

# Parathyroid Imaging by $^{18}\text{F}$ -Fluorocholine PET/CT in Patients With Primary Hyperparathyroidism and Inconclusive Conventional Methods: Clinico-Pathological Correlations

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## Summary

$^{18}\text{F}$ -fluorocholine positron emission tomography/computed tomography (FCH) was performed after inconclusive neck ultrasound and  $^{99\text{m}}\text{Tc}$ -sestaMIBI SPECT (MIBI) scintigraphy in patients with primary hyperparathyroidism (PHPT) to localize abnormal parathyroid glands before surgery. The results were retrospectively evaluated and compared to postoperative histopathological findings. 13 patients with PHPT were enrolled (mean age 64.3 years, preoperative calcium 2.74 mmol/l and parathyroid hormone 114.6 ng/l). FCH localized hyperfunctioning parathyroid glands in 12 patients of 13 (per patient sensitivity 92 % and positive predictive value (PPV) 100 %). Fourteen parathyroid lesions (11 adenomas, 3 hyperplastic glands) were resected with a mean size of 11.9 mm (per lesion sensitivity 93 % and PPV 81 %). Four adenomas and one hyperplastic gland were composed of only chief cells, whereas five lesions contained both chief and oxyphil cells. In three patients an exclusively oxyphil adenoma was found, surprisingly with negative MIBI scintigraphy in spite of a high mitochondria content in the oxyphil parathyroid cells. 12 of 13 patients had thyroid disease. In our limited study sample, FCH correctly identified parathyroid adenomas and/or hyperplastic glands in 92 % of patients with previously inconclusive conventional imaging. Unlike MIBI, FCH successfully localized small, hyperplastic and multiple hyperfunctioning parathyroid glands, irrespective of their histopathological composition.

## Key words

Primary hyperparathyroidism •  $^{18}\text{F}$ -fluorocholine PET/CT • Oxyphil parathyroid adenoma • Thyroid oncocytes

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## Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder caused in more than 80 % of cases by a single parathyroid adenoma (Bilezikian *et al.* 2018). Parathyroid surgery still represents the only curative approach (Bilezikian *et al.* 2014, Žofková *et al.* 2016). The correct preoperative localization of enlarged parathyroid glands is one of the prerequisites for focused parathyroid surgery. Neck ultrasound and  $^{99\text{m}}\text{Tc}$ -sestaMIBI scintigraphy (MIBI), often in a combination with SPECT/CT, are the first line localization techniques (Kunstman *et al.* 2013). Each method has its strong and weak points, but complements each other with sensitivity of up to 80 % (Kuzminski *et al.* 2018). The general factors influencing their positive predictive value are the size of the parathyroid adenoma and concomitant thyroid disease (Kuzminski *et al.* 2018).

In incidental case reports,  $^{18}\text{F}$ -fluorocholine PET/CT (FCH) has shown a promising ability to identify enlarged parathyroid glands (Quak *et al.* 2013, Hodolic *et al.* 2014). Since then, several studies have documented that FCH is capable of localizing parathyroid adenomas in patients with PHPT and negative or inconclusive neck ultrasound and MIBI (Michaud *et al.* 2014, Michaud *et al.* 2015, Kluijfhout *et al.* 2016, Fischli *et al.* 2018, Grimaldi *et al.* 2018).

In this report, we retrospectively evaluated the sensitivity and positive predictive value (PPV) of FCH in patients with PHPT and negative or equivocal localization studies using neck ultrasound and MIBI. Moreover, we correlated the results of localization techniques to the histopathological composition of parathyroid adenomas and to the presence or absence of thyroid disease.

## Methods

### Patients

From January 2016 to December 2017, twenty patients with PHPT and negative or inconclusive standard localization methods were offered additional imaging with FCH. All patients gave written consent after having been informed that FCH was a diagnostic imaging technique for indications other than PHPT. A total of 13 patients (1 male, 12 females, mean age of 64.3 years) were considered for a retrospective analysis (Table 1). The mean preoperative level of calcium was 2.74 mmol/l (2.6-3.03) and of parathyroid hormone (PTH) 114.6 ng/l (78.9-145) (Table 1).

The remaining 7 patients were excluded: 4 patients declined parathyroid surgery, 1 patient was diagnosed with secondary hyperparathyroidism, and in 2 patients PHPT persisted postoperatively in spite of positive foci on FCH. In both cases, lymph nodes and concomitant thyroid nodules very likely contributed to the false positivity of fluorocholine imaging and to the failure of the neck surgery. However, lacking a histopathological correlate, neither case was included in the analysis.

