Original Article

The role of ^{18}F-fluoromethylcholine-positron emission tomography-computed tomography for preoperative localization of hyperfunctioning parathyroid glands with special emphasis on multiglandular disease: a retrospective cohort study

Himam Murad[1]^, Camelia Ciacoi-Dutu[2], Gunnar Lindblom[2], Martin Almquist[3]^

[1]Department of Surgery, Highland Hospital, Eksjö, Sweden; [2]Department of Nuclear Medicine, Ryhov Hospital, Jönköping, Sweden; [3]Department of Surgery and Department of Clinical Sciences, Skåne University Hospital, Lund University, Lund, Sweden

Contributions: (I) Conception and design: H Murad, M Almquist; (II) Administrative support: All authors; (III) Provision of study materials or patients: H Murad, C Ciacoi-Dutu, G Lindblom; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: H Murad, M Almquist; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Himam Murad, MD. Consultant Endocrine Surgeon, Head of Endocrine Surgery, Department of Surgery, Highland Hospital, Västanågatan 9, 57581 Eksjö, County of Jönköping, Sweden. Email: himam.murad@rjl.se.

Background: Primary hyperparathyroidism (PHPT) is a common endocrine disorder. Definitive treatment is surgical. Preoperative localization of diseased glands increases the chance of successful treatment. The aim of this study is to investigate the diagnostic performance of ^{18}F-fluoromethylcholine-positron emission tomography-computed tomography (^{18}F-FCh-PET-CT) in preoperative localization of diseased parathyroid glands, when first-line examinations were inconclusive.

Methods: This is a retrospective study. All patients with PHPT who underwent ^{18}F-FCh-PET-CT, after inconclusive ultrasound examination and ^{99m}Tc-methoxyisobutylisonitrile/single-photon emission CT-CT, were included in cohort I. Patients who were subsequently operated for their parathyroid disease, were included in cohort II. The performance of ^{18}F-FCh-PET-CT was analyzed in two sets: per-lesion, and per-gland analysis.

Results: Out of 52 patients in cohort I, ^{18}F-FCh-PET-CT identified single or multiple parathyroid lesions in 43 patients (83%). Nine patients had multiglandular disease. Thirty-four (65%) patients were subsequently operated and included in cohort II. Forty-four lesions were removed from these patients and 33 patients (97%) were cured. ^{18}F-FCh-PET-CT localized 40 out of 44 lesions, with per-lesion and per-gland sensitivities of 97% and 95%, and positive predictive values (PPVs) of 93% and 87%, respectively, in addition to a specificity of 97% and a negative predictive value (NPV) of 94% in the per-gland analysis. Comparable excellent results were detected in multiglandular disease with sensitivity of 94.1%, specificity of 89%, PPV of 84%, and NPV of 94%.

Conclusions: Our study demonstrates the high diagnostic performance of ^{18}F-FCh-PET-CT in the preoperative localization of diseased parathyroid gland in patients with PHPT, especially in multiglandular PHPT.

Keywords: Primary hyperparathyroidism (PHPT); parathyroid surgery; minimally invasive parathyroidectomy (MIP); ^{18}F-fluoromethylcholine-positron emission tomography-computed tomography (^{18}F-FCh-PET-CT)

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^ ORCID: Himam Murad, 0000-0002-9854-3956; Martin Almquist, 0000-0002-0953-1188.

Introduction

The only cure for primary hyperparathyroidism (PHPT) is surgical removal of diseased gland(s) (1-6). Preoperative localization methods, such as ultrasound (US) examination and ^{99m}Tc-methoxyisobutylisonitrile/single-photon emission computed tomography-computed tomography (^{99m}Tc-MIBI/SPECT-CT), lead to increased cure rates, minimized dissection and operative time, and lower complication rates (1,2,7). However, no single method accurately localizes all diseased glands in all patients. US examination and ^{99m}Tc-MIBI/SPECT-CT have variable sensitivity and specificity, poor performance in multiglandular disease, in ectopic locations and in patients with big goiters (3,4,7-12). Four-dimensional CT (4D-CT) was initially thought to have high accuracy, recent data suggest that it has comparable accuracy to US examination and ^{99m}Tc-MIBI/SPECT-CT in localizing small and ectopic parathyroid glands but has less sensitivity in multiglandular disease, with the disadvantages of high radiation exposure and the need for iodinated contrast medium (9,13,14). In many patients with PHPT, all preoperative localization images are inconclusive. In these patients, cure rates are lower, complication rates increased, and operative time longer (15).

Since the report of an incidental finding of a parathyroid adenoma in a patient with prostate cancer undergoing ^{18}F-fluoromethylcholine-positron emission tomography (^{18}F-FCh-PET), the use of this method has increased (3,7,16). An advantage of ^{18}F-FCh-PET-CT is its superior spatial resolution, and lower radiation exposure, in comparison with ^{99m}Tc-MIBI/SPECT-CT (7,17).

Recent studies have shown promising results with ^{18}F-FCh-PET-CT for localizing diseased parathyroid glands, with a sensitivity as high as 90% in some studies (3,7,13,17). As far as we know, there are no previous data from Scandinavia on this method.

The aim of this study is to assess the diagnostic performance of ^{18}F-FCh-PET-CT in localizing diseased parathyroid glands, with or without previous surgery for PHPT, when conventional imaging (US examination and ^{99m}Tc-MIBI/SPECT-CT) was inconclusive. Special emphasis will be placed on investigating the role of ^{18}F-FCh-PET-CT in patients with multiglandular PHPT. We present this article in accordance with the STARD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-232/rc).

