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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 : Initial work-up for thyroid nodules

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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 initial work-up for thyroid nodules in adult patients, including clinical and biological evaluation, standardized ultrasound characterization and EU-TIRADS-based nodule selection for fine-needle aspiration biopsy. Indications for thyroid core-biopsies or open surgical biopsies and for cross-sectional imaging of the neck and upper chest are also mentioned.

1. History and clinical assessment

In the diagnostic work-up for thyroid nodules, medical history-taking should record family history of thyroid disease, the patient's personal history, including previous neck and/or supraclavicular radiation therapy, and a detailed history of the onset and course of thyroid-related clinical symptoms. Syndromic presentations with increased risk of thyroid cancer are also to be noted, given the high penetrance of medullary thyroid cancer (MTC) in the context of multiple endocrine neoplasia type 2, and the risk of developing papillary or follicular differentiated thyroid cancer in Cowden's syndrome, Carney's complex, familial adenomatous polyposis and/or Gardner's syndrome, Werner's syndrome, and DICER1 syndrome [1]. There are also factors and conditions to consider for medical decision-making: age, gender, with special attention in children, pregnant women, the elderly and patients with significant comorbidities or limited life-expectancy.

The clinical examination comprises inspection and careful palpation of (1) the thyroid gland (volume, pain, consistency), (2) the nodular formation(s) (size, topography, regularity, hardness, mobility, number) and (3) the cervical lymph-node areas, plus any voice changes (hoarse, weakened), swallowing disorder or signs of venous compression in case of goiter (collateral venous circulation, Pemberton's sign) or inspiratory laryngeal dyspnea. Symptoms compatible with hyperthyroidism or hypothyroidism should also be monitored. Clinical signs suggestive of malignancy may comprise rapid asymmetric nodular growth, aspect of large firm-to-hard irregular adherent nodule, compressive symptoms such as dysphonia due to tumor infiltration of the recurrent laryngeal nerve, dysphagia, positional laryngeal dyspnea, and evidence

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Table 1
Clinical and biological factors affecting the risk of thyroid malignancy (excluding ultrasound and cytological characteristics of the nodule).

High risk
Newly formed or rapidly growing solid nodule
Hard, irregular or fixed nodule
Suspect cervical lymph node(s)
Compressive signs (dysphonia or recurrent nerve palsy, dyspnea, dysphagia) with no extra-thyroidal cause
Hypermetabolic nodule discovered on ^{18} F-FDG-PET
Nodule discovered with calcitonin elevation > 100 pg/mL
Personal history of multiple endocrine neoplasia type 2
Intermediate risk
History of cervical irradiation
Male gender
Age < 18 or > 65 years
Solitary nodule occurring at young age
Family history of multiple endocrine neoplasia type 2
Personal or family history of familial adenomatous polyposis, Carney's complex, Cowden's syndrome, DICER1 syndrome
Family history of thyroid cancer of follicular origin (≥ 3 cases)
Low risk
Soft, elastic or purely cystic nodule
Nodule with slow or no progression

of ipsilateral or bilateral cervical lymph nodes in advanced thyroid cancer states [2]. Chronic diarrhea associated with elevated carcinoembryonic antigens in the presence of a thyroid nodule should be investigated by calcitonin (CT) assay to screen for MTC.

Likelihood of thyroid malignancy can be assessed on several clinical features and medical history [3–8] (Table 1). However, a normal clinical examination does not rule out thyroid cancer, which may have a non-suspect clinical presentation or even appear as a non-palpable nodule. To decide between treatment and surveillance, one needs to take into account not only the clinical characteristics of the nodule, along with the ultrasound evaluation and cytological study if indicated, but also the patient's health status and wishes.

Recommendation 2.1: Medical history-taking should include diagnostic circumstances and the time course of thyroid nodule development, age, gender, comorbidities, history of neck radiation therapy, family history of thyroid nodules or thyroid cancer, and genetic disorders that can increase the risk of thyroid cancer.

Level of evidence +++ Grade A

Recommendation 2.2: Clinical examination should assess thyroid volume, signs of hyper- or hypothyroidism, consistency of the nodule or nodules, their size, topography and mobility with respect to surrounding tissue, thyroid pain, compressive signs and their progression, and screen for cervical lymph nodes.

Level of evidence +++ Grade A

2. Initial laboratory work-up

2.1. TSH measurement to assess thyroid function

All international guidelines agree that plasma TSH measurement is the only essential test for a thyroid nodule [4,5,9–12]. Five to ten percent of thyroid nodules secrete thyroid hormones excessively, most often resulting in subclinical hyperthyroidism or, more rarely, in overt thyrotoxicosis. The risk of malignancy in autonomous nodules is extremely low. TSH measurement can thus identify a possible autonomous nodule and may indirectly alter the risk of malignancy. In the case of any abnormal TSH concentration, the result should be confirmed on a second sample and interpreted according to the clinical findings. In the presence of abnormal TSH, testing for FT4 and possibly FT3 is useful to assess the severity of thyroid dysfunction and, depending on the results, the etiological work-up (including thyroid scintigraphy in the case of a low TSH) should be completed, regardless of the diagnostic procedure for thyroid nodule evaluation. In the case of hyperthyroidism without evidence of an autonomous nodule, TSH receptor antibodies can be measured to screen for associated Graves' disease. If TSH is elevated, anti-thyroperoxidase antibodies may be tested to screen for associated autoimmune thyroiditis. Anti-thyroglobulin antibody testing should be proposed only in second line if TSH is elevated and anti-thyroperoxidase antibodies are negative.

