

Nuclear Imaging in Thyroid Diseases - An Overview

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ABSTRACT

Radionuclide imaging is an integral part of functional evaluation of thyroid diseases. Since thyroid gland has the unique ability to concentrate iodine, isotopes of Iodine like ¹³¹I or ¹²³I has been in use for thyroid imaging and uptake studies over the past several decades. Technetium-99m with its similar uptake mechanism and physical properties ideal for imaging with gamma camera is also used for imaging and uptake studies in a routine clinical setting. Together with ultrasonography and other imaging modalities, radionuclide methods are complementary and provides information that can help in the appropriate management of various thyroid disease. In this article, a comprehensive review of all these imaging, their clinical indication, other radionuclide studies including PET and recent advances in imaging technology will be discussed.

INTRODUCTION

Nuclear or Radionuclide imaging or Scintigraphy is a diagnostic test where radioisotopes either by themselves or tagged to protein or other molecules are administered intravenously or orally that travel specifically to an organ or tissue and the emitted radiation is captured by specialized scanners known as Gamma Camera to form two-dimensional images. Thyroid scintigraphy therefore images the thyroid gland *in vivo*. Unlike X-ray (Radiography) where a part of the body is exposed to ionizing radiation in the form of X-rays to form an image, in scintigraphy the internally distributed radioactivity emits gamma radiation that generates images of the body and facilitates whole body imaging whenever required.

Radionuclide imaging has been an integral part of thyroid evaluation along with neck ultrasound and plays a key role in the functional evaluation and management of thyroid disease. ^{131}I - Sodium Iodide (**NaI**) or Radioiodine is a well established isotope that has been in use for thyroid imaging and uptake studies over the past several decades because of its unique ability of being concentrated by the thyroid gland, and an essential component of thyroid hormones. Owing to its beta emissions, ^{131}I - Sodium Iodide is also used for the treatment of hyperthyroidism and thyroid cancer. $^{99\text{m}}\text{Tc}$ -Pertechnetate is another isotope emitting gamma rays with a short half life and similar uptake mechanism based on sodium iodide symporter pump. Together with ^{131}I - Sodium Iodide, $^{99\text{m}}\text{Tc}$ -Pertechnetate forms the main isotopes used for thyroid imaging [1].

In this chapter, the radiopharmaceuticals used for thyroid imaging, imaging equipments, imaging protocols and clinical indications will be discussed.

THYROID ANATOMY AND PHYSIOLOGY

The Thyroid gland is the largest endocrine gland in the human body. It is located in the neck anterior to the trachea and below the thyroid cartilage. The normal thyroid gland weighs 15 to 20 g in adults. It has two lobes attached to each other by a rim of thyroid tissue known as isthmus in the midline. The pyramidal lobe, a remnant of the thyroglossal duct extends superiorly toward the hyoid bone. It is found almost entirely in patients with autoimmune disease such as Graves's disease or Hashimoto's thyroiditis.

The internal carotid arteries and internal jugular veins are located posterolateral to the thyroid lobes, whereas the strap muscles of the neck are located anteriorly. Thyroid is among the most vascular organs gram for gram. A euthyroid gland has a flow rate of about 5 ml/g/min.

The thyroid gland plays a critical role in regulating metabolic functions of our body including heart rate, cardiac output, lipid metabolism, heat regulation, and skeletal growth.

The thyroid gland secretes two physiologically important thyroid hormones; L-triiodothyronine (T_3) and L-thyroxine (T_4). While T_4 is more abundant in the circulation, T_3 is the more important hormone at cellular level. Formation and secretion of T_3 and T_4 are controlled by Thyroid

Stimulation Hormone (**TSH**) which is produced and secreted from specific cells in the anterior pituitary. TSH is regulated by Thyrotrophin Releasing Hormone (**TRH**) from the hypothalamus and the negative feedback from increased levels of T_3 and T_4 levels [2].

The thyroid follicular cells are the functional unit of the thyroid gland that traps iodide by an active high energy sodium iodide symporter (thyroid pump) mechanism situated at the base of the cell. The trapped Iodide is rapidly transported across the follicular cell, is oxidized to Iodine by an enzyme thyroid peroxidase and subsequently organified. Organification is a biochemical process that involves combination of Iodine with tyrosine which is incorporated into thyroglobulin molecules. The iodotyrosines are coupled to form thyronines, for e.g. two iodotyrosines are coupled to form iodothyronine (two diiodotyrosines produce T_4 and a monoiodotyrosine combined with diiodotyrosine forms T_3). The coupling step is catalyzed by the same peroxidase enzyme which is involved in oxidation of iodide and organification of tyrosine [2].

RADIO PHARMACEUTICALS

The most frequently used isotopes for thyroid scintigraphy are ^{99m}Tc Technetium pertechnetate and Iodine based radionuclides such as ^{131}I Iodine and ^{123}I Iodine.

^{99m}Tc - Pertechnetate is the chemical form of ^{99m}Tc eluted from the ^{99m}Tc / ^{99m}Tc generators. 'm' in Tc-99m indicates metastable or an excited state that comes to a stable state 'Tc-99' by isomeric transition. It is readily available in any Nuclear Medicine department, has a short half life of 6 hours with no particulate emissions and hence imparts low radiation absorption by the thyroid gland. It has a low energy of 140 KeV gamma photons which is ideally suited for use with a gamma camera. ^{99m}Tc -pertechnetate is an analogue of iodine and is therefore transported to the thyroid cells in a similar way as the isotopes of iodine, i.e. by the means of NIS [2,3]. However it is not organified nor incorporated into thyroid hormone. After IV administration, Tc-Pertechnetate reaches a peak after 15 minutes, thereafter the uptake curve plateaus after 15-30 minutes and subsequently decreases i.e. it is not retained in the thyroid. Imaging must therefore be performed early, usually at 20-30 minutes after injection.

Iodine-123 (^{123}I) decays by electron capture with a half life of 13.2 hours. The principle gamma emission is a low energy 159 Kev photon with 83.4% abundance, which is well suited for Gamma camera imaging. Compared to ^{131}I , normal thyroid gland receives lower radiation of 1.5 to 2.6 rads from a 200 μCi dose of ^{123}I . The persistence of accumulation of the radiotracer in the thyroid caused by organification results in considerably better image quality. ^{123}I has infact become the agent of choice for most adult thyroid imaging [3].

Iodine-131 (^{131}I) undergoes beta-minus decay (89% abundance of 0.606 MeV) and emits principle primary gamma photon of 364 KeV (81% abundance) which is not optimal for gamma camera imaging. It has a long physical half life of 8 days which along with the high energy beta emissions results in high radiation dose to patients (1 rad/ μCi). ^{131}I is therefore not used for

routine thyroid scans owing to its high dosimetry and poor image quality. A low dose is sometimes used for uptake calculations. It is also used for whole-body imaging in thyroid cancer patients to evaluate residual thyroid tissue or metastatic disease after thyroidectomy or thyroid ablation. The high energy beta emissions are used in effective therapy for Graves disease, toxic nodules and thyroid cancer [2,3].

Other isotopes used are ^{18}F - fluoro-deoxy-glucose in PET imaging and ^{67}Ga Citrate. Radionuclide scanning using $^{99\text{m}}\text{Tc}$ - pertechnetate and $^{123/131}\text{I}$ is used in the evaluation of focal thyroid nodule as hot, warm, or cold on the basis of relative uptake of radioactive isotope by the nodule. ^{131}I Sodium Iodide in addition is also used in the treatment of patients with thyroid cancer to evaluate for residual/recurrent disease, to assess distant metastasis, and in the follow-up of patients after thyroidectomy. ^{67}Ga Citrate imaging was routinely performed in assessment of thyroid lymphoma which has now been replaced by PET-CT.

THYROID UPTAKE STUDIES AND IMAGING

Radioiodine uptake and thyroid scans are often performed together, using different instrumentation. Uptake studies are acquired using a non imaging gamma scintillation probe detector and scans are acquired with a gamma camera. Camera based uptakes can also be routinely performed with $^{99\text{m}}\text{Tc}$ -pertechnetate scans.

Radioiodine Uptake (RAIU)

RAIU is commonly performed to help in the differential diagnosis of thyrotoxicosis. The percentage uptake is elevated in Graves' disease but decreased in thyroiditis. It is also a prerequisite for I-131 therapy dose in patients with Graves' disease.