Highlight box

Key findings

- Superior diagnostic performance of ^{18}F-fluoromethylcholine-positron emission tomography-computed tomography (^{18}F-FCh-PET-CT) over ^{99m}Tc-sestamibi/single-photon emission CT-CT and US.
- High diagnostic performance of ^{18}F-FCh-PET-CT in preoperative localization of parathyroid gland in multiglandular primary hyperparathyroidism (PHPT) and can accurately detect ectopic parathyroid glands.

What is known and what is new?

- Through its high specificity and negative predictive value, ^{18}F-FCh-PET-CT minimizes the risk for false negative results, decreasing the risk for persistent and recurrent PHPT.

What is the implication, and what should change now?

- We believe that ^{18}F-FCh-PET-CT is an excellent imaging tool, which can be used when first-line parathyroid imaging fails, but after the decision of surgery has been made, and can probably replace them within few years.
- Randomized study to evaluate the efficacy of choline PET as first-line examination for preoperative localization of diseased parathyroid glands.
- The cost-effectiveness of using ^{18}F-FCh-PET-CT as a first-line imaging should be investigated in prospective studies.

Methods

Patients

In November 2020, ^{18}F-FCh-PET-CT was introduced for parathyroid imaging at Ryhov Hospital, Jönköping, Sweden. Thereafter, patients with newly diagnosed, persistent or recurrent PHPT, referred for parathyroid surgery to the Highland Hospital, Eksjö, or Ryhov Hospital, Jönköping, and with inconclusive findings on US examination and scintigraphy, underwent ^{18}F-FCh-PET-CT.

All patients with a biochemical diagnosis of PHPT, i.e., hypercalcemia with elevated or inappropriately normal parathyroid hormone (PTH) levels on at least two occasions at 2–3 months intervals, who underwent an ^{18}F-FCh-PET-CT between 1st November 2020 and 31st March 2022 were included in the study. Patients were followed until 30th November 2022. Investigations for familial forms of PHPT were not routinely done in the absence of clinical suspicion. ^{18}F-FCh-PET-CT was done when US examination and/or ^{99m}Tc-MIBI/SPECT-CT were negative or inconclusive, when there were discrepancy in their results, and when there were suspicion of multiglandular disease.

Two study cohorts were created. Cohort I includes all

patients who underwent ^{18}F-FCh-PET-CT, regardless of whether they were operated or not. In cohort II, only patients who underwent ^{18}F-FCh-PET-CT and subsequently were operated for PHPT at one of the two hospitals (Highland or Ryhov) were included. Patients with inconclusive US examination, scintigraphy, and ^{18}F-FCh-PET-CT, were not operated.

Preoperative localization

US examination was performed by the examining surgeons with more than 12 years' experience in neck US examination and more than 20 years' experience in endocrine surgery of the neck, at the outpatient clinic of the department of surgery in both hospitals. The number and position of any enlarged parathyroid glands was documented in patients' electronic health records. The examination was regarded inconclusive if no parathyroid gland could be identified, or the examiners were uncertain about the findings, especially in patients with concomitant nodular goiter.

^{99m}Tc-MIBI/SPECT-CT

^{99m}Tc-MIBI/SPECT-CT was used. Images were acquired on a Siemens Symbia Intevo Bold (Siemens Healthcare GmbH, Erlangen, Germany). An activity of 500 MBq (sestamibi) was administered intravenously. Planar images, anteroposterior and posterior-anterior images over neck and upper chest were taken 15 and 120 min after injection. Imaging was performed using a large field-of-view gamma camera with low energies high-resolution (LEHR) collimators, a matrix size of 128×128, zoom 2.67, and a 15% energy window centered at the 140 keV (^{99m}Tc) photon peak. A SPECT/CT acquisition at 30 min covering the area between the skull base and the heart base was performed. SPECT acquisition covered a rotation of 180° with 60 projections. Low-dose helical CT images were obtained for attenuation correction and anatomic localization (detector row configuration 16 mm × 0.625 mm, pitch 0.8, gantry rotation time 0.6 s, slice thickness 1 mm, increment 0.6 mm; 130 KVp, and quality ref. 30 mAs using automatic tube current modulation). No intravenous contrast was administered at the CT examination. The examination was regarded inconclusive if no parathyroid gland could be identified, when there was faint tracer uptake, or when there were multiple but uncertain tracer uptake.

^{18}F-FCh-PET-CT

^{18}F-FCh-PET-CT images were acquired on a Siemens Biograph mCT Flow Edge scan PET/CT tomograph. Dual-time-point images were acquired at 5 and 60 min after intravenous injection of approximately 150 MBq FCH (1.5 MBq/kg body weight), ranging from the temporomandibular joint to the diaphragm. Images were acquired at 4 min per bed position with matrix size 256×256 and low-dose CT for attenuation correction using a tube current of quality ref. 275 mAs, ref. kV Sn100, CarekV on, with CareDose4D modulation, Carek on, collimation of 128 mm × 0.6 mm and a pitch of 0.8. CT at 60 min 128×0.6, quality ref. 46 mAs, ref. kV 120, pitch 0.8, rotation time 1.0 s, CarekV on. PET images were reconstructed with 400×400 matrix, TrueX + time-of-flight (TOF), Gaussian 4.0, Iterations 2, attenuation correction computed tomography (ACCT) 3 mm high-definition extended field of view (HD-FOV). No intravenous contrast were administered at the CT examination. All readers were unaware of the laboratory results and any other examinations, if any, of all patients. Localization with ^{18}F-FCh-PET-CT was classified as upper and lower hyperfunctioning parathyroid tissue on the right or left sides of the neck. A parathyroid gland was regarded to be in an ectopic location, if it was found in any of the following locations: mediastinum; retroesophageal space; within the carotid sheath, thymus; thyroid gland; or >1 cm above the upper pole of the thyroid.

