EANM-SNMMI JOINT GUIDELINES ON MOLECULAR THYROID IMAGING AND RADIOIODINE UPTAKE
INTRODUCTION

Normal thyroid tissue is characterized by the unique capability of its follicular cells to trap and to process stable iodine (I) which is subsequently incorporated in thyroglobulin (Tg)-bound thyroid hormones. The Iodide uptake into the follicular cells is executed by the Natrium Iodide Symporter (NIS), a transmembrane protein located on the basolateral membrane of the thyroid follicular cells which functions as an energy (Na+/K+-ATPase)-dependent co-transport mechanism. [Baker CH, Morris JC. The sodium-iodide symporter. Current Drug Targets Immune Endocrology Metabolism Disorders 2004; 4: 167-174] Under physiological conditions the expression and activity of NIS is regulated by TSH and also modulated by cytokines such as TNF or TGF-1. Iodide is then translocated via an I- channel across the apical membrane into the colloid; pendrin, a chloride-iodine transport protein, is assumed to play a major role in this process. [Dohán O, De la Vieja A, Paroder V et al. The sodium/iodide Symporter (NIS): characterization, regulation, and medical significance. Endocrine Reviews 2003;24:48-77] Finally, the iodide oxidation into iodine and iodine organification into thiosyl residues on the Tg molecule takes place at the outer (luminal) surface of the apical membrane of the epithelium. Because iodine plays a major role in the physiology and pathophysiology of the thyroid gland, iodine or iodine analogues (i.e. NIS-targeting) radiopharmaceuticals are well suited for thyroid imaging and radioiodine uptake (RAIU) study. Additionally, imaging with aspecific oncotropic tracers [i.e. $^{99m}$Tc-sesta-Methoxy-Iso-Butyl-Isonitrile ($^{99m}$Tc-sestaMIBI)] and $^{18}$F-fluorodesoxyglucose ($^{18}$FDG)] may be useful in selected cases to discriminate benign from malignant thyroid nodules. [Giovanella L, Ceriani L, Treglia G. The role of isotope scan, including positron emission tomography/computed tomography, in nodular goitre. Best Pract Res Clin Endocrinol Metab. 2014;28:507-518] The aim of this guideline is to assist nuclear medicine physicians in recommending, performing, interpreting and reporting molecular thyroid imaging with different radiopharmaceuticals and RAIU study.
GOALS

Thyroid scintigraphy with NIS-targeting tracers provides the detection and localization of focal and/or diffuse abnormalities of follicular thyroid cells. Radioiodine uptake test quantifies the global iodine metabolism within the thyroid gland as reflected by the radiopharmaceutical accumulation by and kinetics within the thyroid gland. Thyroid imaging with $^{99m}$Tc-sestaMIBI and $^{18}$F-FDG provide informations about the biological behaviour of cytologically indeterminate thyroid nodules (i.e. aggressive vs indolent).

INDICATIONS AND CONTRAINDICATIONS

Indications

**Thyroid scintigraphy with NIS-targeting tracers**

It is useful in:

- Evaluation and differential diagnosis of hyperthyroidism.
- Assessment of function of thyroid nodules identified on clinical examination or imaging.
- Evaluation of congenital abnormalities.

*Evaluation and differential diagnosis of hyperthyroidism.*

Thyroid scintigraphy may easily differentiate productive from destructive hyperthyroidism and diffuse from focal overactivity of thyroid cells. The common features of productive hyperthyroidism are:

- Diffuse thyroid overactivity with homogeneous distribution of the tracer, reduced uptake in major salivary glands and low background (i.e. Graves’ disease).
- Unifocal or multifocal overactive areas with reduced or suppressed uptake in the remaining thyroid tissue (i.e. autonomously functioning thyroid nodules).
- Multiple mixed areas of focal increased and suppressed uptake (i.e. toxic multinodular goitres).

On the other hand, decreased uptake is typically observed in early phases of destructive thyroiditis or in the presence of exogenous iodine overload.
Assessment of function of thyroid nodules identified on clinical examination or imaging.

