

Original Article

Combination of dual-phase and dual-tracer SPECT/CT imaging with voxel-based subtraction in the assessment of normocalcemic primary hyperparathyroidism in patients with osteoporosis: a pilot study

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Abstract: Objective: We hypothesized that parathyroid (PT) scintigraphy could be clinically valid in identifying patients, indicated for parathyroidectomy, presenting with consistently elevated PTH and normal serum calcium concentrations. Methods: The parathyroid was examined using ^{99m}Tc-MIBI and ^{99m}TcO₄ SPECT imaging in 75 patients with a BMD ≤ -2.5 T (lumbar spine, proximal femur, or distal one-third of the radius) with concomitantly elevated serum PTH concentration. Results: After excluding patients with secondary hyperparathyroidism, PT scintigraphy indicated the presence of an adenoma in all patients (32) with elevated serum PTH and calcium concentrations. After parathyroidectomy, PT adenoma was confirmed in all surgically treated patients (29). The predictive positive value of PT scintigraphy was 87%. PT scintigraphy indicated the presence of an adenoma in 26/34 patients with elevated serum PTH and normal calcium concentrations. Of these patients, 12 were indicated for parathyroidectomy; PT adenoma was found in all cases. In these patients, the predictive positive value was 85%. In 8 patients with increased PTH and normal serum calcium, scintigraphy did not reveal an enlarged PT. In these patients, serum PTH was significantly lower compared to patients with increased calcium and PTH. Conclusion: The combined dual-phase/dual-tracer SPECT imaging method, including low-dose CT, improves the identification of pathological parathyroid glands and is therefore suitable for presurgical detection of both typical primary hyperparathyroidism and normocalcemic primary hyperparathyroidism. The method should be of value for better management of the increasing number of cases seen in subspecialty metabolic bone practices.

Keywords: Normocalcemic primary hyperparathyroidism, osteoporosis, nuclear medicine, tomography

Introduction

Normocalcemic primary hyperparathyroidism (NPHPT), a variant of the hypercalcemic presentation of primary hyperparathyroidism (PHPT), is characterized by consistently elevated PTH concentrations alongside with normal total and ionized serum calcium concentrations and in the absence of secondary causes for elevated PTH concentrations, such as vitamin D insufficiency, chronic kidney disease, treatment with drugs known to increase PTH (thiazides, bisphosphonate, denosumab, and lithium), hypercalciuria, and occult malabsorption syndromes [1-4]. The condition can proceed to hypercalcemia as part of the disease course, in

which case the hypercalcemic form of the disease becomes evident [5-8]. The elevated PTH concentration in this early phase is postulated to cause reduced cortical bone density, while hand, spine and hip bone density improves in response to parathyroidectomy for NPHPT [9].

In this study, parathyroid SPECT imaging was used as a consequent confirmation and identification of parathyroid adenoma, to facilitate the clinical judgment on parathyroidectomy in patients presenting with consistently elevated PTH concentrations and normal serum calcium concentrations. Parathyroid SPECT imaging is based on dual-phase and dual-tracer comparisons employing a volume rendering view, spa-

