^{18}F-fluorocholine PET/CT semi-quantitative analysis in patients affected by primary hyperparathyroidism: a comparison between laboratory and functional data.

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Research Article

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Abstract

Introduction: this retrospective study aims to establish ^{18}F-fluorocholine (FCH) positron emission tomography / computed tomography (PET/CT) performance in finding hyperfunctioning parathyroid glands, analyse a potential role for semi-quantitative PET parameters and assess factors that may influence PET/CT outcome.

Methods: forty patients with suspect primary hyperparathyroidism (pHPT) and negative/equivocal conventional imaging underwent FCH-PET/CT in our Institution.

For every lesion, visual and semi-quantitative analyses were performed on PET/CT images. In qualitative analysis, a lesion was considered positive if a clear focus of uptake, significantly higher than normal thyroid tissue, was identifiable. Ectopic focal uptake was also regarded as positive PET result. Lesion SUV_{Max} was measured by assigning a spheric VOI to the suspect area of uptake. Thyroid SUV_{Mean} was assessed by placing a spheric VOI inside the contralateral thyroid lobe, and SUV_{ratio} was calculated using this background region.

All patients were subsequently submitted to surgery and histopathologic workup.

Sensitivity, positive predictive value (PPV) and accuracy were calculated based on histopathologic reports for every lesion.

Pearson's test was used to assess a correlation between laboratory and histopathologic features with SUVr.

Results: four out of the 40 patients who underwent surgery for pHPT had more than one histologic proven unhealthy parathyroid and three had papillary thyroid cancer (PTC). A total of 48 lesions were analysed.

We found 42/48 lesions (87.5%) to have true-positive uptake, whereas three lesions (6.7%) had false-positive uptake (PTC). Three histologic proven parathyroid adenomas showed no uptake (6.7%); the sensitivity/PPV were 93.3% and accuracy was 87,8%.

Pearson's test showed a significant correlation between PTH values and parathyroid size with SUVr values ($r=0.56$ and 0.55 respectively, $p<0.01$ for both features).

Discussion: as stated in recent literature, we observed excellent diagnostic sensitivity of FCH-PET/CT in patients with pHPT, providing surgeons a fine tool to optimize treatment.

More studies are needed to improve the evaluability of semi-quantitative parameters towards a further improvement of diagnostic accuracy.

Introduction

Primary hyperparathyroidism (pHPT) is one of the most common endocrine disorders, generally discovered incidentally during routine blood tests which show hypercalcemia.

Inappropriate levels of parathyroid hormone (PTH) (> 20 pg/mL) in a patient with hypercalcemia are consistent with the diagnosis of pHPT, although sometimes pHPT may be normocalcemic. It is brought about by abnormal secretion of parathyroid hormone (PTH) from a solitary adenoma (80%), four-gland hyperplasia (10–15%), multiple adenomas (5%) or parathyroid cancer (< 1%), respectively [1]. It is generally sporadic, but it could be part of hereditary syndromes.

Manifestations of pHPT include osteoporosis, vertebral fractures and nephrolithiasis; surgery is considered the only curative treatment in most cases, recommended for those with symptoms and suggested for asymptomatic patients at risk of progression or with subclinical evidence of end-organ effects [1].

Correct pre-operative localization of the hyperfunctioning gland(s) represents a crucial step, mainly if a minimally invasive procedure (MIP) is contemplated. This approach may reduce the extent of surgery, incision length and recovery time; furthermore, it is associated with a high cure rate as well as bilateral neck exploration [2].

Guiding surgeons towards the exact location, pre-operative imaging is usually performed to reveal glands located at typical sites as well as ectopically, anywhere along the migratory path. Ectopic sites include high cervical position, carotid sheath, intra-thyroidal, intra-thymic, mediastinal or para-oesophagal location and even the pericardium [3].

The most common imaging assessment is the combination of neck ultrasonography (US) and ^{99m}Tc-MIBI scintigraphy with single photon emission tomography / computed tomography (SPECT/CT), yielding a sensitivity of 81–95%, which is mainly contributed by radionuclide imaging [4, 5]. In patients with equivocal or negative conventional imaging, second-line tests can be used, such as positron emission tomography / computed tomography (PET/CT) with ^{18}F-Fluorocholine (^{18}F-FCH) or ^{11}C-Methionine (^{11}C-MET), four-dimensional CT (4D-CT), magnetic resonance imaging (MRI) or, where available, ^{18}F-FCH PET/MRI.

