



# Dual-Tracer Subtraction Scintigraphy Combined with SPECT/CT in Preoperative Patients with Primary Hyperparathyroidism

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## Abstract

**Introduction:** Hyperparathyroidism is an endocrine disorder caused by overproduction of parathyroid hormone secreted from the parathyroid glands. Although this disorder is associated with a plethora of symptoms, the majority of people are now asymptomatic and discovered during routine laboratory screening.

**Aim:** The study presents the diagnostic accuracy of our dual tracer subtraction parathyroid scintigraphy combined with SPECT/CT imaging protocol.

**Materials and methods:** A retrospective study was conducted between June 1st, 2021, and June 1st, 2023. A cohort of 30 patients – 29 women (96.7%) and 1 man (3.3%), aged 37 to 86 years (mean: 61.2, standard deviation: 11.6) with clinical suspicion for primary hyperparathyroidism underwent parathyroid imaging for preoperative localization of parathyroid adenoma or ectopic parathyroid gland.

**Results:** Twenty-six out of the thirty patients with primary hyperparathyroidism had positive scan results, while four patients had negative results. The results showed adenoma of the inferior parathyroid glands in 18 patients. Adenoma of the superior parathyroid glands was found in 3 patients. Ectopic parathyroid gland was found in 4 patients. In one patient multiglandular parathyroid involvement was observed. Planar scintigraphy was positive for presence of hyperfunctioning parathyroid in 15 patients (50%), whereas SPECT/CT imaging was positive in 26 patients (86.7%) and negative in 4 patients (13.3%).

**Conclusions:** The combination of functional and morphological data obtained from a single examination through dual-radiopharmaceutical subtraction imaging and SPECT/CT allows increased diagnostic accuracy, which influences the choice of surgical technique and treatment result.

## Keywords

image subtraction, parathyroid adenoma, single photon emission computed tomography with computer tomography

## INTRODUCTION

The endocrine disorder known as hyperparathyroidism (HPT) is brought on by an excess of parathyroid hormone (PTH), which is secreted by the parathyroid glands and

regulates blood levels of calcium, phosphorus, and vitamin D.<sup>[1]</sup> Usually, this condition is associated with elevated levels of serum calcium and PTH. In some patients, the PTH levels may be within the normal range but accompanied by hypercalcemia.<sup>[2]</sup>

Elevated levels of serum calcium as a result of excessive parathyroid hormone in blood circulation is associated with fatigue, weakness, pain in muscles and bones, polyuria, polydipsia, nocturnal urinary frequency, renal calculi, memory loss, constipation, pyrosis, and depression. Nowadays, most patients are asymptomatic and are diagnosed during routine laboratory screening.<sup>[3]</sup>

HPT can be either primary, secondary, or tertiary. Primary HPT is a relatively common endocrine condition, with an incidence of 0.5/1000 in the general population, and it affects women nearly three times more than males.<sup>[4]</sup> It is typically caused by a solitary parathyroid adenoma in the majority of patients (80%–85%). Of them, 95% are sporadic, and the other 5% are associated with hereditary syndromes, for example, multiple endocrine neoplasia types 1, 2, and 4. In 15%–20% of all patients with primary hyperparathyroidism, the identified cause is either hyperplasia of the glands or multiple parathyroid adenomas. In rare cases, less than 1%, parathyroid carcinoma is the underlying cause.<sup>[5]</sup>

An anatomical understanding of the parotid glands is needed since there are variations in their localization, justified by their embryological development, which can pose a significant challenge for nuclear medicine physicians, radiologists, and surgeons.

The parathyroid glands are small, lentil-sized glands that are normally found behind the upper and lower poles of both thyroid lobes. There are typically four of these glands.

The superior parathyroid glands arise from the dorsal wing of the 4th pharyngeal pouch. During the 7th gestational week, the glands detach from the pharynx, attach themselves to the thyroid tissue and descend with it caudally. The superior parathyroid glands have more constant location than the inferior parathyroid glands, because of their shorter migration length. Their final point of migration is usually on the dorsal surface of the upper thyroid poles, dorsally to the recurrent laryngeal nerve outside of the thyroid fibrous capsule.<sup>[6]</sup>

The inferior parathyroid glands are more likely to vary in position because they arise from the dorsal wing of the third pharyngeal pouch, which differentiates at approximately the fifth or sixth week of pregnancy, with the ventral wing developing into the thymus. The thymus then descends together with them further inferiorly compared to the superior parathyroid glands. Their migration usually ceases close to the lower thyroid poles, at the dorsal surface of the thyroid gland, outside of the fibrous capsule anteriorly to the recurrent laryngeal nerve.<sup>[7]</sup>

