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SFE-AFCE-SFMN 2022 consensus on the management of thyroid nodules

SFE-AFCE-SFMN 2022 Consensus on the management of thyroid nodules : What is the role of functional imaging and isotopic treatment?

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ABSTRACT

The SFE-AFCE-SFMN 2022 consensus deals with the management of thyroid nodules, a condition that is a frequent reason for consultation in endocrinology. In more than 90% of cases, patients are euthyroid, with benign non-progressive nodules that do not warrant specific treatment. The clinician's objective is to detect malignant thyroid nodules at risk of recurrence and death, toxic nodules responsible for hyperthyroidism or compressive nodules warranting treatment. The diagnosis and treatment of thyroid nodules requires close collaboration between endocrinologists, nuclear medicine physicians and surgeons, but also involves other specialists. Therefore, this consensus statement was established jointly by 3 societies: the French Society of Endocrinology (SFE), French Association of Endocrine Surgery (AFCE) and French Society of Nuclear Medicine (SFMN); the various working groups included experts from other specialties (pathologists, radiologists, pediatricians, biologists, etc.). This section deals with the role of thyroid scintigraphy in the diagnosis of autonomous thyroid nodules, nuclear medicine in nodules with indeterminate cytology and iodine treatment for autonomous thyroid nodules.

1. Thyroid scintigraphy

1.1. When should thyroid scan be performed in case of thyroid nodule?

Thyroid scintigraphy (TS) is a prime example of molecular imaging. TS is the only technique that provides functional information regarding a nodule. It is systematically indicated in the assessment of thyroid nodules associated with clinical or subclinical hyperthyroidism (below the lower limit of normal, generally around 0.4 mIU/L). It determines whether the nodule is autonomous or not and possibly associated with diffuse functional autonomy. The risk of malignancy is very low in autonomous nodules [1]. TS is classically not recommended if serum TSH is in the normal range. However, TSH may remain normal in autonomous nodules when iodine intake is suboptimal, suggesting a slightly higher TSH threshold for TS [2,3], especially when fine-needle cytology (FNAC) is indicated. The prevalence of doubtful FNAC results (Bethesda III and, more rarely, IV) is higher for autonomous than for non-functional nodules, and FNAC is not indicated in this setting [1], as it could lead to unnecessary surgeries.

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Table 1
Comparison of ^{99m}Tc and ^{123}I.

Radio	Advantages	Disadvantages
^{99m}Tc	• Low cost • More readily available (generator product) • Faster examination (images obtained 20 min after injection)	• Risk of false positives (trapped but not organified) • Measurement of fixation rate not very informative
^{123}I	• Superior diagnostic capability (organification) • Quantitative analysis of uptake, which is tightly linked to TSH concentration.	• Higher cost • Less readily available (cyclotron product needs to be ordered) • Less rapid examination, usually performed at 2 h

1.2. What type of radiotracer should be used?

TS can be performed with iodine-123 (123I) or technetium-99 m (^{99m}TcO4-, ^{99m}Tc). Qualitatively, images with ^{99m}Tc and ^{123}I are grossly equivalent but ^{123}I offers additional quantitative information. ^{123}I uptake is proportional to the NIS protein density and the integrity of the organification process. By contrast, ^{99m}Tc is taken up by thyrocytes via the same iodine symporter, but rapidly released from the cells [4]. Elimination is mainly urinary. These isotopes are chosen for their short half-life, their imaging quality and lower radiation exposure compared to iodine-131 (^{131}I). Low-activity iodine-131 (2 to 5 MBq) is no longer used for thyroid nodule characterization, but can be used for dosimetric purposes. The advantages and disadvantages of ^{99m}Tc and ^{123}I are presented in Table 1. Although both are readily available, ^{123}I has to be ordered specifically and at higher cost, which may limit its use in daily practice. ATA guidelines favor ^{123}I [1], in contrast to the EANM and the AACE/ACE/AME guidelines [5,6].