The use of choline-labelled radiopharmaceuticals in this setting is based on occasional findings while performing ^{18}F-FCH PET/CT for other purposes (e.g., prostate cancer staging or restaging): choline is a precursor of phosphatidylcholine, a cellular membrane phospholipid component avidly taken up by neoplastic cells with increased cell membrane turnover as well as hyperfunctioning parathyroid cells. However, the biological uptake mechanism of choline is not fully understood. Thanks to its positive electric charge, choline-labelled radiopharmaceuticals enter the cells through a membrane transporter and accumulate in mitochondria; choline is also phosphorylated by choline-kinase, which is overexpressed in patients with pHPT, and used as a component of cell membranes [2]. This double mechanism could explain the advantage of ^{18}F-FCH PET/CT over ^{99m}Tc-MIBI scintigraphy, where ^{99m}Tc-MIBI enters the cells and accumulate only in mitochondria [6].

Published data show the higher sensitivity and overall accuracy of ^{18}F-FCH-PET/CT compared to conventional imaging [7]. Despite higher costs, false-positive results (e.g., inflammatory uptakes in lymph nodes or thyroid nodules) and potential local reimbursement issues, ^{18}F-FCH PET/CT shows several advantages over ^{99m}Tc-MIBI scintigraphy, such as lower radiation exposure [8], shorter time consumption and higher spatial resolution allowing the identification of smaller lesions.

Furthermore, recent data support ^{18}F-FCH PET/CT as a first-line method whenever possible [9]. This study aims to assess ^{18}F-FCH PET/CT performance in finding hyperfunctioning parathyroid glands, analyse a potential role for semi-quantitative PET parameters and evaluate possible factors which may influence ^{18}F-FCH PET/CT outcome.

Material And Methods

Patient population

All patients underwent diagnostic and therapeutic procedures at Candiolo Cancer Institute, Candiolo (TO), Italy, in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent for the use of anonymized data for scientific purposes was provided to all patients.

We retrospectively reviewed all ^{18}F-FCH PET/CT scans performed between February 2018 and June 2021 as a second-line test for pre-operative localization of hyperfunctioning parathyroids in patients with biochemically-diagnosed pHPT.

Patients were eligible for inclusion if they met the following criteria: (I) biochemically proven pHPT, (II) negative or discordant US and ^{99m}Tc-MIBI scintigraphy results, and (III) availability of imaging and histopathologic data. The following exclusion criteria were applied: (I) severe kidney failure (creatinine clearance < 30 mL/min), (II) profound vitamin D deficiency, (III) previous diagnosis of Multiple Endocrine Neoplasia-1 (Men-1) syndrome.

Pre-operative laboratory exams

Serum calcium, phosphate, PTH and 25-OH-vitamin D levels were measured twice: within two weeks before ^{18}F-FCH PET/CT and 2–5 days before surgery. Serum calcium and phosphate were measured by a colorimetric assay (reference range 8.8–10.4 mg/dL and 2.5–4.5 mg/dL, respectively). PTH and 25- OH-vitamin D were measured using a chemiluminescence assay (reference range 15–65 pg/mL and 30–100 ng/mL, respectively).

Scan protocol

All patients fasted for at least 4 hours before intravenous administration of a standard amount of 110 MBq of ^{18}F-FCH. Moreover, to reduce muscle radiopharmaceutical uptake, the patients were requested to avoid vigorous exercise before scanning, according to published data [10].

PET and CT images were acquired using a PET/CT scanner (Gemini TF by Philips® Medical Systems). PET/CT study was performed 60 minutes after ^{18}F-FCH administration, in a supine position with arms along the body from the skull base to the diaphragm. Hydration was obtained during the resting period in a comfortable chair, with oral administration of 500 mL of water.

Acquisition started with a scout view (30 mA, 120 kV) followed by a low-dose CT scan from the diaphragm to the base of the skull (80 mAs, 120 kV, 3 mm slice thickness, 4-mm table feed per rotation and 0.5 seconds per rotation). CT scan was used for both attenuation correction and anatomic localization. PET emission data were acquired in list-mode at 3 minutes per bed position; PET images were reconstructed onto a 128x128 matrix using a BLOB-OS-TF algorithm (Time of Flight).

