Am J Nucl Med Mol Imaging 2021;11(3):207-217
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0132836

Original Article

Influence of medication and PTH levels on detection of parathyroid adenomas with dual isotope parathyroid scintigraphy

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Received March 8, 2021; Accepted May 7, 2021; Epub June 15, 2021; Published June 30, 2021

Abstract: Localization of parathyroid adenomas is a crucial step to facilitate minimally invasive parathyroidectomy. In this study, we investigated sensitivity and positivity rate of SPECT-based dual isotope parathyroid scintigraphy in detecting parathyroid adenomas, and the effect of medication and parathyroid hormone (PTH)-level on detection of adenomas. Two hundred and thirty-seven patients with primary hyperparathyroidism undergoing dual isotope parathyroid scintigraphy with SPECT-CT in our centre between January 1st 2013 and December 31st 2017 were included in this retrospective study. Sensitivity and positivity rate for accurate location of parathyroid adenomas, based on histopathological findings after surgery and follow-up PTH and calcium, were calculated. The impact of pre-operative medication (thyroxin, calcium-antagonists, antacids, vitamin D, bisphosphonates and calcium) and PTH-levels between positive and negative scans was evaluated by using univariate and multivariate analysis, and a ROC analysis respectively. Overall patient-based sensitivity of scintigraphy for finding parathyroid adenomas was 72% for scintigraphy, with a positivity rate of 60%. No significant effect of investigated medication on positivity rate was found. PTH-level was significantly higher in patients with positive scintigraphy (median 96.3 ng/L vs 75.2 ng/L, $P < 0.01$). Optimum cut-off for detection of adenomas for PTH was 79.4 ng/L with a sensitivity of 67% and a specificity of 63%. In this retrospective cohort, sensitivity and positivity rate of dual-isotope SPECT-CT for parathyroid adenomas were in line with previous studies. No statistically significant influence of medication on positivity of scintigraphy was found, suggesting these medication types should not be stopped prior to scintigraphy. PTH level was no useful parameter to predict positivity of scintigraphic imaging.

Keywords: Parathyroid scintigraphy, dual isotope, PTH, medication

Introduction

Hyperparathyroidism is a relatively frequent endocrine disorder. The prevalence of primary hyperparathyroidism is 6.7 per 1000 in the UK [1]. Hyperparathyroidism is caused by an increased activity of the parathyroid glands and can be divided in primary, secondary, and tertiary hyperparathyroidism, depending on the cause. Primary and tertiary hyperparathyroidism are caused by an intrinsic change in excretion of parathyroid hormone, whereas secondary hyperparathyroidism is caused by extrinsic changes affecting the calcium homeostasis leading to an altered parathyroid hormone excretion (response to a low ionized calcium blood-level caused by kidney or bowel disease and typically caused by vitamin D deficiency) [2]. Diagnosis of hyperparathyroidism is usually made in asymptomatic patients, with a routine blood analysis showing a hypercalcemia. Further exploration then shows an inadequate normal or elevated PTH level in patients with a normal vitamin D status and a persisting hypercalcemia [2]. Complications of hyperparathyroidism include nephrolithiasis, impaired renal function, osteoporosis and depression [2]. Primary hyperparathyroidism is best treated by resection of the parathyroid adenomas (in most cases single adenoma) or foci of hyperplasia (like in MEN-1 syndrome), though this can be treated conservative as well when there are no symptoms or complications [2, 3]. Standard treatment consists of vitamin D and calcium, and for patients who are no candidates for surgery, other medical therapies can also be used to reduce complications of hyperparathyroidism (e.g. calcimimetics, antiresorptive therapy (like bisphosphonates) and thiazide diuretics) [2].

Adequate localization of the parathyroid adenomas is an important premise for minimally invasive parathyroidectomy (MIP) avoiding a bilateral neck exploration. MIP implies lower complication ratios, a lower cost and better cosmetic results [4, 5]. Furthermore, visualization of ectopic locations of parathyroid adenomas resulting from aberrant embryological migration processes, which are a relatively common finding with a reported incidence of 16-22% of parathyroid adenomas [6, 7], is of great importance to avoid failed surgery [8, 9].

Ultrasound, MRI and parathyroid scintigraphy are the most used imaging modalities [2, 10]. Parathyroid scintigraphy is usually performed with technetium-99m-based tracers such as N-(2-methoxy-2-methylpropyl)methanimine;technetium(6+) (Sestamibi) or 2-[bis(2-ethoxyethyl)phosphanyl]ethyl-bis(2-ethoxyethyl)phosphane;dioxo(99Tc)technetium-99 (Tetrofosmin). These tracers accumulate in mitochondria in cells with a high metabolic rate [11-13], such as in parathyroid adenoma. To distinguish an adenoma from physiological uptake in the thyroid gland, a comparison with imaging of the thyroid using iodine-123 or [^{99m}Tc]Tc-pertechnetate can be used or, making use of differential kinetics of the thyroid and parathyroid adenoma, the washout of the tracer can be evaluated [14].

