^{18}F-Fluorocholine PET/CT in Primary Hyperparathyroidism: Superior Diagnostic Performance to Conventional Scintigraphic Imaging for Localization of Hyperfunctioning Parathyroid Glands

Anka Cuderman[1,2], Katra Senica[1,2], Sebastijan Rep[1,3], Marko Hocevar[2,4], Tomaz Kocjan[2,5], Mojca Jensterle Sever[2,5], Katja Zaletel[1,2], and Luka Lezaic[1,2]

[1]Department of Nuclear Medicine, University Medical Centre Ljubljana, Ljubljana, Slovenia; [2]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; [3]Faculty of Health Sciences, University of Ljubljana, Ljubljana, Slovenia; [4]Department of Surgical Oncology, Institute of Oncology, Ljubljana, Ljubljana, Slovenia; and [5]Department of Endocrinology, Diabetes and Metabolic Diseases, University Medical Centre Ljubljana, Ljubljana, Slovenia

Primary hyperparathyroidism (PHPT) is a common endocrine disorder, definitive treatment usually requiring surgical removal of the offending parathyroid glands. 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:** In total, 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 histologic analysis, as well as intact parathyroid hormone and serum calcium values obtained 1 d after surgery and on 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 the group with multiple hyperfunctioning glands, with sensitivity of 88%, whereas conventional imaging was significantly inferior, with sensitivity of 22%–34% (44% combined). **Conclusion:** ^{18}F-fluorocholine PET/CT is a diagnostic modality superior to conventional imaging methods in patients with PHPT, allowing for accurate preoperative localization.

Key Words: primary hyperparathyroidism; ^{18}F-fluorocholine PET/CT; scintigraphy; ^{99m}Tc-sestamibi SPECT/CT

J Nucl Med 2020; 61:577–583
DOI: 10.2967/jnumed.119.229914

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by parathyroid hormone (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 (4%–15% of cases). Surgical removal of the offending gland is the only curative treatment. A minimally invasive surgical approach has become the standard of care in selected patients. However, to perform focused approaches, it is necessary to localize all hyperfunctioning glands and rule out possible multiple-gland disease (*2*).

Currently, the most commonly used imaging for this purpose is parathyroid scintigraphy with ^{99m}Tc-sestamibi supplemented by neck ultrasonography. Although subtraction scintigraphy (preferentially using ^{123}I as a thyroid-specific tracer in place of the 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 anatomic data coregistration. PET is of interest because of its inherently higher spatial resolution and shorter imaging times. In hyperparathyroidism, PET was limited to the use of ^{11}C-methionine, a revived parathyroid imaging tracer of poor availability, which was used when conventional parathyroid imaging findings were 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 an expanded role for 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 PHPT (median serum albumin-corrected calcium, 2.78 mmol/L; range, 2.3–4.1 mmol/L; reference range, 2.10–2.60 mmol/L; and median intact PTH [iPTH], 145 pg/mL; range, 40–1076 pg/mL; reference range, 12–65 pg/mL) were prospectively

Received Apr. 18, 2019; revision accepted Aug. 12, 2019.
For correspondence or reprints contact: Luka Lezaic, Department of Nuclear Medicine, University Medical Centre Ljubljana, Zaloska 7, 1525 Ljubljana, Slovenia.
E-mail: luka.lezaic@kclj.si
Published online Sep. 27, 2019.

included in the study, excluding patients with the atypical form of PHPT (familial hypocalciuric hypercalcemia), other known familial syndromes (familial PHPT, multiple endocrine neoplasia syndromes), or previous parathyroid resection. All patients had neck ultrasonography before surgery, not necessarily before scintigraphic imaging.

The study was approved by the National Committee for Medical Ethics (approval 77/11/12, NCT03203668). Each participant gave written informed consent on 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-h fast. PET/CT imaging of the neck and upper mediastinum to the level of the aortic arch was performed 5 and 60 min after injection. A Siemens mCT 128-slice CT scanner was used. Acquisition consisted of low-dose CT (25 mAs, CARE Dose 4D [Siemens], 120 kV) followed by PET imaging (1 bed position, 4 min per bed position). Images were reconstructed using proprietary Siemens HD PET software with iterative TrueX + time-of-flight ordered-subsets expectation maximization (2 iterations, 21 subsets), a matrix of 400 × 400 pixels, a zoom level of 1, and a gaussian filter of 4 mm in full width at half maximum.

Conventional Scintigraphic Imaging and Image Processing

Conventional (i.e., non-PET/CT) scintigraphic imaging 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 3 modalities.