### Neck ultrasound

Ultrasonography was performed by several endocrinologists in combination with a color Doppler to differentiate various hypoechoic lesions in the thyroid gland and in adjacent tissues. Transverse and longitudinal views were recorded with a complete evaluation of the thyroid gland.

### <sup>99m</sup>Tc-sestaMIBI scintigraphy

A combined dual-phase and dual-tracer SPECT/low-dose CT imaging protocol was used with a weight-adjusted standard activity of 700 MBq <sup>99m</sup>Tc-sestamibi (CARDIO-SPECT, Medi-Radiopharma Ltd., Erd, Hungary) and <sup>99m</sup>Tc-pertechnetate (Tc). The first scan (early MIBI) was performed 5-7 min after

intravenous administration of MIBI. A second scan (late MIBI) followed 2-2.5 h p.i. The SPECT/low-dose CT covered an area from the skull base to the diaphragm in both examinations.

The Tc scan was performed on another day approximately 30 min after the intravenous administration of a weight-adjusted activity of 200 MBq Tc. All data were recorded using a GE Infinia Hawkeye dual-head gamma camera (GE Healthcare, Milwaukee, WI, USA) and reconstructed with a Xeleris workstation (GE) using standard acquisition and reconstruction protocols. More detailed technical information is behind the scope of this article and is available through the authors.

The studies were assessed visually by the consent reading of two nuclear medicine physicians with 10+ years of practice. Slices in conventional 3 orthogonal planes and volume rendered maximal intensity projections were evaluated. Focal hyperactivity on the MIBI scan in a possible PT location without a corresponding finding on the Tc scan was taken as diagnostic for an enlarged PT. In the case of a negative or equivocal scintigraphy finding, the patients were scheduled for FCH on another day.

### <sup>18</sup>F-fluorocholine PET/CT

All PET/CT examinations were performed on the same integrated PET/CT system (Discovery 690, GE Healthcare, Milwaukee, WI, USA). The PET center in the General University Hospital in Prague holds a European Association of Nuclear Medicine (EANM) Research 4 Life Ltd. EARL Accreditation since 2014. The administered dose was 180±48 MBq (mean ± SD) of <sup>18</sup>F-fluorocholine (IASOcholine, IASON GmbH, Graz-Seiersberg, Austria).

The mean postinjection resting time was 30±20 min. PET/CT was performed in the supine position, with arms stretched overhead. The scans were acquired from the base of the skull to the diaphragm, with 7 min per bed position in the neck and upper chest region and 5 min in the lower chest region.

The PET acquisition and reconstruction parameters were: a 70 cm transaxial field of view, Time-Of-Flight, Resolution Recovery, VuePoint algorithm with 3 iterations, 32 subsets, and 6.0 mm filtering, and matrix 256 x 256. CT parameters were: helical mode, voltage 120-140 kV, modulated current 30-250 mA, 0.7 s per rotation, and standard FBP reconstruction with 512 x 512 matrix.

**Table 1.** Characteristics of patients, laboratory, imaging results and postoperative histological findings.

Patient no.	Sex	Age (years)	US	sestaMIBI	FCH-PET/CT	Histology	Cell type	Resected lesions (mm)	Preop. calcium (mmol/l)	Postop. calcium (mmol/l)	Preop. PTH (ng/l)	Postop. PTH (ng/l)	FCH-PET/CT accuracy
1	M	35	RL (?)	neg	RL <sup>e</sup>	RL adenoma	<b>oxyphil</b> >>chief	6x4x5	3.03	2.49	101	39	
2	F	72	neg	neg	RU	RU hyperplasia	chief>>oxyphil	12x5x4	2.71	2.53	101	64.6	
3	F	64	neg	neg	LL	LL adenoma	chief>>oxyphil	20x10x10	2.83	2.4	139	89.5	
4	F	67	neg	RL (?)	RL	RL adenoma	chief	13x9x4	2.66	2.52	107	73.9	
5	F	76	neg	LL (?)	RL	RL adenoma	chief	10x8x2	2.6	2.5	78.9	66	
6	F	66	neg	LL/RU <sup>e</sup>	RU <sup>e</sup>	RU hyperplasia	chief	unavailable	2.74	2.36	131.7	83.5	True positive
7	F	62	neg	RL	LU	LU adenoma	chief	7x5x3	2.75	2.29	125.1	18.3	
8	F	61	neg	neg	RU	RU adenoma	<b>oxyphil</b>	17x11x4	2.83	2.36	106.8	65	
9	F	67	neg	neg/LU?	LU	LU adenoma	chief+ oxyphil	10x7x5	2.8	2.38	125.7	60.5	
10	F	74	LL	neg/LL?RL?	LL	LL adenoma	chief	12	2.65	2.34	117.5	47.6	
11	F	74	neg	neg	RU <sup>e</sup> , RL <sup>e</sup> , LU, pancreas	RU/LU adenoma/hyperplasia	<b>oxyphil</b>	8x5x3 / 10x6x3	2.61	2.31	123.2	100.5	
12	F	68	LU	neg	RU, LU, LL, ect.	LU adenoma	chief> oxyphil	10x6x5	2.62	2.33	88.3	42.5	False positive in part
13	F	50	neg	neg	neg	LU adenoma	chief> oxyphil	20x8x8	2.85	2.31	145	72	False negative

