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Challenging pre-surgical localization of hyperfunctioning parathyroid glands in primary hyperparathyroidism: the added value of ^{18}F-Fluorocholine PET/CT

Serena Grimaldi , Jacques Young , Peter Kamenicky, Dana Hartl, Marie Terroir, Sophie Leboulleux, Amandine Berdelou, Julien Hadoux, Segolene Hescot, Hervé Remy, Eric Baudin, Martin Schlumberger, Désirée Deandreis

INTRODUCTION

Primary hyperparathyroidism (HPT) is due to parathyroid hormone (PTH) overproduction caused by a single parathyroid adenoma in more than 80% of cases and by multiple parathyroid hyperplasia or adenomas in the remaining cases [1]. In about 5-10% of patients, primary HPT occurs in the familial context of multiple endocrine neoplasia syndromes (MEN 1, 2a and 4) or in other rare syndromes (HPT-Jaw tumor syndrome, familial hypocalciuric hypercalcemia, familial isolated HPT, neonatal severe HPT or autosomal dominant moderate hyperparathyroidism) [2].

Surgery is the treatment of choice in many cases of primary HPT, in particular in symptomatic patients. A correct pre-surgical localization of the hyper-functioning parathyroid gland by imaging allows for a mini-invasive approach that results in a successful surgical resection in 95-98% of patients [3, 4]. When the pre-surgical localization is inconclusive, a surgical exploration of the four glands is mandatory, but the risk of unsuccessful intervention is increased. [5].

The most commonly used pre-surgical imaging assessment is a combination of parathyroid scintigraphy with ^{99m}Tc-sestaMIBI (2-methoxyisobutylisonitrile) and neck ultrasonography (US) [6]. Different scintigraphic protocols are used, such as the single-tracer (^{99m}Tc-sestaMIBI) dual-phase protocol or the dual tracer (^{99m}Tc-sestaMIBI + $^{99m}TcO_4^-$ (pertechnetate) or ^{99m}Tc-sestaMIBI + 123Iodine) subtraction protocol, sometimes in combination with a Single Photon Emission Tomography (SPECT) or SPECT/Computed Tomography (CT) acquisition [7, 8]. The overall sensitivity of parathyroid scintigraphy ranges from 30% to 92% without significant differences between the two protocols. On the other hand, SPECT or SPECT/CT acquisitions increase sensitivity of planar images alone. In a meta-analysis, a pooled sensitivity of 88% was reported for SPECT/CT both on a per lesion basis and on a per patient basis [9], compared to a previously reported pooled sensitivity of 58% for planar images alone [9–11]. Neck US has a sensitivity ranging from 48% to 96% [12]. The Doppler-technique may increase US performance, parathyroid adenoma being highly vascularized, with a sensitivity exceeding 90% in some studies [13, 14].

Factors associated with lower performances of ^{99m}Tc-sestaMIBI scintigraphy and neck US are small increases of serum levels of PTH and ionized calcium, low parathyroid gland weight (small adenoma), the presence of multi-glandular disease and concomitant thyroid disease. Neck US is highly operator dependent and, in some cases, is not able to differentiate parathyroid adenomas from reactive cervical lymph nodes. Furthermore, ectopic parathyroid glands in the upper mediastinum are often inaccessible to neck US [7, 11].

The pre-surgical assessment of a recurrent disease is more difficult than the localization of a newly diagnosed parathyroid adenoma. In case of persistence or recurrence of HPT after a previous surgical treatment, the localization of the hyper functioning gland is challenging for both ^{99m}Tc-sestaMIBI scintigraphy and US, because most recurrent HPT are due to multi-glandular disease or ectopic parathyroid glands and because previous surgery creates anatomical variations in the neck [15, 16] .

Since 2012, incidental findings of parathyroid adenomas have been reported in patients undergoing ^{11}C-choline and ^{18}F-Fluorocholine (^{18}F-FCH) PET/CT for prostate cancer assessment [17–20]. Preliminary studies showed that ^{11}C-choline and ^{18}F-FCH PET/CT may localize hyper-functioning parathyroid glands both in primary and in secondary HPT, with higher sensitivity compared to ^{99m}Tc-sestaMIBI scintigraphy [21–23]. However, because of the high costs of the tracer, ^{18}F-FCH PET/CT may be not cost-effectively enough to substitute standard imaging techniques in all patients with primary HPT.

