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EXPERT REVIEW

A multicenter survey of current practices of ^{99m}Tc-methoxy-isobutyl-isonitrile (MIBI) imaging for the diagnosis of thyroid nodules: more standardization is essential

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Abstract

Purpose Molecular imaging with ^{99m}Tc-methoxy-isobutyl-isonitrile (^{99m}Tc-MIBI, MIBI) has been used in the assessment of thyroid nodules (TNs) for more than two decades. Many studies showed that MIBI imaging is a suitable tool to rule-out malignancy when negative. However, relatively low specificity and accuracy have been described, thus, limiting its acceptance in clinical practice. Additionally, different technologies, protocols, and interpretation criteria are adopted accounting for heterogeneous data reported in the literature. Therefore, the present study was undertaken to assess the clinical use and methodology of MIBI imaging in patients with nodular thyroid disease in Europe.

Methods A questionnaire was sent to 12 European centers of Nuclear Medicine. The questionnaire encompassed ultrasound (US) and fine-needle aspiration cytology (FNAC) procedures and their evaluation as well scintigraphy imaging indications, technical procedures, and interpretation criteria of MIBI imaging.

Results The survey showed a good agreement of different centers in approaching TNs by TSH measurement, US evaluation and ^{99m}Tc-pertechnetate thyroid scintigraphy. MIBI imaging is mainly used to assess TNs with inconclusive/indeterminate cytological findings and selection of target nodule(s) for FNAC in patients with multi-nodular goiter. Technical procedures adopted in different centers are globally comparable and the recorded differences are unlikely to impact clinical results. However, as the main result of the present study, substantial differences were found in interpretation criteria adopted in different centers.

Conclusions Our survey supports the urgent need of standardized interpretation criteria of thyroid MIBI imaging in order to improve its diagnostic performance and make results comparable in clinical practice.

Keywords Thyroid · Nodule · Ultrasound · Cytology · Scintigraphy · ^{99m}Tc-methoxy-isobutyl-isonitrile

Introduction

Because of the widespread use of ultrasound (US) thyroid nodules (TNs) are a common finding, especially in currently and previously iodine-deficient countries. Although the majority of TNs are benign, non-autonomous TNs on ^{99m}Tc-pertechnetate or ^{123}I scintigraphy may need further diagnostic work-up to exclude thyroid cancer [1, 2]. Depending on the detection of suspicious US features by using risk stratification systems (TIRADS) and the size of the nodule, fine-needle aspiration cytology (FNAC) represents the next step in this diagnostic algorithm [2–4]. However, in 25–40% the FNAC, results can be indeterminate or non-diagnostic [5]. Moreover, FNAC can be challenging in patients with multinodular goiter or nodules in an unfavorable location (i.e. below the thoracic aperture), and should not be performed on patients on anticoagulant therapy [6]. Molecular imaging with ^{99m}Tc-methoxy-isobutyl-isonitrile (^{99m}Tc-MIBI, MIBI) has been used in the assessment of TNs for more than two decades [7–9]. MIBI is a lipophilic cation and member of the isonitrile family. It accumulates within the mitochondria, which have a high negative transmembrane potential. Thus, MIBI uptake is related to high mitochondria

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Table 1 Survey questionnaire

Items	Question/request
1	Imaging equipment (ultrasound devices and gamma-cameras), type, manufacturer, country
2	Thyroid ultrasound interpretation criteria
3	Indications for thyroid scintigraphy (^{99m}Tc-pertechnetate)
4	Indications for FNAC and cytology reporting
5	Indications for ^{99m}Tc-MIBI thyroid imaging
6	^{99m}Tc-MIBI imaging protocols 1 (MIBI activities, timing of planar images, use of SPECT(-CT)
7	^{99m}Tc-MIBI imaging protocols 2 (acquisition parameters)
8	^{99m}Tc-MIBI imaging: interpretation criteria

FNAC fine-needle aspiration cytology, *SPECT* single-photon emission computed tomography, *CT* computed tomography

content and increased vascularity, which are commonly seen in lung and thyroid malignant tumors as well as parathyroid adenomas [10–12]. Many studies showed that a MIBI negative TN has a high probability of being a benign lesion [10, 13–15], thus, making MIBI imaging a suitable tool to rule-out malignancy. On the other hand, relatively low specificity and accuracy have been described [6–8]. Selecting hypofunctioning nodules for MIBI imaging increases the overall accuracy, as hyperfunctioning nodules are commonly benign but MIBI positive due to an increased vascularization and higher proliferation rate of hyperfunctioning follicular cells. Even in hypofunctioning nodules, however, different technologies (i.e., planar and SPECT images), injected activities, protocols, and image interpretation criteria account for heterogeneous results reported in the literature [7]. Therefore, the present study was undertaken to assess the clinical use and methodology of MIBI imaging in patients with nodular thyroid disease in Europe.

Materials and methods

The study was approved by the ethics committee of Magdeburg University Hospital (No. RAD 378-32/20) and the need for informed consent was waived. Firstly, 12 nuclear medicine centers offering complete clinical management of thyroid patients (i.e., including US and FNAC in addition to nuclear imaging and therapy) agreed to participate in the present study during the EANM Thyroid Committee Interesting Group meeting (Düsseldorf 2018).

