REVIEW

Usefulness of accessible imaging methods in thyroid nodules with indeterminate cytology

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Abstract

In thyroid nodules (TN) submitted to fine-needle aspiration (FNA), Bethesda categories III and IV are considered 'indeterminate' cytology. This result corresponds to 10–25% of all FNAs and the risk of malignancy (RoM) ranges from 10% to 30% for category III and from 15% to 40% for category IV. This review analyzed the practical applicability of accessible imaging method in the management of patients with cytologically indeterminate TN > 1 cm (ITN). When ITN are highly suspicious on ultrasonography (US), the RoM supports surgical indication even in the absence of additional tests. The same can be applied to ITN of intermediate suspicion but with elevated stiffness on elastography. Follow-up without additional tests is acceptable in the case of ITN with low-risk cytology and low-suspicion appearance on US and elastography (if obtained). In the case of ITN without highly suspicious US appearance, ^{123}I scintigraphy may be obtained in patients with TSH < 1–1.5 mIU/L to rule out hyperfunctioning nodules before requesting diagnostic methods that are more expensive and less accessible. In addition, in ITN with not very suspicious US appearance, ^{18}F FDG-PET may be obtained. If this method does not reveal nodular uptake, the risk of the nodule corresponding to a macrocarcinoma is sufficiently low in order to allow follow-up. The positive predictive value of focal nodular uptake on ^{18}F FDG-PET depends on the pre-test RoM, cytological findings, and maximum SUV. There is currently no evidence for the use of CT, MRI or imaging using $^{99\text{m}}\text{Tc}$ -MIBI to define the nature of ITN.

Key Words

- ▶ thyroid nodule
- ▶ indeterminate cytology
- ▶ imaging methods

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Introduction

Thyroid nodules are common in the adult population. Initial assessment consists of excluding functionality and defining whether there is an indication for fine-needle aspiration (FNA). Usually, autonomous nodules, purely cystic nodules or nodules less than 0.5 cm do not require FNA. This procedure may be indicated in nodules with a diameter between 0.5 and 1 cm and a suspicion for malignancy on ultrasonography (US) depending on their location, suspicion of metastases, family or personal history, and need for surgery if they correspond to microcarcinomas (Gharib *et al.* 2016, Russ *et al.* 2017, Tessler *et al.* 2017, Pacini *et al.* 2018). For nodules larger

than 1 cm, the risk of malignancy (RoM) estimated by US defines the diameter that would indicate FNA (Perros *et al.* 2014, Gharib *et al.* 2016, Haugen *et al.* 2016, Russ *et al.* 2017, Tessler *et al.* 2017, Pacini *et al.* 2018, Giovannella *et al.* 2019).

In the case of nodules with an indication for FNA, cytology is classified using one of the known systems (Table 1). Traditionally, categories III (B-III) and IV (B-IV) of the Bethesda System (Ali & Cibas 2018), Thy3 of the UK Royal College of Pathologists Classification System (Perros *et al.* 2014), and TIR3 of the Italian Reporting System (Pacini *et al.* 2018) are defined as 'indeterminate' cytology

Table 1 Terminology and nomenclatures schemes for reporting thyroid cytopathology.

System		
Royal College of Pathologists Classification System (Perros <i>et al.</i> 2014)	Italian Reporting System (Pacini <i>et al.</i> 2018)	Bethesda System (Ali & Cibas 2018)
Categories		
Thy 1: Non-diagnostic	TIR 1: Non-diagnostic	I: Non-diagnostic
Thy 2: Non-neoplastic	TIR 2: Benign	II: Benign
Thy3a: Neoplasm possible - Cytological/nuclear or architectural atypia	TIR 3A: Indeterminate - Low-risk lesions	III: Atypia or follicular lesion of undetermined significance
Thy3f: Neoplasm possible - Follicular neoplasms	TIR 3B: Indeterminate - High-risk lesions	IV: Follicular neoplasm or suspicious for a follicular neoplasm
Thy4: Suspicious of malignancy	TIR 4: Suspicious of malignancy	V: Suspicious for malignancy
Thy5: Malignant	TIR 5: Malignant	VI: Malignant

(Table 1). This result corresponds to approximately 10–25% of all FNAs (Gharib *et al.* 2016, Pacini *et al.* 2018).

