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Original

The usefulness of [^{99m}Tc]MIBI scintigraphy in the diagnostic algorithm of ultrasonographical suspected thyroid nodules by using EU-TIRADS criteria

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Abstract

Background: Although not yet involved in the algorithm of thyroid nodules, 99mTc-methoxy-isobutyl-isonitrile ([^{99m}Tc]MIBI) scintigraphy may help in the individual diagnostic workup of a thyroid patient, especially where indeterminate fine needle aspiration biopsy (FNAB) is present. The aim of this study was to evaluate the usefulness of [^{99m}Tc]MIBI thyroid scintigraphy in the diagnostic algorithm of thyroid nodules, particularly in ultrasound EU-TIRADS 4 or 5 lesions, that cytologically were either indeterminate or benign.

Material and methods: A retrospective randomized study, including 42 thyroid patients, with mean age 47 ± 17 years, was conducted. [^{99m}Tc]MIBI scan was compared with ultrasound (US) EU-TIRADS criteria, pertechnetate scan, FNAB and histopathological findings for the differentiation of malignant thyroid nodules from benign lesions.

Results: The US mainly detected hypoechoic inhomogeneous presentation of the thyroid nodules (35/42, 83.33%), 4 cases with isoechoic nodules and 2 cases presented with hyperechoic thyroid nodules. Histopathology revealed malignancy in 15/42 (35.71%), while all other patients 27/42 (64.29%) were benign. Visual analysis score showed that patients scored with 1+ and 2+ were statistically significant to be benign, while 13 *vs.* 10 pts that were visual score 3+ were malignant vs. benign ($p > 0.05$). Sensitivity was 100%, while specificity was very low 22.22%, PPV was 41.67%.

Conclusions: Even [^{99m}Tc]MIBI scan is not routinely used as a daily practice diagnostic tool of thyroid nodules, we will further apply it on a larger group of patients and try to quantify the uptake of the radiotracer to see whether it will help in the diagnostic algorithm of thyroid nodules.

KEY words: thyroid nodule, [^{99m}Tc]MIBI, cytology ultrasound, EU-TIRADS

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Introduction

The most common clinical problem in the investigation of the thyroid gland is the entity of thyroid nodular disease. Thyroid nodule incidence varies from 40 000 to 71 000/100 000 persons, worldwide, with an average of 50 000/100 000 persons [1]. Various studies have found that the prevalence of thyroid nodules in China ranges from 10.12% to 46.56% [2]. The prevalence of nodular thyroid disease is dependent on the population investigated, as well as the imaging modalities used to determine the lesions. The reasons that cause an increase in the incidence of nodules are as follows: advanced age, female gender, iodine deficit or exposition to radiation. According to many studies, prevalence percentages differ based on the method used; palpation detects 2–6% of cases, while ultrasonography (US) detects 19–35% of cases [3].

Thyroid US is frequently used as a first diagnostic tool in detecting thyroid nodules. US-guided fine needle aspiration biopsy (FNAB), improves the sensitivity in detecting highly suspicious thyroid nodules as being malignant. When it comes to identifying benign from malignant thyroid lesions, FNAB has high sensitivity and specificity. Yet, this distinguishment is sometimes impossible. This is either because the specimen is inadequate for diagnosis (in 2–16%), requiring a new FNAB, or because indeterminate

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cytology is found, (in 5–20% of the cases), such as follicular growth and atypia of unknown significance (AUS) [4, 5].

Although not yet involved in the algorithm of thyroid nodules, ^{99m}Tc-methoxy-isobutyl-isonitrile ([^{99m}Tc]MIBI) scintigraphy may help in the individual diagnostic workup of a thyroid patient, especially where indeterminate FNAB is present, or when Bethesda II is confirmed, in a patient with a highly suspicious thyroid nodule. Taking into account the laboratory tests, thyroid US, thyroid scintigraphy with pertechnetate, and the FNAB, the scan with [^{99m}Tc]MIBI presents an individual approach of thyroid work-up.

