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Original article

^{18}F-Fluorocholine PET/CT in primary hyperparathyroidism: superior diagnostic performance to conventional scintigraphic imaging for localization of hyperfunctioning parathyroid glands

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ABSTRACT

Primary hyperparathyroidism (PHPT) is a common endocrine disorder, definitive treatment usually requiring surgical removal of the offending parathyroid glands. In order to perform focused surgical approaches, it is necessary to localize all hyperfunctioning glands. The aim of the study was to compare the efficiency of established conventional scintigraphic imaging modalities with emerging ^{18}F-Fluorocholine PET/CT imaging in preoperative localization of hyperfunctioning parathyroid glands in a larger series of PHPT patients.

Methods: 103 patients with PHPT were imaged preoperatively with ^{18}F-Fluorocholine PET/CT and conventional scintigraphic imaging methods, consisting of ^{99m}Tc-sestaMIBI SPECT/CT, ^{99m}Tc-sestaMIBI/pertechnetate subtraction imaging and ^{99m}Tc-sestaMIBI dual-phase imaging. The results of histological analysis as well as intact parathormone and serum calcium values obtained one day after surgery and on the follow-up served as the standard of truth for evaluation of imaging results.

Results: Diagnostic performance of ^{18}F-Fluorocholine PET/CT surpassed conventional scintigraphic methods (separately or combined), with calculated sensitivity of 92% for PET/CT and 39-56% for conventional imaging (65% for conventional methods combined) in the entire patient group. Subgroup analysis, differentiating single and multiple hyperfunctioning parathyroid glands, showed PET/CT to be most valuable in multiple hyperfunctioning gland group with sensitivity of 88%, while conventional imaging with sensitivity of 22-34% (44% combined) was significantly inferior.

Conclusion: ^{18}F-Fluorocholine PET/CT is the superior diagnostic modality in comparison to the conventional imaging methods, allowing for accurate preoperative localization in patients with PHPT.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a common endocrine disorder, characterized by parathormone (PTH) overproduction (*1*) due to parathyroid adenoma in 85-96% of cases (2-5% may represent a double adenoma) and less often due to parathyroid hyperplasia in 4-15% of cases. Surgical removal of the offending gland is the only curative treatment. Minimally invasive surgical approach has become standard of care in selected patients. However, in order to perform focused approaches, it is necessary to localize all hyperfunctioning glands and rule out possible multiple gland disease (MGD) (*2*).

Currently, the most commonly used imaging for this purpose is parathyroid scintigraphy with ^{99m}Tc-sestaMIBI supplemented by neck ultrasonography. While subtraction scintigraphy (preferentially using ^{123}I as a thyroid-specific tracer in place of more commonly used pertechnetate, $^{99m}TcO_4^-$) is still considered to be a scintigraphic method of choice, the sensitivity can be improved by SPECT, but is nonetheless suboptimal in patients with multiple parathyroid lesions (*3*). With the advent of hybrid imaging methods ^{99m}Tc-sestaMIBI SPECT/CT is increasingly considered to be the most accurate imaging modality (*4*) offering attenuation correction as well as functional and anatomical data co-registration. PET imaging modality is of interest due to its inherent higher spatial resolution and shorter imaging times. In hyperparathyroidism it was limited to the use of ^{11}C-methionine, a revived parathyroid imaging tracer of poor availability, which was utilized when conventional parathyroid imaging was negative or discordant. Recently, ^{18}F-Fluorocholine, a radiopharmaceutical commonly used in prostate cancer imaging, has demonstrated promising results in several small studies possibly leading to expanded role of this tracer in the future (*5-7*) .

The aim of this study was to compare the efficiency of established conventional nuclear medicine imaging methods with emerging ^{18}F-Fluorocholine PET/CT in preoperative hyperfunctioning parathyroid gland localization in a larger series of PHPT patients.

MATERIALS AND METHODS

Patients

Patients with biochemically confirmed primary hyperparathyroidism (PHPT) (median serum albumin-corrected calcium (Ca) 2.78 mmol/L, range 2.3-4.1 mmol/L, normal range 2.10-2.60 mmol/L; median intact parathormone (iPTH) 145 pg/mL, range 40-1076 pg/mL; normal range 12-65 pg/mL) were prospectively included in the study excluding patients with atypical form of pHPT (familial hypocalciuric hypercalcemia), other known familial syndromes (familial pHPT, MEN syndromes) and patients with previous parathyroid resection. All patients had neck ultrasonography prior to surgery, not necessarily prior to scintigraphic imaging.