The aim of this study was to evaluate the added value of ^{18}F-Fluorocholine-PET/CT in challenging localizations of hyper-functioning parathyroid glands in patients with primary HPT who were referred to two centers (Gustave Roussy (GR) and Bicetre Hospital (KB)) for surgery. Patients with sporadic primary HPT and non-conclusive pre-surgical localization on ultrasonography (US) and ^{99m}Tc-sestaMIBI scintigraphy, patients with suspicion of multiple gland disease and patients with a persistence or recurrence of HPT after previous surgery were included in the study.

PATIENTS AND METHODS

Patients

Forty-six consecutive patients between September 2014 and December 2016 underwent a ^{18}F-FCH PET/CT for pre-surgical evaluation of HPT.

For this analysis we considered patients meeting the following criteria: 1) biochemical diagnosis of primary hyperparathyroidism; 2) indication for surgical treatment according to guidelines [3, 4] ; 3) (i) non-conclusive pre-surgical localization imaging on ^{99m}Tc-sestaMIBI scintigraphy and neck US or (ii) suspicion of multiple gland disease (ie, familiar forms of HPT) or (iii) persistence/relapse of HPT after previous surgical treatment. A total of 27 patients met the inclusion criteria and were considered for analysis.

The remaining 19 patients were excluded from the present analysis because of diagnosis of secondary HPT (n=1), absence of complete standard imaging with ^{99m}Tc-sestaMIBI scintigraphy and neck US (n=7), positive and concordant ^{99m}Tc-sestaMIBI scintigraphy and neck US (n=3) or absence of follow up (n=8).

^{99m}Tc-sestaMIBI Scintigraphy

A dual-phase ^{99m}Tc-sestaMIBI protocol was performed in all 27 patients, with a median administered activity of 448 MBq (range: 390-728).by (GE Discovery 690 at GR and Siemens Symbia T2 at KB gamma camera respectively[24] The median activity was administered was slightly lower than that recommended by EANM guidelines (600-900Mq). In all patients a dynamic acquisition was obtained immediately after injection with subsequent planar images. Subsequent planar images of the neck were obtained 30 and at least 90 minutes after the tracer injection, using a pinhole collimator. Furthermore planar image at 90 minutes including the mediastinum was obtained with a parallel hole collimator searching for ectopic parathyroid glands. Three patients underwent a dual-isotope ^{99m}Tc-sestaMIBI/I123 subtraction protocol in addition to the dual-phase protocol described above in case of known thyroid disease after administration of a median administered activity of I123 of 11 MBq (range: 7-15). A supplementary SPECT/CT acquisition was performed in 17 (63%) patients with dubious findings at planar images. In completely negative exams SPECT/CT was not performed.

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Neck ultrasound

Ultrasonography (US) was performed by expert US operator in both centers, using a linear high frequency transducer of 10 MHz. A real-time sonography combined with color-Doppler imaging was used to evaluate vascularity of the lesion and to aid differentiating thyroid and lymph nodes from parathyroid lesions. Transverse and longitudinal views were recorded. A complete evaluation of the thyroid gland was performed in addition to the search of abnormal parathyroid glands.

^{18}F-Fluorocholine PET/CT

All 27 patients underwent a ^{18}F-FCH PET/CT. PET/CT imaging acquisitions were performed on a GE Discovery 690 PET/CT (General Electric Healthcare), 30 minutes after injection of a median ^{18}F-FCH activity of 100 MBq (range 77-230) [25]. We administered an industrial preparation of fluoromethyl-(18F)-dimethyl-2-hydroxyethyl-ammonium, registered in oncology for pathologies, organs and tissues in which an increase of choline metabolism is expected, in particular for the assessment of prostate cancer and hepatocellular carcinoma. Despite some promising results, the use of this tracer in parathyroid imaging is off-label [21–23]. All patients gave their consent. The exam included a low dose CT (120 kV; 210 mA, slice thickness 3.75 mm) and a PET acquisition of the head, neck and mediastinum (3 min/bed position). All foci of uptake located behind the thyroid lobes or in the upper mediastinum were considered as positive findings for hyper functioning parathyroid glands.

Statistics

Sensitivity and positive predictive values of ^{18}F-Fluorocholine PET were calculated in a per-patient analysis. Sensitivity, specificity, positive and negative predictive values were calculated in per-gland analysis.

The combination of histological findings and biochemical resolution of HPT after surgery was considered as the gold standard.