The aim of this study was to evaluate the usefulness of [^{99m}Tc]MIBI thyroid scintigraphy in the diagnostic algorithm of thyroid nodules, particularly in ultrasound EU-TIRADS 4 or 5 lesions, that cytologically were either indeterminate (Bethesda III or IV) or benign (Bethesda II) cytology.

Material and methods

We performed a retrospective randomized study, including 42 thyroid patients, routinely checked at the outpatient Thyroid unit at the Department of Pathophysiology and Nuclear Medicine, 34 females, 8 males, age ranging from 19–75 years, mean age 47 ± 17 years.

Inclusion criteria were patients with detected thyroid nodules by US evaluated by EU-TIRADS criteria as EU-TIRADS IV (oval shape, smooth margins, mildly hypoechoic, without any feature of high risk) or EU-TIRADS V (nodules with at least one of the following high-risk features: non-oval shape, irregular margins, microcalcifications, and marked hypoechogenicity) [6].

Exclusion criteria: breastfeeding or pregnant patients as well as patients who denied performing either FNAB or [^{99m}Tc]MIBI scan.

Ultrasound

Ultrasound was performed using Phillips H.D. 6, Version 1.1, probe 7.5 Hz. by 2 nuclear medicine physicians with more than 10 years' experience in the field of expertise.

^{99m}Tc-pertechnetate

^{99m}Tc-pertechnetate was performed 20 minutes after iv application of 185 MBq of ^{99m}Tc-pertechnetate in planar AP position using a dedicated gamma camera (static image of 10 minutes, 600 counts, with and without zoom). ^{99m}Tc-pertechnetate scan was performed to objectively determine the functionality of the nodule. Patients with hypofunctioning or cold nodule(s) were included in this study.

US-guided FNAB

US-guided FNAB is the standardized and most relevant diagnostic procedure in the preoperative evaluation of thyroid nodules and the diagnosis of TC and is a simple, affordable and safe method, in which the only possible side effect is the appearance of post-interventional hematoma and pain. The patient is in a supine position, neck into the extension when performing US FNAB. After detecting the nodule with US, the puncture is made carefully in the direction below the placed probe, whit 22–25 gauge needle. After taking the sample, FNAB smears are prepared for fixation and dyeing, for further cytopathological analysis [7, 8].

[^{99m}Tc]MIBI scintigraphy acquisition protocol

Twenty minutes after injection of 740 MBq of ^{99m}Tc-pertechnetate, anterior neck image was acquired with a large field-of-view gamma camera (DDD, Solo Mobile) equipped with a low-energy, high-resolution collimator. We performed planar images at 10 minutes (or 100 000 counts) using a 256 × 256 matrix with a digital zoom of 1.0. The energy window was set at 20% and centered at the 140 keV photopeak of ^{99m}Tc. After that, another planar image and afterward a SPECT/CT study was done at 2 hours post-injection using GE NM Optima 640 gamma camera. (SPECT-LEHR collimator, matrix 128 × 128, zoom 1.5, view angle 3/number of views 120, stop and shoot 15 s; CT — matrix 512 × 512, helical pitch 1.25/rotation time 1 s, voltage 120V/Current 25 mA, slice thickness 2.5 mm/Kernel Standard/DFOV 50 cm).

We visually evaluated [^{99m}Tc]MIBI uptake of nodular thyroid disease and compared it with US EU-TIRADS criteria, pertechnetate scan, FNAB and histopathological findings for the differentiation of malignant thyroid nodules from benign lesions. According to the intensity of the retention of the [^{99m}Tc]MIBI, the findings from the late phase of the scan (at two hours) after intravenous administration of the radiopharmaceutical were visually scored as:

- 1+ — uptake similar as the rest of the thyroid tissue
- 2+ — uptake that is higher than the rest of the thyroid tissue, with still showing the other thyroid lobe on the late scan
- 3+ — uptake that is the highest, with almost no accumulation in the rest of the thyroid tissue on the late scan.