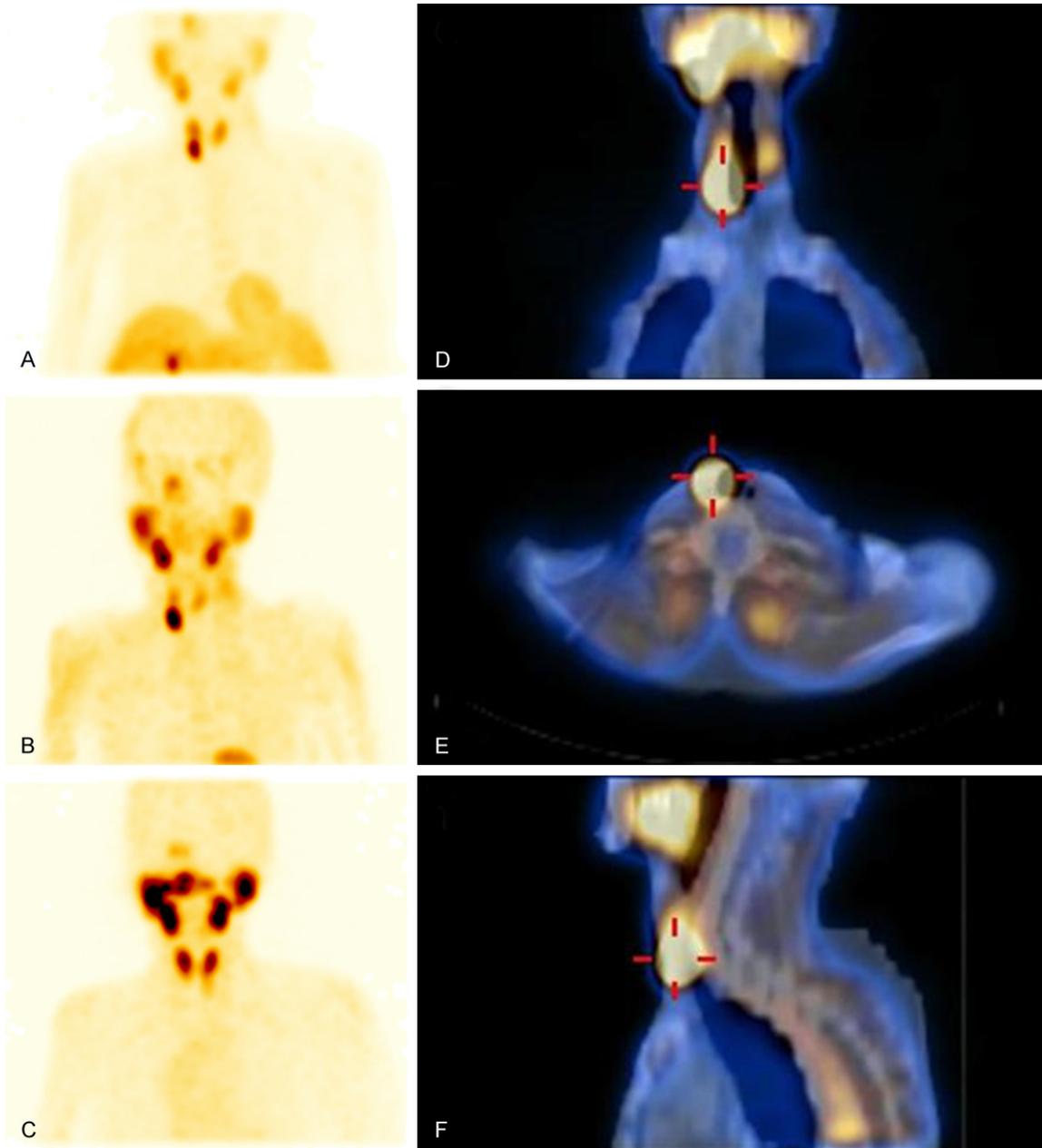


Figure 1. Adenoma of the right lower parathyroid gland in a 70-year-old woman with osteoporosis and normocalcemic hyperparathyroidism (lesion of the increased activity in the lower right parathyroid gland adenoma); serum calcium, 2.28 mmol/l, phosphorus, 0.98 mmol/l, iPTH 37 pmol/l. Left images from (A) early ^{99m}Tc -MIBI SPECT, (B) late ^{99m}Tc -MIBI SPECT, (C) $^{99m}\text{TcO}_4$ SPECT and right images of ^{99m}Tc -MIBI SPECT/CT from (D) coronal view, (E) transverse view, (F) sagittal view with lower right parathyroid gland adenoma.

tial registration, and voxel-based semi-quantitative comparisons [10-12]. These two methods together, both of which are based on Single Photon Emission Computed Tomography (SPECT) images, aid in better sensitivity regarding location of the hyper-producing parathyroid glands [13]. Moreover, a thyroid scan can be helpful in differentiating a thyroid nodule from a hyper-functional parathyroid gland [14].

