18F-Fluorocholine-Positron Emission Tomography/Computerized Tomography (FCH PET/CT) Imaging for Detecting Abnormal Parathyroid Glands: Indication, Practice, Interpretation and Diagnostic Performance

Lucia Noskovicova, Sona Balogova, Cyrielle Aveline, Marc Tassart, Jules Zhang-Yin, Khaldoun Kerrou, Ivan Jaksic, Françoise Montravers, Jean-Noël Talbot

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^{18}F-Fluorocholine-Positron Emission Tomography/Computerized Tomography (FCH PET/CT) Imaging for Detecting Abnormal Parathyroid Glands: Indication, Practice, Interpretation and Diagnostic Performance

Lucia Noskovicova, MD,[†,#] Sona Balogova, MD, PhD,[†,‡,#] Cyrielle Aveline, MD,[‡] Marc Tassart, MD,[§] Jules Zhang-Yin, MD, PhD,[‖] Khaldoun Kerrou, MD,[‡] Ivan Jaksic, MD,[¶] Françoise Montravers, MD, PhD,[‡] and Jean-Noël Talbot, MD, PhD[‡,**]

In patients with confirmed hyperparathyroidism (HPT) scheduled for surgical treatment, the preoperatory imaging permits to optimize the operatory protocol of parathyroidectomy (PTX), in particular by selecting those patients who can benefit from minimally invasive PTX (MIPTX). The MIPTX has the merit to shorten the operative time, incision length, and to reduce the operatory risks. With preoperative localization studies, the rate of PTX failure, in particular due to nonsuspected multiglandular or ectopic disease, has been profoundly decreased. The first cases of incidental localization of abnormal parathyroid glands (PTs) on FCH PET/CTs performed for another indication were reported more than one decade ago. Since then, significant amount of data from heterogeneous series of patients consistently confirmed better diagnostic performances of FCH PET/CT (sensitivity for detection of abnormal PT 97%, range 96%-98%) in comparison with other radiopharmaceuticals, ultrasonography or 4D-CeCT in localizing hyperfunctioning parathyroid glands (HFPTGs) in case of primary HPT. Utility of FCH PET/CT in case of renal HPT has been reported in fewer series. The article discusses and summarizes the bibliographic evidence on documented indications of FCH PET/CT in patients with HPT, its safety profile, the practice of FCH PET/CT and interpretation of FCH PET/CT findings, including potential interpretation pitfalls and tips to avoid them. Our real-world experience over 12 years reinforces published evidence supporting the use of FCH PET/CT as the first-line radionuclide imaging technique in patients with all types of HPT in whom surgery is an option.

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[†]Department of Nuclear medicine, Comenius University Bratislava, St. Elisabeth Oncology Institute and Bory Hospital a.s., Bratislava, Slovakia.
[‡]Service de médecine nucléaire, Hôpital Tenon, Assistance Publique-Hôpitaux de Paris, Paris, France.
[§]Service de radiologie, Hôpital Tenon, Assistance Publique-Hôpitaux de Paris, Paris, France.
[‖]Department of Nuclear Medicine, Clinique Sud Luxembourg, Arlon, Belgium.
[¶]Department of Nuclear medicine, Comenius University Bratislava and Bory Hospital a.s., Bratislava, Slovakia.
[**]Institut National des Sciences et Techniques Nucléaires (INSTN), Saclay, France.
Address reprint requests to Sona Balogova, MD, PhD, Department of Nuclear medicine, Comenius University Bratislava, St. Elisabeth Oncology Institute and Bory Hospital a.s., Ivana Kadlecika 2, 841 01, Bratislava, Slovakia. E-mail: Sona.balogova@fmed.uniba.sk
[#]Contributed equally to this work.

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Introduction

As it has been widely demonstrated, in patients with confirmed hyperparathyroidism (HPT) scheduled for surgical treatment, the preoperative imaging permits to optimize the operatory protocol of parathyroidectomy (PTX), in particular by selecting those patients who can benefit from minimally invasive PTX (MIPTX).[1] The MIPTX has the merit to shorten the operative time, incision length, and to reduce the operatory risks.[2]

According to a recent meta-analysis,[3] 81.4% of patients have 4 parathyroid glands (PTs) (two superior and two inferior); five or more PTs have been observed in 4.9% and 6.3% of healthy and HPT patients, respectively. The superior gland is located posterior to the upper pole or interpolar area of the thyroid gland, whereas the inferior gland is located near the lower pole of the thyroid gland. However, PTs may be found within a rather large area, exceeding the thyroid bed, which is both a challenge and a justification for preoperative imaging. Short embryonic course of superior PTs issued from the 4th pharyngeal pouch (P4) resutls in a relatively limited area of dispersal and in less than 1% of cases located above upper thyroid pole. Inversely, long embryonic course of inferior PTs issued from the 3rd pharyngeal pouch (P3) results in an extensive area of dispersal (from the angle of the mandible to pericardium) and in approximately 2% of cases, P3 PTs can be located above upper thyroid pole. The P4 PTs are located posteriorly to the plane of the recurrent laryngeal nerve within the tracheoesophageal groove, whereas the P3 PTs are located anteriorly to this plane. As a consequence, 15.9% of PTs are present in ectopic locations, with 11.6% in the neck: 3.6% in the retroesophageal/paraesophageal space, 2.4% in the thyroid gland, 2.1% in the carotid sheath, 2.0% in the thyrothymic ligament, 0.6% in the tracheoesophageal groove, and 1.0% in other locations (thyroid cartilage, retropharyngeal space, adjacent to hyoid bone). The majority of the 4.3% PTs in mediastinum are located in the thymus.[3]

With preoperative localization studies, the rate of PTX failure, in particular due to nonsuspected multiglandular or ectopic disease, has been profoundly decreased.[4]

For this imaging work-up to improve the guidance of surgery, the association of a high-resolution anatomic modality and a functional nuclear medicine modality has been recommended for a long time.[5]

In the 1980s, parathyroid gland scintigraphy was performed with ^{201}Tl-thallous-chloride[6] in combination with ^{99m}Tc-pertechnetate to subtract thyroid uptake as a dual-tracer method.[7] The success rate in operated patients was comparably good, reaching 92% in 24 patients who underwent subsequent PTX, but two of the 4 subcentimetre resected abnormal glands were missed at preoperative scintigraphy.[8] Furthermore, ^{201}Tl has poor physical characteristics as an imaging agent, due to suboptimal photon energy (69–81 keV). Additionally, it has a long physical half-life (73 h) and thus results in a nowadays unacceptably high whole-body radiation exposure. Therefore, ^{201}Tl is no longer recommended for parathyroid imaging.[9]

Since the end of the eighties, ^{99m}Tc-sestaMIBI (MIBI) scintigraphy,[10] has been routinely used as the functional imaging modality for HPT imaging, further improved by double phase study,[11] thyroid uptake subtraction with ^{99m}Tc-pertechnetate[12] or preferably with ^{123}I, [13] and subsequently single photon emission computed tomography (SPECT) and hybrid SPECT/X ray computed tomography (CT).

Another technique of functional imaging has emerged in nuclear medicine: positron emission tomography (PET) which yields images of a better resolution than SPECT and is routinely performed thanks to hybrid machines, associated with CT (PET/CT) or magnetic resonance imaging (PET/MR). After an early surge in 1964,[14] methionine labeled with ^{75}Se for localization of hyperfunctioning parathyroid glands (HFPTGs) using rectilinear scanners and then gamma-cameras had progressively been abandoned. But thirty years later, methionine labeled with ^{11}C has been proposed for PET imaging in this indication.[15]

However, evidence has been further provided that the performance of PET/CT with ^{11}C-methionine to detect abnormal PTs is inferior to that with a fluorinated analogue of choline, ^{18}F-fluorocholine (FCH),[16,17] which had been previously introduced as a PET imaging agent in search for HFPTG in 2014.[18,19] On this same year, ^{11}C-choline was reported as a PET tracer for localization of parathyroid adenoma in a series of 40 patients.[20] In a recent comparative study on 32 patients with negative first-line imaging, the sensitivity of PET/CT with ^{11}C-choline was superior to that with ^{11}C-methionine in localizing parathyroid adenomas.[21] Those authors also reported that, in 12 out of 14 patients in whom FCH PET/CT performed as part of first line imaging for pHPT was negative or inconclusive, ^{11}C-choline PET/CT could identify a lesion suspicious of a HFPTG, possibly in relation with differences in imaging protocols, consisting for ^{11}C-choline PET/CT in an uptake duration of 20 minutes and a scan duration of 10 minute.

^{11}C labeled radiopharmaceuticals have a very short half-life of 20 minutes, which results in a low radiation exposure of the patient but requires an on-site cyclotron for the production of ^{11}C, and a GMP radiopharmacy facility for the labeling of ^{11}C-choline, logistics that is not easy to implement and is currently available in very few PET centers. In contrast, FCH is widely available. Another fluorinated choline analogue with a slightly different chemical structure from FCH, ^{18}F-fluoroethylcholine (FEC), has been used for prostate cancer PET imaging, almost exclusively in Germany, but reported for HFPTG detection in one article only.[22]

Rationale for FCH PET/CT in the Imaging Work-Up of HPT

Choline and its analogue ^{18}F-Fluorocholine (FCH)

Choline is a quaternary ammonium base which is crucial for animals and plants as well as an important component of phospholipids in the cell membranes. All cells utilize choline as a precursor for the biosynthesis of

phospholipids, eg, phosphatidylcholine (lecithin), which are essential components of all membranes. After crossing the cell membrane by a carrier-mediated mechanism, choline is phosphorylated by choline kinase to phosphorylcholine which is converted to cytidine diphosphatecholine and subsequently incorporated into phosphatidylcholine, a component of the cell membrane.

The choline analogue FCH has been shown to closely follow the metabolism of choline. According to its first marketing authorization granted in 2010 in France, FCH is used for imaging in patients undergoing oncologic diagnostic procedures describing function or diseases where enhanced choline influx of specific organs or tissues is the diagnostic target.

The activity of choline kinase has been found to be up-regulated in malignant cells, providing a mechanism for the enhanced accumulation of radiolabelled choline by neoplasm. An increase in phospholipid-dependent choline kinase activity has also been observed in parathyroid (PT) adenoma arising from hypersecretion of parathyroid hormone (PTH).[23]

FCH has been used in Europe, in clinical trials and then as a registered radiopharmaceutical, for more than 20 years. During this period, FCH PET/CT has been widely used mainly in the detection of prostate and hepatocellular carcinoma.

FCH uptake by Hyperfunctioning Parathyroid Glands (HFPTG)

More than a decade ago, a few teams in Europe observed that HFPTGs took-up FCH, appearing as incidental hot foci on FCH PET/CT examinations performed for prostate cancer.[24-26] In several of these patients, unknown HPT was then researched and confirmed; some underwent PTX and histology confirmed that the FCH focus matched an HFPTG.

These findings motivated the research focused on clinical efficacy of FCH PET performed deliberately, in men and women, in search for HFPTGs.[18,19]

Ten years later, an important amount of bibliographic evidence documenting the clinical efficacy of FCH in preoperative localization of HFPTGs is available. Moreover, the acceptance of FCH in this indication by the scientific community is documented by the fact that FCH PET/CT is now explicitly recommended for the detection of abnormal PT(s) in HPT by the European Association of Nuclear Medicine (EANM) in its guideline on parathyroid imaging published in 2021 by Petranovič Ovčariček et al.[9] and by the inclusion of HPT in the list of indications in the marketing authorization of a commercial preparation of FCH in France in January 2024[27]. Apart from the analysis of published evidence, our seminar approach includes the practical aspects of FCH PET/CT performed for HPT, from indication to image interpretation, derived from the experience of our teams in this setting, over 12 years at hospital Tenon, Paris, France, and over 11 years at Bratislava, Slovakia.

Indication, Cost Effectiveness and Place of FCH PET in the Imaging Strategy of HPT

Primary (pHPT)

Presurgical Work-Up in Patients with pHPT

FCH PET is indicated in case of biochemically proven HPT (either pHPT or rHPT), above all as part of a presurgical work-up.

The clinical and biochemical elements on which the diagnosis has been suspected and further based have been detailed in a recent issue of the Seminars in Nuclear Medicine by the team in Lausanne,[28] in the 2021 version of the EANM practice guidelines for parathyroid imaging,[9] and in the Guidelines from the 5th International Workshop on pHPT;[29] hence they will not be further developed.

In patients with pHPT, FCH PET/CT has been suggested to be performed as a second-line imaging modality by several teams for further evaluation of patients with inconclusive or discrepant results of MIBI scintigraphy and/or SPECT/CT and neck ultrasonography (US)[18,19,30-39] in patients with expected orthotopic or ectopic HFPTG (Figs. 1A, 1B).

In a partial retrospective analysis of the series from Hôpital Tenon[40] including 323 FCH PET/CTs for pHPT and 78 for rHPT, the positivity rate of FCH PET/CT was 67% (CI: 56-76) in a subgroup of 96 FCH PET/CT examinations performed as the first line imaging modality vs 75% (CI: 70-80) in 305 FCH PET/CTs performed later in the work-up. The corresponding positivity rates of 37% (CI: 30-44) for MIBI and 47% (CI: 42- 52) for US were impacted negatively by the recruitment bias, patients being selected for FCH PET/CT in case of nonconclusive or discordant results of MIBI and US.

Broos et al.[41] also reported a retrospective study of FCH PET/CT as a first-line imaging method in 271 patients with pHPT; its positivity rate was 75%, the rate of correct detection was 96% patient-based and 90% lesion-based. In a more recent similar study, of 271 patients with overt pHPT, first-line FCH PET/CT showed sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of 99%, 91%, 100%, 80%, and 99%, respectively.[42]

In the APACH2 trial,[43] 57 patients with pHPT needing functional imaging before their initial PTX were randomized: 29 in the arm FCH PET/CT vs 28 in the arm MIBI SPECT/CT. The positivity rate of first-line examination was 24/29=83% for FCH vs 18/28=64% for MIBI, corresponding values for sensitivity being 82% (CI: 62-93) for FCH vs 63% (CI: 42-80) for MIBI. Calcemia was normal 1 month after positive first-line imaging guided MIPTX in 23 of 27 patients (85%) in the first-line FCH group vs 14 of 25 patients (56%) in the first-line MIBI group.