Despite the limited migration path of their embryological development, there are still, however, cases of ectopy of parathyroid glands, which is a cause of hyperparathyroidism. Ectopic parathyroid glands may be located within thymus in the anterior mediastinum, within the thyroid or along the paraesophageal space and carotid sheath.<sup>[8]</sup>

The most favorable treatment of hyperparathyroidism is minimally invasive parathyroidectomy, but this focused

approach is applicable only in those cases when the solitary adenoma is preoperatively identified.<sup>[9]</sup>

Parathyroid scintigraphy plays a crucial role in the preoperative localization of hyperfunctioning parathyroid adenomas, multiglandular parathyroid involvement or ectopic parathyroid glands allowing the selection of personalized surgical approach.

However, the success of the appropriate parathyroid surgery does not only depend on the expertise of the surgeon, but also on the sensitivity and accuracy of the chosen preoperative imaging modality.<sup>[10]</sup>

## AIM

Our study presents the diagnostic accuracy of our dual-tracer subtraction parathyroid scintigraphy combined with SPECT/CT imaging protocol.

## MATERIALS AND METHODS

### Patients

We conducted a retrospective study between June 1st, 2021, and June 1st, 2023. A cohort of 30 patients – 29 women (96.7%) and 1 man (3.3%), aged 37 to 86 years (mean: 61.2, standard deviation: 11.6) with clinical suspicion for primary hyperparathyroidism underwent parathyroid imaging at the Department of Nuclear Medicine in Sofia Cancer Center for preoperative localization of parathyroid adenoma or ectopic parathyroid gland. Written informed consent was obtained from each patient before the imaging. Biochemical diagnosis of primary hyperparathyroidism was based on elevated serum calcium levels, elevated PTH levels accompanied with normal renal function.

### Imaging protocol

Scanning was performed using a Siemens Symbia T2 SPECT/CT gamma camera. Anterior planar thyroid gland imaging viewing the neck and the mediastinum was performed using a low energy high-resolution parallel hole collimator (matrix 128×128, 500 000 counts) 15 minutes after injecting 74 MBq of <sup>99m</sup>Tc-pertechnetate. Afterwards, 740 MBq of <sup>99m</sup>Tc-MIBI was injected via cannula, and serial planar images were obtained using 140 KeV energy window center for 15 minutes. Subtraction of both planar scans followed, resulting in the visualization only of the hyperfunctioning parathyroid lesions. A SPECT/CT acquisition was performed immediately after the planar imaging.

Overall, 120 projections (a 128×128 matrix) were obtained, 15 seconds per view using low dose CT scan with a 15-minute duration for the SPECT/CT imaging.

The acquired images were evaluated on a Syngo workstation. Analysis of statistical data was not conducted since

the number of examined patients was not applicable to extract reliable conclusions.

## RESULTS

After reviewing the results from the dual-tracer subtraction, combined with SPECT/CT imaging of 30 patients, predominantly female 29 (96.7%) with primary hyperparathyroidism, we found positive scans in 26 patients and negative in 5 patients. Of these 30 patients, one had a previous parathyroid surgery, but still clinical and laboratory evidence of primary HPT. The positive lesions revealed by the method were visually classified as foci of high, moderate or mild uptake. All included patients were either operated or treated conservatively. In the group of operated patients, the diagnosis was confirmed histopathologically, while in the conservatively treated group, the diagnosis was based on clinical examination and biochemical results – persistent elevation of calcium serum levels and PTH. Four patients (13.33%) with clinical suspicion of primary hyperparathyroidism and positive result from the hybrid dual-tracer imaging refused surgical treatment, while a parathyroidectomy was carried out on the other 26 patients (86.67%). The results showed adenoma of the inferior parathyroid glands in 18 patients (60%) of them 10 were with adenoma of the right inferior

and 8 with adenoma of the left inferior parathyroid gland (Fig. 1).