In the per-gland analysis, independently of the number of glands explored during the surgical procedure, we considered 4 parathyroid glands for patients with newly diagnosed HPT and the number of remaining parathyroid glands for patients already operated for HPT.

Parathyroid glands with abnormal ^{18}F-FCH uptake, confirmed to be abnormal at histopathological examination (adenoma or hyperplasia), associated with a biochemical resolution of HPT after surgery, were classified as true positive findings. ^{18}F-FCH uptake was considered a true positive also in case of resolution of HPT after resection of a single parathyroid gland with normal appearance at histopathological examination.

The absence of ^{18}F-FCH uptake in a parathyroid gland confirmed to be normal at surgical exploration and/or histopathological examination was classified as a true negative finding. The absence of ^{18}F-FCH uptake in parathyroid glands that were not explored during surgery was considered as a true negative finding in case of biochemical resolution of HPT after resection of another gland.

In case of persistent HPT after surgery, one of the not removed glands without ^{18}F-FCH uptake was classified as a false negative finding.

An ^{18}F-FCH uptake in a parathyroid gland found to be normal at surgical exploration and histopathological examination was classified as a false positive finding.

Patients that did not undergo surgery were followed-up and, in the absence of a gold standard, they were not considered for sensitivity, specificity, PPV and NPV analysis.

RESULTS

Among 40 patients that underwent FCH PET/CT a total of 27 patients (8 M, 19 F; median age: 58 years; range: 22-87) were considered for the analysis. Patient population characteristics are summarized in Table 1. In particular, 18 (67%) patients had ^{18}F-FCH PET/CT for a newly diagnosed primary hyperparathyroidism and 9 (33%) for persistent or recurrent primary HPT after previous surgery. Seven (26%) cases of familial HPT were evaluated in the study, among whom 5 were operated.

In 23/27 patients (85%) the assessment by ^{99m}Tc-sestaMIBI scintigraphy and neck US was inconclusive: in 5 patients both ^{99m}Tc-sestaMIBI scintigraphy and neck US were normal, in 5 ^{99m}Tc-sestaMIBI scintigraphy was normal and neck US was positive or dubious, in 7 neck US was normal and ^{99m}Tc-sestaMIBI scintigraphy was positive or dubious, in 6 patients ^{99m}Tc-sestaMIBI scintigraphy and neck US were both dubious or discordant.

^{18}F-FCH PET/TC showed at least one abnormal uptake in 24/27 (89%) cases (single uptake in 17 patients and multiple uptakes in 7 patients), including in the 6 patients who did not undergo surgery for patient refusal (n=1), comorbidities (n=2) or for stable calcium serum levels (n=3). In the remaining 3 cases, ^{18}F-FCH PET/CT was normal, but patients underwent surgery according to clinical indications.

Twenty one patients underwent surgery (Table 1), with a minimally invasive approach in case of single uptake on ^{18}F-FCH PET/CT (n=8), four gland exploration in case of familial HPT and/or multiple uptakes at ^{18}F-FCH PET/CT (n=9) and total or partial thyroidectomy with parathyroid resection in case of concomitant thyroid disease (n=4).

The histological examination revealed 14 adenomas, 11 hyperplastic glands and 2 hyper-functioning parathyroid glands with normal histological appearance. The hyper-function of these two histologically normal glands was confirmed by the resolution of HPT after their surgical removal.

One parathyroid gland was ectopic in the superior mediastinum, another one was an intrathyroidal hyperfunctioning gland. The other glands were retro-thyroidal: 11 left superior, 7 left inferior, 4 right inferior, 3 right superior.

Among the 21 operated patients, 19 (90%) had a biochemical resolution of HPT after surgery. At histology, 16 had a single abnormal gland (13 adenomas, 1 hyperplastic gland in a patient with a previously operated multiple gland disease, 2 parathyroid glands with normal histological appearance) and 3 had multiple abnormal glands (3 hyperplastic glands in 2 patients, 2 hyperplastic glands and one adenoma in one patient).

The remaining two patients had persistent HPT after surgery. In one patient, in a context of a MEN type 1, ^{18}F-FCH PET/CT found one abnormal uptake, while surgery found two hyperplastic glands and one normal gland that was re-implanted in the forearm. The fourth gland was not found during surgical exploration. In the second patient, in a context of sporadic HPT, ^{18}F-FCH PET/CT found one abnormal uptake corresponding to the left inferior parathyroid gland that was resected and appeared to be normal at histological examination.