Despite those results, FCH PET is still performed only as a second line modality for HPT imaging in some nuclear medicine centers. The main arguments to select HPT patients for FCH PET on basis of the negative or discrepant results of MIBI scintigraphy or SPECT/CT are the lower availability of PET machines compared to gamma-cameras and the higher cost of FCH compared with MIBI. The argument of low PET

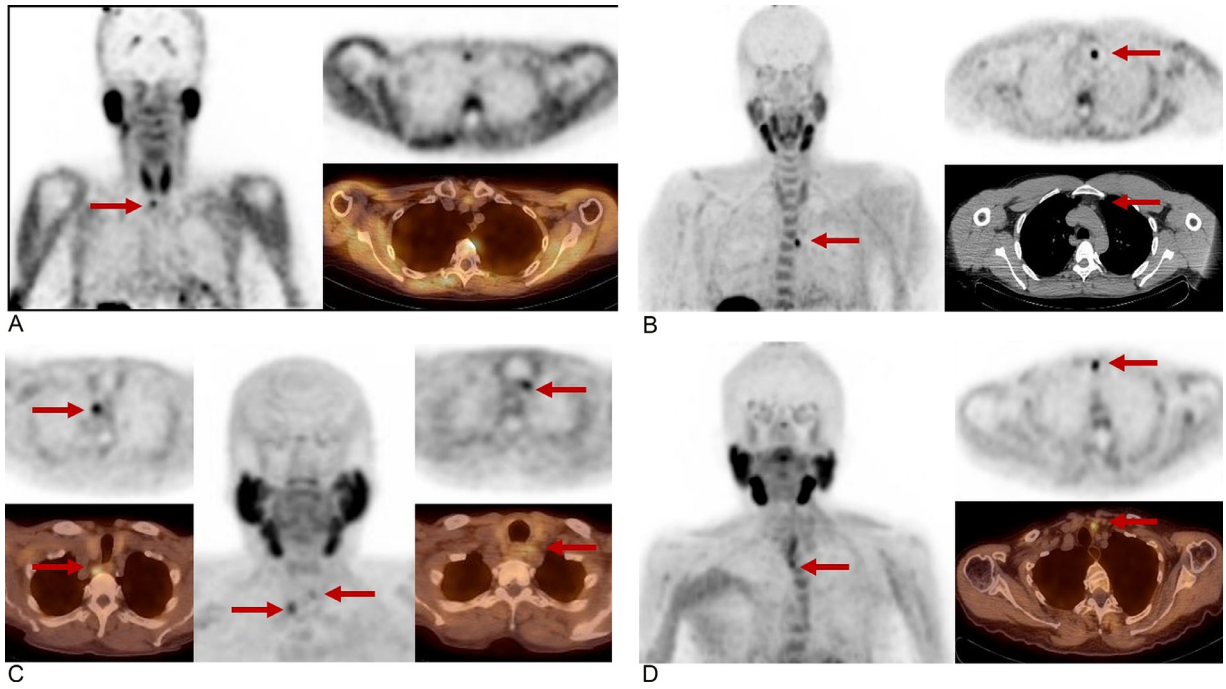


Figure 1 Successful localization of hyperfunctioning parathyroid gland(s) (arrow) by ^{18}F-fluorocholine (FCH) PET/CT in patients with biochemically confirmed primary hyperparathyroidism. (A) Right inferior hyperfunctioning parathyroid gland (HFPTG), SUVmax 2.05 detected after inconclusive standard imaging (ultrasound and parathyroid scintigraphy), (B) left inferior HFPTG detected in a patient with suspected ectopic HFPTG, SUVmax 7.13, (C) right inferior and left superior HFPTGs (SUVmax 3.86 and SUVmax 2.88) detected in patient with suspected multiple gland disease, or (D) left inferior HFPTG (SUVmax 4.76) detected in a patient with persistent pHPT after surgery. Maximum intensity projection, MIP, PET, PET/CT and CT, axial slices. Parathyroid adenoma was confirmed by histology in all cases

availability is less and less valid with the rapid development of PET in countries with nuclear medicine centers. Concerning the cost, recent studies have shown that, even if the activity of FCH per patient is still more expensive than that of MIBI, the procedure is cost-effective in relation with the better diagnostic performance of FCH PET compared to both MIBI and US. Yap et al.[44] developped a decision tree modelled patients who underwent PTX for pHPT using single preoperative localization modalities: FCH PET/CT, or 4D-contrast-enhanced CT (4D-CeCT), or US, or MIBI SPECT, in the health system of United States. All patients underwent either focused PTX or bilateral neck exploration, with associated cost ($) and clinical outcomes measured in quality-adjusted life-years gained. FCH PET/CT gained the most quality-adjusted life-years (23.9) and was the costliest ($2,096), with a total treatment cost of $11,245 or $470/quality-adjusted life-year gained. MIBI SPECT and US were dominated strategies.

In the context of the Dutch healthcare system, Van Mossel et al.[45] compared two strategies for patients suffering from pHPT: a preoperative FCH PET/CT-based one-stop-shop imaging vs FCH PET/CT only recommended after negative or inconclusive MIBI SPECT/CT. The simulated long-term health effects and costs were similar for both imaging strategies.

The strategy of FCH PET/CT as the single functional imaging modality is not only cost-effective in Europe and United States, it also has major advantages compared with MIBI SPECT/CT: a shorter mobilization of the patient and a lower radiation exposure[46], in particular if exposed to SPECT/CT followed by PET/CT, a better detection of abnormal PT including multiglandular disease (MGD) and hyperplastic HFPTG.

MGD is present in 15% to 20% of pHPT, which encompasses a high risk of recurrence after PTX if MIPTX is performed. In the partial analysis of the series from Hôpital Tenon, there was 29/167=17% of histologically proven MGD among 167 pHPT patients;[40] 21 of the 29 FCH PET/CTs (72%) have been indicated on basis of nonconclusive or discrepant results of MIBI and US. In the context of this large selection bias, patient-based sensitivity for MGD was 38% for FCH vs 0% with MIBI as explained by the predominance of the selective strategy, 38% of MGD appearing as a single abnormal focus on MIBI SPECT, with discordant US results. In those patients, a MIBI-based strategy would not prompt FCH PET/CT that actually detects additional abnormal PT. In contrast, MGD was expected and then better detected on FCH PET/CT in 88% of patients with rHPT, with a lesser selection bias (11 after MIBI out of 24 = 46%).[40] Concordant results were reported in short series. Four MGDs among 17 pHPT patients appeared as one single focus on scintigraphy in three cases, whereas FCH correctly localized six pathological PTs in three patients, and surgery was successful[37,47] (Fig. 1C). Of 15 MGDs, nine were recognized on FCH PET/CT vs 4 on MIBI scintigraphy.[48] The prospective study of Cuderman et al.[49] included 103 patients with pHPT who

underwent both FCH PET/CT and MIBI scintigraphy according to a comprehensive protocol combining SPECT/CT, thyroid subtraction and dual phase acquisition, avoiding the aforementioned selection bias of real-world series such as ours. On histology reports, 14 patients (14%) had MGD consisting in 4 dual adenomas and 31 hyperplastic glands. In this subgroup, FCH PET/CT had a sensitivity of 88% and specificity of 100%, whereas MIBI scintigraphy had a sensitivity of 44%. FCH PET/CT revealed MGD in six of 14 patients (43%) who were falsely classified as having a single HFPTG on MIBI scintigraphy.

The risk of selecting patient for FCH PET/CT on basis of nonconclusive results of MIBI scintigraphy or SPECT/CT was recently confirmed in a series of 64 patients with positive finding on MIBI scintigraphy. Subsequent FCH PET/CT identified nine HFPTGs not detected by MIBI scintigraphy in eight patients (12.5%), including 4 patients with MGD. Moreover, negative FCH PET/CT allowed the reassessment of eight false-positive results of scintigraphy diagnosis in seven patients (11%). Only one HFPTG in one patient was missed on FCH PET/CT and correctly identified by MIBI scintigraphy.[47]

Furthermore, the partial analysis of the series from Hôpital Tenon confirmed that FCH is able to detect not only adenomas but hyperplastic PTs as well, which are hardly localized with MIBI and US; for localizing 155 hyperplastic PTs, sensitivity of FCH PET/CT was 72% vs. 39% for US and 25% for MIBI when it was also performed.[40]

Therefore, first-line FCH PET/CT is particularly indicated in the clinical settings of HPT with a high prevalence of hyperplastic HFPTG: persistent or recurrent pHPT in relation with MGD, rHPT at initial imaging work-up, persistence or recurrence, and hereditary HPT, particularly multiple endocrine neoplasia type-1 (MEN1).

The preoperative serum PTH level might potentially be able to predict success of FCH PET imaging in pHPT, with higher lesion-to-background ratios being expected in patients with high serum PTH levels.[30,50,51] However, it was not possible to determine cut-off values of serum PTH or calcium levels permitting to identify subgroups of pHPT patients with a very high or a very low probability for a positive result of FCH PET. In patients with an evocative clinical context but basal serum PTH levels within the normal range, potentially associated with normocalcemia, the diagnosis of pHPT can be assessed by testing the response to an oral or intravenous calcium load, resulting in the absence of the normal decrease of PTH serum level.[52] In 2011, nonelevated basal serum PTH level was observed in 5.5-7% of pHPT patients undergoing PTX;[53,54] with a trend toward lower sensitivity of conventional preoperative imaging. In 50 pHPT patients with nonelevated PTH levels or calcemia reported by Seyedinia et al.,[42] first-line FCH PET/CT showed a patient-based sensitivity of 93% and a specificity of 75%. In a preliminary analysis of the series from Hôpital Tenon reported as an abstract, the sensitivity of FCH PET/CT was still high in pHPT with nonelevated serum PTH level and/or calcemia, 156/192=81% patient-based and 165/256=64% gland-based,[55] the sensitivity gap with "overt" pHPT being largest in case of normocalcemia. FCH PET/CT is thus indicated in this biochemical setting of "mild" pHPT.

Persistent or Recurrent HPT after Previous Parathyroidectomy

In case of persistent or recurrent HPT after PTX, the remaining abnormal PT(s) must be accurately identified before recommending reoperation, because of the high risk of complications (Fig. 1D). The partial analysis of the series from Hôpital Tenon[40] found for FCH PET/CT in patients suspicious for persistence or recurrence after a previous PTX a patient-based positivity rate of FCH of 42/54=78% and a gland-based sensitivity of 24/27=89% vs, in patients without previous PTX, 291/347=84% and 169/186=91%, respectively, no difference being significant. 4D-CeCT has been proposed in this aim, which may be integrated in FCH PET/4D-CeCT. In the study of Latge et al.,[56] 37 patients with persistent or recurrent pHPT underwent FCH PET/CT and 4D-CeCT. The positivity rate and sensitivity were 88% and 95% for FCH PET/CT vs 63% and 70% for 4D-CeCT; dynamic 4D-CeCT identified no additional PT missed by PET/CT, and the combination of the two techniques did not improve the detection rate or sensitivity.

Therefore, recurrent or persistent HPT after PTX is an indication for FCH PET/CT.

Suspicion, Staging or Restaging of Parathyroid Carcinoma

In rare cases, the persistence of pHPT after surgery can be caused by recurrent or metastatic parathyroid carcinoma, a rare malignant endocrine tumor. According to the "3+3 rule"[57] and a recent review,[58] malignant pHPT should be considered in case of serum PTH levels three to 10 times above the upper limit of normal, markedly elevated calcemia >3 mmol/L, lesion size >3 cm possibly palpable in the neck, inhomogeneous, hypoechoic and lobulated masses on US, severe symptoms of bone (osteitis fibrosa cystica) disease and renal disease (renal stones and nephrocalcinosis). Parathyroid carcinoma is prone to recurrence and metastasis, and postoperative reviews should be carried out routinely. FCH PET/CT imaging was reported as early as 2015 in a patient with recurrent parathyroid carcinoma and yielded a better detection than FDG PET/CT and various scintigraphic modalities.[59] Subsequent case reports confirmed that PET/CT imaging with FCH and/or FDG can detect lesions of (recurrent) parathyroid carcinoma[60,61,62] as well as synchronous recurrence of another malignancy.[60] FCH PET/CT is indicated in this setting as it can guide surgeons to perform selective metastasectomy, to control tumor load and hypercalcemia, along with concomitant use of the monoclonal antibody denosumab and diphosphonates, as needed.[63] However, liver metastases may be missed with PET, in relation with the accumulation of the radiopharmaceuticals in the liver. In three patients with recurrent parathyroid carcinoma[58] ^{11}C-choline and FDG PET/CT as well as MIBI showed lesions in the neck, but failed to identify liver metastases visualized on contrast enhanced CT or MRI.

A differential diagnosis in case of recurrent HPT with distant lesions is parathyromatosis in which several hyperfunctioning PT nodules are scattered. It is generally attributed to improper handling of the PTs during PTX; both pathologies may even be concomitant.[64]

Heritable HPT

Approximately 10% to 15% of pHPT consists of heritable forms with Multiple Endocrine Neoplasia type 1 (MEN1) being the most common heritable form, affecting 2% to 4% of patients with pHPT.

HPT is often the first manifestation of the syndromic forms of heritable pHPT, MEN types 1 and 4, and HPT-jaw tumor syndrome (HPT-JT).[65] Early diagnosis of these syndromic disorders is useful in planning the extent of surgery and establishing an optimal surveillance for recurrence of pHPT and the associated extraparathyroidal manifestations of these disorders, with the help of a patient-tailored imaging-work-up.

MEN type 1 (MEN1 previously Wermer's syndrome) is a rare genetic disorder that mainly affects the PTs, the pituitary gland, the pancreas and other components of the digestive tract. The French Guidelines on the management of MEN1 recommend to start biochemical screening for HPT at the age of 10 and then annually, followed by imaging if screening is positive and surgery is planned.[66] The pHPT in the context of MEN1 frequently consists in a MGD with small hyperplastic glands rather than adenomas, a pattern which is challenging for imaging modalities. Even though ^{68}Ga-DOTATOC, a ligand of the somatostatin receptors that targets most types of neuroendocrine neoplasia, may sometimes be taken-up by HFPTG, its detection rate is not sufficient to rule out their presence. In contrast, FCH PET/CT is now recommended in the French guidelines in this setting, before parathyroid surgery and in screening for ectopic PT. Compared to MIBI scintigraphy and/or SPECT/CT, FCH PET/CT provides with additional information regarding the number of pathologic PT(s) and their localization in MEN1.[67,68]

In MEN type 2 (MEN2 previously Sipple's syndrome), medullary thyroid cancer (MTC), pheochromocytoma, and pHPT can be associated, but pHPT is rarer in MEN2 than in MEN1 and the results of PET/CT with FCH have not been reported yet, in contrast with the recognized utility of ^{18}F-fluorodopa to localize MTC.[67-70,84]

MEN type-3 (formerly MEN2B) does not involve pHPT. MEN type-4 (MEN4) is caused by a CDKN1B germline mutation first described in 2006. Its estimated prevalence is less than one per million. It most frequently affects women around 50 years of age; pHPT as a uniglandular disease is the leading pathology;[71] the single reported case with FCH PET/CT was interpreted as negative[68] but a hyperplastic PT was resected.

MEN type-5 (MEN5) has been recently identified, in relation with germline MAX variant; pHPT may be present among various endocrine disorders, of which the localization of abnormal PTs with FCH PET/CT has not been reported yet.