Image analysis

Using Philips® IntelliSpace Portal workstation (v.5.0), PET images were reviewed by two expert nuclear medicine physicians (A.R. and M.R.), starting with visualization of multiple intensity projections (MIPs), then analyzing attenuation-corrected images in the three planes, with and without CT, according to the EANM Practice Guidelines [3]. Possible disagreements were discussed in a consensus meeting.

Qualitative analysis: PET/CT was considered positive when the following characteristics were satisfied: well-defined, focal, non-physiological tracer uptake discriminable from surrounding tissue in typical or ectopic areas. PET/CT was scored as negative when a normal distribution of ^{18}F-FCH was found or when abnormal uptake could be related to alternative explanations rather than hyperfunctioning parathyroid, such as reactive lymph nodes.

Semi-Quantitative analysis: in every lesion considered positive in qualitative analysis, the maximum standardized uptake value ($SUV_{Max)}$ was measured by assigning a spherical VOI. Furthermore, thyroid mean standardized uptake value (SUV_{Mean}) was measured by placing a 1 cm diameter-spherical VOI inside the contralateral lobe, and SUV_{Ratio} was calculated using this as background region.

Surgery

Focused parathyroidectomy or bilateral neck exploration was performed by two experienced endocrine surgeons (N.P. and M.F.), using a transverse collar incision or a minimally invasive median or lateral approach. In the case of mediastinal adenoma, a thoracoscopic resection approach was applied by an experienced thoracic surgeon (C.M.).

A focused parathyroidectomy or a bilateral neck exploration was done according to the results of pre-operative localization studies and intraoperative PTH (ioPTH) determination. A thyroid resection was also performed in the case of nodular thyroid disease.

Histology

Histological analysis of frozen sections was used if requested to confirm the presence of parathyroid tissue.

Final histological analysis was performed on paraffin-wax embedded sections stained with hematoxylin and eosin and for every hyperfunctioning parathyroid longest diameter was measured.

Outcome

PTH was determined intraoperatively after induction of general anaesthesia, and 10 min after removal of the last enlarged parathyroid tissue and serum calcium was determined on the 1st and 2nd postoperative day. A decrease greater than 50% of ioPTH, normalized serum calcium postoperatively, and confirmation of the removal of pathological parathyroid tissue on histopathological examination were defined as surgical success. The patient was considered cured if serum calcium normalization persisted six months after surgery.

Data interpretation and statistical analysis

The gold standard for diagnosis was the presence of a pathological gland (adenoma or hyperplasia) and its removal, resulting in a cure of the condition. Every removed gland was classified as follows:

- True positive: a PET-positive finding histologically confirmed as pathologic parathyroid gland.
- False positive: a PET-positive finding negative for pathological parathyroid gland at histologic examination (e.g., thyroid nodule).
- False negative: a removed pathologic parathyroid gland negative in PET examination.

Quantitative variables were described with median and interquartile range (IQR), whereas qualitative variables were reported with numbers and percentages.

Sensitivity, positive predictive value (PPV) and accuracy were calculated using histopathologic analysis as a reference standard using the χ^2 test.

Pearson's test was used to evaluate a possible correlation between laboratory (PTH, serum calcium, and phosphate) and histopathologic (longest diameter) features with SUV_{Ratio}.

All data analyses were performed using MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium). In every analysis, a P-value < 0.05 was considered statistically significant.

Thyroid nodule sub-analysis

In patients who underwent thyroid surgery alongside parathyroidectomy, PET/CT images were reviewed to assess the presence (or absence) of ^{18}F-FCH uptake in thyroid nodules.

A nodule was considered positive if it showed focal uptake above the surrounding background.

Afterwards, functional data were compared to histological findings to observe if there were qualitative differences between benign and malignant nodules.

Considering the low number of included patients and nodules, sensitivity, specificity, PPV, and NPV of ^{18}F-FCH PET/CT in detecting malignant thyroid lesions were not calculated as the results may have poor relevance.

Results

Study group

A total of 40 patients (M/F: 4/36; median age: 60y IQR: 50–68) with sporadic pHPT and inconclusive conventional imaging results were enrolled; their clinical characteristics are reported in table I.