A questionnaire (Table 1) was sent to these centers in December 2018. The questionnaire encompassed US and FNAC procedures and their evaluation as well as thyroid MIBI imaging indications, technical procedures, and interpretation criteria. The survey was carried out from

Table 2 Thyroid ultrasound devices and gamma-cameras used in the different study centers

Study site	Scintigraphy gammacamera, type, country	Thyroid ultrasound device, type, country
Rijeka, Croatia	Siemens-Symbia T, Siemens, Germany	Aloka Prosound Alpha 6, 5–10 MHz linear probe, Aloka Co.,LTD, Japan
Hacettepe, Turkey	Optima NM/CT 640, General Electric (GE), USA	Logic P9, 3.6–12 MHz Linear Probe, General Electric (GE), USA
Bellinzona, Switzerland	Symbia, Siemens, Germany	Siemens Acuson3000, Germany
Messina, Italy	Brightview-X, Philips, Cleveland, OH	Logiq3 Expert (GE Healthcare, Little Chalfont, United Kingdom), 7.5–10 MHz linear probe
Giessen, Germany	Mediso Nucline Spirit, DH-V, Mediso, Germany	Hitachi EUB 500, 5–10 MHz linear probe, Hitachi, Japan
Genoa, Italy	Millenium, GE Medical Systems, Milwaukee	LOGIQ S8 General Electric Medical Systems, Milwaukee,
Istanbul, Turkey	Mediso Nucline Spirit, DH-V,Mediso, Hungary	GE Healthcare, Logiq 9, M12L linear probe modular frequency (5–13 MHz), GE Ultrasound
Mostar, Bosnia and Herzegovina	Mediso, AnyScan S, Hungary	GE Healthcare, Logiq P6 PRO, linear probe modular frequency (10 MHz), GE Ultrasound, South Korea
Duisburg, Germany	Up to 11/2018: Axis or Forte JETStream, Philips, since 12/2018: E.CAM /Scintron, MIE, Germany	(a) DC-6, Small part tansducer 7L6, 10 MHz, Mindray, China (b) MyLab 40, Small part transducer LA523, 12 MHz, Esaote, Italy
Mersin, Turkey	Siemens-Symbia E, Siemens, Germany	Siemens Acuson X150, Siemens, Germany
Frankfurt, Germany	Mediso, TH22, Hungary	(a) Siemens Acuson S1000, Germany, 18L6HD, 6–13 MHz linear probe (b) Sonix TOUCH, Ultrasonix, Kanada, 5–14 MHz linear probe
Düsseldorf, Germany	Gaede Medizinsystem, Schilddrüsen Gammakamera, GKS-1, Germany	Xario Prime Ultrasound, 5–12 MHz probe, Toshiba Medical Systems GmbH, Germany

Table 3 Indications for ^{99m}Tc-pertechnetate thyroid scintigraphy

Study site	Indications for ^{99m}Tc-pertechnetate scintigraphy
Rijeka, Croatia	Every TN size 10 mm or larger with TSH ≤ 0.55 mIU//L
Hacettepe, Turkey	Every TN size 10 mm or larger with TSH ≤ 0.50 mIU//L
Bellinzona, Switzerland	Every TN size 10 mm or larger with TSH ≤ 2.50 mIU//L
Messina, Italy	Every TN size 10 mm or larger with TSH ≤ 3.00 mIU//L
Giessen, Germany	Every TN size 10 mm or larger regardless of the TSH
Genoa, Italy	Every TN size 10 mm or larger with TSH ≤ 1.00 mIU//L
Istanbul, Turkey	Every TN size 10 mm or larger with TSH ≤ 0.50 mIU//L
Mostar, Bosnia and Herzegovina	Every TN size 10 mm or larger with TSH ≤ 0.50 mIU//L
Duisburg, Germany	Every TN size 10 mm or larger regardless of the TSH
Mersin,Turkey	Every TN size 10 mm or larger with TSH ≤ 0.50 mIU//L
Frankfurt, Germany	Every TN size 10 mm or larger regardless of the TSH
Düsseldorf, Germany	Every TN size 10 mm or larger regardless of the TSH