The study was approved by the National Committee for Medical Ethics (No. 77/11/12, NCT03203668). Each participant gave a written informed consent upon entering the study in accordance with provisions of the Declaration of Helsinki.

^{18}F-Fluorocholine PET/CT Imaging and Image Processing

Patients were administered 100 MBq of ^{18}F-Fluorocholine intravenously after a 6-hour fast. PET/CT imaging of neck and upper mediastinum to the level of the aortic arch was performed 5 minutes and 60 minutes after injection with Siemens mCT® 128 slice CT scanner. Acquisition consisted of low-dose CT (25 mAs, CARE DOSE 4D, 120 kV) followed by PET imaging (one bed position, 4 minutes per bed position). Image reconstruction was performed with proprietary Siemens HD PET software with iterative TrueX + time-of-flight OSEM method (2 iterations, 21 subsets), using matrix 400x400 pixels, zoom 1, Gaussian filter, FWHM 4 mm.

Conventional Scintigraphic Imaging and Image Processing

Conventional (i.e., non-PET/CT) scintigraphic imaging methods consisted of ^{99m}Tc-sestaMIBI SPECT/CT, ^{99m}Tc-sestaMIBI/pertechnetate subtraction imaging and ^{99m}Tc-sestaMIBI dual-phase imaging. A combined imaging protocol was used enabling same-day acquisition of all three modalities. Patients were administered 600 MBq of ^{99m}Tc-sestaMIBI intravenously. Planar acquisition of neck and upper mediastinum was performed on Siemens BASICAM gamma camera 10 minutes after injection (''early'' sestaMIBI planar image; matrix 128x128 pixels, zoom level 2.5, 10 minutes), followed by SPECT/CT acquisition of the same area on Siemens Symbia T2 dual head gamma camera (matrix 128x128, zoom level 1.78, 32 projections, 20s/frame, low-dose CT at 25mAs and 130kV). Image reconstruction was performed with proprietary Siemens Flash3D software with iterative OSEM method (4 iterations, 16 subsets), attenuation and scatter correction. Planar acquisition was repeated at 90 minutes after injection (''delayed'' sestaMIBI planar image) using identical parameters. Immediately after the second planar imaging and without change in position patients were administered 150 MBq of $^{99m}TcO_4^-$ and after 10 minutes planar imaging of neck and upper mediastinum was performed using identical parameters as for the planar sestaMIBI imaging.

Surgery, Intraoperative iPTH Measurement and Histology, Follow-up

Surgery was generally recommended when any one of the criteria for surgery according to guidelines were met: hypercalcemia consistently 0.25 mmol/L above normal; fracture; renal stones, hypercalciuria, and other stone risk factors; T-score < -2.5 SD at any site; and age < 50 years (*8*). When the above criteria were not met, patients were referred to parathyroidectomy on the basis of an expert opinion that surgery is an appropriate option if no medical contraindications are present (*9*).

Surgical approach was chosen according to preoperative imaging results: patients with a single identified hyperfunctioning gland underwent minimally invasive focused approach, while patients with multiple lesions, non-localization or disagreement among imaging methods underwent bilateral neck exploration. iPTH was measured upon the general anesthesia induction and 10 minutes after the removal of the last hyperfunctioning gland. A decrease of iPTH by 50 % or more from baseline at the second measurement was considered to represent a successful surgical procedure; for determination of iPTH, blood samples were collected into K2-EDTA Vacutainer™ tubes (Becton-Dickinson, Plymouth, UK). After collection, tubes were immediately transported to the laboratory, centrifuged (2500 G, 10 min, room temperature) and analysed. For analysis commercial available kits "Cobas, PTH STAT" and analyser "Cobas e 411", (Roche Diagnostics, Mannheim, Germany) were used.

The total number, location (upper left, lower left, upper right, lower right and ectopic), weight (g) and measurements in three dimensions (mm) of the removed parathyroid glands were recorded; the volume of the removed tissue was approximated from measurements ($V = a \times b \times c \times \pi / 6$; a, b, and c referring to the diameters of the gland). Specimens were submitted to histological analysis which served as the standard of truth for comparison with imaging results. Control iPTH and Ca values were obtained one day after surgery and normalization of both values was considered as an early indication of successful surgery. If the normal calcium homeostasis persisted for at least 6 months, the patient was considered cured.