Among the forty analysed patients, 33 were novel diagnoses of pHPT, while 7 were pHPT patients with disease relapse undergoing a second surgery.

With regard to laboratory data, all 40 patients had high PTH and average 25-OH-vitamin D values, and serum calcium was above reference levels in 26 patients (65%) and normal in 14 (35%).

All patients were submitted to parathyroidectomy or bilateral neck exploration according to the results of ^{18}F-FCH PET/CT imaging studies and ioPTH determination. In twelve patients (30%), a thyroid resection was also performed (total thyroidectomy in 5 cases, one of which with central neck dissection; lobo-isthmectomy in 6 cases; isthmusectomy in one case).

Four out of the 40 analysed patients (10%) had more than one histologic proven unhealthy parathyroid gland and three had additional papillary thyroid cancer nodule (PTC).

At follow-up, 37 patients (92.5%) resulted as cured, while 3 (7.5%) had persistent high serum calcium and PTH values, and were considered as not cured.

Based on histological results, a total of 48 lesions were analysed; among them, 29 were parathyroid adenomas (60%), 16 were classified as parathyroid hyperplasia (34%), and 3 were PTC nodules (6%).

FCH-PET/CT performance

^{18}FCH-PET/CT detected 45 areas of abnormal uptake classified as pathological findings. Functional data of analysed lesions are reported in table II.

We found 42/48 lesions (87.5%) to have true positive ^{18}F-FCH uptake, whereas three lesions (6.7%) had false positive uptake. Three histologic proven parathyroid adenomas showed no uptake (6.7%). Consequently, sensitivity and PPV were 93.3%, while accuracy was 87.8%.

Pearson's test showed a significant correlation between PTH values and parathyroid size with SUV_{ratio} values ($r = 0.56$ and 0.55 respectively, $p < 0.01$ for both features).

No significant correlation was found between serum calcium and phosphate levels and functional data (Fig. 1).

Thyroid nodules sub-analysis

As already stated, in twelve patients partial or total thyroidectomy was associated with parathyroid surgery and a total of 18 nodules were analyzed. Among them, three nodules (17%) were found to be classical variant of PTC, whereas 15 (83%) were expressions of benign nodular thyroid disease (four follicular adenomas and eleven nodular hyperplasias).

At the revision of ^{18}F-FCH PET/CT images, none of the 15 benign thyroid nodules showed ^{18}F-FCH uptake superior to the surrounding background, while three nodules classified as PTC showed higher ^{18}F-FCH uptake than the surrounding background.

Discussion

Since parathyroid was discovered as an anatomic entity in humans less than 150 years ago and the first patient underwent parathyroidectomy in 1925, the history of parathyroid disease and treatment emphasizes the importance of pre-surgery localization of unhealthy parathyroid glands [11].

Choline is an essential component for the biosynthesis of membrane phospholipids, necessary for correct physiological cell function. Its primary role in current medical practice is focused on staging and restaging prostate cancer and, to a lesser extent, managing well-differentiated hepatocellular liver cancer [12]. In these pathologies, a higher cell membrane turnover due to an upregulation of choline kinase has been widely described in the literature [13]. As far as the main topic is concerned, in benign parathyroid adenomas, increased choline avidity may be caused by lipid-dependent choline kinase abnormal activity due to PTH hypersecretion [11].

In this monocentric retrospective study, we investigated the performance of ^{18}F-FCH PET/CT in patients with suspect pHPT and negative or inconclusive conventional imaging. We explored possible correlations between ^{18}F-FCH uptake functional semi-quantitative data and laboratory results. The underlying issue was identifying a potential role for functional data to discriminate different findings relying on the laboratory.

In a recent meta-analysis including 14 studies with a total of 517 patients, Treglia et al. evaluated the overall performance of choline PET in localizing hyperfunctioning parathyroid glands [14]. Their findings indicate that choline PET/CT or PET/MRI has a sensitivity and PPV of 92% in per-lesion analysis. According to previously published data, in our study ^{18}F-FCH PET/CT showed a sensitivity and PPV of 93,3%.

