Update

Physiopathologic atlas of thyroid scintigraphy

Gupta V

Department of Nuclear Medicine, Rajiv Gandhi Cancer Institute & Research Centre, Sector –V, Rohini, Delhi-110085, India

Abstract

Nuclear medicine is an excellent example of functional imaging. It has an established role in the evaluation and management of thyroid disorders. The physiologic and pathologic basis of radiotracer based thyroid imaging has been presented in this article. The same principles apply to the treatment of thyroid disorders using radioactive iodine.

Keywords: Thyroid scan, radioiodine, I-131 ablation therapy.

Nuclear Medicine employs open sources of radioactivity (radioisotopes) for studying the function of an organ of interest for the diagnosis and/or treatment of a disease. Its one of the first applications was in the field of thyroid disorders (in 1942 by Hertz & Roberts) which was then extended to several other organs. Since then it has remain irreplaceable especially for the adjuvant treatment of thyroid cancer with a proven safety record.

The field of nuclear medicine offers a gamut of procedures for the comprehensive evaluation of thyroid function including treatment of thyroid disorders. This radioisotope based imaging of thyroid gland is called 'Thyroid Scintigraphy' (or loosely as scanning). It can evaluate both regional as well as global thyroid function and can also evaluate function of anatomical defects in thyroid. The major advantage of using radioisotopes is that the thyroid disorders can be evaluated in a physiological manner. This atlas will focus on radioisotope applications in thyroid disorders.

Thyroid & Iodine

Thyroid is a symmetrical gland situated in the anterior part of the neck. It usually lies between thyroid cartilage and 4th or 5th tracheal ring. This region is called as 'Thyroid bed'. Thyroid consists of two lobes, each of which is ellipsoid in shape. Their longitudinal axis lies along the longitudinal axis of the trachea, thus have upper and lower poles. They are separated at their upper poles but tend to come closer at their lower poles. Most of the times there is a thin layer of thyroid tissue in front of the trachea called as 'Isthmus' which connects the two lobes at their lower poles. A rudiment of embryological structure thyroglossal duct can sometimes be seen as an accessory lobe originating from isthmus or either of the lobes. It is called as Pyramidal lobe.

Each lobe of thyroid gland is structurally organised into multiple lobules which in turn have multiple follicles. These follicles which are spheroid in shape comprise of cuboidal cells lying at periphery which secrete colloid that accumulates in the centre of follicles. The colloid is the site of storage of thyroid hormones. Thyroid has a rich vascular supply through paired superior and inferior thyroidal arteries.

Thyroid has an important endocrine function which regulated through pituitary-thyroid axis. Under the influence of Thyroid Stimulating Hormone (TSH) thyroid produces hormones called thyroxine and tri-iodothyronine, which play an important role in growth and metabolism. The stable form of iodine, i.e. I-127 is one of the essential substrates for thyroid hormone synthesis. Iodine as iodide is actively trapped by the thyroid follicular cells. This process is helped by a cell membrane transport protein- 'sodium iodide symporter' (NIS) which is produced by NIS gene expressed in thyroid cells (Smanik). Trapping mechanism can help to increase the intrathyroidal iodine concentration 25 times more than that of serum. This ratio can go up to 100:1 or more under the influence of TSH as in hyperthyroidism. Once inside the thyroid cells, iodide is oxidised to its active form. The active form binds tyrosine molecules present on thyroglobulin molecules in colloid of the thyroid follicles. The process is called as organification. Further reaction of organified molecules (coupling) results in formation of thyroid hormones. All these reactions i.e. oxidation of iodine, organification and coupling occurs under the influence of an enzyme called thyroid peroxidase (TPO). Thyroid peroxidase function defect is seen in thyroiditis and Pendred's syndrome.

Correspondence
Dr. Vijay Gupta
Department of Nuclear Medicine, Rajiv Gandhi Cancer Institute & Research Centre, Sector –V, Rohini, Delhi-110085, India
Email:drvj@yahoo.com

NIS can also trap various other isotopes of iodine like iodine-123/131 etc. and analogues of iodine, like Tc99m-pertechnetate (*its short name Tc99m would be used for this article*), perchlorate etc. Thus, for instance, one can trace the movement of iodine, more precisely indirectly study thyroid function/iodine metabolism using different isotopes of iodine (I-123 or I-131). Radioisotopes of iodine get incorporated into thyroid hormones (get organified) whereas analogues of iodine like Tc99m don't. Even though not organified, Tc99m can practically give a reliable idea about thyroid function, if not metabolism.

