emitters there are several choices with respect to energy of the b emission. Lower energy b particles can travel a few cell diameters, or at most in the sub-millimeter range. These may be useful for microscopic targets and reducing normal tissue damage. Higher energy b particles

such as those emitted by P-32, Y-90, and Ho-166 have excellent tissue penetration with a range beyond the source of several millimeters (Janet et al., 2007). Thismay be desirable when a high homogeneous dose to a large target such as a lymphoma nodule or the bone from a bone surface or marrow source is being treated. Intermediate-range b particles such as those from iodine-131 (I-131) have a shorter path length and may result in less dose homogeneity to the tissue, but still retain excellent therapeutic effect. Proponents of Auger emitters for radionuclide therapy posit that these low-energy b particles can cause therapeutic effect without excess tissue toxicity because of their short energy deposition range. A somewhat similar argument has garnered favor for support of the use of a-particle emitters for therapy. At-111, Bi-213, and some of the transuranic elements have been studied with varying degrees of success. alpha particles are highly energetic with these emitters. Investigators hypothesize that the heavy particle has such momentum that it results in high levels of cell killing close to the origin of the radionuclide deposition. This is thought to result in low surroundingtissue toxicity and high levels of cell killing in tumors where the radiation is deposited. Gamma emissions from therapeutic radionuclide such as the 364 KeV in I- 131 are energetic enough to cause a generalized dose effect in an organ, or in the whole body and should be considered in treatment planning for the enhanced treatment effect they might provide as well as the toxicity they may cause.

The physical half-life of the therapeutic radionuclide is an important consideration and underlying principle for therapy planning. Rarely, except in thyroid treatment, is the simple salt form of the radionuclide used. It is most likely attached to a drug or particle that controls its biodistribution. The ideal therapeutic radiopharmaceutical is one that remains attached to the parent drug or its metabolites, and is excreted rapidly through a known simple route. Radiopharmaceuticals that undergo complex metabolism that results in free radio nuclides as well as labeled metabolites that are excreted by several routes are more difficult to use(Janet et al., 2007).They also create greater difficulty for realistic radiation absorbed dose estimation

based on their observed biodistribution. In most cases, the most optimal combination is a radionuclide with a physical half-life that is similar to the drug or biologic agent half-life, so that the resulting effective half-life represents a length of time appropriate for maximum therapeutic effect and minimal non target toxicity (Janet et al., 2007).

2.5.2. Bio-distribution:

An important aspect of therapy with radio-nuclides is bio-distribution of the radiopharmaceutical. While high target tissue binding is the most important goal, nonspecific binding or blood pool residence of the compound is an important consideration. Also important is the bio-distribution of metabolized components and their excretion routes. Ideally, a therapeutic radiopharmaceutical has high target binding and rapid excretion without redistribution to non-target tissues and compartments. A major responsibility of the nuclear medicine physician is to know and understand completelythe bio-distribution patterns of a radionuclide therapy combination. Not only is this important for safety, but for accurate dosimetry estimation. Often, observation of bio-distribution requires imaging and quantification of radionuclide tissue concentration and time-activity data. Additionally, knowledge of the bio-distribution of the pharmaceutical that will be radiolabeled will give an indication of the correct radioisotope to be chosen for the therapy indication (Janet et al., 2007).

Iodine-131:Iodine-131 has a convenient half-life and energy characteristics (T1/2 ¼ 8.1 days; E_{max} beta ¼ 600 keV). Normal physiological uptake of iodide (and hence its radioactive form) in functioning thyroid tissue is the primary reason for its role in treating several thyroid disorders and malignancies. This fact, coupled with the energetic beta emission, has made it a treatment standard. Sodium iodide has the convenience of easy oral administration, which further improves patient compliance. Its high-energy gamma radiation (364 keV), which requires additional radiation safety measures, can be considered advantageous for

biodistribution studies and radiation-absorbed dose evaluation. Sodium iodide in liquid form is highly volatile and needs special handling in a fume hood with exhaust system to avoid inhalation of the iodide vapor during labeling. It also means that personnel handling the radiopharmaceutical should be subjected to periodic assays to exclude uptake in their thyroid glands. However, I-131 remains the most commonly used therapy radionuclide in nuclear medicine. When used for treating nonthyroid malignancies, unwanted uptake of 131I in normal thyroid gland needs to be blocked by administering elemental iodide, in the form of Lugol's iodine or Strong Solution of Potassium Iodide (SSKI). It's easy labeling characteristics with the ability to covalently label proteins have made it the primary choice for labeling monoclonal antibodies while its longer half-life (eight days) is ideal in situations where there is slower penetration into a tumor(Janet et al., 2007).

2.5.3. Beta particles:

Radioisotopes with high proportion of beta emission have been used clinically and represent the largest group used in therapy. Beta particles have a finite and limited range in tissues and dissipate most of their energy (95%) within an organ. While beta particles are ideal for treating larger tumors because of longer path range in tissues, much of their energy (up to 99.9%) can fall outside the small diameter microscopic tumors(McEwan et al 2000). A plastic syringe shield is used for pure beta emitters to avoid bremstrahlung that would contribute radiation dose to the hands. Several beta emitters have found appropriate role in the palliation of patients with painful bone metastases (Silberstein et al., 2000, Howell et al., 1994). In theory, the dose rate of particle emission has some bearing on treatment effects. Generally, radionuclides with higher dose rates are effective in treating tumors with shorter cell cycle time, that is, rapidly proliferating cells and vice versa (Howellet al.,1994, Fowler et al., 1990). Radioisotopes without

any gamma ray emission provide the advantage of convenient outpatient treatment, because of the lack of gamma radiation.

2.5.4. Radioiodine Therapy:

Radiotherapy with radioactive iodine-131 (RAI) has been used to treat benign thyroid diseases for over 50 years (Becker et al 1996). Diseases of thyroid hyperfunction that can be treated with RAI include Graves' disease (GD), solitary hyper-functioning nodule, and toxic multinodular goiter. RAI may also benefit patients with subclinical hyperthyroidism, particularly patients at risk for cardiac or systemic complications. RAI is used less frequently for the treatment of euthyroid goiters. The preferred method for treating hyperthyroidism varies in different countries. In a survey of American Thyroid Association (ATA), European Thyroid Association (ETA), and Japanese Thyroid Association (JTA) members, 69%, 22%, and 11% of respondents, respectively, chose RAI as the therapy of choice for an index patient with GD (Wartofskyet al., 1991). In the same survey, anti-thyroid drugs were regarded as initial therapy in 30.5%, 77%, and 88% of ATA, ETA, and JTA respondents, respectively. Such variation likely stem from differences in perceived risks of prescribing radioactive treatments, differences in cost, local requirements for hospitalization during treatment, patient compliance, response to anti-thyroid medications, and natural history of autoimmune thyroid disease in different populations. Differences in dietary iodine content may also significantly affect treatment response in various populations (Solomon et al., 1987).

2.5.7. Dose for Graves' disease:

The amount of RAI to be administered for treating hyperthyroidism related to GD may be selected empirically or determined by a dose calculation based on the assessments of thyroid mass and function. Standard treatment usually involves a single administration of RAI. The

administration of small amounts of activity (e.g., 2 mCi) at frequent intervals is not recommended, because it allows patients to remain hyperthyroid for longer periods of time, and has not been proven superior at preventing iatrogenic hypothyroidism.