Depending on the exact technique that is used (dual-tracer vs wash-out, planar vs SPECT(-CT)), the sensitivity of scintigraphy ranges from 56% to 100% [15-17]. Prior to parathyroid scintigraphy, the advocated patient preparation includes stopping thyroid hormone replacement therapy, thyreostatics and calcimimetics, as well as active vitamin D therapy (European Association of Nuclear Medicine Guidelines) [14]. However, the United States Society of Nuclear Medicine and Molecular Imaging (SNMMI) practice guidelines for parathyroid scintigraphy do not mention any precautions regarding medication intake [18].

The aim of this retrospective study was twofold. In view of the large variation reported in literature, we wanted to evaluate sensitivity of SPECT-CT based parathyroid scintigraphy in detecting adenoma, using dual isotope parathyroid scintigraphy ([^{99m}Tc]Tc-sestamibi or -tetrofosmin and iodine-123), as well as the positivity rate. The confirmation of a surgically resected adenoma and follow-up of calcium and PTH levels served as gold standard for image localization. Furthermore, as the possible influence of medication on parathyroid scintigraphy remains unclear, we aimed to assess the influence of medication prior to scanning on the correct scintigraphic localization of parathyroid adenomas, as well as the influence of calcium and PTH level on finding a positive or negative scintigraphy.

Materials and methods

Patient population

In this retrospective study, inclusion criteria were: patients with a) clinical suspicion of primary or tertiary hyperparathyroidism, who b) underwent dual isotope parathyroid scintigraphy with [^{99m}Tc]Tc-sestamibi or -tetrofosmin and iodine-123 in our center, c) between January 1st 2013 and December 31st 2017. Baseline laboratory data (intact PTH pre-surgery and total calcium pre-surgery), preoperative medication independent of dosage (thyroxine, thyreostatics, calcium-antagonists, antacids, iodine, vitamin D, bisphosphonates, calcium and calcimimetics), clinical data (indication for parathyroid scintigraphy, surgery report), peroperative PTH, histological findings (presence of normal parathyroid tissue, hyperplasia or parathyroid adenoma) and follow-up PTH and calcium levels were retrospectively extracted from medical charts. Overall, exclusion criteria were: patients that lacked in adequate follow-up with calcium/PTH (until 6 months after parathyroid scintigraphy) and lack of surgery. For the sub analysis of the role of preoperative PTH, all patients without a known PTH level within a window of 120 days around the day of scintigraphy and preceding surgery were excluded. For the sub analysis of the influence of medication use on the outcome of parathyroid scintigraphy, all patients without known medication schedule were excluded. The study protocol was approved by the local Ethics Committee.

Parathyroid scintigraphy

All patients underwent iodine-123 planar scintigraphy, directly followed by a dual isotope ([^{99m}Tc]Tc-sestamibi or -tetrofosmin/iodine-123) planar scintigraphy and dual isotope SPECT-CT. Scans were performed on a Discovery NM-CT 670 (GE Healthcare, Haifa, Israel) or a Symbia T16 camera (Siemens, Erlangen, Germany). First, 10 MBq of iodine-123 was administered intravenously, followed by planar imaging with parallel-hole collimators LEHR (Low Energy High Resolution) (128×128 matrix, zoom of 2) for 10 minutes two hours post injection. Afterwards, 550 MBq [^{99m}Tc]Tc-sestamibi or -tetrofosmin was injected, followed by planar imaging of the thyroid region plus mediastinum for 10 minutes (dual isotope setting with photopeaks centered over 140 keV and 159 keV with a 11% window for Tc-99m and iodine-123, respectively). The SPECT-CT study was then started using parallel-hole collimators LEHR (128×128 matrix, zoom of 1.23, 25 seconds per projection using 60 angles; low-dose CT at 110 kV, 36 mAs). SPECT images were reconstructed using OSEM (12 iterations with 15 subsets).

Subtraction planar and SPECT-CT images were produced using Hermes Medical Solutions software (Stockholm, Sweden). A variable normalization factor based on visual assessment was used for the planar images, yielding a series of images with a gradually increasing amount of subtraction. For the subtraction SPECT, a visually determined scaling factor was used to normalise the iodine-123 and [^{99m}Tc]Tc-sestamibi or -tetrofosmin images before subtraction. The calculated subtraction images, along the original iodine-123 and [^{99m}Tc]Tc-sestamibi or -tetrofosmin images were then reviewed alongside the CT and SPECT-CT fusion images.