Principle of Nuclear Medicine Studies
Some of the atoms of an element become unstable due to disproportionate ratio of protons and neutrons in their nucleus. To achieve stability they expel surplus energy in the form of radiation which may be as alpha, beta or gamma rays. Such atoms are called 'Radioactive' and this phenomenon is called Radioactivity.

When a very small amount (traces) of radioactive form of a substrate of a metabolic pathway (compound tagged with radioisotope- called 'radiotracer') is made to enter a biological system, its chemical behaviour is identical to that of the stable form of that metabolite. Therefore, it undergoes similar metabolic changes like its natural (non-radioactive) counterpart without influencing the normal metabolism. The detection of radiation emitted from the radioactive atoms present in that metabolite permits to follow the pathway taken by that metabolite. It is possible to detect even extremely minute concentrations (traces) of radioactive compounds, hence the term 'Tracer Principle' (Hevsey). Very low number of radioactive atoms employed also ensures very low radiation exposure to the patient as well as to the radiation personnel carrying out such studies. One can also study iodine metabolism and thus, thyroid function in a similar manner.

Thyroid Scintigraphy is done using an instrument which can detect gamma rays, called as 'Gamma Camera'. Using it an image of the distribution of radiotracer in the organ/body can be obtained, which is called as 'Scintigraphy'. For instance, if radioiodine containing capsule is given orally, when it is in mouth the radiation detector will show radioactivity to be in mouth. On swallowing, the maximum radioactivity would be detected in stomach and then over a period of time this radioactivity is absorbed from GIT into circulation and after distribution by the blood it will be detected all over the body. It will also be selectively concentrated in normal thyroid, whereby the thyroid gland can be imaged. Alternatively on intravenous injection the tracer

gets circulated in the body through blood and taken up by thyroid. Kindly refer to Figure 6b, consecutive gamma camera images of upper chest have been acquired after the radiotracer has been injected intravenously in a left upper limb vein. In Frame 1 of this figure radiotracer arrives in heart, in frame 2, 3 it enters lungs, in frame 4 it reaches carotid arteries and in frame 5 it reaches thyroid and so on. In this fashion the life-processes can be studied in a dynamic manner. Thus, nuclear medicine is a functional imaging modality. If Radiology usually shows anatomical aspects of body, Nuclear medicine shows related physiological aspects.

The radioisotopes used for thyroid scintigraphy:

a) **Technetium-99m** (Tc99m) in the form of pertechnetate is generally used for thyroid scintigraphy and where available, radioisotope Iodine-123 (I-123) can be used instead. Tc99m is a preferred isotope due to its ready availability, economy, less radiation dose, short half-life and better image quality. There are no side effects.

b) **Iodine-123** (I-123), a cyclotron product, is expensive and is usually not readily available. It is considered to be more physiologic as compared to Tc99m due to the fact that iodine gets incorporated into thyroid hormones and stays in thyroid, whereas Tc99m is not organified.

Further, on comparing it with I-131, I-123 has an advantage over I-131 of short half life and less radiation dose. I-123 is also preferred over I-131 when iodine based thyroid imaging is contemplated to detect iodine organification defect. It is called perchlorate discharge test (PDT) and used in thyroiditis, Pendred's syndrome (details of PDT are beyond the scope of this article).

c) **Iodine-131** (I-131) is used for imaging if goitre is suspected to be retrosternal or intrathoracic, where, highly penetrating gamma rays of I-131 are helpful as they can pass through sternum. It is also used in detection of functioning (I-131 concentrating) metastasis of thyroid cancer. If I-131 is concentrated by thyroid cancer cells then it is very useful for their ablation when administered in high doses. This forms the basis of radioiodine therapy.

Isotope based studies of Thyroid function:
Out of 25 known isotopes of iodine, only I-127 is stable. Though many radioisotopes of iodine are available, but commonly used isotope is analogue of iodine, i.e. Technetium-99m or alternatively Iodine-123.

For routine thyroid scintigraphy, 5-10 mCi of Tc99m is injected intravenously. Neck images are acquired 20-30 minutes post-tracer injection in anterior projection. Additional oblique views are taken, if needed, with a pin-hole collimator to detect/analyse cold nodules.