Materials and methods

Subjects

We examined parathyroid SPECT imaging from 75 consecutive patients (71 females, 4 males) referred for parathyroid (PT) scintigraphy by cooperating osteoporosis clinics between 20-09 and 2015. Patients were found to have a

BMD \leq -2.5 T (lumbar spine, proximal femur, or distal one-third of the radius) and concomitantly elevated serum PTH concentrations (mean of 2 measurements). The patients underwent a clinical examination (a full clinical history including details of co-morbidity, a detailed personal history of the rheumatic disease, fracture history, alcohol intake, smoking habits, height loss, family history of osteoporosis, and hip fracture) as well as physical and laboratory examinations. Serum calcium concentrations were corrected for variations in albumin (mean of 2 measurements). If indicated, surgery was performed within 2 months of clinical, laboratory and parathyroid SPECT examination.

Patients with vitamin D insufficiency (25-hydroxyvitamin D concentrations \leq 50 nmol/l) were not included in the final analysis [15]. Other secondary causes of hyperparathyroidism were also excluded, including renal insufficiency (glomerular filtration rate \leq 40 ml/min per 1.73 m²); liver disease; significant hypercalciuria (urinary calcium \geq 88 mmol per 24 h); use of thiazide diuretic or lithium. To exclude other metabolic bone diseases (e.g. Paget's disease) [1], a whole body scintigraphic bone scan was performed in 39/69 patients, using the GE Infinia-Hawkeye dual-head gamma camera, with LEHR collimator. The scan was started two to three hours after administration of 500-700 MBq ^{99m}Tc-HDP (hydroxymethylendiphosphonate). Whole body images were supplemented with SPECT images of regions of interest with the following acquisition parameters: 120 views, 20 sec/frame, matrix 128 × 128.

Parathyroid SPECT imaging

Each patient underwent two SPECT examinations: a dual-phase ^{99m}Tc-MIBI SPECT study was performed followed by a single-phase ^{99m}TcO₄ SPECT study on a subsequent day. The dual-phase study consisted of an early phase acquired 5 minutes after intravenous (IV) administration of 700 MBq ^{99m}Tc-MIBI and a late phase acquired 2-2.5 hours later. Late images were accompanied by a low-dose CT. The single-phase ^{99m}TcO₄ SPECT was acquired immediately after the IV administration of 200 MBq ^{99m}TcO₄. The examinations were performed using a GE Infinia-Hawkeye dual-head gamma camera using the standard acquisition protocol: 120 projections with 3° angular steps in a 128 × 128 matrix at 20 seconds per view using

a low energy high-resolution parallel-hole collimator with broad field of view covering the neck and mediastinum extending from the parotid glands to the diaphragm. Data were reconstructed on Xeleris workstation (GE) using standard reconstruction parameters. The low-dose CT parameters involved a current of 2.5 mA, 140 kV voltage, and a 5 mm slice thickness reconstructed in 256 × 256 matrixes. The CT rotated at 2.6 rotations per minute (**Figure 1A-F**). The dual-phase ^{99m}Tc-MIBI SPECT images were evaluated and compared visually using the volume rendering (maximum intensity projection) method. Dual-tracer comparisons between early ^{99m}Tc-MIBI and ^{99m}TcO₄ SPECT images was performed as voxel-by-voxel subtraction after automatic spatial registration based on the area covering the region from the top of the salivary glands to the bottom of the thyroid gland (**Figure 2**). All MIBI scans were evaluated by at least two experienced nuclear medicine physicians.

Biochemical analysis

Blood samples were collected the morning, after an overnight fast. Serum intact PTH (iPTH, reference range, 1.6-6.9 pmol/l) and 25-hydroxyvitamin D (reference range, 50-200 nmol/l) was measured using electro-chemiluminescence-based immuno-analysis (Cobas Analyzer, Roche Diagnostics GmbH, Germany). The within run imprecision of the PTH was below 6%. The serum concentration of calcium (reference range, 2.20-2.65 mmol/l) was determined using the colorimetric color test Calcium Arsenazo III on a Beckman Coulter AU 400 analyzer. Corrected calcium was calculated [16].