We observed a correlation between the longest parathyroid diameter and ^{18}F-FCH uptake. This phenomenon may be explained by the well-known partial-volume effect, which negatively affects image quality visually and semi-quantitatively, decreasing signal and image smoothing in the smaller lesion [15]. This finding is consistent with a recent study by Liberini et al., which enhanced the same correlation using ^{18}F-FCH PET/MRI in 31 parathyroid adenomas [16]. Furthermore, Gatu et al. observed a significant correlation between pre-surgical PTH levels and parathyroid volume [17]; based on these premises, more prospective studies are needed to define this kind of correlation properly and to investigate if different reconstruction modalities may increase sensitivity in patients with suspect pHPT and PTH levels slightly above average values.

Consistently with the data reported by Alharbi et al. [18] and Liberini et al. [16], linear regression analysis showed a strong correlation between serum levels of PTH and ^{18}F-FCH uptake (Fig. 2). These results support the hypothesis postulated by Hishitzuka et al. in 1987. They observed a higher expression of membrane-associated cyclic AMP-dependent protein kinase C activity in parathyroid adenomas than in atrophic parathyroid glands, suggesting a close association between protein kinase C activity and hypersecretion of PTH [19].

Conversely from what Liberini et al. [16] and Alharbi et al. [18] observed in the casuistic they published, in our study, linear regression analysis did not show a significant correlation between functional PET data and serum calcium levels. This difference may be brought about by the presence of normocalcemic hyperparathyroidism in about one-third of the patients we examined. In a recent study, Bossert et al. revealed an overwhelming performance of ^{18}F-FCH PET/CT in identifying hyperfunctioning parathyroid glands in patients with normocalcemic pHPT compared to standard imaging with a detection rate of 71% [20]; furthermore, Musumeci et al. observed that ^{99m}Tc-MIBI SPECT/CT has a lower sensitivity in this clinical setting [21]. These results suggest a possible role for ^{18}F-FCH PET/CT as first-line imaging in patients with normocalcemic pHPT.

Ciappuccini et al. investigated the performance of ^{18}F-FCH PET/CT in predicting malignancy of thyroid nodules with indeterminate cytology in 81 patients undergoing surgery; they observed impressive NPV (96%) and sensitivity (90%) but poor specificity (49%) due to an increased uptake in benign oncocytic nodules [22]. In our study, we retrospectively analyzed ^{18}F-FCH behaviour in 18 thyroid nodules in patients submitted to partial or total thyroidectomy alongside parathyroidectomy and observed increased ^{18}F-FCH uptake in PTC nodules, whereas benign thyroid nodules did not show significant phospholipids membrane turnover. According to the literature [22], the absence of benign nodules with high ^{18}F-FCH uptake may be explained by the lack of histologically proven oncocytic nodules in our casuistic. Interestingly, none of the examined patients underwent fine needle aspiration before surgery, suggesting a possible role for ^{18}F-FCH PET/CT in selecting which nodules deserve more diagnostic procedures and cytology. More prospective studies are needed to establish the most cost-effective application of ^{18}F-FCH in this clinical setting and if it could guide or even substitute fine needle aspiration in selected cases.

The present study accounts for several limitations. First, it is a retrospective study with a low number of included patients and analysed lesions due to the limited number of patients with negative or equivocal standard parathyroid imaging. Second, according to the current guidelines, only patients with negative or discordant conventional parathyroid imaging were enrolled. This inclusion criterion induced a patient selection bias about hyperfunctioning parathyroid location and size.

Conclusion

As reported by recent literature, ^{18}F-Fluorocholine PET/CT showed overwhelming performances while employed as second-line imaging for parathyroid adenoma or hyperplasia.

Furthermore, our findings suggest that ^{18}F-Fluorocholine PET/CT may be a valuable instrument for researching unhealthy parathyroid glands in patients with normocalcemic hyperparathyroidism.

Based on our results, ^{18}F-choline uptake in unhealthy parathyroid might be associated with circulating serum parathyroid hormone and parathyroid size; this finding needs to be further explored in prospective studies to define better which patients may benefit from ^{18}F-choline as first-line imaging.

Declarations

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Author contribution: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Alessio Rizzo, Manuela Racca and Nicola Palestini. The first draft of the manuscript was written by Alessio Rizzo and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Tables

Table I. Patients characteristics.