Recommendation 2.3a: TSH should be measured as part of the initial work-up of thyroid nodules, to screen for thyroid dysfunction.

Level of evidence +++ Grade A

Recommendation 2.3b: A low TSH level between 0.1mIU/L and 0.4mIU/L should be checked after a few weeks. If the TSH is below 0.1 mIU/L, or if low TSH is confirmed, FT4 and possibly FT3 should be measured to assess the severity of hyperthyroidism or to distinguish between overt and subclinical hyperthyroidism.

Level of evidence +++ Grade A

Recommendation 2.3c: A moderately elevated TSH level (<10 mIU/L) should be checked after a few weeks, as it may normalize during follow-up. If TSH is >10 mIU/L, or if moderately elevated TSH is confirmed, a FT4 assay should be performed to assess the severity of hypothyroidism or to distinguish between overt and subclinical hypothyroidism.

Level of evidence +++ Grade A

2.2. Role of calcitonin measurement

The low prevalence of medullary thyroid cancer (MTC) and microMTC, estimated at between 0.23% and 1.4%, and the development of C-cell hyperplasia in some benign situations do not justify systematic calcitonin (CT) measurement in the presence of all thyroid nodules, since moderate CT elevation may lead to unnecessary surgery [13]. Indeed, CT elevation was reported in chronic renal failure, autoimmune dysthyroidism, hypergastrinemia (including when induced by proton-pump inhibitors), alcohol intake, smoking, infection, in the presence of heterophilic anti-CT antibodies and in some bronchial or pancreatic neuroendocrine tumors. However, it is important not to ignore an MTC for which the surgical treatment (thyroid surgery and lymph node dissection) must be adapted to the tumor burden and the presumed lymph-node extension related to the CT level [5,10,11,14]. The quality of this initial surgery is known to be a major prognostic factor of MTC. For this reason, calcitonin measurement should always be performed before any thyroid surgery or thyroid thermal ablation.

The predictive diagnostic value of elevated basal CT concentration to identify an MTC is to be assessed in relation to the volume of the thyroid nodule investigated, the data of the cytological examination, or even the immunocytochemistry profile, or the measurement of CT in the fine-needle aspiration biopsy (FNAB) washout fluid. Comparison with age, gender, weight, renal function and current or former smoking is essential: CT levels are moderately increased in middle-aged overweight men who smoke.

If the CT concentration exceeds 100 pg/mL, MTC is very likely.

In case of moderate CT elevation (between 10 and 100 pg/mL), a second check is recommended after 3–12 months (depending on the clinical context); then, in case of persistent CT elevation:

- surgery should be considered if, in the absence of any other identified cause, basal CT exceeds 30 pg/mL in women and 60 pg/mL in men or if there is >20% progression [14];
- measurements should be repeated, doubling the monitoring interval if CT level is stable;
- monitoring should be discontinued if CT levels have decreased.

Recent studies compared procalcitonin (PCT), usually used in biochemistry for the evaluation of sepsis, versus CT as a tumor marker for MTC. Analytically, the data obtained in the various studies showed a good correlation between CT and PCT values in patients with MTC, both at diagnosis and during follow-up (patients in remission, or with residual disease with or without metastases). With PCT, there was little inter-technique variability, no pre-analytical difficulties, compared to the need for rapid freezing for CT, and the half-life of PCT is longer [15]. A disadvantage is that PCT is elevated in case of infection. The effectiveness of PCT for diagnosing and monitoring MTC and its prognostic role remains to be clarified.

Recommendation 2.4: Routine calcitonin testing is not recommended for all thyroid nodules.
Level of evidence ++ Grade A

Recommendation 2.4a: Calcitonin testing should be performed in the following situations: personal or family history of MTC or MEN2; thyroid nodule associated with diarrhea, flushing or lymph node metastasis; suspect thyroid nodule.
Level of evidence +++ Grade A

Recommendation 2.4b: Calcitonin should be measured before any thyroid surgery or thyroid thermal ablation.
Level of evidence +++ Grade A

Recommendation 2.4c: A normal calcitonin test should not be repeated in the absence of a genetic predisposition to MTC.
Level of evidence +++ Grade A

2.3. Value of serum calcium and PTH measurement

The prevalence of primary hyperparathyroidism is 0.9%, affecting 1-7 persons/1,000. The vast majority of patients with thyroid nodules have normal blood calcium levels. However, serum calcium assay is useful if a parathyroid adenoma is suspected on ultrasound examination for thyroid nodule. Before thyroid surgery, serum calcium assay should screen for hypercalcemia and provide a baseline for comparison with the postoperative blood calcium level.