To deliver a specific dose to the thyroid, it is necessary to know the gland size, maximal uptake, and effective half-life of iodine in the targeted thyroid tissue. It may be assumed that the effective biological half-life of RAI is four to six days in the majority of patients with GD. For dosimetry calculation, most physicians use a formula prescribing an activity per estimated gram of thyroid, corrected for the 24-hour uptake. A simple, commonly used formula for treating GD prescribes 2.96–7.4 MBq (80–200 mCi) per estimated mass of thyroid tissue in grams (Cooper et al., 1996):

Administered activity = Thyroid tissue mass (g) * Activity per g tissue/RAI uptake at 24 hour

With RAI uptake expressed as a fraction of 100% uptake. (e.g., 30% uptake is 0.30).Although it may be possible to estimate thyroid mass by palpation, it is difficult to estimate the degree of thyroid hyperfunction (i.e., thyroid uptake) on the basis of clinical findings alone. Thus, most methods for calculating administered activity will require thyroid RAI uptake measurements, typically at 24 hours. A more complicated, but potentially efficacious approach has been the use of late RAI uptake measurements to allow the estimation of physiologic half-life of RAI (Bajnok et al., 1999).

Most recommended administered activities range between 3.7 and 7.4 MBq (100–200 mCi) per gram, corrected for percentage thyroid uptake. Administration of 2.96–4.44 MBq (80–120 mCi) per gram will generally deliver doses of 50– 100 Gy to the thyroid (Dayan CM,2001). Lower doses may reduce the incidence of hypothyroidism following treatment, but will increase the

likelihood that a second treatment will be needed. Administration of 5.5 MBq (150 mCi) per gram will yield a dose of approximately 120 Gy to the thyroid. Larger doses can increase the likelihood of developing hypothyroidism in the post-treatment period, but should reduce morbidity related to prolonged hyperthyroidism. If a high success rate is the primary goal, doses between 200 and 300 Gy may be used.Occasionally, patients with GD may demonstrate RAI uptake more at four to six hours than at 24 hours. This condition of "rapid turnover" may necessitate the administration of larger amounts of radioactivity (5.5–7.4 MBq/g), owing to the shorter physiologic half-life of iodine in this situation. Larger amounts of radioactivity may also be reasonable in patients with relatively low iodine uptake (Cooper et.al., 1996).

Patients with persistent hyperthyroidism following a first treatment with RAI may benefit from additional treatments. Higher doses are often used for retreatment, which are typically given three to six months after the initial treatment. Previous RAI treatment failure does not lessen the chance of a successful retreatment (Leslie et al., 1998).

Although treatments based on dose calculations appear efficacious, they have not proven superior to the use of empirically selected administered activities. The advantages of using a fixed administered activity for treating hyperthyroidism are its simplicity and successful outcome in an acceptable number of patients. The effectiveness of such an approach appears comparable to a dose calculation method. In one prospective trial, patients with GD, hyper-functioning solitary nodules and multinodular goiters, were randomized to receive a fixed radioiodine dose (5, 10, or 15 mCi, based on palpable gland size), versus Iodine-131 calculated dose based on thyroid gland size and 24-hour radioiodine uptake (Jarlov et al., 1995). Comparable rates of euthyroidism, hypothyroidism, and persistent hyperthyroidism were seen in both groups. There were also comparable reductions in gland size. A number of other studies have also supported the equivalence of using several fixed administered activities versus a

calculated activity for the treatment of GD or toxic multinodular goiter (Leslie et al 2003, Kok et al., 2000).

If a fixed amount of activity is chosen, it is still important to keep in mind that the effectiveness of therapy remains dependent on the total radiation dose to the target tissue. In a randomized trial comparing the administration of a standard activity (15 mCi) to an administered activity, calculated to give a target dose of 100 Gy, it was shown that the success rate of the treatment in either arm was dependent on both the thyroid volume and target dose (Peters et al., 1997). If the estimated dose to the thyroid exceeded 200 Gy in patients receiving a standardized treatment with 15 mCi, a success rate of 80% was obtained.

2.6.10 Dose for toxic nodular goiter:

In addition to GD, thyrotoxicosis can also result from a single hyperfunctioning nodule, or multiple hyperfunctioning nodules (i.e., toxic multinodular goiter). Although antithyroid drugs can ameliorate hyperthyroidism, definitive treatment is more commonly accomplished with RAI or surgery. Less commonly, percutaneous ethanol injection has also been used for large solitary nodules (Del et al 2001,Erickson et al 1998). Compared with treatment with RAI, hypothyroidism is a more common sequel of surgery (Erickson et al 1998). The choice of surgery versus radiation for nodular goiters is beyond the scope of this chapter, although surgery should be considered strongly in patients with goiters causing significant airway obstruction or an increased risk of harboring thyroid cancer. Treatment decisions for these patients should be made in consultation with a surgeon with expertise in thyroid surgery.

Most patients with toxic nodular goiters will remain hyperthyroid until definitively treated. Occasionally, central necrosis may occur in a single hyperfunctioning nodule with spontaneous resolution of hyperthyroidism, although this should not be anticipated in lieu of more definitive

treatment. An initial course of antithyroid drugs may be considered in order to render the patient euthyroid before surgical or radioiodine treatment. Nodular goiters are believed to be more radio resistant than the diffuse goiter of GD. Large doses, between 150 and 300 Gy, have frequently been used for toxic adenomas (Gorman et al 1987). A calculated administered activity of 7.4 MBq (200 mCi) per gram to the nodule, corrected for 24-hour uptake, has been used successfully. Standardized administered activities at appropriate doses (e.g., 740–1110 MBq) may also prove effective. With administered activities of less than 370 MBq (10 milliCuries), treatment failures are common (Estour et al 1997).

Radiation exposure to normal thyroid tissue in the setting of solitary toxic nodules has never been shown to increase the incidence of thyroid cancer. This is likely because uptake in the normal thyroid tissue is suppressed. Suppressed thyroid tissue may still receive a dose as high as 23 Gy (Gorman et al 1987). However, hypothyroidism following RAI treatment does seem to occur less frequently for solitary hyperfunctioning nodules compared with GD or multinodular goiter. In order to minimize the risk of hypothyroidism following treatment, a suppressed thyroid-stimulating hormone (TSH) level should be present, and a thyroid scan should be performed to exclude significant extranodular uptake (Huysmans et al 1991). A reduction in the nodule size can be expected following RAI treatment (Nygaard et al 1999).

For toxic multinodular goiters, doses of 150 Gy may be adequate to resolve hyperthyroidism. Administered activities between 3.7 and 7.4 MBq (100–200 mCi) per gram have been shown to be effective (Erickson et al 1998). Fixed administered activities (e.g., 1110 MBq) have also been used. Not uncommonly, patients with toxic multinodular goiters may have large glands and 24-hour RAI uptake measurements that are not significantly elevated. This may necessitate the administration of relatively large amounts of radioactivity. In the United States, higher administered activities may be used for nonhospitalized patients, if it can be documented that

radiation exposure to the public is not likely to exceed 5 mSv (0.5rem) (US Nuclear Regulatory Commission 1997).

2.5.6. Pretreatment procedure's:

Thyroid function tests should confirm results that are consistent with the disease to be treated. Women of childbearing age should have documentation that they are not pregnant at the time of treatment. Routine pregnancy testing should be offered prior to RAI therapy (Stofferet al., 1967).

Traditionally, RAI uptake measurements have been used to determine the amount of radioactivity to administer for treatment. However, this amount may also be empirically determined. Regardless of the method for dose selection, routine thyroid uptake measurements are useful for confirming increased thyroid gland function prior to treatment. This helps avoid inappropriate treatment of hyperthyroid conditions not associated with increased thyroid function, such as silent thyroiditis or factitious hyperthyroidism. RAI uptake measurements can also help exclude a hyper-functioning gland with "blocked" uptake. This condition, which will significantly reduce the effectiveness of RAI treatment, may follow exogenous iodine exposure, such as from intravenous contrast agents. Other substances which may contain large amounts of iodine include expectorants, kelp, agar, carageenan, Lugol's solution, potassium iodide solutions, and drugs, such as amiodarone. RAI uptake measurements should be performed following the withdrawal of such interfering materials in the same manner as done for treatment. Typically, thyroid gland uptake measurements are acquired at four to six hours and 24 hours following the ingestion of a test capsule of 0.15–0.37 MBq (4–10 mCi) of iodine-131. Alternatively, 3.7–7.4 MBq (100–200 mCi) of iodine-123 may be used. An estimate of the 24-hour iodine-131 uptake measurement may be also being derived from the early measurement, allowing for testing and treatment to be completed in one day (Hayes et al 1990). Scanning is

useful for the confirmation of hyper-functioning nodules and the exclusion of cold nodules which need to be further evaluated. Although it is debatable whether a thyroid scan adds information that would alter the management of GD, scanning does provide confirmation of the diagnosis of GD while excluding the rare possibility of incidental thyroid cancer, which may manifest as a hypo-functioning nodule. Such nodules should be evaluated for possible malignancy prior to treatment with RAI.