Patients were administered 600 MBq of ^{99m}Tc-sestamibi intravenously. A planar acquisition of the neck and upper mediastinum was performed on a Siemens BASICAM γ-camera 10 min after injection ("early" sestamibi planar image; matrix, 128 × 128 pixels; zoom level, 2.5; 10 min), followed by a SPECT/CT acquisition of the same area on a Siemens Symbia T2 dual head γ-camera (matrix, 128 × 128; zoom level, 1.78; 32 projections; 20 s/frame; low-dose CT at 25 mAs and 130 kV). Images were reconstructed using proprietary Siemens Flash3D software with iterative ordered-subsets expectation maximization (4 iterations, 16 subsets), attenuation correction, and scatter correction. The planar acquisition was repeated at 90 min after injection ("delayed" sestamibi planar image) using identical parameters. Immediately after the second planar imaging and without a change in patient position, the patients were administered 150 MBq of $^{99m}TcO_4^-$ and, after 10 min, planar imaging of the neck and upper mediastinum was performed using parameters identical to those 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, was met: hypercalcemia consistently 0.25 mmol/L above normal; fracture; renal stones, hypercalciuria and other stone risk factors; T score of less than −2.5 SDs at any site; and an age of less than 50 y (*8*). When these criteria were not met, patients were referred for parathyroidectomy on the basis of an expert opinion that surgery is an appropriate option if no medical contraindications are present (*9*).

A surgical approach was chosen according to preoperative imaging results: patients with a single identified hyperfunctioning gland underwent a minimally invasive focused approach, whereas patients with multiple lesions, nonlocalization, or disagreement among imaging methods underwent bilateral neck exploration. iPTH was measured on the general anesthesia induction and 10 min after the removal of the last hyperfunctioning gland. A decrease in 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). After collection, the tubes were immediately transported to the laboratory, centrifuged (2,500*g*, 10 min, room temperature), and analyzed. For analysis, commercially available kits (Cobas, PTH STAT; Roche Diagnostics) and analyzer (Cobas e 411; Roche Diagnostics) were used.

The total number, location (upper left, lower left, upper right, lower right, and ectopic), weight (g), and measurements in 3 dimensions (mm) of the removed parathyroid glands were recorded; the volume of the removed tissue was approximated from measurements (volume = $a \times b \times c \times \pi/6$, with a, b, and c referring to the diameters of the gland). Specimens were submitted for histologic analysis, which served as the standard of truth for comparison with imaging results. Control iPTH and calcium values were obtained 1 d after surgery, and normalization of both values was considered an early indication of successful surgery. If the normal calcium homeostasis persisted for at least 6 mo, the patient was considered cured.

Image Interpretation and Analysis

Images were read separately by 2 nuclear medicine specialists with 3 and 6 y of experience in parathyroid imaging with ^{18}F-fluorocholine PET/CT and more than 8 y and 15 y in conventional parathyroid scintigraphic imaging.

There were 5 interpretation sessions. The first was of ^{18}F-fluorocholine PET/CT imaging, where regional uptake on the PET image (and the corresponding soft-tissue lesion, if seen, on the CT image) not associated with the thyroid gland was considered to represent hyperfunctioning parathyroid tissue. The second was of ^{99m}Tc-sestamibi SPECT/CT imaging, where regional uptake on the SPECT image (and the corresponding soft-tissue lesion, if seen, on the CT image) not associated with the thyroid gland was considered to represent hyperfunctioning parathyroid tissue. The third was of ^{99m}Tc-sestamibi/pertechnetate subtraction imaging, where the remaining activity (after subtraction of the pertechnetate planar image from the early sestamibi planar image after normalization and anatomic coregistration) was considered to represent hyperfunctioning parathyroid tissue. The fourth was of ^{99m}Tc-sestamibi dual-phase imaging, where ^{99m}Tc-sestamibi uptake with slower washout than from the thyroid gland on the delayed planar image in comparison to the early planar image was considered to represent hyperfunctioning parathyroid tissue. The fifth was a 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 analyzed in random order. As for the histologic analysis, 5 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 with surgical and histologic findings classified using the same site-based 5-location scheme and interpreted as follows: true-positive location with regional tracer uptake as well as histologic confirmation of parathyroid adenoma/hyperplasia; false-positive location with regional tracer uptake and histologic findings other than parathyroid adenoma/hyperplasia; false-negative location without regional tracer uptake but with histologic findings of parathyroid adenoma/hyperplasia; true-negative location without regional tracer uptake and histology findings of normal parathyroid tissue; and locations without regional tracer uptake and without histologic confirmation in patients whose serum calcium and iPTH values were normal at follow-up (i.e., no remnant hyperfunctioning parathyroid tissue). Histologic confirmation of adenoma/hyperplasia or follow-up iPTH and calcium normalization were used as the standard of truth, according to which the diagnostic performance metrics (sensitivity and specificity) were calculated. In cases of persistent hyperparathyroidism, a false-negative result was added to the analysis, assuming that a hyperfunctioning gland negative on imaging must be present.