Image interpretation

All parathyroid scintigraphy images were interpreted in clinical routine with access to all relevant clinical and imaging (e.g. ultrasound) information by board certified nuclear physicians and the reported locations were retrospectively extracted from the medical charts along with the surgery reports and histology reports of the patients. In case of doubt, a reread of the scintigraphy images was performed (by SJ and AG), with access to clinical and imaging information, but blinded for results of surgery. The combination of planar scintigraphy and SPECT-CT was then classified as 'positive' or 'negative' for parathyroid adenoma: a positive finding was defined as focal residual [^{99m}Tc]Tc-sestamibi or -tetrofosmin uptake after subtraction of the iodine-123 image, in most cases corresponding with an underlying CT-correlate or any focal uptake outside of the usual area of physiological distribution of sestamibi or tetrofosmin. Locations were classified in 5 regions (left upper parathyroid, left lower parathyroid, right lower parathyroid, right upper parathyroid and ectopic localization).

Statistical analysis

For descriptive statistics, values of laboratory tests are denoted as mean with standard deviation when results are normally distributed, and as median with IQR when results are not normally distributed. Normality was tested using Shapiro-Wilks test. Findings of the preoperative imaging modalities were correlated with operative findings. True positive findings to calculate sensitivity on a patient-level were defined as positive scintigraphy and the finding of an adenoma on histopathology after surgery, or positive scintigraphy with persisting increased PTH and calcium levels in the cases in which no surgery was performed. False positive findings were defined as positive scintigraphy with a negative investigation with surgery, or positive scintigraphy with normalised PTH and calcium during follow-up when no surgery was performed. False negative findings were defined as negative scintigraphy with the finding of an adenoma on histopathology after surgery, or negative scintigraphy with persisting increased PTH- and calcium-levels in the cases where no surgery was performed. True negative findings were defined as negative scintigraphy with negative investigation with surgery, or negative scintigraphy with normalised PTH and calcium during follow-up. Positivity rate was defined as

Table 1. Patient characteristics

Patient characteristics	Number of patients (% of the population), or laboratory values
Gender	
- Male	54 (23%)
- Female	183 (77%)
Median age (y) (range)	63.0 (range 12.0-88.0)
Median PTH pre-surgery (ng/L) (range)	86.6 (range 7.5-519.5)
Median calcium pre-surgery (mmol/L) (range)	2.7 (range 2.2-3.5)
Mean 25-OH vitamin D (µg/L) (range)	32.6 (range 3-77.5)
- Below 20 µG/L	30/186 (16.1%)
Mean serum creatinine (mg/dL) (range)	0.89 (range 0.35-3.4)
- Above 1.2 mg/dL	19/211 (9.0%)
Medication	
- Thyroxine	26 (11.7%)
- Thyrostatics	2 (0.8%)
- Calcium-antagonists	21 (8.7%)
- Antacids	61 (25.2%)
- Iodine	0 (0%)
- Vitamin D	100 (41.3%)
- Bisphosphonates	21 (8.7%)
- Calcium	13 (5.4%)
- Calcimimetics	1 (0.4%)
Types of surgery performed	
- minimal invasive surgery	65 (41.1%)
- total thyroidectomy	15 (9.5%)
- left hemi-thyroidectomy	3 (1.9%)
- right hemi-thyroidectomy	1 (0.6%)
- exploration	74 (46.8%)

total amount of positive scintigraphies/total amount of scintigraphies performed.

A logistic regression was used to investigate a possible association of medication use with fully (all adenoma locations based on histopathology found with scintigraphy) or partially correct (some, but not all adenoma locations based on histopathology found with scintigraphy) localization on scintigraphy. Median values were calculated with IQR for PTH and calcium levels pre-surgery in a negative versus positive scintigraphy. *P*-values were considered significant if smaller than 0.001.

All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, North Carolina, USA) and R software, version 4.0 (www.r-project.org).

Results

Patient characteristics

Two hundred and forty-two dual isotope parathyroid scintigraphies were performed in 237 patients referred for primary hyperparathyroidism (5 patients were scanned twice), of which 54 male and 183 female patients. The median age was 63.0 years (min-max range 12.0-88.0 years). The median PTH was 86.6 ng/L (min-max range 7.5-519.5 ng/L; normal range 14.9-56.9 ng/L; 85% of the patients had a PTH out of the normal range) and the median calcium level was 2.7 mmol/L (min-max range 2.2-3.5 mmol/L; normal range 2.15-2.55 mmol/L; all patients had hypercalcemia). Nineteen patients had a markedly raised serum creatinine (> 1.2 mg/dL), thus possible tertiary instead of primary hyperparathyroidism can be suspected in these patients. Serum creatinine and vitamin D status of the patient population are discussed in **Table 1**. One hundred and fifty-eight patients underwent exploration and curative surgery: 65 patients had minimally invasive surgery, 15 patients a total thyroidectomy (due to underlying nodules, multinodular goiter, MEN-1 syndrome or important hyperparathyroidism and no adenomas found with exploration), 3 patients had a left hemi-thyroidectomy (due to underlying nodules) and 1 patient had a right hemi-thyroidectomy (due to underlying nodules). Seventy-four patients underwent exploration of all 4 localizations, because scintigraphy did not localize an adenoma (41 patients), insufficient decrease of PTH peroperatively after resection of 1 adenoma (2 patients), underlying thyroid nodular tissue (17 patients), because no adenomas were seen in the indicated location based on scintigraphy (7 patients) or for no clearly stated reason that could be found in the patient file (7 patients). Possible reasons for non-surgical treatment (84 patients) were co-morbidities, loss to fol-