Results

US mainly demonstrated hypoechoic inhomogeneous nodules (35/42, 83.33%), 4 patients had isoechoic nodules and in 3 cases thyroid nodules appeared as hyperechoic. Regarding the thyroid lobe, for 1 patient we had no data, while 23/41 (56.10%) were detected in the right lobe, and the rest 18/41 (43.90%) in the left lobe. The diameter ranged from 14 mm to over 50 mm, with 14 patients having nodules from 20 to 30 mm in diameter. All our patients were sent to the Clinic of Thoracic Surgery for intervention (lobectomy or thyroidectomy in multinodular goiter).

Pertechnetate scan was performed in 36 patients. In 22/36 (61.11%) patients we revealed cold nodules on the pertechnetate scan and from these nodules, 9/42 (21.43%) were found to be malignant that mismatched with the [^{99m}Tc]MIBI scan. Two patients had hot nodules on the pertechnetate, confirmed as thyroid cancer, while 12/36 had isophyxated nodules, 4 out of them being malignant (Tab. 1).

Regarding the FNAB, from 15 confirmed thyroid cancer on histopathology, 7 had Bethesda IV, 4 were Bethesda III and 4 were Bethesda II answered on the cytology findings, (Tab. 2).

Table 1. Scintigraphy findings between pertechnetate scan and [^{99m}Tc]MIBI scan in thyroid cancer patients confirmed on histopathology

Scintigraphy	[^{99m}Tc]MIBI positive scan
Pertechnetate scan positive (hot nodule)	2
Pertechnetate scan negative (cold nodule)	9 (mismatching)
Pertechnetate isofixated nodule	4

Table 2. Histopathological findings regarding Bethesda score by cytology

Cytology score	Bethesda II	Bethesda III	Bethesda IV
Benign	19/23 (82.6%)	5/9 (55.55%)	3/10 (30%)
Malignant	4/23 (17.39%)	4/9 (44.44%)	7/10 (70%)
Total	23	9	10

Table 3. Results of the [^{99m}Tc]MIBI scan and histopathology findings

Histology	[^{99m}Tc]MIBI positive scan	[^{99m}Tc]MIBI negative scan
Benign	21/42 (50%)	6/42 (14.29%)
Malignant	15/42 (35.71%)	0/42

When analyzing the findings of [^{99m}Tc]MIBI scan and histopathology, malignancy was reported in 15/42 (35.71%), all [^{99m}Tc]MIBI positive, while all other patients 27/42 (64.29%) were histopathologically benign (Tab. 3). Their histopathology was as follows:

— tumor of unknown malignant potential, 2 patients ([^{99m}Tc]MIBI scan positive),
— hurthle adenoma, 3 patients (all [^{99m}Tc]MIBI positive),
— follicular adenoma, 10 patients (all [^{99m}Tc]MIBI positive),
— struma nodosa, 10 patients (6 [^{99m}Tc]MIBI positive, 4 being [^{99m}Tc]MIBI negative) and

Hashimoto thyroiditis, 2 patients (1 [^{99m}Tc]MIBI positive, 1 [^{99m}Tc]MIBI negative).

All histopathology findings, according to FNAB results and the results of [^{99m}Tc]MIBI scan are reported in Table 4.

Visual analysis score revealed patients being 1+ and 2+ to be statistically significant to be benign, while 13 *vs.* 10 pts that were visual score 3+ were malignant *vs.* benign respectively, $p > 0.05$ (Fig. 1). Sensitivity was 100%, while specificity was very low 22.22%, PPV was 41.67%.