2.5.5. Contraindications to Radioactive Iodine Therapy:

A patient who is pregnant should not be treated with RAI (Stoffer et al., 1967). RAI crosses freely into the placenta, and the fetal thyroid tissue is capable of accumulating iodine after the 12th week of gestation. Administration of RAI during this period may result in severe neonatal hypothyroidism. Fetal and neonatal thyroid irradiation may also increase the risk of developing thyroid cancer later. Retained activity in the maternal bladder may also increase the risk of malignancy by direct radiation exposure to the fetus. Women who are actively lactating or nursing also should not receive RAI. Iodine is excreted in breast milk. Nursing should not be resumed until the birth of the next child. RAI has no role for the treatment of hyperthyroid conditions that are self-limited or when thyroid tissue is not hyper-functioning. These conditions include silent, sub-acute and postpartum thyroiditis in addition to factitious thyroid disease.

2.5.8. Capsule versus Liquidiodine:

Radioiodine is available in a liquid solution or capsule. Capsules are more convenient, but have generally been more expensive. Liquid formulations may require extra measures to minimize radiation contamination at the time of administration. RAI in capsules and liquid are generally believed to be equivalent in efficacy, although there has been some concern regarding a

reduction in RAI bioavailability from capsules, because of incomplete dissolution related to the amount of magnesium stearate in the capsule (Huysmans et al., 1994).

2.5.9. Goals and expected outcomes of treatment:

With adequate doses of radioactivity, an 80% response rate should be expected. A primary goal of treatment is to resolve hyperthyroidism in as short time as possible. However, with RAI doses calculated to achieve this goal in the majority of patients, a significant number of patients will ultimately become hypothyroid. The incidence of hypothyroidism was first estimated at 20% to 40% of patients one year after RAI therapy (Yu et al., 2002). With more conservative doses of RAI, the incidence of hypothyroidism may be lower, although, often at the expense of higher rates of persistent hyperthyroidism. Patient preferences, the availability of close follow-up, and potential risks from persistent hyperthyroidism should be considered when deciding between more definitive treatment with higher doses and the use of more conservative doses. Some authorities have maintained that hypothyroidism, which is easily and inexpensively treated with thyroid hormone supplementation, is preferable to persistent hyperthyroidism, which, if not optimally treated, may produce significant morbidity.Hypothyroidism tends to occur more frequently in patients with small thyroid glands and lower 24-hour uptake measurements (Hagen et al., 1967). Other independent predictors of hypothyroidism following RAI treatment include a diagnosis of GD, the level of thyroid auto antibodies, and no anti-thyroid treatment given prior to RAI, non-palpable goiter, and high RAI dose. In one series, the absence of risk factors was associated with a 12% probability of developing hypothyroidism, whereas with all factors, the probability increases to 96% (de Bruin et al., 1994). Hypothyroidism may occur several years following RAI treatment, and may be more likely in patients who have had multiple RAI treatments (Ahmad et al., 2002). Regardless of whether the goal is to achieve euthyroidism or acceptable rates of hypothyroidism, all patients who have

been treated with RAI should receive longitudinal clinical follow-up along with thyroid function studies. Patients with autoimmune thyroid disease should also be monitored for complications, such as Graves' ophthalmopathy.In addition to abolishing hyperthyroidism, treatment with radioiodine should significantly reduce thyroid gland size in patients with GD. A 50% to 80% reduction in gland volume may be seen in proportion to the radiation dose given (Holm et al., 1982).

2.5.10. Patient preparation for treatment:

Beforethe oral administration of the therapeutic dose of I131, the diagnosis of toxic goiter must have been firmly established on the basis of physical examinations, history, and evaluated circulating serum thyroid hormones levels and suppressed TSH. An I131 uptake should be routinely performed to exclude hyperthyroidism due to certain diseases such as silent, painless thyroiditis and to gauge the dose required. The patient should take nothing by mouth after midnight the evening before treatment. Female patients should be carefully screened for possible pregnancy, which is contraindication of radioiodine treatment because of possible carcinogenic risk to the fetus and risk of injury to fetal thyroid gland after first trimester. In lactating mother therapy should be instituted only if the patient willing to completely cease breast feeding because iodine is secreted in milk(Fred et al.,2006)

If anti-thyroid drugs are already in use, they should be discontinued for 5 to 7 days before radioiodine treatment is administered depend on the clinical status of the patient, if clinically necessary, these drugs may be re-administered 7 to 10 days after therapy without adversely affecting the results of treatment. As an alternative, beta adrenergic blocking agents such as propanol, may be used throughout the therapy period because they don't affect thyroid function and therefor permit recirculation of I131 in the gland for maximum radiation effect. (Fred et al., 2006)

2.5.11. Side effects of radioiodine therapy:

2.5.11.1 Acute side effects:

Silo adenitis, Radiation thyroiditis, Neck edema, Nausea, Gastritis, Thyroid storm, Edema and acute cerebral hemorrhage

2.5.11.2 Long-term side effects:

Decrease white blood cells, Myleodepression, Oligospermia, Transient ovarian failure, Long-term xerostomia, Infertility, Pulmonary fibrosis, Secondary malignancies acute myelocytic leukemia

2.5.12. Patient instructions, precautions, and follow-up:

Following the administration of therapeutic doses of RAI, contamination from excretion of RAI in urine, perspiration, breast milk, and saliva, can be associated with internal accumulation of RAI by others who come in contact with the patient. Potential avenues of radiation exposure to others include ingestion of iodine-131 excreted by the patient, and from emitted gamma rays from iodine- 131 Although there is little evidence to suggest that small amounts of radiation from iodine-131 treated patients can cause significant problems to others, guidelines have provided simple recommendations to reduce unnecessary radiation exposure, especially to pregnant women, infants, and children. It is a requirement of the United States Nuclear Regulatory Commission to give patients verbal and written instructions prior to treatment with RAI (Dotsch et al., 2003).

The Society of Nuclear Medicine has recommended that patients sleep alone for the first few days after treatment. For the first 72 hours, patients should not spend prolonged periods of time closer than three feet to any adult, or within the same room as any child. An easy to follow

guideline is to maintain a distance of one arm's length between treated persons and others. Short periods of contact are acceptable. If caring for an infant, patients should minimize the amount of time spent in close proximity with the infant during this time (Shulman et al., 1997). Specifically, infants should not be held for prolonged periods because of proximity to the thyroid or bladder. It is also recommended that time spent with pregnant women and young children be minimized for four to seven days after treatment. Work restrictions should be given to patients who may potentially expose pregnant women or children when performing their occupation (Ron et al., 1995).

Fluid intake and frequent voiding should be encouraged for at least the first 24 hours following treatment. Patients should be instructed to wake up at least once the night following treatment to empty their bladder. The toilet should be flushed two or three times. Hand washing should be performed routinely and frequently (Robbins et al., 2000). If patients perspire heavily, clothing should be washed separately. Because of contamination concerns, it is not recommended to treat women during their menses. Sharing food and eating utensils should be prohibited (Dobynset al., 2008). Patients should wash their utensils separately or use disposable utensils. Lactating women who wish to be treated should be instructed to discontinue breastfeeding. Treatment should be withheld until lactation ceases. It may be possible to detect radioactivity in breast milk for several months following treatment. Patients should be instructed not to resume breastfeeding until the birth of another child.