TN thyroid nodule, *TSH* thyroid-stimulating hormone

Table 4 Thyroid ultrasound interpretation criteria

Study site	US reporting system	
Rijeka, Croatia	EU-TIRADS	High-risk features: non-oval/round shape, irregular margin, microcalcifications, marked hypoechogenic (and solid); Risk of malignancy: EU-TIRADS 2 (0%), EU-TIRADS 3 (2–4%), EU-TIRADS 4 (6–17%), EU-TIRADS 5 (26–87%) [16]
Hacettepe, Turkey	EU-TIRADS	High-risk features: non-oval/round shape, irregular margin, microcalcifications, marked hypoechogenic (and solid); Risk of malignancy: EU-TIRADS 2 (0%), EU-TIRADS 3 (2–4%), EU-TIRADS 4 (6–17%), EU-TIRADS 5 (26–87%) [16]
Bellinzona, Switzerland	EU-TIRADS	High-risk features: non-oval/round shape, irregular margin, microcalcifications, marked hypoechogenic (and solid); Risk of malignancy: EU-TIRADS 2 (0%), EU-TIRADS 3 (2–4%), EU-TIRADS 4 (6–17%), EU-TIRADS 5 (26–87%) [16]
Messina, Italy	EU-TIRADS	High-risk features: non-oval/round shape, irregular margin, microcalcifications, marked hypoechogenic (and solid); Risk of malignancy: EU-TIRADS 2 (0%), EU-TIRADS 3 (2–4%), EU-TIRADS 4 (6–17%), EU-TIRADS 5 (26–87%) [16]
Giessen, Germany	Kwak-TIRADS	Five suspicious features: solid, (marked) hypoechogenic, irregular margin, microcalcifications, taller-than-wide shape; TIRADS 3: no features (risk of malignancy 1.7%); TIRADS 4A: one feature (3.3%), TIRADS 4B: two features (9.2%), TIRADS 4C: three/four features (44.4–72.4%), TIRADS 5: five features (87.5%) [17]
Genoa, Italy	EU-TIRADS	High-risk features: non-oval/round shape, irregular margin, microcalcifications, marked hypoechogenic (and solid); Risk of malignancy: EU-TIRADS 2 (0%), EU-TIRADS 3 (2–4%), EU-TIRADS 4 (6–17%), EU-TIRADS 5 (26–87%) [16]
Istanbul, Turkey	EU-TIRADS	High-risk features: non-oval/round shape, irregular margin, microcalcifications, marked hypoechogenic (and solid); Risk of malignancy: EU-TIRADS 2 (0%), EU-TIRADS 3 (2–4%), EU-TIRADS 4 (6–17%), EU-TIRADS 5 (26–87%) [16]
Mostar, Bosnia and Herzegovina	EU-TIRADS	High-risk features: non-oval/round shape, irregular margin, microcalcifications, marked hypoechogenic (and solid)); Risk of malignancy: EU-TIRADS 2 (0%), EU-TIRADS 3 (2–4%), EU-TIRADS 4 (6–17%), EU-TIRADS 5 (26–87%) [16]
Duisburg, Germany	Kwak-TIRADS	Five suspicious features: solid, (marked) hypoechogenic, irregular margin, microcalcifications, taller-than-wide shape; TIRADS 3: no features (risk of malignancy 1.7%); TIRADS 4A: one feature (3.3%), TIRADS 4B: two features (9.2%), TIRADS 4C: three/four features (44.4–72.4%), TIRADS 5: five features (87.5%) [17]
Mersin,Turkey	EU-TIRADS	High-risk features: non-oval/round shape, irregular margin, microcalcifications, marked hypoechogenic (and solid)); Risk of malignancy: EU-TIRADS 2 (0%), EU-TIRADS 3 (2–4%), EU-TIRADS 4 (6–17%), EU-TIRADS 5 (26–87%) [16]
Frankfurt, Germany	ACR-TIRADS	Five categories (composition, echogenicity, shape, margin, echogenic foci) point-based descriptors; TR2 (1.5%), TR3 (4.8%), TR4 (5.9–12.8%), TR5 (20.8–68.4%) [3]
Düsseldorf, Germany	Descriptive	Echogenicity, intranodular composition, node margins, calcifications

TIRADS thyroid imaging reporting and data system, *EU* European, *ACR* American College of Radiology

Table 5 Indications for FNAC and cytology reporting systems

Study site	Criteria	FNAC criteria	Cytology reporting
Rijeka, Croatia	EU-TIRADS	EU-TIRADS 4 and 5 any size EU-TIRADS 3 > 2 cm	Bethesda system
Hacettepe, Turkey	EU-TIRADS	EU-TIRADS 5 > 1 cm EU-TIRADS 4 > 1.5 cm EU-TIRADS 3 > 2 cm	Bethesda system
Bellinzona, Switzerland	EU-TIRADS	EU-TIRADS 4 and 5 > 1 cm EU-TIRADS 3 > 2 cm	SIAPEC-IAP
Messina, Italy	EU-TIRADS	EU-TIRADS 4 and 5 EU-TIRADS 3 ≥ 1.5 cm	SIAPEC-IAP
Giessen, Germany	Kwak-TIRADS	Hypofunctioning TN ≥ 10 mm at intermediate or high risk	Bethesda classification (German version)
Genoa, Italy	EU-TIRADS	EUTIRADS 4 > 1.5 cm EUTIRADS 5 > 1 cm EUTIRADS 3 > 2 cm	SIAPEC-IAP
Istanbul, Turkey	EU-TIRADS	EU-TIRADS 4 and 5 any size EU-TIRADS 3 > 2 cm	Bethesda system
Mostar, Bosnia and Herzegovina	EU-TIRADS	EU-TIRADS 5 any size EU-TIRADS 4 > 1.5 cm EU-TIRADS 3 > 2 cm	Bethesda system
Duisburg, Germany	99mTc-pertechnetate scintigraphy	Scintigraphically non-autonomous nodules with substantial solid component	Bethesda system (German version)
Mersin,Turkey	EU-TIRADS	EU-TIRADS 4 and 5 EU-TIRADS 3 > 2 cm	SIAPEC-IAP
Frankfurt, Germany	ACR-TIRADS	ACR-TIRADS 3 ≥ 2.5 cm ACR-TIRADS 4 ≥ 1.5 cm ACR-TIRADS 5 ≥ 1.0 cm Highly suspicious nodules < 1 cm	UK RCPath
Düsseldorf, Germany	99mTc-pertechnetate scintigraphy	Hypofunctioning TN	Bethesda system

TIRADS thyroid imaging reporting and data system, *EU* European, *ACR* American College of Radiology, *SIAPEC-IAP* Società Italiana Anatomia Patologica e Citopatologia-International Association of Pathology, *UK RCPath* United Kingdom Royal College of Pathologists

December 2019 until December 2020. The responses were collected by the coordinators (SAS, LG) and summarized in Tables 2, 3, 4, 5, 6, 7, 8, 9. To allow comparison, the collected qualitative/descriptive data were merged into new categories.