HPT-jaw tumor syndrome (HPT-JT) is related to a pathogenic variant of cell division cycle 73 (CDC73).[72] Jaw tumors may be found only in approximately one third of cases, while the most common, and sometimes the only feature of HPT-JT, is primary pHPT. HPT-JT is associated with a higher prevalence of PT atypical adenomas and carcinomas than in other heritable pHPT in which most PT tumors are benign. For the moment, FDG PET/CT[73] and MIBI SPECT[74] have been the only functional imaging modalities reported for the detection of abnormal PTs in HPT-JT.

Familial hypocalcemic hypercalciuria (FHH) is the most frequent nonsyndromic heritable HPT. In general, patients with FHH should not undergo PTX as it would not correct the hypercalcemia (unless the PTX were total).[65] Consequently, indication for imaging appears limited in FHH.

Renal HPT at Initial Imaging Work-Up, Persistence or Recurrence

Renal HPT (rHPT) alone is not an indication for imaging and subsequent PTX without other findings. In rHPT, the pattern of secondary HPT (sHPT) is expected: several foci corresponding to MGD of hyperplastic PTs. However, in our experience, HPT in mild or moderate chronic kidney disease (CKD) with a moderate increase in PTH serum level is the most frequently due to pHPT,[40] an association that is not rare in elderly people (Fig. 2).

Tertiary HPT (tHPT) consisting of autonomous secretion of PTH with persistent hypercalcemia despite resolution of the cause of sHPT may also be present, mainly after renal transplantation. PTX is an option, particularly in case of symptomatic hypercalcemia and/or to prevent or palliate the consequences of rHPT in CKD patients, eg, cognitive decline.[75] PTX can be expected to improve prognosis of HPT in kidney transplant recipients that negatively impacts allograft and patient survival rates.[76] A choice between total, subtotal or limited PTX must be made.[77] The preoperative imaging before a first PTX for rHPT remains controversial because bilateral neck exploration is usually needed for identification of all abnormal PTs. Moreover, accurate preoperative localization of abnormal PTs can guide the surgeon for faster and more appropriate intervention, especially in high-risk patients with renal transplant.

Imaging with FCH PET/CT has been proposed[78,79] and shown to be particularly useful for the detection of the most active HFPTG, of an abnormal congenital number of PTs (3 or more than 4), or of ectopic HFPTG(s).

Conclusion on the Indications and Place in the Imaging Strategy of FCH PET/CT

Our team, as well as others,[41,42,80,122] recommend that FCH PET/CT will be indicated, in pHPT and in all other types of HPT if considering a surgical option, as the front line of functional modalities in the sequence of presurgical imaging. If the availability of FCH PET/CT is limited in a center, the priority should be given to patients with a high likelihood of

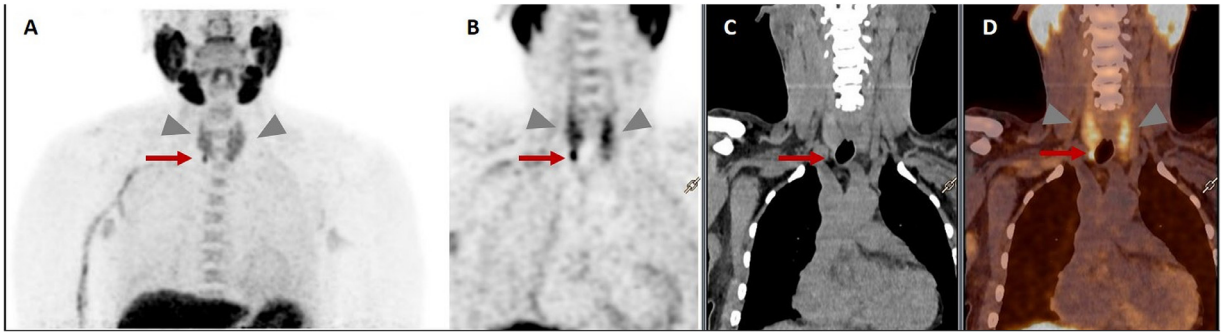


Figure 2 FCH PET/CT was performed in the context of hypercalcemia (2.65 mmol/l) and elevated serum parathyroid hormone (PTH) level (74 ng/L) in a 56-year-old woman with chronic kidney disease (CKD) grade G3a (glomerular filtration rate 52 mL/min/1.73 m^2). A focus corresponding to right inferior parathyroid gland (RP3) was detected, SUVmax 7.13 (arrow) and confirmed by histology as 7 mm parathyroid adenoma. A rapid normalization of calcemia and serum PTH level was observed after surgery and the occurrence of pHPT in a CKD patient was concluded. Diffuse moderate FCH uptake by thyroid gland, SUVmax 4.88 (arrow head) in relation with chronic autoimmune thyroiditis. (A) MIP, (B) PET, (C) CT and (D) PET/CT, coronal slices.

MIBI scintigraphy or SPECT/CT failure due to expected hyperplastic PT, as in heritable HPT or rHPT, or in recurrent pHPT.

Practice of ^{18}F-Fluorocholine PET in Search for Hyperfunctioning Parathyroid Glands (HFPTG)

Patient Preparation

No particular patient preparation is needed before administration of FCH.

As for most PET examinations, patients should drink adequately and urinate as often as possible, before and after the examination to reduce radiation exposure. In order to avoid a high uptake of the tracer at the muscular level, it is recommended to avoid any significant physical activity before the examination and between the injection and the examination.

As choline is a dietary component which is found in foodstuff and dietary supplements, concomitant intake of choline may compete with cellular uptake of FCH in target tissues, with a potential risk of false negative PET results. Therefore, on empirical ground, it was initially recommended that patients fast for at least 4h before the FCH administration of FCH. Based on a case report,[81] some teams recommend discontinuation of colchicine for 48h, if applicable. Those recommendations no longer appear in the marketing authorization of FCH revised to include HPT.[27]

In the absence of intraindividual comparative data, no detectable impact of cinacalcet treatment on diagnostic performance of FCH in preoperative localization of HFPTG have been evidenced.[33,41,47,56,82-84] The discontinuation of a justified and effective cinacalcet treatment seems not to be necessary prior FCH PET imaging for localization of HFPTG.

Fine needle aspiration (FNA) for cytology[85] may cause local inflammation or even hematoma and should not be performed on the days prior to FCH PET. It is recommended to schedule FNA after FCH PET, which may contribute to FNA targeting or lead to revise its indication.

FCH Posology for PET

According to majority of studies in a series of patients, the activity of FCH administered for localization of HFPTG ranged between 1.5 and 4 MBq/kg of body mass or between 100 and 300 MBq.[86] Those values for injected activity of FCH are in line with current recommendations for parathyroid imaging: 1.5 to 3.2 MBq/kg of body mass or 100-300 MBq,[9] or 140 to 280 MBq for a body mass of 70 kg, according to its marketing authorization.[27]

In all cases, the administered activity has to be adapted according to the type and the generation of the imaging machine: PET alone (not recommended) or PET/CT or PET/MRI.

FCH PET/CT Image Acquisition Protocol

Various FCH PET or PET/CT acquisition protocols have been proposed for localization of HFPTG.

- Dynamic acquisition:
  - up to 20 minute after administration of FCH, either without[18,33,79,87-90] or with a late static acquisition of images 60 minute after administration of FCH.[33]
  - Static dual time point acquisition:
  - 2-5 minute and 50-90 minute after administration of FCH[19,41,46,48-50,91-97]
  - 10-15 minute and 45-60 minute after administration of FCH[35,51,94,98]
  - 60 minute and 120 minute after administration of FCH[99]
  - 60 and 90 minute after administration of FCH[100]
  - Static single point acquisition:
  - 30 minute after administration of FCH[32,82,84]
  - 45-60 minute after administration of FCH[31,34,38,39,47,56,83,101-107]
  - 10-50 minute after administration of FCH[31,36,38,40,67,68,104,108-110]

Standardization of the FCH PET imaging protocol may be expected in future, according to the current EANM guideline

on parathyroid imaging which recommends to perform either a dual acquisition consisting in an early acquisition of images 5 minute after administration of FCH, as some lesions may show uptake in the early phase only, and a delayed acquisition 1 hour after administration of FCH, or one acquisition 20 minute after injection of FCH completed, in case of a negative or equivocal result, with a delayed image acquisition.[9] The current SmPC of the marketing authorization of FCH considers those two options for the imaging protocol.[27] We initially performed FCH PET/CT only as a second line examination in HPT (2012-2016); at that time, our imaging protocol consisted in a dynamic acquisition followed by whole-body scan; but in 2017 we proposed FCH PET/CT as the first-line functional imaging modality and we opted for a static acquisition at 20 minute with an optional second static acquisition at 60 minute, both on a field of view (FOV) dedicated to HFPTG detection.

This FOV can be limited from the nose, below the eye lenses, to the chest down to the base of the heart (Fig. 2) as for SPECT/CT, to obtain a low radiation exposure from CT. But thanks to the more rapid acquisition with PET than with SPECT, it may easily be extended, on a case by case basis, to the whole head[26] (Fig. 1) or to the whole torso or even the whole-body according to the patient's history (neoplasia, skeletal disease, infection...) or incidental findings.[9] Information about a previous cervical surgery is important for the determination of the FOV, as reimplantation of parathyroid tissue in the forearm[111] or in a cervical muscle may have been performed, which may become a culprit HFPTG.

To avoid beam-hardening artifacts on PET/CT fusion images in the cervical region, the arms of the patient should not be placed over the head but along the torso (Fig. 1-6).

The duration of image acquisition depends on the extension of the FOV and on the speed of the translation of the examination bed, either step by step or continuous. The optimal translation speed of the bed is chosen according to the generation and characteristics of the PET machine, the actual injected activity and the clinical status of the patient (pain, claustrophobia, ...) and a general recommendation concerning the duration of the image acquisition is not possible. A new generation of PET machines is becoming available with a long axial FOV,[112] allowing the FCH PET/CT acquisition to be performed without motion of the bed, and to reduce both the injected activity and the duration of the examination. Currently no application of FCH with long-axial FOV PET to human HPT has been published.

Safety Profile of FCH, Dosimetry and Use in Special Populations

During more than 20-year experience with use of FCH in adult patients of all categories of age, including patients with renal of hepatic impairment, and in few pediatric reported cases, no serious adverse reactions related with use of FCH have been reported, permitting to conclude to its highly favorable benefit/risk profile. The acquisition of images and the whole FCH PET/CT procedure are shorter than with conventional planar scintigraphy or SPECT/CT and is well tolerated by patients.

From dosimetry point of view, according to the fourth addendum to ICRP (International Commission on Radiological Protection) Publication 53 of May 24th, 2013, the effective dose per activity unit is 0.020 mSv/MBq of FCH in adults. The effective dose resulting from an administration of 280 MBq of FCH is about 5.6 mSv. In comparison with planar scintigraphy or dual phase MIBI SPECT/CT, as reported by Rep et al.,[46] the highest radiation exposure was caused by conventional planar subtraction scintigraphy (7.4 mSv), followed by dual-phase MIBI SPECT/CT (6.8 mSv). The radiation exposure was the lowest for dual-phase FCH PET/CT imaging (2.8 mSv). The added CT component for both hybrid approaches (PET/CT and SPECT/CT) generates a limited additional radiation exposure (1.4 mSv for MIBI SPECT/CT, adding 26% to overall exposure; 0.8 mSv for FCH PET/CT, adding 42% to overall exposure). However, it should be noted that, in this study, the median injected activity of FCH was only 99.2 MBq (range 88.0-149.4), at the lower end of the interval of recommended activity[9] or even lower,[27] whereas it was 603.1 MBq (range 535.8-671.3) for MIBI, around the middle of the corresponding interval of recommended activity.[9] This low FCH injected activity, which may become the reference in future as the imaging performance of PET/CT machine improves, explains a low radiation exposure. In conclusion, the radiation exposure with FCH PET/CT is clearly not greater than with MIBI SPECT/CT.

After injection of FCH, close contact of the patient with young children should be avoided for 12 hours.[27]

FCH PET in paediatric population has initially been reported mainly in oncological indications.[113] Currently the use of FCH in localising HFPG in paediatric population is considered as safe and proposed as a method of choice after US.[9,46]

Women are affected twice as often as men by pHPT which is the most common endocrine disorder after diabetes and thyroid disease. Moreover, 25% of pHPT are diagnosed in childbearing age. In case of pHTP during pregnancy, the maternal complications occur in approximately 67% of cases, including nephrolithiasis (24%-36%), bone disease (13%-19%), pancreatitis (7%-13%), (pre)eclampsia (25%) and spontaneous abortion, hyperemesis, muscle weakness, confusion, and hypercalcaemic crisis. Foetal complications of pHPT occur in 80% of cases including postpartum hypocalcemia (50%) or even neonatal death (27%-31%).[114] It appears that, with higher awareness of pHPT and its impact on maternal and foetal morbidity and mortality, there may be more evidence to support PTX regardless of gestational age, particularly for pregnant women in the third trimester,[114] highlighting the importance of accurate preoperative localising of abnormal PT(s). The choice between medical or surgical treatment must be based on assessment of the risks by obstetricians and endocrinologists, with the help of imaging to optimize a potential surgical intervention. In this context, radiation-free US is the front-line imaging modality. When preoperative US fails to localize an abnormal PT,

functional nuclear medicine imaging can be performed according to the technique preferred by the nuclear medicine physician.[115] The choice of the imaging modality and protocol is therefore essentially based on three elements in a pregnant woman: reduction of radiation burden of the foetal thyroid and of whole-body as low as reasonably achievable, compliance with approved indications, and ensure the most sensitive imaging possible. This decision must be based on multidisciplinary consultation.[116]

Nevertheless, as the experience with administrating FCH to a pregnant woman is missing, according to its marketing authorization[27], FCH is currently contraindicated during pregnancy, whereas FDG, that has been reported to be used to localize the recurrence of a parathyroid adenocarcinoma during pregnancy[117] or MIBI[116] are not contraindicated, despite a similar dosimetry profile. A case report illustrates the potential interest of pre-PTX imaging with FCH, the most sensitive modality, in this context: in a 40-year-old patient, a bilateral neck exploration with PTX during the second trimester of pregnancy was unsuccessful and the patient remained hypercalcemic. Postpartum imaging assessment with MIBI scintigraphy could not supply conclusive diagnostic results, whereas FCH PET/CT provided the accurate localization of an ectopic parathyroid adenoma in the anterior mediastinum, which was successfully resected by a thoracoscopic approach.[118]

After injection of FCH in a lactating woman, breastfeeding should be interrupted for 12 hours and milk produced during this period should be eliminated.[27]

Interpreting and Reporting FCH PET/CT

A request for FCH PET in search for HFPTG must be submitted to a nuclear medicine physician. It should provide sufficient information to assess the indication and to optimize the acquisition protocol of the examination, as well as to interpret the images. This include relevant events of patient's medical history (such as thyroid or parathyroid dysfunction, cervical or thoracic surgery, chronic renal disease, kidney stones, fractures, digestive pathology, treatment with lithium, thyroxine or calcimimetics, any malignancy ...) and data about the current episode (biology, cervical imaging ...).