Statistical analysis

Data are presented as means and 95% CI. Two-group comparisons were analyzed using the Mann-Whitney Rank Sum test and three-group comparisons were analyzed using One-way ANOVA on Ranks, Dunn's Method. In all instances, significance was assigned at P < 0.05.

Results

Initially, we identified 37 patients with elevated serum PTH and elevated calcium concentrations, and 38 patients with elevated serum PTH and normal total serum calcium concentrations. For statistical analysis, we excluded 3

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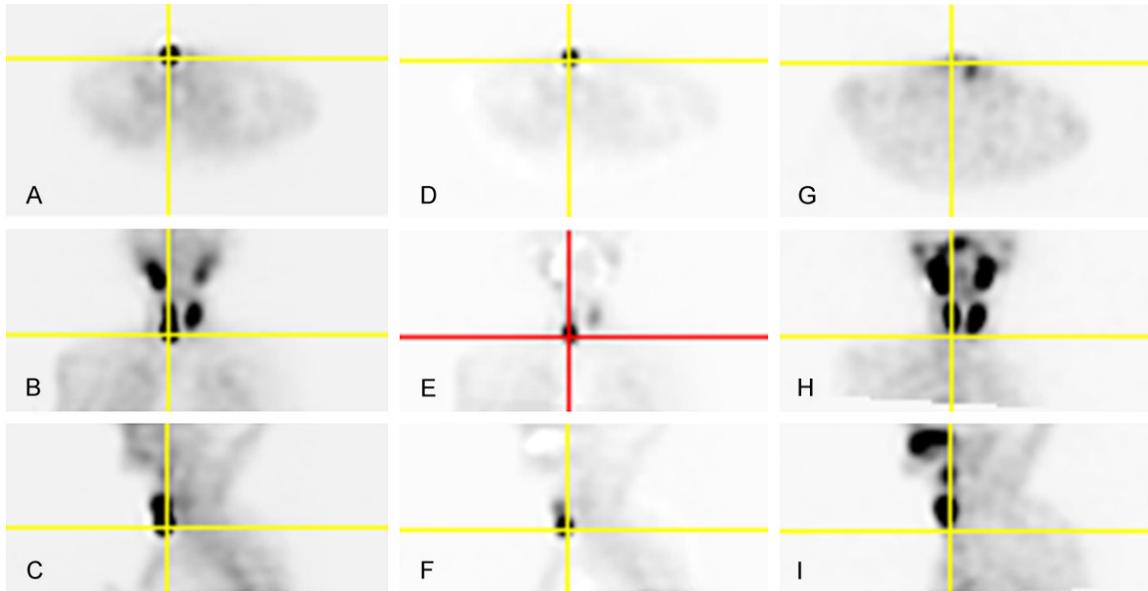


Figure 2. Voxel-based dual tracer subtraction: After spatial registration and uptake normalization, the images were subtracted: ^{99m}Tc -MIBI (A-C) in all views (axial, coronal and sagittal) minus ^{99m}Tc -O₄ (G-I) in all views. (D-F) All views represent a suspicious finding that consists of a small group of voxels, which is visible in the contrast image as a residue of ^{99m}Tc -MIBI and records a difference in an order of tens or hundreds of percent.