Although Bethesda category V (B-V) (Ali & Cibas 2018), Thy4 (Perros *et al.* 2014) and TIR4 (Pacini *et al.* 2018) can also be considered indeterminate, we do not include them in this definition. The RoM of these categories is elevated and significantly higher than that expected for categories B-III and B-IV (Thy3, TIR3) (Perros *et al.* 2014, Gharib *et al.* 2016, Haugen *et al.* 2016, Ali & Cibas 2018, Pacini *et al.* 2018). In addition, the management for category B-V (Thy4, TIR4) differs from that recommended for categories B-III and B-IV (Thy3, TIR3), and is very similar to or even the same as that recommended for category B-VI (Thy5, TIR5) (Gharib *et al.* 2016, Haugen *et al.* 2016, Ali & Cibas 2018, Pacini *et al.* 2018). In the case of B-III cytology (Thy3a, TIR3A), the change of category in a new FNA or after revision by an experienced cytopathologist is common. For this reason, repetition of FNA or revision by an experienced cytopathologist is desirable in category B-III (Thy3a, TIR3A) before additional tests are carried out for the definition of management (Perros *et al.* 2014, Gharib *et al.* 2016, Haugen *et al.* 2016, Ali & Cibas 2018, Pacini *et al.* 2018). Exceptions would be patients with an already defined surgical indication, even if the new result is benign, or individuals for whom observation will be the management, even if cytology remains indeterminate.

The RoM of nodules with indeterminate cytology generally ranges from 10% to 30% for category B-III (Thy3a, TIR3A) and from 15% to 40% for category B-IV (Thy3f, TIR3B) (Perros *et al.* 2014, Gharib *et al.* 2016, Haugen *et al.* 2016, Ali & Cibas 2018, Pacini *et al.* 2018, Giovanella *et al.* 2019). Considering that FNA is indicated correctly, this RoM is too high to recommend the follow-up of all patients without any additional investigation. However, the opposite management, that is, thyroidectomy for all patients will result in many unnecessary surgeries.

Thus, parameters that refine the RoM for these nodules are important. These include imaging methods that are accessible in clinical practice, which are the focus of this review.

Ultrasonography

US should be performed on all individuals with thyroid nodules and the nodules should be categorized using one of the current ultrasonographic classifications. This information is also necessary for the indication of FNA (Perros *et al.* 2014, Gharib *et al.* 2016, Haugen *et al.* 2016, Russ *et al.* 2017, Tessler *et al.* 2017, Pacini *et al.* 2018, Giovanella *et al.* 2019). Thus, in nodules with indeterminate cytology, the use of the already known ultrasonographic category to estimate RoM is an available and simple approach.

US is of value in defining the management of patients with thyroid nodules and indeterminate cytology but its role is not consensual. The British Thyroid Association (BTA) (Perros *et al.* 2014) recommends US in order to rule the need for surgery in patients with B-III cytology (Thy3a). US is also recommended by the American Association of Clinical Endocrinologists (AACE) (Gharib *et al.* 2016) and Italian Societies (Pacini *et al.* 2018) in order to rule out the need for surgery in patients with B-III cytology (TIR3A) and only exceptionally in those with B-IV cytology (TIR3B). The American Thyroid Association (ATA) (Haugen *et al.* 2016) considers US to be of value for the direct indication of surgery in individuals with B-III and B-IV cytology or to rule out its need without molecular tests in those with B-III cytology.

We analyze here the two classifications most used today (ATA (Haugen *et al.* 2016) and Thyroid Imaging Reporting and Data System (TI-RADS) of the American

Table 2 Ultrasonography Classification of the American Thyroid Association (ATA) (Haugen *et al.* 2016) and Thyroid Imaging Reporting and Data System (TI-RADS) of the American College of Radiology (ACR) (Tessler *et al.* 2017).