The reading of PET/CT to localize HFPTG usually starts with visualizing maximum intensity projections (MIP) in search for foci adjacent to the posterior face of thyroid gland and for evocative ectopic foci. The analysis of attenuation-corrected slices in the three planes with and without CT fusion is necessary in all cases, to precise the anatomical landmarking and the size of CT images matching abnormal FCH foci. The analysis of nonattenuation-corrected images may sometimes be useful in the case of artifacts on CT or of incidental foci in the lungs. For the neck region, the soft-tissue CT window should be used. A reading of PET and PET/CT fused images of organs or structures out of the neck but included in the whole FOV, should not be omitted. The soft-tissue CT window is adapted to the mediastinum and the breast (and the liver in the absence of a specific window), but other CT windows are recommended for lung and bone (and liver if this window is available).[9]

In the FOV extending from the nose down to the base of the heart, FCH physiologically accumulates in the salivary glands, the liver, and usually with a lower intensity in the thyroid gland and the bone marrow.[119] The interpretation of FCH PET/CT in children or adolescents referred for localization of HFPTG must consider the particularities of biodistribution of FCH at that age, particularly the variable physiologic uptake by thymus and eventual FCH uptake by brown adipose tissue[120] or growth plates (Figs. 3A, 3B).

Orthotopic HFPTG

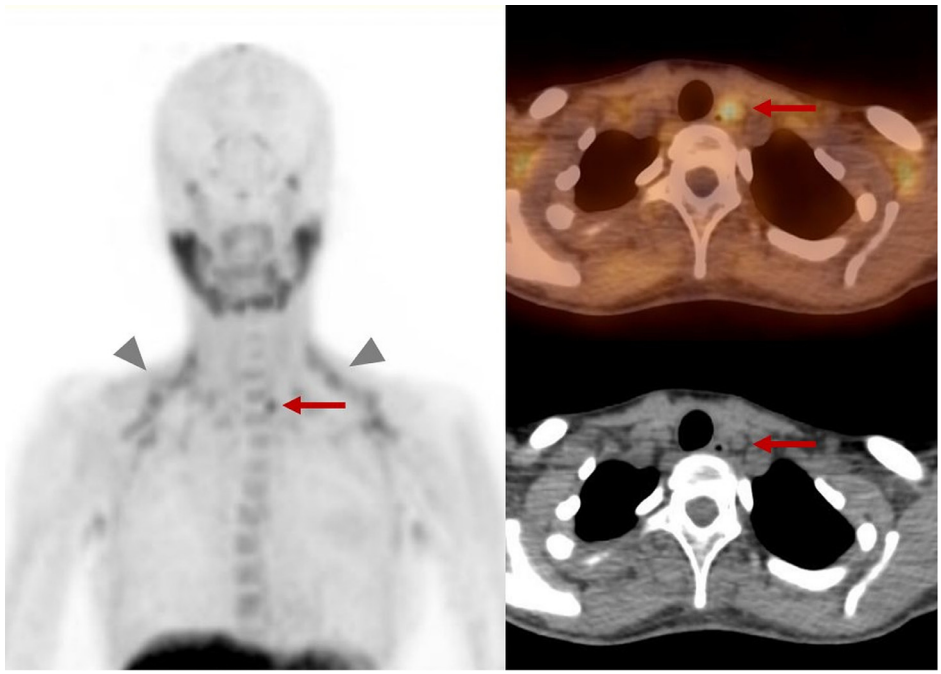
Focal accumulation of radiopharmaceutical in a nodule behind the thyroid gland is the most typical FCH PET/CT image for HFPTG. But all foci with an increased tracer uptake compared with the adjacent background located in an area from the upper neck to the base of the heart should be considered as potentially corresponding to a HFPTG. As a complement to visual assessment, the measurement of SUVmax of the focus, its uptake ratio to the liver or the thyroid may reinforce the confidence in detecting a HFPTG.[79,87,121-123] Compared with the thyroid parenchyma, a greater SUVmax of the focus and a hypodense character of the corresponding lesion on CT are further positive arguments for HFPTG, but they may be lacking, in particular for small-sized foci or in case of thyroid pathology. If dual-time point acquisition has been performed, the persistence and reinforcement of uptake intensity in the late acquired images (related to clearance from healthy structures) of foci visible but equivocal on the early acquired images is a further argument for a HFPTG, but the disappearance on the late acquired images of a focus that was equivocal on early acquired images could be due to an actual HFPTG with rapid FCH clearance.

Ectopic PTs

The three most common ectopic locations of PT are the thymus, para- or retroesophageal space, and thyroid.[3]

Intrathyroidal HFPTG

Intrathyroidal HFPTGs are usually FCH-positive; the main diagnostic problem is to identify the FCH focus as PT, since thyroid anomalies are much more frequent in HPT patients and may take-up FCH. In pHPT, favoring arguments can be a lack of evocative of extrathyroidal FCH focus, recurrence after PTX, matching a low density structure on CT or a profoundly hypoechoic solid nodule on US with well-defined border, abundant blood flow and polar feeding vessels originating from the superior or inferior thyroid artery.[124,125] But the presence of an extrathyroidal FCH focus does not rule out an intrathyroidal HFPTG that can be part of a MGD. The frequency of intrathyroidal PT in pHPT was 17/808=2.1% in



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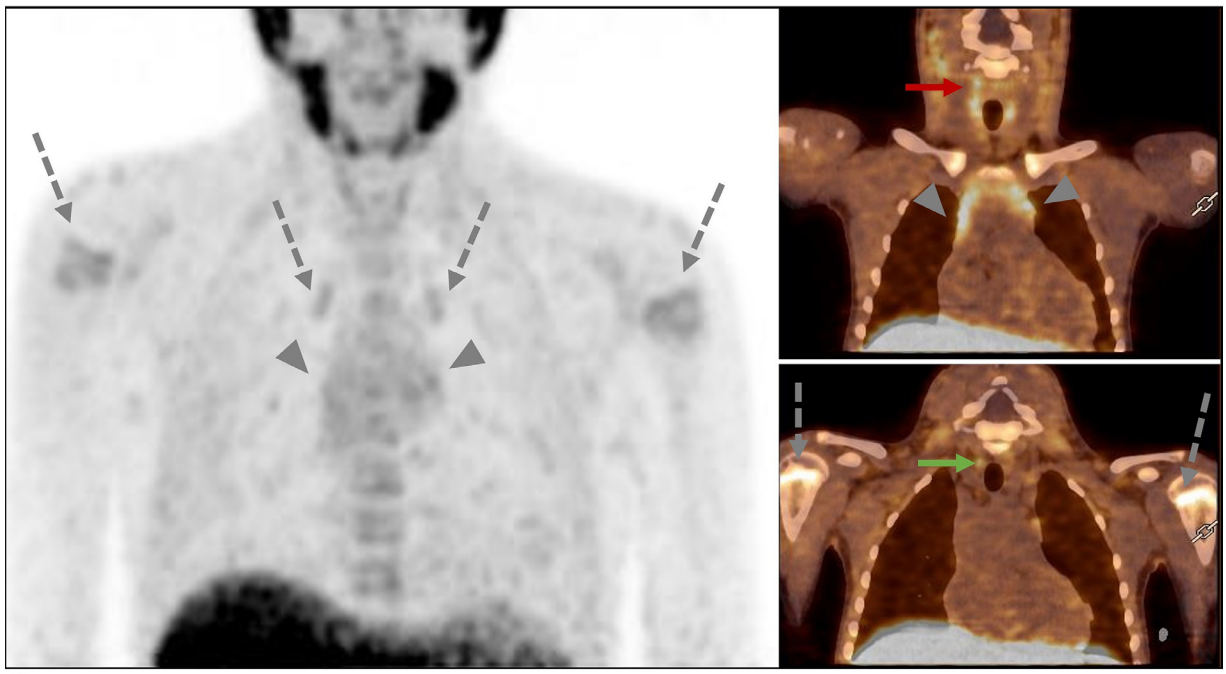

B

Figure 3 (A) FCH uptake by brown fat SUVmax 4.07 (arrowheads) in 14 year-old girl with pHPT (calcemia 2.96mmol/L, serum parathyroid hormone level 168 ng/L (normal level<60 ng/L). Left inferior parathyroid gland (LP3) was detected SUVmax 4.07 (arrow), and confirmed as adenoma by histology. No recurrence of HPT was observed during follow-up of 6 months. (B) FCH uptake by thymus (arrowheads) and growth plates in both humeri (dashed arrows) in 11 year-old girl with primary hyperparathyroidism (calcemia 3.2 mmol/L, serum parathyroid hormone level 63 ng/L (normal level <34 ng/L). Right superior, SUVmax 2.1 (red arrow) and inferior SUVmax 2.0 (green arrow) parathyroid glands (RP4 and RP3) were detected (arrows) and confirmed as adenomas by histology. No recurrence of HPT was observed during follow-up of 6 months.

one recent study.[126] No series are currently available concerning this detection with FCH PET, the sparce reported cases being FCH-positive[41,79,94] whereas 2/3 were MIBI-negative in the study of Xue et al.[94]

Cervical Ectopic PTs

The frequency of PT in the carotid sheath is around 2%. Libé et al.[127] reported a highly vascularized hypoechoic solid lesion on US between the carotid artery and the jugular vein,

which was suspicious at cytology for a carotid body paraganglioma; a high serum PTH level prompted FCH PET/CT that showed an intense FCH uptake (SUVmax=15) and an ectopic PT adenoma was confirmed.

Intrathoracic PTs

The study of Dream et al.[128] included 2291 patients who underwent PTX for HPT by one surgeon, 158 (7%) were identified to have an ectopic intrathymic PT, of which 42% were hyperplastic HFPTGs. To date, no data on the detection of intrathymic HFPTGs with FCH PET have been reported.

Erroneous or Nonconclusive Interpretation

False-negative results may result from inadequate technical options such as too low injected activity, too late image acquisition, too short acquisition duration, too restricted FOV, in particular in case of recurrence after PTX, to presence of metal induced artefacts on hybrid PET/CT images. Even though the uptake of FCH by healthy thyroid tissue is usually moderate (Figs. 1BCD, 3-6), it is diffusely intense in case of thyroiditis Fig. 4 or of Graves' disease, making it difficult to detect HFPTG(s) adjacent to the thyroid gland. Similarly, multiple FCH-positive lymph nodes in the neck or the median part of the upper mediastinum may mask the actual HFPTG foci and lead to false-negative results. FCH foci corresponding to aforementioned ectopic HFPTG(s) may be overlooked or attributed to other origins, a false-negative result for culprit PT(s).

False negative results may also be in relation wild mild HPT or with the particulars of HFPTG, such as small size, PT hyperplasia, MGD overlooked since one intense FCH focus was evident ... These situations will be discussed below about the FCH diagnostic performance.

As FCH is a nonspecific tracer of increased intracellular influx of choline, several malignant and nonmalignant lesions may show increased FCH uptake on PET/CT. Concerning the false-positive results, we will distinguish (somehow arbitrarily but in order to organize a long enumeration) "pitfalls," that are uncertain or inappropriate interpretation as HFPTG of foci of nonpathologic origin or of nature that will require no consequence on the patient's management, from "incidental findings" that may or should impact on patient's management.

Pitfalls

Accessory thyroid tissue or small remnants in case of partial or total thyroidectomy are likely to take-up FCH and appear as foci on PET, leading to a false-positive result. This pitfall may be avoided by referring the patient to thyroid sodium ^{123}I-iodine scintigraphy (as ^{124}I for PET imaging is hardly available), providing no injection of iodine CT contrast agent has been recently performed and a possible thyroid hormone substitution has been paused.

The most frequent nonspecific FCH uptake outside of the thyroid bed is due to inflammatory and reactive lymph nodes.[119] They are usually easy to differentiate from HFPTG (s) just based on their topographic distribution, generally out of the area of extension of ectopic PT, the most frequent locations being the axilla and the pulmonary hilum.

In 2007, some of us reported a "washout" phenomenon: FCH uptake within benign lymph nodes, including cervical lymph nodes, observed during the first 5 minute of injection diminishes rapidly by 20 minute.[129] Nevertheless, residual FCH uptake by reactive lymph nodes is still frequent, even on delayed imaging.

Incidental Findings

Diffuse Intense Thyroid Uptake of FCH

In 19 of a series of 107 patients (18%) planned for thyroid surgery, chronic autoimmune thyroiditis (CAT) was evidenced. Of these, 13 (68%) displayed an increased and diffuse FCH thyroid uptake correlated with pathology and thyroperoxidase antibodies titers.[130] This uptake pattern was highly predictive of CAT.

Thyroid Nodules

Inside the thyroid area, the post-thyroidectomy remnants may create a potential interpretation pitfall, but the most frequent and main interpretation problem is a focal FCH uptake inside the thyroid gland. It corresponds in most cases to a benign thyroid nodule (Fig. 4), in particular oxyphil adenomas that are very FCH avid,[131,132] or more rarely to a thyroid malignancy,[133] but may also correspond to an intrathyroidal HFPTG as aforementioned.[41,79,94]

As thyroid anomalies are frequent in HPT patients, the potential of dual-time-point PET/CT acquisition in characterising centimetre thyroid nodules as benign or malignant has been tested. In the pilot study of Bani et al.[134] on 27 pHPT patients, FCH early uptake ratio and washout index were significantly higher in malignant lesions than in benign thyroid nodules. On the same year, Ciappuccini et al.[131] gathered and analysed with a similar goal a larger prospective series of 107 patients. It was confirmed that FCH PET/CT offers high negative predictive value (NPV = 96% 20 minute after injection) to reliably exclude cancer in FCH-negative indeterminate thyroid nodules, but suffers from low positive predictive value (PPV= 29%), particularly in those lesions with oncocytic cytology. There was no difference in the predictive values between acquisitions at 20 minute or 60 minute postinjection. Broos et al.[90] found a more rapid clearance of FCH from thyroid anomalies than from PTs.