Table 1. Characteristics of study participants. Values are median and 95% CI

	All patients	Scintigraphy		Parathyroid histology in patients with positive scintigraphy		
		Parathyroids enlarged	Parathyroids not enlarged	Increased calcium, increased PTH	Normal calcium, increased PTH	
Women/men (No.)	62/4	31/1	24/2	7/1	28/1	11/1
Age (years)	67.0	65.5	69.0	75.0	65.0	68.5
	42.4-80.0	43.1-76.9	39.2-80.0	49.0-85.0	42.4-76.1	42.4-76.1
Corrected calcium (mmol/l)	2.61	2.81 ^a	2.51	2.50	2.81	2.53
	2.34-3.13	2.66-3.38	2.33-2.60	2.35-2.60	2.66-3.42	2.29-2.60
iPTH (pmol/l)	12.1	16.2	11.3	9.9 ^b	15.8	19.7
	7.7-45.5	8.0-38.6	8.0-74.1	7.0-11.9	8.0-41.1	9.4-90.1
25-hydroxyvitamin D (nmol/l)	67.2	61.2	68.3	67.6	64.4	73.6
	50.6-98.0	50.4-84.5	51.9-116.6	50.9-78.7	50.3-84.6	62.0-127.3

^a: P < 0.05 vs patients with normal calcium (One-way ANOVA on Ranks, Dunn's Method); ^b: P < 0.05 vs patients with increased PTH and increased calcium (One-way ANOVA on Ranks, Dunn's Method); ^c: P < 0.001 vs patients with normal calcium (Mann-Whitney Rank Sum test).

patients in whom the 25-hydroxyvitamin D value was not available, and 6 patients with PT hyperplasia and vitamin D deficiency documented through parathyroidectomy. The characteristics of the final patient population are presented in **Table 1**.

In 32 patients with elevated serum PTH and elevated calcium concentrations, PT scintigra-

phy indicated the presence of an adenoma (**Table 1**). Three patients with primary hyperparathyroidism refused the surgical intervention. A parathyroidectomy was performed on 29 patients and PT adenoma was confirmed in all 29 cases (**Table 2**).

In the 34 patients with elevated serum PTH and normal calcium concentrations (corrected for

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Table 2. Scintigraphic and surgical findings in 29 patients with primary hyperparathyroidism

Scintigraphic findings	Surgical findings						Total
	Dx upper PG	Dx Lower PG	Sin upper PG	Sin lower PG	Multi-focal. lesions	Ectopia	
Dx upper PG	1						1
Dx lower PG		7			2		9
Sin upper PG			8	1			9
Sin lower PG				6			6
Multi-focal. lesions		2	1		2		3
Ectopia						1	1
Total	1	9	9	7	2	1	29

Dx/Sin upper PG-right/left parathyroid gland; Dx/Sin lower PG-right/left parathyroid gland; Corresponding findings are in the grey cells.

Table 3. Scintigraphic and surgical findings in 12 patients with normocalcemic primary hyperparathyroidism

Scintigraphic findings	Surgical findings						Total
	Dx upper PG	Dx Lower PG	Sin upper PG	Sin lower PG	Multi-focal. lesions	Ectopia	
Dx upper PG	3						3
Dx lower PG		3					3
Sin upper PG			3				3
Sin lower PG				3			3
Multi-focal. lesions		1	1		2		2
Ectopia						1	1
Total	3	4	1	3		1	12

Dx/Sin upper PG-right/left parathyroid gland; Dx/Sin lower PG-right/left parathyroid gland; Corresponding findings are in the grey cells.

variations in albumin), PT scintigraphy was positive in 26 patients (**Table 1**). Of the 26 cases, 12 were indicated for parathyroidectomy. PT histology revealed PT adenoma in all 12 cases (**Table 3**). The other 14 patients were not elected for surgery, mostly by decision of the referring physician (9 patients). Five patients refused the surgical intervention.

In 8 patients with increased PTH and normal serum calcium, scintigraphy did not reveal an enlarged PT; however, serum PTH was significantly lower compared with patients with increased calcium and increased PTH (**Table 1**). **Figures 1 and 2** depicts an adenoma of the lower right parathyroid gland in a patient with osteoporosis and normocalcemic hyperparathyroidism (lower right parathyroid gland adenoma). **Figure 3** depicts the ^{99m}Tc-HDP whole body bone scan in the same patient.

In patients with PHPT, complete agreement between the scintigraphic and surgical findings with regard to location, including the number of lesions, was found in 23 of 29 patients (79%),

5 patients differed in the number of lesions; 3 parathyroid glands were scintigraphically false positive, and 2 were false negative. The predictive positive value was 87%.