I-123 is not usually used for imaging due to less availability, more expense, more radiation dose and imaging time involved. With I-123, the images are acquired 4/24 hours after tracer administration.

Patient Preparation for Thyroid Scintigraphy:

* Usually no prior patient preparation is needed for thyroid scintigraphy. However, if the patient is taking any antithyroid drugs, the drugs should be stopped and thyroid scintigraphy is done 72 hours later.

* In case the patient is taking thyroid hormone replacement therapy or iodine, the study should be done six weeks after stopping these drugs.

* The female patients who are pregnant or breast feeding the babies should inform the nuclear medicine physician before taking a diagnostic test. Although the radiation exposure involved is very low, however, in case of pregnancy the procedure would be performed only when the benefit outweighs the

---

Tc99m Scintigraphic Images, Salient features:
Tc99m-pertechnetate being an analogue of stable form of iodine, i.e. I-127, behaves like it and is actively trapped by the thyroid gland depending on the integrity, level of thyroid (especially NIS gene) function and gland vascularity.

Thyroid scintigraphy produces an image of distribution of radiotracer in thyroid parenchyma. It helps to diagnose thyroid diseases on the basis of level of radiotracer uptake as compared to surrounding structures, radiotracer distribution in thyroid, any extrathyroidal uptake etc. It gives an idea about thyroid location. It also helps to know thyroid morphology including its size and overall & regional level of thyroid function both qualitatively and quantitatively.

The important thyroid imaging findings seen in nuclear medicine practice are as follows:

I. Normal Findings
Just like natural iodine, the tracer Tc99m after intravenous injection will be delivered to thyroid through its blood vessels. It would be available for trapping by NIS present in thyroid follicular cells. Trapped tracer will then accumulate in thyroid. For instance, for a normal thyroid gland (Figure 1) the tracer trapping is 0.4-4 % of total injected dose with uniform tracer distribution. Normally the gland is symmetrical and the lateral borders of lobes are straight to convex. Tracer is normally seen in salivary glands and in capillary network of the neck tissue also, called as 'blood pool'.
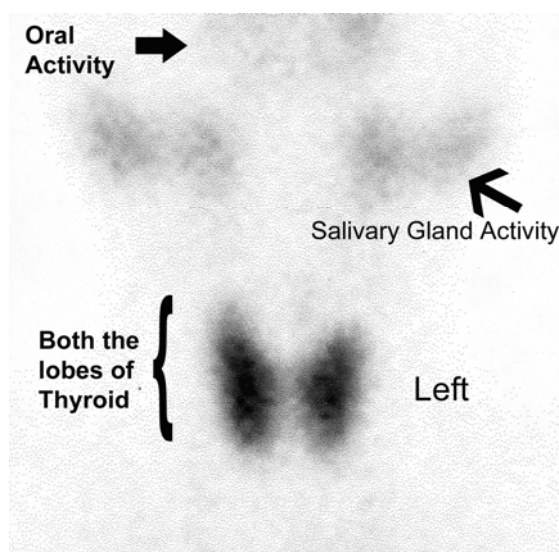

**Figure 1: Scintiscan of Normal Thyroid**

II. Abnormal Findings
While interpreting a thyroid scintiscan one is looking for abnormality in its shape, size, location. Both regional and global level of tracer uptake and its distribution is also evaluated. Any abnormal extrathyroidal tracer trapping is also looked for. In addition, final interpretation of the findings should be done in the light of clinical history, physical examination, serum thyroid hormone levels and when available correlative information should be derived from other diagnostic tests like-ultrasonography, FNAC, thyroid antibodies etc. Many times thyroid scintigraphy alone can give a reliable diagnosis.

The regional distribution of tracer in the thyroid depends on the level of vascularity of thyroid and function of different areas of thyroid. For instance, when the vascularity of thyroid is high, more tracer would be delivered to it due to more volume of blood passing through it per unit time. This means more tracer would be available to thyroid for

trapping. Hence, more tracer can concentrate in the thyroid independent of level of NIS gene expression. Sometimes, focal areas are affected by thyroiditis resulting in focal loss of function, the areas with loss of function show decreased tracer trapping.

In Graves' disease, in addition to increased vascularity, cardiac output is also increased. Further, NIS expression is also increased. Both these latter factors also result in enhanced tracer trapping by thyroid (Figure 2) i.e. higher than normal (> 4%), it can be >60% or more. Thyroid usually shows uniform diffuse enlargement. Tracer is uniformly distributed in the thyroid. Not normally seen pyramidal lobe (a remnant of thyroglossal duct) can be seen in a hypertrophied gland. Tracer is barely trapped in salivary glands due to less tracer availability for extraction to them consequent to higher trapping by thyroid.