Thyroid scintigraphy is the only examination able to demonstrate the presence of autonomously functioning thyroid nodules (AFTN). Notably, AFTN very rarely harbour malignancy and current clinical guidelines suggest refraining from fine-needle aspiration cytology (FNAC) of AFTN. Importantly, although most thyroid cancers are nonfunctioning and therefore cold nodules, the majority of these nodules are benign (i.e. up to 80-90%), which greatly reduces the specificity of a thyroid scintigraphy. The relationship between thyroid autonomy and TSH levels is affected by the degree of iodine sufficiency and varies widely regionally [Giovanella EJCI/Endocrine]. Consequently, different indications are given in clinical guidelines (Table X). As an example, a thyroid scan is recommended when the TSH level is low or low-normal in the United States [ATA2015] while it is recommended in all patients with a nodule > 10 mm, independently of the TSH level, in Germany [Musholt T, Clerici T, Dralle H, Frilling A, Goretzki PE, Hermann MM, et al. German Association of Endocrine Surgeons practice guidelines for the surgical treatment of benign thyroid disease. Langenbecks Arch Surg 2011;396:639-649]. Indeed, AACE, AME and ETA joined guidelines suggest the use of thyroid scans taking into account the iodine supply in different geographical areas [Gharib H, Papini E, Paschke R et al. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules. Endocrine Practice 2010;16 (Suppl 1):S1-S43].

Table 2. Thyroid nodules: indications for thyroid scintigraphy in different clinical guidelines.

<table>
<thead>
<tr>
<th>ATA 2015</th>
<th>AACE/AME/ETA 2010 and 2016</th>
<th>German Endocrine Surgeons 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Thyroid nodules &gt;10-15 mm&lt;br&gt;-TSH subnormal</td>
<td>-TSH &lt;lower reference limit&lt;br&gt;-Consider scintigraphy even if TSH is normal in iodine-deficient regions.</td>
<td>-Thyroid nodules &gt;10 mm&lt;br&gt;-Any TSH</td>
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</table>

Thyroid scan is also recommended for suspicious retrosternal goiter (i.e. mediastinal masses), for multinodular goitre to identify suspicious nodules for FNAC, for thyroid nodules with indeterminate biopsy results and for eligibility for radioiodine therapy.
Evaluation of patients with congenital hypothyroidism

Congenital hypothyroidism (CH), is a disorder characterized by inadequate thyroid hormone production, and is the most common cause of preventable intellectual disability and growth failure. It affects approximately 1:2000 to 1:4000 newborns in iodine-sufficient regions, with higher incidence in areas with iodine deficiency. Apart from iodine deficiency the etiology includes thyroid dysgenesis (ectopia, hypoplasia, agenesis), defects in thyroid hormone synthesis (dyshormonogenesis), hypothalamic-pituitary CH and the transient CH due to iodine overload, maternal antithyroid antibodies or antithyroid drug intake during pregnancy [Klett M. Epidemiology of congenital hypothyroidism. Exp Clin Endocrinol Diabetes 1997;105:19–23]. Measurement of TSH and T4, on the 2nd and 5th day of life, has been established in the developed world to diagnose CH early and begin hormone replacement treatment. Thyroid scintigraphy and thyroid sonography reveal the underlying etiology of CH [Clerc J, Monpeyssen H, Chevalier A, Amegassi F, Rodrigue D, Leger FA, Richard B. Scintigraphic imaging of paediatric thyroid dysfunction. Mol Imaging Radionucl Ther 2015;24:47-59]. Ultrasonography evaluates the presence of the thyroid gland and measures thyroid volume but has less sensitivity in cases of ectopia [Meller J, Becker W. The continuing importance of thyroid scintigraphy in the era of high-resolution ultrasound. Eur J Nucl Med Mol Imaging 2002;29 (Suppl 2):S425-438].


Radioiodine uptake test

It is useful to:

- differentiate productive hyperthyroidism from destructive and factitious thyrotoxicosis.
- detect intrathyroidal defects of organification with the perchlorate discharge test.
Differentiate productive hyperthyroidism from destructive and factitious thyrotoxicosis

RAIU is increased in productive hyperthyroidism while destructive and factitious thyrotoxicosis are typically related to low or suppressed RAIU.