Recommendation 2.5a: Routine measurement of serum calcium, corrected serum calcium and/or PTH in the presence of a thyroid nodule is not recommended.
Level of evidence ++ Grade B

Recommendation 2.5b: Prior to thyroid surgery, measurement of serum calcium is recommended.
Level of evidence +++ Grade B

2.4. Value of thyroglobulin assay in thyroid nodules

Preoperative serum thyroglobulin (Tg) levels do not discriminate between benign and malignant nodules [5]. Tg is an approximate indicator of functional thyroid volume. It cannot be used as a marker of malignancy in this context.

However, if distant metastases (notably bone and lung) are found in a patient with suspicious thyroid nodule(s) and no obvious primary tumor, Tg measurement together with anti-thyroglobulin antibody assay can rule out or confirm metastatic differentiated thyroid cancer [4,5,9–11].

Recommendation 2.6: Routine measurement of serum thyroglobulin for the initial assessment of thyroid nodules is not recommended.
Level of evidence +++ Grade A

3. Ultrasound assessment

3.1. When should thyroid ultrasound be performed?

The overuse of ultrasound is thought to be responsible for much of the overdiagnosis of subclinical thyroid cancers over the last two decades [16,17]. The Korean experience has also clearly demonstrated that systematic screening only increases the detection of papillary carcinomas, without reducing specific mortality [18]. International consensus therefore recommends that thyroid ultrasound should be performed when a nodule is palpable, in case of discomfort or pressure symptoms for which a thyroid origin is suspected, especially if palpation is difficult (overweight subject, short neck), or to image incidentaloma. The aim is then to describe the characteristics of the nodule(s), stratify cancer risk, define management, and obtain a reference size for subsequent surveillance. Otherwise, routine ultrasound screening is not recommended. However, selective screening may be discussed in populations at increased risk of thyroid cancer: monogenic syndrome of susceptibility to thyroid cancer, cancer treated during childhood with external beam radiation therapy, either with high-dose total body exposure or cervical irradiation, family history of thyroid cancer ($\geq$3 cases), or significant exposure to ionizing radiation. In these cases, it is advisable that overall management and ultrasound should be carried out in a specialized setting.

3.2. Good practice - standardized reporting

Consensus on thyroid ultrasound emphasizes the need to standardize practice by standardizing the report. The minimum information that should be included is the indication for the examination, thyroid volume, the echogenicity and homogeneity of the gland, and the description of significant nodules (in practice, description of 3 to 5 nodules is generally sufficient). For the description, a lexicon should be used (see supplementary lexicon), with representation and numbering on a dedicated diagram (Fig. 1). Malignancy risk should be stratified using a TI-RADS score (Thyroid Imaging and Reporting Data System: for Europe, EU-TIRADS). Nodule selection in the report is stratified according to score and size. It is advisable to describe all nodules with EU-TIRADS score of 5, with EU-TIRADS score of 4 and larger than 5 mm, and with EU-TIRADS score of 3 or 2 and larger than 10 mm. Cervical lymph-node study is mandatory, as well as the region between the upper edge of the isthmus and the hyoid bone, in order not to overlook thyroglossal duct pathology. Finally, the upper mediastinum should be examined for ectopic goiter or lymph nodes. The conclusion of the report gives the scores of the main nodules, assesses progression and suggests a course of action.

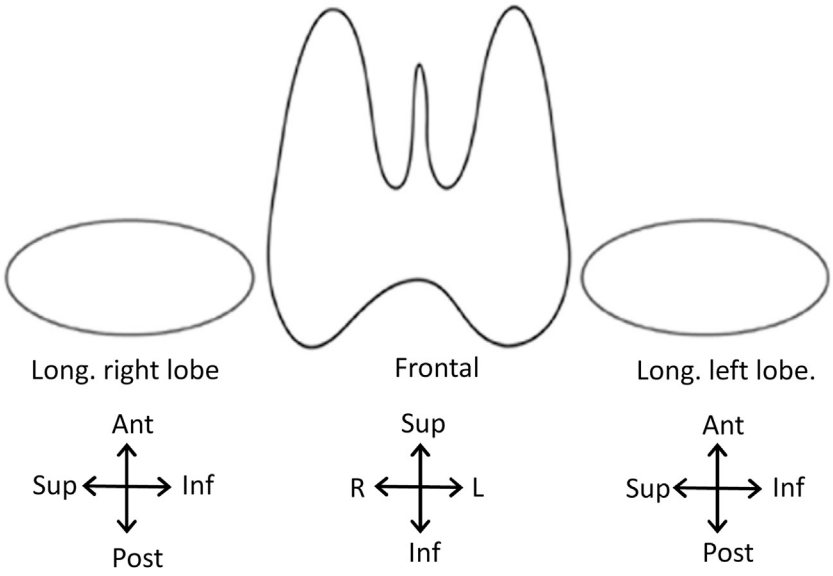

Fig. 1. Diagram accompanying the thyroid ultrasound report (long.: longitudinal, Ant: anterior, Post: posterior, Sup: superior, Inf: inferior, R: right, L: left). Diagram: by courtesy of J Tramalloni.