Statistical Analysis

Continuous data are reported as median and range. Sensitivity and specificity were calculated on a site basis for each imaging modality and for the conventional imaging modalities combined against the standard of truth (histologic analysis or follow-up iPTH and calcium normalization). The McNemar test was performed to compare sensitivity and specificity. A normal-probability plot was used to assess the normality of data distribution. The Wilcoxon rank-sum test was applied to compare continuous variables with nonnormal distribution. A *P* value of less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software (version 22; IBM).

RESULTS

Patients

Between May 2012 and June 2016, 188 patients were enrolled, of whom 103 (78 women and 26 men, with a median age of 64 y [range, 39–77 y]) underwent surgery and were included in the analysis. All included patients had biochemically confirmed PHPT. The median serum calcium level was 2.78 mmol/L (range, 2.3–4.1 mmol/L), and median iPTH was 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, 1 or more thyroid nodules were confirmed on neck ultrasonography. The patient characteristics are detailed in Table 1.

TABLE 1
Patient Characteristics

Characteristic	Data
Age (y)	64 (39–77)
Sex	
Male	26
Female	77
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	
Hypercalcemia	8
Bone disease/osteoporosis	14
Kidney (nephrolithiasis/chronic kidney disease)	17
Nonclassic (neuropsychiatric, cardiovascular, gastrointestinal)	10
None	38
Thyroid nodules	
Yes	43
No	59

Qualitative data are expressed as numbers; continuous data are expressed as median followed by range in parentheses.

Resected Parathyroid Gland Pathologies, Volumes, and Weights

All 103 patients underwent surgery; cumulatively, 131 lesions were removed. The patients were allocated into 2 groups for statistical analysis according to the histologic findings, namely a single-hyperfunctioning-parathyroid group (87 patients; 83 adenomas, 1 parathyroid carcinoma) and a multiple-adenoma/hyperplasia group (4 patients with 2 adenomas and 10 patients with 31 hyperplastic glands). Therefore, 86% of our patient group had single-gland disease and 14% had multiglandular disease. Resected specimens included 1 sample of thyroid tissue beside the parathyroid glands.

In 3 patients, a single hyperfunctioning parathyroid gland that was localized with ^{18}F-fluorocholine PET/CT (in 1 case, ^{99m}Tc-sestamibi SPECT/CT and subtraction scintigraphy were also positive) was classified as normal parathyroid tissue in the histologic report. Because iPTH and calcium 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 3 of these patients, hyperparathyroidism persisted after surgical resection of a single adenoma. Two patients without evidence of parathyroid adenoma or hyperplasia on any imaging modality underwent bilateral neck exploration; both had 2 histologically normal parathyroid glands removed. For statistical analysis, 1 false-negative finding in each imaging modality was assigned to either of these patients. One patient had 2 hyperplastic glands removed despite localization of all 4 on PET/CT; the remaining 2 glands were classified as true-positive in view of persistent PHPT and findings on repeated ^{18}F-fluorocholine PET/CT (the remaining 2 lesions again identified). Definite histology could not be obtained because the patient was unwilling to undergo reoperation despite persistent PHPT.

The volumes and weights of resected hyperfunctioning glands were available for 111 of the 131 removed lesions. The median volume of these lesions was 2.9 cm^3 (range, 0.2–87.9 cm^3), and the median weight was 0.4 g (range, 0.1–10.9 g). Separate analysis of adenomas and hyperplastic glands found that both volume and weight were significantly less for hyperplastic glands than for parathyroid adenomas ($P < 0.001$). For hyperplastic glands, the median volume was 1.5 cm^3 (range, 0.2–71.6 cm^3) and the median weight was 0.2 g (range. 0.1–9.7 g), whereas for adenomas, the median volume was 3.9 cm^3 (range, 0.5–87.9 cm^3) and the median weight was 0.5 g (range, 0.1–10.9 g).