Surgery

All surgical procedures were performed by two endocrine surgeons. Minimally invasive parathyroidectomy (MIP) was the standard operation. Bilateral parathyroid exploration (BPE) was performed when preoperative imaging led to suspicion of multiglandular disease. The decision to convert from MIP to BPE was made intraoperatively by the operating surgeon. Intraoperative PTH was used selectively. All removed glands were sent for histopathological analysis. The anatomical localization of the diseased gland(s) was determined by the operating surgeon and was classified as upper and lower parathyroid lesions on the right or left sides of the neck. Lesions in the territory of lower parathyroid glands, but in a more posterior location, were classified as descended upper gland lesions in the presence of a normal lower parathyroid gland.

Outcome

Cure was defined as normocalcemia, and persistent disease as hypercalcemia, at 6 to 8 weeks after surgery.

Statistical analysis

The efficacy of ^{18}F-FCh-PET-CT, namely the proportion of patients cured after undergoing ^{18}F-FCh-PET-CT was evaluated in cohort I, i.e., all patients who underwent ^{18}F-FCh-PET-CT.

In cohort II, i.e., patients operated after ^{18}F-FCh-PET-CT, the performance of ^{18}F-FCh-PET-CT was assessed in two sets of analyses: one per-lesion and one per-gland analysis. In the per-lesion analysis, sensitivity and the positive predictive value (PPV) of ^{18}F-FCh-PET-CT in detecting diseased parathyroid gland(s) were calculated.

In the per-gland analysis, it was assumed that all patients had four parathyroid glands (upper/lower, right/left). In patients previously operated for PHPT, the remaining number of glands was calculated in accordance with the record of previous surgery. The number of previously removed and histopathologically verified glands was subtracted from the four glands assumed in all patients.

Any surgically removed, histopathologically verified gland that was detected preoperatively on ^{18}F-FCh-PET-CT was classified as a true positive gland. Removed pathological glands not detected on ^{18}F-FCh-PET-CT were classified as false negative, and glands suspected on ^{18}F-FCh-PET-CT, but not found intraoperatively, were classified as false positive. Finally, glands neither removed nor detected on ^{18}F-FCh-PET-CT were classified as true negative. This determination was only made in patients who achieved eucalcemia postoperatively.

Data collection

Electronic health records were used to extract data. Baseline and demographic data, laboratory values and histopathology results, as well as original reports of imaging examinations were collected. Data regarding operative findings were obtained from operative notes made by the operating surgeons for the present surgery and for any previous parathyroid surgery in previously operated patients.

Ethical consideration

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Swedish Ethical Review Authority (No. 2022-05134-01-336690). Since only already collected data were used, and no new contact or intervention with patients were performed, the Swedish Ethical Review Authority waived the need for informed consent.

Results

There were 52 patients with proven or suspected PHPT who underwent ^{18}F-FCh-PET-CT during the study period. These constituted cohort I. Of these, 34 patients were subsequently operated for PHPT at Highland or Ryhov Hospital. These constituted cohort II.

Cohort I

Out of a total of 52 patients, 10 (19%) were males and 42 (81%) were females. Their median age was 67.5 (range, 29.0–84.0) years (*Table 1*). Median ionized calcium was 1.42 (range, 1.24–1.71) mmol/L, and median PTH was 11.2 (range, 6.2–42.0) pmol/L. According to the electronic health records, no patient was suspected of having familial PHPT.

Of the 18 patients not operated at one of the two local hospitals before the end of the study (*Figure 1*), two patients with positive localization of ectopic glands in the superior mediastinum were referred for surgery at another center. Another six were still awaiting a decision on whether to operate or not. Three of these had positive localization, and three had inconclusive findings on ^{18}F-FCh-PET-CT. In 10 patients, a decision was made not to operate—six due to inconclusive ^{18}F-FCh-PET-CT, two because the patient declined, and two were rejected due to advanced comorbidity. Of the six that had inconclusive ^{18}F-FCh-PET-CT, three were found not to have PHPT after re-evaluation: two with hyperparathyroidism secondary to vitamin D deficiency, and one with genetically confirmed familial hypocalciuric hypercalcemia (FHH).

