



Visualizing hyperparathyroidism: A pictorial essay of Tc-99m MIBI parathyroid imaging across different etiologies

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ABSTRACT

Parathyroid scintigraphy is an imaging technique that uses gamma-emitting radionuclide to locate hyperfunctioning parathyroid glands in patients with hyperparathyroidism. It is valuable for preoperative assessment before parathyroidectomy, which is a curative surgery in most cases of primary hyperparathyroidism and some cases of secondary hyperparathyroidism. There are several different techniques for parathyroid scintigraphy. In general, the scintigraphy is performed with Tc-99m MIBI, a mitochondria-targeting radiotracer. Some techniques also supply the Tc-99m MIBI scintigraphy with thyroid scintigraphy to differentiate between thyroid and parathyroid tissue. Parathyroid scintigraphy can detect primary hyperparathyroidism with a sensitivity of 80% and a specificity of 84%. It can also detect secondary hyperparathyroidism with a sensitivity of 58% and a specificity of 93%. The unique advantage of parathyroid scintigraphy is the ability to identify supernumerary and ectopic parathyroid abnormalities, which can significantly affect surgical planning and outcomes.

KEYWORDS

radionuclide imaging, parathyroid scintigraphy, hyperparathyroidism

Introduction

Parathyroid scintigraphy is a general term that is commonly used to refer to parathyroid imaging techniques with gamma-emitting radionuclide. These techniques are performed using gamma cameras or single photon emission computed tomography (SPECT) systems. Parathyroid scintigraphy is useful for the localization of the hyperfunctioning parathyroid gland in patients with hyperparathyroidism [1].

Hyperparathyroidism is a condition in which the blood level of parathyroid hormone (PTH) increases. Hyperparathyroidism can be classified as *primary* or *secondary*. Primary hyperparathyroidism is hyperparathyroidism resulting from inappropriate PTH secretion. The most common cause of primary hyperparathyroidism is single parathyroid adenoma, which accounts for 80% of cases. The remaining primary hyperparathyroidism is the result of primary parathyroid hyperplasia, multiple adenomas, or parathyroid carcinoma. Secondary hyperparathyroidism is hyperparathyroidism resulting from low serum calcium that stimulates the parathyroid glands, which is usually characterized by elevated serum PTH with low or normal serum calcium. Some patients with secondary hyperparathyroidism develop autonomous PTH secretion, resulting in elevated serum calcium. This setting of secondary hyperparathyroidism is sometimes referred to as *tertiary* hyperparathyroidism [2].

Parathyroidectomy is the curative treatment for primary hyperparathyroidism and is indicated in many cases of secondary hyperparathyroidism. Parathyroid imaging plays an important role in surgical planning and parathyroid scintigraphy possesses several unique advantages. In primary hyperparathyroidism, parathyroid scintigraphy can differentiate between single and multiple gland diseases as well as identify ectopic hyperfunctioning parathyroid gland. In secondary hyperparathyroidism, parathyroid scintigraphy can identify supernumerary and ectopic parathyroid glands that need to be removed and may be helpful in selecting the least hyperfunctioning gland as a candidate for autoimplantation [1, 3].

Anatomy and histology of parathyroid glands

Most people have four parathyroid glands located posterior to the upper and lower poles of the thyroid gland. Two parathyroid glands posterior to the upper poles of the thyroid gland, called *superior* parathyroid glands, develop for the fourth pharyngeal pouches. Two parathyroid glands posterior to the lower poles of the thyroid gland are called *inferior* parathyroid glands. The inferior parathyroid glands originate from the third pharyngeal pouches, which also give rise to the thymus.

Variations of the parathyroid glands are relatively common, with approximately 13% of the population having supernumerary parathyroid glands and 16% of the people having ectopic parathyroid glands. Ectopic parathyroid glands may reside within the thyroid gland, along the thyrothymus conduct, in the mediastinum, or elsewhere in the head and neck region [4].

Each of the normal parathyroid glands is 5 mm in diameter and 50 mg in weight [4]. There are two distinct cell types in the parathyroid glands: chief cells, and oxyphil cells. The chief cells are the more abundant cells with smaller size and are responsible for the synthesis of PTH. The oxyphil cells are the larger cells with orange-pink cytoplasm on haematoxylin and eosin (H&E) stain. This staining characteristic reflects a high concentration of mitochondria, which is essential for parathyroid scintigraphy [5].