A known amount of Radioiodine (^{131}I or ^{123}I) is administered orally to the patient and the percentage taken by the thyroid is measured by a thyroid probe. The percentage uptake is measured at 2 hours and 24 hours respectively and always done along with scintigraphy. The thyroid probe is a simple probe with a single 2 cm thick sodium iodine crystal with a single hole lead collimator coupled to a photomultiplier tube. The 5-10 μCi ^{131}I (or 50 -100 μCi ^{123}I) capsule counts are measured before administering to the patient. After administration, counts of the anterior neck over the thyroid are measured at specified times and are corrected for background by subtracting thigh counts. Measuring the counts at 2-4 hours represents the uptake phase and at 24 hours represents the organification phase [4].

Good patient preparation is essential before RAIU studies. Patients should not take any medications such as Thyroxine (Thyroxine should be stopped for 4 weeks and Triiodothyronine 2 weeks before the study), Antithyroid drugs, Iodine containing medications or food etc that can interfere with the thyroid uptake values. Patients should not have had any recent radiographic Iodine contrast studies. Fasting for 4 hours before ingestion of Radioiodine ensures good absorption.

Normal RAIU is 5-15% at 2- 4 hours and 15- 35% at 24 hours [4].

In chronic lymphocytic thyroiditis, the % RAIU at 2 hours will be greater than 24 hour uptake suggestive of peroxidase enzyme (acquired) deficiency while in Grave's disease; the 24 hours uptake will be greater than 2 hours uptake.

% RAIU values are elevated in conditions such as Graves disease, toxic adenoma, toxic multinodular goiter, Iodine deficiency, recovery from thyroiditis (Silent/ Subacute), neonates, dyshormonogenesis except for trapping defect e.g. some cases of Hashimotos's thyroiditis and after stopping antithyroid drugs.

% RAIU is decreased in iodine load, factitious thyroiditis, hypothyroidism and ectopic thyroid.

^{99m}Tc-pertechnetate uptake is not commonly performed even though it can be completed within 20-30 minutes, because of its lower accuracy as compared to % RAIU. This is due to its lack of organification once it is trapped by follicular cells. However, the trapping function of the isotope has been used for thyroid uptake along with the scintigraphy using a Gamma Camera. The pre and post injection syringe counts of the isotope are imaged to calculate the administered counts and the thyroid images are acquired at about 20-30 minutes of injecting 2-5 mCi ^{99m}Tc-pertechnetate. Areas of interest are drawn over the thyroid gland and its background region, which are then normalized for pixel size and for the time of acquisition. Normal uptake is 0.2-4 % [1-4].

Scintigraphy

Thyroid scintigraphy images the distribution of radiotracer in the functional thyroid tissue. Planar images are acquired 20 minutes after injection of the radiotracer (^{99m}Tc- pertechnetate or ¹²³Iodine), with patient in a sitting or supine position with hyperextended neck under a large field of view gamma camera detector equipped with low energy parallel collimator or a pin hole collimator. Anatomical reference is obtained by placing a radioactive marker over the sternal notch and the chin. A 15% to 20% photopeak window is centered at 140 KeV for ^{99m}Tc and 159 KeV for ¹²³I. Images are acquired in anterior, right anterior oblique and left anterior oblique views, with each image for approximately 100,000 counts or for 5 minutes. Additional images can be acquired by placing radioactive markers on a palpable nodule to help determine whether it takes up the radiopharmaceutical or not. Additional images using pinhole collimator can be performed which allows superior image resolution compared to parallel hole collimators [3-5].

Single Photon Emission Computed Tomography (**SPECT**) produces 3-dimensional images of the thyroid gland and is acquired whenever indicated using the same gamma camera, where the detectors rotate around the region of body to be imaged to generate projection images which are reconstructed using filtered back projection to generate cross sectional images [1].

Thyroid scans should be interpreted in conjunction with the patient's clinical history, thyroid function tests and clinical examination of the thyroid. Correlation with ultrasound and % RAIU is often necessary.

Normal thyroid scintigraphy demonstrates symmetric uniform uptake in both the lobes (Figure 1). The uptake in the isthmus may be variable. Thin pyramidal lobe is normally not seen. There may be increased intensity of uptake seen in the middle of the lobes where the gland is thicker as compared to the poles. The salivary glands are routinely visualized on the thyroid images.

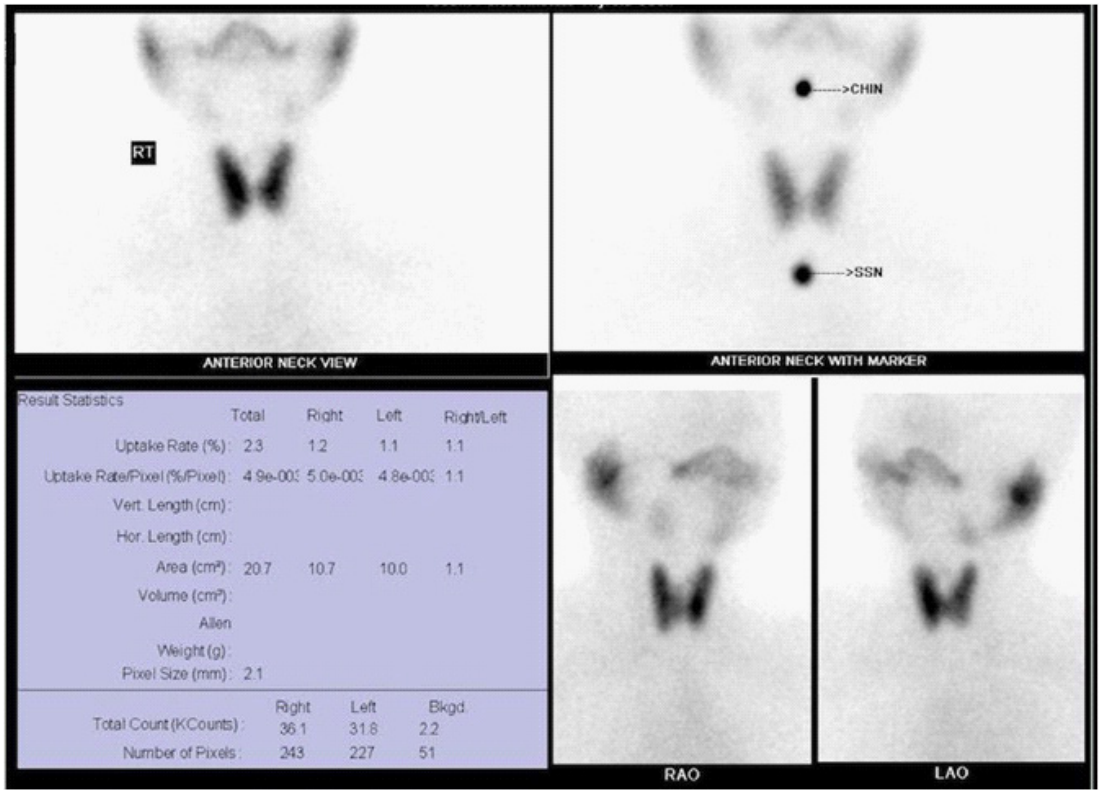


Figure 1: Normal ^{99m}Tc-pertechnetate thyroid scintigraphy showing symmetric uniform uptake in both the lobes. Physiological uptake seen in the salivary glands.

CLINICAL APPLICATIONS

Diagnosing the Cause of Hyperthyroidism

The terminology “Thyrotoxicosis” and “Hyperthyroidism” are not synonymous. “Thyrotoxicosis” refers to the hypermetabolic clinical syndrome resulting from elevated serum thyroid hormone levels, specifically free thyroxine (T₄) and/or triiodothyronine (T₃). Conditions such as subacute thyroiditis and thyroiditis factitia cause thyrotoxicosis due to the release of stored thyroid hormones into the circulation. “Hyperthyroidism” is thyrotoxicosis resulting from hyperfunctioning thyroid gland or accelerated thyroid hormone biosynthesis and secretion by the thyroid gland -for example Grave’s disease and toxic nodular goiter [4].

Thyroid scintigraphy and thyroid uptake measurements can help in the establishment of the diagnosis, when there is a clinical question between Grave’s disease (Figure 2a and 2b) and

toxic multinodular goitre (Figure 2c) and also between Grave’s disease and subacute thyroiditis (Figures 2d). The appropriate patient management is hence based on the above scan information [1,4].

