

Added value of 18F-fluorocholine positron emission tomography-computed tomography in presurgical localization of hyperfunctioning parathyroid glands after dual tracer subtraction scintigraphy failure

A retrospective study of 47 patients

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Abstract

Hyperparathyroidism is a common endocrine disorder. The precise localization of causal parathyroid gland is crucial to guide surgical treatment. Several studies report the added value of 18F-fluorocholine (FCH) positron emission tomography-computed tomography (PET/CT) as second line imaging but rely on suboptimal first-line imaging using 99mTc-sestaMIBI dual phase scintigraphy. The aim of this study is to evaluate the percentage of successful parathyroid localization with FCH PET/CT after failure of a more sensitive first-line detection protocol associating neck ultrasonography and 99mTc-Per technetate/99mTc-sestaMIBI dual tracer subtraction scintigraphy.

We included retrospectively 47 patients who underwent a FCH PET/CT as second line imaging for biologically proven primary hyperparathyroidism from November 2016 to October 2018 in Godinot Institute (Reims, France). 99mTc-Per technetate/99mTc-sestaMIBI dual tracer subtraction scintigraphy and neck ultrasonography were used as first-line imaging and failed to localize the causal parathyroid lesion in all cases.

FCH PET/CT demonstrated at least 1 parathyroid target lesion in 29 patients (62%). 21/29 patients underwent surgery. Target lesions corresponded histologically to hyperfunctioning parathyroid glands for all 21 patients and surgery was followed by hyperparathyroidism biological resolution. Calcium serum levels were associated to FCH PET/CT positivity ($P = .002$) and a trend toward significance was seen for Parathyroid hormone (PTH) levels ($P = .09$).

FCH PET/CT is a promising tool in second-line parathyroid imaging. Large prospective studies and cost-effectiveness analyses are needed to precise its role.

Abbreviation: FCH = 18F-fluorocholine.

Keywords: fluorocholine, parathyroid, PET

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All procedures performed in study involving human participants were in accordance with the ethical standards with the 1964 Helsinki Declaration and its later amendments.

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

Additional consent to publish has been obtained for individual person's data.

The data that support the findings of this study are available on request from the corresponding author [DM]. Raw imaging data are not publicly available due to state restriction as they contain information that could compromise research participant privacy.

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1. Introduction

Hyperparathyroidism is the third most common endocrine disorder after diabetes and dysthyroidism^[1] with prevalence estimates of 1 to 7 per 1000 adults.^[2] Primary hyperparathyroidism affects mostly women after the age of 50 years and is mainly due to solitary parathyroid adenoma (85%). Multiglandular disease accounts for 15% of the cases, either in the form of a double adenoma or parathyroid hyperplasia.^[3]

Parathyroidectomy is the only curative treatment with good efficiency and relatively low morbidity.^[4] Surgical guidelines are well codified.^[5] In the absence of preoperative imaging, bilateral neck exploration with resection of enlarged parathyroid glands is curative in 95%.^[4] The advent of localization imaging, using a combination of neck ultrasonography and radionuclide imaging, allowed the development of minimally invasive approaches and reduced the rate of surgical failure associated with ectopic glands.^[6,7] The possibility of preoperative imaging has profoundly changed the treatment paradigm to the point of noting a decrease in surgical proposals in case of preoperative localization failure in some studies.^[8]

There is growing interest in 18F-fluorocholine (FCH) positron emission tomography-computed tomography (PET/CT) as a second line nuclear imaging technique in preoperative parathyroid localization,^[9,10] in an era where hyperparathyroidism is diagnosed at an asymptomatic early stage with a decrease in weight of the lesions removed.^[11] The few studies available focusing on FCH PET/CT mostly use double phase 99mTc-sestaMIBI scintigraphy as first-line imaging, an acquisition protocol leading to one-third of localization failure.^[12] The question whether FCH PET would still be efficient when using a more sensitive double tracer subtraction protocol^[13] as first-line imaging is unanswered.^[14] The aim of this study is to evaluate the percentage of successful preoperative parathyroid localization with FCH PET/CT after failure of a more sensitive first-line detection protocol associating neck ultrasonography and 99mTc-Pertechnetate/99mTc-sestaMIBI dual tracer subtraction scintigraphy.