ATA Classification	TI-RADS of the ACR ^a
High suspicion: Solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of extrathyroidal extension	TR5: Highly suspicious (≥7 points)
Intermediate suspicion: Hypoechoic solid nodule with smooth margins without microcalcifications, extrathyroidal extension, or taller than wide shape	TR4: Moderately suspicious (4 to 6 points)
Low suspicion: Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid areas, without microcalcification, irregular margin or extrathyroidal extension, or taller than wide shape.	TR3: Mildly suspicious (3 points)
Very low suspicion: Spongiform or partially cystic nodules without any of the sonographic features described in low, intermediate or high suspicion patterns	TR2: Not suspicious (2 points)
Benign: Purely cystic nodules (no solid component)	TR1: Benign (0 point)

^aComposition: cystic or almost completely cystic (0 points), spongiform (0 points), mixed cystic and solid (1 point), solid or almost completely solid (2 points); Echogenicity: anechoic (0 points), hyperechoic or isoechoic (1 point), hypoechoic (2 points), very hypoechoic (3 points); Shape: wider-than-tall (0 points), taller-than-wide (3 points); Margin: smooth (0 points), ill-defined (0 points), lobulated or irregular (2 points), extra-thyroidal extension (3 points); Echogenic foci: none or large comet-tail artifacts (0 points), macrocalcifications (1 point), peripheral (rim) calcifications (2 points), punctate echogenic foci (3 points).

College of Radiology (ACR) (Tessler *et al.* 2017)) (Table 2), specifically in nodules with indeterminate cytology. The primary goal is to determine whether nodules with highly suspicious US features (or TI-RADS 5) have a RoM that renders prompt surgical indication acceptable and/or whether nodules with a very low (or TI-RADS 2) or low (TI-RADS 3) ultrasonographic suspicion have a RoM that permits exclusive follow-up of the patient. Thus, additional investigation using more expensive and less accessible methods would be reserved for patients whose clinical, ultrasonographic and cytological data were not sufficient for the definition of management. When molecular tests are easily available, the role of US is less decisive but this method is still important for estimating the pre-test RoM, which influences the negative (NPV) and positive predictive values (PPV) of molecular tests.

In the largest retrospective study that investigated TI-RADS ACR in nodules with indeterminate cytology, Yoo *et al.* (2020) evaluated 382 nodules with B-III cytology that were subsequently submitted to core needle biopsy (CNB). Final diagnoses of malignancy were confirmed surgically, whereas final diagnoses of benign nodules were determined by surgery or absence of malignancy assessed by CNB and decreased or stable nodule size on US follow-up more than 12 months after initial FNA. The RoM was 8.3%, 14.1%, 32.2% and 67.4% for TI-RADS categories 2 ($n=12$), 3 ($n=92$), 4 ($n=152$) and 5 ($n=126$), respectively. Three other studies analyzed TI-RADS ACR in a reasonable number of nodules with indeterminate cytology that were removed surgically (104 B-III and 29 B-IV (Sahli *et al.* 2019), 103 B-III and 99 B-IV (Ahmadi *et al.*

2019), and 167 B-III (Al Dawish *et al.* 2020)). In general, these studies showed a RoM $\geq 50\%$ for TI-RADS 5 nodules, approximately 25% to 35% for TI-RADS 4 nodules, and 10% to 35 for TI-RADS 3 nodules. The RoM was higher for those with B-IV cytology (Ahmadi *et al.* 2019) and when NIFTP was considered malignant (Sahli *et al.* 2019). As expected, the number of TI-RADS 2 nodules was small, but the RoM was 12.5% (4/32) when the data of the three studies were pooled.

Three studies, although retrospective, evaluated the ATA classification in a large number of nodules with indeterminate cytology. In the first study, Valderrabano *et al.* (2018) analyzed ultrasound images of 463 thyroid nodules (38% B-III and 62% B-IV) with histological follow-up. Images of all thyroid ultrasounds were independently revised by three observers. Considering NIFTP as malignant, the RoM ranged from 0% to 5% for very-low-suspicion nodules, from 20% to 27% for low-suspicion nodules, from 14% to 21% for intermediate-suspicion nodules, and from 43% to 51% for high-suspicion nodules. Considering NIFTP as benign, the differences were even smaller, ranging from 0% to 5% for very-low-suspicion nodules, from 10% to 12% for low-suspicion nodules, from 8% to 14% for intermediate-suspicion nodules, and from 29% to 41% for high-suspicion nodules. In the second study, Hong and Lee (2019) analyzed 683 nodules that had B-III cytology after the initial FNA. Nodules were included if they had undergone surgery ($n=421$), had benign or malignant pathological results on CNB ($n=35$), had benign cytology results from more than two FNAs ($n=177$), or had US