3.3. Malignancy score: EU-TIRADS vs other scores (Table 2)

Description of the ultrasound features of thyroid nodules is marred by poor inter-observer reproducibility. The development of the TI-RADS scores, from 2009 onward, was an attempt to resolve this difficulty, but also to establish a quantitative malignancy risk stratification. Other aims were to homogenize reports, facilitate their understanding (use of a diagram - Fig. 1) and standardize management recommendations. Ten risk stratification systems have been developed [19]. The main ones are compared in Table 2. The main differences consist in the type of analysis, which is called 'pattern-based' when the entire appearance of the nodule is taken into account globally to analyze its risk, or 'point-based' when each ultrasound sign is assigned a certain number of points; the sum of the points is then used to calculate the score. Other differences include whether or not the composition (presence and proportion of a cystic component) and possible extra-thyroidal extension are taken into account.

In terms of gross diagnostic value (application of ultrasound alone), no system has demonstrated superiority over the others. A multicenter retrospective study of the EU-TIRADS score in 1,058 nodules, using final histology as reference, found a cancer rate close to the estimates predicted by the ETA (European Thyroid Association) consensus and a satisfactory diagnostic value, with sensitivity of 93% and negative predictive value of 97% [20]. In a meta-analysis published in 2020, including 7 studies for 5,672 nodules, the prevalence of malignancy per EU-TIRADS class was 0.5%, 5.9%, 21.4% and 76.1% for classes 2 to 5, respectively. Sensitivity, specificity, PPV and NPV of EU-TIRADS class 5 for the detection of malignancy were 83.5%, 84.3%, 76.1% and 85.4%, respectively [21]. Inter-observer reproducibility of the scores was also similar: satisfactory to robust [19]. Each system makes recommendations for the indication of FNAB based on score and nodule size. When applied, all TI-RADS reduce the number of unnecessary FNABs, with the ACR (American College of Radiology) system appearing to be the most effective in this respect. The main shortcoming of these systems is their lack of sensitivity in diagnosing follicular carcinoma and, to a lesser extent, papillary carcinoma of follicular variant and medullary carcinoma. In addition, there are possible false positives, particularly in cystic nodules that have decreased in size and in subacute thyroiditis. Overall, the use of a TI-RADS system is recommended by all consensus statements. In Europe, and therefore in France, the system in use is the EU-TIRADS. Its major advantage is its simplicity. The score is described in Table 2 and Fig. 2. A single feature of high suspicion is sufficient to classify the nodule as EU-TIRADS 5.

3.4. What is the role of elastography?

Elastography has been used in clinical practice since 2008, but its role remains controversial. Indeed, there is a strong contrast between the international consensus against routine clinical use and the published research, most of which supports the effectiveness of the method. In the meta-analysis by Filho et al., combined positive and negative predictive values were respectively 16-94% and 29-100% [22], with highly heterogeneous results. It is therefore not possible to say whether the method should be used routinely, but it may be useful in selected cases or during the learning phase of thyroid ultrasound training.

3.5. What is the role of contrast-enhanced ultrasound?

The meta-analysis by Trimboli et al.of studies using a histological reference obtained pooled sensitivity of 85%, specificity of 82%, and positive and negative predictive values of 83% and 85% respectively, for 14 publications and 1,515 nodules [23]. In the meta-analysis by Liu et al., combined sensitivity and specificity were both 88% [24]. A positive test increased the pre-test risk of malignancy from 49% to 87%, and a normal test reduced it from 49% to 11%. Both meta-analyses concluded that the method was useful. In France, the available ultrasound contrast medium does not have market authorization for exploration of thyroid nodules and it is therefore not possible to recommend its use in clinical routine, but only for research projects.

Recommendation 2.7: Thyroid ultrasound is recommended for the investigation of palpable nodules and incidentalomas. It is not recommended for routine screening.
Level of evidence +++ Grade A

Recommendation 2.8: The ultrasound report should describe the nodules and display them on a diagram. Risk stratification according to the EU-TIRADS score is advised, as well as including

Table 2
Comparison of the main risk stratification systems used worldwide.

System	Number of classes	TI-RADS 1 Meaning	Design	Features of high suspicion	Composition taken into account	Extra-thyroidal extension taken into account
EU- TIRADS	5	No significant nodule	Pattern	Taller than wide Irregular margins Microcalcifications Marked hypoechogenicity	No	No
ATA	5	Benign	Pattern	In a solid, hypoechoic nodule: Irregular margins Microcalcifications Taller than wide Peripheral calcifications with extra-nodular solid extension Extra-thyroidal extension	Yes	Yes
K- TIRADS	5	No nodule	Pattern	In a solid, hypoechoic nodule: Non-parallel orientation Irregular margins Microcalcifications	Yes	No
ACR- TIRADS	5	Benign	Point	Taller than wide All hyperechoic spots without comet tail artifacts Marked hypoechogenicity	Yes	Yes

ATA: American Thyroid Association, TI-RADS: Thyroid Imaging and Reporting Data System, K: Korean, EU: European, ACR: American College of Radiology.