Women capable of childbearing should be asked to avoid pregnancy for at least six months following treatment, in order to confirm resolution of hyperthyroidism in addition to minimizing risks from radiation.Patients should be told that symptoms would resolve over several weeks, and that they would require close follow-up, as hyperthyroidism may worsen during the intervening time (Rivkees et al., 1998). Symptoms of uncontrolled hyperthyroidism

should be described, and patients should be informed to seek medical attention if such symptoms occur. They should also be made aware of the probable need for thyroid hormone supplementation in the future (Rivkeeset al., .2003). The risk of persistent hyperthyroidism and myxedema following treatment necessitates close follow-up that includes clinical examination and thyroid function tests. Patients with GD should be made aware that ophthalmopathy may occur or worsen. Patients should follow-up with their physician in four to six weeks. One study suggests that the assessment of treatment response may be most reliable at 12 to 14 weeks after therapy, although it may be possible to identify non optimal responders as early as six to eight weeks (Daae et al., 1980). Instructions for patients are summarized in Table 3. In the United States, the most current regulations for RAI therapy may be obtained from the U.S. Nuclear Regulatory Commission.

2.5.13 Radiation safety aspect:

The major aspect of radiation therapy that need to be controlled when releasing a patient with radioiodine is the external exposure of the other. However, the typical doses that occur to other person from patients treated with I131 only have a very low risk of cancer induction. Approximate dose rate at 1.0m from the patient treated for hyperthyroidism are 0.185 mrem\mci (0.05msv\MBq) immediately after administration, 0.11mrem/mci (0.03msv/MBq) at 2 to 4 days after administration, and 0.07mrem/mci (0.02msv/MBq) at 5 to 7 days after administration, (Fred et al.,2006). The international Commission on Radiological Protection (ICRP) recommends the concept of a dose constraint of a few rems (a few msv) per episode for caregivers and family, whereas the recommended international annual dose limit to the public is 100 mrem (1 msv). Infants and young children as well as casual visitor should probably be excluded from the dose constraint and be limited to public dose limit. (Fred et al., 2006)

2.6. Previous Study:

Safa et al., (1975) aimed to evaluate the long-term results of ^{131}I therapy for children, we studied the course of 87 patients (three to 18 years old, 24 boys and 63 girls) treated from 1949 through 1968, for hyperthyroidism due to Graves's disease. Dose of ^{131}I per patient ranged from 2.9 to 31 mCi (mean ± S.D., 9.75 ± 6.5). Patients were followed for five to 24 years (mean, 12.3±3.5). Hyperthyroidism was controlled in 85 within one to 14 months (mean, 3.3±2.6). Recurrence of thyrotoxicosis due to toxic diffuse goiter, observed in only one case after 11 years, was successfully re-treated with ^{131}I. Reproductive history and health status of the progeny of ^{131}I-treated patients were not different from those of the general population. No deaths and no cancer or leukemia were observed in patients or their offspring. The major cause of goiter regrowth was Hashimoto's thyroiditis. Hypothyroidism developed in 35 of 76 patients (46 per cent).^{131}I deserves further use in treatment of hyperthyroid children with Graves's disease.

Gutiérrez et al.,(1999) he was stated the detected the incidence and persistence of potential chromosome damage induced by iodine-131 therapy, we applied the cytokinesis-block micronucleus assay to peripheral blood lymphocytes from hyperthyroidism and thyroid cancer patients treated with 131I. Two groups of patients were evaluated in a longitudinal study; one group was composed of 47 hyperthyroid patients and the other of 39 thyroid cancer patients. In the hyperthyroidism group, the micronuclei frequency was determined before 131I therapy and 1 week, 1 month and 3 months after it. Furthermore, an additional sample was taken from a subgroup of 17 hyperthyroidism patients 6 months after treatment. In the thyroid cancer group, the analysis was also conducted over time, and four samples were studied: before treatment and 1 week, 6 months and 1 year later. Simultaneously, a cross-sectional study was performed with 70 control subjects and 54 thyroid cancer patients who had received the last therapeutic dose 1–

6 years before the present study. In the hyperthyroidism group a significant increase in the micronuclei average was found over time. In the sample obtained 6 months after therapy, the micronuclei mean frequency was practically the same as in the sample taken 3 months before. In the thyroid cancer group, a twofold increase in the frequency of micronuclei was seen 1 week after therapy. Although this value decreased across time, the micronuclei frequency obtained 1 year after 131I therapy remained higher than the value found before it. Concerning the data from the cross-sectional study, a significant increase in the frequency of micronuclei was detected in the subgroup of thyroid cancer patients treated between 1 and 3 years before the current study. These results indicate that exposure to 131I therapy induces chromosome damage in peripheral lymphocytes and that the cytokinesis-block micronucleus assay is sensitive enough to detect the genetic damage by exposure to sufficiently high levels of radiation from internal radioactive sources.

Dottorini et al., (1995) he was aimed to study was to evaluate female fertility, carcinogenic, and genetic effects after treatment with 131I of differentiated thyroid carcinoma. Method: A total of 814 females of child-bearing age were studied. The fertility of 627 females who received 131I therapy was compared to 187 untreated females. Birth histories of the children born from these women were registered. The carcinogenic effect was evaluated by comparing the incidence of tumors in 730 patients treated with 131I with an internal control group, as well as with local population incidence. The main result of his study was no significant difference in the fertility rate, birth weight and prematurity between the two groups. Only one case of a ventricular septal defect was observed in a child born to a women treated with 131I. The overall standardized incidence ratio (SIR) of second tumors was 1.19 (95% CI: 0.76-1.77) in patients treated with 131I. An elevated SIR was registered for salivary gland tumors and melanoma. No case of leukemia was registered. Finally, he concludes that the risk of long-term effects of I^{131}

treatment of differentiated thyroid carcinoma is quite low. Iodine-131 may be safely used in treating cases with a high risk of recurrence.

Earle etal., (1946) Roentgen treatment has been used for hyperthyroidism for many years. In 1923 Means and Holmes1 pointed out that in this form of treatment about one third of the patients are cured, another third improved and another third not affected. Since 1923 ordinary iodine by mouth has been used as a preoperative method of quieting the hyperactive thyroid in preparation for surgery. Under iodine alone occasionally the patient and the doctor have been agreeably surprised to find that the symptoms and signs of hyperthyroidism disappeared, and a permanent remission apparently was effected. That x-ray treatment and iodine treatment sometimes cure hyperthyroidism led to the hope that someday a more effective, nonsurgical agent would be found. Then the MacKenzies2 and Astwood3 discovered that several chemical compounds inhibit the function of the thyroid in hyperthyroidism as well as under other circumstances. Several of these agents have been investigated, and Concern about the side effects of radiation exposure has deterred physicians from using radioiodine treatment for Graves' disease, although the efficacy and safety of this treatment have been established in the 35 years since its introduction. In that time, no significant side effects have been discovered. We believe iodine-131 should be considered the treatment of choice in most patients with Graves' disease. This article reviews the current understanding of the risks in radioiodine treatment of Graves' disease, including the risks for teratogenicity, genetic damage, carcinogenesis, and cellular dysfunction.