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

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

False-negative results consisted of 5 nonlocalized hyperplastic glands, 1 upper right adenoma incorrectly identified as lower right adenoma and false-negatives we added to the statistical analysis in patients with persistent hyperparathyroidism after surgery. Nonlocalized 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 1 patient, ^{18}F-fluorocholine PET/CT localized all 4 hyperfunctioning glands, followed by surgical resection of 2 upper parathyroid glands, both histologically reported as hyperplastic. Because of a sufficient intraoperative iPTH reduction and the surgeon's visual assessment, both lower parathyroid glands were not resected. On follow-up, iPTH remained elevated, and a repeated ^{18}F-fluorocholine PET/CT study 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 because of the ^{18}F-fluorocholine PET/CT false-positive finding of thyroid tissue (i.e., a finding that was not localized on any of the conventional imaging modalities); the diagnostic performance of all modalities is presented in Table 2.

Calculation of sensitivity included 131 lesions proven by histology and 6 cases of persistent PHPT described above and interpreted in the individual clinical context.

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

Diagnostic Performance of Imaging Modalities According to Parathyroid Gland Pathology

In the subgroup with a 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, 1 upper right adenoma was incorrectly identified as a lower right adenoma, 3 patients had persistent PHPT after single-adenoma resection, and in 1 patient 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. The combined conventional imaging assessment amounted to a sensitivity of 76%. In 1 patient, a parathyroid carcinoma was identified with ^{18}F-fluorocholine PET/CT whereas 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, at 34%, followed by ^{99m}Tc-sestamibi dual-phase imaging and ^{99m}Tc-sestamibi/$^{99m}TcO_4^-$ subtraction imaging, with identical sensitivities of 22%. The combined conventional imaging assessment had a sensitivity of 44%.

The diagnostic performance of ^{18}F-fluorocholine PET/CT was significantly higher than that of conventional imaging modalities (separately or combined) in both the single-parathyroid-adenoma group and the multiple-adenomas/hyperplasia group ($P < 0.001$). Specifically, 6 of 14 patients in the subgroup with multiple adenomas/hyperplasia were falsely classified as having a single hyperfunctioning parathyroid gland on conventional imaging, whereas ^{18}F-fluorocholine PET/CT correctly localized multiple offending glands. Three of these patients had a dual adenoma, and 3 had several hyperplastic glands, as confirmed by histology reports.

DISCUSSION

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

Hyperfunctioning parathyroid localization with conventional imaging approaches is currently suboptimal, particularly in cases of hyperplasia, which is of concern because PHPT persistence is caused mostly by failure to recognize multiple-gland disease (*10*). The reported sensitivities of conventional scintigraphic imaging modalities are in the range of 58%–86% (*11–13*), with lower performance in smaller lesions and multiple-gland disease (*3,4*). Emerging studies show a slow but steady growth of evidence establishing ^{18}F-fluorocholine as the most promising PET tracer investigated for localizing hyperfunctioning glands. In comparison to conventional scintigraphic imaging, ultrasonography, or in 1 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 had negative results, was inconclusive, or was discordant with ultrasonographic examination of the neck. Excluding our pilot study and the present work, to our

TABLE 2
Diagnostic Performance of ^{18}F-Fluorocholine PET/CT and Conventional Modalities for Localization of Hyperfunctioning Parathyroid Tissue

Patient group	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*
Specificity (%)	100	100	100	100	100

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

TABLE 3
Comparison of Histologically Confirmed Hyperfunctioning Parathyroid Glands with Discordant Results* and True-Positive Results on Conventional Modalities

Modality	Parameter	Discordant	True-positive	P
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

*True-positive on ^{18}F-fluorocholine PET/CT and false-negative on conventional modalities.
Data are median followed by range in parentheses.

