



# <sup>99m</sup>Tc-MIBI SPECT/CT SCINTIGRAPHY AND ULTRASOUND OF THE ANTERIOR NECK REGION IN DIAGNOSING PARATHYROID GLAND PATHOLOGY IN PATIENTS WITH THYROID NODULES

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**SUMMARY** – Parathyroid scintigraphy with <sup>99m</sup>Tc-MIBI is an imaging technique used in nuclear medicine and performed in patients with suspected hyperparathyroidism (HPT). The objective of this study was to evaluate the role of this technique in patients who, along with suspected HPT, also have thyroid nodules. Retrospective analysis included a period of 8 years (2006-2013). The study included 91 patients with clinical or laboratory suspected HPT. Pathologic changes in parathyroid glands were demonstrated in 47 (70%) of 67 patients with positive scintigraphy. Pathologic changes in parathyroid glands were not evident in the remaining 20 (30%) patients. Out of nine patients with negative scintigraphy results but with suspected enlargement of the parathyroid gland examined by ultrasound, eight (89%) patients did not show pathologic changes in the parathyroid gland, whereas one (11%) patient had evident changes. Eight (54%) of 15 patients with suspected scintigraphy had positive ultrasound findings, as well as fine needle aspiration cytology (FNAC) findings with parathyroid hormone (PTH) determination in the aspirate. Seven (46%) patients had negative FNAC findings and PTH in the aspirate. The study showed scintigraphy to have high sensitivity (98%) in detecting patients with pathologic changes in the parathyroid glands. In patients with suspected HPT, scintigraphy needs to be combined with FNAC and PTH determination in the aspirate due to its low specificity of 28%.

**Key words:** <sup>99m</sup>Tc-MIBI, SPECT/CT; Hyperparathyroidism; Parathyroid hormone; Fine needle aspiration

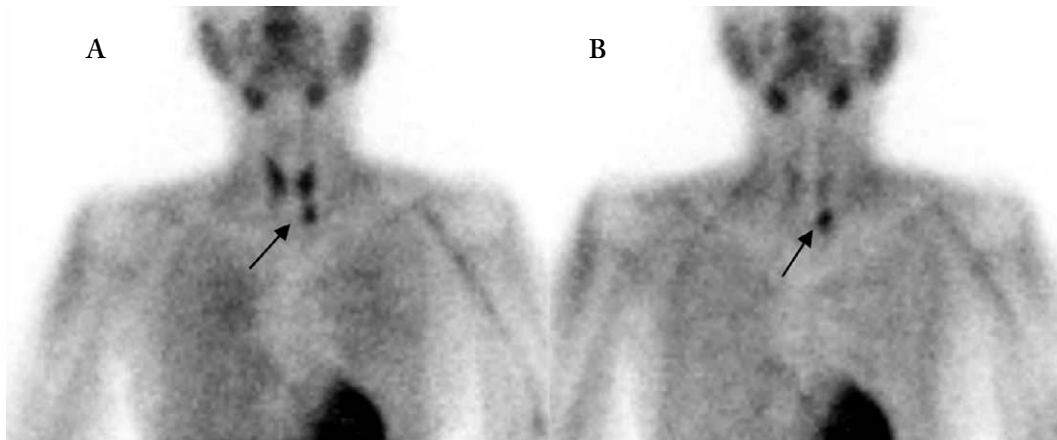
## Introduction

Parathyroid gland scintigraphy scan with <sup>99m</sup>Tc-methoxyisobutylisonitrile (<sup>99m</sup>Tc-MIBI, sestamibi) is an imaging technique used in nuclear medicine as a reliable, simple and noninvasive technique in diagnosing parathyroid diseases, and is performed in patients with clinical or laboratory suspicion of hyperparathy-

roidism (HPT). The presence of thyroid nodules complicates the diagnosis of parathyroid diseases due to the anatomic localization of normally located (eutopic) parathyroid glands (adjacent to the superior and inferior poles of both thyroid lobes), as well as the possible ectopic location (mediastinum, intrathyroid location)<sup>1-5</sup>. Thyroid nodules are common, their prevalence increases with age, and can be found in approximately 50% of individuals over 40 years of age. Most commonly, they are benign nodules, and in cytologic examination, 70% of nodules are nodular goiter (struma nodosa), whereas 5%-15% of the nodules in adults are malignant<sup>1,2</sup>.