Image Interpretation and Analysis

Images were read separately by two nuclear medicine specialists (A. C. and L. L.) with 3 and 6 years of experience with ^{18}F-Fluorocholine PET/CT in parathyroid imaging, respectively and more than 8 years and 15 years in conventional parathyroid scintigraphic imaging, respectively in five sessions:

1.) ^{18}F-Fluorocholine PET/CT imaging, where regional uptake on the PET image (and corresponding soft tissue lesion on the CT image, if seen) not associated with thyroid gland was considered to represent hyperfunctioning parathyroid tissue;

2.) ^{99m}Tc-sestaMIBI SPECT/CT imaging, where regional uptake on the SPECT image (and corresponding soft tissue lesion on the CT image, if seen) not associated with thyroid gland was considered to represent hyperfunctioning parathyroid tissue;

3.) ^{99m}Tc-sestaMIBI/pertechnetate subtraction imaging, where the remaining activity after subtraction of pertechnetate planar image from early sestaMIBI planar image after normalization and anatomical co-registration was considered to represent hyperfunctioning parathyroid tissue;

4.) ^{99m}Tc-sestaMIBI dual-phase imaging, where uptake of ^{99m}Tc-sestaMIBI with slower washout than from thyroid gland on the delayed planar image in comparison to the early planar image was considered to represent hyperfunctioning parathyroid tissue;

5.) Combined assessment of conventional scintigraphic imaging methods (i.e., simultaneous reading of all conventional scintigraphic studies), where any positive finding according to the interpretation criteria described above was considered to represent hyperfunctioning parathyroid tissue.

The results of conventional scintigraphic imaging or neck ultrasonography were not known before ^{18}F-Fluorocholine PET/CT interpretation, as the studies were anonymized; the studies were analysed in random order. As for the histological analysis, five locations were evaluated in each patient for the presence of tracer uptake considered to represent hyperfunctioning parathyroid tissue: upper left, lower left, upper right, lower right and ectopic.

Imaging results were compared to surgical and histological findings classified using the same site-based five-location scheme and interpreted as follows: *true-positive* location with regional tracer uptake as well as histological confirmation of parathyroid adenoma/hyperplasia; *false-positive* location with regional tracer uptake and histological findings other than parathyroid adenoma/hyperplasia; *false-negative* location without regional tracer uptake but with histological findings of parathyroid adenoma/hyperplasia; *true-negative* location without regional tracer uptake and histology findings of normal parathyroid tissue; locations without regional tracer uptake and without histological confirmation in patients whose serum Ca and iPTH values were normal at follow-up (i.e., no remnant hyperfunctioning parathyroid tissue). Histological confirmation of adenoma/hyperplasia and/or follow-up iPTH and Ca normalization were used as the standard of truth, according to which the diagnostic performance metrics (sensitivity, specificity) were calculated. In cases of persistent hyperparathyroidism a false negative result was added to the analysis based on the assumption that a hyperfunctioning gland negative on imaging must be present.

Statistical Analysis

Continuous data are reported as median (range). Sensitivity and specificity were calculated site-based for each imaging modality and conventional imaging modalities combined against the standard of truth (histological analysis and/or follow-up iPTH and Ca normalization). McNemar's test was performed for sensitivity and specificity comparison. Normal probability plot was used to assess the normality of data distribution. The Wilcoxon rank-sum test was applied for comparison of continuous variables with non-normal distribution. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS software (version 22).

RESULTS

Patients

Between May 2012 and June 2016, 188 patients were enrolled, of which 103 patients (78 women, 26 men) were operated and included in the analysis, with the median age of 64 years (range 39-77 years). All included patients had biochemically confirmed primary hyperparathyroidism with median serum Ca 2.78 mmol/L (range 2.3-4.1 mmol/L) and median iPTH 145 pg/mL (range 40-1076 pg/mL). Long term follow-up identified 2 patients with recurrent hyperparathyroidism and 6 patients with persistent hyperparathyroidism. In 40 % of our study group, one or more thyroid nodules were confirmed on neck ultrasonography. Patient characteristics are detailed in Table 1.

Resected Parathyroid Gland Pathologies, Volumes and Weights

All 103 patients underwent surgery and had cumulatively 131 lesions removed. The patients were allocated into two groups for statistical analysis according to the histological findings, namely single hyperfunctioning parathyroid group (87 patients; 83 adenoma, 1 parathyroid carcinoma) and multiple adenoma/hyperplasia group (4 patients with two adenomas and 10 patients with 31 hyperplastic glands). Therefore, 86% of our patient group had a single gland disease and 14% of patients had multiglandular disease. Resected specimens included one sample of thyroid tissue beside parathyroid glands.