1.3. Interpretation of thyroid scintigraphy

A hot (hypercontrasted) nodule on TS means that uptake is greater than in the normal thyroid parenchyma. It may be classified as an autonomous nodule in case of low TSH. When TSH is detectable (compensated autonomy), normal parenchyma is often visible on TS. Autonomous nodules should not be confused with "hyperplastic" nodules, but may appear more contrasted than the adjacent non-nodular parenchyma because of its thickness, in which case TSH is usually normal.

Recommendation 5.1
In case of thyroid nodule, we recommend thyroid scintigraphy if the serum TSH is below the lower limit of normal (< 0.4 mIU/L). If serum TSH is between 0.4 and 1 mIU/L, we recommend thyroid scintigraphy only if fine-needle aspiration cytology is indicated. Grade A ++.

Recommendation 5.2
R5.2a If TSH is ≥ 1 mU/l, thyroid scintigraphy is not recommended as a first-line procedure to characterize a solitary or prevalent nodule. Grade A ++.
R5.2b The presence of a hot nodule on thyroid scintigraphy performed despite serum TSH being ≥1 mU/l should not prevent to perform thyroid ultrasound and FNAC. Grade B Expert opinion.

Recommendation 5.3
For purely diagnostic purposes, thyroid scintigraphy be performed with either ^{99m}Tc or ^{123}I. Grade A ++.

Recommendation 5.4
Fine-needle aspiration cytology is not recommended for autonomous nodules with serum TSH in the low range of normal (< 1 mU/L). Grade A ++

2. ^{123}I/^{99m}Tc, ^{99m}Tc-MIBI and ^{18}F-FDG-PET/CT thyroid scintigraphy for the characterization of indeterminate nodules (Bethesda III and IV)

Techniques with high sensitivity and negative predictive value (NPV) need to be developed to reduce the number of inappropriate thyroidectomies in case of nodules with indeterminate cytological findings (Bethesda class III and IV). Additional imaging options include 123-iodine (^{123}I) or pertechnetate (^{99m}Tc) thyroid scintigraphy, ^{99m}Tc-methoxyisobutylisonitrile (^{99m}Tc-MIBI) scintigraphy and ^{18}F-Fluoro-deoxyglucose (^{18}F-FDG) PET.

2.1. Performance of ^{123}I or ^{99m}Tc thyroid scintigraphy for the diagnosis of indeterminate nodules (Bethesda III and IV)

When FNAC is indeterminate (Bethesda III or IV) or not feasible for technical reasons or contraindicated (hemostasis problems), thyroid scintigraphy can be discussed, to limit unnecessary surgery (if autonomous nodule).

Rosario et al. recently reported use of ^{123}I thyroid scintigraphy for the characterization of thyroid nodules indeterminate on FNAC, in case of TSH < 2mIU/l [3]. Their study was conducted in a geographical region where iodine intake is considered sufficient; only 78 patients with >1 cm nodules (84 nodules), without highly suspicious ultrasound criteria and without history of childhood irradiation, increased calcitoninemia or family history of thyroid cancer, all operated on, were included. Twenty-one nodules (25%) were hot on scintigraphy performed at 24 hours post-injection, with higher frequency when TSH was lower: 50%, 33.3%, 12% and 0% for TSH respectively < 1 mIU/l (n = 16), 1–2 mIU/l (n = 24), 2–3 mIU/l (n = 25) and > 3 mIU/l (n = 13). None of the hot nodules were malignant (20 benign and 1 tumor of uncertain malignancy), confirming the good NPV of nodular hyperfixation on thyroid scintigraphy to rule out malignancy. Of the 63 nodules without iodine uptake, only 7 (11%) were malignant, the others being uncertain (n = 3), NIFT-P (n = 9) or benign (n = 64). Thyroid scintigraphy may be useful to characterize of Bethesda III or IV nodules in some cases. In a recent meta-analysis, including 8 studies and 2761 hot nodules on thyroid scan, 50% (95% CI: 32-68%) of patients had normal TSH. This meta-analysis included series mainly from Europe, where moderate iodine deficiency is common [7]. The study by Chami et al. also showed that nodule size in relation to normal TSH is an imperfect criterion despite the inverse relationship between nodule size and TSH level in autonomous nodules [2]. The contribution of thyroid scintigraphy therefore needs to be assessed by comparing TSH level with nodule size and ultrasound characteristics, and should be validated prospectively.