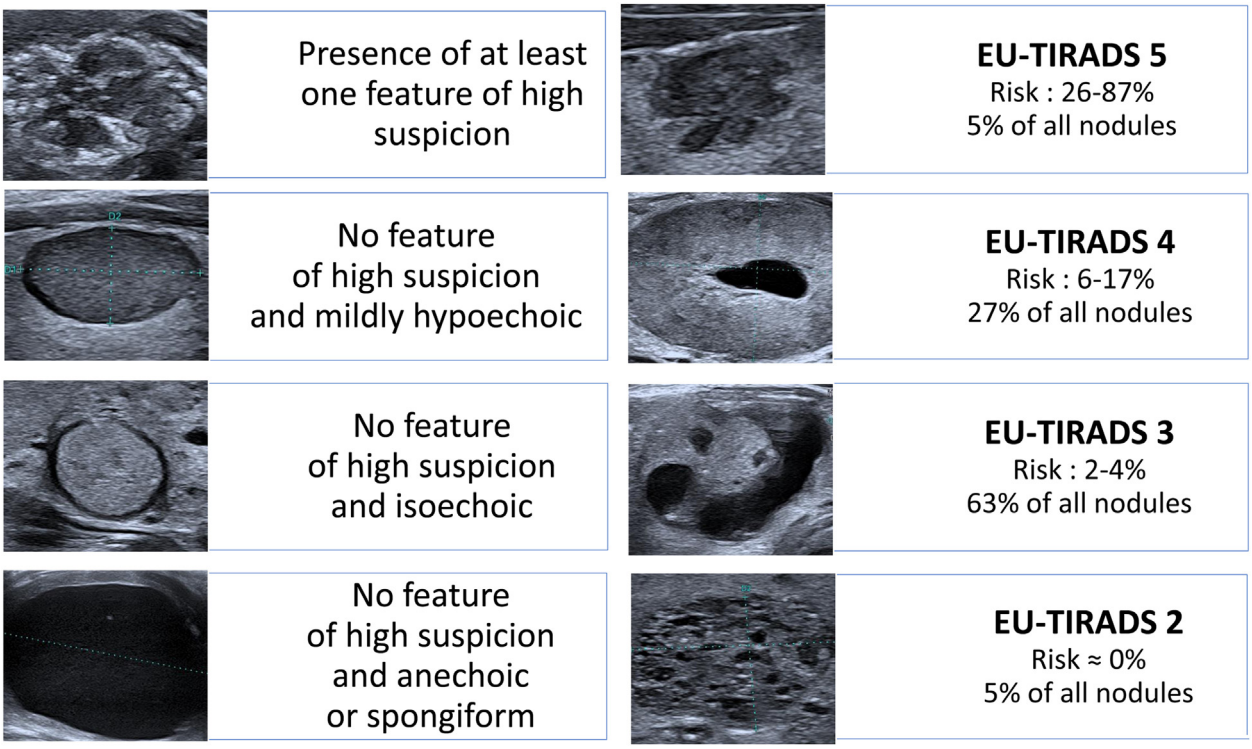

Fig. 2. Illustration of EU-TIRADS scores.

cervical lymph nodes and areas of the thyroglossal tract and upper mediastinum in the description.

Level of evidence +++ Grade A

4. When to implement fine-needle aspiration biopsy of thyroid nodules

The indication for thyroid nodule fine-needle aspiration biopsy should be discussed on the basis of symptoms, EU-TIRADS score, nodule size and the patient's medical situation, with the patient's agreement. In all cases where there is a cervical lymph node suspected of thyroid metastasis, FNAB of the most suspicious thyroid nodule or nodules is indicated, without size criteria. Fine-needle aspiration biopsy should also be performed on the suspected node with in situ Tg (or CT) measurement: i.e., Tg (or CT) measurement in washout of fine-needle aspirates.

4.1. Indications for FNAB according to size and EU-TIRADS score

The indication for FNAB depends on the risk of cancer: high, intermediate, low or very low [5,25]. This risk is assessed according to ultrasound characteristics: shape, contour, presence of microcalcifications and echogenicity. The size of the nodule is also taken into account, and thresholds vary somewhat according to current