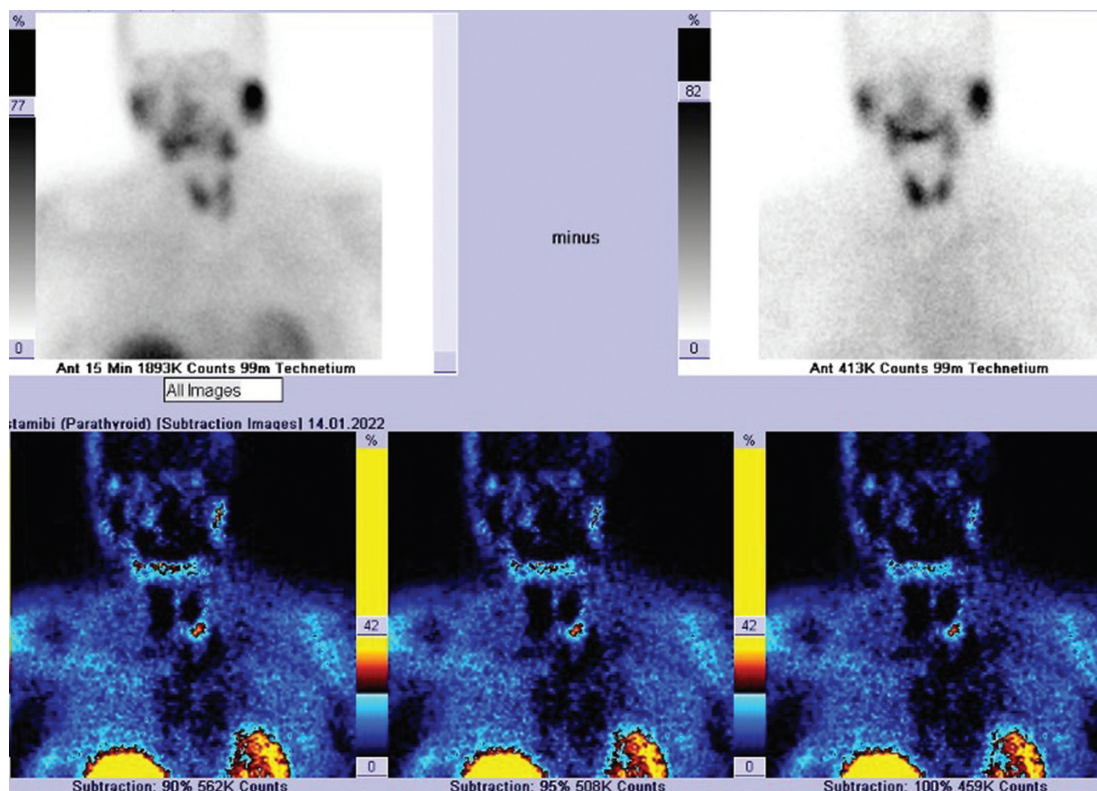
No evidence of adenoma was found in 4 patients (13.33%), ectopic parathyroid gland was found in 4 patients (13.33%) – either in the anterior mediastinum or along the paraesophageal space and carotid sheath (Fig. 2).

Adenoma of the superior parathyroid glands was found in 3 patients (10%) – in all of them in the right superior gland. In one patient (3.33%) multiglandular parathyroid involvement was observed - multifocal adenomas of the right parathyroid glands.