Parathyroid scintigraphy

There are two techniques in parathyroid scintigraphy: the dual tracer technique and the dual phase technique. Both techniques require a mitochondria-targeting radiotracer, the most common of which is technetium-99m sesta-methoxyisobutylisonitrile (Tc-99m MIBI). This tracer is the gamma-emitting isotope Tc-99m coordinated with six molecules of the cationic lipophilic ligand MIBI. Its lipophilic nature allows the tracer to diffuse passively through the plasma membrane from the extracellular compartment to the cytosol and from the cytosol to the mitochondria. Within the mitochondria, the cations of the tracer bind to the negative charges on the inner surface of the mitochondrial membrane; therefore,

resulting in the high tracer concentration in the mitochondria. This higher concentration will show up as high Tc-99m avidity of the mitochondria-rich tissue [3, 6].

Because Tc-99m-based imaging typically has a spatial resolution limit around 6 mm, normal parathyroid glands are too small to visualize on parathyroid scintigraphy. Although the enlarged parathyroid glands can be detected on parathyroid scintigraphy, identification of parathyroid gland on parathyroid scintigraphy is challenging due to the Tc-99m MIBI avidity of the adjacent thyroid gland 10–15 min after Tc-99m MIBI injection [2].

The dual tracer technique can help identify parathyroid glands by performing an additional thyroid scintigraphy, either with Tc-99m pertechnetate or I-123. In this technique, the enlarged parathyroid glands can be identified as the Tc-99m MIBI-avid lesion which is negative on thyroid scintigraphy. Identification can be done visually or with the assistance of image processing software.

The dual phase technique substitutes thyroid scintigraphy with an additional delayed Tc-99m MIBI scan 90–150 min after tracer injection. Normally, the thyroid gland washes out the Tc-99m MIBI at a much faster rate than the enlarged parathyroid glands and the enlarged parathyroid gland is seen as the lesion with Tc-99m MIBI retention on the delayed Tc-99m MIBI scan [3].

Causes of hyperparathyroidism

Parathyroid adenoma

Parathyroid adenoma is the most common cause of primary hyperparathyroidism. Most parathyroid adenomas arise from one gland, but up to 15% of primary hyperparathyroidism results from multiple gland adenomas. It is reported that single gland adenomas are more frequent in the inferior glands and multiple gland adenomas are more frequent in the superior glands [7]. Differentiating single gland adenomas from multiple gland adenomas and parathyroid hyperplasia is essential for surgical planning because single gland adenomas allow minimally invasive surgery, which has lower morbidity compared to surgical removal. Because ectopic adenomas represent 10% of all cases of parathyroid adenomas, parathyroid scintigraphy, which has superior sensitivity to computed tomography and magnetic resonance imaging in the detection of ectopic parathyroid glands, has a significant impact on the treatment of the patients [3].

There are multiple variations among parathyroid adenomas. Most parathyroid adenomas consist mainly of chief cells, which is consistent with excess PTH secretion. Some variants of parathyroid adenoma include oncocytic changes, water-clear cells adenomas, cystic degeneration, and lipoadenomas. Variants with a high component of oxyphil cells are expected to be more Tc-99m MIBI avid, but clinical evidence is still inconclusive and the effects of different parathyroid adenoma variants on the accuracy of parathyroid scintigraphy have not been established [8] (Fig. 1).