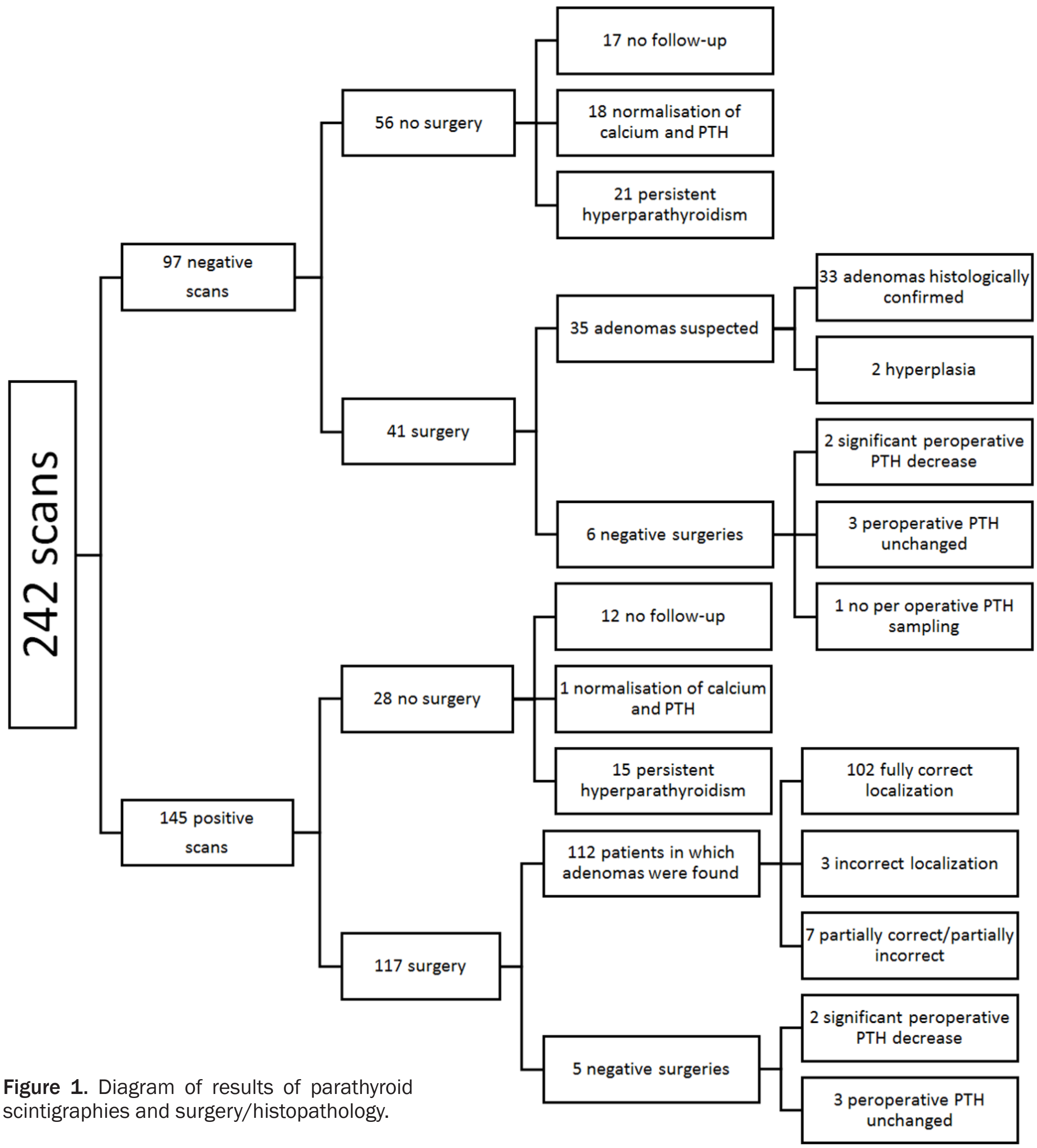

Figure 1. Diagram of results of parathyroid scintigraphies and surgery/histopathology.