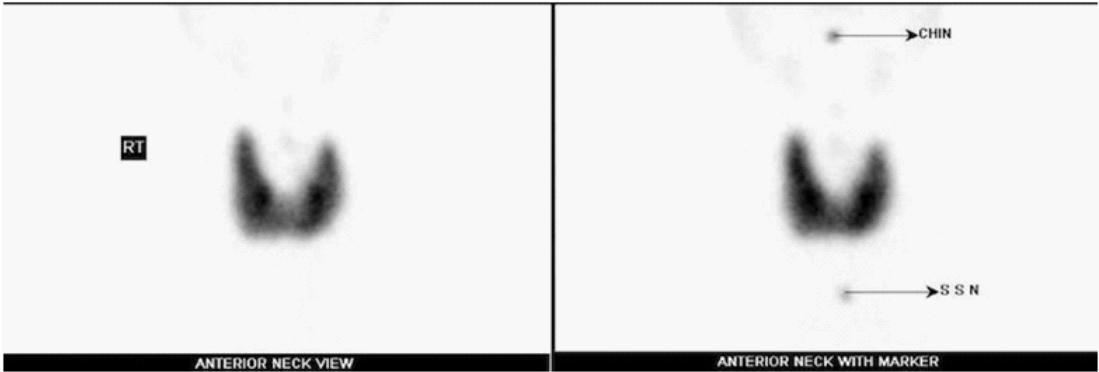


Figure 2a: Graves’ Disease: ^{99m}Tc-pertechnetate thyroid showing homogenously increased tracer uptake in both the lobes with faint background activity. 20 minutes uptake was calculated as 17% (normal: 1-4%).

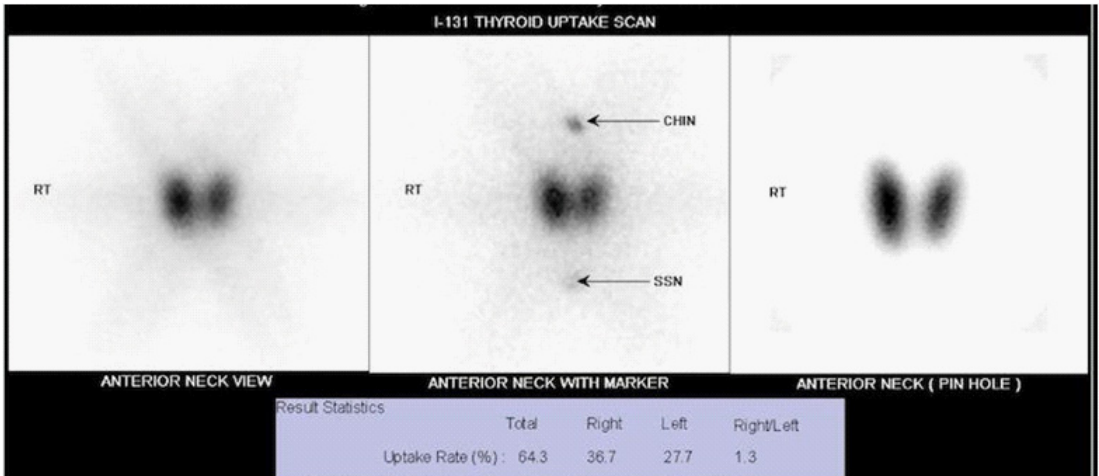


Figure 2b: Graves’ Disease: ¹³¹I scintigraphy showing uniformly increased tracer distribution in both lobes of the thyroid gland with elevated 24 hours uptake value.



Figure 2c: Toxic multinodular goiter: ^{99m}Tc -pertechnetate scan demonstrates inhomogenous tracer distribution with high uptake within the hyperfunctioning nodules and suppression of the extranodular non autonomous tissue. 20 minute uptake of 3.5% is at the upper level of normal range.

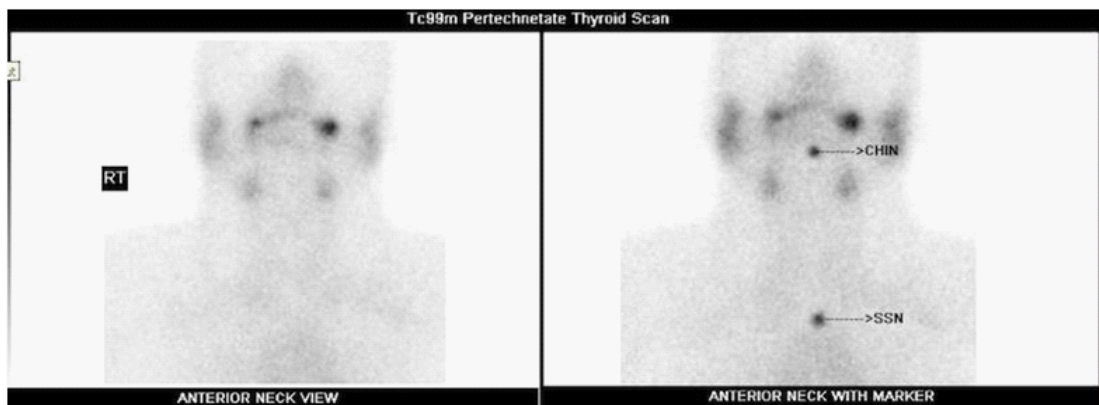


Figure 2d: Subacute Thyroiditis: Markedly suppressed ^{99m}Tc -pertechnetate uptake in the thyroid gland in a patient clinically presenting with thyrotoxicosis.

Conditions with elevated thyroid uptake

In Graves disease (Figure 2a and 2b) the scan will typically show uniformly increased thyroid uptake and percent uptake greater than 4% in ^{99m}Tc -pertechnetate scans and 50-80 % RAIU; confirming the diagnosis and excludes most other causes of thyrotoxicosis which have suppressed values.

Toxic multinodular goiter (Plummer's disease) demonstrates inhomogenous tracer distribution with high uptake within the hyperfunctioning nodules and suppression of the extranodular non autonomous tissue (Figure 2c). The % RAIU is only moderately elevated or may be in the high normal range. In some cases Grave's disease can be superimposed on a nontoxic multinodular goiter that may have warm or hot nodules, but the extranodular tissue is not suppressed.

Thyroid scan can help in diagnosing Autonomously Functioning Thyroid Nodules (AFTN) that are independent of TSH for growth and function. The nodule concentrates the radiotracer avidly with suppression of the remainder of the gland and low background activity (Figure 3). % RAIU may be elevated but often remains in the normal range. The decision to treat an AFTN depends upon the size and degree of function of the nodule and the patient's age with surgery and ^{131}I -Radioiodine being effective therapies.

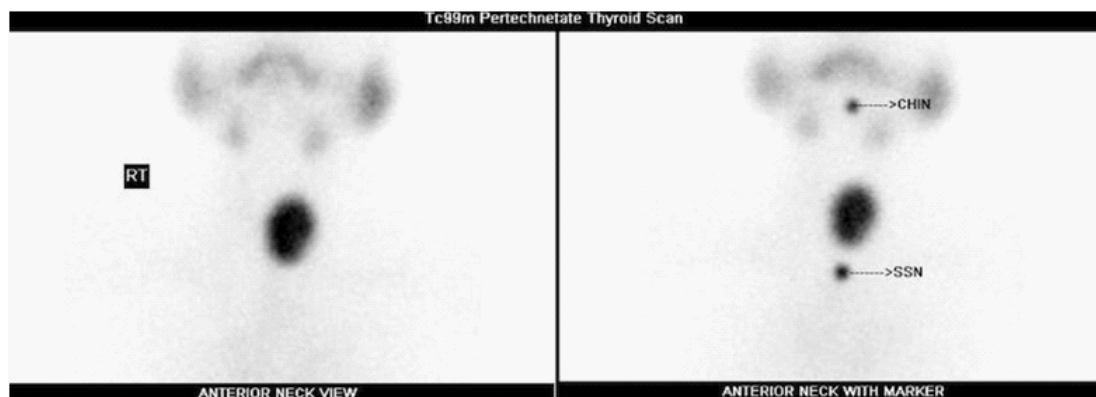


Figure 3: AFTN: Solitary hot nodule seen with suppression of the remainder of the gland and low background activity (20 minute uptake 0.9%).

Hashimotos's disease is an uncommon cause of thyrotoxicosis (hashitoxicosis). During the thyrotoxic phase, %RAIU is elevated and the scan shows diffusely increased uptake similar to Grave's disease (Figure 4). This is thought to be an overlap syndrome with Grave's and is treated with ^{131}I - Radioiodine.