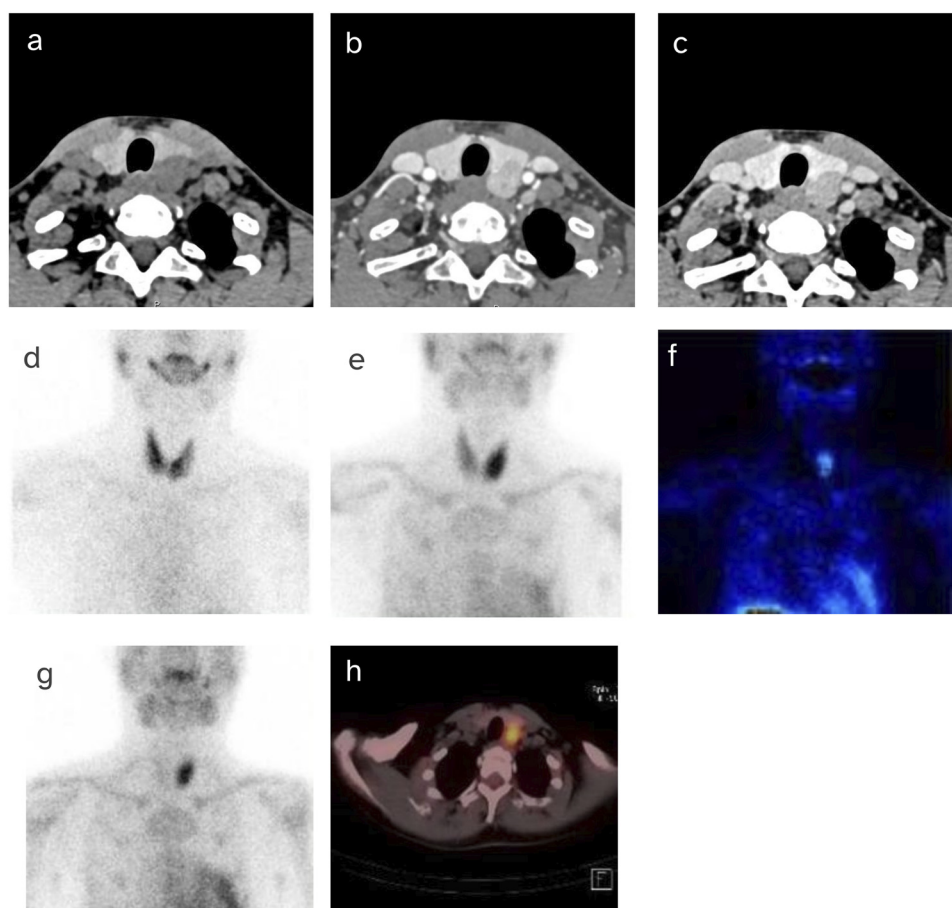


Fig. 1. An 18-year-old man presented with multiple fractures. His blood test reveals serum intact PTH = $2,560 \text{ pg mL}^{-1}$ (15–65), calcium 13.7 mg dL^{-1} (8.5–10.5), phosphate 1.8 mg dL^{-1} (2.5–4.5) and 25-hydroxyvitamin D 10.9 ng mL^{-1} (30–100). His parathyroid CT showed a well defined hypodense nodule (a) with arterial enhancement (b) and venous washout (c) posterior to the left lower pole of the thyroid gland. The dual tracer parathyroid scintigraphy revealed a non Tc-99m pertechnetate-avid (d) and Tc-99m MIBI-avid (e) lesion at the left lower pole. The lesion was clearly visible on subtraction image (f) and was Tc-99m MIBI-avid in the delayed planar image (g) and the SPECT/CT (h). A left parathyroidectomy was performed, revealing a 4.2 cm parathyroid adenoma. After surgery, the patient's blood test results were as follows: Intact PTH = 10.3 pg mL^{-1} (15–65), calcium = 8.9 mg dL^{-1} (8.5–10.5), and phosphate = 2.7 mg dL^{-1} (2.5–4.5). His serum 25-hydroxyvitamin D was not measured

Parathyroid hyperplasia

Parathyroid hyperplasia is a condition in which the masses of all parathyroid glands increase. It is the pathological finding of 15–20% of primary hyperparathyroidism and all secondary hyperparathyroidism. Conventionally, parathyroid hyperplasia is classified into nodular and diffuse patterns [8]. Some evidence suggested that parathyroid scintigraphy is more sensitive to detect the nodular subtype. However, recent investigations showed overlaps in molecular markers between parathyroid hyperplasia and multiple gland parathyroid adenomas in primary hyperparathyroidism and more studies are required to make a clear distinction between these two entities (Fig. 2) [5, 9].

Parathyroid carcinoma

Parathyroid carcinoma is a rare cause of primary hyperparathyroidism, accounting for less than 1% of cases. The clinical course of parathyroid carcinoma is usually indolent but progressive. Some characteristics that may differentiate

between parathyroid adenomas and parathyroid carcinoma are local invasion and metastasis. However, metastasis is rarely present at initial presentation (Fig. 3) [10].

Discussion

Parathyroid scintigraphy is a diagnostic imaging technique that is used to locate the hyperfunctioning parathyroid gland in patients with hyperparathyroidism. One major benefit of parathyroid scintigraphy is its ability to identify abnormalities in the supernumerary and ectopic parathyroid glands, which is valuable for surgical planning. In primary hyperparathyroidism, parathyroid scintigraphy has a sensitivity and specificity of 80% and 84%, respectively. For secondary hyperparathyroidism, the sensitivity and specificity are 58% and 93%, respectively [11, 12]. Compared to other modalities, the sensitivity of parathyroid scintigraphy was not significantly different from those of ultrasonography, computed tomography, or magnetic resonance imaging [12].