Characteristics	Results (n. patients: 40)
Male/female	4 (10%)/36 (90%)
Age	
Median (IQR)	60 y (50-68)
PTH	
Median (IQR)	121 pg/mL (95-146)
Serum Calcium	
Median (IQR)	10.6 mg/dL (10.2-11.0)
25- OH-vitamin D	
Median (IQR)	42.4 ng/mL (35.6-48.1)
Surgery	
Parathyroidectomy	40 (100%)
Associated partial thyroidectomy	5 (12%)
Associated total thyroidectomy	7 (18%)
Number and location	
Patients with single hyperfunctioning parathyroid	36 (90%)
Patients with more than one pathologic gland	4 (10%)
Orthotopic	38 (95%)
Ectopic	2 (5%)
Clinical outcome	
Cured / not cured	37 (93%)/ 3 (7%)

Table II. ^{18}F-FCH PET-positive lesions characteristics.

Characteristics	Results (n. lesions: 48).
SUV_{Max}	
Median (IQR)	3.6 (2.5-4.3)
SUV_{Ratio}	
Median (IQR)	2.0 (1.4-2.9)
Histology	
Parathyroid adenoma	29 (60%)
Parathyroid hyperplasia	16 (34 %)
Papillary thyroid cancer	3 (6%)
Longest diameter	
Median (IQR)	1.4 cm (0.8-2.0)

Figures

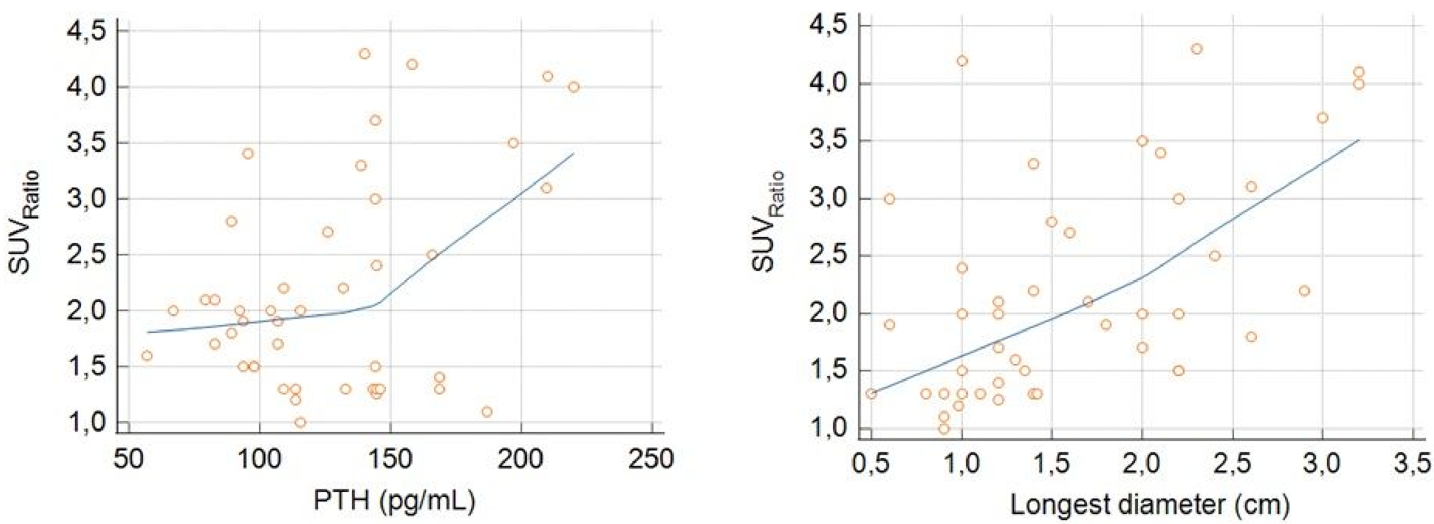

Figure 1

Linear regression analysis showing (A) significant correlation of SUVratio and PTH values(R =, P <0.05) and (B) longest parathyroid diameter (R=0.728, P < 0.05).