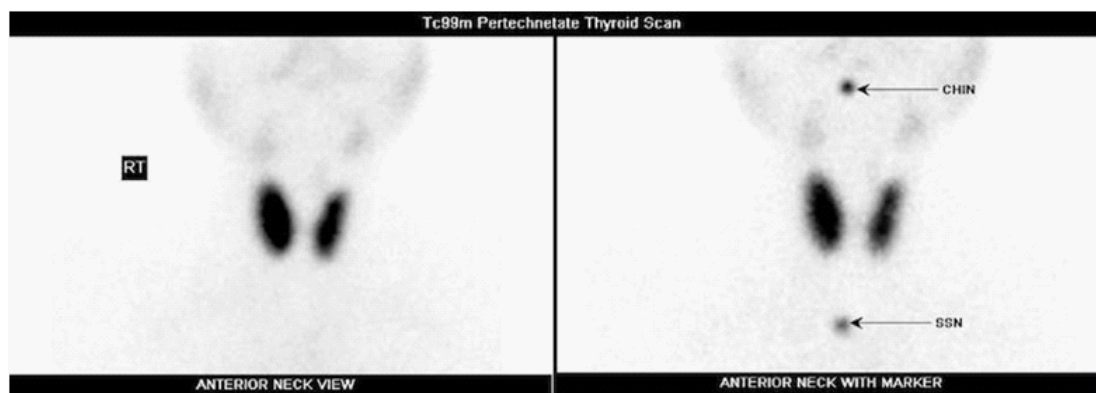


Figure 4: Hashimotos's disease: $^{99\text{m}}\text{Tc}$ -pertechnetate shows diffusely increased tracer uptake similar to Grave's disease in a 33 year old lady with elevated TSH levels (20 minute uptake 3.7%).

Conditions with suppressed thyroid uptake

Subacute thyroiditis is the most common cause of thyrotoxicosis associated with a decreased %RAIU. The RAIU depends on the stage of the disease and the damaged gland's ability to respond to endogenous TSH stimulation. Hypothyroidism resolves over weeks or months. The decreased uptake that occurs initially with subacute thyroiditis during the thyrotoxic stage (Figure 2d) is the result of an intact pituitary feedback mechanism, not damage or dysfunction of the gland. Uptake is suppressed in the entire gland although the disease may be patchy or regional [1,3].

During recovery, the appearance is variable depending on the severity of the thyroid damage. Scan may show in homogeneity of uptake or regional or focal areas of hypofunction in figure 7.

Hashimoto thyroiditis, also known as chronic autoimmune thyroiditis, is an autoimmune destruction of the thyroid characterized by goiter, autoimmunity to thyroid antigens, and lymphocyte infiltration. This condition is the most common of all thyroid disorders and affects people of all ages [6-8]. The autoimmune reaction results in lymphocytic and plasma cell infiltration with formation of lymphoid follicles, which in turn leads to thyroid follicle deterioration. As a result of the ongoing replacement of the normal thyroid follicles by lymphocytes and fibrous tissue, there is eventual reduction in thyroid function because thyroid hormone production by the gland is impaired leading to goiter and hypothyroidism [6]. The most common thyroid scan appearances are that of an enlarged gland with diffusely increased tracer uptake, a pattern identical to that found in Graves' disease (Figure 4). This is because of the compensatory rise in TSH secretion in response to the initial decline in thyroid hormones that stimulates the gland to synthesize more thyroid hormone and hence results in diffusely increased radionuclide activity throughout the thyroid [7]. Eventually, as more thyroid parenchyma is replaced by fibrous tissue, serum thyroid hormone levels decrease as the gland fails to respond to the elevated TSH level and overt hypothyroidism ensues, with nonuniform decreased uptake in varying degrees throughout the thyroid [6].

Postpartum thyroiditis is believed to be an autoimmune disease very similar to Hashimoto's thyroiditis. It manifests in the postpartum period when there are fluctuations in immune function as thyrotoxicosis followed by hypothyroidism [6,8].

Functional Assessment of Thyroid Nodules Identified on Clinical Examination or Ultrasound or by other Diagnostic Imaging

Radionuclide scanning can functionally evaluate a focal thyroid nodule as hot, warm, or cold on the basis of relative uptake of the radiotracer by the nodule. A thyroid nodule is cold (hypofunctional) if there is a focal photopenic defect devoid of the tracer uptake (Figure 5a), hot (hyperfunctional) if there is focal increased accumulation of the radiotracer (Figure 5b) or warm (indeterminate) if the uptake is similar to the surrounding normal parenchyma.

Most clinically or incidentally detected thyroid nodules are benign and are typically evaluated with ultrasound, Fine Needle Aspiration Cytology (**FNAC**) or core biopsy and serum TSH, wherein a thyroid scintigraphy is seldom required, unless the serum TSH is suppressed.

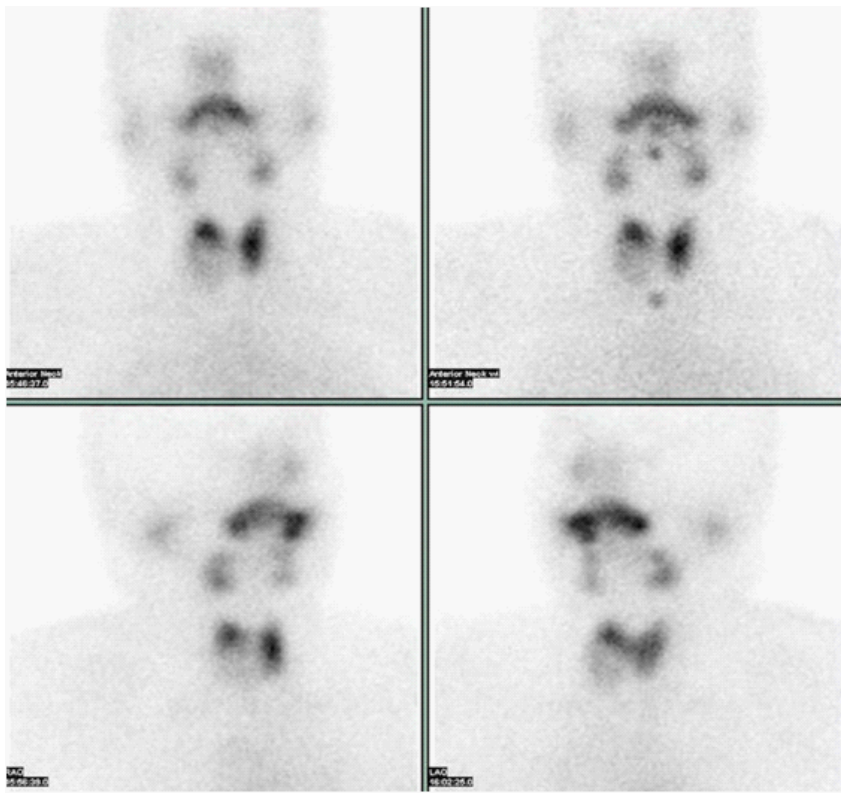


Figure 5a: Cold or hypofunctional thyroid nodule appearing as a photopenic defect in the right lobe.

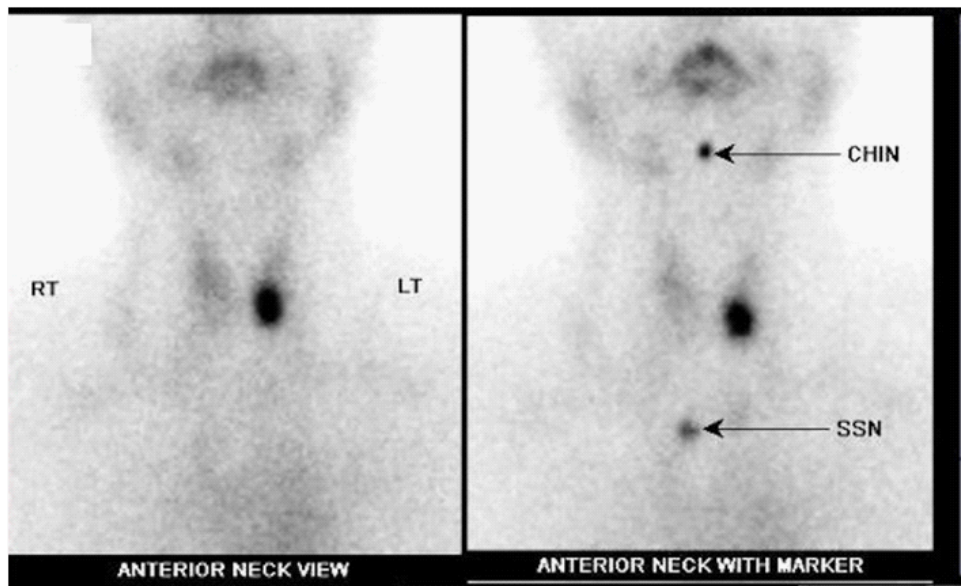


Figure 5b: Hot or hyperfunctional nodule in the lower pole of left lobe.