Per patient analysis

Among the 21 patients who underwent surgery, ^{18}F-FCH PET/CT correctly identified at least one parathyroid lesion in 17 patients. In the remaining 4 patients, PET was classified as a false negative: no abnormal uptake was visible in 3 cases (resection of 2 parathyroid adenomas and one normal parathyroid gland without ^{18}F-FCH uptake, with postoperative resolution of HPT in all these patients), while in one case PET did not correctly identify the abnormal parathyroid gland, even in the presence of an abnormal uptake (uptake focus corresponding to a resected normal parathyroid gland, with persistent HPT after surgery).

Sensitivity and PPV of ^{18}F-FCH PET/CT in operated patients were 81% and 94%, respectively. Sensitivity and PPV in overall population and in different subgroups of patients are reported in Table 2.

^{18}F-FCH -PET identified at least one lesion in all patients with familial or multi-glandular HPT and in all patients with persistent or recurrent HPT after surgery. Resolution of HPT after surgery was achieved in 5/6 (83%) patients with familial or multi-glandular HPT and in all patients (6/6) with persistent or recurrent HPT after surgery.

Age, sex, PTH and calcium serum levels in patients with a positive ^{18}F-FCH PET/CT and patients with a normal ^{18}F-FCH PET/CT are summarized in Table 3. In particular, median PTH serum levels was similar in patients with either a negative or a positive PET/CT.

Per gland analysis

In the per gland analysis, we considered a total of 74 analyzed parathyroid glands in the 21 operated patients (the 4 parathyroid glands for patients with newly diagnosed HPT and the remaining parathyroid glands for patients already operated for HPT). Based on histology results, we considered 29 lesions, the 27 resected parathyroid glands confirmed to be hyperfunctioning at histology and at follow-up after surgery and the 2 hypothetic lesions that were not removed in the two patients with persistent HPT after surgery.

^{18}F-FCH PET/CT correctly identified 22 out of 29 lesions. Four ^{18}F-FCH uptakes were classified as false positive: two faint uptakes found to be normal parathyroid glands at surgery, a thyroid uptake due to a differentiated thyroid cancer and an undetermined thyroid uptake that was not explored, with post-operative normalization of HPT. There were 7 false negatives at ^{18}F-FCH PET/CT: two hyperplastic glands in two patients with a multi-glandular parathyroid disease (MEN1 in both cases), one ectopic adenoma in the thyro-thymic ligament that was found at surgery, one right inferior sporadic single adenoma, one hyper-functioning parathyroid gland with a normal histologic appearance, and two lesions not found at surgery with persistent HPT after surgery (sporadic HPT in one case and familiar HPT in one case). Per lesion sensitivity, specificity, PPV and NPV were 76%, 91%, 85% and 86 %, respectively. Sensitivity, specificity, PPV and NPV in patients with single sporadic parathyroid adenoma, familiar or multi-glandular parathyroid disease and relapse of HPT after previous surgery are reported in Table 4.

In 7/21 (33%) patients, ^{18}F-FCH PET/TC was able to detect 8 lesions that were not detected on ^{99m}Tc-sestaMIBI scintigraphy nor neck US (4 adenomas, 4 hyperplastic glands). Among these 7 patients, three had a first diagnosis of sporadic parathyroid adenoma, one had a relapse of a previously treated sporadic adenoma, one had a familial multiple gland disease and two had a relapse of a multiple parathyroid hyperplasia.

In patients with multi-glandular parathyroid disease, despite good values of sensitivity, specificity and PPV, the NPV was 63% compared to 89% in patients with sporadic adenoma. In patients with a relapse of a previously treated HPT, ^{18}F-FCH PET/CT properly localized all sites of recurrence in both patients with sporadic HPT (n=3) and familiar forms of HPT (n=3).

Median SUVmax was similar in case of true positive uptakes and false positive uptakes (4.5 (range 2.6-10.7) and 3.1 (range 1.9-5.0), respectively). Median size of true positive lesions was 15 mm (range: 4-50) compared to 14 mm in false negative lesions (range 9-24).

DISCUSSION

Our study demonstrates that ^{18}F-FCH PET/CT could have an important role in patients in whom the pre-surgical detection of hyper-functioning parathyroid gland is challenging. On a per-patient analysis, sensitivity and PPV of ^{18}F-FCH PET/CT were 81% and 94%, respectively. On a per gland analysis, sensitivity and PPV of ^{18}F-FCH PET/CT were 76 % and 85%, respectively. In one third of patients, ^{18}F-FCH PET/TC correctly identified 8 lesions that neither ^{99m}Tc-sestaMIBI scintigraphy nor neck US were able to detect (Fig.1).

