Dual Tracer ^{99m}Tc-Pertechnetate / ^{99m}Tc-MIBI Dual-Time-Point SPECT/CT Parathyroid Gland Assessment Regarding to Parathyroid Gland Size and Biochemical Parameters – Two Years Single Imaging Centre Experience

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ABSTRACT

Introduction: Preoperative parathyroid imaging is inevitable part of focused parathyroid surgery. The aim of our study was assessment of parathyroid scintigraphy diagnostic accuracy regarding to size and metabolic parameters of hyperfunctioning parathyroid tissue.
Material and methods: Parathyroid scintigraphy for suspected primary hyperparathyroidism was performed in 95 patients during years 2015 and 2016. Of them, 75 patients with known clinical outcome (40 underwent surgery, 35 had documented laboratory follow-up) were further retrospectively evaluated. The performance of dual tracer ^{99m}Tc-pertechnetate and ^{99m}Tc-MIBI subtraction and dual-time-point ^{99m}Tc-MIBI imaging with SPECT/CT was analysed. Serum parathyroid hormone (PTH), calcaemia, ionized calcaemia and phosphataemia and ultrasound detected adenoma volume and largest diameter in false negative and true positive findings were compared using Mann-Whitney test.
Results: Sensitivity and specificity of parathyroid scintigraphy was 74.5% and 95.8%, respectively. NPV was 63.8% and PPV 97.4%. Hyperfunctioning parathyroid tissue detectability was almost significantly associated with hypophosphataemia and PTH levels.
Conclusion: Parathyroid scintigraphy provides high sensitivity and superior specificity in parathyroid adenoma location, nevertheless the diagnostic accuracy tends to decline in smaller adenomas and in less metabolically active parathyroid tissue causing only subtle biochemical changes. ^{18}F-Fluorocholine PET/CT or 3D SPECT/CT subtraction should be a reasonable option for those cases.

KEYWORDS

hyperparathyroidism; primary; single photon emission computed tomography; computed tomography; ultrasonography; parathyroid hormone; hypercalcemia; hypophosphatemia

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INTRODUCTION

Primary hyperparathyroidism (pHPT) is a common endocrine disorder, nowadays most frequently disclosed in asymptomatic patients during their routine laboratory check-ups including calcaemia measurements (1, 2). Consequently, the patients are referred to parathyroidectomy during the early disease stage. This trend leads to a shift in surgical approach from bilateral neck exploration to mini-invasive surgery. However, this less invasive approach is suitable only for patients with successfully localized solitary adenoma (3).

Parathyroid scintigraphy plays an essential role in selecting patients for appropriate surgical treatment, allowing precise solitary adenomas location as well as disclosure of supernumerary or ectopic parathyroid glands.

^{99m}Tc labelled lipophilic cation methoxyisobutilisonitrile (^{99m}Tc-MIBI) is used for parathyroid scintigraphy. The tracer is accumulated in tissues with intensive oxidative metabolism (due to its high mitochondrial affinity) including thyroid and parathyroid glands (4). Dual-time-point ^{99m}Tc-MIBI imaging is based on markedly delayed ^{99m}Tc-MIBI wash-out from hyperfunctioning parathyroid tissue (5) (Fig. 1a, b). Scintigraphy spatial resolution is enhanced by single photon emission tomography combined with CT (SPECT/CT) (Fig. 2) and accuracy is improved employing ^{99m}Tc-pertechnetate subtraction (6) (Fig. 3a, b, c). ^{99m}Tc-pertechnetate uptake, limited to the thyroid gland, enables us to distinguish "hot" or "cold" nodules which may interfere with ^{99m}Tc MIBI scan (6).

However, the recent trend to operate patients during the early disease course could potentially lead to decreased sensitivity of preoperative localization procedures, due to lower preoperative serum ionised calcium levels and smaller adenoma size (7).

Thus the aim of our study was to evaluate sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of our parathyroid imaging protocol. Our secondary aim was to compare serum calcaemia (both total and ionized), phosphataemia, serum parathyroid hormone (PTH) levels and sonographically (US) assessed volume and the longest diameter between true positive and false negative findings.