In patients with NPHPT, complete agreement between the scintigraphic and surgical findings with regard to location, including the number of lesions, was found in 10 of 12 patients (83%), 2 patients differed in the number of lesions, but all patients had at least one positive parathyroid gland. The predictive positive value was 85%.

Discussion

To our knowledge, this is the first study using parathyroid SPECT imaging to facilitate the clinical judgement on parathyroidectomy in patients presenting with consistently elevated PTH concentrations and normal serum calcium concentrations. In this report, we document our experience with normocalcemic PHPT in 12 patients who had clinical features of osteoporo-

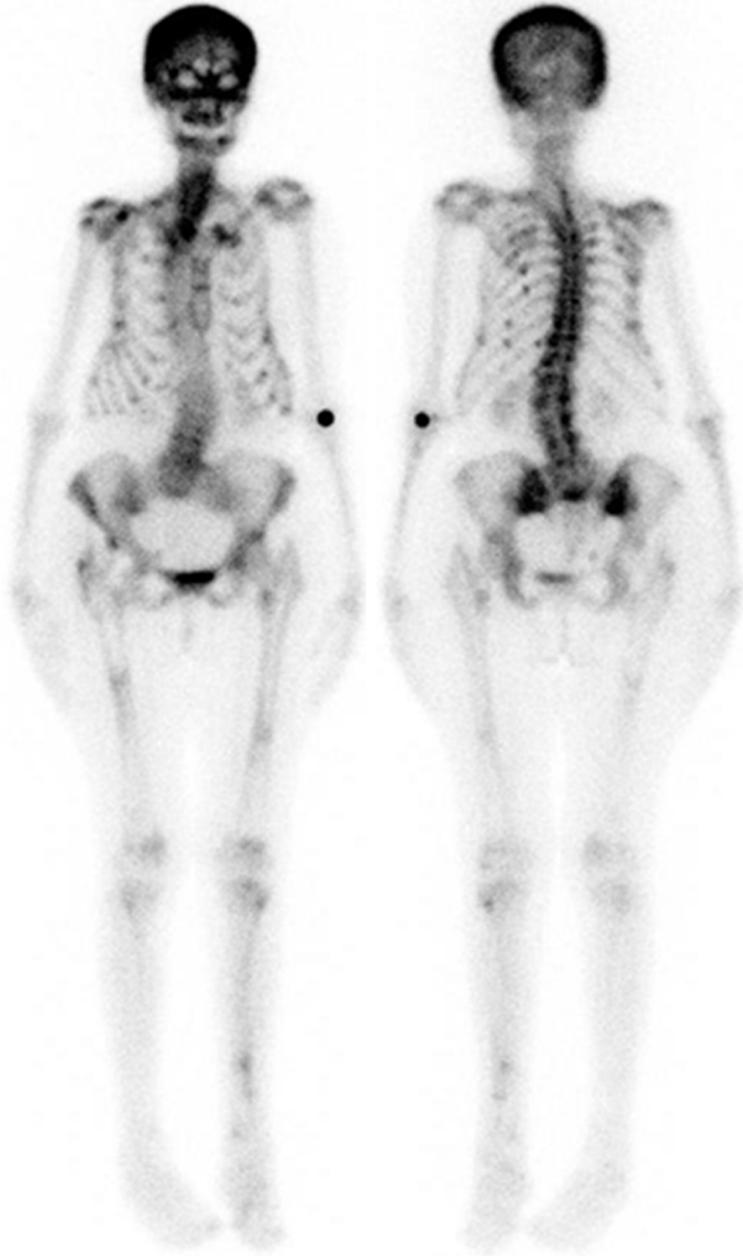


Figure 3. ^{99m}Tc -HDP whole body bone scan in the same 70-year-old patient (Figure 1) with osteoporosis and normocalcemic hyperparathyroidism (lower right parathyroid gland adenoma). Typical patterns of metabolic bone disease are seen in calvaria, ribs, costochondral junction, pelvis, and long bones.