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*Fig. 1. Early (A) and delayed (B) static  $^{99m}\text{Tc}$ -MIBI scintigraphy images of the neck and thorax in anteroposterior projection; (A) evident accumulation of radiopharmaceutical in both thyroid lobes and caudally to the inferior pole of the left thyroid lobe; (B) evident elimination of radiopharmaceutical from thyroid tissue while the accumulation caudally to the inferior pole of the left thyroid lobe persists.*

The aim of this study was to evaluate the role of the neck and thorax scintigraphy with  $^{99m}\text{Tc}$ -MIBI in combination with ultrasound (US) of the anterior neck region and targeted fine needle aspiration cytology (FNAC) with parathyroid hormone (PTH) determination in the aspirate when diagnosing parathyroid diseases. The combination of these diagnostic methods is particularly important in patients with suspicion of primary (pHPT) or secondary (sHPT) hyperparathyroidism, who also have changes in thyroid nodules.

## Patients and Methods

### *Scintigraphy of the neck and thorax with $^{99m}\text{Tc}$ -MIBI*

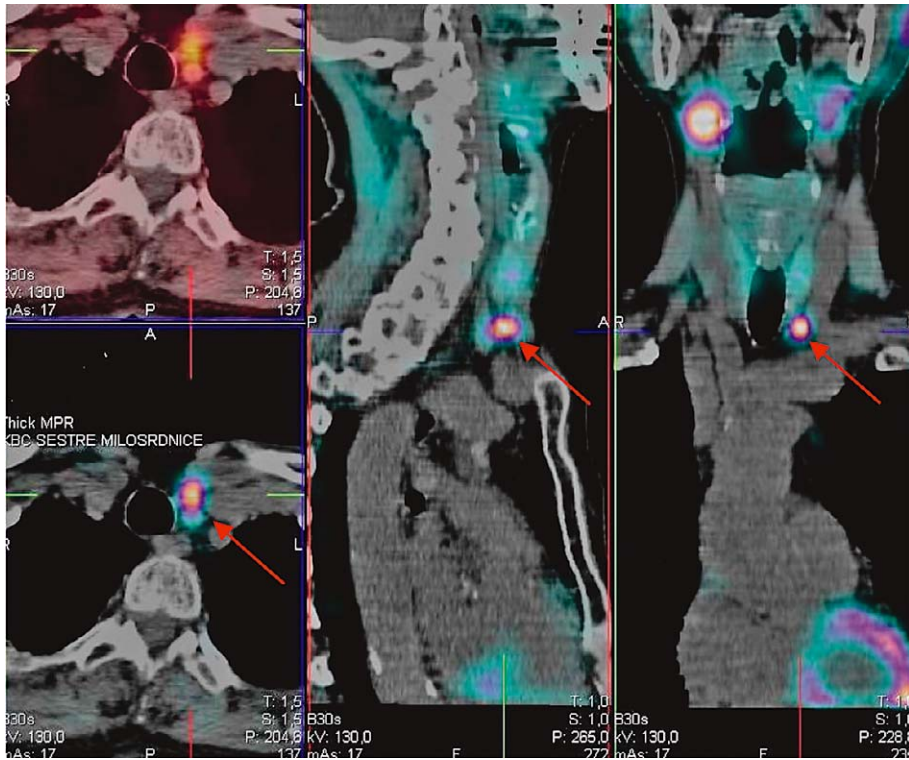
In patients with clinical or, even more common, laboratory suspicion of hyperthyroidism (hypercalcemia and/or elevated serum PTH concentration), scintigraphy is a required diagnostic technique. It is performed with a technetium sestamibi radiopharmaceutical agent, and is based on different velocity of elimination of the radiopharmaceutical accumulated in both thyroid and parathyroid gland tissue with pathologic changes. Normal, healthy parathyroid glands are metabolically inactive, do not accumulate radiopharmaceuticals, and cannot be seen with this method<sup>3,4</sup>.

$^{99m}\text{Tc}$ -MIBI is a nonspecific radiopharmaceutical agent that is accumulating in mitochondria-rich cells (cells of certain tumors, myocardial cells), together with oxyphilic cells of the parathyroid glands with

pathologic changes, most commonly due to an adenoma or hyperplasia of one or more parathyroid glands, and very rarely due to parathyroid carcinoma. It enters the cells by active transport and passive diffusion, as well as by mitochondrial sequestration<sup>3,4</sup>.