follow-up for at least 2 years with a decrease in size and subsequent benign cytology findings ($n=50$). The RoM of nodules with a very low-, low- intermediate- and high-suspicion US pattern was 0%, 3.3%, 33.54% and 87.67%, respectively. Finally, in the study of [Yoo *et al.* \(2020\)](#) described previously and involving 382 nodules with B-III cytology, the RoM for the low-, intermediate- and high-suspicion US categories was 16.3%, 36.4% and 66.1%, respectively.

Some aspects need to be addressed when estimating the RoM of nodules with indeterminate cytology based on US. First, clinical data and cytology findings (whether B-IV or B-III, nature of the atypias in the latter) can modify the estimated RoM for a given ultrasonographic category ([Rosario 2014](#), [Ahmadi *et al.* 2019](#), [Barbosa *et al.* 2019](#), [Yoo *et al.* 2020](#)).

Second, studies that evaluate the performance of US include only the subgroup of patients who are submitted to surgery or CNB. It is expected that highly suspicious nodules (or TI-RADS 5) are almost always referred for surgery and the reported RoM should therefore be close to the true risk. However, it is possible that nodules with a very-low/low-suspicion US pattern (or TI-RADS 2 or 3) are referred for surgery when other data are worrisome and the reported RoM may therefore be overestimated. To accurately assess the RoM based on US findings, we conducted a prospective study in which all euthyroid patients with nodules > 1 cm with an indication for FNA and indeterminate cytology, who were consecutively seen over a given period, were submitted to surgery. Considering NIFTP/TUMP as malignant, the RoM was 10% for the very low, 13% for the low, 42.8% for the intermediate, and 80% for the high-suspicion categories ([Rocha *et al.* 2018](#)). Using TI-RADS ACR, the RoM was 0% for TI-RADS 2, 14.3% for TI-RADS 3, 38.8% for TI-RADS 4, and 90% for TI-RADS 5 ([Rocha *et al.* 2019](#)). Considering NIFTP/TUMP as benign, the RoM was 0% for the very low, 4.3% for the low, 22.4% for the intermediate, and 72% for the high-suspicion categories ([Rocha *et al.* 2018](#)). Using TI-RADS ACR, the RoM was 0% for TI-RADS 2, 4% para TI-RADS 3, 22.4% for TIRADS 4, and 80% para TI-RADS 5 ([Rocha *et al.* 2019](#)).

Third, recently, tumors considered malignant were reclassified as borderline and these tumors more frequently exhibit indeterminate cytology in FNA ([Rosario *et al.* 2016, 2019](#)). It is therefore important to know whether the RoM considered refers only to malignant tumors or whether it includes borderline tumors and, if so, what is the contribution of the latter. A significant difference is observed especially in nodules with low or intermediate

suspicion by ATA or TI-RADS 3 or 4 ([Rosario *et al.* 2016](#), [Rocha *et al.* 2018, 2019](#), [Valderrabano *et al.* 2018](#), [Rosario & Mourão 2019](#), [Sahli *et al.* 2019](#)). We reported the RoM considering NIFTP to be either benign or malignant because some authors define NIFTP as malignant. However, we believe that the RoM should not include NIFTP.

Fourth, a proportion of thyroid nodules do not meet any of the categories of the ATA classification. In these nodules not classified by ATA and whose cytology was indeterminate, [Valderrabano *et al.* \(2018\)](#) found a RoM of 29% to 41% considering NIFTP as malignant and of 20% to 21% considering NIFTP as benign. In the study of [Yoo *et al.* \(2020\)](#), the RoM was 30%. Finally, in our prospective study the RoM was 23% considering NIFTP/TUMP as malignant and 15.4% considering NIFTP/TUMP as benign ([Rocha *et al.* 2018](#)). Using TI-RADS, all nodules with indeterminate cytology are classified.