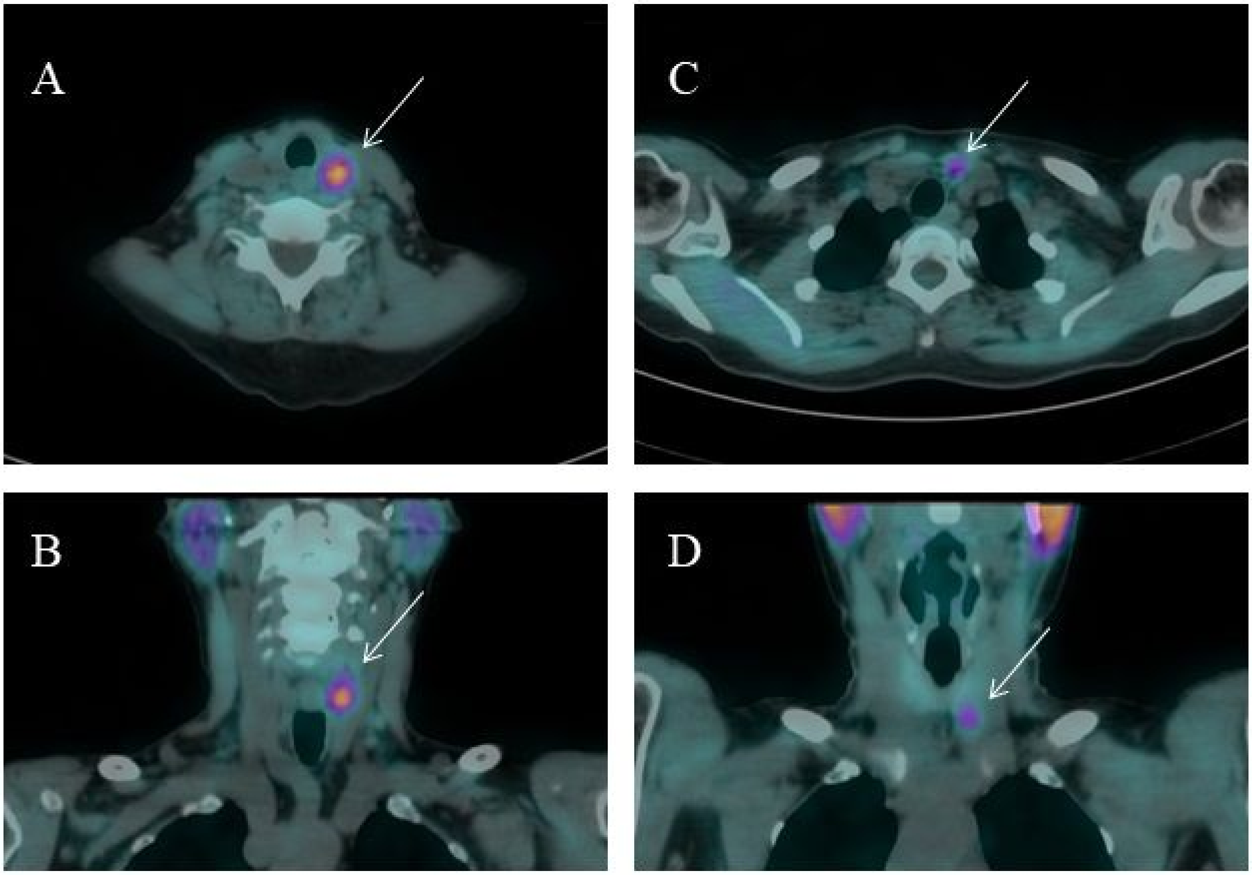

Figure 2

Two examples of ^{18}F-FCH PET/CT images in patients with parathyroid adenomas selected according to PTH levels. Left column (A: axial fused PET/CT image, B: coronal fused PET/CT image): a 56-year-old female patient underwent ^{18}F-FCH PET/CT for pHPT (PTH: 144 pg/mL, serum calcium: 11,3 mg/dL); PET/CT images showed focal and intense uptake in the upper left parathyroid gland (white arrow), suspect for the presence of unhealthy parathyroid (SUV_{Max}: 8.6, SUV_{Ratio}: 3,9); subsequent parathyroidectomy confirmed the presence of parathyroid adenoma. Right column: a 44-year-old female patient underwent ^{18}F-FCH PET/CT for pHPT (PTH: 89,2 pg/mL, serum calcium: 10,8 mg/dL); PET/CT images showed focal and intense uptake in the lower left parathyroid gland (white arrow), suspect for the presence of unhealthy parathyroid (SUV_{Max}: 3.7, SUV_{Ratio}: 1.5); subsequent parathyroidectomy confirmed the presence of parathyroid adenoma.