low-up, advanced age of the patient, refusal by the patient, normalization of PTH and calcium, no localization on scintigraphy and absence of complications of the hyperparathyroidism. For the analysis of the influence of medication use on the outcome of parathyroid scintigraphy, medication usage was known for 239 scans. Patient demographic, surgical and medication characteristics can be found in **Table 1**. Out of the 148 surgical explorations in 144 different patients, 127 patients had 1 adenoma, 7 patients were found to have 2 adenomas and 3 patients had 3 locations of parathyroid hyperplasia. Out of all these surgical explored patients, 19 patients had persisting elevated PTH with normalised calcium levels, 6 patients had persisting elevated PTH with elevated calcium levels and 2 patients had persisting hypercalcemia with normalised PTH levels. In the subgroup of patients with negative histopathology during surgery, 2 patients had persisting hypercalcemia and elevated PTH levels, while 5 other patients showed a normalisation of calcium with persisting elevated PTH and 4 patients had a normalised PTH and calcium after surgery (**Figure 1**).

Sensitivity and positivity rate of dual isotope parathyroid scintigraphy

The findings of 39 scans could not be assessed with respect to the gold standard, due to a lack of adequate follow-up with calcium/PTH and lack of surgery in these patients at the same time. Overall patient-based sensitivity of dual isotope parathyroid scintigraphy was 73%.

Out of the 242 included scans, 145 were positive (positivity rate = 60%). Of these, 117 patients underwent surgery in which scintigraphy fully correctly localized the adenoma (all adenoma localizations were visualized with scintigraphy) in 102 cases. In 3 patients, an incorrect localization was found on scintigraphy, in 7 patients a partially correct localization was found (2 patients in which scintigraphy suggested 2 localizations and histopathology confirmed only 1 localization, 2 patients in which scintigraphy suggested 1 localization and histopathology confirmed 2 localizations, and 3 findings of multiple localizations of hyperplasia instead of parathyroid adenomas) and in 5 patients no adenoma or hyperplasia was found (**Figure 1**). Four ectopic localizations were confirmed by the gold standard. Four ectopic localizations were confirmed by the gold standard, an example of a positive scintigraphy for an ectopic localization can be seen in **Figure 2**.

Predictive factors for negative scintigraphy

All patients with a known PTH level within a window of 120 days around the day of scintigraphy and preceding surgery were included for analysis of influence of PTH level, resulting in 132 patients in the group with positive scintigraphy and 92 patients in the group with negative scintigraphy. PTH levels were significantly higher ($P < 0.01$) in positive versus negative scintigraphies, albeit with wide overlap between both (median 96.3 ng/L with IQR 69.0-143.0 ng/L in patients with a positive scintigraphy; median 75.2 ng/L with IQR 60.2-93.7 ng/L in patients with a negative scintigraphy). A Receiver Operating Characteristic (ROC) analysis using SAS-software showed an Area Under the Curve (AUC) of 0.68 for an optimal cut-off PTH-value of 79.4 ng/L, resulting in a sensitivity of 67% and a specificity of 63%. This result suggests the PTH level before scintigraphy is an insufficient predictor of a positive scintigraphy (**Figure 3**). No statistically significant difference was found in the calcium value between patients with a negative (median 2.7 mmol/L; min-max range 2.2-3.1 mmol/L) or positive scintigraphy (median 2.7 mmol/L; min-max range 2.4-3.5 mmol/L), $P = 0.63$.

In univariate logistic regression, serum calcium concentration and PTH level were significant predictors of a negative scintigraphy, although in a multivariate regression analysis only PTH level remained a significant predictor of the scintigraphy outcome (**Table 2**). No significant predictors were found for any of the studied medication types (thyroxine, thyrostatics, calcium antagonists, antacids, iodine, bisphosphonates, vitamin D, calcium and calcimimetics), using univariate and multivariate analysis (**Table 2**). We could not demonstrate an interaction, though this might be due to limited power.

Discussion

Pre-operative localization of parathyroid adenomas is important to reduce the complication rate and the cost of surgery, as well as to obtain better cosmetic results by opting for minimal invasive parathyroidectomy instead of bilateral neck exploration where possible. Parathyroid scintigraphy is a routinely used imaging modality to guide surgeries in this context. A range of sensitivity has been published for dual isotope parathyroid scintigraphy in this setting. Our study, with an overall sensitivity of 73% on a patient-based level, is in line with Cepkova et al. (75%) also using SPECT-CT [19]. Raruenrom et al. reported a slightly higher value using SPECT-CT scintigraphy of 80% [20]. In contrast, Ishii et al., using planar imaging only, found a lower sensitivity of 64% [21]. Factors influencing sensitivity include scanning modality (planar vs SPECT-CT), observer bias and patient population selection. In the current study, performed in a tertiary referral hospital, a higher number of patients can be included as they can be referred after previous failed imaging or surgery in localizing parathyroid adenomas and a higher rate of hyperplasia as compared to adenomas, thus increasing chances of a negative scintigraphy.