About 80 to 85% of thyroid nodules are cold, with only 10% of these representing malignancies. Approximately 30 to 40% of clinically diagnosed Solitary Nodules (**STN**) are infact multiple on scans that considerably decreases the probability of thyroid cancer (to 2-10%) in the absence of any clinical suspicion. A dominant cold nodule in a gland with multiple nodules should however be investigated as an STN and excised if indicated. The potential of malignancy in hot nodules is extremely rare (less than 1% incidence).

The current role of nuclear scintigraphy using $^{123/131}\text{I}$ or $^{99\text{m}}\text{Tc}$ -pertechnetate is therefore adjunctive rather than as a first-line diagnostic test. The thyroid scan may be useful in the following circumstances [9,8];

- (1) To determine the functional status of a nodule in a patient with biochemical or clinical evidence of hyperthyroidism and to obviate the need for FNAC in a hot nodule (Figure 5b) as per the American Thyroid Association guidelines.
- (2) To determine the functional status of a nodule shown to be a follicular neoplasm by FNAC/ biopsy.
- (3) In the case of goiter without clear dominance of one of the nodules, scintigraphy is used to select the biopsy site (Figure 5c).



Figure 5c: Multinodular goitre with a dominant cold nodule appearing as a large photopenic defect in the right lobe.

- (4) To determine substernal extension of a nodule or goiter.
- (5) To detect ectopic thyroid tissue and
- (6) In the postoperative management of patients with thyroid cancer.

Retrosternal goitres are associated with palpable enlargement of the cervical thyroid and diagnosed clinically if the lower border of the goitre cannot be felt. To confirm, a radiograph of the thoracic inlet and a thyroid scan with $^{123/131}\text{I}$ should be performed to evaluate the extent when ultrasound is not able to visualize the lower pole of the thyroid gland (Figure 5d). Mediastinal CT or MRI may be necessary to assess the extent and to evaluate tracheal compression. Retrosternal

or posterior intrathoracic goitres should be removed surgically if there is evidence of increasing tracheal or esophageal compression as the goitre enlarges.

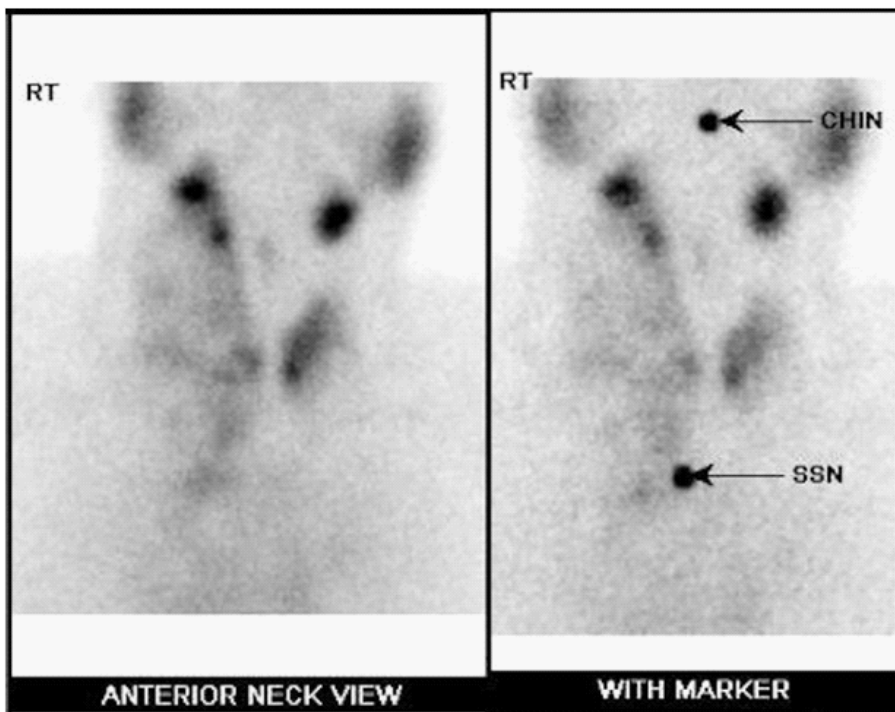


Figure 5d: ^{99m}Tc -pertechnetate scan showing a large goiter with retrosternal extension.

Other radiopharmaceuticals for thyroid nodule evaluation

One of the limitations of FNAC has been its non diagnostic results in about 5-15% cases despite ultrasound guided FNA. It is unable to characterize follicular neoplasms because of its inability to detect capsular invasion and vessel infiltration of the tumor. Few radiopharmaceuticals such as ^{201}Tl Thallium, ^{67}Ga Gallium Citrate or ^{99m}Tc Sestamibi have been evaluated in thyroid nodules particularly those with indeterminate FNAB results. At present, there is no radiopharmaceutical that has satisfactory specificity in the detection of thyroid cancer.

^{99m}Tc -sestamethoxyisobutylisonitryl (Sestamibi) has been reported to accumulate in differentiated thyroid carcinoma and medullary thyroid carcinoma. The probability of thyroid malignancy increases in hypofunctioning (cold) and MIBI-positive thyroid nodules (Figure 5e), whereas nodules with absent MIBI uptake have generally proved to be benign. However, the overall published data on its effectiveness have been inconclusive, where a SESTAMIBI scan was not specific in differentiating benign oncocyctic from malignant lesions [8]. The cellular accumulation of Sestamibi depends on the tumour size, its vascularity and richness of mitochondria in the tumor cells and is concentrated across a potential gradient [9]. While it's use is limited when the cytologic results are follicular oncocyctic neoplasm, the diagnostic accuracy of sestamibi

scans in non oncocytic follicular neoplasms were found to be 94.44%, with better sensitivity and specificity than visual analysis (100% and 73.33% vs. 90.48% and 80.95%, respectively) and can therefore be used when the FNAB results are indeterminate [10]. The authors of the above study therefore propose to adopt close monitoring when Sestamibi scan results and those of molecular markers Galectin-3 and HBME-1 are negative and to refer patients for thyroidectomy when both the scan and markers are positive [10].

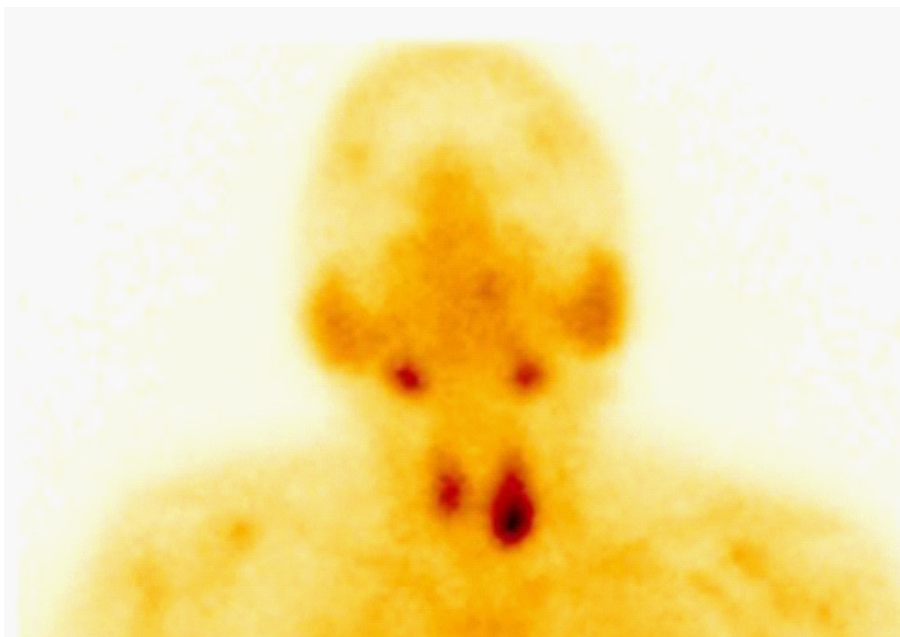
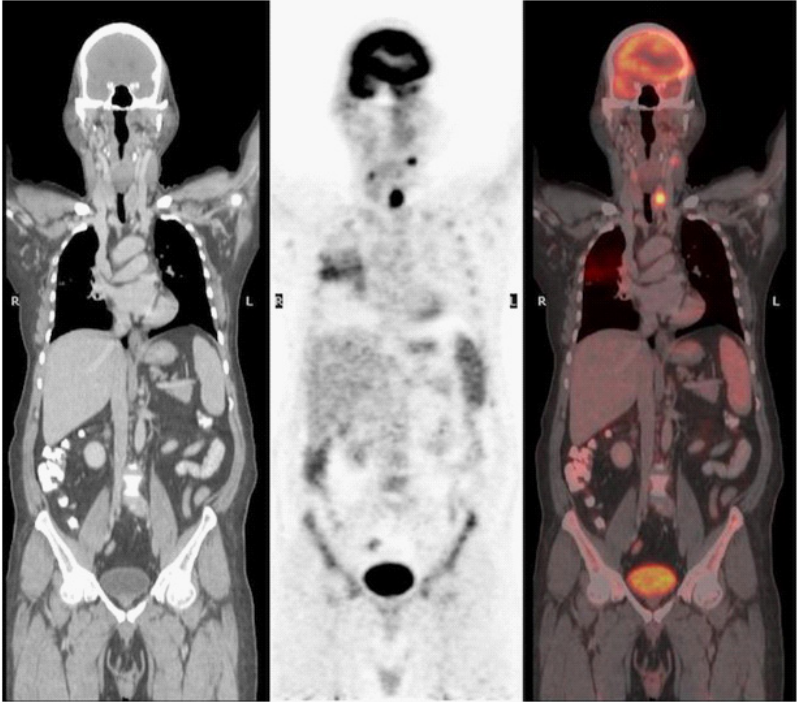