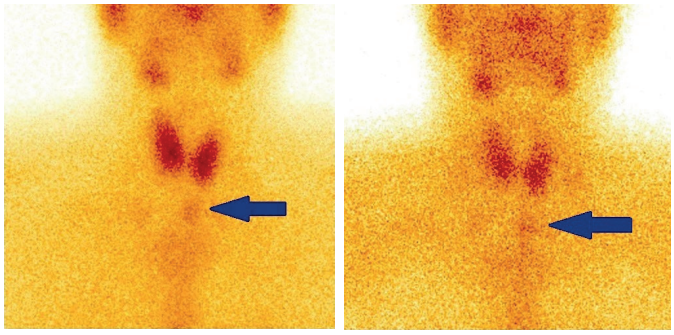

Fig. 1 (a) Early planar scan acquired 10 minutes after ^{99m}Tc-MIBI administration. Arrow shows suspected parathyroid adenoma. (b) Delayed scan obtained 2 hours after ^{99m}Tc-MIBI administration. Arrow shows the same suspected adenoma with markedly delayed radiotracer wash-out.

MATERIALS AND METHODS

We retrospectively reviewed 96 patients with suspected pHPT who underwent parathyroid imaging at the Nuclear Medicine Department of the University Hospital in Hradec Králové from January 2015 till December 2016. Only patients with known clinical outcome (total 75; 40 of them operated and 35 managed conservatively) were further evaluated. In the operated patients, the diagnosis of pHPT was derived from histopathology. In the conservatively managed patients, the diagnosis was assessed from clinical and laboratory follow-up data: ongoing hypercalcaemia and hyperparathyroidism were considered strongly suggestive of pHPT.

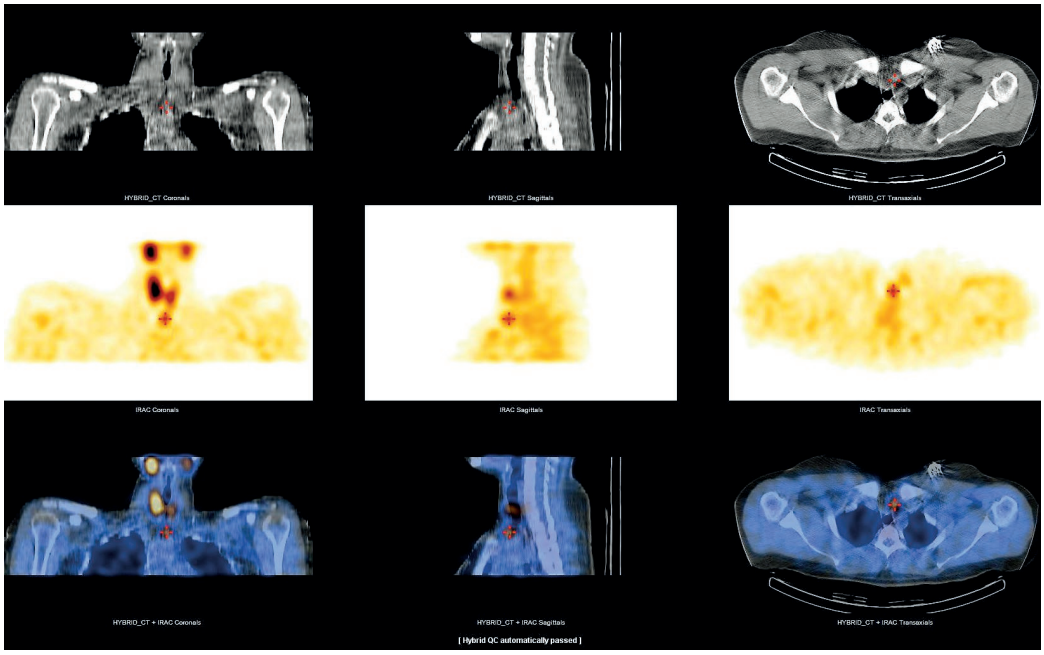

Fig. 2 Neck ^{99m}Tc-MIBI SPECT/CT. Parathyroid adenoma is clearly visible behind the left clavicle.