Laurberg etal., (2001) stated that the relationship between the iodine intake level of a population and the occurrence of thyroid diseases is Ushaped with an increase in risk from both low and high iodine intakes. Developmental brain disorders and endemic goiter caused by severe iodine deficiency may seriously deteriorate overall health status and economic

performance of a population. Severe iodine deficiency with a median 24-hour urinary iodine excretion of the population below 25 μg needs immediate attention and correction. Less severe iodine deficiency with median urinary iodine excretion below 120 μg per 24 hours is associated with multinodular autonomous growth and function of the thyroid gland leading to goiter and hyperthyroidism in middle aged and elderly subjects. The lower the iodine intake, the earlier and more prominent are the abnormalities. At the other end of the spectrum, severely excessive iodine intake starting at median urinary iodine excretion levels around 800 μg per 24 hours is associated with a higher prevalence of thyroid hypo-function and goiter in children. A number of studies indicate that moderate and mild iodine excess (median urinary iodine >220 μ g per 24 hours) are associated with a more frequent occurrence of hypothyroidism, especially in elderly subjects. The exact mechanism leading to this has not been clarified, and more studies are needed to define the limits of excessive iodine intake precisely. Due to the frequent occurrence of thyroid disorders, proper monitoring and control of the population iodine intake level is a cost-effective alternative to diagnosing, therapy and control of the many individual cases of thyroid diseases that might have been prevented

Michael et al., (1998) he stated that radioactive iodine (RAI) therapy for hyperthyroidism was first used in 1941 by physicians at Massachusetts General Hospital in Boston.7 and 58 the first nuclide used was 130I, which has a half-life of 12.4 hours. In 1946, 131I became readily available from the Oak Ridge National Laboratory in Tennessee as a spin-off of atomic energy research conducted during World War II. The relatively low cost convenient half-life of 8 days and the effectiveness of treatment of hyperthyroidism with 131I rapidly led to its widespread adoption. It has become one of the standard therapies for hyperthyroidism and is now used throughout the world. Attempts have been made to use another isotope, 125I, for the treatment of hyperthyroidism in the hope of avoiding subsequent long-term hypothyroidism; however, it has no advantage over 131I. The properties of 123I that make it excellent for thyroid imaging—

a short half-life, an appropriate gamma radiation emission energy, and a low radiation dose delivered to the thyroid gland—also make it ineffective for the ablation of thyroid tissue. Thus, only 131I is currently used for ablative thyroid therapy, both for hyperthyroidism and thyroid cancer.

Teng etal., (2006) stated that the iodine is an essential component of thyroid hormones; either low or high intake may lead to thyroid disease. We observed an increase in the prevalence of overt hypothyroidism, subclinical hypothyroidism, and autoimmune thyroiditis with increasing iodine intake in China in cohorts from three regions with different levels of iodine intake: mildly deficient (median urinary iodine excretion, 84 μg per liter), more than adequate (median, 243 μg per liter), and excessive (median, 651 μg per liter). Participants enrolled in a baseline study in 1999, and during the five-year follow-up through 2004, we examined the effect of regional differences in iodine intake on the incidence of thyroid disease. Of the 3761 unselected subjects who were enrolled at baseline, 3018 (80.2 percent) participated in this follow-up study. Levels of thyroid hormones and thyroid autoantibodies in serum, and iodine in urine, were measured and B-mode ultrasonography of the thyroid was performed at baseline and follow-up. Among subjects with mildly deficient iodine intake, those with more than adequate intake, and those with excessive intake, the cumulative incidence of overt hypothyroidism was 0.2 percent, 0.5 percent, and 0.3 percent, respectively; that of subclinical hypothyroidism, 0.2 percent, 2.6 percent, and 2.9 percent, respectively; and that of autoimmune thyroiditis, 0.2 percent, 1.0 percent, and 1.3 percent, respectively. Among subjects with euthyroidism and antithyroid antibodies at baseline, the five-year incidence of elevated serum thyrotropin levels was greater among those with more than adequate or excessive iodine intake than among those with mildly deficient iodine intake. A baseline serum thyrotropin level of 1.0 to 1.9 mIU per liter was associated with the lowest subsequent incidence of abnormal thyroid function. More than adequate or excessive iodine intake may lead to hypothyroidism and autoimmune thyroiditis.

Gharibetal., (2007) In the general population, thyroid nodules are found in 5% by palpation and in 50% by ultrasonography (US). Initial evaluation of nodules should include serum thyroid-stimulating hormone measurement, fine-needle aspiration (FNA) biopsy, and US. Thyroid micronodules are being detected with increasing frequency and are currently evaluated by US-FNA. Routine measurement of in the general population, thyroid nodules are found in 5% by palpation and in 50% by ultrasonography (US). Initial evaluation of nodules should include serum thyroid-stimulating hormone measurement, fine-needle aspiration (FNA) biopsy, and US. Thyroid micronodules are being detected with increasing frequency and are currently evaluated by US-FNA. Routine measurement of serum calcitonin and thyroglobulin and FNA rebiopsy are not recommended. Cytologically benign thyroid nodules should be followed rather than treated. Novel treatment options including iodine 131, percutaneous ethanol injection, and percutaneous laser thermal ablation have specific indications, advantages, and adverse effects.

Chapter Three

Methodology

3.1. Materials:

Thyroid function test: 5 ml Blood sample, test tube, centrifuge, I^{125}, antibodies and gamma counter (PC-RIA.MAS STRATEC,Germany).Thyroid uptake: Radioisotope Tc99m (Tc99m/Mo99 generator-Monrol company, Turkey), Dose calibrator (PTW CURIEMENTOR – Germany) and Gamma camera (Dual Head –FOV: 53*39cm^2, Nucline^{TM} SPIRIT DH-V, Mediso company, Hungary).

3.2. Method:

A cross-sectional (descriptive) hospital based prospective study carried out to evaluate and to assess the role of I^{131} treatment of hyperthyroidism, patient referred to the thyroid clinic in Khartoum Oncology Hospital (KOH), C/O enlarged thyroid gland with thyroid hormone disturbance; physician advice the patient to perform laboratory investigation, and thoracic inlet x-ray used to evaluate the hormone level and the airway passage, thyroid function test performed using 5ml of blood, test tube, centrifuge to separate the plasma from the blood component, I125, antibodies, and Gamma counter (PC-RIA.MAS STRATEC, Germany), An elevated RAIU confirms that endogenous thyroidal secretion is the source of the hyperthyroidism and aids in excluding other etiologies of hyperthyroidism, such as silent thyroiditis, sub-acute thyroiditis, postpartum thyroiditis, iodine-induced hyperthyroidism, and factitious hyperthyroidism, all of which are associated with a low RAIU. Tc99m/ Mo99m generator, Dual head gamma Camera (FOV= 53X49cm2, Nucline^{TM} SPIRT DH-V, MEDISO-Company, Hungary) SPECT imaging was used to scan the patient to assess cause of hyperthyroidism and the thyroid uptake was recorded, the level of thyroid hormone was recorded before starting radioiodine treatment and 3, 6, 9, 12 months after treatment in order to

assess the level of thyroid hormone in these periods and therefore assessing the treatment response and the outcome.

3.2.1. Study Design:

This was analytical nuclear medicine study aimed to assess I^{131} treatment of hyperthyroidism

3.2.2. Area of Study:

This study was conducted at Khartoum State, Khartoum Oncology Hospital, Nuclear Medicine Department.

3.2.3. Duration of the Study:

This study conducted in period from October 2018 to December 2019.

3.2.4. Sample of the Study:

This study consists of 120 patients drown from hyperthyroidism patients treated by radioactive iodine131 referred to KOH.

3.2.5. Inclusion Criteria:

The study was carried out in patient having ages between 17 To 55 Years from both sexes.

3.2.6. Exclusion Criteria:

Patient undergoing anti thyroid medication for more than one year, ages below 17 and over 55years, Patients receiving radioactive iodine as a second dose and patient taking propylthiouracil (PTU) was clearly excluded from this study.

3.2.7. The study populations:

This study was conducted in Sudanese population who underwent treatment in KOH on periods of the study.

3.2.8. Method of Data Collection:

The data were collected using standard master data sheet contain the necessary study variables.

3.2.9. Data Collection Variables:

Patient age, gender, thyroid hormone level (T3, T4 and TSH), RIA dose, and thyroid uptake.