Results

Technical instrumentations available in the different study centers are listed in Table 2.

Initial approach in patients with thyroid nodules

Patients with TNs first underwent TSH measurement and neck US in all centers. Then, a ^{99m}Tc-pertechnetate scintigraphy was performed for nodules with a maximum diameter ≥ 10 mm and different TSH levels (any value in four centers, values from 0.50 to 3.0 mUI/L in others) (Table 3). Hyperfunctioning nodules were excluded from FNAC, while the management of hypofunctioning nodules and those not evaluated by ^{99m}Tc-pertechnetate scintigraphy (i.e., TSH above the local threshold) is centered on neck US to stratify the risk of malignancy and yardstick for additional FNAC. Among 12 participating centers, 11 (92%) use TIRADS (EU-TIRADS: eight, Kwak-TIRADS: two, ACR-TIRADS: one) for stratifying the risk of malignancy, while a descriptive report is provided by one (8%), center, respectively (Table 4). In two centers, hypofunctioning nodules larger than 10 mm underwent FNAC, one for nodules at intermediate or high risk; the other centers applied TIRADS criteria, combined with nodule's size, for stratification. In general, FNAC is not used in nodules with a low-risk TIRADS score. Intermediate-risk nodules underwent FNAC when larger than 20 mm. Finally, high-risk nodules underwent FNAC in all cases, with some differences for nodules < 10 mm where FNAC and wait-and-see strategy are applied in different centers.

Table 6 Indications for ^{99m}Tc-MIBI thyroid scintigraphy

Study site	Indications for ^{99m}Tc-sestaMIBI scintigraphy
Rijeka, Croatia	Repeated Bethesda I-nondiagnostic Bethesda III-Atypia of undetermined significance/follicular lesion of undetermined significance Multinodular goiters (hypofunctioning nodules)
Hacettepe, Turkey	Cytologically indeterminate hypofunctioning nodules (Bethesda, AUS/ FLUS)
Bellinzona, Switzerland	Non-diagnostic cytology (SIAPEC-IAP: TIR1, except TIR1C, cystic) Cytologically indeterminate hypofunctioning nodules (SIAPEC-IAP: TIR3B) Multinodular goiters (hypofunctioning nodules)
Messina, Italy	Cytologically indeterminate hypofunctioning nodules (SIAPEC-IAP: TIR3 A and B) Cytologically suspicious hypofunctioning nodules (SIAPEC-IAP: TIR4) Multinodular goiters (hypofunctioning nodules)
Giessen, Germany	Hypofunctioning thyroid nodules if FNAC is not applicable
Genoa, Italy	Cytologically indeterminate hypofunctioning nodules (SIAPEC-IAP: TIR3A and TIR3B)
Istanbul, Turkey	Cytologically indeterminate hypofunctioning nodules Multinodular goiters (hypofunctioning nodules)
Mostar, Bosnia and Herzegovina	Hypofunctioning nodules with indeterminate cytology results (suspected follicular neoplasm, follicular proliferation w/ and wo/ atypia). Bethesda III and suspected IV
Duisburg, Germany	Scintigraphically hypofunctioning nodules with a substantial solid component, If patient refuses FNAC If FNAC is contraindicated (e.g., while taking anticoagulants, in case of hemorrhagic diathesis) In difficult anatomical conditions for FNAC In the case of multinodularity In case of a previous FNAC with an equivocal result
Mersin,Turkey	Cytologically indeterminate hypofunctioning nodules (SIAPEC-IAP: TIR3B) Multinodular goiters (hypofunctioning nodules)
Frankfurt, Germany	Cytologically indeterminate hypofunctioning nodules (Thy 3) Multinodular goiters (hypofunctioning nodules)
Düsseldorf, Germany	Hypofunctioning nodule in ^{99m}Tc-pertechnetate scan (in parallel to FNAC)

AUS/FLUS Atypia of Uncertain Significance/Follicular Lesion of Uncertain Significance, *SIAPEC-IAP* Società Italiana Anatomia Patologica e Citopatologia-International Association of Pathology, *FNAC* fine-needle aspiration cytology

Fine-needle aspiration cytology and cytopathology reporting

Cytopathology findings are reported using the Bethesda ($n=5$), SIAPEC-IAP ($n=4$), German modified Bethesda ($n=2$) and UK RCPath ($n=1$) system respectively (Table 5).

^{99m}Tc-MIBI imaging: indications, methodology and interpretation criteria

As summarized in Table 6 ^{99m}Tc-MIBI is mainly indicated in patients with equivocal/indeterminate FNAC results (10/12, 83%). Some differences are observed, however, in cytological subclasses selected for MIBI imaging: while most centers include all indeterminate categories (i.e., Bethesda III-IV, SIAPEC-IAP TIR3A/3B, Bethesda Germany 3, and UK RCPath Thy 3), one also includes lesions suspicious for cancer (SIAPEC-IAP TIR4), two centers only select high-risk indeterminate nodules (SIAPEC-IAP TIR 3B) and one center only selects low-risk indeterminate nodules (Bethesda III AUS/FLUS), respectively. Additional indications are non-diagnostic cytology ($n=2$, 17%), multinodular goiters, to address FNAC on hypofunctioning and MIBI-positive nodules ($n=7$, 58%), inapplicable FNAC (refused by patients, anticoagulant therapy and other contraindications, difficult anatomical conditions/locations) ($n=2$, 17%). Finally, MIBI imaging and FNAC are simultaneously performed in one center (8%).