In three patients a single hyperfunctioning parathyroid gland localized with ^{18}F-Fluorocholine PET/CT (in one case ^{99m}Tc-sestaMIBI SPECT/CT and subtraction scintigraphy were also positive) was classified as normal parathyroid tissue in histological report. As iPTH and Ca normalized and remained normal on follow-up (i.e., biochemical remission), we classified these imaging findings as true positive and analyzed them in the single adenoma patient group.

Six patients had persistent hyperparathyroidism on follow-up. In three of these patients hyperparathyroidism persisted after surgical resection of a single adenoma. Two patients without evidence of parathyroid adenoma or hyperplasia on all imaging modalities underwent bilateral neck exploration; both had two histologically normal parathyroid glands removed. For statistical analysis one false negative finding in each imaging modality was assigned to either of these patients. One patient had two hyperplastic glands removed despite PET/CT localizing all four; the remaining two glands were classified as true-positive in view of persistent primary hyperparathyroidism and repeated imaging with ^{18}F-Fluorocholine PET/CT (remaining two lesions again identified). Definite histology could not be obtained because the patient was unwilling to undergo reoperation despite persistent primary hyperparathyroidism.

The volumes and weights of resected hyperfunctioning glands were available for 111 of the 131 removed lesions measuring 2.9 (median; range 0.2-87.9) cm^3 and 0.4 (median; range 0.1-10.9) g. Separate analysis of adenomas and hyperplastic glands demonstrated both volume and weight being significantly smaller for hyperplastic glands than for parathyroid adenomas (p-value < 0.001): 1.5 (median; range 0.2-71.6) cm^3 and 0.2 (median; range 0.1-9.7) g for hyperplastic glands and 3.9 (median; range 0.5-87.9) cm^3 and 0.5 (median; range 0.1-10.9) g for adenomas.

Diagnostic Performance of ^{18}F-Fluorocholine PET/CT and Conventional Imaging Modalities

^{18}F-Fluorocholine PET/CT correctly localized 122/131 resected lesions. The majority of lesions were visible on both phases of imaging with better lesion-to-background and lesion-to-thyroid ratio on the delayed images on visual assessment.

False-negative results consisted of non-localization of 5 hyperplastic glands, one upper right adenoma incorrectly identified as lower right adenoma and previously identified patients with persistent hyperparathyroidism. Five non-localized glands were significantly smaller and lighter than localized glands ($p < 0.05$). One false-positive result was histologically classified as thyroid tissue and slightly reduced the specificity of the test.

In one case ^{18}F-Fluorocholine PET/CT localized all four hyperfunctioning glands followed by surgical resection of two upper parathyroid glands, both histologically reported as hyperplastic. Due to a sufficient intraoperative iPTH reduction and surgeon's visual assessment both lower parathyroids were not resected. Upon follow-up iPTH remained elevated, a repeated ^{18}F-Fluorocholine PET/CT again demonstrated uptake in both lower parathyroid gland locations. Only the lower left parathyroid gland was correctly visualized on all conventional imaging studies.

The sensitivity of ^{18}F-Fluorocholine PET/CT was significantly higher than that of any of the conventional imaging methods separately or combined , with specificity being slightly lower due to ^{18}F-Fluorocholine PET/CT false-positive finding of thyroid tissue not being localized on any of the conventional imaging modalities; diagnostic performance of all modalities is presented in Table 2.

Calculation of sensitivity included 131 lesions proven by histology and also six cases of persistent primary hyperparathyroidism described above and interpreted in the individual clinical context.

Discordant findings (i.e. true-positive on PET/CT that were false-negative on conventional modalities) were compared to true-positive findings on conventional imaging modalities. The analysis (Table 3) showed significantly smaller volumes and weights of lesions that were correctly identified only on PET/CT imaging.

Diagnostic Performance of Imaging Modalities according to the Parathyroid Gland Pathology

In the subgroup with single parathyroid adenoma (87 patients) ^{18}F-Fluorocholine PET/CT had a sensitivity of 95.5% and specificity of 99.7% for lesion localization. As previously noted, one upper right adenoma was incorrectly identified as lower right adenoma, three patients had persistent PHPT after single adenoma resection and in one case thyroid tissue (as reported by histology) was falsely interpreted as a hyperfunctioning parathyroid gland on imaging. ^{99m}Tc-sestaMIBI SPECT/CT had a sensitivity of 67%, followed by ^{99m}Tc-sestaMIBI dual-phase imaging and ^{99m}Tc-sestaMIBI/$^{99m}TcO_4^-$ subtraction imaging with sensitivities of 48% and 49%, respectively. Combined conventional imaging assessment amounted to a sensitivity of 76%. In one patient a parathyroid carcinoma was identified with ^{18}F-Fluorocholine PET/CT, while conventional imaging modalities were all false-negative.