Detect intrathyroidal defects of organification with the perchlorate discharge test

Iodine organification defects (IOD) presents with high early uptake sensitive to perchlorate. In particular, a reduction >10% of the RAIU levels at 2 hours after oral administration of sodium perchlorate was considered positive for an iodide organification defect. Patients with iodide discharge of 10% to 90% were considered to have a partial IOD, whereas patients with iodide discharge greater than 90% were considered to have a total IOD, respectively. [Clerc J, Monpeyssen H, Chevalier A, Amegassi F, Rodrigue D, Leger FA, Richard B. Scintigraphic imaging of paediatric thyroid dysfunction. Horm Res 2008;70:1-13.

Provides informations for calculating the administered therapeutic activity of radioiodine

Refer to the EANM / SNMMI Procedure Guidelines

Thyroid imaging with oncotropic tracers $^{99m}Tc$-sestaMIBI and $^{18}$F-FDG

It is useful to assess the biological behaviour and aggressiveness of hypofunctioning thyroid nodules. In the case of sestaMIBI and/or FDG-avid hypofunctioning thyroid nodules, the risk of malignancy is about 35% [Treglia G, Caldarella C, Saggiorato E at al. Diagnostic performance of 99mTc-MIBI scan in predicting the malignancy of thyroid nodules: a meta-analysis. Endocrine 2013;44:70-78]. [Bertagna F, Treglia G, Piccardo A, Giubbini R. Diagnostic and clinical significance of F-18-FDG-PET/CT thyroid incidentalomas. J Clin Endocrinol Metab 2012;97:3866-3875]. At the same time, a nodule characterized by low or absent tracers uptake should be considered at very low risk of malignancy [Giovanella L, Campenni A, Treglia G, Verburg FA, Trimobili P, Ceriani L, Bongiovanni


**Contraindications**

For the pregnant and potentially pregnant see that ACR Practice Guideline/others? for imaging pregnant or potentially pregnant adolescents and women with ionizing radiations. Overall, in women of childbearing age, it is necessary to verify the absence of pregnancy. In a patient who is known or suspected to be pregnant evaluation by other techniques such as ultrasonography is preferred. If medically justified, radiation exposure should be delayed until after both pregnancy and breastfeeding.

**SPECIFICATIONS OF THE PROCEDURES**

**Qualifications and responsibilities of personnel**
All physicians and personnel involved in performing and reporting thyroid imaging and RAIU should be sufficiently qualified and experienced in accordance with applicable laws, and individual responsibilities should be documented in standard operating procedures.

**Request, examination planning and patient preparation**

The written or electronic request for thyroid imaging procedures and RAIU must be originated by a physician or other appropriately licensed health care provider. It should provide sufficient information to demonstrate the medical necessity of the examination and allow for its proper performance and interpretation. Documentation should include signs, symptoms, relevant clinical history (including medications), the results of all other relevant examinations that have already been performed (laboratory, ultrasonography or other) and the specific reason for the examination or a provisional diagnosis. When making an appointment, the patient should receive information on how the examination is performed and its estimated duration. Patients should be informed that they may eat and drink and of the need to report a pregnancy, any delay in menstrual cycle, or active breastfeeding. Information leaflets and/or displays should be available in the waiting area of the nuclear medicine service, and all information should preferably be accessible through the website of the institution. The image quality and informations provided by imaging procedures and RAIU are influenced by a variety of factors which can be identified and managed carefully. The percent thyroid uptake is dependent on the dietary iodine intake (which varies greatly in geographical location). The dietary iodine intake in the U.S.A. ranges from 0.2 to 0.7 mg/day. Continuous iodine excess intake of as little as 1 mg/day for 2 weeks will significantly diminish the RAIU. A single dose of 30 mg or larger will suppress the RAIU to very low levels and the effect will last for days to weeks. Therefore, previous ingestion of iodine, various drugs, or use of iodinated radiocontrast agents may alter uptake and make interpretation difficult (Table 1).

**Table 1.** Factors that influence the thyroid uptake of iodine and iodine-analogues radiopharmaceuticals and respective withdrawal time.
The thyroid uptake of aspecific oncotropic tracers, as $^{99m}$Tc-sestaMIBI and $^{18}$F-FDG, is not dependent by NIS expression and activity. Therefore, drugs and substances interfering iodine uptake should not be discontinued before imaging.