Cohort II

In total, 34 patients (65%), six males and 28 females, underwent parathyroid surgery at Highland or Ryhov Hospital after ^{18}F-FCh-PET-CT during the study period (*Table 2*). In these 34 patients, a total of 44 parathyroid glands were removed. Multiglandular disease was detected in nine patients and in these nine patients, 19 glands were

Table 1 Characteristics of patients who underwent ^{18}F-FCh-PET-CT (cohort I)

Characteristics	Values
Age (years)	67.5 [29.0–84.0]
Sex	
Male	10 (19.2)
Female	42 (80.8)
Diagnosis	
PHPT	
Newly diagnosed	41 (78.8)
Persistent	6 (11.5)
Recurrent	1 (1.9)
SHPT	2 (3.8)
FHH	2 (3.8)
Preoperative laboratory results	
Ionized calcium (Ca^{2+}) (mmol/L)	1.42 [1.24–1.71]
PTH (pmol/L)	11.2 [6.2–42.0]
^{18}F-FCh-PET-CT	
No diseased parathyroid gland identified	9 (17.3)
Single parathyroid gland identified	34 (65.4)
Two parathyroid glands identified	9 (17.3)
^{99m}Tc-MIBI/SPECT-CT	
No diseased parathyroid gland identified	35 (67.3)
Single parathyroid gland identified	11 (21.2)
Two parathyroid glands identified	2 (3.8)
Three parathyroid glands identified	1 (1.9)
Not performed	3 (5.8)
US examination	
No diseased parathyroid gland identified	19 (36.5)
Single parathyroid gland identified	28 (53.8)
Two parathyroid glands identified	2 (3.8)
Not done	3 (5.8)
Previous surgery	
BPE	6 (11.5)
MIP	1 (1.9)
RHT	1 (1.9)
Surgery	
Operated at our center	34 (65.4)
Referred to another center	2 (3.8)
Not operated	16 (30.8)
Waiting for decision	6
No surgery	10

Values are presented as median [range] or n (%). ^{18}F-FCh-PET-CT, ^{18}F-fluoromethylcholine-positron emission tomography-computed tomography; PHPT, primary hyperparathyroidism; SHPT, secondary hyperparathyroidism; FFH, familiar hypoclaciuric hypercalcemia; PTH, parathyroid hormone; ^{99m}Tc-MIBI/SPECT-CT, ^{99m}Tc-methoxyisobutylisonitrile/single-photon emission computed tomography-computed tomography; US, ultrasound; BPE, bilateral parathyroid exploration; MIP, minimally invasive parathyroidectomy; RHT, right hemithyroidectomy.

removed (*Table 3*).

Of all 34 patients, 33 achieved normocalcemia at 6 to 8 weeks after surgery and were considered cured. Thus, the overall cure rate in patients undergoing ^{18}F-FCh-PET-CT was 33/52 (63%), and the cure rate among those operated was 33/34 (97%). The patient with persistent hypercalcemia had two positive glands on ^{18}F-FCh-PET-CT. Both were removed surgically, and histopathology showed adenomas of the chief cell type. At postoperative re-evaluation, this patient was found to have FHH, which was confirmed genetically. In five patients, ^{18}F-FCh-PET-CT detected five parathyroid lesions in an ectopic location. Three lesions were identified in an intrathyroidal location, and in these patients, a hemithyroidectomy was performed. The other two patients had lesions in the superior mediastinum, and they were referred to another center.

Per-lesion analysis

In the per-lesion analysis (*Table 4*), ^{18}F-FCh-PET-CT correctly localized 40 of 44 removed lesions, which were classified as true positive. As for the remaining four lesions, three were false positive. The fourth lesion was not shown on ^{18}F-FCh-PET-CT but was identified during surgery, and hyperplasia was confirmed on histopathology (false negative). In this analysis, ^{18}F-FCh-PET-CT had a

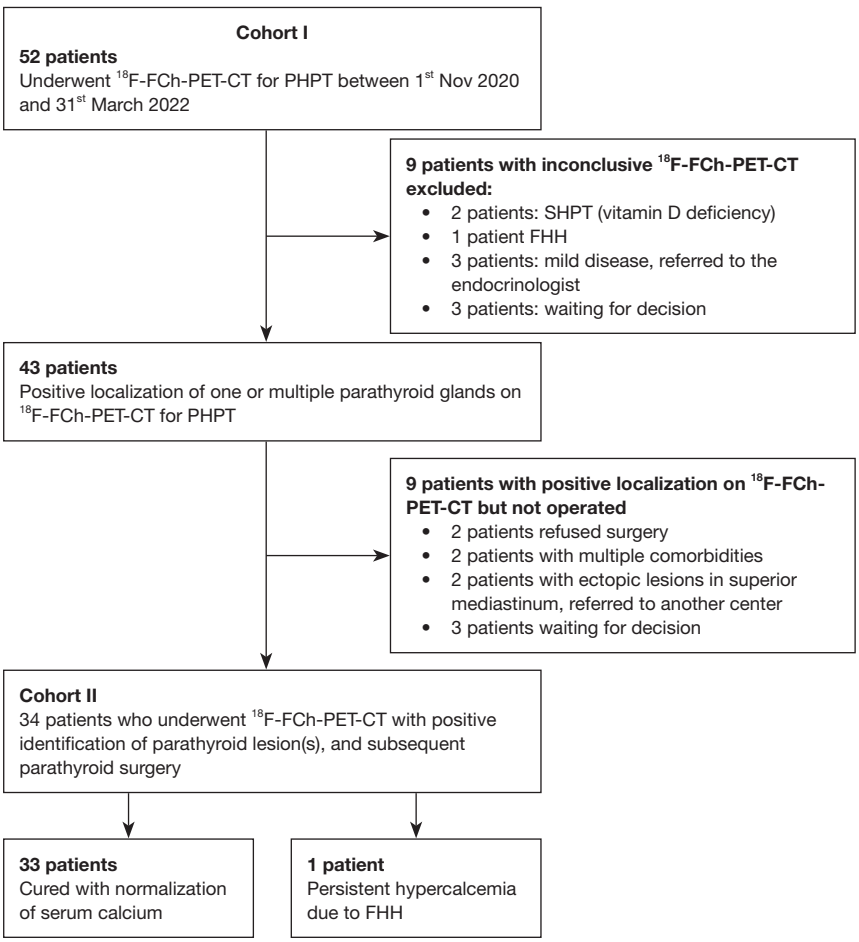

Figure 1 Inclusion/exclusion flowchart for cohort I and II. ^{18}F-FCh-PET-CT, ^{18}F-fluoromethylcholine-positron emission tomography-computed tomography; PHPT, primary hyperparathyroidism; SHPT, secondary hyperparathyroidism; FHH, familiar hypoclaciuric hypercalcemia.

