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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Received: 19 April 2021 / Accepted: 26 May 2021 / Published online: 2 June 2021
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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
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

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

**Table 1** Survey questionnaire

| 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 Acuson 3000, 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 | LOGIQ58 General Electric Medical Systems, Milwaukee, Germany |
| Istanbul, Turkey      | Mediso Nuclide 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 |
| 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 

| Study site     | Indications for \( ^{99m} \)Tc-pertechnetate thyroid 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   | EU-TIRADS                                                                 |
|---------------------------------|-----------------------|---------------------------------------------------------------------------|
| Rijeka, Croatia                 | EU-TIRADS             | High-risk features: non-oval/round shape, irregular margin, microcalcifications, marked hypoechoic (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 hypoechoic (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 hypoechoic (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 hypoechoic (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) hypoechoic, 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 hypoechoic (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 hypoechoic (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 hypoechoic (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) hypoechoic, 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 hypoechoic (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
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 mU/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 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                         | Bethesda system            |
|                                   |                | EU-TIRADS 3 > 2 cm                                 |                             |
| Hacettepe, Turkey                 | EU-TIRADS      | EU-TIRADS 5 > 1 cm                                 | Bethesda system            |
|                                   |                | EU-TIRADS 4 > 1.5 cm                               |                             |
|                                   |                | EU-TIRADS 3 > 2 cm                                 |                             |
| Bellinzona, Switzerland           | EU-TIRADS      | EU-TIRADS 4 and 5 or 1 cm                          | SIAPEC-IAP                 |
|                                   |                | EU-TIRADS 3 > 2 cm                                 |                             |
| Messina, Italy                    | EU-TIRADS      | EU-TIRADS 4 and 5                                  | SIAPEC-IAP                 |
|                                   |                | EU-TIRADS 3 ≥ 1.5 cm                               |                             |
| Giessen, Germany                  | Kwak-TIRADS    | Hypofunctioning TN ≥ 10 mm at intermediate or high risk | Bethesda classification (German version) |
| Genoa, Italy                      | EU-TIRADS      | EU-TIRADS 4 > 1.5 cm                               | SIAPEC-IAP                 |
|                                   |                | EU-TIRADS 5 > 1 cm                                 |                             |
|                                   |                | EU-TIRADS 3 > 2 cm                                 |                             |
| Istanbul, Turkey                  | EU-TIRADS      | EU-TIRADS 4 and 5 any size                         | Bethesda system            |
|                                   |                | EU-TIRADS 3 > 2 cm                                 |                             |
| Mostar, Bosnia and Herzegovina    | EU-TIRADS      | EU-TIRADS 5 any size                               | Bethesda system            |
|                                   |                | EU-TIRADS 4 > 1.5 cm                               |                             |
|                                   |                | EU-TIRADS 3 > 2 cm                                 |                             |
| 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                                  | SIAPEC-IAP                 |
|                                   |                | EU-TIRADS 3 > 2 cm                                 |                             |
| Frankfurt, Germany                | ACR-TIRADS     | ACR-TIRADS 3 ≥ 2.5 cm                              | UK RCPath                  |
|                                   |                | ACR-TIRADS 4 ≥ 1.5 cm                              |                             |
|                                   |                | ACR-TIRADS 5 ≥ 1.0 cm                              |                             |
|                                   |                | Highly suspicious nodules < 1 cm                    |                             |
| 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
Fine-needle aspiration cytology and cytopathology reporting

Cytopathology findings are reported using the Bethesda 

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

| Study site                  | Indications for $^{99m}$Tc-sestaMIBI scintigraphy                                      |
|-----------------------------|----------------------------------------------------------------------------------------|
| Rijeka, Croatia             | Repeated Bethesda I-nondiagnostic                                                    |
| Hacettepe, Turkey           | Cytologically indeterminate hypofunctioning nodules (Bethesda, AUS/FLUS)              |
| Bellinzona, Switzerland     | Non-diagnostic cytology (SIAPEC-IAP: TIR1, except TIR1C, cystic)                      |
| Messina, Italy              | Cytologically indeterminate hypofunctioning nodules (SIAPEC-IAP: TIR3A and TIR3B)     |
| Giessen, Germany            | Hypofunctioning thyroid nodules if FNAC is not applicable                             |
| Genoa, Italy                | Cytologically indeterminate hypofunctioning nodules (SIAPEC-IAP: TIR3A and TIR3B)     |
| Istanbul, Turkey            | 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: Thy 3)              |
| Frankfurt, Germany          | Multinodular goiters (hypofunctioning nodules)                                       |
| Düsseldorf, Germany         | Hyofunctioning nodules in $^{99m}$Tc-pertechnetate scan (in parallel to FNAC)         |

$^{99m}$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 cyto-

99mTc-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 cyto-

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.
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., ≥ 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 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 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

| 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                              | Not performed                 |
| Mostar, Bosnia and Herzegovina            | 500            | 70                                   | 20                              | 90                              | Not performed                 |
| Duisburg, Germany                         | 555, since 2020 | 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
### Table 8 99mTc-MIBI imaging: imaging protocols

| Study site                     | Planar imaging matrix, 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 99mTc-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 99mTc-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 |
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 99mTc-MIBI scintigraphy reliably excludes malignancy, many benign follicular proliferation will frequently show isointense or hyperintense 99mTc-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 99mTc-MIBI in nodular thyroid diseases are encouraging.

Wale and colleagues evaluated the diagnostic performance of 99mTc-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 99mTc-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 99mTc-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 (99mTc-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.

Acknowledgements The authors would like to thank Ms. Rema Markous from Duisburg Practice of Nuclear Medicine (partly contains data from her doctoral thesis).

Author’s contributions SAS, LG: writing–original draft, formal analyses, conceptualization, methodology, investigation; AC, AP, MT, SS, TB, DR, RG, PPÖK, DG, HH, RK, MCK: investigation, writing–review, and editing, methodology.

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.

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