RL – right low, RU – right upper, LL – left low, LU – left upper, neg – negative, RL<sup>e</sup> – right low ectopic, RU<sup>e</sup> – right upper ectopic, PTH – parathyroid hormone, preop. – preoperative, postop. – postoperative, ect. – ectopic. Total calcium normal range: 2.20-2.55 mmol/l, PTH normal range: 15-65 ng/l.

The data were recorded and reconstructed on a proprietary Advantage Workstation (ADW v. 4.6). FCH scans were evaluated by the joint reading of an experienced nuclear medicine physician and radiologist. Slices in conventional 3 orthogonal planes and volume rendered maximal intensity projections were evaluated.

The diagnosis of hyperplastic PT was based on the presence of well circumscribed focal hyperactivity, with the intensity clearly exceeding background activity, and a corresponding morphological finding on CT images.

### Statistics

The reports of MIBI and FCH were reviewed by an endocrinologist (KZ), the findings were summarized for each patient and all FCH images were later visually reviewed by a nuclear medicine physician (DZ) in joint reading with the endocrinologist (KZ) to validate the information in the reports and to provide complex correlation of all data. Sensitivity and the positive predictive value of FCH were calculated in per patient and per lesion analysis. The biochemical resolution of PHPT and the histological findings were considered as the gold standard.

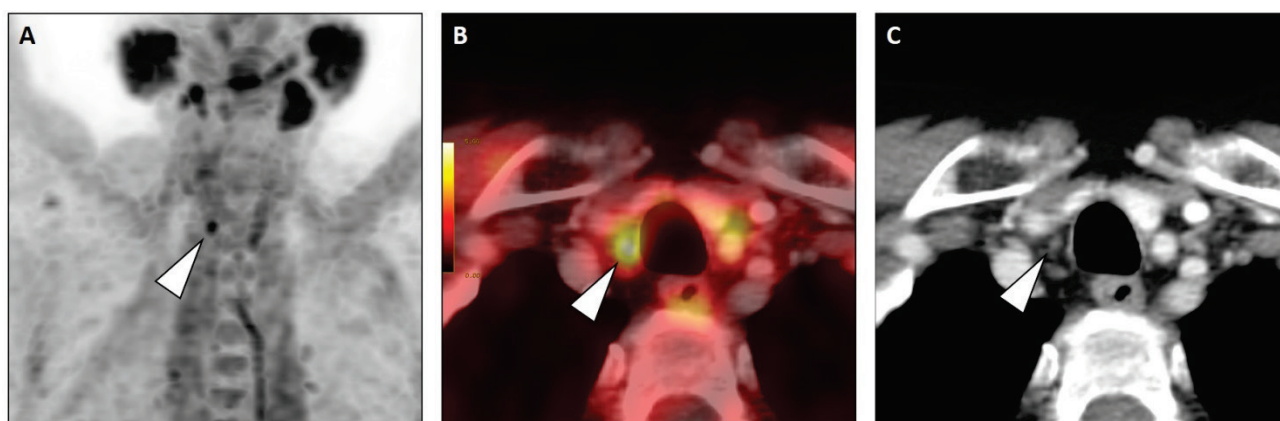
A combination of active foci on FCH, corresponding postoperative histology and the biochemical resolution of PHPT were considered as true positive imaging of FCH. In one case, 3 additional fluorocholine foci were considered as false positives after the removal of one parathyroid adenoma with fluorocholine uptake and with a biochemical normalization of PHPT after surgery. In another case, the absence of fluorocholine uptake in a parathyroid gland that was removed during neck surgery, subsequently

confirmed as a parathyroid adenoma with normalization of calcium and PTH, was considered as a false negative.