2. Material and methods

2.1. Inclusion and exclusion criteria

We retrospectively screened all patients who underwent a FCH PET/CT for biologically proven primary hyperparathyroidism from November 2016 to October 2018. The inclusion criteria were as follows:

- (1) biologically proven hyperparathyroidism (retrospectively reconfirmed by experienced endocrinologists based on available biological results);
- (2) first-line imaging involving at least a 99mTc-Pertechnetate/99mTc-sestaMIBI dual tracer subtraction scintigraphy and a neck ultrasonography;
- (3) parathyroid disease localization failure on first-line imaging (no target lesion on neither ultrasonography nor scintigraphy; in case of doubtful results on 1 modality, target lesion should not be confirmed by the other examination).

The exclusion criteria were as follows:

- (1) previous cervical surgery;
- (2) first-line imaging involving 99mTc-sestaMIBI dual phase scintigraphy;
- (3) FCH PET/CT performed as first-line imaging.

2.2. First-line imaging

First-line imaging (neck ultrasonography and 99mTc-Pertechnetate/99mTc-sestaMIBI dual tracer subtraction scintigraphy) was performed either in Godinot Institute (Reims, France) or Troyes Hospital (Troyes, France) by experienced nuclear medicine specialists (at least 5 years of experience in parathyroid imaging). Images were retrospectively reviewed for the study purpose to confirm localization failure before inclusion.

Dual-tracer scintigraphy included at least, and in this order:

- (1) a 10-minute pinhole thyroid acquisition performed 20 minutes after an intravenous administration of 150MBq of 99mTc-Pertechnetate,
- (2) a 15-minute pinhole cervical acquisition and a 5-minute parallel cervico-mediastinal planar acquisition performed 15 minutes after an intravenous acquisition of 600 MBq of 99mTc-sestaMIBI. Single Photon Emission Computed Tomography (SPECT)/CT was optionally performed.

Dual tracer scintigraphy was rated as negative if no target lesion was identified on either conventional scintigraphy (pinhole cervical subtracted image, cervico-mediastinal planar acquisition) or SPECT/CT, if it was performed.

2.3. FCH PET/CT

All FCH PET/CT were performed at Godinot Institute (Reims, France) and followed the acquisition protocol used in clinical routine. Immediately after an intravenous administration of 2.5 MBq/kg of FCH, patients underwent a cervical dynamic acquisition (30 frames of 1 minute) followed by a late cervico-mediastinal acquisition at 60 minutes post-injection. Acquisitions were performed on a Discovery 710 Elite PET/CT system (General Electrics, Milwaukee, Wisconsin). Images retrospective analyses were conducted on a dedicated console (AW Server 3.2, General Electrics) by 2 experienced nuclear medicine physicians (more than 8 years of experience in parathyroid imaging). In case of discrepancy between the 2 observers, the final decision was reached by consensus. The cervical dynamic acquisition was reviewed in cine mode along with the late cervico-mediastinal acquisition. Criteria used to retain parathyroid target lesions were as follows: mandatory focal FCH uptake on dynamic and/or late acquisition; compatible target lesion on CT. The precise localization of target lesions was noted.

2.4. Surgery and follow-up

Patients were referred to general surgeons experienced in endocrine surgery (more than 10 years of experience) in Reims University Hospital (Reims, France) and Godinot Institute (Reims, France). They underwent minimally invasive surgery or bilateral neck exploration when no target lesions were identified.

Calcium and PTH levels were monitored to assess hyperparathyroidism resolution at least 1 month after surgery.

2.5. Histopathological analysis

Parathyroidectomy samples were analyzed by pathologists with more than 20 years of experience in Reims University Hospital (1 observer per analysis). The final histopathological results and weight of the parathyroid samples were noted.

2.6. Statistical analysis

When patients underwent surgery, we considered FCH PET/CT as successful when 2 conditions were met: first, all identified lesions corresponded to histologically proven hyperfunctioning parathyroid; second, the remaining parathyroid glands were unaffected, confirmed by the normalization of calcium and PTH levels. When surgical treatment could not be performed, FCH PET/CT was considered as positive when it identified a plausible target lesion. Fisher exact test and Student *T* test were used to determine whether patients' characteristics significantly differ between positive and negative FCH PET/CT. All statistical analyses were conducted using R software.^[15]

3. Results

We screened 48 patients and excluded 1 patient who underwent FCH PET/CT as first-line imaging. Forty-seven consecutive patients were thus retrospectively included (Fig. 1). No patient had previous neck surgery. First-line imaging results were as follow: 18 patients had an additional SPECT/CT; doubtful lesions were seen on either neck ultrasonography or scintigraphy alone in respectively 12 and 4 patients (2/4 had had SPECT/CT). No patients were negative on planar scintigraphy and doubtful on SPECT/CT. Both ultrasonography and scintigraphy were negative in 31/47 patients.