In the subgroup with multiple adenomas/hyperplasia (14 patients; 4 dual adenomas and 31 hyperplastic glands) ^{18}F-Fluorocholine PET/CT had a sensitivity of 88% and specificity of 100%. Among the conventional imaging modalities ^{99m}Tc-sestaMIBI SPECT/CT had the highest sensitivity of 34%, followed by ^{99m}Tc-sestaMIBI dual-phase imaging and ^{99m}Tc-sestaMIBI/$^{99m}TcO_4^-$ subtraction imaging with identical sensitivities of 22%. Combined conventional imaging assessment had a sensitivity of 44%.

Diagnostic performance of ^{18}F-Fluorocholine PET/CT was significantly higher in comparison to conventional imaging modalities (separately and combined) in both single parathyroid adenoma as well as multiple adenomas/hyperplasia patient group ($p < 0.001$); specifically, 6/14 patients in the subgroup with multiple adenomas/hyperplasia were falsely classified as having a single hyperfunctioning parathyroid gland on conventional imaging, while ^{18}F-Fluorocholine PET/CT correctly localized multiple offending glands – three of these patients had dual adenoma and three had several hyperplastic glands as confirmed by histology reports.

DISCUSSION

The results of the present study provide further proof of ^{18}F-Fluorocholine PET/CT as a promising imaging modality for parathyroid localization in PHPT patients, surpassing conventional imaging modalities in single gland adenoma and more notably in MGD.

Hyperfunctioning parathyroid localization with conventional imaging approaches is currently suboptimal – particularly in case of hyperplasia, which is of a concern as PHPT persistence is mostly caused by failure to recognize MGD (*10*). Reported sensitivities of conventional scintigraphic imaging modalities are in the range of 58-86% (*11-13*), with lower performance in small lesions and MGD cases (*3,4*). Emerging studies show a slow but steady growth of evidence establishing ^{18}F-Fluorocholine as the most promising PET tracer investigated for hyperfunctioning gland localisation. In comparison to the conventional scintigraphic imaging, ultrasonography or in one case 4D CT, ^{18}F-Fluorocholine had superior performance with reported sensitivities ranging from 94% to 100% (*6,7,14,15*). Typically, ^{18}F-Fluorocholine PET/CT was performed as a "second line" investigation when conventional scintigraphic imaging was negative, inconclusive or discordant with US examination of the neck. Excluding our pilot study and present work, only two studies have directly compared ^{18}F-Fluorocholine PET/CT and conventional scintigraphic methods, both demonstrating superior diagnostic performance of PET/CT with a sensitivity of 100% and 94%; as a reference scintigraphic method, the studies used planar ^{99m}Tc-sestaMIBI dual-phase imaging with an addition of optional early ^{99m}Tc-sestaMIBI (*16*) or routine late ^{99m}Tc-sestaMIBI/^{99m}Tc-tetrofosmin (*17*) SPECT/CT imaging for a sensitivity of 76% and 61%, respectively. Current recommendations (*18,19*) allow several approaches to parathyroid imaging (dual-phase ^{99m}Tc-sestaMIBI protocol, subtraction protocol with ^{99m}Tc-sestamibi or ^{99m}Tc-tetrofosmin as parathyroid-specific tracers and $^{99m}TcO_4^-$ or ^{123}I as thyroid-specific tracers, addition of SPECT or SPECT/CT to parathyroid-specific imaging). While subtraction scintigraphy may still be considered as the method of choice due to its proven diagnostic value (*20*), the use of hybrid (SPECT/CT) ^{99m}Tc-sestaMIBI imaging is increasing as a result of accumulating evidence of diagnostic advantage over alternative protocols; a recent meta-analysis reported superior performance of ^{99m}Tc-sestaMIBI SPECT/CT over planar imaging approaches with a pooled sensitivity of 86 % (*4*).