A patient is injected intravenously with 16–24 mCi (592–888 MBq) of  $^{99m}\text{Tc}$ -MIBI, and gamma-camera imaging (Symbia T2, Siemens, Munich, Germany) is performed in two different periods<sup>5</sup>. First imaging is performed 10–15 minutes after injection with early static images of the neck and thorax in anteroposterior (AP) and posteroanterior (PA) projections, as well as single photon emission computed tomography (SPECT) scan. Scintigrams show distribution of the radiopharmaceutical in both thyroid and parathyroid gland tissue with pathologic changes based on blood flow and tissue cellularity (Fig. 1A). Second imaging is performed 90–180 minutes after injection, when planar imaging of the same region is performed in AP and PA projections (Fig. 1B), as well as SPECT scan with low-dose CT fusion (Fig. 2). In this phase, the accumulation of the radiopharmaceutical is based on tissue cellularity<sup>3–6</sup>.

In the early phase, the activity of the radiopharmaceutical in the delayed phase decreases by 40%–60% in thyroid tissue and by 15%–35% in parathyroid gland tissue with pathologic changes, which makes parathyroid gland more noticeable on scintigram in relation to the surrounding thyroid tissue. SPECT scan with low-dose CT fusion (SPECT/CT) enables better evaluation of the location of the hyperfunctional parathyroid



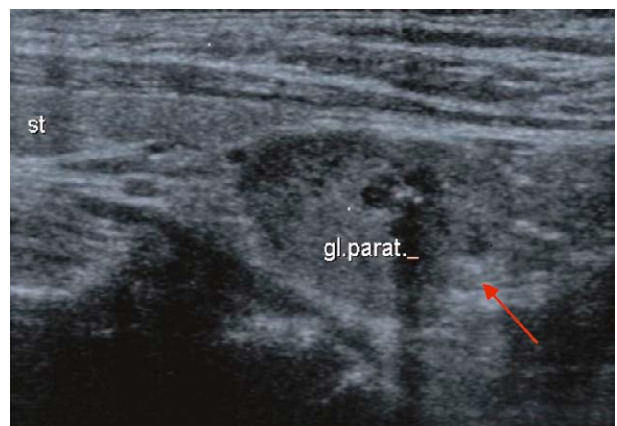
*Fig. 2.  $^{99m}\text{Tc}$ -MIBI SPECT/CT scan of the neck and thorax; arrows show parathyroid gland with pathologic changes (adenoma) caudally to the inferior pole of the left thyroid lobe.*

tissue, in particular ectopic tissue (mediastinum, intra-thyroidal location), and can also show results that cannot be identified by planar scanning<sup>3-6</sup>.

#### *Ultrasound of the anterior neck region and targeted FNAC with PTH determination in the aspirate*

After scintigraphy, patients also underwent neck and thyroid US examination with special attention to parathyroid glands with a linear-array transducer (7.5–12 MHz). Thyroid size and weight were determined, as well as its morphological features, i.e. quantity and prevalence of thyroid nodules and nodule size. Based on the US and scintigraphy findings, US guided FNA biopsy was performed at the neck sites with enhanced radiopharmaceutical accumulation. However, localized areas without radiopharmaceutical accumulation were also aspirated if they presented as enlarged parathyroid gland (Fig. 3). Normal, healthy parathyroid glands cannot be visualized by US imaging<sup>4</sup>.

The 23–24 G needles are used during the free-hand FNA technique, and the material obtained is stained



*Fig. 3. Ultrasound image of enlarged parathyroid gland (arrow).*

with May-Grünwald-Giemsa method and examined by cytopathologists<sup>7</sup>. PTH concentration is determined in the aspirate with electrochemiluminescence immunoassay (Roche Cobas e 601, Indianapolis, USA) after 1:0.5 mL dilution (Diluent MultiAssay, Roche, Mannheim, Germany). There is no consensus on PTH

values in the aspirate which would indicate positive findings; however, it is considered that PTH concentration in the aspirate higher than serum PTH value indicates the presence of hyperfunctional parathyroid tissue at the FNA site<sup>7-10</sup>.