FCH PET/CT performed as second line imaging failed to localize a target lesion in 18/47 patients (38%). In the remaining 29 patients (62%), FCH PET/CT showed 1 target lesion in 28/29 patients and multiglandular disease in 1/29 patient (bilateral double adenoma). An example is shown in Figure 2. Twenty-one patients underwent surgery. Eight patients did not undergo surgery for various reasons: 3 were lost to follow-up, 2 refused surgical treatment, 3 suffered from intercurrent pathology, which delayed surgical treatment. Among the 21 operated patients (including the patient with multiglandular disease), 21 hyperparathyroidism resolutions were obtained (100%). Histopathological results showed 16 solitary chief cell adenomas, 1 double chief cell adenoma, 1 chief cell hyperplasia, and 3 oxyphil cell adenomas. Removed parathyroid glands weight (Table 1) ranged from 0.10 to 8.80 g (median weight: 0.55 g) and were mostly

located in cervical paraesophageal areas (43%), anterosuperior mediastinum (24%) or in orthotopic position (33%).

Of the 18 FCH PET/CT negative patients, only 1 underwent surgery by bilateral neck exploration (1 clear cell adenoma in orthotopic position), the remaining 17 patients were followed up.

Three patients over 47 had concomitant thyroid nodular goiter: 2 patients had a positive FCH PET/CT and 1 patient had a negative FCH PET/CT.

Regarding patient characteristics (Table 2), Calcium serum levels were significantly higher when FCH PET/CT was positive ($P=.002$). PTH levels were also higher in the positive FCH PET/CT group but the difference was not statistically significant ($P=.09$). FCH PET/CT was performed under Cinacalcet treatment for 5/29 patients (17%) in positive FCH PET/CT group and 1/18 (6%) patient in negative FCH PET/CT group.

Only 1 patient met the criteria to perform genetic predisposition assessment: HRPT2 mutation was found (solitary chief cell adenoma on histopathological results)

4. Discussion

FCH PET/CT allowed to localize parathyroid target lesions in 29/47 (62%) patients after inconclusive first-line imaging including neck ultrasound and ^{99m}Tc -Pertechnetate/ ^{99m}Tc -sestaMIBI dual tracer subtraction scintigraphy. Histological confirmation was obtained for 21/29 patients and hyperparathyroidism resolution was obtained in 100% of the operated patients.

This rate of 62% is markedly lower than previously reported. Grimaldi et al^[16] included 27 consecutive patients with primary hyperparathyroidism with non-conclusive preoperative localization, recurrence of previously operated hyperparathyroidism or familial hyperparathyroidism: FCH PET/CT was positive in 24/27 (89%) patients.

The prospective study of Quak et al^[9] including 25 patients with negative or inconclusive localization on conventional scintigraphy and neck ultrasound reported FCH PET/CT positivity in 19/25 patient and more equivocal findings in 3/25, with only 2/25 negative studies.

These 2 studies used however dual-phase ^{99m}Tc -sestaMIBI scintigraphy as first-line imaging. Reported sensitivity of this protocol is low by comparison to dual-tracer^[13] or dual-isotope scintigraphy.^[17] Dual-phase scintigraphy leads to approximately one-third of localization failure.^[12]

The only available meta-analysis provided by Treglia et al^[18] gathered 14 studies and 517 patients with a pooled estimate sensitivity of FCH PET/CT of 95% (92%–97%) but gathered again studies where first-line imaging relied on ^{99m}Tc -sestaMIBI dual-phase scintigraphy.

FCH PET/CT positivity is associated with higher calcium levels. To the best of our knowledge, it is the first study to identify this association. A trend toward significance is seen for PTH levels and is presumably due to a lack of power of our study. This trend is also reported in another study.^[19]

Cinacalcet is a modulator of the calcium-sensing receptor strongly expressed on the surface of parathyroid cells.^[20] It reduces serum calcium and PTH levels^[21] and is indicated in particular in patients with primary hyperparathyroidism based on calcium levels in patients for whom surgery is not clinically indicated or contraindicated.^[20] We did not find any significant negative impact of Cinacalcet on the FCH PET/CT success. Patients displaying positive FCH PET/CT tended to be more frequently under Cinacalcet treatment, presumably because of higher calcium levels.