An image similar to Graves' disease (Figure 2) may also be seen in 'acute' phase of thyroiditis-'Hashitoxicosis', due to the increased vascularity of gland consequent to inflammation, which causes increased delivery of tracer to thyroid resulting in increased tracer trapping in the thyroid. Sometimes it is difficult to differentiate this condition from Graves' disease. Perchlorate discharge test (PDT) is another nuclear medicine procedure which can be used to differentiate the two. In thyroiditis, the TPO function is impaired. Hence, the trapped iodine would not be organified. This can be verified by PDT. Finally, if PDT is not done then on follow-up the thyroiditis can resolve, whereas, Graves' disease will persist.

[SSN: Suprasternal Notch]
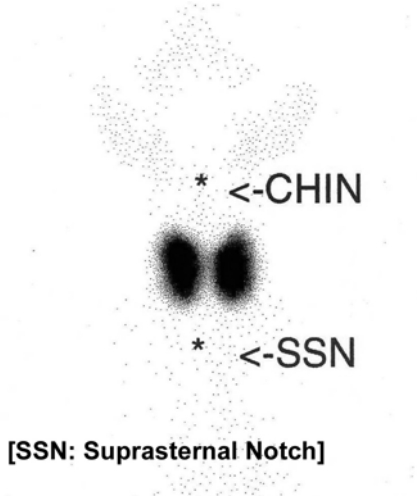
Figure 2: Graves' Disease

Other differential diagnoses:
In goitre of iodine deficiency, high serum TSH causes hyper-stimulation of gland resulting in hyperplasia, hypertrophy and increased vascularity of thyroid gland. However, this condition can be differentiated from the above two conditions because the patient would be hypothyroid clinically [Low Serum T4, High Serum TSH].

Note: In thyroiditis, on thyroid scan, heterogeneous tracer distribution can be seen. The areas with increased vascularity due to inflammation can cause more tracer trapping. Whereas, areas with the loss of functioning parenchyma will show decreased tracer trapping.

Radioactive Iodine Uptake (RAIU): A Non-Imaging Thyroid Test

I-131 is used in extremely low doses (50 microcuries) for radioactive iodine uptake (RAIU). RAIU is done using a thyroid probe 24 hours after oral administration of I-131 in a capsule. No images can be acquired. The normal values are usually 10%–35% at 24 h and vary from region to region depending on dietary (stable) iodine intake, therefore, each laboratory defines its own normal range. RAIU is now usually done-

a) To differentiate hyperthyroidism from thyroiditis (usually low uptake in thyroiditis).
b) To decide about the therapeutic dose of I-131 to be administered.
c) Rarely, it is used for PDT.

Thus, scintigraphy also helps to evaluate functional status of a clinically palpable nodule(s) in the thyroid. These nodules can be labelled on the basis of tracer uptake as:
• **Warm**: Tracer uptake equivalent to normal tissue, usually means normal level of function in that area. Have a low probability of malignancy.
• **Cold**: Tracer uptake nil or less than normal tissue, means nil or less than normal level of function. Such nodules could result from cystic changes, fibrosis, haemorrhage, adenoma, malignancy etc. Have a high probability of malignancy.
• **Hot**: Tracer uptake higher than normal tissue, means more than normal level of function. They can be autonomously functioning thyroid nodules (AFTN). Have a low probability of malignancy.

Multinodular Goitre:
It usually develops in the population living in iodine deficient regions due to periods of nutritional iodine deficiency interspersed with iodine sufficiency resulting in compensatory thyroid hypertrophy and regression to normalcy respectively. This causes nodularity, focal haemorrhages, calcifications, cyst formation and