^{18}F-FCH PET/CT allowed identifying the hyper-functioning gland in two thirds of patients with sporadic HPT and negative/inconclusive standard work up. In patients with familiar or multiple gland disease, sensitivity was 79% and 100% on a per lesion and a per patient basis respectively. In these patients, however, some abnormal glands could be missed, and NPV is lower in comparison to those with a sporadic single gland disease (NPV 57% and 90%, respectively). This suggests the need for a complete exploration of the four parathyroid glands in case of clinically suspected multi-glandular disease (i.e. familial HPT, secondary HPT) and when two or more abnormal foci are found at imaging. Interestingly, in patients with a persistence or relapse of a surgically treated HPT, all lesions were correctly identified by ^{18}F-FCH PET/CT, in both sporadic and familiar forms of HPT. In these patients, a correct localization of the hyper-functioning gland is essential to avoid complex and often invasive surgery in an already operated neck, with a higher rate of complications [26, 27] .

Recently published studies suggest that ^{18}F-FCH PET/CT is a promising tool in the localization of hyper-functioning gland(s) in patients with HPT, with higher sensitivity compared to ^{99m}Tc-sestaMIBI scintigraphy [21, 28]. In patients with a negative or inconclusive pre-surgical evaluation with ^{99m}Tc-sestaMIBI scintigraphy and/or US, a detection rate of hyper-functioning parathyroid gland by ^{18}F-FCH PET/CT ranging between 77% and 94% was reported on a per patient analysis and between 80 and 96% on a per lesion analysis [22, 25, 29, 30]. Consistent with previous preliminary studies, our results suggest high detection rate of hyper-functioning parathyroid glands in patients with primary HPT and negative or non-conclusive standard work-up. Nevertheless, several differences with the previous studies are relevant. In a recently published prospective study, among 24 subjects with primary HPT and negative or inconclusive standard imaging, ^{18}F-FCH PET/CT was able to guide the surgical procedure in 22 cases and 21/24 patients (88%) were cured after surgery [30]. Considering the APACH1 study a higher sensitivity in a per lesions analysis was found compared to our study (91.3% versus 76%). However the two series are not completely comparable, due to the different inclusion criteria. Compared to other studies, in our study there was a high prevalence of patterns known to negatively influence the pre-surgical localisation imaging, such as the presence of familial multiple gland hyperplasia and the recurrence of HPT after previous surgery. Second, we did not include secondary HPT, surgery being of limited interest in these patients [22, 23]. Third, in the present study even when the pre-surgical localization imaging was negative, patients underwent surgery if there was formal indication, and the 6 patients who did not undergo surgery despite a positive ^{18}F-FCH PET/CT were not considered for the analysis. In contrast to our criteria, in previous studies a histological gold standard was sometimes available only in a small proportion of cases and a negative localisation on ^{18}F-FCH PET/CT was the main reason to avoid surgery and therefore the diagnostic impact could not be evaluated [29].

A retrospective study including 151 subjects with primary HPT showed that ^{18}F-FCH PET/CT allows minimally invasive targeted surgery in most patients with parathyroid adenoma, with a 96.8% cure rate [31]. Similarly in our series the cure rate was high, reaching 90%. Nevertheless, the number of minimally invasive interventions was lower, due to a higher proportion of multiple gland disease and concomitant thyroid disease, requiring a four gland exploration or a total/partial thyroidectomy.

Even if ^{18}F-FCH PET/CT localization performances are quite good, false positive or false negative findings may occur. In our series, we observed 4 false positive findings related to thyroid gland uptakes in 2 patients (one corresponding to a differentiated thyroid carcinoma) or to a faint uptake in normal parathyroid glands in 2 patients. Similarly, false positive results have been reported in previous studies in case of thyroid nodules (including differentiated thyroid carcinoma and oncocytic thyroid adenoma) and normal lymph nodes [18, 22, 23, 31]. Interestingly, ^{18}F-FCH uptakes were also described in parathyroid carcinoma tissue both in local persistent disease and in distant metastases [32].