3.2.10. Example of master data sheet used for data analysis:

Age	Sex	Uptake	Dose	T3 before TX	T4 before TX	TSH before TX

3.2.11. Method of Data Analysis

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

3.2.11. Ethical issues:

- There was official written permission to Khartoum Oncology Hospital to take the data.
- No patient data were published also the data was kept in personal computer withpersonal password.

Chapter Four

Result

This study aimed to discuss the role of thyroid treatment of hyperthyroidism by using of I^{131} radioisotopes in hyperthyroidism patients. The data were collected using standard master data sheet contain the necessary study variables and consist of 120 patients drown from hyperthyroidism patients treated by radioactive iodine131 referred to thyroid clinic inKhartoum Oncology Hospital (KOH)in period from October 2018 to December 2019,the results described as follow for both technical variables and some patient related variables as showed below:

Table (4.1): showed the mean±STD of thyroid function test values before and at constant interval after the treatment.

Period	T3	T4	TSH
Before treatme	6.94±6.28	222.124±110.4	0.3699±0.663
After 3 month	4.18±7.949	134.01±88.36	6.337±15.50
After 6 month	2.78±3.5	119.24±66.73	5.309±13.142
After 9 month	2.768±2.9	119.15±59.47	2.765±4.058
After 12 mont	2.46±1.79	113.36±47.16	2.265±2.66

Table (4.2): showed the mean and STD values for patient age and the percentage of thyroid uptake.

Variables	N	Mean	Std. Deviation
Age	120	42.98	12.099
uptake	120	18.2852	12.17988

Table (4.3): showed the frequency distribution of the age groups for 120 patients with I-131 treatment

Age group	Frequency	Percent
10-19	3	2.5
20-29	16	13.3
30-39	24	20.0
40-49	33	27.5
50-59	32	26.7
60-69	10	8.3
70-79	2	1.7
Total	120	100.0

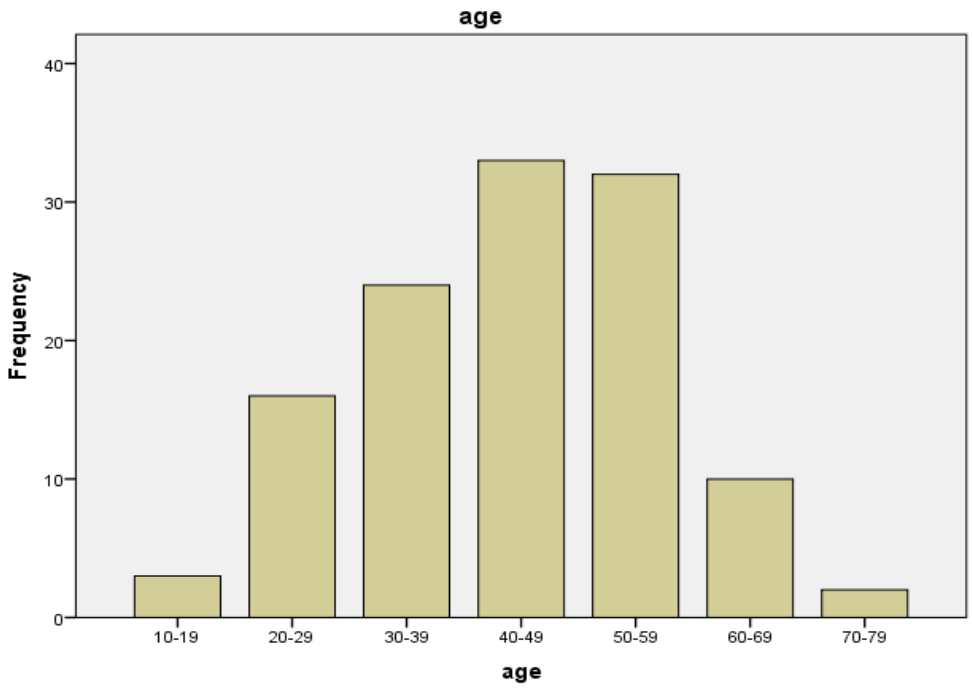

Figure (4.1) par graph demonstrate the frequency of age group distribution of collected data

Table (4.4): frequency distribution of male and female for 120 patient

Variables	Frequency	Percent
Female	97	80.8
Male	23	19.2
Total	120	100.0

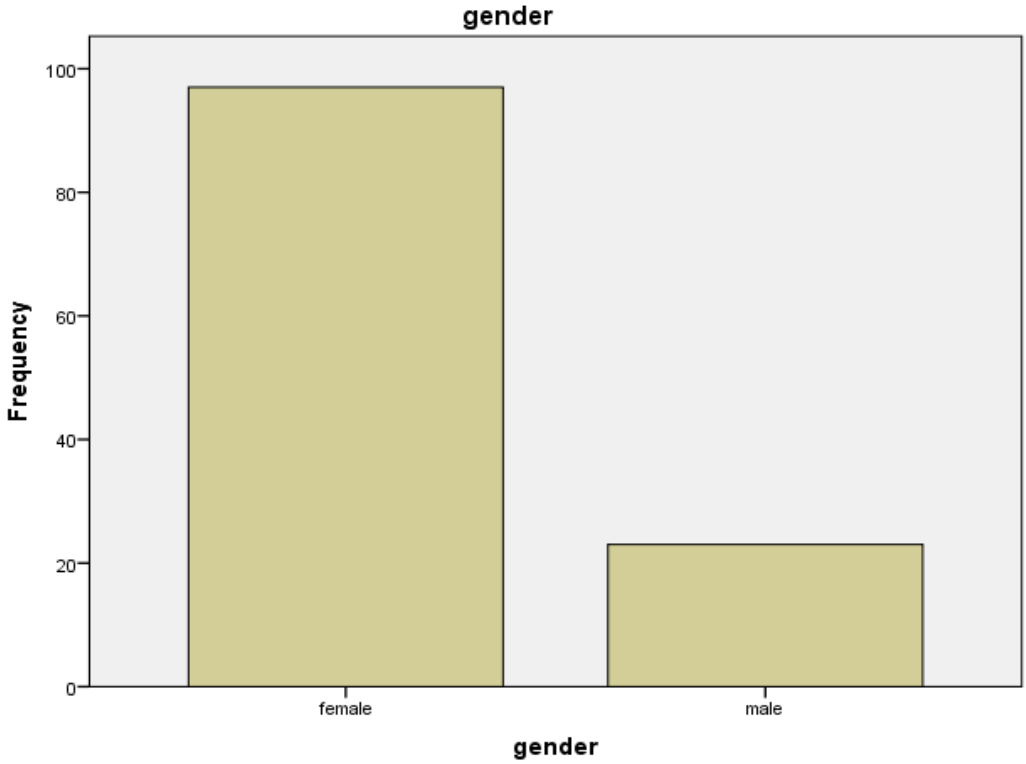

Figure (4.2): frequency distribution of male and female for 120 patient

Table (4.5): showed the frequency distribution of the most causes of the hyperthyroidism

Variables	Frequency	Percent
GRAVES	54	45.0
TMNG	28	23.3
DTG	30	25.0
Nodules	8	6.7
Total	120	100.0