sis, high PTH, normal serum calcium, and were diagnosed with PT adenoma. In our setting, parathyroid SPECT imaging provided a reasonably high positive predictive value for detecting parathyroid adenomas in PHPT and NPHPT (79% and 83%, respectively), which is in accordance with other studies in PHPT [17, 18]. High PTH levels increase bone turnover and decrease

bone mineral density (BMD). Screening an unselected population for normocalcemic PHPT could lead to the identification of a normocalcemic cohort whose parathyroid disease is minimal [19].

Our data suggest that parathyroid scintigraphy used for large-scale evaluations of PTH levels in association with normocalcemic individuals with osteoporosis would succeed in identifying those with the earliest forms of truly asymptomatic primary hyperparathyroidism. Moreover, preoperative localization of a parathyroid adenoma is crucial, especially when a targeted surgical approach is planned (i.e., minimally invasive parathyroidectomy) [20].

^{99m}Tc -Sestamibi; 2-methoxy-isobutyl-isonitril (^{99m}Tc -MIBI) scintigraphy is considered to be very useful technique for detection of parathyroid hyperplasia or adenoma [10, 20-22]. ^{99m}Tc -MIBI as the sole imaging agent washes out of normal thyroid tissue faster than it washes out of abnormal parathyroid adenomas and hyperplasia [21-26]. This difference increases with time, so delayed images are usually compared to earlier ones. Radiotracer washout from hyperplastic parathyroid gland can be undesirably fast and that is why a second study with ^{99m}Tc -pertechnetate (^{99m}Tc - O_4) was performed, and compared with the early (i.e., 5 min. post-administration) ^{99m}Tc -MIBI. ^{99m}Tc - O_4 is trapped by, but not incorporated into, the functioning thyroid tissue and does not accumulate in the parathyroid glands.

Using the MIBI washout technique, it is possible to detect parathyroid adenoma in approximately 60% of PHPT cases. Nevertheless, the washout rate in the thyroid and hyper-function-

ing parathyroid glands may be similar and so parathyroid hyperplasia (or adenoma) could be overlooked on the late (i.e., 2-2.5 hrs post-administration) MIBI scan. Generally, the subtraction technique (i.e., planar MIBI images-Tc) is considered more accurate than the washout technique [11, 25]. In our patients with NPHPT, as with patients with PHPT, a significant correlation was observed between the combination of dual-phase and dual-tracer SPECT/CT studies with voxel-based subtraction and parathyroid surgery in identification of enlarged parathyroid glands. Combining radionuclide imaging with (low dose) CT provides the highest accuracy (**Figure 1D-F**) with regard to structural anatomical detail and leads to the optimal surgical strategy [27-29].

This pilot study has several limitations. First, it was an observational study using consecutive patients during a specific period. Second, the data suffers from selection bias since patients were discovered during an evaluation for osteoporosis or fragility fractures. Third, ultrasonography examinations were not performed in our patients. Fourth, ionized calcium, which is the preferred method, was not measured in this study [30]. Sixth, the study excluded patients with diseases associated with hypo- or hyperproteinemia. And last, the relatively small sample size limited the strength of our conclusions regarding possible false negatives or false positive scintigraphy results. A multicenter, randomized, prospective study of different preoperative imaging modalities in NPHPT might be needed for a more accurate and objective investigation.

Conclusion

The proposed combined dual-phase and dual-tracer SPECT imaging method, including low-dose CT, improves identification of pathological parathyroid glands and therefore may be suitable not only for detection of PHPT but also for NPHPT, and may help in the management of the increasing number of such patients seen in subspecialty metabolic bone practices. Our patients with NPHPT, who underwent parathyroidectomy, had a positive surgical finding with histological confirmation of parathyroid gland adenoma. SPECT/CT-based localization was also very helpful in selection of the best therapeutic strategy.

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Disclosure of conflict of interest

None.

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