Recommendation 5.5
In Bethesda III nodules, when TSH is < 1 mIU/l, thyroid scintigraphy, ideally with iodine 123, may be considered to search for an autonomous nodule. However, the added value of combined ultrasound/cytological classification approach has not been assessed. Grade C ++

2.2. ^{99m}Tc-methoxyisobutylisonitrile (^{99m}Tc-MIBI) scintigraphy for the diagnosis of indeterminate nodules (Bethesda III and IV),

MIBI is a lipophilic monovalent cation of the isonitrile family, which crosses the cell membrane and concentrates in the mitochondria due to the electrical potential. In thyroid nodules, ^{99m}Tc-MIBI uptake reflects mitochondrial activity and consequently cellular oxidative metabolism. Intense ^{99m}Tc-MIBI uptake is thus expected in cancer cells, but is not specific for malignancy.

There is a large body of literature, mainly before 2016, on the role of ^{99m}Tc-MIBI scintigraphy in the characterization of thyroid nodules. Nodule selection criteria were heterogeneous, and imaging procedures and interpretation criteria were not standardized. Probably because of these disparities, and the lack of specificity of ^{99m}Tc-MIBI fixation, the technique has not become widespread, despite an excellent NPV of 80 to 100%, depending on the study [8].

False positives are numerous with ^{99m}Tc-MIBI, including situations as diverse as hyperplastic nodular goiter, macro- or micro-follicular adenoma, oncocytic adenoma or autoimmune or subacute nodular thyroiditis.

Recent reports indicate that the performance of ^{99m}Tc-MIBI scintigraphy can be improved by coupling the examination to a thyroid scan (to avoid study of usually benign hot nodules), by performing a tomoscintigraphy (3D scan) coupled to the CT scan, and by studying the retention of the tracer [9–11].

The results of two prospective studies by the same team [10,11], involving 105 and 61 operated patients, showing excellent results in terms of sensitivity and NPV, are presented in Table 2. Semi-quantitative analysis (^{99m}Tc-MIBI washout analysis) also improved the performance of the examination, which was superior to that of molecular analysis (KRAS, HRAS, NRAS, BRAF mutations and translocations of PAX8/PPARγ, RET/PTC1 and RET/PTC3) [11].

In conclusion, ^{99m}Tc-MIBI scintigraphy has an excellent NPV for ruling out malignancy in thyroid nodules, but low specificity and PPV due to tracer uptake by many benign tumor types.

Recommendation 5.6

^{99m}Tc-MIBI scintigraphy can be performed for thyroid nodules >15 mm, not hot on thyroid scintigraphy (^{99m}Tc or ^{123}I) and indeterminate on FNAC (Bethesda III-IV), due to its high NPV. Grade C ++.

The level of evidence and standardization of imaging procedures need to be validated prospectively in a multi-center setting.

2.3. ^{18}F-FDG-PET/CT for diagnosis of indeterminate nodules (Bethesda III and IV), and cost-benefit ratio

^{18}F-FDG is a labeled glucose analogue. It is used primarily to assess the metabolic characteristics of tissues. Like for ^{99m}Tc-MIBI, intense uptake of ^{18}F-FDG is observed in many cancer cells, but is not always specific enough to differentiate a benign process from malignant pathology.