## Radiopharmaceuticals

As opposed to the use of iodine-131 ($^{131}$I), which is strongly discouraged for routine imaging because of its much higher radiation burden to the thyroid, Iodine-123 sodium iodide ($^{123}$I) is an ideal radiopharmaceutical for NIS targeting due to low radiation burden and optimal imaging quality. The thyroid uptake of $^{99m}$Tc-pertechnetate, a stereo isomere of iodine, is also related to NIS activity. $^{99m}$Tc-pertechnetate is the tracer most commonly used for thyroid scintigraphy in Europe. Compared with $^{123}$I it has the advantages of daily availability in every nuclear medicine department, of shorter physical half-life (6 h vs 13 h) and of preferable energy (140 keV) for scintigraphic imaging. Importantly, it is not a substrate for any metabolic pathways and a complete wash-out from thyroid cells occurs in about 30 minutes. Although the thyroid gland does not organify $^{99m}$Tc-pertechnetate,
in the majority of cases the uptake and imaging data provide sufficient information for accurate diagnosis in most cases. However, in very rare cases the appearance of a thyroid nodule may be discordant on radioiodine and pertechnetate scans due to iodide organification defects in the nodule that results in a rapid washout of radioiodine (i.e. so-called “trapping only nodule”) [Kusic Z, Becker DV, Saenger EL, Paras P, Gartside P, Wessler T, Spaventi S. Comparison of Technetium-99m and Iodine-123 imaging of thyroid nodules: correlation with pathological findings. J Nucl Med 1990;3:393-399].

The $^{99m}$Tc-sestaMIBI is a lipophilic cation that crosses the cell membrane and penetrates reversibly into the cytoplasm via thermodynamic driving forces and then irreversibly passes the mitochondrial membrane using a different electrical gradient regulated by a high negative inner membrane potential. The cancer cells, with their greater metabolic turn-over, are characterized by a higher electrical gradient of mitochondrial membrane thus determining an increased accumulation of $^{99m}$Tc-MIBI compared to normal cells [Bongiovanni M, Paone G, Ceriani L, Pusztaszeri M. Cellular and molecular basis for thyroid cancer imaging in nuclear medicine. Clin Transl Imaging 2013;1:149-161]. The $^{18}$F-FDG is able to trace an accelerated glucose metabolism in the thyroid tissue as in the other principal organs. The FDG uptake mechanism is classically mediated by an up-regulation of transmembrane glucose transporter proteins (GLUTs), able to introduce the tracer into the cell, and by an overexpression of hexokinases (HK) able to phosphorylate FDG to FDG-6-phosphate and thus trapping the tracer into the cell [Bongiovanni M, Paone G, Ceriani L, Pusztaszeri M. Cellular and molecular basis for thyroid cancer imaging in nuclear medicine. Clin Transl Imaging 2013;1:149-161 ALREADY CITED].

The activity of the radiopharmaceuticals to be administered should be determined after taking into account [Directive 2013/59/EURATOM of the Council of the European Union, 1728 Eur J Nucl Med Mol Imaging (2016) 43:1723–1738] which guarantees health protection of individuals with respect to the dangers of ionizing radiation in the context of medical exposure. According to this directive, member states are required to bring into force such regulations as may be necessary to comply with the directive. One of the criteria is the designation of Diagnostic Reference Levels (DRL) for radiopharmaceuticals; these are defined as levels of activity for groups of standard-sized patients and for broadly defined types of equipment. These levels are expected
not to be exceeded for standard procedures when good and normal practice regarding diagnostic and technical performance is applied. For the reasons discussed above, the activities recommended below for different tracers should be considered only a general indication, based on data in the literature and current experience. However, nuclear medicine physicians in each country should respect the DRLs and the rules set out in local laws. The activities administered to children should be a fraction of those administered to adults calculated in relation to body weight according to the factors given by the EANM/SNMMI Paediatric Dosage Harmonization Working Group [Lassmann M, Treves ST. Paediatric radiopharmaceutical administration: harmonization of the 2007 EANM paediatric dosage card (version 1.5.2008) and the 2010 North American consensus guidelines. Eur J Nucl Med Mol Imaging. 2014;41:1036–1041].