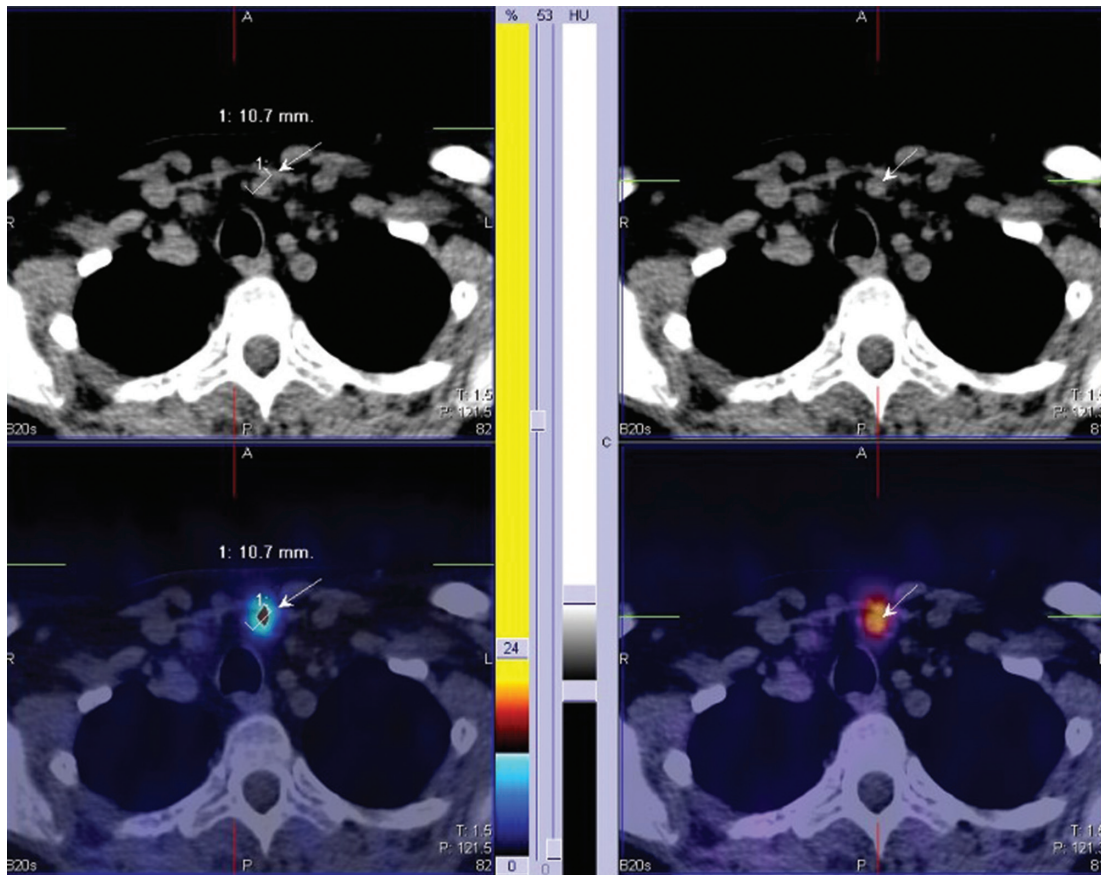
Planar scintigraphy was positive for presence of hyperfunctioning parathyroid in 15 patients (50%), whereas SPECT/CT imaging was positive in 26 patients (86.7%) and negative in 4 patients (13.3%). SPECT/CT was able to identify hyperfunctioning parathyroid tissue in 11 patients (36.7%) with negative planar scintigraphy, allowing appropriate surgical intervention (Fig. 3).

## DISCUSSION

The findings of this study suggest that SPECT/CT enhances the diagnostic utility of dual-phase scintigraphy for the preoperative identification of hyperfunctioning parathyroid lesions in patients with primary HPT. This technique provides a less invasive means of identifying affected



**Figure 1A.** Dual-tracer subtraction of both  $^{99m}\text{Tc}$ -pertechnetate and  $^{99m}\text{Tc}$ -MIBI planar scans of a 37-year-old woman. A focal MIBI uptake is visualized below the lower pole of the left thyroid lobe, suggestive of adenoma of left lower parathyroid gland.



**Figure 1B.** Axial view of the subsequent SPECT/CT images by the same patient, showing a round lesion with a diameter of around 11 mm with focal MIBI uptake localized to a single abnormal left lower parathyroid gland. The patient underwent minimally invasive parathyroidectomy for a single left lower parathyroid adenoma and experienced an appropriate drop in intraoperative parathyroid hormone.

glands in cases where there is only one, thereby reducing the possibility of an extended intraoperative examination of the remaining parathyroid glands. The added value of 3D imaging for detection of adenomas is advocated in the medical literature. Similar results are reported in a study by Assante et al., which highlights the importance of the three-dimensional method in the selection of surgical approach and the achievement of better therapeutic outcomes. The study proves the superiority of SPECT/CT over dual-phase scintigraphy in preoperative patients with primary HPT and uncertain ultrasound findings.<sup>[11]</sup>

SPECT/CT may give additional information in patients with ectopic parathyroid adenoma in the neck and mediastinum, providing accurate anatomical location of the pathology.<sup>[12]</sup>