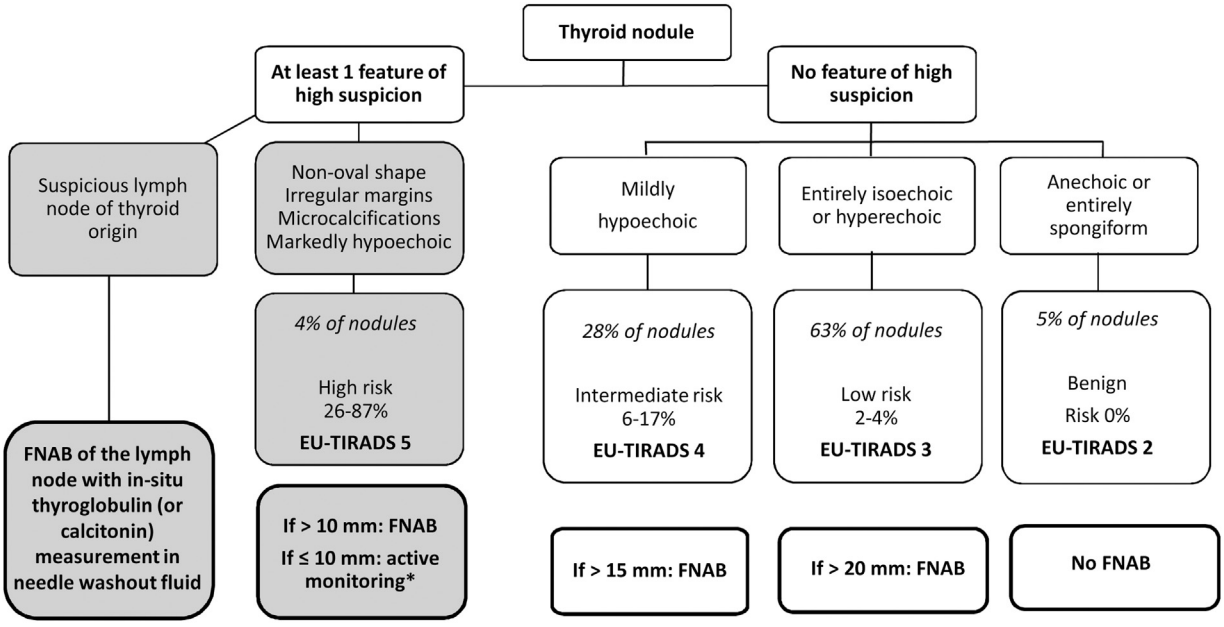

Fig. 3. Indications for thyroid nodule fine-needle aspiration biopsy according to EU-TIRADS score and size. *: except particular cases (Monitoring section).

recommendations [19]. Screening for adenopathy in at least cervical lymph-node levels III, IV and VI is essential. According to the American Thyroid Association, nodules with intermediate or high risk of cancer should undergo FNAB as of 10 mm size, nodules with low risk as of 15 mm and nodules with very low risk as of 20 mm. Entirely cystic nodules are a-priori benign and do not require FNAB. In France, recommendations for FNAB are based on the stratification described by G. Russ, detailed in Fig. 3.

There is no indication for diagnostic thyroid FNAB for EU-TIRADS 2 nodules, whatever their size. The risk of malignancy is < 2%. The sonographer must ensure that the nodule is entirely cystic (or anechoic) or spongiform so as not to miss a solid portion of a different nature the size or sonographic features of which would in itself require a diagnostic sample.

In the case of EU-TIRADS 5 nodule > 10 mm in a patient who is not operable and/or has low life expectancy, the indication for FNAB must be discussed on a case-by-case basis in specialized multidisciplinary board.

4.2. Should EU-TIRADS 5 nodule ≤ 10 mm without lymph-node involvement undergo FNAB?

Nodules measuring ≤ 5 mm should not undergo FNAB [4]. Nodules measuring 6–10 mm do not require routine FNAB either, except when they have several ultrasound malignancy criteria and do not meet the criteria for active surveillance laid out in Section 6 (Surveillance).

Recommendation 2.9: Thyroid fine-needle aspiration biopsy (FNAB) is recommended for the following nodules, based on EU-TIRADS score and size:

- EU-TIRADS 3 nodules > 20 mm where the risk of malignancy is between 2% and 4% (very low risk);
- EU-TIRADS 4 nodules > 15 mm where the risk of malignancy is between 6% and 17% (low to intermediate risk);
- EU-TIRADS 5 nodules > 10 mm where the risk of malignancy is between 26% and 87% (intermediate to high risk);
- most suspicious nodules, when there is a lymph node suspected of metastasis of thyroid origin. FNAB should also be performed on the suspicious lymph node with in situ thyroglobulin/calcitonin measurement.

Level of evidence +++ Grade A

Recommendation 2.10: A EU-TIRADS 5 nodule of size ≤ 10 mm should not undergo routine FNAB.
Level of evidence ++ Grade B

4.3. Indications for FNAB in multiple nodules

The indications for fine-needle aspiration biopsy should be prioritized according to the score and size of each nodule and the risk of cancer. The sonographer should look for >10 mm nodules at intermediate or high risk of thyroid cancer. If all nodules have the same sonographic features (not suspect for cancer) according to EU-TIRADS score, the sonographer will select the 2 or 3 largest (>20 mm) nodules for thyroid FNAB. Several studies have shown that risk of cancer is lower with multiple nodules than with a single nodule [6].

In the case of multiple nodules associated with subnormal TSH or TSH in the low range of normal, indications for FNAB may be guided by scintigraphy.