Table 1. Thyroid radiopharmaceuticals

<table>
<thead>
<tr>
<th></th>
<th>131I</th>
<th>123I</th>
<th>99mTcO4−</th>
<th>99mTc-sestaMIBI</th>
<th>18F-FDG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administration</td>
<td>o.a.</td>
<td>o.a.</td>
<td>i.v.</td>
<td>i.v.</td>
<td>i.v.</td>
</tr>
<tr>
<td>Activity [MBq] (adults)</td>
<td>7.4-14.8</td>
<td>74-111</td>
<td>185-370</td>
<td>200-370</td>
<td></td>
</tr>
<tr>
<td>Energy [Kev] (γ peak)</td>
<td>364</td>
<td>159</td>
<td>140</td>
<td>140</td>
<td>511 KeV</td>
</tr>
<tr>
<td>Physical half-live</td>
<td>8.06 days</td>
<td>13.2 hours</td>
<td>6.04 hours</td>
<td>6.04 hours</td>
<td>110 minutes</td>
</tr>
<tr>
<td>Effective dose (mSv/MBq)</td>
<td>11</td>
<td>0.20</td>
<td>0.013</td>
<td>0.009</td>
<td>-0.02 (PET)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- 0.04 (PET/CT)</td>
</tr>
</tbody>
</table>

Legend: 99mTcO4−, 99mTc-pertechnetate; i.v., intravenous; o.a., oral administration; mSV, milliSievert.

Diagnostic procedures

**Thyroid scintigraphy with NIS-targeting radiopharmaceuticals**

Iodine-123 sodium iodide activity (7.4 to 14.8 MBq) is administered orally (in a capsule or as a liquid) while 99mTc-pertechnetate (74 to 111 MBq) and 99mTc-sestaMIBI (185 to 370 MBq) are administered intravenously. The calculation of pediatric activity can be based on the EANM dosage card (version 5.7.2016) [Lassmann M, Treves ST. Paediatric radiopharmaceutical administration: harmonization of the 2007 EANM paediatric dosage card (version 1.5.2008) and the 2010 North American...
Prior to tracer administration, the nuclear medicine physician or technologist must explain the purpose of the examination, the expected benefits, and answer any questions. The patient is informed as to how the examination is to be performed (i.e. taking into account the specific clinical problem). Relevant information that may assist in interpretation of imaging findings are checked with the patient.

Instrumentation

Scintigraphic evaluation of the thyroid gland is normally performed with a conventional or small field gamma-camera equipped with a parallel-hole high-resolution or pinhole collimator with a 20% window centered on the 159 KeV ($^{123}$I) or 140 KeV ($^{99m}$Tc-pertechnetate) photo peak. A 128x128 or 256x256 collimator matrix size and a zoom factor of 1.5 to 2 are generally used. Notably, significant geometric distortion occurs and additional views with a parallel-hole collimator may be useful to search for ectopic tissue or to estimate the thyroid size.

Imaging protocols

Imaging are generally acquired 2 to 6 and 24 hours after $^{123}$I administration; 15-20 minutes after $^{99m}$Tc-pertechnetate administration and 10-30 minutes and 60-120 minutes after $^{99m}$Tc-sestaMIBI. Administration, respectively. Immediately prior to imaging, the patient should be invited to swallow water to clear activity from mouth and esophagus. The patient should be placed in a supine position, with the neck comfortably extended. It may be helpful to immobilize the head with gentle restraints. An anterior image of the neck is acquired for 100-200 x $10^3$ counts or 5-10 minutes, whichever occurs first. The distance between the neck and the collimator should be minimized. At the end of acquisition the thyroid should be palpated with the patient in position for imaging. Anatomical landmarks as well as palpable nodules should be identified by radioactive or radiopaque markers. Duplicate view should be obtained without markers. The images should be appropriately labeled including the purpose of the marker when indicated (e.g. "sternal notch"). Beside an anterior image of the neck, additional oblique views and/or SPECT(-CT) acquisitions can be performed on
indication, especially if substernal or ectopic thyroid is an issue. The following SPECT/CT protocol should be adopted: SPECT zoom 1/128x128/32 step/180°/10-15° x step; CT 4 mm acq/5 mm rec FoV 500 mm/Kernel B08s SPECT AC/kV 130/90m As with CARE Dose4D.
Assessment of $^{123}$I thyroid uptake and kinetic (RAIU) can be obtained by using a specific gamma-probe or gamma-camera (see Radioiodine uptake test paragraph). A semiquantitative evaluation of $^{99m}$Tc-pertechnetate uptake (TcTU) can be also obtained by measuring the syringe before and after injection and subtract counts in a background ROI from counts in a ROI drawn following the contour of the thyroid. Then, to determine the percentage of the injected dose present in the gland the TcTU is calculated as:

$$\text{TcTU} = \frac{\text{counts over thyroid} – \text{background counts}}{\text{counts of injected activity}} \times 100$$

TcTU results depend, as RAIU, on iodine intake and patients-related factors, such as the thyroid volume and, to a minor extent, the patient’s age. Therefore, a local normal range should be established.