In all centers, ^{99m}Tc-MIBI imaging is only performed after exclusion of autonomously functioning thyroid nodules (AFTNs) using ^{99m}Tc-pertechnetate scintigraphy. Administered activities of ^{99m}Tc-MIBI ranged from 185 to 700 MBq, respectively. After tracer injection early (10–30 min) and late (60–90 min) planar images were acquired in 10 (83%) and 12 (100%) centers, respectively. An additional single-photon emission computed tomography (SPECT) is performed on a routine basis in six (50%) centers and selectively, on the decision of the attending nuclear medicine physician in two centers (16%) while it is not performed on the remaining four centers (34%) (Table 7). Two centers also perform hybrid SPECT/CT imaging in selected patients. Acquisition protocols and parameters for planar and tomographic emission imaging as well as CT imaging are summarized in Tables 7 and 8, respectively.

Table 7 ^{99m}Tc-MIBI imaging: administered activities, number of examinations per year, and acquisitions timing

Study site	Activity (MBq)	Number of MIBI examinations per year	MIBI early images time (minutes)	MIBI late images time (minutes)	SPECT(-CT) timing
Rijeka, Croatia	370	80	15	90	Yes, selective (40%) After late planar
Hacettepe, Turkey	555	25	20	90	Yes, all cases After late planar
Bellinzona, Switzerland	185	120	10	60	Yes, all cases After late planar
Messina, Italy	370	50	10	60	Not performed
Giessen, Germany	500	95	Not performed	60	Yes, all cases After late planar
Genoa, Italy	700	20	30	90	Not performed
Istanbul, Turkey	500	30	30	90	Yes, all cases After late planar
Mostar, Bosnia and Herzegovina	500	70	20	90	Not performed
Duisburg, Germany	555, since 2020 370	120	20	90	Yes, all cases
Mersin, Turkey	555	260	30	90	Yes, all cases
Frankfurt, Germany	500	175	10	60	Yes, individual cases After late planar
Düsseldorf, Germany	300	50	Not performed	60	Not performed

MBq Megabecquerel, *SPECT* single-photon emission computed tomography, *CT* computed tomography

Finally, three different interpretation criteria are adopted in different centers: (i) comparison between ^{99m}Tc-MIBI and ^{99m}Tc-pertechnetate uptake within the nodule (four centers, 33%); (ii) comparison of ^{99m}Tc-MIBI uptake within the hypofunctioning nodule and normal thyroid tissue (six centers, 50%); (iii) semiquantitative evaluation of ^{99m}Tc-MIBI washout from the nodule (i.e., Wash-Out Index, WOI) (one center, 8%). In one center (8%) different criteria are combined (Table 9).

The concordance rate of relevant issues is summarized in Fig. 1.

Discussion

In this manuscript, the procedures, the indications, and the imaging interpretation criteria for MIBI imaging in various areas of Europe were investigated by a survey that showed a good agreement of different centers in approaching TNs by TSH measurement, US evaluation and selective use of ^{99m}Tc-pertechnetate thyroid scintigraphy based on nodule's size (i.e., $\geq$10 mm) and TSH levels. A notable exception is observed in the German centers, where ^{99m}Tc-pertechnetate thyroid scintigraphy is performed independently of the TSH levels. Due to the fact, that the majority of AFTNs in Germany present with normal TSH levels [18], the German Society of Nuclear Medicine recommends thyroid scintigraphy for all TNs of 10 mm or larger independent of the TSH level [19]. In other centers, however, the adopted TSH thresholds are significantly higher than those proposed by clinical guidelines such as the 2015 ATA guideline reflecting differences in iodine intake and prevalence of AFTNs between the United States and Europe, as well as between different European regions. After excluding AFTNs, all but two centers based the decision to perform FNAC or not on ultrasound TIRADS patterns. Even if different US TIRADS and cytological reporting systems are adopted in different centers, significant differences are unlikely as all methods proved to be accurate and are comparable in terms of accuracy [20–22]. In this clinical context, ^{99m}Tc-MIBI imaging is mainly used to assess TNs with inconclusive/indeterminate cytological findings and selection target nodule(s) for FNAC in patients with multi-nodular goiter. Injected ^{99m}Tc-MIBI activities range from 185 to 700 MBq (mean 465 MBq). Early (10–30 min after intravenous injection) and late (60–90 min after intravenous injection) anterior planar images are obtained in 10 (83%) centers, while late images only are obtained in the remaining two centers (16%), respectively. An additional SPECT is also obtained as a standard in seven centers (52%) and in selected cases in two centers (16%), respectively. Hybrid SPECT/CT is also performed in two centers (16%) in selected cases (i.e., mediastinal goiters, preoperative evaluation). When performed, SPECT and SPECT/CT are performed after the late image acquisition. Visual interpretation is based on the evaluation of intranodular ^{99m}Tc-MIBI uptake compared to the normal