In our study, in 102 of the 117 patients with a positive scintigraphy who underwent full exploratory surgery, the adenoma was found to be correctly localized by the scintigraphy. This indicates that in 87% of cases a minimally inva-

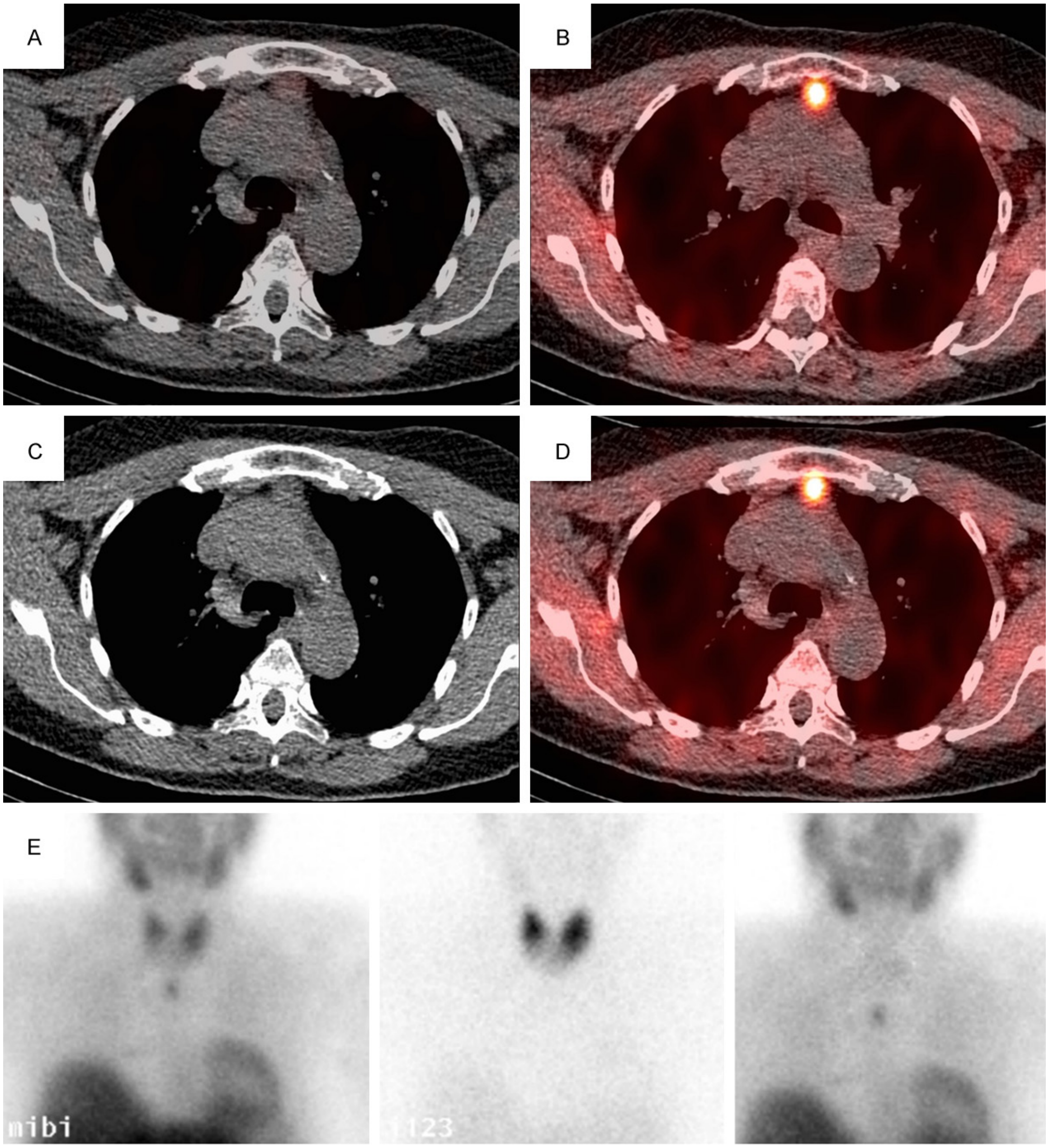

Figure 2. Example of an ectopic parathyroid adenoma, localized at the left retrosternal area. Iodine-123 image showing no increased uptake (A), Tc-99m MIBI image with a focal increased uptake retrosternal (B), native CT showing a nodule retrosternal (C), subtraction of Tc-99m MIBI and iodine-123 showing a high residual uptake in the left retrosternal area (D), planar Tc-99m MIBI, planar Iodine-123 and planar subtraction image (E).