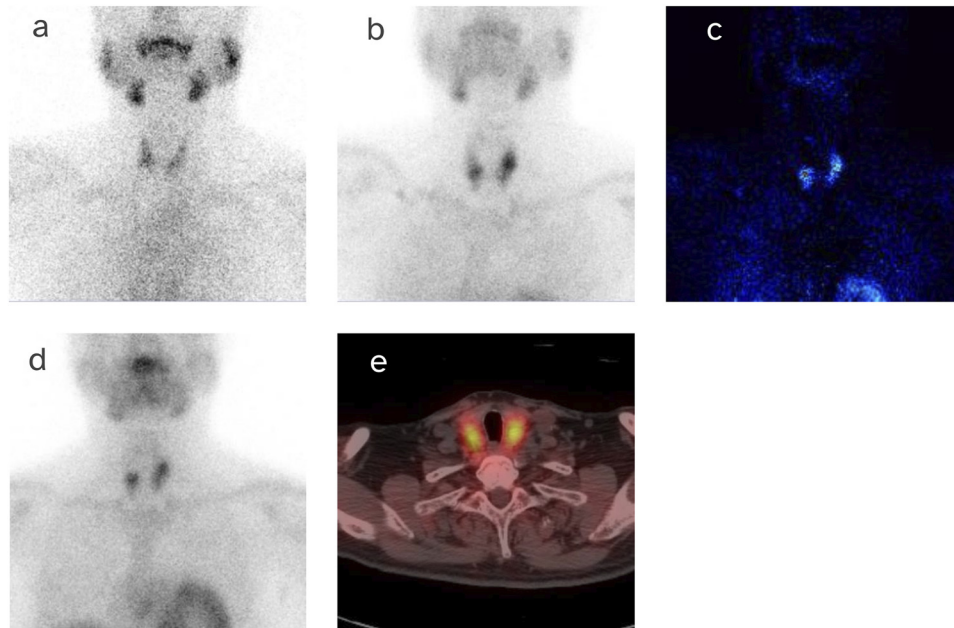


Fig. 2. A 51-year-old man with chronic kidney disease presented with elevated serum parathyroid hormone. His blood test reveals serum intact PTH = $3,229 \text{ pg mL}^{-1}$ (15–65), calcium 10.9 mg dL^{-1} (8.5–10.5), phosphate 5.8 mg dL^{-1} (2.5–4.5) and 25-hydroxyvitamin D 33.4 ng mL^{-1} (30–100). His dual tracer parathyroid scintigraphy revealed non Tc-99m pertechnetate-avid (a) and Tc-99m MIBI-avid lesions (b), most obvious at bilateral lower poles of the thyroid gland. The subtraction image (c), delayed planar Tc-99m MIBI image (d), and SPECT/CT (e) also showed lesions at bilateral lower poles. A four-gland parathyroidectomy was performed, revealing hyperplasia of all glands. The blood test results after surgery were as follows: intact PTH = 24.6 pg mL^{-1} , calcium 7.3 mg dL^{-1} , phosphate 2.9 mg dL^{-1} , 25-hydroxyvitamin D 41.4 ng mL^{-1} (30–100)