Recommendation 2.11: In the case of multiple nodules, indications for FNAB are case-by-case according to the size and EU-TIRADS score of each nodule. Priority should be given to nodules most likely to be cancerous (2 to 3 nodules maximum).
Level of evidence ++ Grade A

4.4. Indications for FNAB in mixed nodules

Mixed nodules have a solid and a liquid component, in varying proportions. Some studies estimate that the risk of malignancy in mixed nodules is inversely proportional to the percentage of the cystic portion. Nevertheless, 13-26% of thyroid cancers have a cystic component and 2-18% of mixed nodules (partially cystic) are cancerous. It appears that mixed nodules with >50% solid tissue component are associated with a higher risk of malignancy,

especially if the tissue component is eccentric [26–28]; conversely, the risk of malignancy decreases with >75% cystic component [6]. To date, there are no specific validated scores to assess the risk of malignancy in mixed nodules.

These nodules are more difficult to characterize on ultrasound, with the risk of non-expert sonographers misjudging the indication for fine-needle aspiration biopsy. Technically, FNAB may be more difficult if the solid part is small or posterior.

Recommendation 2.12: In mixed nodules, the solid tissue portion of each nodule should be accurately described, with size (or volume) and EU-TIRADS score, separately from the fluid portion. The indication for fine-needle aspiration biopsy depends on the EU-TIRADS score, ensuring that the tissue portion of the mixed nodule is accessible for FNAB and >10 mm in size.

Level of evidence +++ Grade B

4.5. Indications for fine-needle aspiration biopsy in case of lymph nodes, and role of in-situ Tg and CT markers

Node involvement is present in 20-50% of patients with vesicular thyroid carcinoma, including cancers <10 mm in size [5]. If lymphadenopathy is present, FNAB should be proposed to all patients if the expected result is likely to alter management.

Ultrasound criteria that strongly suggest metastatic cervical lymph-node involvement of thyroid origin comprise the presence within the suspected lymph node of cystic areas, microcalcifications, a thyroid tissue-like echostructure, and peripheral or anarchic lymph-node vascularization [29].

Measurement of Tg in the washout fluid of lymph-node fine-needle aspiration is appropriate and valid even in patients with anti-Tg antibodies [30]. A Tg concentration <1 ng/mL is reassuring, and the likelihood of lymph-node metastasis increases with increasing Tg levels measured in situ. Levels >100 ng/mL are typical for metastatic lymphadenopathy of differentiated cancer. The study by Pak et al. suggested that a Tg cut-off value of 32 ng/mL gives the best ratio of sensitivity and specificity when measuring Tg in the lymph-node washout fluid in patients with non-operated thyroid gland [31].

For patients with or suspected of having MTC, lymph-node FNAB with CT measurement in the needle washout fluid can also be used. A study published in 2020 showed 100% sensitivity and specificity for a CT cut-off value of 23 pg/mL for the diagnosis of lymph-node metastasis [32].

Recommendation 2.13: Lymph-node fine-needle aspiration biopsy should be performed for ultrasound-diagnosed lymph-node disease. Depending on the case, thyroglobulin or calcitonin measurement in the washout fluid of the suspicious lymph-node FNAB is indicated.

Level of evidence +++ Grade A

4.6. When should thyroid biopsy be performed in first line?

When the thyroid nodule is suspected of being an aggressive cancer because of compressive symptoms such as dysphonia, dyspnea, dysphagia or rapid progression of an indurated thyroid mass associated with lymphadenopathy, thyroid FNAB and microbiopsy or surgical biopsy should be performed urgently by an experienced operator to rule out or confirm anaplastic thyroid carcinoma or thyroid lymphoma [33]. These two rare pathologies, where delayed diagnosis can profoundly alter prognosis, require urgent oncological management in an expert center. In some centers, microbiopsy and FNAB are performed at the same time to shorten diagnostic time. It is advisable to perform an ultrasound-guided procedure, to avoid areas of necrosis and to take multiple samples to collect sufficient material for molecular biology analysis (with tissue freezing if necessary). In the case of anaplastic cancer, the sample will allow BRAF analysis by immunohistochemistry to screen for a potential therapeutic target, pending further somatic genetic analysis.

Other possible diagnoses to be considered in the presence of a symptomatic and/or rapidly progressive thyroid mass include intra-thyroid metastasis of an extra-thyroid cancer, tumor infiltration by another cervical cancer (esophagus, etc.) and Riedel's thyroiditis [34,35].

Recommendation 2.14: In the case of a symptomatic thyroid tumoral mass and/or rapid clinical progression suggesting anaplastic cancer or lymphoma, the patient should be referred urgently to an expert center for surgical biopsy or thyroid microbiopsy (possibly combined with FNAB) under ultrasound guidance, for diagnostic purposes and molecular genotyping.

Level of evidence ++ Grade A

5. Thyroid incidentaloma on 18F-FDG PET/CT and 18F-FCholine PET/CT

18F-FDG positron emission tomography coupled with X-ray computed tomography (18F-FDG-PET/CT) is a widely used imaging technique for the exploration of malignant and inflammatory pathologies. Thyroid incidentaloma on 18F-FDG-PET/CT is defined by the presence of focal uptake incidentally discovered on an examination performed for another reason, with incidence varying between 2% and 3% of 18F-FDG-PET/CT scans [36–38]. Focal 18F-FDG uptake corresponds in the vast majority of cases to a thyroid nodule, with a malignancy rate estimated in a meta-analysis at 30-35% [36,38]. SUVmax (maximum standardized uptake value) is generally significantly higher in malignant nodules (6.9 vs. 4.8, $p < 0.001$); however, no studies have been able to demonstrate a threshold of SUVmax that would completely exclude risk of malignancy [36].