Coexistence of PT adenoma with papillary thyroid carcinoma (PTC), both detected on FCH but also on FDG PET/CT, was reported.[135] FCH PET/CT may also reveal collision tumor composed of both PTC and PT carcinoma within one thyroid nodule, PTC metastases being found in lymph nodes.[136]

In 2022, Broos et al.[137] reviewed 388 FCH PET/CTs for HPT and retrieved 247 incidental findings in 226 patients (58%): 82 FCH-positive findings with corresponding

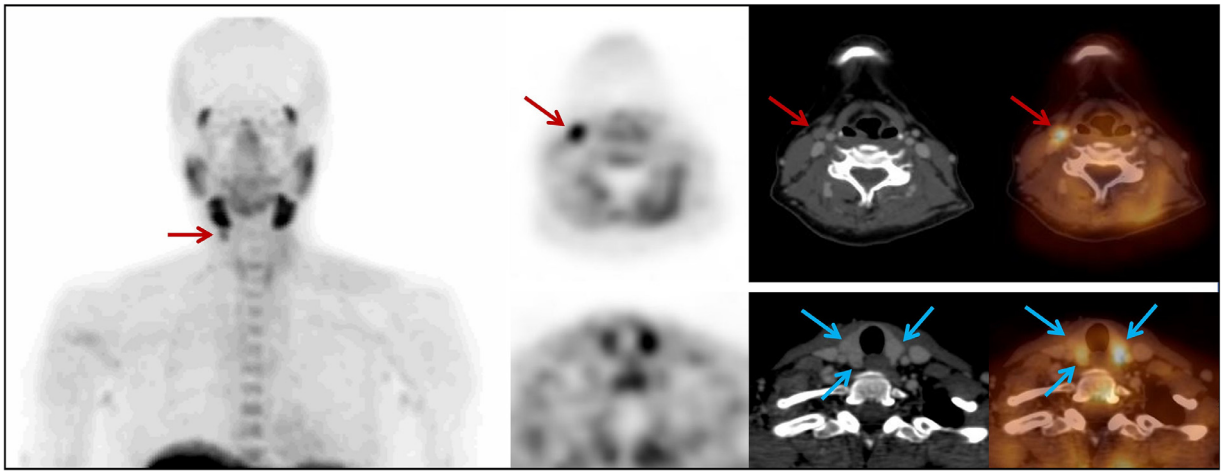

Figure 4 ^{18}F-fluorocholine PET/CT in 36 year-old asymptomatic woman with mild elevation of serum parathyroid hormone level, mild hypercalcemia, and low serum vitamin D3 levels. Uptake of FCH by reactive cervical lymph node on the right side of the neck confirmed by cytology (SUVmax 3.5), potentially mimicking ectopic nondescended right inferior HFPTG, and by thyroid nodules (SUVmax 2.3 in the right lobe and 2.7 in the left lobe). Localization of lesions, their pattern on low dose CT image and biological context were helpful in yielding a correct interpretation of images. Moreover, higher significantly increased serum parathyroid hormone level would be expected in case of FCH avid hyperfunctioning parathyroid gland of 20mm in largest diameter, which was not the case of this patient.

pathology on low-dose CT, 16 without CT substrate, and 149 FCH-negative abnormalities on the low-dose CT. In 20 patients, a solitary thyroid nodule was detected; in 6 of the 10 FCH-positive nodules, histology was acquired showing one PTC, one metastasis of renal cell carcinoma, and 4 benign aetiologies (colloid cysts and hyperplastic nodules). Multinodular goitre with irregular FCH uptake was described in 35 patients and a diffusely increased uptake was seen in five patients (two hyperthyroid patients, two hypothyroid patients, and 1 patient with normal thyroid function).

Further characterization of FCH thyroid foci may be obtained by matching the FCH PET/CT images with those of thyroid scintigraphy (best with sodium ^{123}I-iodine), similarly to the dual isotope protocols for MIBI scintigraphy. Maximum intensity projection (MIP) and coronal slices of PET/CT are particularly useful in this aim, to check how PET/CT foci match with the location and the iodine uptake by FCH-positive thyroid nodules: an intense ^{123}I uptake is likely to correspond to a thyroid adenoma, whereas a ^{123}I-cold nodule can correspond to a thyroid adenoma but also to an adenocarcinoma or to an intrathyroidal HFPTG as aforementioned.

Thymus

In three adult patients with prostate cancer, Calabria et al.[119] documented abnormal FCH uptake in the thymus corresponding to thymomas.

Lymph Nodes

FCH-positive lymph nodes may be observed as a reactive condition in case of infection or inflammation in the area of head and neck (Fig. 4) or may reveal clinically significant inflammatory conditions, such as sarcoidosis which is frequently presenting with hypercalcemia and may be associated with HPT; in typical cases, the symmetrical distribution of the mediastinal foci will orientate the diagnosis. The case was reported of a 63−year-old woman with persistent hypercalcaemia, osteoporosis, a history of sarcoidosis and suspected pHPT,[138] a lower left HFPTG was highly likely on FCH PET. But the results were judged inconclusive because of metabolically active granulomas resulting in FCH foci in the right mediastinal, supraclavicular, pectoral and axillary lymph nodes with comparable SUVmax. At focused PTX under general anaesthesia, a lower left PT adenoma was confirmed and removed.

Nonthyroidal Malignancies

In the aforementioned study by Broos et al.,[137] nonthyroidal cancer was detected in 10/388 patients (2.6%) harbouring 13 malignant incidental foci, including three metastases and 10 primary malignancies: breast carcinoma (n=7), lung carcinoma (n=2), and one skin melanoma (which had been reported earlier by the same team[139]).

Attention should especially be paid to breast lesions, as women are typically over-represented in HPT, particularly in case of MEN1, which is linked with an enhanced risk of breast cancer: two cases of 25 women in our dedicated study.[68]

Diffuse Skeletal FCH Uptake

A FCH SUVmax of the HFPTG greater than 4.4 could be predictive of disease severity in terms of reduced values of bone mineral densitometry.[39] In a patient referred to our center for FCH PET/CT, a large focus evocative of HFPTG was evidenced, and furthermore an intense and diffuse FCH uptake by the axial and peripheral skeleton was also reported; after the removal of an abnormal PT, a severe and prolonged hungry bone syndrome (HBS) was observed.[140] HBS occurs on average 3 days (1-7) after PTX, most frequently for rHPT, in relation with severe hypocalcemia and nonlow serum PTH,

which differentiates HBS from hypoparathyroidism, requiring high doses of calcium and active metabolites of vitamin D.[141]

A diffuse increase of FCH bone uptake on preoperatory PET/CT could be a predictive factor for HBS, various others being proposed such as high serum level of bone alkaline phosphatase and of PTH in a context of pHPT. FCH uptake by the cortical bone should be distinguished on CT-fused images from the metabolic activation of bone marrow, in relation with erythropoietin treatment[142] observed in two haemodialyzed patients of the series from Hôpital Tenon, or in another haemodialyzed patient, with myelofibrosis, a previously reported association.[143]

Focal Skeletal FCH Uptake

Brown tumors (or osteitis fibrosa cystica) are a bone complication of severe HPT, in relation with long-standing, elevated PTH-induced osteoclast activation causing multinucleated giant cell conglomerates with hemosiderin deposits in addition to the local production of cytokines and growth factors. Multiple FCH foci, osteolytic on CT, spread in the skeleton may be located, corresponding to brown tumors. They were rarely reported in case of severe pHPT, as in a patient from Hôpital Tenon[144] or in a very rare condition, HPT secondary to untreated pseudohypoparathyroidism, due to PTH resistance in target organs, ie, kidney resistance, but with conserved bone cell sensitivity.[145] More frequently, in patients with rHPT, particularly with long history of hemodialysis or tertiary rHPT, brown tumors appear as FCH- and/or FDG-positive high turn-over lesions, belonging to renal osteodystrophy[146] (Fig. 5). As the result of a systematic review of 52 articles reporting the use of nuclear medicine imaging in the detection of 392 brown tumors, Jacquet-Francillon et al.[147] conclude that, if this diagnosis is evoked on a known lesion, performing FCH PET/CT imaging seems the most appropriate. In the series from Hôpital Tenon, brown tumors took-up FCH in seven patients, 6 referred for rHPT and 1 for pHPT.

These brown tumors may mimic FCH-positive bone lesions related with multiple myeloma[148] that can be confirmed or excluded by biology, or metastases of osteophilic cancer (eg, prostate cancer). If such lesions are localized in the FOV of parathyroid imaging (head, neck and thorax), it is considered as useful to complete with whole-body imaging and to use all CT windows for analysis, to characterize the bone lesions and to localize a potential primary cancer.

The metabolic activity of brown tumors is reduced when HPT is cured, which is not the case of malignant bone involvement.

Jaws are thus among the potential localizations of brown tumors in HPT. Other bone pathologies of the jaws can take-up PET/CT tracers, such as osteonecrosis. But the association

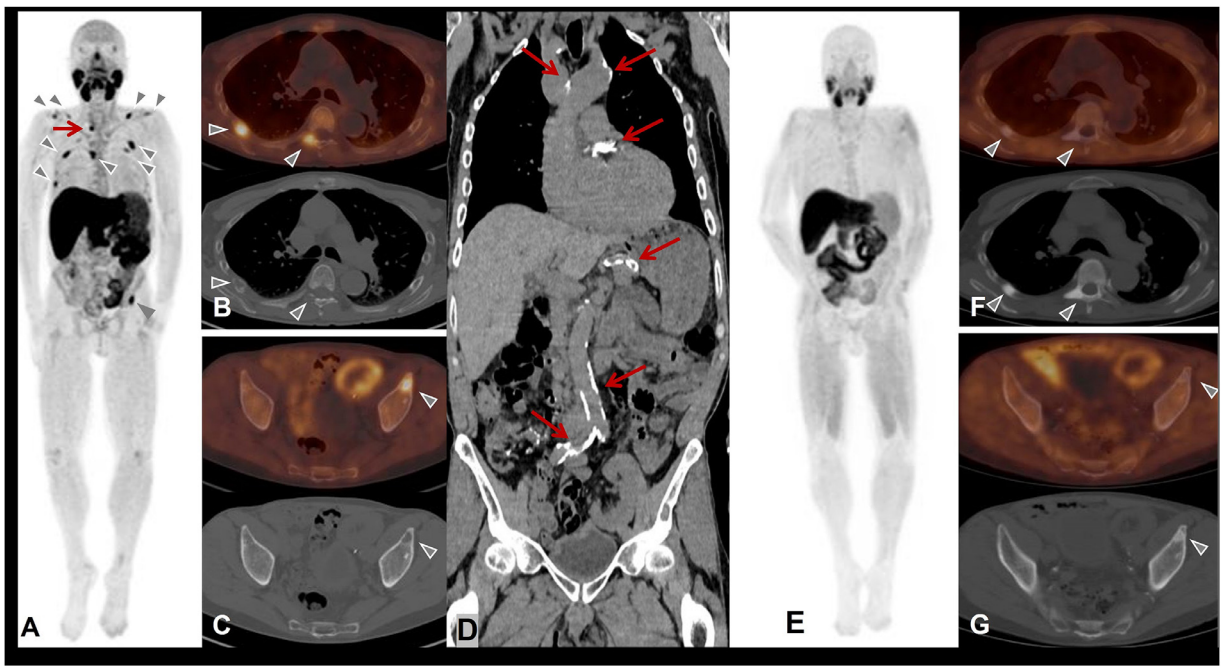

Figure 5 Patient on haemodialysis for 8 years with rejection of 2 kidney grafts. Parathyroidectomy of both superior and the left inferior hyperplastic parathyroid glands (RP4, LP4, LP3) has been performed, but 2 months later, serum parathyroid hormone level increased to 1300 ng/L. Hence FCH PET/CT was performed and showed a right inferior hyperfunctioning parathyroid gland (RP3) SUVmax 14.71 (A, arrow) but also numerous skeletal foci (A, B, C, arrow heads), osteolytic on low dose CT image (B, C) and generalized atherosclerosis (D, arrows). (A, E) MIP, (B, C, F, G) PET/CT and CT, axial slice, (D) CT, coronal slice, Following right inferior parathyroidectomy (more than 7/8 of PTs resected) the serum parathyroid hormone level dropped to 185 ng/L. On FCH PET/CT performed 5 months after this parathyroidectomy, the bone foci disappeared on PET and the corresponding osteopenic lesions on CT showed remineralization (arrow heads), permitting to conclude that they corresponded to brown bone tumors.

of jaw-ossifying fibroma with HPT is evocative of the very rare HPT-jaw tumor syndrome (HPT-JT), aforementioned among the hereditary forms of HPT. In the absence of a clear alternative aetiology, in particular bisphosphonate therapy, the discovery of an isolated hypermetabolic focus in the jaw may prompt genetic search of a pathogenic variant of cell division cycle 73 (CDC73).[72] For the moment, FDG PET/CT[73] and MIBI SPECT[74] have been the only functional imaging modalities reported in this rare disease, which is associated with a high prevalence of PT atypical adenomas and carcinomas.

On the CT Component of PET/CT: Cardiovascular Calcifications and Arteria Lusoria

In addition, relevant information on cardiovascular calcifications may be obtained on CT of FCH PET/CT, even low dose (Fig. 5), a potential detection of vulnerable atherosclerotic plaques by uptake of ^{18}F choline analogue on the corresponding PET image being reported[149] and then contradicted.[150]

Finally, the presence of lusoria artery (retroesophageal right subclavian artery or aberrant right subclavian artery) should be checked on the CT component (even low-dose) of PET/CT and reported if discovered. This rare anatomical variant is strongly correlated with the presence of a nonrecurrent inferior laryngeal nerve that is at risk of injury during right neck surgery[151]

Diagnostic Performance of FCH PET in Primary Hyperparathyroidism (pHPT)

Evangelista et al. published a metaanalysis in 2020[86], FCH PET results of diagnostic performance in pHPT, evaluated according to an independent reference-standard (or standard-of-truth), were available in 18 studies as patient-based, and in 14 studies as lesion-based. Overall, true-positive findings were reported in 686 patients and 530 lesions. Conversely, the number of false-negative results were 35 patient-based and 23 lesion-based. Pooled sensitivities of FCH PET were 93.7% patient-based and 91.3% lesion-based.

In the metaanalysis of Whitman et al.,[152] 20 studies were gathered resulting in a total of 796 HPT patients (4 studies also included rHPT patients), FCH PET had a high sensitivity of 97% (range, 96%-98%), for the detection of abnormal PT. In the subpopulation for which both FCH and MIBI were reported, FCH also had a sensitivity of 96% (94%-98%) higher than 54% (29%-79%) observed with MIBI ($P < 0.001$).

The meta-analysis of Lee et al.[153] gathered a total of 8495 patients from 119 direct comparative studies published between 1985 and September 2020, comparing two or more imaging modalities for localization of abnormal PT in pHPT. Eleven "choline" studies were included, 10 with FCH and 1 with ^{11}C-choline. The sensitivity of choline PET/CT was significantly higher than that of MIBI SPECT in both patient-based and lesion-based analyses (patient-based analysis: odds ratio, 5.22; CI: 2.36-11.80; lesion-based analysis: odds ratio, 17.70; CI: 5.79-60.10). Among eight representative imaging modality categories, choline PET/CT obtained the highest surface under the cumulative ranking curve (SUCRA) values in both patient-based and lesion-based analyses. In patient-based analysis of articles published after 2010, choline PET-CT showed the highest SUCRA value, followed by the CT category, overpassing MIBI SPECT that had the highest SUCRA value before 2009.