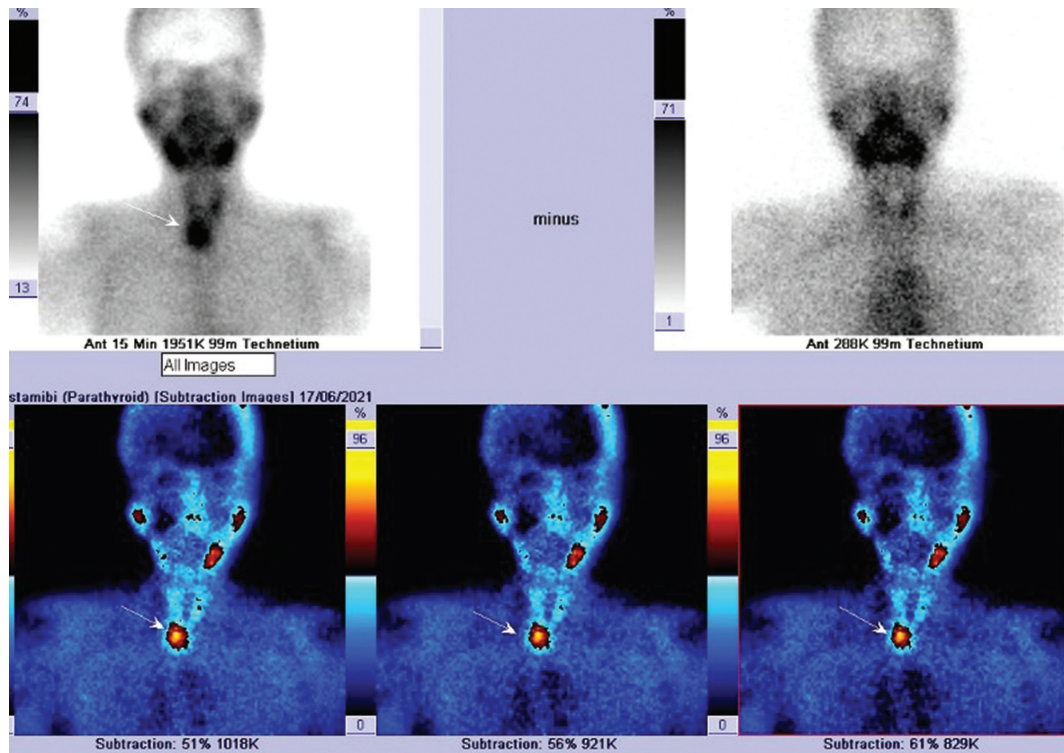
The dual-tracer method (the  $^{99m}\text{Tc}$ -pertechnetate/ $^{99m}\text{Tc}$ -MIBI method in our case) is a very useful tool in patients with thyroid nodules or goiter, in whom performing a subtraction of the images allows easy visualization of the parathyroid adenoma.<sup>[13]</sup> Another advantage of our dual-tracer protocol is its low cost for a nuclear medicine technique using  $^{99m}\text{Tc}$  tracers. There are many tracers ( $^{99m}\text{Tc}$ ,  $^{123}\text{I}$ , or  $^{131}\text{I}$ ) that could be applied in the thyroid gland mapping in the dual-tracer subtraction. However,

the costs of administering  $^{99m}\text{Tc}$  to a single patient are twenty times as low as those when  $^{123}\text{I}$  is applied, and using a MIBI kit is 10 times cheaper than using  $^{123}\text{I}$ .<sup>[14]</sup>