The results of major studies and meta-analyses on the value of ^{18}F-FDG-PET/CT in cytologically indeterminate thyroid nodules (Bethesda III–IV) are presented in Table 3. A review of the literature and meta-analysis published in 2011 [12] found excellent diagnostic performance, with a sensitivity of 96% and NPV of 95%, partly in contradiction with a more recent meta-analysis of 2019, including 8 studies ($n = 8$) [13], where sensitivity and NPV were only 74%. Several studies showed improvement in both parameters in patients with >1 cm thyroid nodules [14,15]. In 2011, the meta-analysis by Vriens et al. found 100% sensitivity and NPV in the subgroup with >15 mm lesion [12]. Again, these excellent performances do not seem to have been confirmed in more recent studies [16,17] and data for ^{18}F-FDG-PET/CT performance according to nodule size are finally quite limited [13]. Specificity and PPV values are also rather disappointing. The use of a SUVmax threshold [18] or SUVmax ratio (SUVmax nodule/SUVmax contralateral thyroid lobe) [19] has been proposed to improve specificity and positive predictive value (PPV), but without consensus or optimal threshold recognized in the literature.

Several studies investigated the contribution of ultrasound and FNAC subgroups and the additional or combined value of ^{18}F-FDG-PET/CT in this context (Table 3), without finding any added value of ^{18}F-FDG-PET/CT over and above ultrasound characterization with TIRADS or EU-TIRADS score [16,19].

In conclusion, the most recent data on ^{18}F-FDG-PET/CT showed lower sensitivity and NPV than previously reported. Semi-quantitative analysis (i.e., SUV) increases specificity and PPV but at the expense of sensitivity and NPV, and there is no consensual threshold reported in the literature.

Data combining ultrasound/cytological classifications and visual analysis of ^{18}F-FDG-PET/CT do not appear to show any added value of ^{18}F-FDG-PET/CT in predicting malignancy in all thyroid nodules with indeterminate FNAC.

Finally, a recent prospective study investigated the value of another PET tracer, ^{18}F-Fluorocholine in the characterization of ≥ 15 mm thyroid nodules, indeterminate on FNAC (Bethesda III-IV). The results showed a high NPV of 96% but a low PPV of 29%. Further studies are needed to better assess the contribution of this radiotracer in this indication [20].

Recommendation 5.7:

^{18}F-FDG-PET/CT is not recommended for FNAC-indeterminate thyroid nodules (Bethesda III-IV), due to suboptimal NPV in recent studies and the lack of added value over and above combined ultrasound/cytology classification approach. Grade A ++

3. Radioactive iodine therapy for autonomous thyroid nodules

Iodine-131 is a high-energy emitter with a sufficiently long half-life (8.04 days) to be used in therapy. In autonomous nodules, treatment is given as a single dose, in the form of a capsule, usually in an outpatient setting. In exceptional cases, treatment can be delivered in hospital, and/or in liquid form (subject to a specific temporary authorization).

Autonomous nodules are treated radically, surgically or with radioactive iodine (RAI) when they are the cause of frank hyperthyroidism, whatever the patient's age, and in sub-clinical hyperthyroidism, depending on the context.

Thus, in overt hyperthyroidism with TSH < 0.1 mIU/L, radical treatment is recommended for all subjects over 65 years of age, and in symptomatic or asymptomatic patients under 65 years of age but with cardiac comorbidity, osteoporosis or menopause without hormone replacement. Treatment may be discussed for asymptomatic patients under 65 years of age.

In subclinical hyperthyroidism with TSH between 0.1 and 0.4 mIU/L, treatment is discussed on a case-by-case basis, depending on age, symptomatic features of the hyperthyroidism, and comorbidities [21].

The choice of RAI therapy rather than surgery depends on the patient's age and comorbidities, contraindications to surgery, tolerance of the hyperthyroidism, compressive nature of the nodule and the patient's wishes. RAI therapy is the treatment of choice for non-compressive autonomous nodules, not suspicious on ultrasound, and for hyperthyroidism not requiring an urgent therapeutic solution. It is, of course, contraindicated in case of pregnancy and breastfeeding.

Table 2
Performance of 99mTc-MIBI scintigraphy in predicting malignancy of thyroid nodules. Results obtained with 99mTc-MIBI washout analysis.