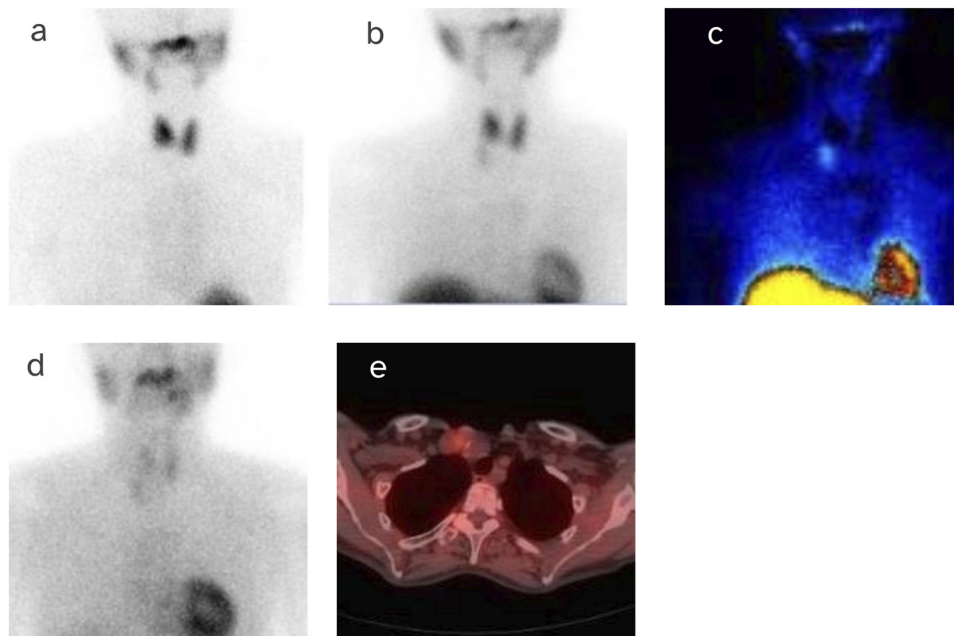


Fig. 3. A 66-year-old woman presented with asymptomatic hypercalcemia. Her blood test reveals serum intact PTH = $1,643 \text{ pg mL}^{-1}$ (15–65), calcium 12.84 mg dL^{-1} (8.5–10.5), phosphate 1.74 mg dL^{-1} (2.5–4.5), and 25-hydroxyvitamin D 19.5 ng mL^{-1} (30–100). Her dual tracer parathyroid scintigraphy revealed non Tc-99m pertechnetate-avid (a) and Tc-99m MIBI-avid lesion (b) inferior to the right lower pole of the thyroid gland, which was confirmed on the subtraction image (c). The delayed planar Tc-99m MIBI image (d), and SPECT/CT (e) shows minimal retention of tracer in the same area. Her parathyroid scan revealed a discordant Tc-99m MIBI-avid focus inferior to the right lower pole of the thyroid gland. A right inferior parathyroidectomy was performed, revealing a 3.3-cm parathyroid carcinoma. After surgery, the patient's blood test results were as follows: intact PTH = 62.5 pg mL^{-1} (15–65), calcium 10.0 mg dL^{-1} (8.5–10.5), phosphate 2.2 mg dL^{-1} (2.5–4.5). Her serum 25-hydroxyvitamin D was not measured

Each of the parathyroid scintigraphy techniques - dual tracer and dual phase - has its own advantages and disadvantages. The dual phase technique is simpler, but the dual tracer might be advantageous in patients with rapid Tc-99m MIBI clearance from the parathyroid glands, which is often observed in parathyroid hyperplasia or parathyroid adenomas with p-glycoprotein overexpression [13].

Cellular biology and molecular ultrastructure studies confirmed that mitochondria are the ultrastructure responsible for Tc-99m MIBI uptake in hyperfunctioning parathyroid glands. A clear correlation between Tc-99m MIBI uptake and cellular mitochondria content under electron microscopy has been established [9]. An in vitro study also demonstrated that mitochondria extracted from parathyroid adenomas expressed the ability to accumulate Tc-99m MIBI [15].

Whether the oxyphil content within the functioning parathyroid gland can determine the Tc-99m MIBI avidity remains controversial. A study in cases of primary hyperparathyroidism found that parathyroid adenomas with oxyphil content greater than 20% had a 10-fold increase in Tc-99m MIBI positivity rate [14]. Furthermore, parathyroid adenomas with positive Tc-99m MIBI scans are found to have a significantly higher oxyphil content [5]. However, a study in cases of secondary hyperparathyroidism found no correlation between the percentage of oxyphil cells and Tc-99m MIBI uptake [15].

Almost all evidence agreed that the implementation of SPECT could significantly enhance the efficacy of parathyroid scintigraphy. However, the evidence of the added benefit of hybrid SPECT/CT over SPECT is still conflicting [12, 16].

Recent developments of positron emitting radiotracer provided some newer promising tracers such as fluorine-18 fluorocholine that provided added benefits of superior resolution of positron emission tomography (PET).

Conclusions

Parathyroid scintigraphy is a parathyroid imaging modality with significant roles in the preoperative assessment of patients with hyperparathyroidism. In dual tracer parathyroid scintigraphy, hyperfunctioning parathyroid glands are characterized by Tc-99m MIBI-avid lesions without uptake on Tc-99m pertechnetate or I-123 thyroid scan. In dual phase parathyroid scintigraphy, hyperfunctioning parathyroid glands are characterized by Tc-99m MIBI-avid lesions with Tc-99m MIBI retention at delayed scan. One distinct advantage of parathyroid scintigraphy over other parathyroid imaging modalities is its ability to localize supernumerary and ectopic hyperfunctioning thyroid tissue, which is essential for successful a curative operation in cases of hyperparathyroidism.

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SV contributed to the interpretation of parathyroid scintigraphy, and to writing the manuscript.

Both authors edited, reviewed the final version of the manuscript, and agreed to submit it to IMAGING for publication.

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Consent for publication: The institutional review board approved this retrospective study, and the requirement to obtain informed consent was waived.

Availability of data and material: The data are available upon reasonable request to the corresponding author.

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