Table 8 ^{99m}Tc-MIBI imaging: imaging protocols

Study site	Planar imagingmatrix, zoom factor	SPECT imaging acquisition parameters	SPECT/CT imaging CT-parameters
Rijeka, Croatia	256 × 256 pixels; zoom 2	360°, 128 × 128 pixels, 10 s per view, iterative reconstruction	30 mA (AEC + DOM), 130 kV, slice 5 mm Acq 2 × 1.5 mm, PITCH: 1.5 mm RECON: B08s SPECT AC; B30s
Hacettepe, Turkey	256 × 256 pixels; zoom 1.5	360°, 128 × 128 pixels, 25 s per view, iterative reconstruction	Not performed
Bellinzona, Switzerland	128 × 128 pixels; zoom 2.67	360°, 128 × 128 pixels, 20 s per view, iterative reconstruction	40 mA (Care Dose) 120 kV, slice 3 mm, PITCH 1.5, mm recon 3 mm, filter L30F medium smooth
Messina, Italy	256 × 256 pixels; zoom: 1 and/or 1.4	Not performed	Not performed
Giessen, Germany	256 × 256 pixels; zoom 1.5	360°, 128 × 128 pixels, 20 s per view, iterative reconstruction	Not performed
Genoa, Italy	256 × 256 pixels; zoom 1.8	Not performed	Not performed
Istanbul, Turkey	256 × 256 pixels; zoom 1.5	360°, 128 × 128 pixels, 20 s per view, iterative reconstruction	Not performed
Mostar, Bosnia and Herzegovina	256 × 256 pixels; zoom 2.0	360°, 128 × 128 matrix, 64 views, 30 s per view, zoom 1.45	Not performed
Duisburg, Germany	256 × 256 pixels; zoom 308 × 308 mm	360°, 128 × 128 pixels, 25 s per view;zoom 461 × 461 mm, iterative reconstruction	Not performed
Mersin,Turkey	256 × 256 pixels; zoom 2.0	180°, 128 × 128 pixels, 32 views, 20 s per view, zoom 1.23	Not performed
Frankfurt, Germany	256 × 256 pixels; zoom 1.45	360°, 128 × 128 pixels, 25 s per view, iterative reconstruction	Not performed
Düsseldorf, Germany	128 × 128; zoom 1.74	Not performed	Not performed

SPECT single-photon emission computed tomography, *CT* computed tomography

Table 9 ^{99m}Tc-MIBI imaging: interpretation criteria

Study site	Criteria for a positive (i.e., suspicious) hypofunctioning thyroid nodules
Rijeka, Croatia	Hypofunctioning nodule with any intranodular uptake higher than normal parenchyma
Hacettepe, Turkey	Hypofunctioning nodule with any intranodular MIBI uptake same or higher than normal parenchymal MIBI uptake
Bellinzona, Switzerland	Hypofunctioning nodule with any intranodular MIBI uptake ≥ Tc uptake
Messina, Italy	Semi-quantitative analysis (wash-out index; WOI)
Giessen, Germany	MIBI uptake in the hypofunctioning thyroid nodule compared to the paranodular thyroid tissue (visual evaluation): isointense and hyperintense pattern
Genoa, Italy	Hypofunctioning nodule with any intranodular MIBI uptake higher than normal parenchyma
Istanbul, Turkey	Hypofunctioning nodule with any intranodular MIBI uptake higher than normal parenchyma
Mostar, Bosnia and Herzegovina	Hypofunctioning nodule with any intranodular MIBI uptake ≥ Tc uptake
Duisburg, Germany	Hypofunctioning nodule in ^{99m}Tc-pertechnetate scintigraphy with pronounced MIBI accumulation OR isointense MIBI accumulation AND with a WOI > − 40%
Mersin,Turkey	Hypofunctioning nodule with any intranodular MIBI uptake ≥ Tc uptake
Frankfurt, Germany	Hypofunctioning nodule with any intranodular MIBI uptake ≥ Tc uptake
Düsseldorf, Germany	Hypofunctioning nodule with any intranodular MIBI uptake same or higher than normal parenchymal MIBI uptake

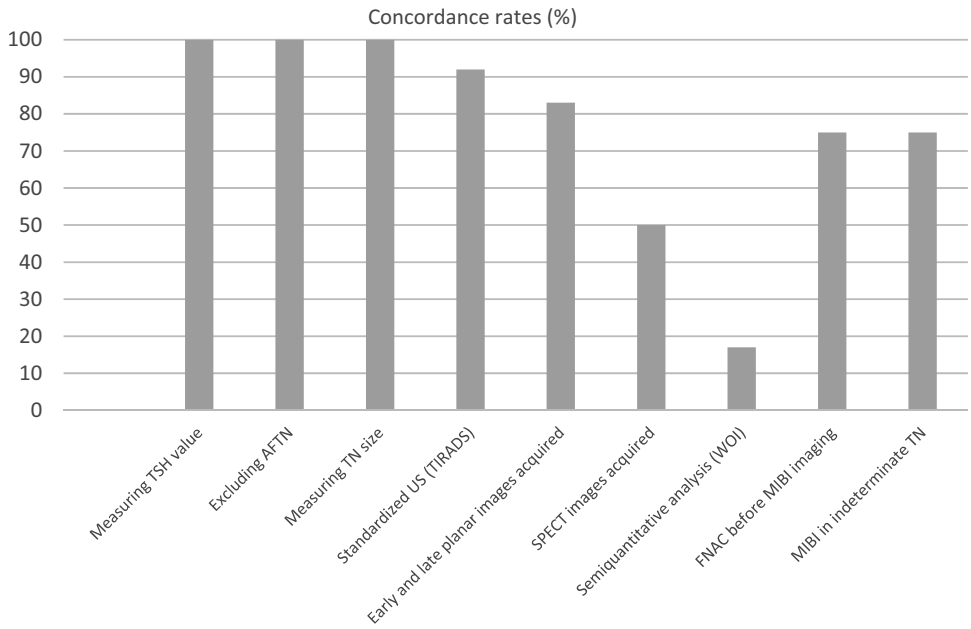

Fig. 1 Concordance rates of all study centers. AFTN: autonomously functioning thyroid nodule; US: Ultrasound; TIRADS: Thyroid Imaging Reporting and Data System; SPECT: Single-photon emission computed tomography; WOI: Washout index; TN: Thyroid nodule