### Results

FCH correctly localized hyperfunctioning parathyroid glands in 12 patients of 13, yielding per patient sensitivity of 92 %. FCH identified five enlarged parathyroid glands that were entirely undetectable on both neck ultrasound and MIBI (Table 1). True positive FCH imaging led to the successful reoperation of hyperfunctioning parathyroid glands in 2 patients in whom first surgery failed in part due to false positive sestaMIBI scintigraphy (patients 6 and 7, Table 1). The per patient positive predictive value (PPV) of FCH parathyroid imaging was 100 % (Fig. 1, a representative case of a patient 5, Table 1).

False negativity was documented in one subject in whom the thyroid gland showed a diffusely enhanced uptake of fluorocholine, probably linked to the presence of autoimmune thyroid disease (patient 13, Table 1). Parathyroid adenoma was afterwards successfully found by a surgeon. In two patients (11 and 12),  $^{18}\text{F}$ -fluorocholine PET/CT localized 3-4 foci suggestive of parathyroid hyperplasia and/or multiglandular disease. In patient 12, prior to surgery, fine needle aspiration cytology was carried out from one of the lesions visualized on ultrasound. The cytopathology was suggestive of parathyroid tissue. Subsequently, a single adenoma was found by a surgeon. Postoperatively, calcium and PTH normalized (Table 1). Three other fluorocholine foci were probably linked to hypermetabolic thyroid nodules and/or a mediastinal lymph node (false positivity).



**Fig. 1.**  $^{18}\text{F}$ -fluorocholine PET/CT showing focal hyperactivity dorsal to the right caudal pole of the thyroid gland, histologically confirmed as parathyroid adenoma (arrowheads). Previous imaging by neck ultrasound and MIBI was inconclusive (patient 5, Table 1). (A) Maximal intensity projection. (B) PET/CT fusion, axial slice. (C) CT, axial slice.

In patient 11, <sup>18</sup>F-fluorocholine PET/CT identified 3 foci suggestive of enlarged right upper, right lower and left upper glands. The superior parathyroid glands were excised by a surgeon and histopathology revealed one oxyphil parathyroid adenoma and one oxyphil hyperplasia. Postoperatively hypercalcemia normalized, but PTH still remained elevated although 25-hydroxyvitamin D was sufficient and renal functions were normal (not shown). The biochemical picture of normocalcemic hyperparathyroidism in accordance with fluorocholine imaging raises the possibility of a third enlarged parathyroid gland (probably the right lower) left unremoved during the surgery.

The mean size of fourteen resected parathyroid lesions (11 adenomas/3 hyperplastic tissues) was 11.9 mm (6-20) with a per lesion sensitivity of 93 % and per gland PPV of 81 %. Four adenomas and one hyperplastic gland were composed only of chief cells whereas five lesions contained both chief and oxyphil cells (Table 1). The total cell population of three parathyroid adenomas and one hyperplastic gland contained more than 80 % of oxyphil cells, defining them as exclusive oxyphil adenomas (Howson *et al.* 2015, Paul *et al.* 2015). Surprisingly, in all cases, MIBI was falsely negative in spite of high mitochondria content in oxyphil parathyroid cells. Unlike MIBI, FCH did not seem to be dependent on the histopathological composition of parathyroid lesions.

12 of 13 patients had thyroid disease (7 cases with nodular thyroid disease and 5 cases with autoimmune thyroid disease). An underlying thyroid pathology, in particular thyroid oncocytes, may complicate nuclear medicine imaging. In two patients with inconclusive FCH either oncocytic thyroid cells or oncocytic metaplasia were found by aspiration cytology or postoperative histopathology (patients 12 and 13, Table 1).

## Discussion

In this report we retrospectively analyzed patients with PHPT who underwent FCH because previous standard localization methods gave either negative or inconclusive results. FCH correctly identified enlarged parathyroid glands with per patient sensitivity of 92 % and PPV of 100 %, thus providing superior diagnostic ability in comparison with conventional methods. By virtue of this functional imaging technique, parathyroid surgery led to a cure in 12 of 13 patients with

PHPT. Our results are in agreement with other studies reporting a high detection rate using FCH in patients with PHPT and inconclusive MIBI and neck ultrasound (Michaud *et al.* 2014, Michaud *et al.* 2015, Kluijfhout *et al.* 2016, Fischli *et al.* 2018, Grimaldi *et al.* 2018).