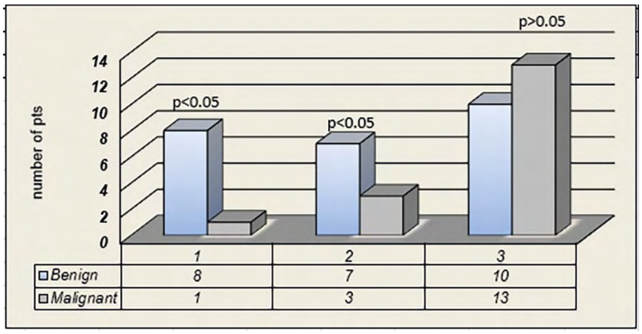

Figure 1. Significance of visual score analysis in benign and malignant thyroid nodules

Discussion

Thyroid nodules are a frequent finding, especially in presently and formerly iodine-deficient regions, due to the increasing use of US [9]. Ultrasonography of the thyroid gland is the first imaging and diagnostic tool for evaluating of thyroid nodules. It is widely available, affordable and easy to perform method, but depended on the experience of the performing physician. The introduced EU-TIRADS criteria further helped in distinguishing between benign and malignant thyroid nodules [6]. Nodules that are hypoechoic inhomogeneous, with irregular margins, presenting with micro- or macrocalcifications, well-vascularized present as EUTIRADS 5 and are highly suspicious of being malignant. Sometimes because of extended calcification, it is really difficult to prepare a good smear with enough cellularity, leaving the pathologist to answer the sample as Bethesda II. The echogenicity of the solid section of the nodule distinguishes the low-risk and intermediate-risk categories. Other characteristics may influence the risk of malignancy in this group. A thin halo, partly cystic composition, comet-tail artifacts, peripheral vascularity, and low stiffness all reduce the likelihood of cancer [6].

In our study group, we cytologically evaluated all thyroid nodules. Out of 23 patients, that were benign on cytology (Bethesda II), 4 of them turned out to be malignant on the histopathology report.

Table 4. Histopathology according to FNAB and [^{99m}Tc]MIBI results

Histology	Number	[^{99m}Tc]MIBIPositive	[^{99m}Tc]MIBINegative	FNAB AUS/FLUS	FNAB Positive	FNAB Negative
Papillary carcinoma	10	10	0	7	0	3
Follicular carcinoma	2	2	0	1	0	1
Hurthle cell carcinoma	2	2	0	2	0	0
Anaplastic carcinoma	1	1	0	1	0	0
Tu of unknown malignancy	2	2	0	2	0	0
Hurthle adenoma	3	3	0	1	0	2
Follicular adenoma	10	10	0	3	0	7
Struma nodosa/colloides	10	5	5	2	0	8
Hashimoto thyroiditis	2	1	1	0	0	2

AUS — atypia of unknown significance; FLUS — follicular lesion of undetermined significance; FNAB — fine needle aspiration biopsy

Most of the cases (70%) that were cytologically Bethesda IV, were diagnosed as thyroid cancer. Even large majority of the thyroid lesions presented as benign, the US-features increased the need for additional investigations, since the risk of inappropriate thyroid surgery is significant. Especially cold nodules on pertechnetate scan rise the suspicion of malignancy in the thyroid nodule, which seeks further diagnostic follow-up — either another biopsy or the dual phase [^{99m}Tc]MIBI scan, for assessing the mitochondrial activity in the nodule. [^{99m}Tc]MIBI is becoming more widely employed in the diagnosis of thyroid nodules. [^{99m}Tc]MIBI is a lipophilic cation and non-specific radiopharmaceutical for tumor imaging that targets mitochondria, where the positive charge traps them. In hyperplasia, malignant tumors, and parathyroid adenomas, the tracer accumulates in mitochondria-rich cells [10].

Thyroid nodules have been independently evaluated by both US and [^{99m}Tc]MIBI scintigraphy. There are limited studies in the literature regarding the comparison between these two modalities in the evaluation of thyroid suspected nodules. We tried in this study to see if ultrasound diagnostic criteria (EU-TIRADS) can predict malignancy even in thyroid nodules that were cytologically benign or indeterminate. Can we rely only on the "nuclear physician's eye" or only on the FNAB result? Should we use [^{99m}Tc]MIBI scan in the diagnostic algorithm in these cases when we are not sure how to follow up — watch and wait (if Bethesda II), lobectomy (Bethesda III and IV). Very often subsequently after initial lobectomy and confirming thyroid carcinoma second intervention is needed, leading to increasing risk for postoperative complications for the patient.