Figure 5e: ^{99m}Tc Sestamibi scan: Patient with solitary thyroid nodule showing increased concentration of ^{99m}Tc SESTAMIBI in the left lobe nodule.

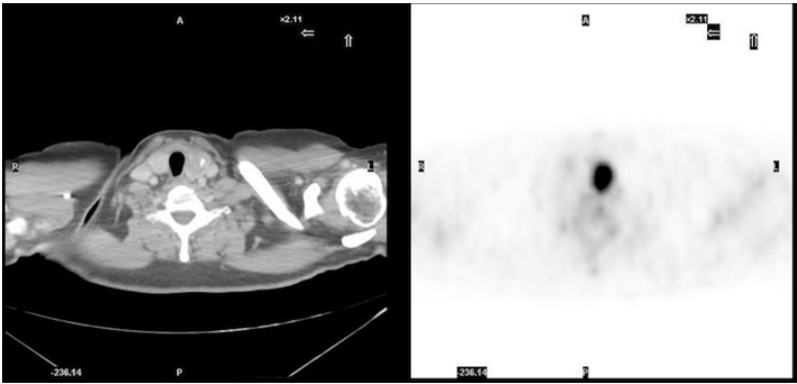
^{99m}Tc -MIBI has also been shown to be a substrate for the MDR1 gene coded P-glycoprotein (P-gp) and multidrug resistance-associated protein-1 (MRP1) demonstrating rapid washout from the tumor cells expressing high levels of P-gp or MRP1 [10] providing tissue information on the possible molecular mechanisms of Sestamibi uptake in thyroid lesions.

Thyroid nodules are incidentally detected in about 2% - 3% of PET imaging with ^{18}F - Fluoro-2-Deoxy-d-Glucose (**FDG**). Both benign and malignant thyroid lesions tend to show increased FDG uptake that can be quantified with the Standardized Uptake Value (**SUV**) relative to normal background thyroid parenchyma. Although studies have showed higher SUV measurements in malignant thyroid nodules than in benign nodules, there is no accepted threshold SUV for prediction of malignancy. Nonetheless, given that FDG uptake in a nodule increases the risk for malignancy to 14%-40%, further evaluation with ultrasound and FNAB is recommended (Figures 5f and 5g). In several prospective studies image of a metabolically active thyroid nodule was characterized by relatively low positive predictive value (33 to 50%). ^{18}F -FDG uptake may

also occur in a number of benign lesions [11]. Retrospective studies performed on thousands of PET and PET/CT images, showed that the probability of thyroid cancer in case of incidentally detected focal metabolic activity in the thyroid varies from 27 to 47% (Incidentalomas). In some centres positron-emitting iodine isotope ^{124}I is available with a half-life of 4.2 days and allows for more precise images than routine ^{131}I scintigraphy, with the advantage of no effect on the thyroid stunning.



5 f



5 g

Figure 5f and 5g: ^{18}F -FDG PET/CT showing intensely increased FDG uptake in a left lobe thyroid nodule with additional cervical nodal metastasis in a patient being evaluated after for lung mass. Biopsy revealed papillary carcinoma of thyroid.

Evaluation of Congenital Hypothyroidism

Congenital Hypothyroidism (CH) during neonatal screening represents a spectrum of disease ranging from transient under activity to complete absence of a thyroid gland. It is one of the most common preventable causes of mental retardation. The clinical and biochemical parameters fail to distinguish between the presence of an ectopic or hypoplastic thyroid, athyrosis, dyshormonogenesis and transient hypothyroidism [12,13].

Thyroid dysgenesis is the commonest accounting for 80-85% of all cases of CH. 10 to 15% cases are due to dyshormonogenesis, which along with developmental anomalies are responsible for permanent hypothyroidism. Among patients with thyroid dysgenesis, 23-67% was due to ectopic thyroid gland and one third due to thyroid agenesis. Any genetic defect regarding thyroid biosynthesis pathway (most frequently thyroid peroxidase deficiency) or hormone secretion may lead to thyroid dyshormonogenesis [12,13].

Once the diagnosis is established, further investigations to determine the etiology should be done. Thyroid scintigraphy helps in confirming the cause of hypothyroidism by the typical appearances of athyreosis (Figure 6a), ectopic location (Figure 6b) as well as goitrous hypothyroidism due to dyshormonogenesis (Figure 6c). Scan should be done before commencing replacement thyroxine. However, one should not withhold therapy if it is not possible to get it performed immediately.

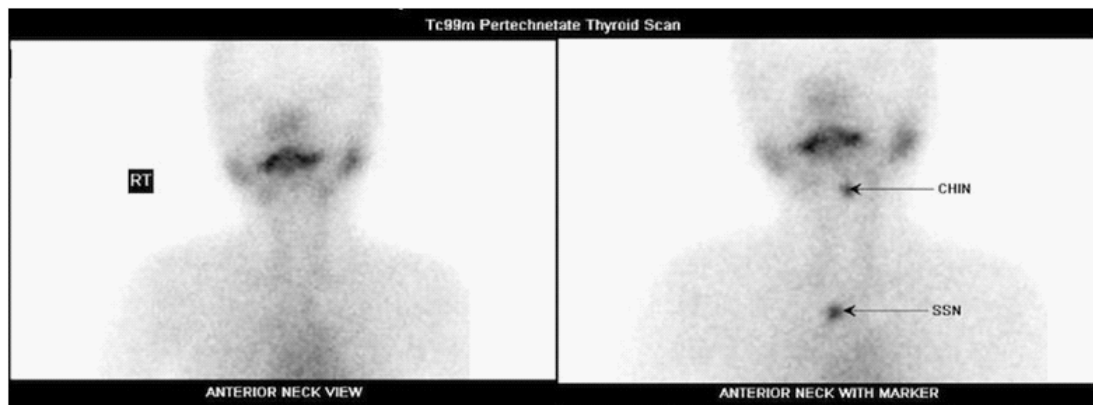


Figure 6a: 3 year child with hypothyroidism. ^{99m}Tc -pertechnetate scan showing no tracer uptake in the neck or at ectopic sites in favour of hypoplastic gland or athyreosis. Ultrasound of the neck also failed to identify the thyroid gland.

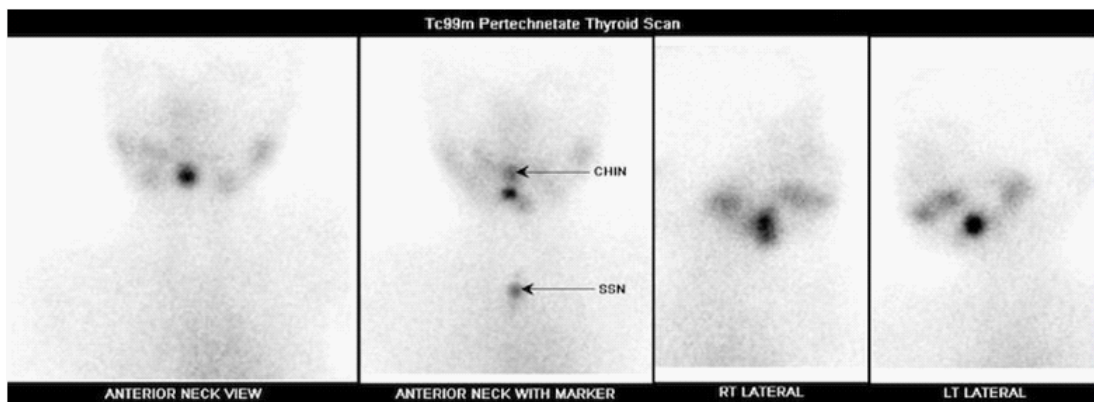


Figure 6b: Lingual thyroid gland: 4 year child with hypothyroidism. ^{99m}Tc -pertechnetate showing a small focus of tracer uptake ectopically in the lingual region. No other functional thyroid tissue seen in its normal location suggesting this as the only functional thyroid tissue.