Underlying thyroid disease often complicates the correct localization of enlarged parathyroid glands either by neck ultrasound or by MIBI (Kuzminski *et al.* 2018, Kunstman *et al.* 2013, Krátký *et al.* 2014). In the present cohort, thyroid disease was present with higher frequency than in previous reports (92 % of patients) and very likely contributed to both cases with false negative and false positive FCH findings. One case with a false positive FCH had nodular thyroid disease. We might only indirectly speculate that the presence of thyroid nodules led to the false uptake of fluorocholine in the thyroid bed, because the patient did not undergo thyroidectomy. A high uptake of fluorocholine has been documented in oncocytic thyroid adenomas (Aziz *et al.* 2015, Soelberg *et al.* 2012). Thyroid oncocytes were described in the thyroid cytology after fine needle aspiration of one of the thyroid nodules in this individual.

The false negative FCH result was documented in one patient with autoimmune thyroid disease. The thyroid gland showed a diffuse uptake of fluorocholine. It has been described that the presence of inflammation in Hashimoto thyroiditis can lead to a higher uptake of either MIBI or <sup>18</sup>F-fluorodeoxyglucose (FDG) (Boi *et al.* 2013, Yasuda *et al.* 1998). The concomitant thyroid uptake of fluorocholine may result in decreased sensitivity for lesions adjacent to the thyroid. False negative results of MIBI scans in the diagnosis of hyperfunctioning parathyroids have been documented in patients with either Hashimoto thyroiditis or Graves' disease (Boi *et al.* 2013). Whether there is any interfering mechanism of uptake, retention and washout of MIBI needs to be clarified. On the other hand, in a recent study the presence of autoimmune thyroid disease did not prevent the use of FCH from an accurate localization of parathyroid adenoma (Fischli *et al.* 2018).

Regarding the cytopathological composition of excised parathyroid glands, chief cells prevailed. A low number of oxyphil cells could explain the false negativity of MIBI in the present cohort. SestaMIBI is a mitochondrial marker and oxyphil cells contain a large amount of mitochondria (Mehta *et al.* 2005). Previous reports have shown a correlation between the percentage of oxyphil cells in parathyroid adenomas and MIBI sensitivity (Bleier *et al.* 2006). Surprisingly, three cases

with exclusively oxyphil adenomas were also associated with negative MIBI scans in our sample. It is likely that factors other than mitochondrial content, such as a parathyroid adenoma size/weight, may have played a role. Howson *et al.* (2015) showed that oxyphil parathyroid adenomas are also related to MIBI negativity more often than chief cell parathyroid adenomas. These findings raise the question if the advanced oncocyctic transformation of parathyroid chief cells might alter oxyphil cell properties with respect to MIBI avidity. In the thyroid gland, oncocytes in the thyroid nodules and/or oncocyctic metaplasia in the Hashimoto thyroiditis are linked to the false positivity of either MIBI or FDG (Boi *et al.* 2013, Yasuda *et al.* 1998). Whether oncocyctic transformation in the thyroid gland and the parathyroid glands might influence MIBI sensitivity in opposite ways needs to be addressed in further *in vitro* studies.

One of the patients with an oxyphil adenoma had multiglandular parathyroid disease. Moreover, an active focus was described in the pancreas. If this is a sporadic form of PHPT or a part of a familial syndrome like multiple endocrine neoplasia is being currently investigated. Furthermore, this particular case demonstrated the ability of FCH to appropriately localize enlarged parathyroid glands when being multiply involved.

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The major limitations of this study are the retrospective design with a low number of patients with PHPT. On the other hand, to the best of our knowledge, FCH sensitivity in parathyroid imaging was correlated for the first time with the cytopathological composition of the adenomatous and/or hyperplastic parathyroid glands.

In conclusion, in our limited sample of patients with PHPT, FCH correctly identified parathyroid adenomas or hyperplastic glands in 92 % patients with previously inconclusive conventional imaging. These patients thus became candidates for focused parathyroid surgery that afterwards led to the resolution of PHPT in 12 of 13 individuals. Unlike MIBI, FCH successfully localized small, hyperplastic and multiple hyperfunctioning parathyroid glands, irrespective of their histopathological composition. There was a high frequency of simultaneous thyroid disease in our patients, which contributed to both false negativity and false positivity in the FCH parathyroid imaging.

## Conflict of Interest

There is no conflict of interest.

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