sensitivity of 98% and PPV of 93%. In the multiglandular disease group of patients, 19 lesions were removed, with 16 true positives, and ^{18}F-FCh-PET-CT showed a sensitivity of 94% and PPV of 89%.

Per-gland analysis

In the per-gland analysis (*Table 4*), the original number of glands was calculated as 134 glands (four in previously non operated patients, and the remaining number of glands in previously parathyroid operated patients). Forty-four glands were removed, 40 true positive glands, 89 assumed to be true negative, three false positive and two false negative. In this analysis, ^{18}F-FCh-PET-CT had a sensitivity of 95%, specificity of 97%, PPV of 87%, and NPV of 98%. In patients with multiglandular disease, sensitivity was 94%, specificity 90%, PPV 84%, and NPV 94%.

Discussion

In this study, ^{18}F-FCh-PET-CT had high sensitivity and PPV both in the per-lesion analysis and the per-gland analysis. Per-gland analysis had a sensitivity of 95%, specificity of 96%, PPV of 87%, and NPV of 98%. This indicates that ^{18}F-FCh-PET-CT is not only superior for localizing diseased parathyroid glands, but also, through its high specificity and NPV, minimizes the risk for false negative results, decreasing the risk for persistent and recurrent PHPT. This is consistent with previous results (1,3-7,18-20).

In this study, nine patients had multiple parathyroid lesions on ^{18}F-FCh-PET-CT. Of the 19 lesions which were

Table 2 Characteristics of patients who underwent ^{18}F-FCh-PET-CT and subsequent parathyroid surgery (cohort II)

Characteristics	Values
Age (years)	68 [33–82]
Sex	
Male	6 (17.6)
Female	28 (82.4)
Diagnosis	
PHPT	
Newly diagnosed	30 (88.2)
Persistent	3 (8.8)
Recurrent	0 (0.0)
FHH	1 (2.9)
Preoperative laboratory results	
Ionized calcium (Ca^{2+}) (mmol/L)	1.43 [1.35–1.64]
PTH (pmol/L)	12.2 [8.0–42.0]
^{18}F-FCh-PET-CT	
Single parathyroid gland identified	25 (73.5)
Two parathyroid glands identified	9 (26.5)
^{99m}Tc-MIBI/SPECT-CT	
No diseased parathyroid gland identified	23 (67.6)
Single parathyroid gland identified	7 (20.6)
Two parathyroid glands identified	2 (5.9)
Three parathyroid glands identified	1 (2.9)
Not performed	1 (2.9)
US examination	
No diseased parathyroid gland identified	10 (29.4)
Single parathyroid gland identified	21 (61.8)
Two parathyroid glands identified	2 (5.9)
Not done	1 (2.9)
Type of surgery	
BPE	10 (29.4)
MIP	19 (55.9)
MIP converted to BPE	3 (8.8)
UPE	2 (5.9)
Previous surgery	
BPE	3 (8.8)
MIP	0 (0.0)
Histopathology (n=44)	
Adenoma	24 (54.5)
Hyperplasia	18 (40.9)
Normal parathyroid gland	2 (4.5)

^{18}F-FCh-PET-CT, ^{18}F-fluoromethylcholine-positron emission tomography-computed tomography; PHPT, primary hyperparathyroidism; FFH, familiar hypoclaciuric hypercalcemia; PTH, parathormone hormone; ^{99m}Tc-MIBI/SPECT-CT, ^{99m}Tc-methoxyisobutylisonitrile/single-photon emission computed tomography-computed tomography; US, ultrasound; BPE, bilateral parathyroid exploration; MIP, minimal invasive parathyroidectomy; UPE, unilateral parathyroid exploration.

Table 3 Patients with multiglandular PHPT

Patients no.	Age (years)/sex	Diagnosis	Ionized Ca (mmol/L)	PTH (pmol/L)	^{18}F-FCh-PET-CT (gland)	Sestamibi (gland)	US (gland)	Type of surgery	Removed glands	Pathology	PET # GS
6	76/M	PHPT	1.47	13.6	2	0	1	BPE	2	Hyperplasia	TP + TP
9	55/F	PHPT	1.40	14.8	2	3	1	BPE	3	Hyperplasia	TP + TP + FN
12	67/F	PHPT	1.50	12.9	2	1	1	BPE	2	1 hyperplasia, 1 normal	TP + FP
17	53/F	FHH	1,64	13.5	2	1	1	BPE	2	Adenoma	TP + TP
20	72/F	PHPT	1.43	13.2	2	1	1	BPE	2	Hyperplasia	TP + TP
27	61/F	PHPT	1.42	11.5	2	0	1	BPE	2	Hyperplasia	TP + TP
29	77/F	PHPT	1.42	8.5	2	0	1	BPE	2	Hyperplasia	TP + TP
33	69/F	PHPT	1.41	10.0	2	0	1	BPE	2	1 normal, 1 adenoma	FP + TP
49	46/F	PHPT	1.54	17.8	2	0	0	UPE	2	1 hyperplasia, 1 adenoma	TP + TP