Notably, in the presence of unsuppressed TSH, scintigraphic diagnosis and quantification of compensated autonomy are only possible if suppressible thyroid tissue has been switched off by a standardised exogenous suppression with thyroid hormones []


*Interpretation criteria and reporting*

On planar scintigrams the normal gland is butterfly shaped and does not extend substernally. The isthmus may or may not be visualised and a pyramidal lobe can be recognised in about 10% of patients. Tracer activity is normally evenly distributed throughout the thyroid and both salivary glands and gastric mucosa are normally visualised because they also express the NIS glycoprotein. Grey-scale documentation of the results is preferable because a discontinuous colour documentation will
hinder recognition of details and may produce artefacts. The interpretation of the thyroid scan should comment on thyroid gland location, size and morphology; radiotracer distribution throughout the gland and correlation with palpitation findings and available imaging (i.e. ultrasonography). The abnormal scan may show thyroid gland enlargement, variations from normal shape, or focal areas of increased or decreased uptake which may be single or multiple. Mild thyroid gland enlargement may be suggested by the appearance of a "U-shaped" thyroid. The presence of uptake within a thyroglossal duct remnant and/or a pyramidal lobe are typically demonstrated in the setting of Graves' disease. The thyroid uptake of $^{123}$I and $^{99m}$Tc-pertechnetate compared to that demonstrated in the salivary glands (i.e. less than, equal to, more than) may serve as a rough approximation of the overall thyroid activity. However, an accurate assessment of iodine uptake and kinetic can only be obtained by performing a RAIU test (see below).

**Radioiodine uptake test**

Thyroid uptake determination is the measurement at selected times (e.g. 6 and/or 24 hours after ingestion) of the fraction of an administered amount of radioactive iodine that is retained in the thyroid gland. The percentage of radioactive iodine uptake by the thyroid usually reflects the overall function of the gland. RAIU test is performed by administering activities as little as 3.7 MBq of $^{123}$I or 0.15 MBq of $^{131}$I. A benefit of 123-I is that it allows concurrent imaging of the gland (see above).

**Instrumentation**

A thyroid probe is normally used. A gamma-camera with a parallel-hole collimator may be used instead of a probe: the use of a standardized neck phantom, however, remains necessary (see above).

**Protocols**

The usual time of measurement for diagnostic purposes is 4-6 and 24 hours after radiopharmaceutical administration. Multiple measurements may be necessary for calculating the administered therapeutic activity of radioiodine in patients with hyperthyroidism or non-toxic
There are several acceptable measurement and calculation techniques; the following is an example. Counts are taken over the thyroid gland and the patient’s mid-thigh for 1 minute each at the same distance (i.e. 20-30 cm), taking care to exclude the urinary bladder from the field of view from the detector field. A source of the same radionuclide of identical activity to that given to the patient is placed in a standardized neck phantom and is counted for 1 minute using the same geometry. The room background is also counted for 1 minute. The RAIU is calculated using the formula:

$$RAIU = \left( \frac{\text{Unshielded neck} - \text{Shielded neck}}{\text{Phantom counts} - \text{Background}} \right) \times 100$$

Interpretation criteria

Normal ranges varies in different regions, depending on iodine intake, and should be settled locally. but proper interpretation requires knowledge of the patients physical findings, immediately recent thyroid function tests, and assessment of iodine and drug intake as outlined below. As an indication, any result in excess of 25% in iodine-sufficient regions and within the setting of clinical hyperthyroidism is compatible with thyroid hyperfuntion. A small subset of hyperthyroid patients (generally affected by Graves’ Disease) turnover iodide so rapidly that their highest uptake is at 6-12 hours, however, almost all of these patients maintain an abnormally elevated 24 hour RAIU. Elderly patients with hyperthyroidism may may have a RAIU value within the normal range. Destructive hyroiditis (injury phase); extrathyroidal source of thyroid hormone; thyrotoxicosis, factitia, ectopic thyroid tissue (note: increased RAIU may be demonstrated at the site of ectopic tissue), functional metastatic thyroid carcinoma, mediastinal goiter reduce RAIU values. Of note, given the dynamic events of destructive thyroiditis, it is crucial that RAIU measurements in this setting be interpreted in the light of recent thyroid function tests (e.g. within 1 week). Finally, patients with severe renal failure tend to have somewhat increased RAIU while a severe stressful illness of any kind may reduce the RAIU (euthyroid sick syndrome).