Authors	Number and types of nodules	Number of cancers	Sensitivity	Specificity	PPV	NPV
Campenni [10]	≥ 15 mm 40 Bethesda III 65 Bethesda IV	11/40 (27.5%) 17/65 (26.1%)	100%	91%	80%	100%
Giovanella [11]	10–42 mm (median: 22 mm) 61 Bethesda IV + ultrasonographic criteria: EU-TIRADS 5	16/61 (26.2%)	100%	96%	88%	100%

Table 3
Performance of 18F-FDG-PET/CT in the prediction of malignancy of thyroid nodules according to recent meta-analyses and studies.

Authors	Type of study	Number and type of nodules	Number of cancers	Sensitivity	Specificity	PPV	NPV
Vriens et al., 2011 [12]	Meta-analysis (6 studies)	225 patients Bethesda III/IV	58/225 (25.8%)	95%	48%	39%	96%
Castellana et al., 2019 [13]	Meta-analysis (8 studies)	331 nodules Bethesda III/IV	104/331 (24.1%)	74%	58%	34%	74%
Deandreis et al., 2012 [16]	Prospective study	56 nodules Bethesda III/IV Median: 21 mm	10/56 (17.8%)	77% 80%[a]	62% 52%[a]	57% 27%[a]	81% 92%[a]
Piccardo et al., 2016 [15]	Prospective study	87 nodules TIR3[b] > 10 mm Median: 20 mm	18/87 (20.7%)	94%	58%	37%	98%
Nguyen et al., 2018 [17]	Prospective study	108 nodules Bethesda III/IV Median: 31 mm	31/108 (28.7%)	79%	32%	31%	79%
Rosario et al., 2019 [18]	Prospective study	63 nodules Bethesda III/IV > 10 mm Median: 28 mm	7/63 (11.1%)	90% 100%[a]	68% 57%[a]	55% 23%[a]	94% 100%[a]
Piccardo et al., 2020 [13]	Retrospective study	111 TIR3[b] 67 TIR3A 44 TIR 3B All > 10 mm Median 19 mm	27/111 (24.3%)	85%	41%	32%	90%

PPV: positive predictive value; NPV: negative predictive value.
[a] Considering thyroid tumors of uncertain malignant potential (TUMP and NIFT-P) as benign.
[b] TIR3: from the Italian ICCRTC cytological classification of thyroid nodules.

Preparing the patient for therapeutic administration of iodine 131 involves several stages:

- ultrasound evaluation of the volume of the autonomous nodule, possibly weighted by functional volume on scintigraphy [22];
- informing the patient about the procedure for this type of metabolic radiotherapy and the associated radiation protection measures [23];
- checking possible iodine overload;
- if synthetic anti-thyroid drugs have been used previously, it is strongly recommended that they should be discontinued 5-7 days before treatment, to avoid increasing the risk of permanent secondary hypothyroidism [24]. Any synthetic anti-thyroids may be resumed at a minimum 7 days after RAI therapy.

If the TSH is low but not suppressed and there is still iodine uptake in the non-autonomized thyroid parenchyma, a short course of LT3-based hormone therapy may be considered in preparation for RAI therapy, after assessment of the clinical context and depending on tolerance. A short course of LT3 is generally well tolerated in the absence of cardiac co-morbidity and, by extinguishing iodine uptake in the non-autonomized thyroid parenchyma, may reduce the risk of secondary hypothyroidism, although this was not demonstrated in case-control cohort studies [25–27].

The therapeutic goal in hyperthyroidism due to an autonomous nodule is ideally the restoration of euthyroidism, avoiding both too low a level of radioactivity, leading to failure, and too high a level, leading to hypothyroidism in the long term.

There is no international consensus to determine radioactivity level 131. The data on therapeutic efficacy and tolerance come from studies of heterogeneous patient populations, all causes of hyperthyroidism combined. Similarly, practices in France are heterogeneous [24].