scarring in the gland. Thyroid size is usually grossly increased with non-uniform enlargement in general. The tracer distribution can also be inhomogeneous in case of a nodular pathology because different areas/nodules can have different levels of function. Therefore, on scintigraphy the tracer trapping is variable, higher / lower than normal in some areas (Figure 3). Tracer is normally seen in salivary glands. Some nodules may become autonomous i.e. independent of TSH control and can show hyperfunction resulting in toxic MNG. In such cases areas of increased radiotracer uptake i.e. hot nodules can be seen. However, radiotracer uptake in them is not as high as in Graves' hyperthyroidism. The perinodular regions may show decreased tracer uptake due to suppression. The salivary glands may also show less tracer uptake. The areas of fibrosis, cyst formation don't have functional thyroid tissue, hence don't take up radiotracer. Therefore, they are seen as cold areas. Sometimes huge MNGs can have retrosternal extension.
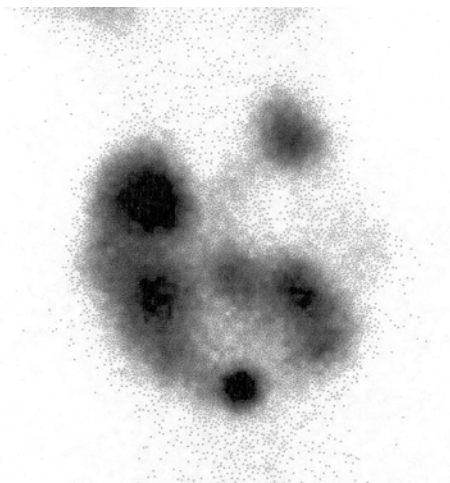
Figure 3: Multinodular Goitre

Toxic autonomous nodule:
It is also called as Autonomously Functioning Thyroid Nodule (AFTN) i.e. independent of TSH control. Image shows a focal increased tracer uptake confined to a nodule that occupies most or all of the thyroid lobe. When an autonomous nodule produces excessive thyroid hormones it causes near-total suppression of TSH. In absence of TSH the rest of normal thyroid tissue (perinodular tissue) does not get a stimulus for even normal function resulting in its suppression (Figure 4).

Tracer is barely trapped in salivary glands due to less tracer availability for extraction to it consequent to higher trapping by thyroid, a situation similar to Graves' disease. Once such nodules are treated, the TSH is no more suppressed and is available for stimulation of normal but

previously suppressed perinodular thyroid tissue, resulting in its functional recovery.


Figure 4: AFTN

Thyrotoxicosis vs Hyperthyroidism
Thyrotoxicosis means high serum thyroid hormone (TH) levels with consequent hypermetabolic state irrespective of source of TH i.e. high production from thyroid or exogenous etc. In hyperthyroidism the thyroid hyperfunction leads to excessive TH such as in Graves' disease, toxic adenoma, toxic multinodular goitre. Whereas, in conditions like early phase of Hashimoto's thyroiditis there is no thyroid hyperfunction but due to the excessive release of stored TH high serum TH levels with consequent hypermetabolic state are seen (hashitoxicosis). Here the scintigraphic findings can help to differentiate these conditions i.e. whether thyrotoxicosis is due to hyperfunction of thyroid or otherwise. Further, multiple hot nodules may be seen in an apparently non-nodular goiter changing the diagnosis from Graves' disease to toxic MNG. Thus, it helps to decide further management.

Chronic thyroiditis:
In case of chronic thyroiditis if the functional thyroid tissue is decreased significantly, then despite the enlargement of thyroid (goitre) the tracer trapping is less than normal or may be absent, sometimes even thyroid outline is poorly seen. Tracer may be inhomogenously distributed in the thyroid (Figure 5). Tracer trapping is apparently highly increased in salivary glands due to more tracer availability to it consequent to lesser trapping by thyroid. Decreased tracer uptake can also be seen in sub-acute thyroiditis, Hashimoto's thyroiditis and primary hypothyroidism, however, the thyroid may not be felt in primary

hypothyroidism whereas in thyroiditis the goitre may be present due to inflammatory oedema and/or fibrosis. Image similar to thyroiditis is also obtained if the patient is taking exogenous thyroid hormones or excessive iodine, this can be confirmed by interview with the patient. This occurs due to suppression of thyroid stimulating hormone resulting in decreased thyroid function and blockage of iodine transport mechanism respectively.
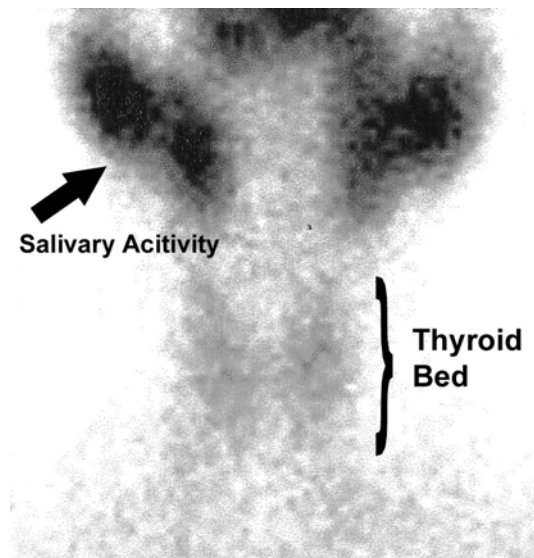
Figure 5: Thyroiditis