Our aim was to compare ^{18}F-Fluorocholine PET/CT to all curently recommended conventional parathyroid scintigraphy protocols. We found the diagnostic performance of ^{18}F-Fluorocholine PET/CT was superior to all conventional scintigraphic protocols, both separately and combined. In the two similarly designed studies, the performance of conventional scintigraphy was comparable (*17*) or better (*16*). However, a median gland weight in the two studies was 1 g and only 0.4 g in the present study, which may have contributed to the lower diagnostic performance of conventional scintigraphy; in solitary adenomas with the median weight of 0.5 g, the sensitivity of conventional scintigraphy was in the expected range of 78 % (Table 2). It must also be noted that the diagnostic performance of conventional scintigraphy in our study may potentially be limited by the imaging protocol. Ideally, $^{99m}TcO_4^-$ injection and imaging is performed first and no patient movement is allowed between $^{99m}TcO_4^-$ and ^{99m}Tc-sestaMIBI injection in order to enable optimal alignment and subtraction (*18,19*); the use of ^{123}I as a thyroid-specific tracer would obviate patient movement during subtraction imaging. Nevertheless, this approach offers the benefit of combining three conventional scintigraphy protocols for improved sensitivity, as demonstrated in a large retrospective single-centre analysis of 462 patients (*21*) and also in the present study.

Because of its technical characteristics including high spatial resolution and sensitivity, PET/CT theoretically enables localization of smaller lesions. Lesion size is probably a very important factor contributing to the exceptional diagnostic accuracy of PET/CT ^{18}F-Fluorocholine in comparison to the conventional scintigraphic imaging due to the superior spatial resolution of the PET system. We demonstrated this fact by comparing the discordant results (true-positive on ^{18}F-Fluorocholine and false-negative on conventional modalities) with the true-positive results on conventional scintigraphic modalities, where the glands in discordant cases were significantly smaller (Table 3); these results are again in concordance with previous reports (*16,17*).

In most previous studies, ^{18}F-Fluorocholine PET/CT in PHPT was performed as a "second-line" investigation. However, this approach may be suboptimal. Recent reports (*16,17*) and present study results demonstrate significantly lower diagnostic value of conventional imaging methods (including ^{99m}Tc-sestaMIBI SPECT/CT) in comparison to ^{18}F-fluorocholine PET/CT, requiring additional imaging when negative and thereby increasing radiation exposure and cost. These findings are even more important in case of multiple hyperfunctioning parathyroid glands, where the diagnostic performance of conventional imaging methods is poor. Frequently, only one (usually the largest) offending gland is localized and subsequently removed, leading to persisting or recurrent endocrine disorder. Similarly, intraoperative iPTH measurement can fail to detect multiglandular disease leading to premature termination of surgery based on sufficient fall of iPTH values after removing the largest offending gland (*20*). Initial assessment by ^{18}F-Fluorocholine PET/CT would preclude this complication and thus avoid the need for repeated surgery; a typical case is shown in Figure 1. Moreover, if a solitary gland is localized by ^{18}F-Fluorocholine PET/CT, there is usually no need for either additional imaging or intraoperative iPTH monitoring due to the exquisitely high sensitivity of the method; the surgical procedure is therefore simplified and accelerated. Several authors have reported success rates as high as 97% in patients undergoing minimally invasive parathyroidectomy without intraoperative iPTH

(*22,23*). In our experience, intraoperative iPTH was not used in 126 patients where a single gland disease was localized preoperatively by ^{18}F-Fluorocholine PET/CT (*24*). Although intraoperative iPTH is not an expensive test by itself, it prolongs the procedure for about 30 minutes, marginally increases the cure rate in minimally invasive parathyroidectomy but incurs an approximately 4% additional cost (*25*).

If applying the approach of "second-line PET/CT" to our patient group, 12 patients with negative conventional imaging (all methods combined) would benefit from PET/CT as they had a single adenoma identified and were therefore suitable candidates for MIP. But at the same time 6/14 patients in our group would be falsely selected for MIP based on conventional imaging results if PET/CT would not reclassify them as MGD patients.

^{18}F-Fluorocholine PET/CT currently represents the most widely available PET modality for hyperfunctioning parathyroid gland localisation due to its widespread indication for prostate cancer imaging. While it inevitably includes the use of ionizing radiation, using an identical imaging approach as described above recently showed that the radiation exposure is lowest for ^{18}F-Fluorocholine PET/CT in comparison to conventional imaging approaches (*26*). Short scanning time also speaks in favor of the method. Nevertheless, the availability of ^{18}F-Fluorocholine is still considerably lower in comparison to conventional scintigraphy. Another significant limitation of the method may be the price of the investigation.