### Study design

A retrospective analysis was conducted including a period of eight years (from January 1, 2006 until December 31, 2013). Ninety-one patients with clinical or laboratory suspected HPT were included in the study and diagnostically processed at the Department of Oncology and Nuclear Medicine, Sestre milosrdnice University Hospital Centre, Zagreb, Croatia.

There were 84 (92%) women and seven (8%) men, yielding a 12:1 male to female ratio. The median age of patients was 59 years and they all had normal thyroid size (weight) (18 ccm, 20 g). The median age was 59.2 years in female patients and 60.5 in male patients. <sup>99m</sup>Tc-MIBI SPECT/CT scintigraphy of the neck and thorax, US of the anterior neck region with special attention to parathyroid glands, and if needed, FNAC with PTH determination in the aspirate were performed in all patients.

### Results

Fifty-nine (65%) of 91 study patients with suspected HPT also had changes in thyroid nodules, while the rest of them had regular or diffuse changes in the thyroid parenchymal structure shown on US.

The <sup>99m</sup>Tc-MIBI SPECT/CT scintigraphy findings are classified as positive, negative, or equivocal. Positive findings show accumulation of the radiopharmaceutical, which is more intensive in delayed phase images as compared with the early phase, or the accumulation of the radiopharmaceutical is persisting in the early and delayed images<sup>3,6</sup>. Negative findings do not show any increased accumulation of the radiopharmaceutical, and the presence of pathologic changes in the parathyroid gland is excluded by scintigraphy. Equivocal scintigraphy findings show the accumulation of the radiopharmaceutical not found at typical locations on the neck, or is not of high intensity; however, they show the possible presence of hyperfunctional parathyroid tissue or other mitochondria-rich cells and tissues.

Out of our 91 patients, scintigraphy findings were positive in 67 (74%), negative in nine (10%) and equivocal in 15 (16%) patients. Out of 67 patients with positive scintigraphy, 47 (70%) patients also had positive findings at targeted FNA sites monitored by US, as well as PTH determined in the aspirate (suspicious cytology of parathyroid gland cells and elevated PTH level in the aspirate). In the remaining 20 (30%) patients, cytologic findings were negative, i.e. there was no parathyroid gland with pathologic changes (false-positive scintigraphy).

Out of nine patients with negative scintigraphy findings but with suspected parathyroid gland enlargement on US examination, eight (89%) patients also had negative FNAC findings and PTH level in the aspirate was not elevated. Only one (11%) patient had positive cytology with elevated PTH level in the aspirate (false-negative scintigraphy).

Out of 15 patients with suspected scintigraphy, eight (54%) patients had positive US and FNAC findings with PTH determined in the aspirate. Seven (46%) patients had negative FNAC findings and PTH levels in the aspirate were not increased.

The results obtained by scintigraphy, US and FNAC showed that the sensitivity of <sup>99m</sup>Tc-MIBI SPECT/CT scintigraphy in diagnosing hyperthyroidism was high, i.e. 98%. At the same time, the specificity of parathyroid gland scintigraphy with this radiopharmaceutical was low, i.e. 28%.

### Discussion

Study results showed that <sup>99m</sup>Tc-MIBI-SPECT/CT scintigraphy of parathyroid glands in patients with suspected HPT could detect a great number of really ill patients (among 91 study patients, scintigraphy was positive in 47 out of 48 patients with parathyroid gland with pathologic changes, with test sensitivity of 98%). At the same time, positive scintigraphy findings were also found in 20 patients with negative FNAC findings, monitored by US, representing false-positive results.

These false-positive findings can be most often found in patients with thyroid nodular changes, which can be explained by the accumulation of the radiopharmaceutical in all mitochondria-rich cells, i.e. parathyroid glands with pathologic changes (most commonly adenoma and hyperplasia, very rarely carcinoma in parathyroid glands), thyroid adenomas, well-differ-

entiated thyroid carcinomas, Hürthle cell adenoma or carcinoma, Hashimoto's thyroiditis, reactive lymph nodes in the neck, granulomatous lymph nodes with clinical changes (sarcoidosis), lymphomas, head and neck cancers, and metastases of certain malignant cancers into lymph nodes of the neck (breast cancer, lung cancer, bronchial carcinoids)<sup>3,5,6,11,12</sup>. This radiopharmaceutical can also have enhanced accumulation in the brown adipose tissue in the neck<sup>13</sup>.