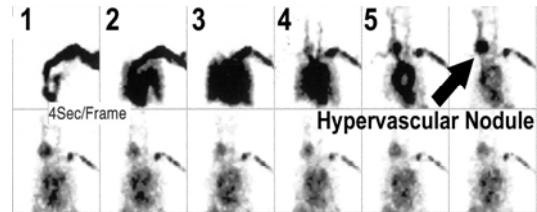**Solitary Nodule in Thyroid:**
A palpable solitary thyroid nodule can harbour malignancy. Dominant nodules in multinodular goitre can also harbour malignancy. The malignant tissue may not be functioning properly, therefore, may show reduced or almost nil tracer uptake i.e. seen as cold nodule (Figure 6b).
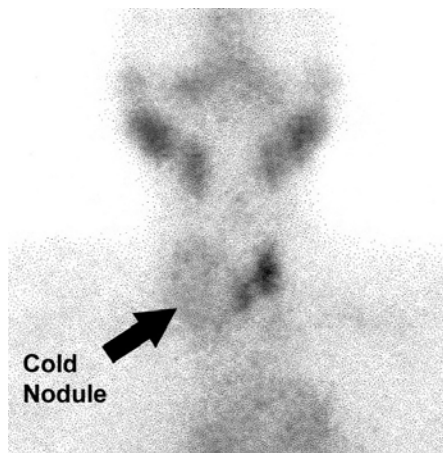
Figure 6a: Cold Thyroid Nodule

Such nodules when are equivocal about their malignant status on cytology, can be evaluated

further by imaging them during intravenous tracer injection, a process called 'Scintiangiography' (Figure 6b). In case of malignancy, these nodules are usually hypervascular. This is because many of the malignant lesions have increased vascularity due to neovascularisation. Whereas, cystic nodules are avascular.


Figure 6b: Scintiangiography of Thyroid Nodule

However, vascularity is not pathognomic of malignancy. Some of the malignant nodules can be 'hypo' or 'normo' –vascular. Finally, if a solitary thyroid nodule is warm or hot, then it is very unlikely that it will be malignant.

Thyroid Dysgenesis:
Scintigraphy can also detect abnormal but functional thyroid tissue by virtue of its iodine/analogue concentrating ability, as may occur in thyroid dysgenesis.

Thyroid arises from fusion of two embryological structures called medial and paired lateral anlages. The medial anlage arises from foramen caecum in base of the tongue and descends into neck during normal human development whereby it is joined by paired lateral anlages, one each on each side of neck. Failure of descent can occur anywhere from base of the tongue to thyroid bed in neck and cause incomplete development of thyroid (thyroid dysgenesis) because median and lateral anlages don't have the chance to fuse. Complete arrest of descent stops medial anlage at base of the tongue resulting in Lingual thyroid. For instance, if only lingual thyroid were seen then only spot 'A' in Figure 7 would have been seen.

Figure 7: Double Thyroid

Anterior views
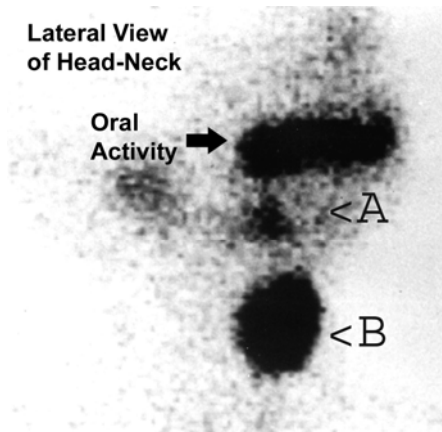
Figure 8: WBI-131 Imaging for Cancer Thyroid

Incomplete descent can also result in multiple rests of incompletely formed thyroid gland anywhere along the path of its normal descent i.e. from foramen caecum in base of tongue to thyroid bed in the neck. In given Figure 7 double thyroid is seen on lateral view of neck whereby two rests of thyroid tissue (A & B) are seen, one at base of the tongue and other lower down in the neck. Sometimes, only one lobe of thyroid develops due to developmental defect: Hemiagenesis. On scintigraphy it may look like an AFTN (Figure 4)