False negative findings (n=7) were related to the ectopic localization of the parathyroid gland in one patient, a hyper-functioning parathyroid gland with a normal histologic appearance in one patient, hyperplastic parathyroid glands in the context of a multi-glandular parathyroid disease in 3 cases, while in two patients, there was no apparent explanation for the negative ^{18}F-FCH PET/CT. False negative results have already been reported in previous studies in case of ectopic glands, but also in case of hyperplastic glands or adenomas with no specific characteristics [22, 23, 31].

To our knowledge, no study was able to identify any predictive factor which can influence the performance of ^{18}F-FCH PET/CT such as calcium levels, PTH levels or lesion size. In one study, PTH serum level was the only parameter which trended towards higher levels in patients with positive ^{18}F-FCH PET/CT results than in those with a negative ^{18}F-FCH PET/CT [29]. In our study median PTH and calcium levels were similar on ^{18}F-FCH PET/CT positive and ^{18}F-FCH PET/CT negative cases.

Finally, our study has some limitations. The sample size is small, but similar to the majority of other studies. This is related to the selection criteria that focused on a subset of patients with primary HPT and led to the inclusion of a small percentage of patients. Moreover, the inclusion of patients with inconclusive standard imaging in most cases does not allow a comparison between ^{18}F-FCH PET/CT and the other techniques. Nevertheless, the selection of patients with challenging detection of hyper functioning parathyroid glands allows evaluating the added value of ^{18}F-FCH PET/CT to standard work up in a “real life” setting. Some limitations are related to the 99mTc-sestaMIBI scintigraphy protocol: in particular, not all patients underwent a SPECT/CT or a dual-tracer protocol, which have been reported to better performances than planar dual-phase imaging alone [9, 33].

Among PET tracers, before ^{18}F-FCH, ^{11}C-Methionine has been investigated in the pre-surgical localization of hyper functioning parathyroid glands. A meta-analysis showed interesting results with a pooled sensitivity of 81% and a detection rate of 70%. However, its short half-life limits its applicability in the daily practice [34]. Four dimensional computed tomography (4D-CT) has been reported to be effective for the same purpose. In a meta-analysis, the sensitivity and PPV were 89.4% and 93.5%, respectively; in studies in which 4D-

CT was performed in patients with previously inconclusive US and scintigraphy, sensitivity and PPV were 71.8% and 74.9%, respectively [12]. Moreover, promising results have been reported with magnetic resonance imaging (MRI), in particular using a 4D-technique [35, 36]. As ^{18}F-FCH PET/CT, these techniques may be good "problem solving" modalities in patients with challenging pre-surgical localization imaging. In the absence of studies comparing their performances, the preference of one technique over the others may be based on the availability and the absence of contraindications.

CONCLUSION

Our study strengthens the interest of ^{18}F-FCH PET/TC in the detection of hyper-functioning parathyroid glands in primary HPT, showing high sensitivity and specificity. Nevertheless, the use of ^{18}F-FCH PET/CT as a first line examination rather than ^{99m}Tc-sestaMIBI scintigraphy and US seems not to be as yet justified in all patients with HPT. The real added value appears to be in patients with inconclusive standard imaging, persistence or recurrence of HPT after previous surgery or suspicion of multiple gland disease.

Compliance with Ethical Standards:

Conflict of Interest: Serena Grimaldi declares that she has no conflict of interest, Jacques Young declares that he has no conflict of interest, Peter Kamenicky declares that he has no conflict of interest, Dana Hartl declares that she has no conflict of interest, Marie Terroir declares that she has no conflict of interest, Sophie Leboulleux declares that she has no conflict of interest, Amandine Berdelou declares that she has no conflict of interest, Julien Hadoux declares that he has no conflict of interest, Segolene Hescot declares that she has no conflict of interest, Hervé Remy declares that he has no conflict of interest, Eric Baudin declares that he has no conflict of interest, Martin Schlumberger declares that he has no conflict of interest, Désirée Deandreis declares that she has 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 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.

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Figures:

Fig.1: Patient with a recurrence of primary hyperparathyroidism after surgical resection of the right superior parathyroid gland, in the context of a familiar form of hyperparathyroidism (MEN1). Histopathological examination found three hyperplastic parathyroid glands. ^{99m}Tc-sestaMIBI scintigraphy correctly identified one hyperplastic parathyroid gland (white arrow, figure 1A: planar images; 1B: SPECT maximum intensity projection; 1C: SPECT/CT axial images). ^{18}F-FCH PET/CT correctly identified three hyperplastic parathyroid glands (white arrows, figure 1D: PET maximum intensity projection, 1E-F: PET/CT coronal images and axial images).