Considering the superior diagnostic performance of ^{18}F-Fluorocholine PET/CT in PHPT, the examination will most likely have an important role in PHPT imaging, but uncertainty remains regarding its place in the diagnostic algorithm. Before considering its role as a first-line modality a dedicated prospective cost-effectiveness study should be performed to analyze the benefits of avoided duplicated imaging and repetitive surgery against the cost of ^{18}F-fluorocholine PET/CT when performed as the only nuclear medicine imaging modality.

CONCLUSION

Our prospective study in the largest patient population to date shows ^{18}F-Fluorocholine PET/CT to be a superior diagnostic modality in comparison to all conventional scintigraphic imaging protocols, most notably surpassing conventional imaging in cases of small adenomas and multiglandular disease. Confirmation of results in a large multicentre study and a dedicated cost-effectiveness analysis is required to consider ^{18}F-Fluorocholine PET/CT as first-line imaging modality in PHPT.

Compliance with Ethical Standards:

Funding: none.

Conflict of Interest: Authors declare no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

KEY POINTS

QUESTION: What is the diagnostic value of ^{18}F-Fluorocholine PET/CT imaging for preoperative localization of hyperfunctioning parathyroid tissue in patients with primary hyperparathyroidism in comparison to conventional nuclear medicine modalities (dual-phase imaging, subtraction scintigraphy, SPECT & SPECT/CT)?

PERTINENT FINDINGS: ^{18}F-Fluorocholine PET/CT was compared to conventional nuclear medicine imaging protocols (dual-phase imaging, subtraction scintigraphy, SPECT & SPECT/CT) in prospectively enrolled patients with biochemically proven primary hyperparathyroidism and indication for surgery; surgical findings and histology were used as the standard of truth for evaluation of imaging results. ^{18}F-Fluorocholine PET/CT was found to be superior to all conventional scintigraphic protocols individually or combined, in particular in patients with small and/or multiple lesions

IMPLICATIONS FOR PATIENT CARE: If used as a first-line imaging modality, ^{18}F-Fluorocholine PET/CT can spare a proportion of patients from repeated imaging and/or repeated surgery, potentially reducing radiation exposure and cost.

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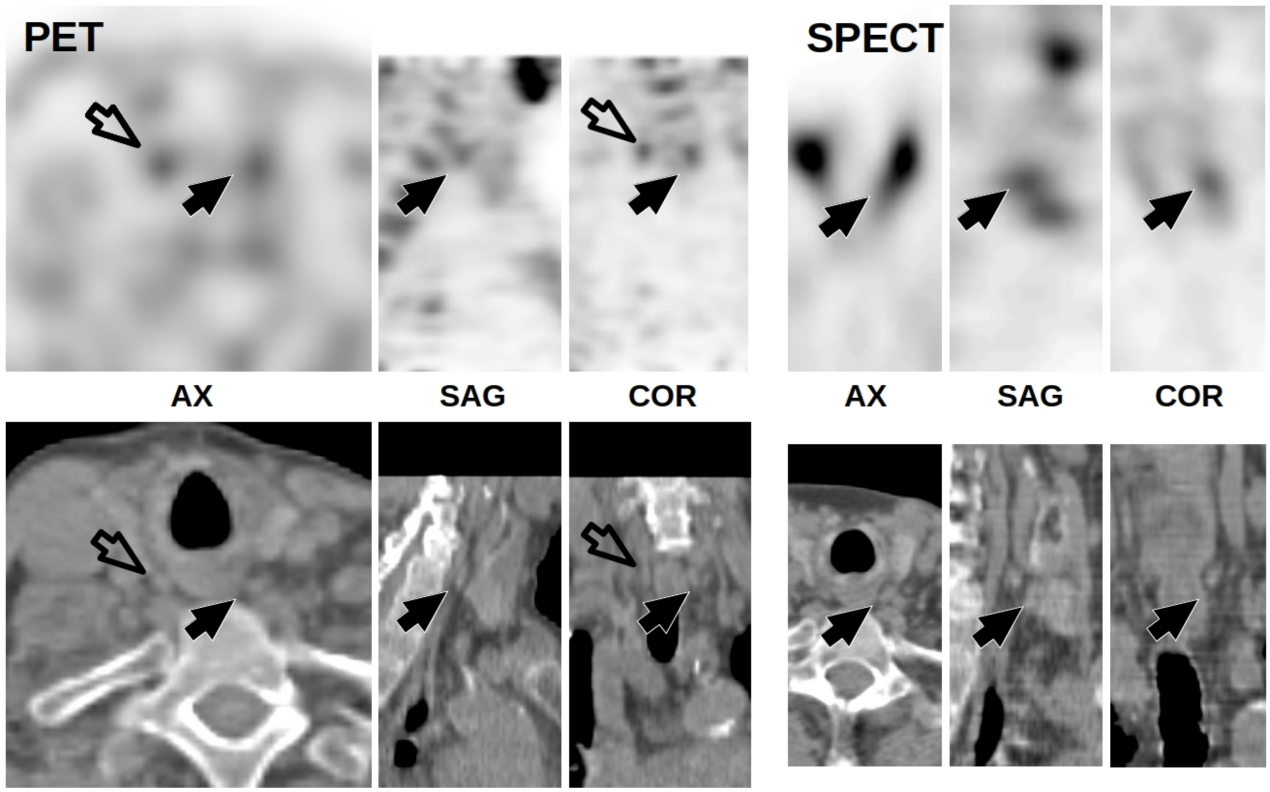