Thus, using scintigraphy true morphology of thyroid could be delineated, both thyroid dysgenesis and ectopically located thyroid tissue can be detected. It can also give an idea about size of the functional thyroid tissue.
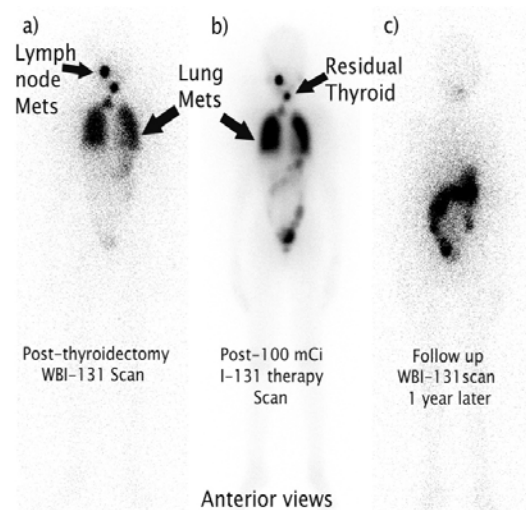
Exclusive Iodine-131 Based Imaging:
Special indication for I-131 based imaging is carcinoma thyroid post thyroidectomy & before I-131 therapy. I-131 scan is done to detect:
-Residual thyroid tissue post-thyroidectomy
-Functioning metastases from carcinoma thyroid

It also helps to decide the dose of radioiodine to be used for therapy, if needed.

Usually, residual thyroid tissue is seen in the thyroid bed post-thyroidectomy. Physiological uptake of radioioidine can be seen in salivary glands, stomach, GIT, urinary tract, breasts, etc. I-131 uptake elsewhere is indicative of abnormal uptake i.e. functioning metastases from carcinoma thyroid. For instance in Figure 8 a,b the whole body I-131 scan of a case of carcinoma thyroid, post thyroidectomy shows I-131 uptake in:
-Thyroid bed
-Neck lymph nodal metastases
-Lung metastases

A repeat study was done 6 months after therapy (Figure 8 c) which shows successful eradication of residual thyroid tissue (also called Thyroid Ablation) and also eradication of nodal and pulmonary metastases.

From the above subject review it is clear that the thyroid scintigraphy finds useful applications in management and diagnosis of thyroid disorders.

Most Common Indications for Thyroid Scintigraphy:

a) **Graves' Disease**: To look for level of hyperfunction in anticipation for radioiodine therapy. Radio-active iodine uptake (RAIU) or technetium uptake is also used.

b) Differentiation of the cause of thyrotoxicosis i.e. hyperthyroidism/Hashitoxicosis etc.

c) **Multinodular Goitre**: To look for functional status of dominant thyroid nodules and sometimes to exclude retrosternal extension in case of huge goitres.

d) **Solitary Thyroid Nodule**: To see the vascularity and functional status of clinically palpable/ultrasonographically detected nodules.

e) Characterisation of neck swelling especially to exclude its thyroid origin e.g. thyroglossal cyst, ectopic thyroid, etc.

f) **Congenital Hypothyroidism**: Its detection, delineating thyroid morphology if thyroid dysgenesis is suspected.

g) **Thyroid Cancer**: Detection of post surgery

References

1. Datz FL - Endocrine System Imaging. In: Osborn AG, Bragg DG editors - Handbooks in Radiology: Nuclear Medicine. Chicago: Year Book Medical Publishers, 1988: 1-34.

2. Scintigraphic Manifestations of thyrotoxicosis. Intenzo CM, dePapp AE, Jabbour S et al. RadioGraphics 2003; 23:857–869.

3. Hedley AJ, Young RE, Jones SJ, et al. Antithyroid drugs in the treatment of hyperthyroidism of Graves' disease: long-term follow-up of 434 patients. Clin Endocrinol 1989; 31:209–218.

4. Hamburger JI. The various presentations of thyroiditis: diagnostic considerations. Ann Intern Med 1986; 104:219–224.

5. Peter HJ, Gerber H, Studer H, et al. Pathogenesis of heterogeneity in human multinodular goiter. J Clin Invest 1985; 76:1992–2002.