Thyroid imaging with proliferation targeting tracers

$^{99m}$Tc-sestaMIBI scintigraphy
**Instrumentation and protocols**

Instrumentation and image acquisition protocols are the same described for conventional thyroid scintigraphy with $^{99m}$Tc-pertechnetate. Anterior planar images are obtained 20-30 minutes and 1-2 hours after intravenous injection of $^{99m}$Tc-sestamibi [185-370 MBq]. A SPECT or SPECT/CT can be also obtained in selected cases after revision of planar images.

**Interpretation criteria**

$^{99m}$Tc-sestamibi images are mostly interpreted visually and findings include a low, an isointense or an increased tracer accumulation in the thyroid nodule in comparison to the paranodular thyroid tissue and in comparison to pertechnetate thyroid scintigraphy. A “match” between pertechnetate and sestamibi scintigraphy is a concordantly decreased uptake in the thyroid nodule in comparison to the normal thyroid gland. A “mismatch” describes a hypofunctioning thyroid nodule on pertechnetate scintigraphy and an increased uptake of sestamibi in comparison to the paranodular thyroid tissue. An “intermediate finding” describes isointense sestamibi uptake within the nodule in comparison to the paranodular thyroid tissue. There is some disagreement how to read isointense sestamibi uptake. [Theissen P, Schmidt M, Ivanova T, Dietlein M, Schicha H. MIBI scintigraphy in hypofunctioning thyroid nodules: can it predict the dignity of the lesion? Nuklearmedizin 2009;48:144-152 ALREADY CITED]. [Hurtado-Lopez LM, Martinez-Dunker C. Negative MIBI thyroid scans exclude differentiated and medullary thyroid cancer in 100% of patients with hypofunctioning thyroid nodules. Eur J Nucl Med Mol Imaging 2007;34:1701-1703] and semiquantitative analysis may greatly increase diagnostic accuracy in this setting [Giovanella L, Campenni A, Treglia G, Verburg FA, Trimboli P, Ceriani L, Bongiovanni M. Molecular imaging with $^{99m}$Tc-MIBI and molecular testing for mutations in differentiating benign from malignant follicular neoplasm: a prospective comparison. Eur J Nucl Med Mol Imaging 2016; 43:1018-1026 ALREADY CITED]. [Campenni’ A, Siracusa M, Ruggeri RM, Laudicella R, Pignata SA, Baldari S, Giovanella L. Differentiating malignant from benign thyroid nodules with indeterminate cytology by $^{99m}$Tc-MIBI scan: a new quantitative method for improving diagnostic approach. Sci. Rep. 7: 6147 | DOI:10.1038/s41598-017-06603-3] For semiquantitative analysis a ROI is placed over the thyroid
nodule, copied to the contralateral lobe and a background ROI is drawn on early and delayed images. The washout index (WOInd) is calculated using the formula WOInd = [(DUR/EUR × 100) − 100] (DUR = delayed uptake ratio, EUR = early uptake ratio). A $^{99m}$Tc-sestaMIBI WOInd cutoff of -19% was found to be significantly more accurate (positive likelihood ratio 4.56 for visual assessment and 12.35 for semiquantitative assessment) than mutation analysis (positive likelihood ratio 1.74) in cytologically indeterminate nodules. In particular, a negative $^{99m}$Tc-sestaMIBI scan reliably excluded malignancy in this setting [Giovanella L, Campenni A, Treglia G, Verburg FA, Trimboli P, Ceriani L, Bongiovanni M. Molecular imaging with $^{99m}$Tc-MIBI and molecular testing for mutations in differentiating benign from malignant follicular neoplasm: a prospective comparison. Eur J Nucl Med Mol Imaging 2016; 43:1018-1026 ALREADY CITED]. Notably, the transferability of WOInd cutoff values reported in literature should be assessed locally before its application in clinical practice.