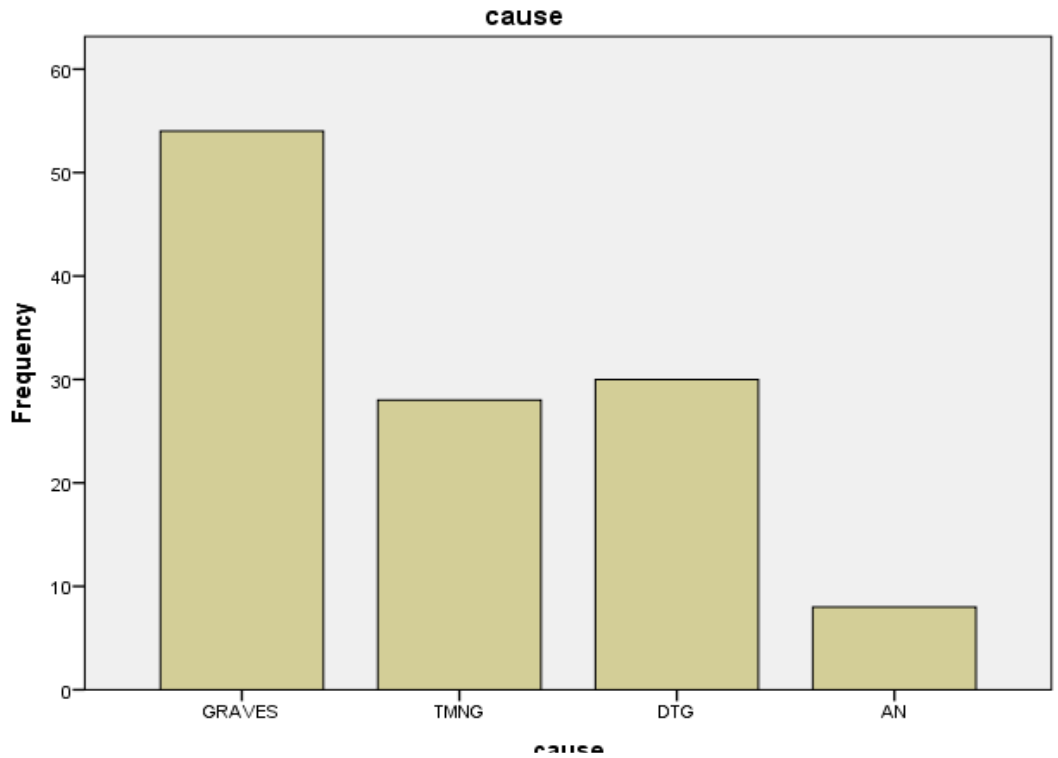

Figure (4.3): a par graph showed the frequency distribution of the most causes of the hyperthyroidism

Table (4.6) Demonstrate the performed significant two tailed t-test for to test the difference in mean values of thyroid hormone values before and after 9 months after the I131 treatment (test were significant at p<0.050

Pairs	Paired Differences					T	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference			
				Lower	Upper		
pT3 – 12mt3	4.5	6.8	0.6	3.3	5.6	7.6	0.000
PT4 -12mT4	108.8	121.4	11.1	86.8	130.7	9.8	0.000
PTSH-12Mtsh	-1.9	2.624	.24	-2.37	-1.42	-7.9	0.000

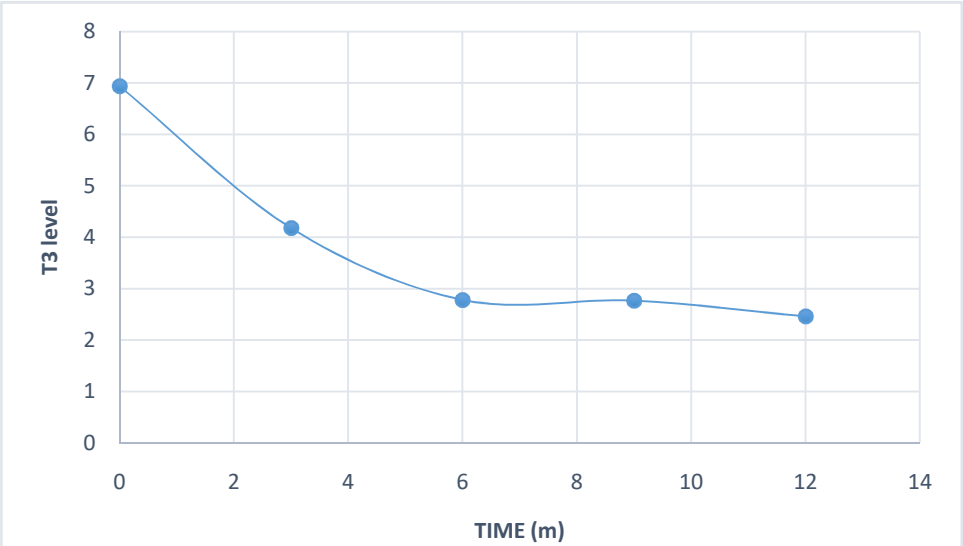

Figure (4.4): a line plot demonstrates the relation between T3 value and time after the treatment linear correlation showed that (y = -0.3455x + 5.8996, *R^2 = 0.7736) in strong indirect relationship.*

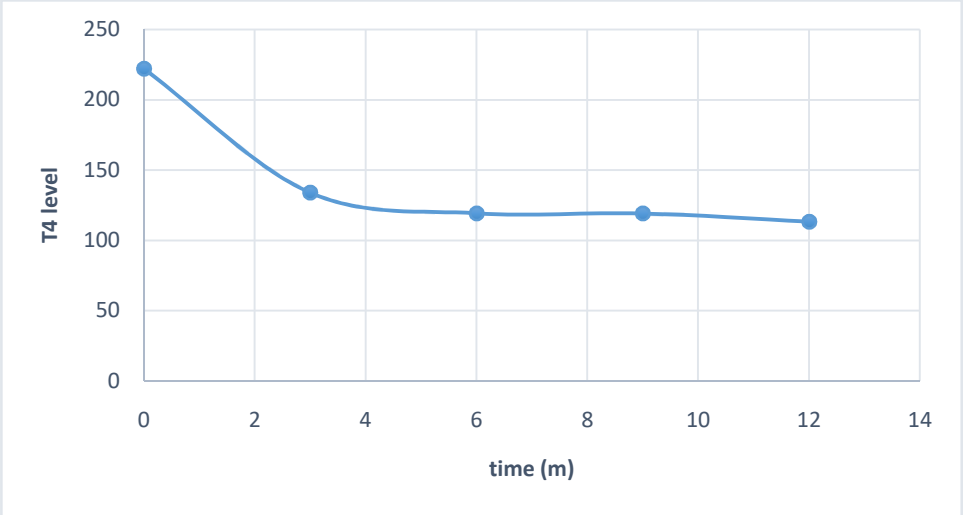

Figure (4.5): a scatter plot demonstrates the relation between T4 value and time after the treatment

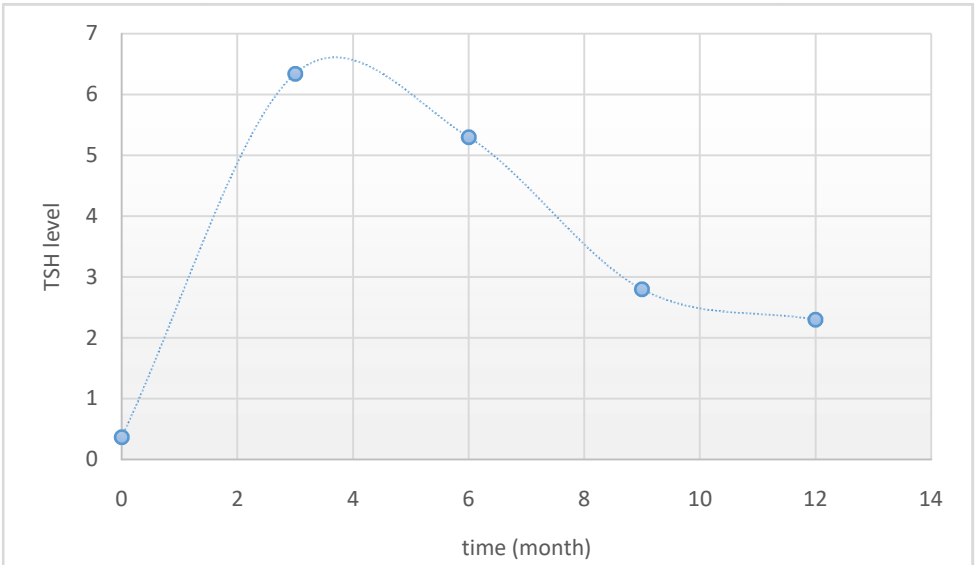

Figure (4.6): a line plot demonstrates the relation between TSH value and time after the treatment in which the value was increased as a function of time after treatment followed by gradual hypothyroidism takes place. Linear correlation showed that y = -0.4347x + 7.3437 R^2 = 0.9446. In period after the treatment.