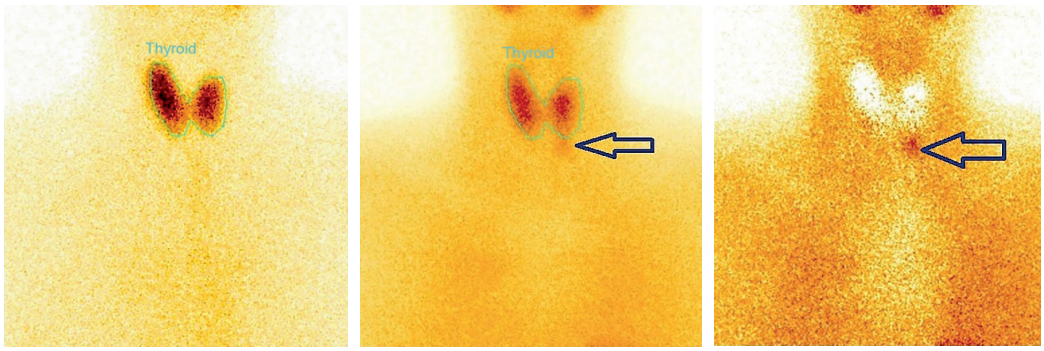

Fig. 3 (a) Planar scan after ^{99m}Tc-pertechnetate administration in another patient. Only thyroid gland is visible. (b) Early planar scan acquired 10 minutes after ^{99m}Tc-MIBI administration, suspected adenoma under the left lobe is faintly visible (arrow). (c) Suspected parathyroid adenoma is clearly depicted using ^{99m}Tc-pertechnetate and ^{99m}Tc-MIBI subtraction (arrow).

Tab. 1 Patients baseline characteristics.

Patients baseline characteristics					
Number of patients, *n*		75			
Gender, *n* (%)	Female	66 (88%)			
	Male	9 (12%)			
Metabolic and ultrasound parameters		**n**	**mean**	**median**	**range**
Calcemia (*mmol/l*)		71	2.73	2.75	2.63–2.86
Serum ionized calcium (*mmol/l*)		53	1.41	1.42	1.29–1.52
Phosphatemia (*mmol/l*)		42	0.84	0.86	0.67–0.97
PTH levels (*pmol/l*)		69	14.69	11.23	8.4–15.7
US lesion largest diameter (*mm*)		45	13.45	12.00	9–15
US lesion volume (*ml*)		30	0.91	0.32	0.21–0.65

Patient characteristics are shown in Table 1. Baseline laboratory parameters and US assessment of suspiciously enlarged parathyroid gland were provided by the referring endocrinologists. 1-84 PTH analyses were performed using chemiluminescence imunoanalysis (system DiaSorin, Stillwater, USA), chemiluminescent microparticle immunoassay (system Architect iSystem, Abbot, Wiesbaden, Germany) and electrochemiluminescence analysis (system Cobas 6000, e601 module Roche diagnostics, Mannheim, DE).

Imaging was performed using a SPECT/CT scanner Infinia Hawkeye 4 (GE Healthcare, Haifa, Israel). Thyroid gland scans (matrix 128 × 128, 500 000 counts) were obtained 20 minutes after 70 MBq ^{99m}Tc-pertechnetate intravenous administration. Subsequently, 700MBq of ^{99m}Tc-MIBI was injected and early planar scan (from upper pole of parotid glands to diaphragm, matrix 128 × 128, 500 000 counts) was acquired 10 minutes thereafter.