sive parathyroidectomy could have been performed with complete resection of all parathyroid adenomas. Only in 3 patients (2.6%) an incorrect localization was found on scintigraphy and in 7 patients (6.0%) a partially correct localization was found. In 3 cases the histological diagnosis of multiple locations of parathyroid hyperplasia instead of parathyroid adenomas was made, giving a possible explanation for the incomplete correct localization. Five patients (4%) with a positive scintigraphy underwent surgery that did not localize any parathyroid adenomas. In 1 patient, a second surgery was performed later, showing a parathyroid adenoma in the left lower parathyroid location (which had previously been suggested on parathyroid scintigraphy). Three other patients of this group had resolution of their hypercalce-

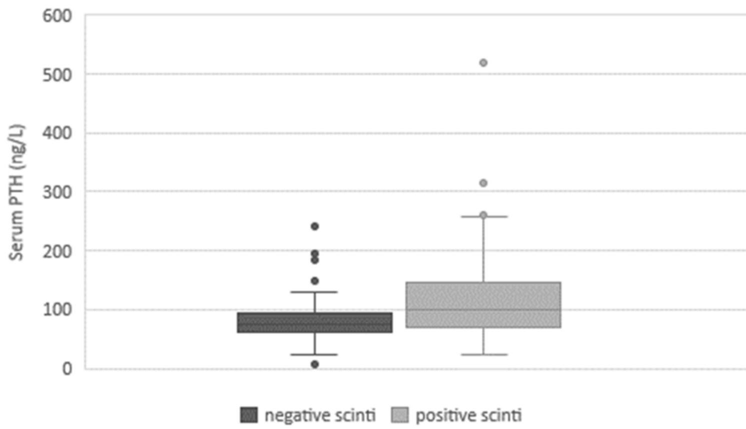

Figure 3. Boxplot of PTH in negative versus positive scintigraphies. Different level of PTH correlated with positive (median 96.3 ng/L) or negative scintigraphy (median 75.2 ng/L). Circles: outliers, boxplot with median, 1st and 3rd IQR and min/max value without outliers. The overlap suggests PTH is insufficient to preselect patients for preoperative scanning. Dark grey = negative scintigraphies, light grey = positive scintigraphies.

mia although no parathyroid adenoma was found, suggesting a different cause for the hypercalcemia or the possibility of sampling error of histopathology. The last patient of this group had an accidental finding of a micropapillar carcinoma of the thyroid, but no parathyroid adenoma.

Furthermore, we found serum PTH and calcium concentration are strong predictors of a positive parathyroid scintigraphy, and PTH levels are significantly higher in patients with a positive parathyroid scintigraphy, but with considerable overlap with the group of patients with a negative scintigraphy. Also ROC analysis (AUC of 0.68) showed that PTH level is not a sufficient discriminator to accurately predict the likelihood of a positive scintigraphy. Therefore, we suggest performing a parathyroid scintigraphy when primary hyperparathyroidism is suspected, independent of the PTH level. This is substantiated by the fact that in the group of patients with high-normal PTH levels, 14 (40%) had a positive parathyroid scintigraphy and 21 (60%) patients had a negative scintigraphy. Previous studies also indicated varying associations between PTH and calcium, and prediction of scan positivity. Some authors found no significant difference in PTH-levels between parathyroid positive and negative scans [27], while Behesti et al. and Chan et al. also did not find a significant difference in serum calcium concentration between both scan outcomes, though there seems to be a trend towards higher PTH and calcium values [28, 29]. On the other hand, Bergenfelz et al. found significantly higher PTH levels in true positive scans (PTH 11.5 ± 11.3 pmol/L for positive scintigraphy vs 8.0 ± 4.6 pmol/L for negative scintigraphy; P = 0.023) [30], and Hoang et al. suggested higher serum calcium was associated with a higher likelihood of a positive scan [31]. These discrepant results of PTH may be population based, but may also be due to the pulsatile nature of PTH secretion over a 24 h period according to Chiavistelli et al. [32], with blood draw timing as another possible factor that can have impact on PTH values [32].