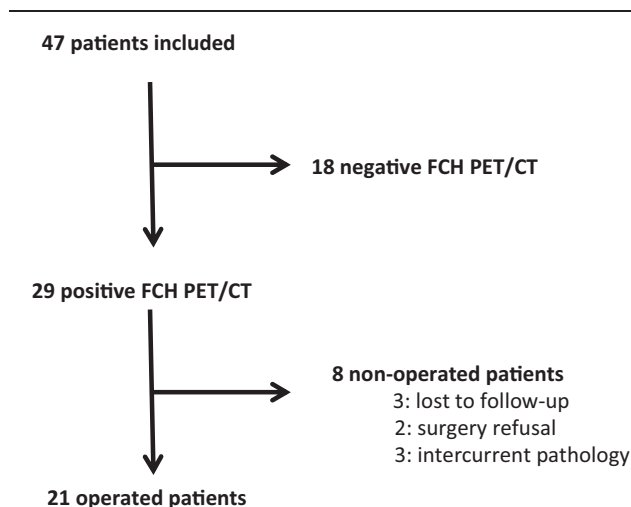


Figure 1. Patients' flowchart.

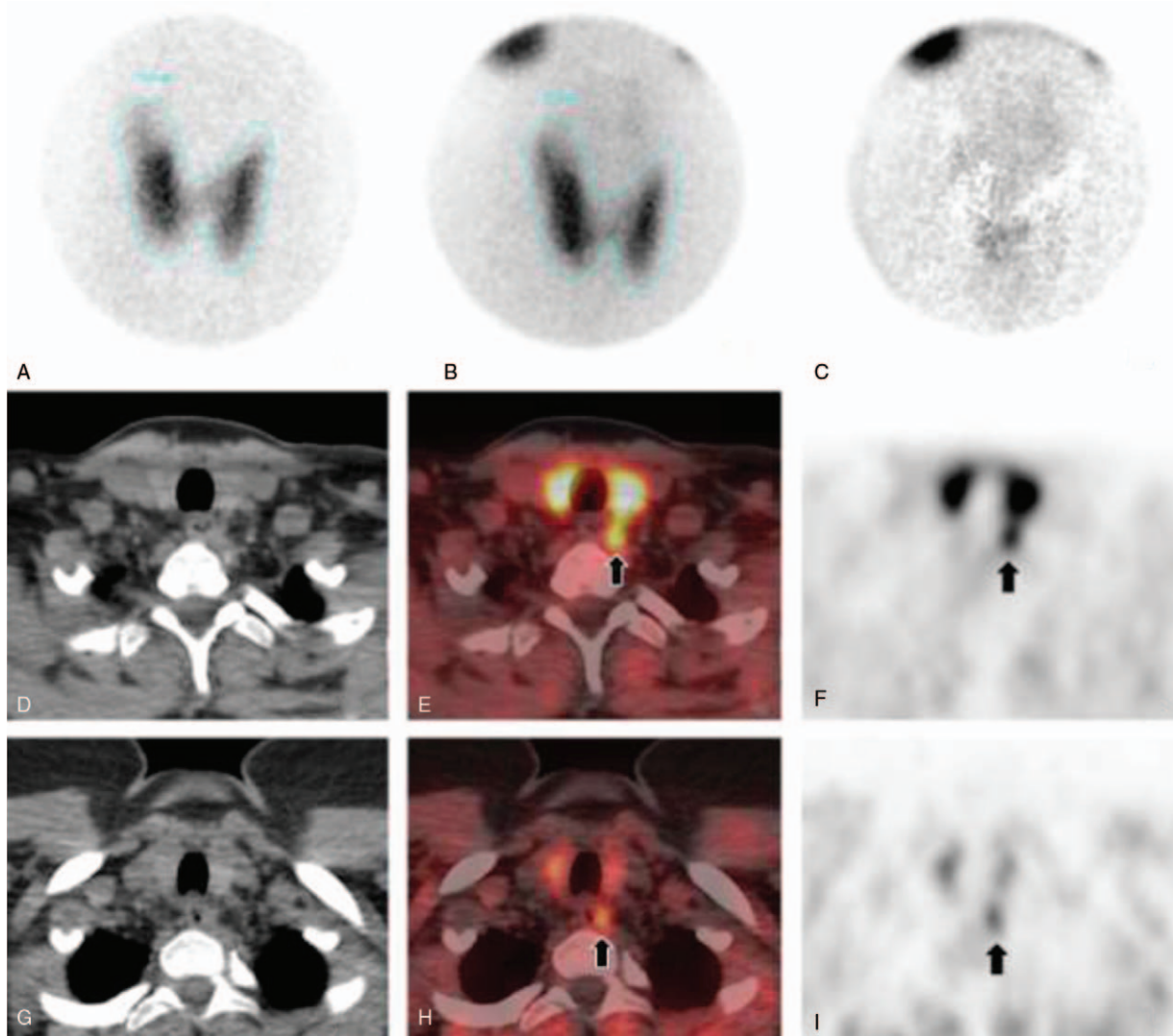


Figure 2. Dual tracer ^{99m}Tc -pertechnetate/ ^{99m}Tc -sestaMIBI subtraction scintigraphy showed no focal uptake compatible with a hyperfunctioning parathyroid (A: $^{99m}\text{TcO}_4$ - thyroid pinhole acquisition, B: pinhole obtained after the administration of ^{99m}Tc -sestaMIBI, C: subtracted image). FCH PET/CT demonstrated a target lesion (arrow) on dynamic acquisition (D, E, F – 2 minutes post injection) and late acquisition (G, H, I). FCH = ^{18}F -fluorocholine, PET/CT = positron emission tomography-computed tomography.

Table 1		
Surgical and histopathological results.		
	Positive FCH PET/CT (n=21)	Negative FCH PET/CT (n=1)
Sample weight (g)		
Median (min-max)	0.55 (0.10–8.80)	0.16
Histological results	16: solitary chief cell adenoma	1: solitary clear cell adenoma
	1: double chief cell adenoma	
	1: chief cell hyperplasia	
	3: solitary oxyphil cell adenoma	
Localization	9: cervical paraesophageal area	1: orthotopic position
	5: anterosuperior mediastinum	
	7: orthotopic position	

FCH = ^{18}F -fluorocholine, PET/CT = positron emission tomography-computed tomography.

Thyroid gland uptake, thyroid nodules, faint uptake in normal parathyroid glands and uptake in normal, reactive or metastatic lymph nodes have been reported as false-positive findings^[18] on FCH PET/CT, but were not encountered in our patients. Only 3/47 patients had concomitant thyroid nodular goiter in our study, mainly because such patients usually undergo double phase scintigraphy in our institution to avoid subtraction artifacts.

Removed operated glands were mostly found in deep cervical area (9/21 paraesophageal localizations) and anterosuperior mediastinum region (5/21) explaining the neck ultrasonography negativity. Their small sizes may explain the false-negative scintigraphy.^[22]

There are several limits to our study aside from its retrospective design.

Additional ^{99m}Tc -sestaMIBI SPECT/CT were not systematically performed in first-line imaging. However although it provides useful anatomical information before surgery,^[23] it is not proven more sensitive than pinhole acquisition.^[2,3]