Figure 1. A patient with primary hyperparathyroidism and three hyperfunctioning parathyroid glands, histologically confirmed as adenomas. ^{18}F-fluorocholine PET/CT (PET, left panel) and ^{99m}Tc-sestaMIBI SPECT/CT (SPECT, right panel) showing an upper left hyperfunctioning gland on functional (PET/SPECT, top row) and anatomical (CT, bottom row) imaging (full arrow on all images), clearly better delineated on PET. An upper right hyperfunctioning gland (outlined arrow) is only demonstrable on PET functional imaging. The hyperfunctioning lower right parathyroid gland is not shown.

AX, SAG, COR: axial, sagittal, coronal slices, respectively, on tomographic functional (PET – positron emission tomography, SPECT – single-photon emission computed tomography; top row) and CT imaging (bottom row)

Table 1. Patient characteristics.

Age (y)		64 (39-77)
Gender		26 male, 77 female
Serum albumin-corrected calcium (mmol/L)		2.78 (2.3-4.1)
Serum phosphate (mmol/L)		0.8 (0.3-1.3)
iPTH (pg/mL)		145 (40-1076)
Symptoms	Hypercalcaemia	8
	Bone disease/osteoporosis	14
	Kidney (nephrolithiasis/CKD)	17
	Non-classical (neuropsychiatric, cardiovascular, gastrointestinal)	10
	Asymptomatic	38
Thyroid nodules	Yes	43
	No	59

iPTH: intact parathormone; CKD: chronic kidney disease. Continuous data are shown as median (range), where applicable.

Table 2. Diagnostic performance of ^{18}F-Fluorocholine PET/CT and conventional imaging modalities for localization of hyperfunctioning parathyroid tissue.

	PET/CT	SPECT/CT	Subtraction	Dual phase	Combined
All patients					
Sensitivity (%)	92	56*	41*	39*	65*
Specificity (%)	99.7	100	100	100	100
Solitary parathyroid adenoma					
Sensitivity (%)	95.5	67*	49*	48*	76*
Specificity (%)	99.7	100	100	100	100
Multiple parathyroid adenomas/hyperplasia					
Sensitivity (%)	88	34*	22*	22*	44*

* ^{18}F-Fluorocholine vs. conventional imaging (McNemar test, $p < 0.001$)

Table 3. Comparison of histologically confirmed hyperfunctioning parathyroid glands with discordant results (true positive on ^{18}F-Fluorocholine PET/CT and false negative with conventional modalities) and true positive results on conventional modalities.

		Discordant	True positive	p-value
SPECT/CT	Volume (cm^3)	1.7 (0.2-42.3)	4.1 (0.5-87.9)	<0.005
	Weight (g)	0.3 (0.1-5.4)	0.5 (0.1-10.9)	<0.005
Subtraction	Volume (cm^3)	2.1 (0.5-54.4)	4.2 (0.2-87.9)	<0.005
	Weight (g)	0.3 (0.1-6.8)	0.6 (0.1-10.9)	<0.005
Dual-phase	Volume (cm^3)	2.5 (0.2-54.4)	5.0 (0.5-87.9)	0.005
	Weight (g)	0.3 (0.1-6.8)	0.5 (0.1-6.9)	0.01
Combined	Volume (cm^3)	2.1 (0.1-42.3)	3.9 (0.2-87.9)	0.01
	Weight (g)	0.3 (0.1-5.4)	0.5 (0.1-10.9)	0.03