Both planar scans were subtracted. This was followed by SPECT/CT acquisition (128 × 128 matrix, 120 projections, 15 seconds per view; low dose CT parameters: 120 kV, 2.5 mAs). Delayed scan (for wash-out assessment) was obtained 2 hours after the early ^{99m}Tc-MIBI scan. The images were evaluated using dedicated software for hybrid imaging (Volumetrix, GE Healthcare). For statistical analysis, SigmaStat software package (Jandel Corporation, San Rafael, CA, USA), version 3.1, was used. As data were mostly non-normally distributed their summary values were expressed as medians (25th–75th percentiles) and comparisons between true positive and false negative findings were performed using non-parametric Mann-Whitney test.

RESULTS

We assessed 75 patients (65 women, 10 men; median age 65 years; range 55–72 years) with suspected pHPT who underwent parathyroid scintigraphy and had reliably documented clinical outcome. Parathyroid scan was true positive in 38 patients, false negative in 13 patients, true negative in 23 patients and false positive in 1 patient as shown in Table 2. The sensitivity of our scintigraphic protocol reached 74.5%, specificity 95.8%, positive predictive value 97.4% but negative predictive value was only 63.8%, as summarized in Table 3.

Tab. 2 Pivot table evaluating parathyroid scintigraphy detection efficiency regarding to clinical outcome (histopatological, imaging or laboratory proof of hyperfunctioning parathyroid tissue).

	Clinical outcome +	**Clinical outcome –**
Scintigraphy +	38	1
Scintigraphy –	13	23

Tab. 3 Patient-based sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy based on true-positive, true-negative, false-positive and false-negative parathyriod scintigraphy results.

No. of patients	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**Accuracy**
(n)	(%)	(%)	(%)	(%)	(%)
75	74.5	95.8	97.4	63.8	81.3

Tab. 4 Comparison of laboratory parameters and ultrasound findings in parathyroid scan true positive and false negative patients. The p value was calculated using Mann-Whitney test, significance level <0.05.

	Serum PTH (pmol/l)	p	Calcaemia (mmol/l)	p	Ionized calcaemia (mmol/l)	p	Phospha-taemia (mmol/l)	p	Longest diameter (mm)	p	Parathyroid gland volume (ml)	p
True positives	14.05 (10.83;23.47) n = 34	0.088	2.8 (2.69;2.93) n = 34	0.454	1.45 (1.36;1.60) n = 25	0.287	0.66 (0.6;0.78)	0.078	14.0 (11.0;16.0) n = 16	0.233	0.47 (0.30;0.73) n = 14	0.156
False negtives	10.20 (8.75;13.10) n = 11		2.78 (2.65;2.89) n = 13		1.32 (1.17;1.57) n = 11		0.845 (0.68;0.92)		11.0 (10;14) n = 9		0.23 (0.19;0.44) n = 7	

All but one true positive patients underwent neck US and enlarged parathyroid glands were detectable in 26 of 37 of them. Neck US was performed in 12 of 13 false negative patients, and revealed enlarged parathyroid tissue in 9 patients. Baseline neck US performed in 69 of all identified patients (n = 75) reached overall sensitivity 71.4%, specificity only 50.0%, PPV 77.0%, NPV only 41.7% and accuracy 65.0%. Because US is highly operator dependent and neck US examinations were performed by referring endocrinologists, the data inevitably vary in quality.

Although the largest diameter was lower in false negative patients than in true positive ones, the difference did not reach statistical significance. The same was true for parathyroid tissue volume and calcaemia (both total and ionized). The differences in PTH levels and phosphataemia between true positive patients and false negative ones were even more obvious but still slightly above statistical significance level (Table 4).

DISCUSSION

We achieved superior specificity and very high PPV using our dual tracer dual-time-point imaging protocol with SPECT/CT in comparison with the recent study by Raruenrom et al. that report sensitivity 80%, specificity 75%, PPV 88.9%, NPV 60% and accuracy 78.6% using the same comprehensive imaging (8). Neumann et al. who performed ^{123}I-NaI/^{99m}Tc-MIBI subtraction and SPECT/CT achieved higher patient-based 88% sensitivity and the same 96% specificity (9). Nevertheless our NPV and sensitivity were lower than expected.