thyroid tissue (six centers, 50%) or pertechnetate thyroid scintigraphy (four centers, 34%). Finally, a semi-quantitative assessment of WOI is employed in one (8%) center while visual and WOI are integrated in the remaining one (8%), respectively.

All in all, our present survey demonstrates a good agreement between the different nuclear thyroidology centers regarding the approach to nodular thyroid diseases. Adoption of different TIRADS systems and cytology reporting systems should be accounted as a potential source of heterogeneity. However, currently available systems are well comparable in terms of accuracy. Nonetheless, a standardization and harmonization are desirable to ameliorate communication between different specialists and allow a better comparison of research data. Technical procedures adopted in different centers are globally comparable and the recorded differences are unlikely to impact clinical results. However, as the main result of the present study, substantial differences were found in visual interpretation criteria adopted in different centers. Indeed, the WOI is only assessed in two centers for all TNs despite it has been supported as the preferred method for differentiating benign from malignant nodules and, especially, differentiate benign from malignant cytologically indeterminate nodules, respectively [10, 13]. The adoption of WOI in daily clinical practice is likely limited by the lengthening of the image analysis times and the need for strict standardization of methods. However, while a qualitatively negative ^{99m}Tc-MIBI scintigraphy reliably excludes malignancy, many benign follicular proliferation will frequently show isointense or hyperintense ^{99m}Tc-MIBI uptake and will only be discriminated by a semi-quantitative assessment. In conclusion, we found satisfactory agreement of different nuclear thyroidology centers concerning indications and technical procedures. At the same time, relevant differences exist in interpretation criteria explaining differences in diagnostic performance reported in the literature.

Preliminary data on the cost-effectiveness of ^{99m}Tc-MIBI in nodular thyroid diseases are encouraging.

Wale and colleagues evaluated the diagnostic performance of ^{99m}Tc-MIBI calculated from a retrospective review of local data on 712 patients combined with a meta-analysis of the published literature. Decision tree analysis was used to calculate the cost-effectiveness and a combined FNAC/MIBI investigative strategy was proved to be useful in avoiding unnecessary thyroidectomies, saving related costs and potential side effect [14].

Another study compared the cost-effectiveness of ^{99m}Tc-MIBI imaging and the Afirma gene expression classifier for the assessment of cytologically indeterminate TNs. Costs were calculated from the perspective of the German health insurance system. A decision tree model was used and results were confirmed by the Monte Carlo simulation. Life expectancy was 34.3 years (estimated costs per patient €1459–€2224) for the MIBI scan and 34.1 years (estimated costs €3560–€4071) for the molecular test. Therefore, the authors concluded that ^{99m}Tc-MIBI imaging is more cost-effective than the gene expression classifier [23].

However, both studies referred to local costs; then for future studies, more standardized approaches will be applied, allowing the evaluation of cost-effectiveness (^{99m}Tc-MIBI imaging combined with FNAC) in a larger and multicentric setting [14].

Conclusions

Our survey supports the urgent need for standardized interpretation criteria of thyroid ^{99m}Tc-MIBI imaging to improve its diagnostic performance and make multicenter results comparable in clinical practice. Based on this, the EANM Thyroid Committee will promote a multicenter prospective study on the clinical results of ^{99m}Tc-MIBI imaging by using harmonized ^{99m}Tc-MIBI imaging interpretation criteria, aiming to develop an EANM standardized protocol for interpreting thyroid ^{99m}Tc-MIBI imaging and improving its clinical relevance.

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Data availability Yes.

Declarations

Conflict of interest All authors declare that there is no conflict of interest.

Ethics approval The study was approved by the ethics committee of Magdeburg University Hospital (No. RAD 378-32/20) and the need for an informed consent was waived.