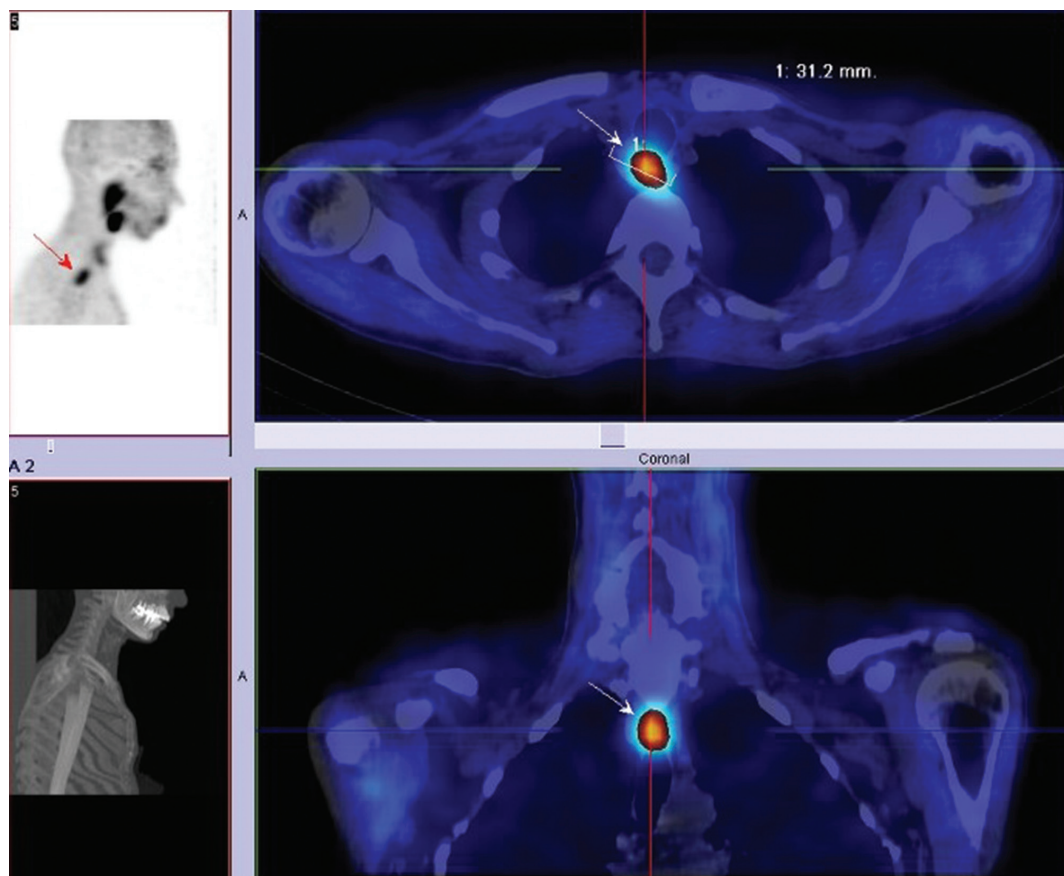
But compared to a dual-phase single-tracer method, this technique comes with a higher radiation dose to the patient. Another disadvantage of this method is that it requires good patient compliance to stay still and relaxed in the required position during the scanning in order to avoid motion artifacts.<sup>[13]</sup>

Possible causes of false negative results when applying our protocol include a low pathological tumor weight, a parathyroid cyst, non-steroidal anti-inflammatory drugs used by the patient, calcium channel blockers, or calcimimetics leading to low or no  $^{99m}\text{Tc}$ -MIBI uptake.<sup>[15]</sup> Another possible reason for a false negative result could be a low concentration of oxyphil cells in the parathyroid adenoma.<sup>[16]</sup>

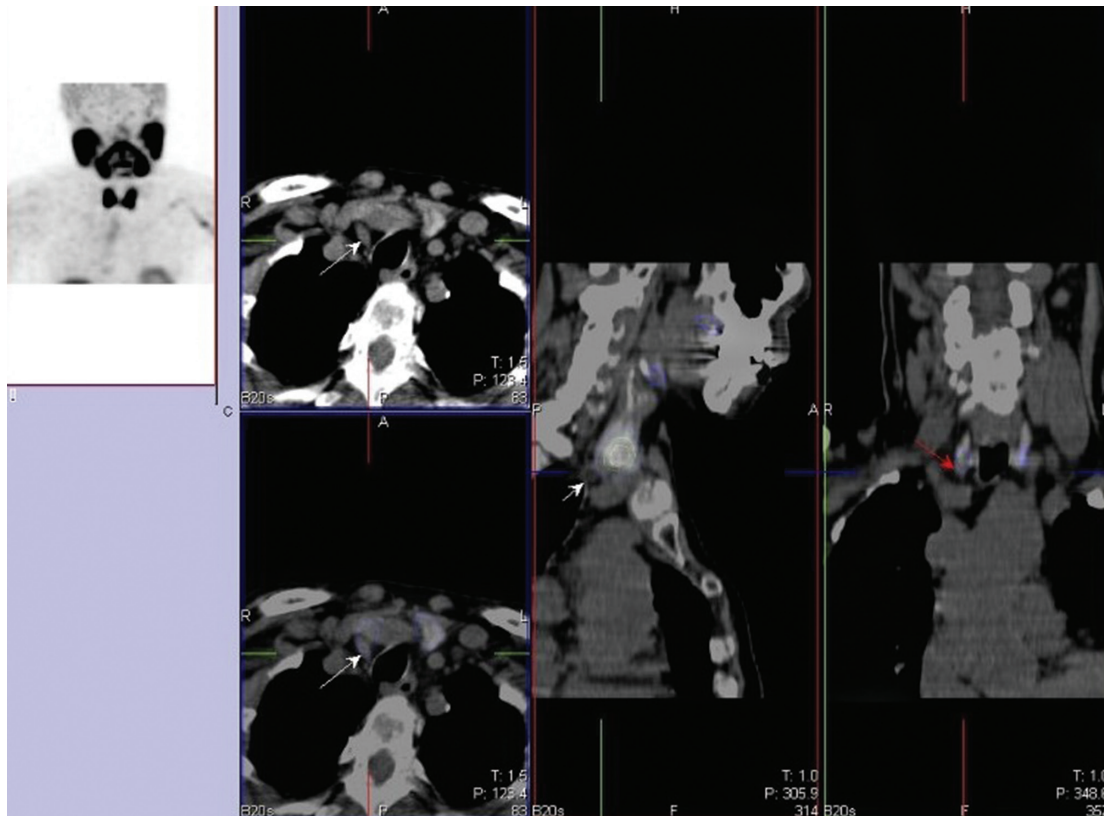
The primary limitation of our research is the limited number of patients we included. However, having in mind the trend towards minimally invasive surgery and the increased demand for hybrid parathyroid imaging, more patients should be examined in order to demonstrate the diagnostic superiority of our dual-tracer subtraction scintigraphy combined with SPECT/CT protocol, so that the collected data could make a significant contribution.