knowledge only 2 studies have directly compared ^{18}F-fluorocholine PET/CT with conventional scintigraphic methods, both demonstrating superior diagnostic performance for PET/CT, with sensitivities of 100% and 94%. As a reference scintigraphic method, the studies used planar ^{99m}Tc-sestamibi dual-phase imaging with the 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 a parathyroid-specific tracer and with $^{99m}TcO_4^-$ or ^{123}I as a thyroid-specific tracer, addition of SPECT or SPECT/CT to parathyroid-specific imaging). Although subtraction scintigraphy may still be considered the method of choice because of its proven diagnostic value (*20*), the use of hybrid (SPECT/CT) ^{99m}Tc-sestamibi imaging is increasing as a result of accumulating evidence of a diagnostic advantage over alternative protocols. A recent metaanalysis reported superior performance for ^{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 with all currently recommended conventional parathyroid scintigraphy protocols. We found the diagnostic performance of ^{18}F-fluorocholine PET/CT to be superior to all conventional scintigraphic protocols, either separately or combined. In the 2 similarly designed studies, the performance of conventional scintigraphy was comparable (*17*) or better (*16*). However, the median gland weight was 1 g in the 2 studies 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 a median weight of 0.5 g, the sensitivity of conventional scintigraphy was in the expected range of 78% (Table 2). The diagnostic performance of conventional scintigraphy in our study may potentially be limited by the imaging protocol. Ideally, $^{99m}TcO_4^-$ injection and imaging are performed first and no patient movement is allowed between $^{99m}TcO_4^-$ and ^{99m}Tc-sestamibi injection 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 3 conventional scintigraphy protocols for improved sensitivity, as demonstrated in a large retrospective single-center analysis of 462 patients (*21*) and 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 an important factor contributing to the exceptional diagnostic accuracy of ^{18}F-fluorocholine PET/CT, in comparison to 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 the present study demonstrate significantly lower diagnostic value for conventional imaging methods (including ^{99m}Tc-sestamibi SPECT/CT) than for ^{18}F-fluorocholine PET/CT, requiring additional imaging when negative and thereby increasing radiation exposure and cost. These findings are even more important in cases of multiple hyperfunctioning parathyroid glands, for which the diagnostic performance of conventional imaging methods is poor. Frequently, only 1 (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 a sufficient fall in iPTH values after removal of 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 because of the exquisitely high sensitivity of the method; the surgical procedure is therefore simplified and accelerated. Several authors have reported success rates of 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 when 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 min, marginally increases the

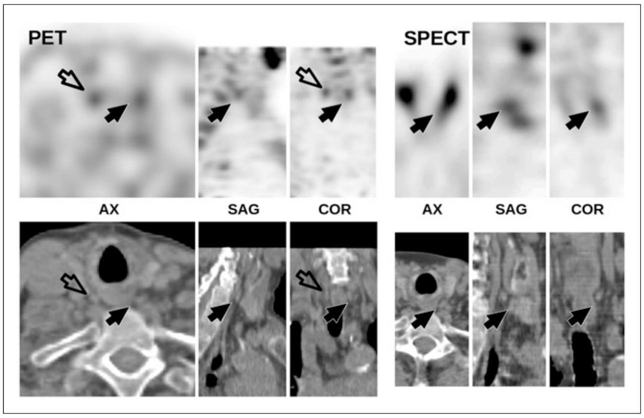

FIGURE 1. Patient with PHPT and 3 hyperfunctioning parathyroid glands, histologically confirmed as adenomas. ^{18}F-fluorocholine PET/CT and ^{99m}Tc-sestamibi SPECT/CT show upper left hyperfunctioning gland on functional (PET and SPECT, top) and anatomic (CT, bottom) imaging (solid arrows on all images), clearly better delineated on PET. Upper right hyperfunctioning gland (open arrows) is demonstrable only on PET. Hyperfunctioning lower right parathyroid gland is not shown. AX, SAG, and COR = axial, sagittal, and coronal slices, respectively.

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 results (all methods combined) would benefit from PET/CT because they had a single adenoma identified and were therefore suitable candidates for minimally invasive parathyroidectomy. But at the same time, 6 of 14 patients in our group would be falsely selected for minimally invasive parathyroidectomy on the basis of conventional imaging results if PET/CT were not to reclassify them as multiple-gland-disease patients.

^{18}F-fluorocholine PET/CT currently represents the most widely available PET modality for hyperfunctioning parathyroid gland localization because of its widespread indication for prostate cancer imaging. Although it inevitably includes the use of ionizing radiation, using an identical imaging approach to that described above recently showed that the radiation exposure is lower for ^{18}F-fluorocholine PET/CT than for the conventional imaging approaches (*26*). The short scanning time also speaks in favor of the method. Nevertheless, the availability of ^{18}F-fluorocholine is still considerably lower than that of conventional scintigraphy. Another significant limitation 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 one can consider 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 on the largest patient population to date showed ^{18}F-fluorocholine PET/CT to be a diagnostic modality superior 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, multicenter study and a dedicated cost-effectiveness analysis is required to consider ^{18}F-fluorocholine PET/CT to be a first-line imaging modality in PHPT.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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 PHPT in comparison to conventional nuclear medicine modalities (dual-phase imaging, subtraction scintigraphy, SPECT, and SPECT/CT)?

PERTINENT FINDINGS: ^{18}F-fluorocholine PET/CT was compared with conventional nuclear medicine imaging protocols (dual-phase imaging, subtraction scintigraphy, SPECT, and SPECT/CT) in prospectively enrolled patients with biochemically proven PHPT and an 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 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 or repeated surgery, potentially reducing radiation exposure and cost.

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