Several recent studies evaluated the contribution of ultrasound scores (EU-TIRADS, K-TIRADS, American Thyroid Association (ATA) criteria) for the detection of malignant nodules among these incidentalomas [39,40]. In a single-center retrospective study of 75 patients, Trimboli et al. reported a <2.9% malignancy risk in EU-TIRADS 3, 4.2% in EU-TIRADS 4 and 78.6% in EU-TIRADS 5 nodules, after exclusion of two patients with intra-thyroid metastasis (sarcoma and renal cancer). Absence of ultrasound criteria of suspicion excluded malignancy with 97.1% specificity. Chung et al., in a single-center retrospective study of a large cohort of 907 nodules, confirmed that there was no increase in malignancy risk associated with nodules with 18F-FDG uptake but classified in the low or very low risk categories according to the ATA ultrasound classification and the Korean K-TIRADS [39]. Ultrasound scores are therefore effective in excluding risk of malignancy in the absence of any ultrasound criteria of suspicion, except for intra-thyroid metastasis: these criteria, which were developed for nodular thyroid disease, may be faulted in case of intra-thyroid metastasis of certain solid cancers [40].

Management of thyroid incidentaloma on 18F-FDG-PET/CT should take account of the general context, initial indication and results of the FDG-PET imaging (extent of disease), patient's prognosis and life-expectancy.

Recently, another tracer, 18F-FCholine, has been widely used, particularly for exploration of prostate cancer, revealing several clinical cases of incidentaloma in relation to benign or malignant thyroid nodules. There are at the moment no large cohort studies assessing the risk of malignancy, but this mode of discovery would appear to be less frequent than with 18F-FDG [41].

Recommendation 2.15: Thyroid ultrasound is routinely recommended for incidental findings of focal thyroid uptake on 18F-FDG PET.

Level of evidence +++ Grade A

Recommendation 2.15a: In the case of a thyroid incidentaloma on 18F-FDG PET/CT, ultrasound criteria remain relevant for discrimination of benign versus malignant nodules. However, as the risk of malignancy is higher in thyroid nodules with focal 18F-FDG uptake, FNAB is recommended for all supracentimetric hypermetabolic nodules classified as EU-TIRADS 4 and 5 and hypermetabolic EU-TIRADS 3 nodules measuring 2 cm or more.

Level of evidence ++ Grade A

Recommendation 2.15b: 18F-FDG PET/CT incidentalomas corresponding to subcentimetric or <2 cm EU-TIRADS 2 and 3 thyroid nodules can be monitored by ultrasound at 6-12 months and then managed according to progression, like thyroid nodules with unknown metabolic status.

Level of evidence ++ Grade B

6. Role of CT (computed tomography) or MRI (magnetic resonance imaging) in nodule assessment

CT exposes patients to radiation, is much more expensive than ultrasound, and is far less effective in differentiating benign from malignant thyroid nodules [42]. Nodule size is often underestimated. Thyroid incidentalomas are detected in 1-25% of cervicothoracic CT or MRI scans [43,44]. The risk of malignancy is in line with the general rate of malignancy, ranging from 0.1% to 11% in thyroid nodules encountered in adults with medical need for CT imaging [43,45]. On CT, the malignancy risk is greater in calcified than non-calcified nodules [46].

The SFE (French Endocrinology Society), ETA (European Thyroid Association) and ATA (American Thyroid Association) guidelines do not recommend routine CT or MRI for initial evaluation of thyroid nodules or for follow-up [4,5,10]. Cross-sectional imaging techniques are, however, useful in patients with compressive symptoms, to characterize substernal nodules and nodules with retrotracheal extension, and for endothoracic mutinodular goiter. In most cases, CT does not require the use of IV contrast-medium. However, to study a suspect thyroid mass or a known cancer relative to other critical anatomic structures such as vessels, to detect accurately both lymph-node and pulmonary extension, and to evaluate the presence of tracheal stenosis or deviation or esophageal invasion, contrast-enhanced cervical or cervicothoracic CT is more appropriate [42,44]. If the TSH is low, MRI may be preferred, which also has the advantage of being non-irradiating, offering better spatial resolution and better visualization of vascular structures, though being more expensive.

Recommendation 2.16: CT and MRI are usually not required in the assessment of thyroid nodules at initial work-up or during follow-up.

Level of evidence +++ Grade A

Recommendation 2.17: CT or MRI may be useful to investigate the substernal extension of a nodule or retrosternal goiter, to assess tracheal or esophageal compression or invasion, to study vascular anatomy preoperatively, and to map lymph nodes, in addition to ultrasound imaging.

Level of evidence ++ Grade A

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ando.2022.10.009.

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