**Figure 2A.** Dual-tracer subtraction of both  $^{99m}\text{Tc}$ -pertechnetate and  $^{99m}\text{Tc}$ -MIBI planar scans of a 53-year-old woman. A focal MIBI uptake is visualized below the lower pole of the right thyroid lobe, suggestive of adenoma of right lower parathyroid gland.



**Figure 2B.** SPECT/CT images of the same patient, showing a round lesion with a diameter of around 32 mm with focal MIBI uptake localized in the thorax retrotracheally at the level of Th3, suggestive of an intrathoracic ectopic parathyroid adenoma.



**Figure 3.** Images of a 71-year-old woman with primary hyperparathyroidism (PHT - 129 pg/ml, Ca - 2.75 mmol/l). Dual-tracer subtraction of both  $^{99m}\text{Tc}$ -pertechnetate and  $^{99m}\text{Tc}$ -MIBI planar images did not show a clear focus suspect for adenoma. The subsequent SPET/CT images showed a small lesion located caudally from the right thyroid gland, suspicious for parathyroid adenoma of the lower right parathyroid gland (white arrow on the axial and sagittal views and red arrow on the coronal slices).

## CONCLUSION

When combined with SPECT/CT, dual-radiopharmaceutical subtraction imaging offers the integration of functional and morphological data, optimizing diagnostic accuracy from a single exam and influencing surgical strategy and treatment outcome.

## Author contributions

T.S.: corresponding author, report writing, data collection, and drafting the manuscript; S.B.S.: report writing and interpretation; B.S.R.: data collection and patient follow-ups; M.T.D: data management and analysis. All co-authors listed here have agreed to have the manuscript submitted for publication.

## Conflict of Interest

We have no conflicts of interest to disclose.

## REFERENCES

- Spanu A, Schillaci O, Piras B, et al. SPECT/CT in hyperparathyroidism. *Clin Transl Imaging* 2014; 2:537–55.
- Madkhali T, Alhefdhi A, Chen H, et al. Primary hyperparathyroidism. *Ulus Cerrahi Derg* 2016; 32:58–66. doi: 10.5152/UCD.2015.3032
- Taubman ML, Goldfarb M, Lew JI. Role of SPECT and SPECT/CT in the surgical treatment of primary hyperparathyroidism. *Int J Mol Imaging* 2011; 2011:141593. doi: 10.1155/2011/141593
- Fraser WD. Hyperparathyroidism. *Lancet* 2009; 374(9684):145–58.
- Duan K, Gomez Hernandez K, Mete O. Clinicopathological correlates of hyperparathyroidism. *J Clin Pathol* 2015; 68(10):771–87.
- Grubbs EG, Edeiken BS, Gule MK, et al. Preoperative parathyroid imaging for the endocrine surgeon. In: *Handbook of Parathyroid Diseases: A Case-Based Practical Guide*. New York, NY: Springer; 2012: 19–40.
- Taterra D, Wong LM, Vikse J, et al. The prevalence and anatomy of parathyroid glands: a meta-analysis with implications for parathyroid surgery. *Langenbeck's Arch Surg* 2019; 404(1):63.
- Rubello D, Pelizzo MR, Boni G. Radioguided surgery of primary hyperparathyroidism using the low  $^{99m}\text{Tc}$ -sestamibi dose protocol: multi-institutional experience from the Italian Study Group on Radioguided Surgery and ImmunoScintigraphy (GISCRIS). *J Nucl Med* 2005; 46:220–6.
- Noureldine SI, Gooi Z, Tufano RP. Minimally invasive parathyroid surgery. *Gland Surg* 2015; 4(5):410–9.
- Hindié E, Ugur O, Fuster D, et al. Parathyroid task group of the