PHPT, primary hyperparathyroidism; PTH, parathormone hormone; ^{18}F-FCh-PET-CT, ^{18}F-fluoromethylcholine-positron emission tomography-computed tomography; US, ultrasound; PET, positron emission tomography; GS, gold standard; M, male; BPE, bilateral parathyroid exploration; TP, true positive; F, female; FN, false negative; FP, false positive; FHH, familiar hypocalciuric hypercalcemia; UPE, unilateral parathyroid exploration.

Table 4 Diagnostic performance of ^{18}F-FCh-PET-CT

Patients group	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
All patients				
Per-lesion analysis (n=44)	97.5	–	93.0	–
Per-gland analysis (n=134)	95.2	96.7	86.9	97.8
Multiglandular disease				
Per-lesion analysis (n=19)	94.2	–	88.9	–
Per-gland analysis (n=36)	94.1	89.5	84.2	94.4

^{18}F-FCh-PET-CT, ^{18}F-fluoromethylcholine-positron emission tomography-computed tomography; PPV, positive predictive value; NPV, negative predictive value.

removed, 16 lesions were pathological, resulting in a DR of 84.2%. ^{18}F-FCh-PET-CT was also accurate in patients with multiglandular disease, with sensitivity of 94% and PPV of 89% in the per-lesion analysis. Furthermore, per-gland analysis showed specificity of 94%, and NPV of 94%. These results are in line with previous studies (2,3,6,17).

^{18}F-FCh is not a specific tracer for parathyroid glands and can accumulate in other tissues. In our study, three false positive lesions were depicted on ^{18}F-FCh-PET-CT. Histopathology showed normal parathyroid glands in two lesions and lymph node in the third. Other potential locations for false positive tracer uptake include well-differentiated thyroid cancer, oncocytic thyroid nodules, metastatic and inflammatory lymph nodes, benign and autoimmune thyroid nodules. In Rizzo *et al.*, 6.7% of removed lesions found to be false positive (3,5,7,19-24).

Furthermore, ^{18}F-FCh-PET-CT also accurately detected ectopic parathyroid glands. In this study, five lesions, in five patients, were found in ectopic locations. ^{18}F-FCh-PET-CT identified three lesions in an intrathyroidal position. Hemithyroidectomy was performed and all three patients were cured. The other two patients had an ectopic parathyroid lesion in the superior mediastinum on ^{18}F-FCh-PET-CT. Both patients were referred to another center for thoracoscopic removal of the lesions. These results are in line with previous studies (5,25).

The high sensitivity and overall accuracy of ^{18}F-FCh-PET-CT in locating hyperfunctioning parathyroid glands is due to a combination of factors. The first factor is the high spatial resolution of PET-CT, allowing detection of much smaller parathyroid lesions. Many studies have shown that ^{18}F-FCh-PET-CT, can correctly locate much smaller parathyroid lesions than conventional scintigraphic imaging, even after the integration of SPECT-CT. This can be one of the reasons why ^{18}F-FCh-PET-CT has a better diagnostic performance in multiglandular PHPT where parathyroid hyperplasia is the dominant etiology, and the parathyroid lesions are generally known to be of smaller size than in the case of adenomas (5,6,12,17,18).

The second factor which affects the diagnostic performance of ^{18}F-FCh-PET-CT and ^{99m}Tc-MIBI/SPECT-CT, is the differences in the pharmacokinetic properties of the radioactive tracer used in these two imaging modalities. ^{99m}Tc-MIBI enters the parathyroid cells and accumulates in the mitochondria, which are more abundant in the oxyphilic cells than the chief cells. On the other hand, radioactive tracer-labeled choline enters both types of parathyroid cells, phosphorylated to phospholipids by choline-kinase, which is upregulated by the increased production of PTH in patients with PHPT, and integrated in the cell membrane of all newly proliferated cells. Thus, choline uptake is a marker of cell wall synthesis. The increased availability of radioactive tracer in all cells increases the diagnostic performance of ^{18}F-FCh-PET-CT (*Figure 2*) (1,17,26-28).

In 10 of 52 patients who underwent ^{18}F-FCh-PET-CT, a decision was made not to operate (*Figure 1*). It could be argued that these patients underwent ^{18}F-FCh-PET-CT unnecessarily. Three patients did not have a diagnosis of PHPT, but FHH (one patient) and hyperparathyroidism secondary to vitamin D deficiency (two patients). A further two patients declined surgery, and two were deemed too ill to undergo surgery. Three had no uptake on ^{18}F-FCh-PET-CT. Perhaps more detailed preoperative counseling could have identified these patients before referral to ^{18}F-FCh-PET-CT. However, FHH can be difficult to diagnose, and there was indeed one patient with FHH who had positive findings on ^{18}F-FCh-PET-CT and was operated with two