Chapter five

Discussion, Conclusion and Recommendation

5.1 Discussion:

In 1941 Radio-iodine treatment of thyroid gland had been proposed as a modality of choiceand has since evolved to the treatment modality of choice for the majority of adult patients particularly in USA, UK and Europe, while the drugs (anti-thyroid drugs) can cause complete remission in 10-40% of patient only, William H. et.al., 2005. Administered dose is usually calculated with the goal of administering approximately 70–120 Gy (7000–12000 rad) to the thyroid gland [4]. *The calculation is made as follows: administered microcuries = μCi/g desired × gland weight (g) × 100 ÷ percent uptake (24 hours).*This equation demonstrates the effect of thyroid uptake in calculation of administered dose.

This study was contained of 120 sample having a mean age of 42.98±12.099 year, and the most frequent gender treated with radioactive iodine was female (97, 80.8%), and male (23, 19.2%) as in table (4.4), the mean value of thyroid uptake percentage during these scan was (18.28±12.17). table (4.2). and the most affected age group was (40-49) having frequency of 33 (27.5%) as in table (4.3).

A mean dose used to ablate thyroid tissue was (13.45mCi). This was being decided upon (1) the amount of radioiodine administered, (2) the fraction deposited in the gland (uptake), (3) the duration of retention by the thyroid (biologic half-life), and (4) the radio sensitivity of the irradiated tissue.The main purpose of this study is to assess the level of thyroid hormones in patients with hyperthyroidism in five periods which are (before treatment, 3months after treatment, 6months, 9 months and 12months after treatment) for T3, T4 and level of TSH. The result showed that the mean value of these hormone was 6.9, 4.2, 2.8, 2.7 and 2.5 (nmol/L) for

T3, 222.1, 134, 119, 119.2 and 113.4 (nmol/L) for T4, and 0.37, 6.34, 5.3, 2.8, and 2.3 (nmol/L) for TSH respectively, table (1). These were compared to the normal level of thyroid hormone which are T3 (0.8-3nmol/L), T4 (50-150nmol/L) and TSH (0.4-4 nmol/L) and we noted an elevated thyroid hormone before treatment and then gradually decreased over the mentioned period of time for assessment this result reveals that the hormone level was decreased in response to the treatment.

A significant paired sample T-test was performed in order to test the difference between these values for the same patients in mentioned period. The result showed that there is a significant difference between the thyroid hormone level before I^{131}adminstration and after 3, 6, 9, and 12 months later after the treatment, at Confidence level of (CL=95%) and (p value= 0.05), the test were significant at P= 0.000, which mean that the thyroid hormone are significantly changing in these period which indicate the effectiveness of the I-131 to treat the hyperthyroidism and its causative factor such as TMNG, or Graves' disease.

Factor or disease that may lead to cause hyperthyroidism was also investigated and our result showed that 45 patients (54%) of the collected samples were caused by Graves' disease, 28 (23.3%) by TMNG, 30 (25%) due to Diffuse toxic goiter and 6.7% related to the autonomous nodules. William H. et.al 2005 stated that 95% of hyperthyroidism caused by Graves' disease and diffuse toxic goiter, as in table (3). Figure (1): showed that linear relationship between the T3 level and the time before and after the treatment which demonstrated the decrement of T3 value with period of time in which decreased by 0.3455 (nmol/L) for every one-month increment in time after treatment by I-131 ***($y = -0.3455x + 5.8996$, $R^2 = 0.7736$).*** Assessment of T3, T4, and TSH value after 6 months is consider significant in term of treatment response as stated by William H et.al., 2005.

A strong correlation between T4 value and the time in similar manner as T3, that result may explained by physiological aspect of T4 value which is derivative from the T3 as normal

physiological process, so when level of T3 decreased T4 is decreased due to lack of T3 synthesized by thyroid tissue related to normal iodine uptake. The correlation showed that T4 level decreased by 7.746 (nmol/L) every month increments in period after thyroid treatment. ***y = -7.746x + 188.05, R^2 = 0.6472. As in Figure*** (2)

The effect of treatment on the level of TSH after the treatment, in normal pathophysiological process of hyperthyroidism TSH level where decreased, due to over expression of T3 and T4 in the blood, as stated by A. zeiessman et al., 2006. our study notes the same result in which TSH having value of 0.37 (nmol/L) then starting to increase until starting the treatment, reaching a value of 6.34 (nmol/L) in three months (peak value), then starting to decrease as a function of time (month) indicating of hypothyroidism, in which decreased by 0.434 (nmol/L) for every one-month increment in period after I131 administration. ***y = -0.4347x+7.3437 R^2 = 0.9446 as in figure (3).***This result was explained by William H et.al., 2005, who stated that following radioiodine therapy, the patient should be advised to have serum thyroid hormone and TSH levels checked within 2 to 3 months. Patients may be symptomatically improved within 4 to 6 weeks, but clinically significant hypothyroidism rarely occurs before 2 to 3 months. Hypothyroidism is only a problem if not adequately treated, and many practitioners will initiate thyroxine replacement therapy at the earliest indication of post-therapy hypothyroidism.

5-2 Conclusion:

A process of introduction of NM treatment options for hyperthyroidism and thyroid disease as general had been evaluated by many literature, Hyperthyroidism is considered as one of common pathological problem associated with thyroid gland, in which thyroid hormone level were increased. This a prospective study attended to assess the efficiency of thyroid treatment using I-131 in treatment of hyperthyroidism patients, 120 patients were treated by using I^{131} at Khartoum Oncology Hospital (KOH) period from October 2018 to December 2019. Imaging procedure was done using Tc99m radiopharmaceutical where the Tc99m/ Mo99m Generator was used to produce Tc99m, dose caliber and Dual head Gama camera was used to scan these patient. The level of thyroid hormone was recorded before, and after 3, 6, 9, and 12 months after treatment in order to assess the decrement level of these hormone and therefore performing a quantitative assessment of hyperthyroidism treatment, the result showed that the mean value of these hormones was 6.9, 4.2, 2.8, 2.7 and 2.5 (nmol/L) for T3, 222.1, 134, 119, 119.2 and 113.4 (nmol/L) for T4, and 0.37, 6.34, 5.3, 2.8, and 2.3 (nmol/L) for TSH respectively. Pair sample two tailed T test was performed; a significant difference between the thyroid hormone level was noted before the RAI treatment and after 3, 6, 9, and 12 months later after the treatment, at Confidence level of (CL=95%) and (p value= 0.05), the test were significant at P= 0.000. Causative disease of hyperthyroid function found to be due to Graves' disease in 45 patients (54%) of the collected samples, 28 (23.3%) by TMNG, 30 (25%) due to Diffuse toxic goiter and 6.7% related to the autonomous toxic nodules. This study concludes that hyperthyroidism treatment using I131 considered effective and cause significant difference in thyroid hormone level after treatment.

5.3 Recommendations:

- Because of increased thyroid avidity to iodine in hyperthyroidism, it is recommending that iodine containing food should be avoided one week prior to iodine administration to maximize RAI trapping and Organification, hence increase the therapeutic effect.
- Empty stomach enhances iodine uptake, so NPO for 6 hours prior to RAI administration is of great importance.
- Thyroid uptake study is of importance for all hyperthyroidism patients to adjust administered dose.
- Written patient instructions for follow up should be given clearly explained to the patients.
- Further researches should focus on the weight factor in both adult and pediatric hyperthyroidism patients.
- Further study should be conducted to compare the differences between high and low doses of radioiodine therapy.

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