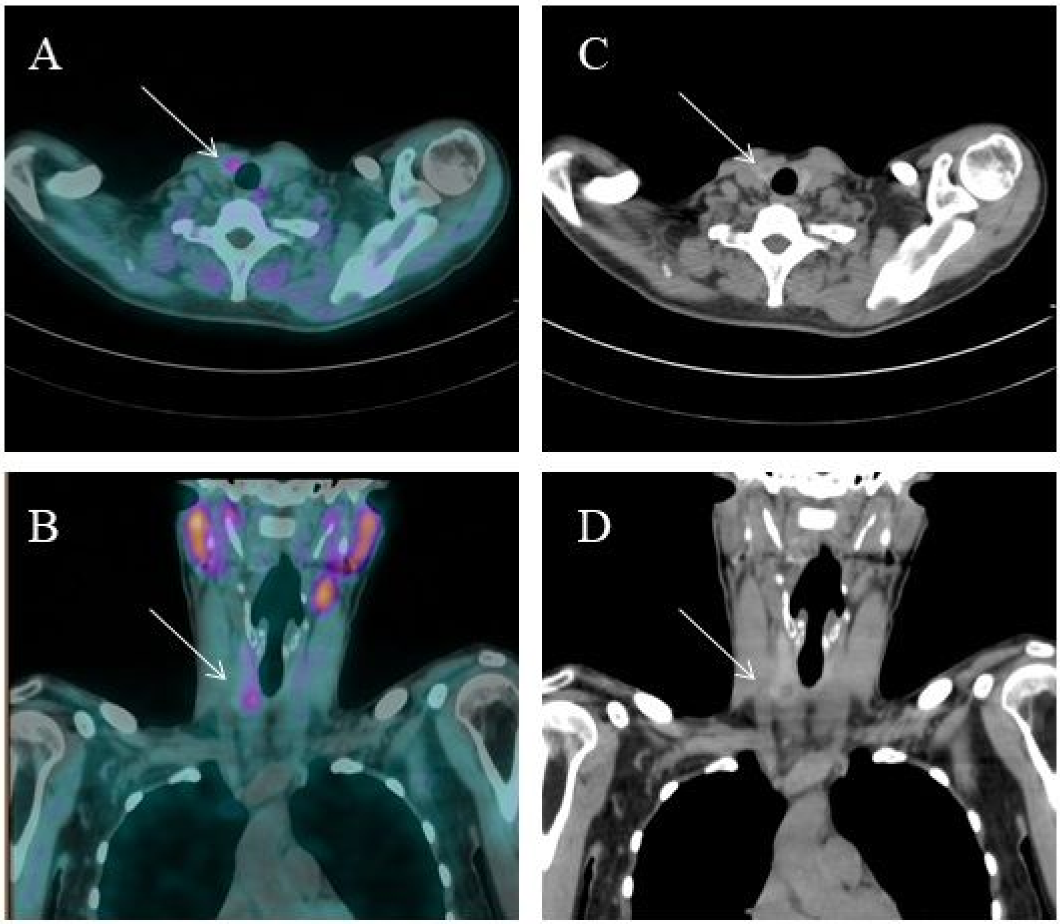

Figure 3

Example of a ^{18}F-FCH PET/CT positive thyroid nodule in a 20-year-old female patient. She was referred to our centre for pHPT (PTH: 82 pg/mL, serum calcium: 10,4 mg/dL). US examination showed a thyroid nodule in the right thyroid lobe and dual-phase ^{99m}Tc-MIBI scintigraphy did not show any abnormal uptake site. ^{18}F-FCH PET/CT images (A: axial fused PET/CT image, B: coronal fused PET/CT image, C: axial low dose CT image, D: coronal low dose CT image) showed focal uptake in the right thyroid lobe (white arrow). Subsequently, the patient underwent right lobectomy and pathology revealed a 14 mm classical papillary thyroid cancer. Considering that 18F-FCH PET/CT imaging did not find the source of abnormal serum PTH levels, nor did surgical neck exploration, the patient was classified as not cured.