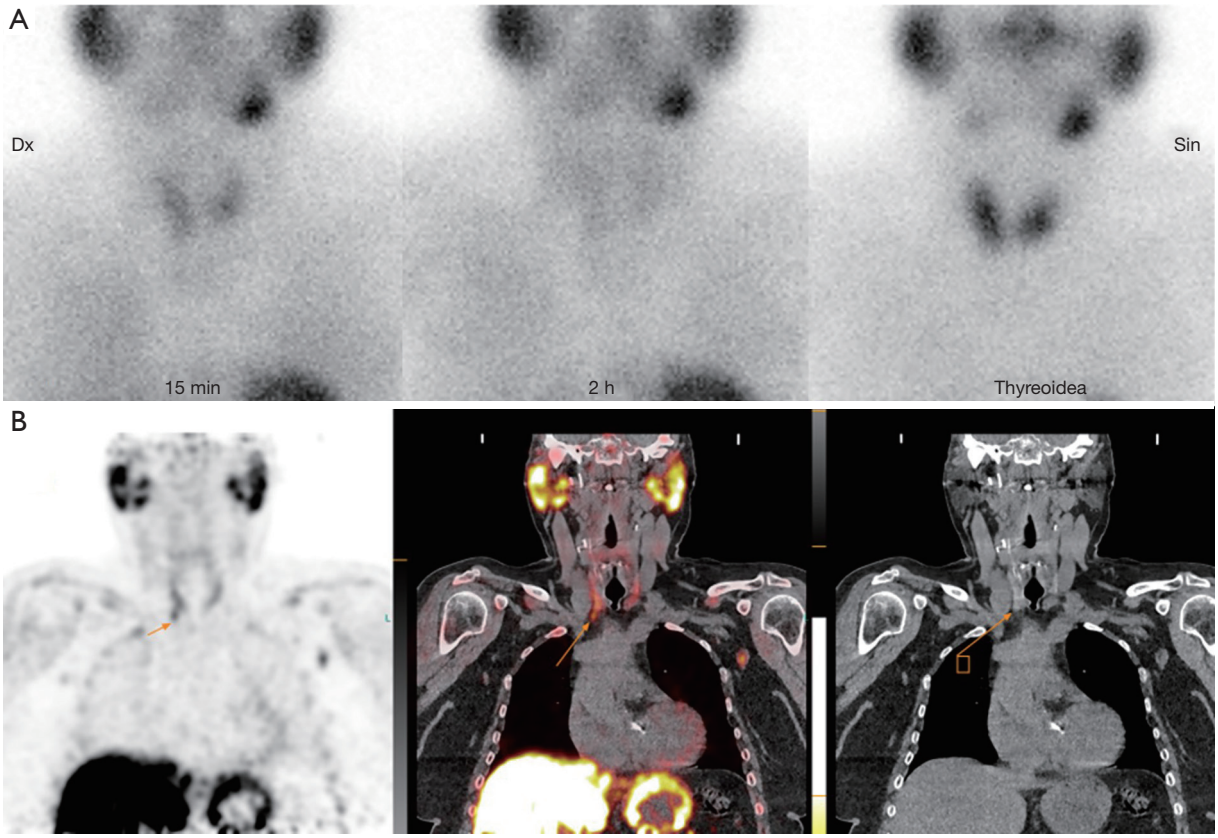

Figure 2 A 74 years old woman with PHPT. (A) ^{99m}Tc-MIBI/SPECT-CT was normal, no parathyroid identified. (B) Positive uptake on ^{18}F-FCh-PET-CT representing a parathyroid adenoma on the right inferior side (arrows). Postoperative histopathology showed chief cell adenoma. Dx, dexter; Sin, sinister; PHPT, primary hyperparathyroidism; ^{99m}Tc-MIBI/SPECT-CT, ^{99m}Tc-methoxyisobutylisonitrile/single-photon emission computed tomography-computed tomography; ^{18}F-FCh-PET-CT, ^{18}F-fluoromethylcholine-positron emission tomography-computed tomography.

pathological glands removed. Although the indication to operate should not be based on findings on preoperative localization, positive localization of diseased parathyroid glands does, in practice, affect the decision to operate in borderline cases. Furthermore, double or triple-negative examinations can be the reason for further, or renewed verification of the primary diagnosis.

The question of whether ^{18}F-FCh-PET-CT should be used as the first-line imaging modality in patients with PHPT is still unanswered. Our study, as well as many others over the last few years, has clearly shown the superior diagnostic performance of ^{18}F-FCh-PET-CT over ^{99m}Tc-MIBI/SPECT-CT and US examination making MIP possible and successful. The same applies for patients with multiglandular PHPT, where ^{18}F-FCh-PET-CT successfully identified all lesions making the choice of BPE correct and easy to perform (*Figure 3*). Moreover, it has lower irradiation and requires a shorter time to perform the examination, making it more convenient for patients.

Nevertheless, the high cost of this modality, and the limited availability of the radioactive tracer make it difficult to recommend ^{18}F-FCh-PET-CT as first-line imaging for PHPT at present (5-8). On the other hand, in our cohort, only 3 patients (6%) were denied surgery due to negative ^{18}F-FCh-PET-CT. This low proportion speaks for the advantage of ^{18}F-FCh-PET-CT also as a first-line examination.

Certain limitations of our study should be highlighted. The retrospective design, the small number of patients, and the fact that no patient with negative localization on ^{18}F-FCh-PET-CT was operated limit the generalizability of this study.