Table 2**Patients' characteristics.**

	Positive FCH PET/CT (n=29)	Negative FCH PET/CT (n=18)	P
Sex ratio M:F	7:22	5:13	P=1.0
Age, yr	66 +/- 12	60 +/- 16	P=.19
Calcemia, mmol/L*	2.77 +/- 0.26	2.56 +/- 0.12	P=.002*
PTH, pg/mL*	144 +/- 81	106 +/- 46	P=.09
Cinacalcet treatment (%)	17%	6%	P=.38

FCH = 18F-fluorocholine, PET/CT = positron emission tomography-computed tomography.

*Local normal laboratory ranges: PTH <60 pg/mL, Ca <2.55 mmol/L.

We used, as in clinical routine, a maximalist FCH PET/CT acquisition protocol. Temporal uptake of parathyroid glands can indeed differ with early washout patterns.^[24] On the other hand, the contrast between parathyroid and thyroid is better on late acquisitions.^[25] We opted for a dynamic cervical acquisition in order not to miss an early washout parathyroid gland, as the precise scan time is not well documented. However, we could have missed mediastinal early washout glands.

We have only scarce information on the FCH PET/CT negative group: only 1 patient in 18 was referred to surgery concluding to an orthotopic clear cell parathyroid adenoma. One of the main hypothesis to explain FCH PET/CT negativity could be the low size of hyperfunctioning parathyroid: in positive FCH PET/CT group, removed parathyroid gland weights ranged from 0.10 to 8.8g, the only operated PET/CT negative patient had a parathyroid gland of 0.16g, on the low side of the range.

FCH PET/CT opens new perspectives for parathyroid glands imaging. Prospective studies are needed to specify its role especially in first-line settings along cost-effectiveness studies. The sources of false-negative studies need also to be investigated.

5. Conclusions

In a first surgery setting, FCH PET/CT allowed the identification of a parathyroid target lesion in 62% of patients after failure of first-line imaging with 99mTc-Per technetate/99mTc-sestaMIBI dual tracer subtraction scintigraphy and neck ultrasonography. High calcemia serum levels were significantly associated with FCH PET/CT positivity.

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