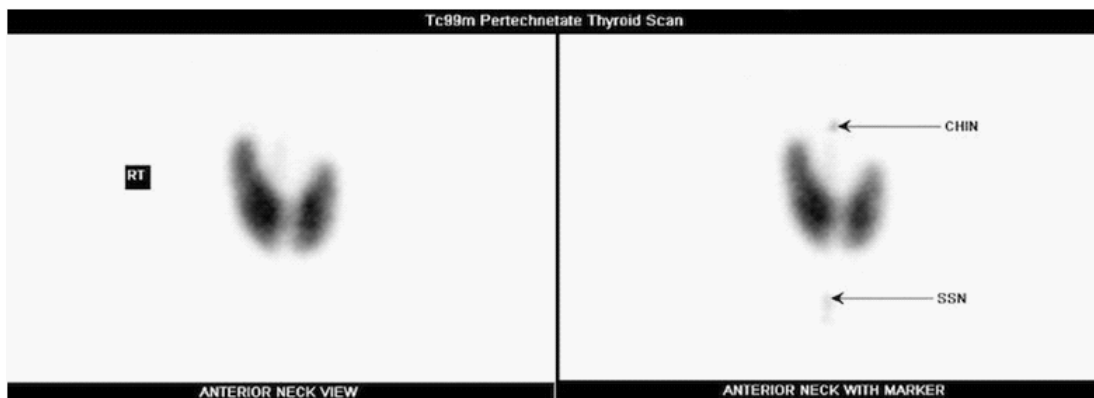


Figure 6c: Dyshormonogenesis. 10 year old child with hypothyroidism showing normal thyroid gland in its normal location with avid tracer uptake typical of dyshormonogenesis in this clinical setting.

For ectopic thyroid glands, ^{123}I is a better isotope because of its higher uptake which avoids confusion with saliva and salivary glands on a ^{99m}Tc -pertechnetate scan. Radiation dose is small compared with ^{131}I . Therefore the scan can be used safely in infants, children or adolescents.

A point to note that is that the thyroid scan should include field of view from mouth to sternal notch. In case of a lingual thyroid, a lateral view is important for accurate 3-dimensional localization. Radionuclide uptake in the nodule confirms the presence of ectopic thyroid whereas other types of nodule (example: a thyroglossal cyst) appears cold.

Thyroid scan also establishes whether a normal thyroid is present or not. If normal thyroid is not visualized, the scan should be repeated after TSH stimulation to exclude the possibility that its function may be suppressed. Nodules that show no uptake of ^{99m}Tc -pertechnetate or ^{123}I can be

excised. A functioning ectopic thyroid nodule in the presence of a normal thyroid in its normal site can also be excised. However, a sublingual thyroid that contains the entire functioning thyroid tissue should be preserved [12,13].

Thyroid Malignancy

Thyroid cancer originates from follicular or parafollicular thyroid cells. The well-differentiated cancers are Papillary and Follicular cancers arising from the follicular cells and Medullary thyroid cancer arising from the C or parafollicular cells that produce the hormone calcitonin. Anaplastic thyroid cancers are poorly differentiated [1].

Ultrasound and ultrasound-guided FNAC or core biopsy is the investigation of choice for diagnosing primary thyroid cancers. Cross sectional imaging with contrast enhanced CT or MRI may be helpful in patients who have extrathyroidal tumour extension into major structures of the neck to guide surgeons in taking decisions regarding operability as well as in planning major reconstructive surgery. Tumour invasion into the trachea and oesophagus (T4a) are two sites where major reconstructive surgery may be required, but these are also sites that are difficult to assess by imaging [1,3].

An $^{131/123}\text{I}$ Whole Body Imaging (**WBI**) is not useful for preoperative surgical staging of a thyroid malignancy. However, it has an important role following total thyroidectomy to identify residual locoregional disease (Figure 7a) and distant metastases (Figure 7b) in well differentiated cancers. $^{131/123}\text{I}$ WBI is routinely performed after Radioiodine ablation at intervals of 6 months to identify recurrent nodal metastases in the neck and mediastinum if the serum thyroglobulin is elevated. In low risk patients, a post ablative WBI may not be necessary if the thyroglobulin level is undetectable under thyroid stimulating hormone stimulation and the post-operative ultrasound is normal [1,3].

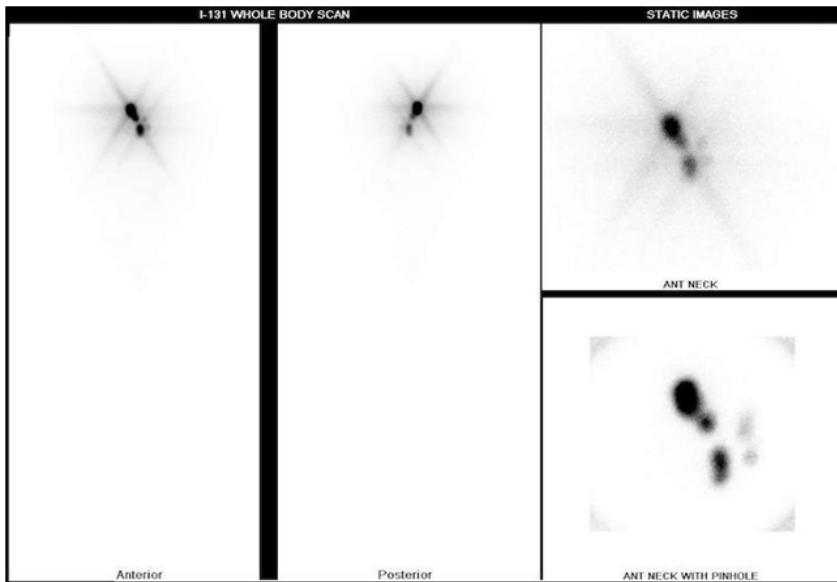


Figure 7a: ^{131}I whole body imaging in a 40 year old female who underwent total thyroidectomy for papillary carcinoma thyroid showing increased radioiodine concentration in the neck residue as well as neck nodal metastasis suggestive of locoregional disease.

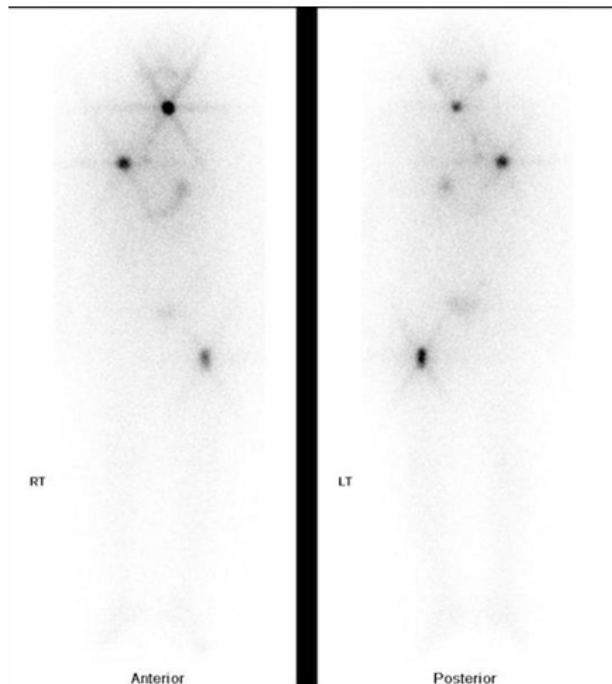


Figure 7b: ^{131}I whole body imaging in a 52 year old gentleman who underwent total thyroidectomy for follicular carcinoma thyroid showing increased radioiodine concentration in the neck residue as well as multiple bony sites.

Limitations of $^{131/123}\text{I}$ WBI include missing iodine negative nodes which arise from medullary cancer thyroid and less differentiated papillary or follicular thyroid cancers including some hurthle cell carcinomas and anaplastic cancers. The above limitations result in a greater role for other imaging modalities such as CT, MRI and other radioisotopic imaging such as ^{111}In - DTPA-octreotide, $^{99\text{m}}\text{Tc}(\text{V})$ -DMSA, ^{131}I -MIBG scans and ^{18}F -FDG PET-CT. Scintigraphy with tracers such as ^{111}In - DTPA-octreotide, $^{99\text{m}}\text{Tc}(\text{V})$ -DMSA, ^{131}I -MIBG offer the prospect of targeted therapy in tumour positive cases [1,3,14].