Reporting $^{99m}$Tc-sestaMIBI thyroid imaging: the following should be assessed and described in the report as appropriate

- Location, morphology and size of the thyroid gland
- Presence of retrosternal extension.
- Presence of diffuse tracer uptake.
- Presence of focal tracer uptake on image corresponding or not to the US/$^{99m}$Tc-pertechnetate scan (i.e. cold nodule).
- The WO-index measurement (if calculated, see above).
- Presence or not of anatomical variants or related compressive pathological conditions (e.g. tracheal deviations or vascular compressions) if concurrent SPECT/CT is performed.

$^{18}$F-fluorodeoxyglucose PET/CT

*Instrumentation and protocols*
18F-FDG imaging evaluation of the thyroid gland should be acquired in the three dimensional mode by means of a conventional PET/CT system routinely used for the other oncological PET/CT examinations. No difference in terms of matrix, field of view [FOV] size and reconstruction parameters have been suggested [Merten MM, Castro MR, Zhang J, Durski J, Ryder M. Examining the Role of Preoperative Positron Emission Tomography/Computerized Tomography in Combination with Ultrasonography in Discriminating Benign from Malignant Cytologically Indeterminate Thyroid Nodules. Thyroid. 2017;27:95-102]. A non diagnostic and low dose CT scan is used for attenuation correction and anatomical localization of the 18F-FDG hot spots. Overall, CT parameters should be selected so as to minimise the exposure dose but to obtain the necessary diagnostic information [35].

**Interpretation criteria**

The healthy thyroid tissue is characterized by a very low FDG activity, allowing the identification even of small nodules with faint uptake. Indeed, FDG PET/CT is able to identify and characterize with high accuracy small thyroid nodules (i.e. ≥1 cm). Indeed, the low dose CT acquired during PET/CT may be helpful in evaluating thyroid morphology and the presence of any anatomical variant or related compressive pathological conditions (e.g. tracheal deviations or vascular compressions). Any focal uptake above normal thyroid parenchyma, corresponding to the nodule with cytological undetermined results, is considered as positive [Piccardo A, Puntoni M, Bertagna F, Treglia G, Foppiani L, Arecco F, et al. 18F-FDG uptake as a prognostic variable in primary differentiated thyroid cancer incidentally detected by PET/CT: a multicentre study. Eur J Nucl Med Mol Imaging. 2014;41:1482-91]. Reporting FDG thyroid imaging: the following should be assessed and described in the report as appropriate

- Location, morphology and size of the thyroid gland
- Presence of retrosternal extension.
- Presence or not of anatomical variants or related compressive pathological conditions (e.g. tracheal deviations or vascular compressions).
• Presence of diffuse tracer uptake.

• Presence of focal tracer uptake on PET/CT image corresponding or not to the US findings (i.e. mandatory).

• The uptake measurement (if calculated, see below).

Standard uptake value (SUV) is a semiquantitative parameter reflecting glucose metabolic activity, but it is not a specific marker of malignancies [Schonberger J, Ruschoff J, Grimm D. Glucose transporter 1 gene expression is related to thyroid neoplasms with an unfavourable prognosis: an immunohistochemical study. Thyroid 2002;12:747–754]. Indeed although many SUV thresholds have been proposed to differentiate benign from malignant lesions in patients with FDG avid thyroid nodules incidentally detected during PET/CT examinations, no safe and highly specific cutoff has been identified [Pak K, Kim SJ, Kim IJ, Kim BH, Kim SS, Jeon YK. The role of 18Ffluorodeoxyglucose positron emission tomography in differentiated thyroid cancer before surgery. Endocr Relat Cancer 2013; 20:R203-13].

Indeed, a high SUV value increases the risk of malignancy [38] [Piccardo A, Puntoni M, Bertagna F, Treglia G, Foppiani L, Arecco F, at al. ¹⁸F-FDG uptake as a prognostic variable in primary differentiated thyroid cancer incidentally detected by PET/CT: a multicentre study. Eur J Nucl Med Mol Imaging. 2014;41:1482-91 ALREADY CITED] but this finding remains not specific enough to confirm the diagnosis of primary differentiated thyroid cancer.