Despite the similarity of mean longest diameters of our true positive and false negative findings with data published by Behesti et al. (15.5 ± 7.9 mm in our true positives versus 12.2 ± 4.6 mm in false negatives compared to their 17.6 ± 7.4 mm and 13.3 ± 6.7 mm, respectively) and the clearly visible trend of missing smaller adenomas, we (unlike them) failed to prove statistical significance of size differences between true positive and false negative findings (10). This is probably caused by our smaller cohort. This may also apply to parathyroid adenoma volume.

Although small size of parathyroid adenomas (below the gamma camera spatial resolution) is limiting for imaging, accurate location of even subcentimetre parathyroid adenomas is required in the minimal invasive surgery era. On the other hand, high tracer uptake in parathyroid adenomas with intensive metabolism enables detection of such lesions (11). In our analysis, successfully detected parathyroid adenomas volume ranged from 0.3 to 0.7 millilitres and metabolic changes (particularly PTH levels and phosphataemia) were more pronounced in those patients. However, the metabolic changes did not reach statistical significance in our study.

In fact, association between metabolic markers and parathyroid scintigraphy positivity differs from study to study. Formerly published data provided evidence that PTH is significantly higher in parathyroid scan true positive patients (12). Also recent study by Hoang et al. found an association between positive ^{99m}Tc-MIBI scan and higher serum ionised calcium, increased intact PTH levels and lower phosphataemia (13). However, an association between PTH and parathyroid scan positivity was not confirmed by Dy et al. (14). In addition, Behesti et al. recently did not prove statistically significant difference in calcaemia and PTH levels regarding to parathyroid adenomas detectability using ^{99m}Tc-MIBI SPECT/CT (10).

Here, it is necessary to address the issue of normocalcaemic hyperparathyroidism and hypercalcaemia with inappropriately high-normal PTH (normohormonal pHPT). Diagnosis of normocalcaemic hyperparathyroidism can only be established if vitamin D deficiency, chronic kidney disease, malabsorption, idiopathic hypercalciuria and PTH increase due to medication are excluded (1). Normohormonal pHPT is defined as hypercalcaemia without suppressed PTH levels, presuming that other causes of hypercalcaemia like malignancy, granulomatous diseases, vitamin D intoxication, renal disease or thiazides or lithium intake have been ruled out (15). The increasing number of recognized normocalcemic pHPT may explain contradictory data regarding to metabolic differences in true positive and false negative findings in recent studies (16). Because parathyroid surgery is required in all asymptomatic patients younger than 50 years as well as in those with proven subclinical bone or renal impairment (17), localization of such lesions is a big challenge for preoperative parathyroid imaging procedures. A very promising scintigraphic method is 3D subtraction of ^{99m}Tc-pertechnetate and ^{99m}Tc-MIBI SPECT data (18). Nuclear medicine option with superior spatial resolution and sensitivity is ^{18}F-Fluorocholine PET/CT. ^{18}F-Fluorocholine (FCH) is marker of cell membrane turnover (19). Sensitivity of 94%, specificity 96%, PPV 90.2%, NPV 97.4% and diagnostic accuracy 95.3% were achieved using this tracer, making it the most promising tracer with high diagnostic performance (10, 20). At present, PET/CT centres in the

Czech Republic depend on FCH supplies from abroad. This dramatically decreases tracer availability due to its short physical half-life (109 minutes). Marketing authorisation of FCH produced in the Czech Republic for parathyroid imaging is an inevitable step forward to precise preoperative localization of even early and asymptomatic forms of primary hyperparathyroidism.

CONCLUSION

We achieved good sensitivity, superior specificity and PPV using our one day dual tracer dual-time-point imaging protocol with SPECT/CT. Our data suggest that the lower NPV probably results from missing smaller adenomas and hyperfunctioning parathyroid tissue in patients in the early stage of disease. In view of recently published data, ^{18}F-FCH PET/CT or 3D SPECT/CT subtraction may be reasonable options for patients with asymptomatic, normohormonal and normocalcemic pHPT.

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