- EANM. 2009 EANM parathyroid guidelines. *Eur J Nucl Med Mol Imaging* 2009; 36:1201–16.
11. Assante R, Zampella E, Nicolai E, et al. Incremental value of sestamibi SPECT/CT over dual-phase planar scintigraphy in patients with primary hyperparathyroidism and inconclusive ultrasound. *Front Med (Lausanne)* 2019; 6:164. doi: 10.3389/fmed.2019.00164
  12. Krausz Y, Bettman L, Guralnik L, et al. Technetium-99m-MIBI SPECT/CT in primary hyperparathyroidism. *World J Surg* 2006; 30:76–83. doi: 10.1007/s00268-005-7849-2
  13. Botushanova AD, Botushanov NP, Yaneva MP. Nuclear medicine methods for evaluation of abnormal parathyroid glands in patients with primary and secondary hyperparathyroidism. *Folia Med (Plovdiv)* 2017; 59(4):396–404. doi: 10.1515/folmed-2017-0054
  14. Chehade F, Kanj A, Ghafari E, et al. Tc-99m-sestamibi/Tc-99m pertechnetate dual-tracer scintigraphy of parathyroid glands with double image subtraction: A dedicated short execution time protocol. *Imaging in Medicine* 2021; 13(6):1–10.
  15. Petranović Ovčariček P, Giovanella L, Hindie E, et al. An essential practice summary of the new EANM guidelines for parathyroid imaging. *Q J Nucl Med Mol Imaging* 2022; 66:93–103.
  16. Ince S, Emer O, Deveci S, et al. Complementary role of parathormone washout test to (99m)Tc-MIBI parathyroid scintigraphy and histopathologic analysis of cell types in parathyroid adenomas. *Rev Esp Med Nucl Imagen Mol (Engl Ed)* 2018; 37:205–10.

# Субтракционная сцинтиграфия с двумя трейсерами в сочетании с SPECT/CT у предоперационных пациентов с первичным гиперпаратиреозом

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## Резюме

**Введение:** Гиперпаратиреоз – это эндокринное заболевание, вызванное избыточной выработкой паратиреоидного гормона, секретируемого паращитовидными железами. Хотя это заболевание сопровождается множеством симптомов, у большинства людей оно в настоящее время протекает бессимптомно и обнаруживается во время рутинного лабораторного скрининга.

**Цель:** Исследование демонстрирует диагностическую точность нашей двойной субтракционной паратиреоидной сцинтиграфии в сочетании с протоколом визуализации SPECT/CT

**Материалы и методы:** Ретроспективное исследование проводилось в период с 1 июня 2021 года по 1 июня 2023 года. Группа из 30 пациентов – 29 женщин (96,7%) и 1 мужчина (3,3%) в возрасте от 37 до 86 лет (среднее: 61,2, стандартное отклонение: 11,6) с клиническим подозрением на первичный гипотиреоз – прошла визуализацию паращитовидных желез для предоперационной локализации аденомы паращитовидных желез или эктопической паращитовидной железы.

**Результаты:** У двадцати шести из тридцати пациентов с первичным гиперпаратиреозом результаты сканирования были положительными, а у четырех пациентов – отрицательными. Результаты показали аденому нижних паращитовидных желез у 18 пациентов. Аденома верхних паращитовидных желез была обнаружена у 3 пациентов. Эктопическая паращитовидная железа была обнаружена у 4 пациентов. У одного пациента наблюдалось мультигландулярное поражение паращитовидных желез. Планарная сцинтиграфия была положительной на наличие гиперфункции паращитовидных желез у 15 пациентов (50%), тогда как SPECT/CT визуализация была положительной у 26 пациентов (86,7%) и отрицательной у 4 пациентов (13,3%).

**Выводы:** Сочетание функциональных и морфологических данных, полученных в результате одного обследования с помощью двойной радиофармацевтической субтракционной визуализации и SPECT/CT, позволяет повысить точность диагностики, что влияет на выбор хирургической техники и результат лечения.

## Ключевые слова

субтракция изображений, аденома паращитовидной железы, однофотонная эмиссионная компьютерная томография с компьютерной томографией