The 2009 EANM parathyroid guidelines advise to avoid iodine-containing contrast media 4-6 weeks prior to subtraction parathyroid imaging, stop treatment with thyroid hormone replacement therapy and calcimimetics 2-3 weeks prior to the investigation and stop active vitamin D therapy or treatment with methimazole or propylthiouracil 1 week before [14]. These guidelines also advocate to temporarily stop thyreostatics [14]. On the other hand, the SNMMI practice guideline for parathyroid scintigraphy 4.0 (2012) does not mention any precautions regarding medication intake [18]. In our study, no significant effect of medication (thyroxine, thyreostatics, calcium-antagonists, antacids, iodine, vitamin D, bisphosphonates, calcium and calcimimetics) on the presence of a positive scintigraphy was found. The absence of significant impact on true positive rates by using calcium channel blockers (CCB) and antacids on [^{99m}Tc]Tc-sestamibi was also found by Ishii et al., though there seems to be a trend towards higher amount of positive scintigraphies when taking calcium channel blockers (CCB) and antacids in this study [33]. This is at odds with Cahid Civelek et al., finding an odds ratio of 2.9 (95% CI, 1.03-8.10; P = 0.045) for a negative scan in patients taking calcium channel blockers [34]. In line with our study, Ayers et al. found no significantly different rate of cor-

Table 2. Predictive factors for negative scintigraphy

	Univariate analysis				Multivariate analysis			
	Odds ratio	95% confidence interval		*p*-value	Odds ratio	95% confidence interval		*p*-value
Age	0.99	0.97	1.01	0.501				
Sex	0.65	0.34	1.21	0.172				
PTH	0.98	0.98	0.99	< 0.001	0.99	0.98	0.99	< 0.001
1,25 OH vit D	0.99	0.98	1.01	0.475				
25 OH vit D	1.02	0.99	1.04	0.150				
Phosphate	8.55	1.95	41.06	0.006	3.59	0.59	22.14	0.165
Serum calcium	0.03	0.00	0.14	< 0.001	0.06	2.51	106.13	0.004
Creatinine	0.63	0.24	1.42	0.297				
Thyroxine	0.89	0.70	2.69	0.780				
Thyrostatics	n/a	n/a	n/a	n/a				
Calcium antagonists	1.05	0.39	2.70	0.922				
Antacids	1.28	0.70	2.35	0.420				
Iodine	n/a	n/a	n/a	n/a				
Bisphosphonates	0.76	0.52	3.65	0.570				
Vitamine D	0.94	0.55	1.60	0.820				
Calcium	3.47	1.09	13.13	0.042	2.06	0.59	8.44	0.274
Calcimimetics	n/a	n/a	n/a	n/a				

n/a = not assessable.

rect Tc-99m-sestamibi scans between patients taking levothyroxine and those who do not [35].

Although the relatively low number of patients taking most of the individual studied medication types (**Table 1**) and the subsequent potential lack of statistical power to prove or exclude a correlation with certainty, our finding of the absence of an influence of medication on the outcome of parathyroid scintigraphy has a great clinical guiding significance. Patients should not stop any of the studied medication prior to imaging. Therefore, further prospective clinical trials focusing on the effect of independent medication use could give more certainty about our findings.

The limitations of this study are mainly due to its retrospective nature. Furthermore, not all patients had surgery as well as pre-operative and follow-up calcium and PTH levels, resulting in fewer patients included in some statistical analyses, though still larger in number or comparable with previous studies. The study suffers from ascertainment bias as in a substantial fraction of patients with a negative scintigraphy, no surgery and thus gold standard assessment was performed. Furthermore, we only calculated sensitivity on a patient-level, and not at the parathyroid-level, because multiple adenomas in 1 patient might not be completely independent of each other and there is no 100% certainty of a true negative localization of parathyroid scintigraphy if not all 4 possible locations are being investigated by the surgeon. In addition, we only found 6 false positive cases in our study, which is probably an underestimation of false positive results because no patients were included when no hyperparathyroidism was clinically suspected. This also applies to the number of true negatives, thus not allowing a calculation of specificity of parathyroid scintigraphy with great certainty. In analyzing the cut-off for PTH, no correction for 25-OH vitamin D status and serum creatinine (possibly adding a secondary raise in PTH) was performed, though these are a minority in our patient population (19 patients with a raised serum creatinine out of 211 known results, and 30 patients with a low 25-OH vitamin D out of 186 known results). Possible other explanations for false negative findings in patients who had no surgery (negative scintigraphy, high PTH and calcium on follow-up after 3-6 months) is familial hypocalciuric hypercalcemia, though this is really uncommon and calciuria is routinely checked in clinical practice before referral for parathyroid scintigraphy, and thus is not expected to have any significant influence on our results.

Conclusion

This study demonstrates a sensitivity of 73% for dual isotope SPECT-CT based detection of parathyroid adenomas on patient-based level, in line with previous literature. Moreover, we found no significant impact of commonly administered medication on scan positivity, though possibly due to insufficient power of this study. Further investigation with larger patient groups in each of the studied medication groups could resolve this question. Finally, although PTH levels were significantly different between positive and negative scans, a large overlap makes this parameter insufficiently predictive to select patients that should undergo preoperative scanning.

Disclosure of conflict of interest

None.

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