The detection of MGD in pHPT patients is still a challenge, some of the multiple abnormal PT(s) being small-sized and possibly metabolically inhibited by the overactivity of the dominant PT, in particular if they are hyperplastic but nonadenomatous. In the partial analysis of the series of hôpital Tenon,[40] MGD was found at post-PTX histology in 29 patients, of whom MGD had been recognized on FCH PET/CT in 11 (38%), one single abnormal PT being located in 12 (41%). Dudoignon et al.[48] reported a somewhat better MGD detection rate of 9/15=60% (nonsignificant difference Fisher's test $P = 0.21$). In both studies, the MGD detection with MIBI was worse 0/21=0% and 4/15=27%, respectively. The mass of abnormal PTs was smaller in case of MGD (mean 178 mg) than in case of uniglandular disease (mean 699 mg) ($p < 0.001$) which substantiates the challenge of detecting MGD with imaging, and the importance of FCH PET/CT, the most sensitive modality.

Dynamic 4D-CeCT has been proposed to localize abnormal PTs. As this imaging procedure is demanding and requires injection of iodine contrast agent, which is contraindicated in rHPT, its potential indication corresponds to discrepant results of imaging work-up in pHPT. Alternatively, the low-dose CT component of PET/CT may be replaced by 4D-CeCT in the composite imaging.[109] The results of five articles in a total of 153 pHPT patients were pooled by Piccardo et al.[154] The pooled detection rate of FCH PET/CT was 86%, vs 69% for 4D-CeCT and 86% for FCH PET/4D-CeCT, while their pooled sensitivity was 89%, 77% and 93% respectively. In conclusion, the sensitivity of FCH PET/CT and FCH PET/4D-CeCT is higher than that of 4D-CeCT, while only a slight difference using FCH was observed between PET/CT and PET/4D-CeCT. Performing routinely FCH PET/4D-CeCT in pHPT seems to be of little benefit and high cost in procedural constraint, radiation exposure and potential side effects of the iodine contrast agent.

Van den Bruel et al.[155] retrospectively evaluated how accurately preoperative imaging localizes PT adenomas in superior vs inferior glands, the reference standard being surgical findings with histopathologic confirmation of adenoma. In case of missed localization on imaging, superior PTs were more often localized as inferior than the reverse on CT, US and FCH PET/CT. Of 30 FCH PET/CTs this error rate was 36% vs 17% of inferior PTs localized as superior.

In nine patients with chronic thyroiditis favouring a high background due to thyroid uptake of FCH as aforementioned, Mazurek et al.[106] did not observe a decline of the performance of FCH PET/CT compared with the 56 other pHPT patients of their study.

Diagnostic Performance of FCH in MEN

In a pilot series of 44 HPT patients with inconclusive conventional imaging were three NEM1 patients: FCH PET detected all their 4 PTs, all hyperplastic, that were resected guided on its images.[84]

A dedicated extraction from our database[68] retrieved 15 MEN1 and 1 MEN4 patients referred to FCH PET/CT as part of their initial pHPT work-up who were subsequently operated; 44 abnormal PTs were resected, of which 32 (73%) had been detected and two considered as equivocal foci on FCH PET/CT. In nine patients referred to FCH PET/CT for recurrent MEN1 pHPT who were subsequently operated, 14 abnormal PTs, all FCH-positive, were resected, a successful unilateral PTX being performed in 4 of them. In a subsequent multicenter study including 71 MEN1 patients,[156] patient-based sensitivity of FCH PET/CT ranged from 98.5 to 100% among the different readers. FCH PET/CT detected more lesions than US or MIBI. Lesion-based sensitivity ranged across different readers from 84.4 to 87%, and specificity ranged from 94.7 to 98.8%. Less than subtotal PTX was performed in 7/13 patients with one or two abnormal FCH foci.

Diagnostic Performance of FCH in Secondary Hyperparathyroidism (sHPT)

The most frequent cause of sHPT is CKD; however, pHPT may occur also in this population of patients.

When PTX is considered, imaging, most recently with FCH PET/CT, is useful for the detection of HFPTGs.

The team from Hôpital Tenon published the first pilot series in rHPT, including 1 dialyzed and 4 transplanted patients, comparing FCH, MIBI and US for the detection of 12 resected hyperplastic PTs and 1 adenoma.[79] Sensitivity of FCH was 5/5=100% patient-based and 12/13=92% gland-based; identical values were found for MIBI but with two false-positive lesions; for US, patient-based sensitivity was 2/4=50% with 1 false-positive and gland-based sensitivity was 6/13=46% with 1 false-positive result.

In the study of Xue et al.,[94] a total of 63 hyperplastic PTs were resected in 17 rHPT patients, of which 53 lesions were detected on FCH PET/CT with no false-positive results. The gland-based sensitivity, specificity, accuracy, PPV, and NPV for FCH PET/CT were 84%, 100%, 86%, 100%, and 52%, respectively. In comparison, the corresponding values for MIBI SPECT/CT were 63%, 91%, 68%, 98%, and 30%, and, for US, 62%, 82%, 65%, 95%, and 27%, respectively. In rHPT, FCH PET/CT appeared as superior over MIBI SPECT/CT and US for all performance criteria. This result was confirmed on the next year by Chen et al.[95] In a total of 107 lesions resected in 27 haemodialyzed patients with sHPT or tHPT, the lesion-based sensitivity of FCH PET/CT was 86%, significantly greater than 55% for MIBI and 62% for US, whereas specificities were similar. FCH PET/CT identified more hyperplastic glands than US in 14/27=52% of patients. The gland-based sensitivity of FCH PET/CT (72% overall) was significantly greater than that of MIBI (35%), US (25%), and 4D-CeCT (40%) as in pHPT. Furthermore, the gland-based sensitivity of FCH PET/CT was greater in case of tertiary rHPT (88%) compared to secondary rHPT (66%).[107]

In summary, preoperatory FCH PET/CT in rHPT may be helpful in localizing ectopic PT and guiding the surgical choice for PT preservation, preventing PTX-induced hypoparathyroidism.

Although the mechanism of rHPT underlying PT hyperplasia is common to all PTs of a given patient, their FCH uptake is generally uneven on preoperative FCH PET/CT (Fig. 6). If partial PTX is performed and the CKD is not corrected, previously nondetectable PTs or PTs with the lowest uptake on preoperatory FCH, particularly ectopic PTs, frequently become obviously FCH-positive on follow-up FCH PET/CT for persistent or recurrent rHPT.

Apart from CKD, sHPT may be induced by chronic calcium depletion in case of severe vitamin D deficiency, long term treatment with lithium, long term hypermagnesemia, malnutrition, stomach or intestine bypass for obesity surgery (gastric stapling, Roux-n-Y or gastric bypass) after at least 10-12 years, celiac disease or Crohn disease, typically in case of severe form during decades, not after few years. Secondary HPT with normal serum calcium levels has also been reported after 2.2 cycles of treatment with sunitinib malate.[157] In this context, indication for imaging is rare, except if the association with pHPT is suspected, particularly in case of current or recent lithium therapy

Sensitivity of FCH PET According to the Histologic Type and the Weight of the Resected Abnormal Parathyroid Glands

This was the main objective of the partial analysis of the series from hôpital Tenon.[40] FCH gland-based sensitivity was 78% (CI: 73-83) overall, 72% (CI: 65-79) for hyperplastic PTs, 86% (CI: 80- 92) for PT adenomas. Discordant results between FCH and MIBI corresponded to 35/75 adenomas, FCH being true-positive and MIBI false-negative in 34, the reverse in one only. Of 41/95 discordant results corresponding to hyperplastic PTs, FCH was true-positive and MIBI false-negative in 39, the reverse in two only ($P < 0.0001$). The mass of the resected hyperplastic PTs was significantly lower than that of the adenomas: mean 0.64 g *vs.* 1.03 g ($P = 0.001$). The mass of the PT adenomas detected on FCH PET/CT was greater than that of the nondetected PT adenomas: mean 1.10 g *vs.* 0.33 g ($P = 0.01$). Accordingly, the mass of the hyperplastic PTs detected on FCH PET/CT was greater than that of nondetected hyperplastic PTs: mean 0.80 g *vs.* 0.21 g ($P < 0.0001$). In contrast, the mass of the abnormal PTs detected on FCH PET/CT did not differ significantly according to their histologic type ($P = 0.06$).The mass

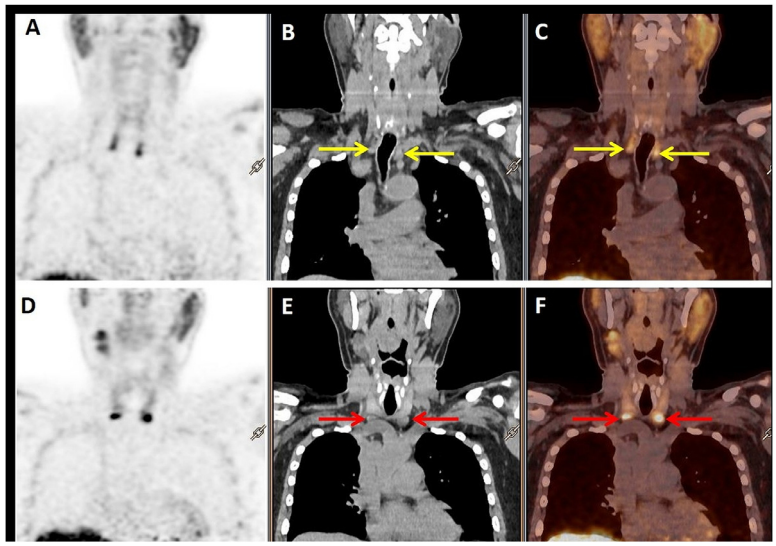

Figure 6 Patient on hemodialysis for 18 years, with serum parathyroid hormone level 2090 ng/L. FCH PET/CT was performed and showed four hyperfunctioning parathyroid glands with uneven FCH uptake: right superior (RP4) SUVmax 7.6, right inferior (RP3) SUVmax 14.3, left superior (LP4) SUVmax 8.5 and left inferior (LP3) SUVmax 14.4. Superior (P4) and inferior (P3) parathyroid glands may be located at the same level in the neck, with P4 located posteriorly to P3 due to embryonic development, which highlights the importance for tomographic imaging for correct localization of HFPTG.

of an abnormal gland appears as a major determinant for its detection with FCH PET/CT.

Impact of FCH PET/CT on Patient Management and Cure Rate After FCH-Guided PTX

The partial analysis of the series from Hôpital Tenon[40] confirmed the influence of FCH PET/CT on the decision of PTX and its acceptance by the patient: PTX rate was 192/264=73% if FCH PET/CT is positive vs 29/83=35% if FCH PET/CT was negative ($P < 0.0001$).

Hocevar et al.[92] concluded from their retrospective analysis of series of 151 patients with pHPT, that patients with a single parathyroid adenoma on FCH PET can safely undergo focused PTX without intraoperative testing of PTH serum levels.

In the study of Quak et al.,[43] of 28 pHPT patients randomized for first-line MIBI SPECT/CT, 10 had inconclusive or negative MIBI SPECT/CT and benefited from second line FCH PET/CT which was positive in 8, of whom seven underwent MIPTX, resulting in normocalcemia at 1 month in 6 patients (one patient lost for follow-up). In this imaging strategy with second line FCH PET/CT that we do not recommend, its rate of impact on patient management was 80%. In this prospective comparative study on 57 pHPT patients,[43] the primary endpoint was the proportion of patients for whom the first-line imaging technique, either FCH PET/CT or MIBI SPECT/CT, guided the surgical procedure appropriately, ie, toward positive MIPTX resulting in normocalcemia 1 month after surgery. Calcemia was normal 1 month after positive first-line imaging guided MIPTX in 23 of 27 patients (85%) who benefited from first-line PET/CT vs 14 of 25 patients (56%) in the group with first-line MIBI. All patients with normocalcemia at 1 month after surgery were still normocalcemic at 6 months.

A meta-analysis included 22 studies in a total of 1129 pHPT patients who underwent surgery after FCH PET/CT, the pooled cure rate was 93% (range 58%-100%, CI: 87%-96%).[24]

In the context of rHPT, the operative endpoint of surgery is not necessarily a return of serum PTH to normal levels, but a >50% drop in serum PTH level, even if it remains above upper normal value. Additionally, "success" or "cure" is defined as normal calcium levels regardless of whether or not serum PTH is elevated. It appears the goal of surgery for tHPT is not a normal serum PTH value, but a normal calcium level at least six months postoperatively.[77] Comparing cure rates after PTX in rHPT is difficult since it widely depends on the PTX practice (partial PTX sparing one detected HFPTG is effective to avoid hypoparathyroidism but favours recurrence) and on the frequency and success rate of post-PTX kidney transplant. One very preliminary result in the context of their center has been published by Gass et al.,[83] 4/4 patients with sHPT or tHPT showed normal calcium and PTH levels after six months and were cured.