The study also showed one <sup>99m</sup>Tc-MIBI SPECT/CT scintigraphy false-negative finding, which can be found in small adenomas or adenomas with cystic changes in parathyroid glands that do not have enough oxyphilic mitochondria-rich cells, therefore, they do not accumulate the radiopharmaceutical but they appear on the US scan as enlarged parathyroid gland<sup>5,6,14</sup>.

Based on the US findings, as well as the FNAC findings in patients with equivocal scintigraphy results, the results show that there is a grey zone in which this radiopharmaceutical rightfully does not show a clear image. That is to say, out of 15 scintigraphy suspicious patients, parathyroid glands with pathologic changes were evident on US scan and FNAC in eight patients, and not evident in seven patients.

Most of the literature references report on <sup>99m</sup>Tc-MIBI SPECT/CT scintigraphy sensitivity in detecting primary HPT ranging between 80% and 90%<sup>14</sup>, and on US as the imaging technique to significantly increase scintigraphy sensitivity<sup>4,15,16</sup>.

Yuan *et al.* report on the <sup>99m</sup>Tc-MIBI SPECT/CT scintigraphy sensitivity of 85% and specificity of 58% in patients with secondary HPT. These authors recorded 93% sensitivity and 61% specificity by combining US and SPECT/CT scintigraphy scan; however, PTH determination in the aspirate was not performed<sup>17</sup>. In the study by Zeng *et al.*, <sup>99m</sup>Tc-MIBI SPECT/CT scintigraphy sensitivity ranged between 70% and 85% in patients with secondary HPT<sup>18</sup>.

## Conclusion

Our study confirmed that <sup>99m</sup>Tc-MIBI SPECT/CT scintigraphy had high sensitivity in detecting patients with pathologic parathyroid glands (98%). However, due to a great number of false-positive scintigraphy findings, the specificity was low (28%), therefore, this method needs to be complemented with

FNAC monitored by US, with PTH determination in the aspirate in patients with suspected HPT<sup>19</sup>. Combined application of these diagnostic techniques has incremental value in diagnosing parathyroid gland diseases, as well as in planning and monitoring the treatment success rate.

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#### Sažetak

### <sup>99m</sup>Tc-MIBI SPECT/CT SCINTIGRAFIJA I ULTRAZVUK PREDNJE VRATNE REGIJE U DIJAGNOSTICI BOLESTI PARATIREOIDNIH ŽLIJEZDA KOD BOLESNIKA S NODOZNI PROMJENAMA ŠTITNJAJE

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Scintigrafija paratireoidnih žlijezda <sup>99m</sup>Tc-MIBI-jem je slikovna metoda nuklearne medicine, a provodi se kod bolesnika sa sumnjom na hiperparatireoidizam (HPT). Cilj istraživanja bio je procijeniti važnost upotrebe ove metode kod bolesnika koji uza sumnju na HPT imaju i nodozne promjene štitnjače. Retrospektivna analiza obuhvatila je razdoblje od 8 godina (2006.-2013.). U studiju je bio uključen 91 bolesnik s klinički ili laboratorijski sumnjivim HPT. Od 67 scintigrafski pozitivnih bolesnika, patološki promijenjena paratireoidna žlijezda dokazana je u njih 47 (70%). U preostalih 20 (30%) bolesnika patološki promijenjena paratireoidna žlijezda nije dokazana. Od 9 bolesnika s negativnim nalazom scintigrafije, a UZV suspektom povećanom paratireoidnom žlijezdom, patološki promijenjena paratireoidna žlijezda nije dokazana u njih 8 (89%), a dokazana je u jednog (11%) bolesnika. Od 15 scintigrafski dvojbjenih bolesnika, njih 8 (54%) je imalo pozitivan nalaz UZV i citološke punkcije uz određivanje PTH u punktatu. U 7 (46%) bolesnika nalaz punkcije i PTH u punktatu bio je negativan. Istraživanje potvrđuje da scintigrafija ima visoku osjetljivost za otkrivanje bolesnika s patološki promijenjenim paratireoidnim žlijezdama (98%). Zbog niske specifičnosti (28%) scintigrafiju treba nadopuniti punkcijom uz određivanje PTH u punktatu u bolesnika sa suspektnim HPT.

Ključne riječi: *<sup>99m</sup>Tc-MIBI, SPECT/CT; Hiperparatireoidizam; Paratireoidni hormon; Punkcija*