There are several approaches to metabolic radiotherapy in hyperthyroidism:

- fixed radioactivity, depending on the cause of hyperthyroidism; however, practices are non-standardized and heterogeneous, varying in France from 185MBq to 740 MBq [24];
- calculated radioactivity level:
  - according to a semi-quantitative method based on the mass of tissue to be treated (depending on the publications from 3.3 MBq to 8 MBq/g of tissue),
  - or according to dosimetric methods taking account not only of mass but also of the dose (in Grays) to be delivered, iodine uptake, and the effective half-life of the iodine in the tissue to be treated (5). This method uses Marinelli's approach based on iodine uptake observed several days after administration of low-activity iodine-131. Dosimetric measurements based on iodine-123 uptake at 2 h, 4 h or 24 h are also feasible, by applying matching factors.

Few studies compared efficacy and safety between these methods in this indication. Only one randomized study in patients with autonomous nodules showed equivalent efficacy with lower risk of hypothyroidism for calculated than fixed radioactivity methods [26,28–30].

However, although more complex to implement, dosimetric methods should ideally be preferred, as internal vectored radiotherapy should be performed with "the lowest effective activity possible" (ALARA principle: As Low As Reasonably Achievable).

The rate of successful restoration of euthyroidism after a single course of iodine-131 in this indication ranges from 75% to 95% [27,29,31], including the case of large nodules weighing more than 50 g [32]. The speed of regression of hyperthyroidism depends on factors influencing iodine uptake, and correlates with radioactivity level [29].

The risk of secondary hypothyroidism persists for up to 20 years after RAI therapy, with cumulative rates of approximately 7% at 6 months to 30% at 20 years [28,32]. The risk of hypothyroidism correlates with patient age, radioactivity level, TSH value at the time of therapy, and pre-existing underlying thyroid disease (presence of antithyroid antibodies before RAI therapy) [27,28,31]. This risk of long-term hypothyroidism justifies regular long-term biological monitoring, with annual TSH assay.

The rate of recurrence or persistence of hyperthyroidism due to incomplete treatment is about 3% to 5.5% [31], favored by rapid turnover of iodine in the thyroid tissue, as shown by the 24 h/4 h iodine fixation ratio, by too low a dose, or underestimation of the mass to be treated. Repeat RAI treatment can be proposed after 6 months, allowing a return to euthyroidism in nearly 80% of cases [32].

Adverse effects consist in increased thyrotoxicosis by hormone release in case of large nodules, and, exceptionally, induction of thyroid autoimmunogenicity after RAI therapy [29].

Recommendation 5.8:

RAI therapy should be performed in first line patients with overt hyperthyroidism (or subclinical hyperthyroidism requiring radical treatment) related to an autonomous nodule. Surgical treatment should be preferred in case of compressive nodule, a suspicious nodule on ultrasound, if pregnancy is planned within 6 months, or according to patient preference. Grade A ++

Recommendation 5.9:

Preparation with beta-blockers (propranolol) and synthetic anti-thyroid drugs is not systematic before RAI therapy, but may be considered in cases of cardiovascular risk and high T3L, preferably using imidazoles, with two precautions:

- maintaining TSH suppression to limit the risk of permanent hypothyroidism secondary to RAI therapy;
- interrupting treatment 5 to 7 days beforehand to preserve the effectiveness of the RAI therapy.

Resumption of synthetic anti-thyroid drugs should be discussed with the endocrinologist.

Grade B ++.

Recommendation 5.10:

The administred activity should be as low as possible, according to the ALARA principle, possibly based on dosimetric methods. Grade B +++

Recommendations 5.11:

After treatment with iodine-131, biological monitoring of TSH is necessary at 1, 3, 6 and 12 months in order to assess therapeutic efficacy. Grade A ++.

After the first year, annual TSH measurements are justified in the long term to detect late hypothyroidism. Grade A ++.

Disclosure of interest

The authors declare that they have no competing interest.

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