Point to note: $^{131/123}\text{I}$ uptake is reduced by intravenous iodinated contrast agents used for CT and these can interfere with the uptake for at least 1-3 months. Hence $^{131/123}\text{I}$ WBI or Radioiodine therapy should be scheduled 2 to 3 months later.

Advanced imaging technology

Single-photon-emission Computed Tomography (**SPECT**) has been used in general nuclear medicine, nuclear cardiology and nuclear neurology for several decades to provide three-dimensional images of radiotracer distribution [1,3]. In onco imaging, use of SPECT data has occasionally been less than optimal because of the inability to provide accurate anatomic localization of an identified abnormality. By combining SPECT with CT, it is now feasible to address this limitation and has clinical applications in the evaluation of thyroid nodules and thyroid malignancies.

The advantages of SPECT/CT parallel those of PET/CT in many ways. The additional anatomic localization provided by CT imaging has proven beneficial in situations where SPECT results alone have been inconclusive. This together with the ability to correct for attenuation and scatter artefacts can provide more accurate image data. While anatomic imaging techniques allow accurate detection and localization of morphologic abnormalities, nuclear medicine studies reflect the pathophysiologic status of the disease process [14]. Using a combined system, one can sequentially acquire both anatomic and functional information that is accurately fused in a single examination [1,3,14]. SPECT/CT imaging provides value to the clinician by allowing accurate localization of radiopharmaceutical accumulations, detection of occult disease sites, characterization of metabolically active areas of known lesions, and providing a means for quantifying tracer uptake (Figure 8). $^{123/131}\text{I}$ SPECT/CT can help in localization of sites of abnormal tracer uptake and improve the diagnostic accuracy of these studies. It can also provide a more reliable determination of the response to treatments received.

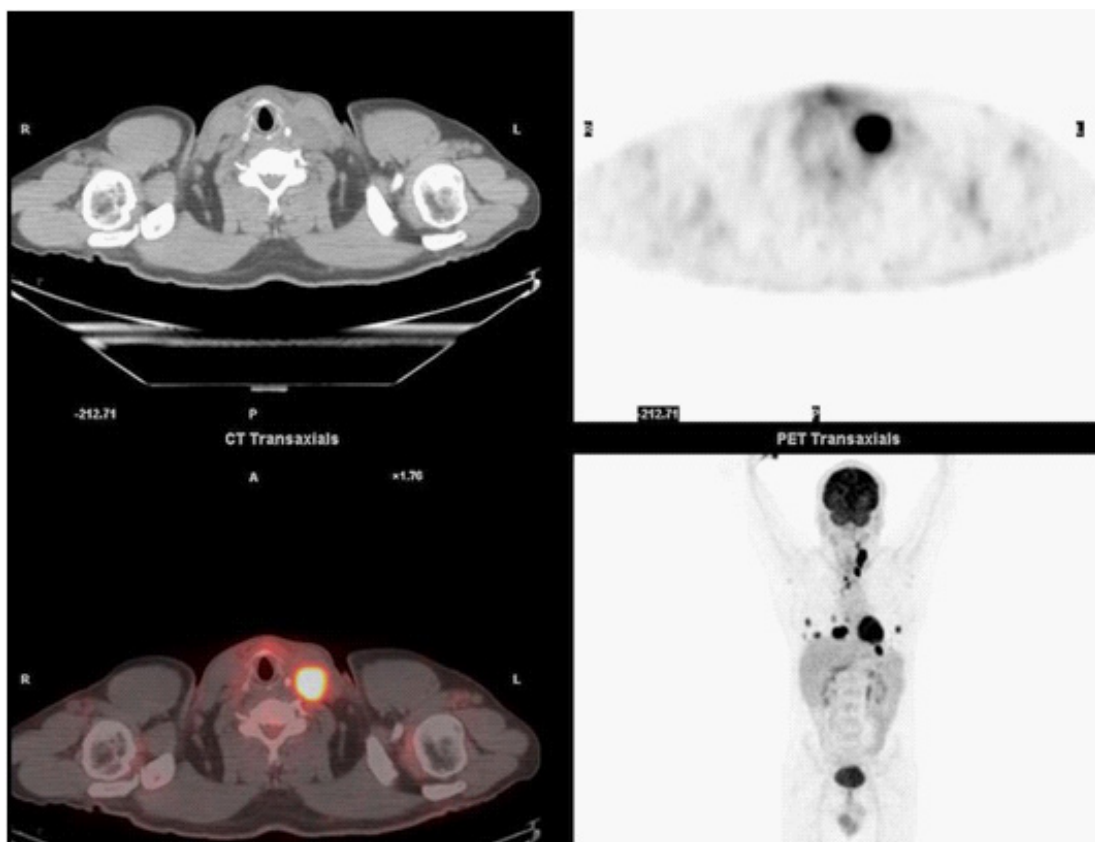


Figure 9: ^{18}F -FDG PET/CT in a case of anaplastic carcinoma showing high great concentration of FDG in multiple lymph nodes in the neck, mediastinum and abdomen. Focal uptake in the left thyroid nodules is well appreciated. Multiple FDG avid lung nodules visualized.

CONCLUSION

Thyroid scintigraphy is an integral part of thyroid evaluation. Despite the recent advances in imaging modalities, the conventional scintigraphic techniques using $^{99\text{m}}\text{Tc}$ -pertechnetate and $^{123}/^{131}\text{I}$ are still indicated in select group of patients with thyroid disease which can impact decision on the management of patients. This article attempts to summarize the current state of knowledge for the most efficient use of nuclear imaging in the investigation of thyroid disease.

References

1. Maisey MN. Thyroid. Clinical Nuclear Medicine 4th Edition. 2006; 491-510.
2. McDougall IR. Thyroid physiology. Thyroid disease in clinical practice. 1992; 12-33.
3. Zeissman AH, O'Malley PJ, Thrall HJ, Fahey HF. Endocrine System. Nuclear medicine: The requisites. 2016; 66-97.
4. McDougall IR. Tests of thyroid function. Thyroid disease in clinical practice. 1992; 34-74.
5. Intenzo CM, Capuzzi DM, Jabbour S, Kim SM, dePapp AE. Scintigraphic Features of Autoimmune Thyroiditis. Radiographics. 2001; 21: 957-964.

6. Ramtoola S, Maisey MN, Clarke SE, Fogelman I. The thyroid scan in Hashimoto's thyroiditis: the great mimic. *Nucl Med Commun*. 1988; 9: 639-645.
7. Cases JA, Surks MI. The Changing Role of Scintigraphy in the Evaluation of Thyroid Nodules. *Semin Nucl Med*. 2000; 30: 81-87.
8. Czepczyński R. Nuclear medicine in the diagnosis of benign thyroid diseases. *Nucl Med Rev Cent East Eur*. 2012; 15: 113-119.
9. Saggiorato E, Angusti T, Rosas R, Martinese M, Finessi M, et al. 99mTc-MIBI Imaging in the Presurgical Characterization of Thyroid Follicular Neoplasms: Relationship to Multidrug Resistance Protein Expression. *J Nucl Med*. 2009; 50: 1785-1793.
10. Bae JS, Chae BJ, Park WC, Kim JS, Kim SH, et al. Incidental thyroid lesions detected by FDG-PET/CT: prevalence and risk of thyroid cancer. *World J Surg Oncol*. 2009; 7: 63.
11. Volkan-Salanc B, Kiratl PO. Nuclear Medicine in Thyroid Diseases in Pediatric and Adolescent Patients. *Mol Imaging Radionucl Ther*. 2015; 24: 47-59.
12. Sood A, Kumar R. The ectopic thyroid gland and the role of nuclear medicine techniques in its diagnosis and management. *Hell J Nucl Med*. 2008; 11: 168-171.
13. Chaudhary V, Bano S. Imaging of the thyroid: Recent advances. *Indian J Endocrinol Metab*. 2012; 16: 371-376.
14. Asa S, Aksoy SY, Vatankulu B, Aliyev A, Uslu L, et al. The role of FDG-PET/CT in differentiated thyroid cancer patients with negative iodine-131 whole-body scan and elevated anti-Tg level. *Ann Nucl Med*. 2014; 28: 970-979.
15. Becker D, Charkes ND, Dworkin H, Hurley J, McDougall IR, et al. Procedure guideline for thyroid scintigraphy: 1.0. society of nuclear medicine. *J Nucl Med*. 1996; 37: 1264-1266.