The usefulness of [^{99m}Tc]MIBI scintigraphy in the diagnostic algorithm of suspected thyroid nodules is yet a matter of discussion. The diagnostic chart of a patient with thyroid nodules differs between colleagues and institutions. In one study of thyroid nodules, it was concluded that the rate of absorption of [^{99m}Tc]MIBI in the 34 operated thyroid nodules confirmed, that this radiopharmaceutical is not specific for malignancy, but is accumulating in thyroid tissue viability [11].

When malignancy was suspected on US, a meta-analysis of 21 selected studies reported that [^{99m}Tc]MIBI scintigraphy had a sensitive diagnostic performance result for detecting malignant lesions, with pooled sensitivity and specificity in a per-lesion study of 85% and 46%, respectively. When only "cold" nodules were evaluated, based on prior iodine-123 or technetium-99m-pertechnetate scintigraphy, the pooled sensitivity and specificity were 82% and 63% respectively, allowing for better diagnostic accuracy [12].

Regarding our study, from all thyroid cancer patients detected on histopathology, cold nodules prevailed on the pertechnetate scan, with mismatch (cold pertechnetate scan and hot [^{99m}Tc]MIBI scan) in 9 patients. Only in 2 patients hot nodules were seen, while 4 patients had isophyxation on the pertechnetate scan, and these nodules turned out to be thyroid cancer.

A negative [^{99m}Tc]MIBI scan consistently excluding malignancy with high sensitivity and NPV has been demonstrated in many retrospective and prospective studies. A visibly positive [^{99m}Tc]MIBI scan, on the other hand, can be observed in both malignant and benign tumors, lowering its specificity and PPV [13, 14]. Our NPV was also 100%, while the PPV was 41.67% and specificity 22.22%.

Lower specificity is related to a non-exclusive metabolic pattern of [^{99m}Tc]MIBI distribution also in hyperplasic nodular goiter, macro and micro-follicular adenoma, Hürthle cell adenoma, or autoimmune or subacute nodular thyroiditis, were also increased mitochondrial activity could be expected. As a result, a [^{99m}Tc]MIBI scan that is positive should be interpreted as "indeterminate" [15].

In the study conducted by Kresnik et al. involving 62 patients with hypofunctional nodules on ^{99m}Tc-pertechnetate scans, 23 of them were revealed to have [^{99m}Tc]MIBI positive uptake, with 5 (22%) of them being malignant [16].

From our visual analysis, patients that were scored as 1+ and 2+ were benign on histopathology ($p < 0.05$), and those that were scored as 3+ were mainly malignant than benign (13 *vs.* 10 pts respectively), although without statistical significance, that may be due to the small number of patients in this group.

Thyroid carcinomas were histopathologically confirmed in 11% (8/73 cases) in the study of Theissen. [^{99m}Tc]MIBI had a NPV of 97%, which was similar to FNAB, 94%. Nonetheless, FNAB was inconclusive in 19.5% of the patients. [^{99m}Tc]MIBI uptake had a low specificity (54%) and PPV (19%), indicating that it cannot distinguish between malignant and benign thyroid nodules. Moreover, when compared to cytological and/or histological data, it was found to be able to distinguish between tumors with variable mitochondrial metabolism processes [17].

Even [^{99m}Tc]MIBI scan is not routinely used as a daily practice diagnostic tool for thyroid nodules, we will further apply in on a larger group of patients and try to quantify the uptake of the radiotracer to see whether it will help in the diagnostic algorithm of thyroid nodules and help nuclear medicine physicians as well as thyroid surgeons in the decision making of thyroid nodule patients. The limitation of our study was the small number of cases included in the analysis and further studies including a larger group of patients and semi-quantitative instead visual interpretation should be performed for a better understanding of the real meaning of the [^{99m}Tc]MIBI scan in the diagnostic algorithm of thyroid nodules.

Conflict of interest

The authors have no conflicts of interest to declare.

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