Conclusion

In conclusion, the available bibliographic data completed by real-world experience of FCH PET/CTs in HPT over 12 years in our centers permit to recommend FCH PET/CT as a safe and efficient first line radionuclide imaging method in patients of all categories of age with HPT referred for localization of HFPTGs.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Lucia Noskovicova: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Sona Balogova:** Conceptualization, Formal analysis, Methodology, Validation, Writing – original draft, Writing – review & editing. **Cyrielle Aveline:** Investigation, Validation, Writing – review & editing. **Marc Tassart:** Investigation, Validation, Writing – review & editing. **Jules Zhang-Yin:** Investigation, Validation, Writing – review & editing. **Khaldoun Kerrou:** Investigation, Validation, Writing – review & editing. **Ivan Jaksic:** Investigation, Validation, Writing – review & editing. **Françoise Montravers:** Investigation, Supervision, Validation, Writing – review & editing. **Jean-Noël Talbot:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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References

1. Bijnens J, Van den Bruel A, Vander Poorten V, et al: Retrospective real-life study on preoperative imaging for minimally invasive parathyroidectomy in primary hyperparathyroidism. Sci Rep 12:17427, 2022
2. Noureldine SI, Gooi Z, Tufano RP: Minimally invasive parathyroid surgery. Gland Surg 4:410-419, 2015
3. Taterra D, Wong LM, Vikse J, et al: The prevalence and anatomy of parathyroid glands: a meta-analysis with implications for parathyroid surgery. Langenbecks Arch Surg 404:63-70, 2019
4. Boggs JE, Irvin GL 3rd, Carneiro DM, et al: The evolution of parathyroidectomy failures. Surgery 126:998-1002, 1999.. discussion 1002-1003
5. Mariani G, Gulec SA, Rubello D, et al: Preoperative localization and radioguided parathyroid surgery. J Nucl Med 44:1443-1458, 2003
6. Makiuchi M, Miyakawa M, Sugenoya A, et al: Diagnostic usefulness of 201Tl-chloride scintigraphy for preoperative localization of parathyroid tumors. Jpn J Surg 11:162-166, 1981
7. Young AE, Gaunt JI, Croft DN, et al: Location of parathyroid adenomas by thallium-201 and technetium-99m subtraction scanning. Br Med J (Clin Res Ed) 286:1384-1386, 1983
8. Ferlin G, Borsato N, Camerani M, et al: New perspectives in localizing enlarged parathyroids by technetium-thallium subtraction scan. J Nucl Med 24:438-441, 1983
9. Petranović Ovčariček P, Giovanella L, Carrió Gasset I, et al: The EANM practice guidelines for parathyroid imaging. Eur J Nucl Med Mol Imaging 48:2801-2822, 2021
10. Coakley AJ, Kettle AG, Wells CP, et al: 99Tcm sestamibi—a new agent for parathyroid imaging. Nucl Med Commun 10:791-794, 1989
11. Taillefer R, Boucher Y, Potvin C, et al: Detection and localization of parathyroid adenomas in patients with hyperparathyroidism using a single radionuclide imaging procedure with technetium-99m-sestamibi (double-phase study). J Nucl Med 33:1801-1807, 1992
12. Wei JP, Burke GJ, Mansberger AR Jr: Preoperative imaging of abnormal parathyroid glands in patients with hyperparathyroid disease using combination Tc-99m-pertechnetate and Tc-99m-sestamibi radionuclide scans. Ann Surg 219:568-572, 1994.. discussion 572-563
13. Wei JP, Burke GJ, Mansberger AR Jr.: Prospective evaluation of the efficacy of technetium 99m sestamibi and iodine 123 radionuclide imaging of abnormal parathyroid glands. Surgery 112:1111-1116, 1992.. discussion 1116-1117
14. Digiulino W, Beierwaltes WH: PARATHYROID SCANNING WITH SELENIUM-75 LABELLED METHIONINE. J Nucl Med 5:417-427, 1964
15. Hellman P, Ahlström H, Bergström M, et al: Positron emission tomography with 11C-methionine in hyperparathyroidism. Surgery 116: 974-981, 1994
16. Bioletto F, Barale M, Parasiliti-Caprino M, et al: Comparison of the diagnostic accuracy of 18F-Fluorocholine PET and 11C-Methionine PET for parathyroid localization in primary hyperparathyroidism: a systematic review and meta-analysis. Eur J Endocrinol 185:109-120, 2021
17. Mathey C, Keyzer C, Blocklet D, et al: 18)F-fluorocholine PET/CT is more sensitive than (11)C-methionine PET/CT for the localization of hyperfunctioning parathyroid tissue in primary hyperparathyroidism. J Nucl Med 63:785-791, 2022
18. Michaud L, Burgess A, Huchet V, et al: Is 18F-fluorocholine-positron emission tomography/computerized tomography a new imaging tool for detecting hyperfunctioning parathyroid glands in primary or secondary hyperparathyroidism? J Clin Endocrinol Metab 99:4531-4536, 2014
19. Lezaic L, Rep S, Sever MJ, et al: ^{18}F-Fluorocholine PET/CT for localization of hyperfunctioning parathyroid tissue in primary hyperparathyroidism: a pilot study. Eur J Nucl Med Mol Imaging 41:2083-2089, 2014
20. Orevi M, Freedman N, Mishani E, et al: Localization of parathyroid adenoma by ^{11}C-choline PET/CT: preliminary results. Clin Nucl Med 39:1033-1038, 2014
21. Noltes ME, Kruijff S, Appelman APA, et al: Head-to-head comparison of [(11)C]methionine PET, [(11)C]choline PET, and 4-dimensional CT as second-line scans for detection of parathyroid adenomas in primary hyperparathyroidism. Eur J Nucl Med Mol Imaging 51:1050-1059, 2024
22. Smaxwil C, Aschoff P, Reischl G, et al: [(18)F]fluoro-ethylcholine-PET Plus 4D-CT (FEC-PET-CT): A Break-Through Tool to Localize the "Negative" Parathyroid Adenoma. One Year Follow Up Results Involving 170 Patients. J Clin Med 10, 2021
23. Ishizuka T, Kajita K, Kamikubo K, et al: Phospholipid/Ca2+-dependent protein kinase activity in human parathyroid adenoma. Endocrinol Jpn 34:965-968, 1987
24. Quak E, Lheureux S, Reznik Y, et al: F18-choline, a novel PET tracer for parathyroid adenoma? J Clin Endocrinol Metab 98:3111-3112, 2013

25. Cazaentre T, Clivaz F, Triponez F: False-positive result in 18F-fluorocholine PET/CT due to incidental and ectopic parathyroid hyperplasia. Clin Nucl Med 39:e328-e330, 2014
26. Hodolic M, Huchet V, Balogova S, et al: Incidental uptake of (18)F-fluorocholine (FCH) in the head or in the neck of patients with prostate cancer. Radiol Oncol 48:228-234, 2014
27. ANSM. PROSTATEP 500 MBq/mL, solution injectable RÉSUMÉ DES CARACTÉRISTIQUES DU PRODUIT. 2023. http://agence-prd.ansm.sante.fr/php/ecodex/frames.php?specid=63885956&typedoc=R&ref=R0414274.htm.
28. Lalonde MN, Correia RD, Syktiotis GP, et al: Parathyroid Imaging. Semin Nucl Med. 53:490-502, 2023
29. Bilezikian JP, Khan AA, Silverberg SJ, et al: Evaluation and Management of Primary Hyperparathyroidism: Summary Statement and Guidelines from the Fifth International Workshop. J Bone Miner Res 37:2293-2314, 2022
30. Benjamin J, Maillard L, Morelec I, et al: Diagnostic performance of (18)F-choline positron emission tomography/contrast-enhanced computed tomography in adenoma detection in primary hyperparathyroidism after inconclusive imaging: a retrospective study of 215 patients. Cancers (Basel) 14, 2022
31. Fischli S, Suter-Widmer I, Nguyen BT, et al: The significance of 18F-fluorocholine-PET/CT as localizing imaging technique in patients with primary hyperparathyroidism and negative conventional imaging. Front Endocrinol (Lausanne) 8:380, 2017
32. Grimaldi S, Young J, Kamenicky P, et al: Challenging pre-surgical localization of hyperfunctioning parathyroid glands in primary hyperparathyroidism: the added value of (18)F-fluorocholine PET/CT. Eur J Nucl Med Mol Imaging 45:1772-1780, 2018
33. Morland D, Lalire P, Deguelte S, et al: 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. Medicine (Baltimore) 99:e18681, 2020
34. Quak E, Blanchard D, Houdu B, et al: F18-choline PET/CT guided surgery in primary hyperparathyroidism when ultrasound and MIBI SPECT/CT are negative or inconclusive: the APACH1 study. Eur J Nucl Med Mol Imaging 45:658-666, 2018
35. Uslu-Beşli L, Sonmezoglu K, Teksoz S, et al: Performance of F-18 fluorocholine PET/CT for detection of hyperfunctioning parathyroid tissue in patients with elevated parathyroid hormone levels and negative or discrepant results in conventional imaging. Korean J Radiol 21:236-247, 2020
36. Zajíčková K, Zogala D, Kubinyi J: Parathyroid imaging by (18)F-fluorocholine PET/CT in patients with primary hyperparathyroidism and inconclusive conventional methods: clinico-pathological correlations. Physiol Res 67:S551-s557, 2018
37. Zajíčková K, Včelák J, Lešková Z, et al: Multiglandular parathyroid disease in primary hyperparathyroidism with inconclusive conventional imaging. Physiol Res 71:233-240, 2022
38. Dekorsy FJ, Beyer L, Spitzweg C, et al: Preoperative imaging with [(18)F]-fluorocholine PET/CT in primary hyperparathyroidism. J Clin Med 11, 2022
39. Araz M, Soydal Ç, Özkan E, et al: The efficacy of fluorine-18-choline PET/CT in comparison with 99mTc-MIBI SPECT/CT in the localization of a hyperfunctioning parathyroid gland in primary hyperparathyroidism. Nucl Med Commun 39:989-994, 2018
40. Talbot JN, Périé S, Tassart M, et al: 18F-fluorocholine PET/CT detects parathyroid gland hyperplasia as well as adenoma: 401 PET/CTs in one centre. Q J Nucl Med Mol Imaging: 67, 2023
41. Broos WAM, Wondergem M, Knol RJJ, et al: Parathyroid imaging with (18)F-fluorocholine PET/CT as a first-line imaging modality in primary hyperparathyroidism: a retrospective cohort study. EJNMMI Res 9:72, 2019
42. Seyedinia SS, Mirshahvalad SA, Schweighofer-Zwink G, et al: Evolving role of [(18)F]flurocholine PET/CT in assessing primary hyperparathyroidism: can it be considered the first-line functional imaging approach? J Clin Med: 12, 2023
43. Quak E, Lasne-Cardon A, Cavarec M, et al: F18-choline PET/CT or MIBI SPECT/CT in the surgical management of primary hyperparathyroidism: a diagnostic randomized clinical trial. JAMA Otolaryngol Head Neck Surg 2024
44. Yap A, Hope TA, Graves CE, et al: A cost-utility analysis of 18F-fluorocholine-positron emission tomography imaging for localizing primary hyperparathyroidism in the United States. Surgery 171: 55-62, 2022
45. van Mossel S, Saing S, Appelman-Dijkstra N, et al: Cost-effectiveness of one-stop-shop [(18)F]Fluorocholine PET/CT to localise parathyroid adenomas in patients suffering from primary hyperparathyroidism. Eur J Nucl Med Mol Imaging 2024
46. Rep S, Hocevar M, Vaupotic J, et al: (18)F-choline PET/CT for parathyroid scintigraphy: significantly lower radiation exposure of patients in comparison to conventional nuclear medicine imaging approaches. J Radiol Prot 38:343-356, 2018
47. Imperiale A, Bani J, Bottoni G, et al: Does (18)F-Fluorocholine PET/CT add value to positive parathyroid scintigraphy in the presurgical assessment of primary hyperparathyroidism? Front Med (Lausanne) 10:1148287, 2023
48. Dudoignon D, Delbot T, Cottereau AS, et al: 18F-fluorocholine PET/CT and conventional imaging in primary hyperparathyroidism. Diagn Interv Imaging 103:258-265, 2022
49. Cuderman A, Senica K, Rep S, et al: 18)F-fluorocholine PET/CT in primary hyperparathyroidism: superior diagnostic performance to conventional scintigraphic imaging for localization of hyperfunctioning parathyroid glands. J Nucl Med 61:577-583, 2020
50. Alharbi AA, Alshehri FM, Albatly AA, et al: [(18)F]fluorocholine uptake of parathyroid adenoma is correlated with parathyroid hormone level. Mol Imaging Biol 20:857-867, 2018
51. Boccalatte LA, Gómez NL, Musumeci M, et al: (18)F-choline PET/4D CT in hyperparathyroidism: correlation between biochemical data and study parameters. Rev Esp Med Nucl Imagen Mol (Engl Ed) 39:273-278, 2020
52. Halimi C, Bor C, Chieze R, et al: Comparison of normocalcemic versus hypercalcemic primary hyperparathyroidism in a hypercalciuric renal stone population. J Clin Endocrinol Metab 2024
53. Amin AL, Wang TS, Wade TJ, et al: Normal PTH levels in primary hyperparathyroidism: still the same disease? Ann Surg Oncol 18:3437-3442, 2011
54. Wallace LB, Parikh RT, Ross LV, et al: The phenotype of primary hyperparathyroidism with normal parathyroid hormone levels: how low can parathyroid hormone go? Surgery 150:1102-1112, 2011
55. Talbot JN, Aveline C, Zhang-Ying J, et al: 18F-fuorocholine (FCH) PET/CT performance to detect hyperfunctioning parathyroid glands in patients with no definite kidney disease and whose PTH serum level and/or calcemia are within the normal range. Eur J Nucl Med Mol Imaging 2023
56. Latge A, Riehm S, Vix M, et al: 18)F-fluorocholine PET and 4D-CT in patients with persistent and recurrent primary hyperparathyroidism. Diagnostics (Basel): 11, 2021
57. Schulte KM, Talat N: Diagnosis and management of parathyroid cancer. Nat Rev Endocrinol 8:612-622, 2012
58. Su C, Zhang J, Yang H, et al: Diagnosis and treatment of liver metastases of parathyroid carcinoma. Front Endocrinol (Lausanne) 13: 982972, 2022
59. Deandreis D, Terroir M, Al Ghuzlan A, et al: (1)(8)Fluorocholine PET/CT in parathyroid carcinoma: a new tool for disease staging? Eur J Nucl Med Mol Imaging 42:1941-1942, 2015
60. Radzikowski KC, Rendl G, Beheshti M, et al: 18F Choline PET/CT in a patient with HRPT2 mutation: detecting parathyroid carcinoma recurrence and concomitant breast carcinoma. Nuklearmedizin 61:62-64, 2022
61. Thanseer NTK, Parihar AS, Sood A, et al: Evaluation of recurrent parathyroid carcinoma: a new imaging tool in uncommon entity. World J Nucl Med 18:198-200, 2019
62. Hatzl M, Röper-Kelmayr JC, Fellner FA, et al: 18F-fluorocholine, 18F-FDG, and 18F-fluoroethyl tyrosine PET/CT in parathyroid cancer. Clin Nucl Med 42:448-450, 2017
63. Morand GB, Helmchen BM, Steinert HC, et al: 18F-Choline-PET in parathyroid carcinoma. Oral Oncol 86:314-315, 2018