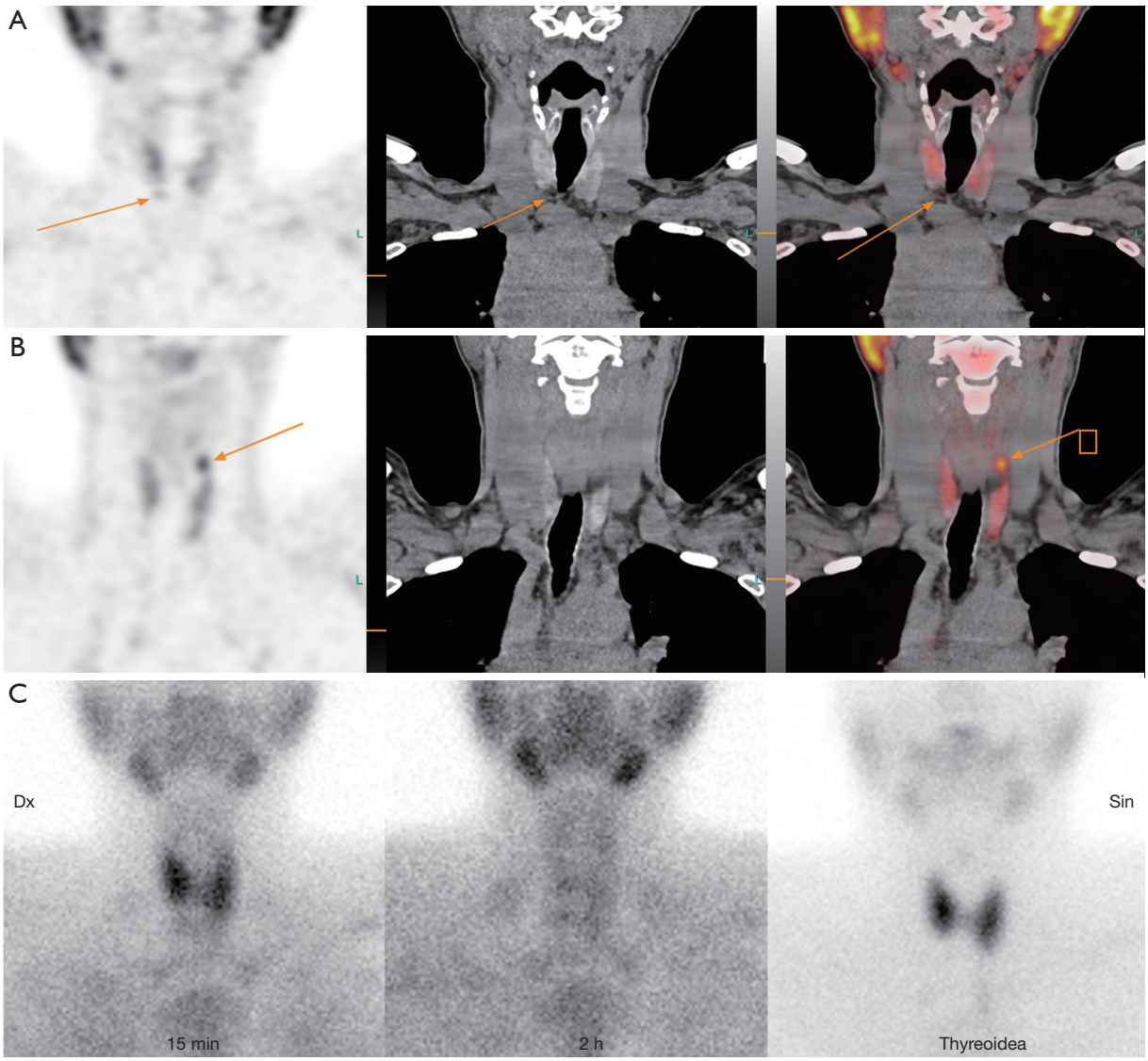

Figure 3 A 56 years old man with multiglandular PHPT verified on postoperative histopathology (hyperplasia). (A) ^{18}F-FCh-PET-CT representing a hyperactive parathyroid tissue on the right inferior side (arrows). (B) Same patient with positive ^{18}F-FCh-PET-CT representing a hyperactive parathyroid tissue on the left superior side (arrows). (C) No positive finding on ^{99m}Tc-MIBI/SPECT-CT. Dx, dexter; Sin, sinister; PHPT, primary hyperparathyroidism; ^{18}F-FCh-PET-CT, ^{18}F-fluoromethylcholine-positron emission tomography-computed tomography; ^{99m}Tc-MIBI/SPECT-CT, ^{99m}Tc-methoxyisobutylisonitrile/single-photon emission computed tomography-computed tomography.

Conclusions

Our study demonstrates the high diagnostic performance and added value of ^{18}F-FCh-PET-CT in the preoperative localization of diseased parathyroid gland in patients with PHPT, especially in multiglandular PHPT, and ectopically located parathyroid glands. We believe that ^{18}F-FCh-PET-CT is an excellent imaging tool, which can be used when first-line parathyroid imaging fails, but after the decision of surgery has been made, and can probably replace them within few years. The cost-effectiveness of using ^{18}F-FCh-PET-CT as a first-line imaging modality in comparison with the present ^{99m}Tc-MIBI/SPECT-CT should be investigated in future, ideally prospective, studies.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-232/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-232/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Swedish Ethical Review Authority (No. 2022-05134-01-336690). Since only already collected data were used, and no new contact or intervention with patients were performed, the Swedish Ethical Review Authority waived the need for informed consent.

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