Scintigraphy with ^{123}I or $^{99\text{m}}\text{Tc}$

There is consensus that autonomous nodules have a low RoM ([Perros *et al.* 2014](#), [Gharib *et al.* 2016](#), [Haugen *et al.* 2016](#), [Russ *et al.* 2017](#), [Pacini *et al.* 2018](#), [Hoang *et al.* 2019](#), [Giovannella *et al.* 2019](#)). Scintigraphy with ^{123}I or $^{99\text{m}}\text{Tc}$ might be indicated for individuals with thyroid nodules in three situations. This method is recommended in patients with low TSH ([Perros *et al.* 2014](#), [Gharib *et al.* 2016](#), [Haugen *et al.* 2016](#), [Russ *et al.* 2017](#), [Pacini *et al.* 2018](#), [Hoang *et al.* 2019](#), [Giovannella *et al.* 2019](#)), even if they are asymptomatic and have normal free T4 and T3 concentrations. Many authors even recommend this method in euthyroid individuals with TSH in the lower half of the reference range, especially in iodine-deficient regions ([Gharib *et al.* 2016](#), [Russ *et al.* 2017](#), [Giovannella *et al.* 2019](#)). With this management, it is believed that part of the nodules with an indication for FNA based on US may not require this procedure because scintigraphy reveals hyperuptake ([Schenke *et al.* 2019](#), [Castellana *et al.* 2020](#), [Noto *et al.* 2020](#)). Finally, the indication that interests us here are euthyroid patients with nodules > 1 cm whose cytology was indeterminate.

In the last situation, the AACE ([Gharib *et al.* 2016](#)) recognizes the value of scintigraphy in iodine-deficient regions and when the TSH level is low-normal (e.g. 0.5–1.0 mIU/L). The European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) ([Giovannella *et al.* 2019](#)) recommend that, to identify a benign autonomously

functioning thyroid nodule (including ‘compensated’ ones), it is reasonable to first perform thyroid scintigraphy (if not previously obtained), particularly if TSH is in the lower end of the normal range (e.g. less than 1.5 mIU/L) and to select only patients with nonfunctioning nodules for molecular testing, molecular imaging, or diagnostic lobectomy.

In a prospective study on 77 euthyroid patients with nodules > 1 cm without highly suspicious US features and with cytology suggesting ‘follicular neoplasm’, radioiodine scintigraphy revealed hyperuptake in the topography of the nodule in 36 patients (46.5%) and none of these nodules was malignant (Rosario *et al.* 2010). Another prospective study evaluated 78 euthyroid patients with 84 nodules > 1 cm with indeterminate cytology that were not very suspicious on US (Rosario *et al.* 2018). Hyperuptake of ^{123}I in the area corresponding to the nodule was detected in 19 patients (24%) and 21 nodules (25%). Of these, 20 were benign and there was one borderline tumor.

However, the probability of scintigraphy showing that hyperuptake in the nodule is inversely correlated with TSH concentrations, which is unlikely in patients with TSH > 2 mIU/L, is much higher in those with TSH < 1 mIU/L (Rosario *et al.* 2018). The relationship between RoM and serum TSH in euthyroid individuals with cytologically indeterminate nodules corroborates this observation. A recent study showed that among 378 euthyroid patients the RoM was 9.8% for TIR3A nodules and 27.3% for TIR3B nodules (Cappelli *et al.* 2020). However, in the subgroup with TSH in the lower quartile (0.4–1.42 mIU/L), the RoM was significantly lower, 5.9% for TIR3A and 12% for TIR3B (Cappelli *et al.* 2020), possibly reflecting a higher probability of the nodules being autonomous in this TSH quartile.

18F-fluorodeoxyglucose positron emission tomography

The EANM and SNMI (Giovannella *et al.* 2019) recommend molecular thyroid imaging using ^{18}F FDG. A nodule characterized by low or absent ^{18}F FDG uptake is considered at a very low RoM. According to these societies, the high NPV of thyroid imaging with ^{18}F FDG is very helpful in characterizing nodules with indeterminate cytological results.

The EANM and SNMI (Giovannella *et al.* 2019) consider that any focal uptake above normal thyroid parenchyma, corresponding to the nodule with cytological indeterminate results, is considered as positive.