References

1. Campennì A, Siracusa M, Ruggeri RM et al (2017) Differentiating malignant from benign thyroid nodules with indeterminate cytology by 99mTc-MIBI scan: a new quantitative method for improving diagnostic accuracy. Sci Rep 7:6147. https://doi.org/10.1038/s41598-017-06603-3
2. Giovanella L, Avram AM, Iakovou I et al (2019) EANM practice guideline/SNMMI procedure standard for RAIU and thyroid scintigraphy. Eur J Nucl Med Mol Imaging 46:2514–2525. https://doi.org/10.1007/s00259-019-04472-8
3. Tessler FN, Middleton WD, Grant EG et al (2017) ACR Thyroid Imaging, Reporting and Data System (TI-RADS): white paper of the ACR TI-RADS Committee. J Am Coll Radiol 14:587–595. https://doi.org/10.1016/j.jacr.2017.01.046
4. Shin JH, Baek JH, Chung J et al (2016) Ultrasonography diagnosis and imaging-based management of thyroid nodules: revised Korean Society of Thyroid Radiology Consensus Statement and Recommendations. Korean J Radiol 17:370–395. https://doi.org/10.3348/kjr.2016.17.3.370
5. Haugen BR, Alexander EK, Bible KC et al (2015) American Thyroid Association Management Guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. Thyroid 26:1–133. https://doi.org/10.1089/thy.2015.0020
6. Yordanova A, Mahjoob S, Lingohr P et al (2017) Diagnostic accuracy of [99mTc]Tc-Sestamibi in the assessment of thyroid nodules. Oncotarget 8:94681–94691. https://doi.org/10.18632/oncotarget.21866
7. Schmidt M, Schenke S (2019) Update 2019 zur MIBI-Szintigrafie bei hypofunktionellen Schilddrüsenknoten. Der Nuklearmediziner 42:174–182. https://doi.org/10.1055/a-0916-6238
8. Treglia G, Caldarella C, Saggiorato E et al (2013) Diagnostic performance of (99m)Tc-MIBI scan in predicting the malignancy of thyroid nodules: a meta-analysis. Endocrine 44:70–78. https://doi.org/10.1007/s12020-013-9932-z
9. Kim S-J, Lee S-W, Jeong SY et al (2018) Diagnostic performance of Technetium-99m Methoxy-Isobutyl-Isonitrile for differentiation of Malignant Thyroid Nodules: a systematic review and meta-analysis. Thyroid 28:1339–1348. https://doi.org/10.1089/thy.2018.0072
10. Campennì A, Giovanella L, Siracusa M et al (2016) (99m)Tc-Methoxy-Isobutyl-Isonitrile Scintigraphy is a useful tool for Assessing the risk of Malignancy in Thyroid nodules with indeterminate fine-needle Cytology. Thyroid 26:1101–1109. https://doi.org/10.1089/thy.2016.0135
11. Melloul M, Paz A, Koren R et al (2001) 99mTc-MIBI scintigraphy of parathyroid adenomas and its relation to tumour size and oxyphil cell abundance. Eur J Nucl Med 28:209–213. https://doi.org/10.1007/s002590000406
12. Arbab AS, Koizumi K, Toyama K et al (1996) Uptake of technetium-99m-tetrofosmin, technetium-99m-MIBI and thallium-201 in tumor cell lines. J Nucl Med 37:1551–1556
13. Giovanella L, Campenni A, Treglia G et al (2016) Molecular imaging with (99m)Tc-MIBI and molecular testing for mutations in differentiating benign from malignant follicular neoplasm: a prospective comparison. Eur J Nucl Med Mol Imaging 43:1018–1026. https://doi.org/10.1007/s00259-015-3285-1
14. Wale A, Miles KA, Young B et al (2014) Combined (99m)Tc-methoxyisobutylisonitrile scintigraphy and fine-needle aspiration cytology offers an accurate and potentially cost-effective investigative strategy for the assessment of solitary or dominant thyroid nodules. Eur J Nucl Med Mol Imaging 41:105–115. https://doi.org/10.1007/s00259-013-2546-0
15. Schenke S, Zimny M, Rink T et al (2014) 99mTc-MIBI scintigraphy of hypofunctional thyroid nodules. Comparison of planar and SPECT imaging. Nuklearmedizin. 53:105–110. https://doi.org/10.3413/Nukmed-0619-13-08
16. Russ G, Bonnema SJ, Erdogan MF et al (2017) European Thyroid Association Guidelines for ultrasound malignancy risk stratification of thyroid Nodules in adults: the EU-TIRADS. Eur Thyroid J 6:225–237. https://doi.org/10.1159/000478927
17. Kwak JY, Han KH, Yoon JH et al (2011) Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. Radiology 260:892–899. https://doi.org/10.1148/radiol.11110206

18. Görges R, Kandror T, Kuschnerus S et al (2011) Scintigraphically „hot“ thyroid nodules mainly go hand in hand with a normal TSH. Nuklearmedizin 50:179–188. https://doi.org/10.3413/nukmed-0386-11-02
19. Dietlein M, Eschner W, Lassmann M et al. Procedure Guideline for thyroid scintigraphy (Version 4) 2014. http://www.nuklearmedizin.de/leistungen/leitlinien/docs/031-011I_S1_Schilddrüsenszintigraphie_2014-10.pdf; Accessed: 25 Mar 2021
20. Seifert P, Görges R, Zimny M et al (2020) Interobserver agreement and efficacy of consensus reading in Kwak-, EU-, and ACR-thyroid imaging recording and data systems and ATA guidelines for the ultrasound risk stratification of thyroid nodules. Endocrine 67:143–154. https://doi.org/10.1007/s12020-019-02134-1
21. Grani G, Lamartina L, Cantisani V et al (2018) Interobserver agreement of various thyroid imaging reporting and data systems. Endocr Connect 7:1–7. https://doi.org/10.1530/EC-17-0336
22. Grani G, Lamartina L, Ascoli V et al (2019) Reducing the number of unnecessary thyroid biopsies while improving diagnostic accuracy: toward the “Right” TIRADS. J Clin Endocrinol Metab 104:95–102. https://doi.org/10.1210/jc.2018-01674
23. Heinzel A, Müller D, Behrendt FF et al (2014) Thyroid nodules with indeterminate cytology: molecular imaging with 99mTc-methoxyisobutylisonitrile (MIBI) is more cost-effective than the Afirma gene expression classifier. Eur J Nucl Med Mol Imaging. 41:1497–500. https://doi.org/10.1007/s00259-014-2760-4

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