Thus, the sensitivity of ^{18}F FDG-PET in identifying malignant tumors > 1 cm is high (Kresnik *et al.* 2003, Kim *et al.* 2007, Sebastianes *et al.* 2007, Traugott *et al.* 2010, Muñoz Pérez *et al.* 2013, Buyukdereli *et al.* 2016, Pathak *et al.* 2016, Piccardo *et al.* 2016, Rosario *et al.* 2019, Piccardo *et al.* 2020).

As observed for molecular tests, the pre-test RoM can influence the NPV of ^{18}F FDG-PET. In this regard, US can be important. In the study of Deandreis *et al.* (2012), among 26 nodules without ^{18}F FDG uptake, 0/21 benign or only suspicious on US vs 2/5 malignant on US were cancer. Considering TUMP/cancer, there were 2/21 vs 3/5, respectively. In the series of Merten *et al.* (2017), among 20 ^{18}F FDG-negative nodules, 1/16 with a very-low-, low- or intermediate-suspicion US pattern vs 1/4 highly suspicious nodules were cancer. In another prospective study that intentionally excluded nodules with highly suspicious US features, of the 32 ^{18}F FDG-negative nodules, 30 were benign (93.8%), 2 were NIFTP/TUMP (6.2%), and none was cancer (Rosario *et al.* 2019). Thus, when the clinical, ultrasonographic and cytological data do not suggest a very high RoM, the absence of nodular uptake on ^{18}F FDG-PET has a sufficient NPV for macrocarcinoma to rule out the need for surgery.

Some factors influence the specificity of ^{18}F FDG-PET, which is higher when the maximum SUV is > 5 (Kresnik *et al.* 2003, Mitchell *et al.* 2005, de Geus-Oei *et al.* 2006, Kim *et al.* 2007, Sebastianes *et al.* 2007, Smith *et al.* 2008, Traugott *et al.* 2010, Deandreis *et al.* 2012, Muñoz Pérez *et al.* 2013, Pathak *et al.* 2016, Merten *et al.* 2017, Nguyen *et al.* 2018, Rosario *et al.* 2019, Piccardo *et al.* 2020) and lower in nodules with cytology with predominance of oxyphilic cells or suspicious for Hürthle cells neoplasm (Kresnik *et al.* 2003, de Geus-Oei *et al.* 2006, Deandreis *et al.* 2012, Muñoz Pérez *et al.* 2013, Pathak *et al.* 2016). Depending on the clinical context (considering pre-test RoM and maximum SUV) and availability of molecular tests, a positive ^{18}F FDG-PET scan does not necessarily represent an indication for surgery. The patient can still be submitted to molecular tests and thyroidectomy can be excluded if these tests suggest benignity.

Other accessible imaging methods

Although assessment of vascularization of the nodule is recommended, using US/Doppler, the ATA classification (Haugen *et al.* 2016) or TI-RADS (Russ *et al.* 2017, Tessler *et al.* 2017) does not consider this parameter in the definition of the level of suspicion for malignancy.

Table 3 Main advantages and limitations of the most accessible and useful imaging methods for thyroid nodules > 1 cm with indeterminate cytology.

Imaging method	Advantages	Limitations
Ultrasonography	Wide availability, low cost, extensively studied, permits to obtain additional features of the nodule (Doppler, elastography), good predictive value for the extreme categories of suspicion of malignancy	Dependence on operator, contributes little to the category of intermediate suspicion of malignancy
Scintigraphy with ¹²³ I or ^{99m} Tc	Easy accessibility, affordable cost, high negative predictive value for hyperuptake in the topography of the nodule	Probability of revealing nodular hyperuptake is inversely correlated with serum TSH, which is unlikely if TSH > 1.5–2 mIU/L; ‘inconclusive’ results are not uncommon; low positive predictive value for nodular hypouptake
¹⁸ FDG-PET	More accessible and less expensive than high-performance molecular tests, high negative predictive value for the absence of ¹⁸ FDG uptake in the topography of the nodule	High cost, low positive predictive value (except for non-Hürthle cell cytology and high SUVmax)

Analyzed separately, the vascularization pattern seems to be of value for defining the benign or malignant nature of nodules with indeterminate cytology (Iared *et al.* 2010), but there is little information about the frequency at which Doppler diverges from US (B-mode) in terms of the suspicion for malignancy and if the RoM estimated by US is indeed modified by the Doppler result in these cases. Regarding this additional value, a prospective study specifically investigating nodules with indeterminate cytology showed a modest increase in the sensitivity of the ATA ultrasonographic classification with the addition of Doppler to US (B-mode) (Rocha *et al.* 2018).

The elasticity of the nodule (elastography) has also been studied. Elastography has many limitations and cannot reliably be applied to large nodules (> 3 cm), nodules with macrocalcifications, cystic, deeply located and/or isthmic nodules, nodules located near the carotid artery, or coalescent nodules (Russ *et al.* 2017). The capacity of elastography to define the nature of nodules with indeterminate cytology is controversial (Trimboli *et al.* 2015, Bardet *et al.* 2017). Rather than its individual value, it is more important to know the frequency at which elastography reveals a level of suspicion for malignancy that differs from that estimated by US (B-mode) and to what extent this level is modified by elastography. Regarding this additional value of elastography specifically in nodules with indeterminate cytology, the results are not uniform (Trimboli *et al.* 2015, Cantisani *et al.* 2016, Bardet *et al.* 2017, Azizi *et al.* 2018, Gay *et al.* 2018, Liu *et al.* 2018, Ríos *et al.* 2018). If obtained, elevated stiffness on elastography is considered a suspicious finding for malignancy but it must be remembered that readings may be low in non-papillary thyroid carcinomas.

There is currently no recommendation for the use of CT or MRI in nodules with indeterminate cytology in

order to define their nature (Hoang *et al.* 2019). These methods can be useful if there is a gross invasion or metastatic disease, if the nodule is part of a goiter that is suspected to extend substernally, or in the case of a suspicion of invasive thyroid cancer (Hoang *et al.* 2019).

The EANM and SNMI (Giovannella *et al.* 2019) consider molecular thyroid imaging using ^{99m}Tc-MIBI of value but this method (i) requires semiquantitative evaluation (using retention index, washout index) to optimize its sensitivity (Saggiorato *et al.* 2009, Campenni *et al.* 2016, Giovannella *et al.* 2016, 2019), (ii) possesses few studies that include a considerable number of patients specifically with nodules with indeterminate cytology (Campenni *et al.* 2016, Giovannella *et al.* 2016, Piccardo *et al.* 2016), and (iii) exhibited lower sensitivity and NPV than ¹⁸FDG-PET in the only direct comparative study (Piccardo *et al.* 2016).

Table 3 shows the main advantages and limitations of accessible imaging methods that are apparently more useful for the definition of the nature of TN > 1 cm with indeterminate cytology.

Conclusions

Regarding the usefulness of accessible imaging methods in euthyroid individuals with nodules > 1 cm with an indication of FNA and indeterminate cytology (B-III (Thy3a, TIR3A) or B-IV (Thy3f, TIR3B)), we conclude that:

- In the case of nodules with a high suspicion US pattern (or TI-RADS 5), the RoM supports surgical indication even in the absence of additional tests. The same applies to nodules with an intermediate suspicion (or TI-RADS 4) but elevated stiffness on elastography (if obtained).

- In nodules with low-risk indeterminate cytology and low-suspicion appearance (or TI-RADS ≤ 3) on US and elastography (if obtained), follow-up is acceptable even without additional tests. Although less consistent, this recommendation may be valid for nodules with high-risk indeterminate cytology (TIR 3B) and with a very-low-suspicion appearance (or TI-RADS 2) on US and elastography (if obtained).
- In patients with TSH $< 1\text{--}1.5$ mIU/L and nodules without a highly suspicious US pattern (or TI-RADS 5), scintigraphy with ^{123}I can be obtained to rule out hyperfunctioning nodules before requesting diagnostic methods that are more expensive and less accessible.
- In the case of nodules that are not very suspicious on US, ^{18}F FDG-PET can be obtained and, if it does not reveal nodular uptake, the risk of the nodule corresponding to a macrocarcinoma is sufficiently low to allow follow-up. The PPV of focal nodular uptake on ^{18}F FDG-PET depends on the pre-test RoM, cytological findings, and maximum SUV.
- There is currently no evidence for the use of CT, MRI or thyroid imaging using $^{99\text{m}}\text{Tc}$ -MIBI to define the nature of cytologically indeterminate nodules.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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