64. Yang J, Lu X, Zhou P, et al: Recurrence hyperparathyroidism caused by synchronous parathyroid carcinoma and parathyromatosis in a patient with long-term hemodialysis. BMC Nephrol 24:293, 2023
65. Jha S, Simonds WF: Molecular and clinical spectrum of primary hyperparathyroidism. Endocr Rev 44:779-818, 2023
66. Goudet P, Cadiot G, Barlier A, et al: French guidelines from the GTE, AFCE and ENDOCAN-RENATEN (Groupe d'étude des Tumeurs Endocrines/Association Francophone de Chirurgie Endocrinienne/Reseau national de prise en charge des tumeurs endocrines) for the screening, diagnosis and management of Multiple Endocrine Neoplasia Type 1. Ann Endocrinol (Paris) 85:2-19, 2024
67. Gauthé M, Dierick-Gallet A, Delbot T, et al: (18)F-fluorocholine PET/CT in MEN1 patients with primary hyperparathyroidism. World J Surg 44:3761-3769, 2020
68. Talbot JN, Zhang-Yin J, Kerrou K, et al: Multiple endocrine neoplasia type 1 or 4: detection of hyperfunctioning parathyroid glands with 18F-fluorocholine PET/CT. Illustrative cases and pitfalls. Q J Nucl Med Mol Imaging 66:130-140, 2022
69. Balogova S, Talbot JN, Nataf V, et al: 18F-fluorodihydroxyphenylalanine vs other radiopharmaceuticals for imaging neuroendocrine tumours according to their type. Eur J Nucl Med Mol Imaging 40:943-966, 2013
70. Slavikova K, Montravers F, Treglia G, et al: What is currently the best radiopharmaceutical for the hybrid PET/CT detection of recurrent medullary thyroid carcinoma? Curr Radiopharm 6:96-105, 2013
71. Singeisen H, Renzulli MM, Pavlicek V, et al: Multiple endocrine neoplasia type 4: a new member of the MEN family. Endocr Connect: 12, 2023
72. Torresan F, Iacobone M: Clinical features, treatment, and surveillance of hyperparathyroidism-jaw tumor syndrome: an up-to-date and review of the literature. Int J Endocrinol 2019:1761030, 2019
73. Nazerani Hooshmand T, Pernthaler B, Szurian K, et al: 18F-FDG PET/CT in the Hyperparathyroidism-Jaw-Tumor Syndrome. Clin Nucl Med 46:497-498, 2021
74. Piciu D, Piciu A, Barbus E, et al: Primary hyperparathyroidism-jaw tumor syndrome: a confusing and forgotten diagnosis. Clujul Med 89:555-558, 2016
75. Crepeau P, Fedorova T, Morris-Wiseman LF, et al: Secondary hyperparathyroidism and cognitive decline. Curr Transplant Rep 10:60-68, 2023
76. Nakamura M, Takiguchi S, Uehara S, et al: Outcome of surgical parathyroidectomy for tertiary hyperparathyroidism in kidney transplant recipients: tertiary hyperparathyroidism should not be ignored, for the sake of precious allografts. Ren Fail 46:2333919, 2024
77. Tang JA, Friedman J, Hwang MS, et al: Parathyroidectomy for tertiary hyperparathyroidism: a systematic review. Am J Otolaryngol 38:630-635, 2017
78. Lee JB, Kim WY, Lee YM: The role of preoperative ultrasonography, computed tomography, and sestamibi scintigraphy localization in secondary hyperparathyroidism. Ann Surg Treat Res 89:300-305, 2015
79. Michaud L, Balogova S, Burgess A, et al: A pilot comparison of 18F-fluorocholine pet/ct, ultrasonography and 123i/99mtc-sestamibi dual-phase dual-isotope scintigraphy in the preoperative localization of hyperfunctioning parathyroid glands in primary or secondary hyperparathyroidism: influence of thyroid anomalies. Medicine (Baltimore) 94:e1701, 2015
80. Treglia G, Piccardo A, Paone G, et al: [(18)F]Fluorocholine PET/CT as First-Line vs. Second-Line Imaging Method to localize parathyroid adenomas in primary hyperparathyroidism: "Game, Set, and Match.". Eur J Nucl Med Mol Imaging 2024
81. Roef MJ, van der Poel H, van der Laken CJ, et al: Colchicine must be stopped before imaging with [18F]-methylcholine PET/CT. Nucl Med Commun 31:1075-1077, 2010
82. Kluijfhout WP, Vorselaars WM, Vriens MR, et al: Enabling minimal invasive parathyroidectomy for patients with primary hyperparathyroidism using Tc-99m-sestamibi SPECT-CT, ultrasound and first results of (18)F-fluorocholine PET-CT. Eur J Radiol 84:1745-1751, 2015
83. Gass JM, Wicke C, Mona C, et al: 18)F-Fluorocholine-PET combined with contrast-enhanced CT for localizing hyperfunctioning parathyroid glands and optimizing surgical treatment in patients with hyperparathyroidism. Endocrine 75:593-600, 2022
84. Kluijfhout WP, Vorselaars WM, van den Berk SA, et al: Fluorine-18 fluorocholine PET-CT localizes hyperparathyroidism in patients with inconclusive conventional imaging: a multicenter study from the Netherlands. Nucl Med Commun 37:1246-1252, 2016
85. Suzuki A, Hirokawa M, Kanematsu R, et al: Fine-needle aspiration of parathyroid adenomas: indications as a diagnostic approach. Diagn Cytopathol 49:70-76, 2021
86. Evangelista L, Ravelli I, Magnani F, et al: (18)F-choline PET/CT and PET/MRI in primary and recurrent hyperparathyroidism: a systematic review of the literature. Ann Nucl Med 34:601-619, 2020
87. Kluijfhout WP, Pasternak JD, Gosnell JE, et al: 18F fluorocholine PET/MR imaging in patients with primary hyperparathyroidism and inconclusive conventional imaging: a prospective pilot study. Radiology 284:460-467, 2017
88. Prabhu M, Kumari G, Damle NA, et al: Assessment of the role of early dynamic PET/CT with 18F-fluorocholine in detection of parathyroid lesions in patients with primary hyperparathyroidism. Nucl Med Commun 39:1190-1196, 2018
89. Khafif A, Masalha M, Landsberg R, et al: The role of F18-fluorocholine positron emission tomography/magnetic resonance imaging in localizing parathyroid adenomas. Eur Arch Otorhinolaryngol 276:1509-1516, 2019
90. Broos WAM, Wondergem M, van der Zant FM, et al: Dynamic 18F-fluorocholine PET/CT for parathyroid imaging in patients with primary hyperparathyroidism. Nucl Med Commun 41:776-782, 2020
91. Rep S, Lezaic L, Kocjan T, et al: Optimal scan time for evaluation of parathyroid adenoma with [(18)F]-fluorocholine PET/CT. Radiol Oncol 49:327-333, 2015
92. Hocevar M, Lezaic L, Rep S, et al: Focused parathyroidectomy without intraoperative parathormone testing is safe after pre-operative localization with 18F-Fluorocholine PET/CT. Eur J Surg Oncol 43:133-137, 2017
93. Bossert I, Chytiris S, Hodolic M, et al: PETC/CT with (18)F-Choline localizes hyperfunctioning parathyroid adenomas equally well in normocalcemic hyperparathyroidism as in overt hyperparathyroidism. J Endocrinol Invest 42:419-426, 2019
94. Xue Y, Li W, Xia Z, et al: The role of (18)F-FCH PET/CT in patients with uremic hyperparathyroidism compared with (99m)Tc-sestaMIBI SPECT/CT and ultrasonography. EJNMMI Res 9:118, 2019
95. Chen YH, Chen HT, Lee MC, et al: Preoperative F-18 fluorocholine PET/CT for the detection of hyperfunctioning parathyroid glands in patients with secondary or tertiary hyperparathyroidism: comparison with Tc-99m sestamibi scan and neck ultrasound. Ann Nucl Med 34:527-537, 2020
96. Broos WAM, Wondergem M, van der Zant FM, et al: Dual-time-point (18)F-fluorocholine PET/CT in parathyroid imaging. J Nucl Med 60:1605-1610, 2019
97. Liu S, Li M, Pang H, et al: Clinical application of (18)F-FCH PET/CT in the diagnosis and treatment of hyperparathyroidism. Front Endocrinol (Lausanne) 14:1100056, 2023
98. Thanseer N, Bhadada SK, Sood A, et al: Comparative Effectiveness of Ultrasonography, 99mTc-Sestamibi, and 18F-Fluorocholine PET/CT in Detecting Parathyroid Adenomas in Patients With Primary Hyperparathyroidism. Clin Nucl Med 42:e491-e497, 2017
99. Beheshti M, Hehenwarter L, Paymani Z, et al: 18)F-Fluorocholine PET/CT in the assessment of primary hyperparathyroidism compared with (99m)Tc-MIBI or (99m)Tc-tetrofosmin SPECT/CT: a prospective dual-centre study in 100 patients. Eur J Nucl Med Mol Imaging 45:1762-1771, 2018
100. Christakis I, Khan S, Sadler GP, et al: (18)Fluorocholine PET/CT scanning with arterial phase-enhanced CT is useful for persistent/recurrent primary hyperparathyroidism: first UK case series results. Ann R Coll Surg Engl 101:501-507, 2019
101. Amadou C, Bera G, Ezziane M, et al: 18F-fluorocholine PET/CT and parathyroid 4d computed tomography for primary hyperparathyroidism: the challenge of reoperative patients. World J Surg 43:1232-1242, 2019

102. Ballester Vázquez E, Pérez García JI, López Mora DA, et al: Identification of occult adenomas in primary hyperparathyroidism with 18F-fluorocholine PET/CT. Cir Esp (Engl Ed) 98:395-402, 2020
103. Pretet V, Rotania M, Helali M, et al: 18)F-fluorocholine PET and multiphase CT integrated in dual modality PET/4D-CT for preoperative evaluation of primary hyperparathyroidism. J Clin Med 9, 2020
104. Graves CE, Hope TA, Kim J, et al: Superior sensitivity of (18)F-fluorocholine: PET localization in primary hyperparathyroidism. Surgery 171:47-54, 2022
105. Goren S, Paladino NC, Laks S, et al: Diagnostic rechallenge with (18)F-FCH PET/CT often allows minimally invasive parathyroidectomy while maintaining exceptional cure rates. World J Surg 2022
106. Mazurek A, Dziuk M, Witkowska-Patena E, et al: The utility of 18F-fluorocholine PET/CT in the imaging of parathyroid adenomas. Endokrynol Pol 73:43-48, 2022
107. Aymard S, Leroy-Freschini B, Kaseb A, et al: (18)F-fluorocholine PET/CT compared with current imaging procedures for preoperative localization of hyperfunctioning parathyroids in patients with chronic kidney disease. Diagnostics (Basel): 13, 2023
108. Huber GF, Hüllner M, Schmid C, et al: Benefit of (18)F-fluorocholine PET imaging in parathyroid surgery. Eur Radiol 28:2700-2707, 2018
109. Piccardo A, Trimboli P, Rutigliani M, et al: Additional value of integrated (18)F-choline PET/4D contrast-enhanced CT in the localization of hyperfunctioning parathyroid glands and correlation with molecular profile. Eur J Nucl Med Mol Imaging 46:766-775, 2019
110. Araz M, Nak D, Soydal Ç, et al: Detectability of 18F-choline PET/MR in primary hyperparathyroidism. Eur Arch Otorhinolaryngol 279: 2583-2589, 2022
111. Garrou F, Rizzo A, Rosso D, et al: 18F-fluorocholine PET/CT in the detection of hyperfunctioning transplanted parathyroid tissue. Clin Nucl Med 48:e580-e582, 2023
112. Ng QK, Triumbari EKA, Omidvari N, et al: Total-body PET/CT - first clinical experiences and future perspectives. Semin Nucl Med 52:330-339, 2022
113. Padma S, Sundaram PS, Tewari A: PET/CT in paediatric malignancies - an update. Indian J Med Paediatr Oncol 37:131-140, 2016
114. Som M, Stroup JS: Primary hyperparathyroidism and pregnancy. Proc (Bayl Univ Med Cent) 24:220-223, 2011
115. McMullen TP, Learoyd DL, Williams DC, et al: Hyperparathyroidism in pregnancy: options for localization and surgical therapy. World J Surg 34:1811-1816, 2010
116. Malheiro E, Chabbert-Buffet N, Talbot JN, et al: Hyperparathyroidism in pregnancy and (99m)Tc-MIBI scintigraphy. Eur Ann Otorhinolaryngol Head Neck Dis 136:501-503, 2019
117. Gill MM, Sia W, Hoskinson M, et al: The use of PET/CT in pregnancy: A case report of malignant parathyroid carcinoma and a review of the literature. Obstet Med 11:45-49, 2018
118. Triantafyllidou M, Strobel K, Leiser A, et al: Localisation of ectopic mediastinal parathyroid adenoma by 18F-fluorocholine PET/CT. BMJ Case Rep 2018, 2018
119. Calabria F, Chiaravalloti A, Ciccio C, et al: PET/CT with 18F-choline: Physiological whole bio-distribution in male and female subjects and diagnostic pitfalls on 1000 prostate cancer patients: 18F-choline PET/CT bio-distribution and pitfalls. A southern Italian experience. Nucl Med Biol 51:40-54, 2017
120. Balogova S, Michaud L, Vereb M, et al: 18F-fluorocholine may be taken-up by brown adipose tissue. Nuklearmedizin 52:N3-N4, 2013
121. Treglia G, Piccardo A, Imperiale A, et al: Diagnostic performance of choline PET for detection of hyperfunctioning parathyroid glands in hyperparathyroidism: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging 46:751-765, 2019
122. Boudousq V, Guignard N, Gilly O, et al: Diagnostic performance of cervical ultrasound, (99m)Tc-sestamibi scintigraphy, and contrast-enhanced (18)F-fluorocholine PET in primary hyperparathyroidism. J Nucl Med 63:1081-1086, 2022
123. Jacquet-Francillon N, Granjon D, Casteillo F, et al: Incidental detection of a small cell lung cancer by 18F-choline pet/ct performed for recurrent hyperparathyroidism after parathyroidectomy. Clin Nucl Med 46: e109-e111, 2021
124. Zhao W, Lu R, Yin L, et al: The value of preoperative and intraoperative ultrasound in the localization of intrathyroidal parathyroid adenomas. J Invest Surg 35:752-757, 2022
125. Gowrishankar SV, Bidaye R, Das T, et al: Intrathyroidal parathyroid adenomas: scoping review on clinical presentation, preoperative localization, and surgical treatment. Head Neck 45:706-720, 2023
126. Knepprath JK, McHenry CR: How often are intrathyroidal parathyroid glands a cause of primary hyperparathyroidism, and how should they be managed? Surgery 175:794-798, 2024
127. Libé R, Calvani J, Cottereau AS, et al: An ectopic parathyroid adenoma mimicking a carotid body paraganglioma. J Endocr Soc 4:bvaa143, 2020
128. Dream S, Lindeman B, Chen H: Prevalence of thymic parathyroids in primary hyperparathyroidism during radioguided parathyroidectomy. Clin Med Insights Endocrinol Diabetes 12:1179551419869917, 2019
129. Kwee SA, DeGrado TR, Talbot JN, et al: Cancer imaging with fluorine-18-labeled choline derivatives. Semin Nucl Med 37:420-428, 2007
130. Ciappuccini R, Saguet-Rysanek V, Dorbeau M, et al: Thyroid 18F-fluorocholine uptake in patients with chronic autoimmune thyroiditis. Eur Thyroid J 11, 2022
131. Ciappuccini R, Licaj I, Lasne-Cardon A, et al: (18)F-fluorocholine positron emission tomography/computed tomography is a highly sensitive but poorly specific tool for identifying malignancy in thyroid nodules with indeterminate cytology: the chocolate study. Thyroid 31:800-809, 2021
132. Talbot JN, Fartoux L, Balogova S, et al: Detection of hepatocellular carcinoma with PET/CT: a prospective comparison of 18F-fluorocholine and 18F-FDG in patients with cirrhosis or chronic liver disease. J Nucl Med 51:1699-1706, 2010
133. Bertagna F, Albano D, Giovanella L, et al: F18-choline/C11-choline PET/CT thyroid incidentalomas. Endocrine 64(2):203-208, 2019
134. Bani J, Morland D, Hubelé F, et al: Dual-time-point 18F-fluorocholine PET/CT improves characterization of thyroid nodules in patients referred for primary hyperparathyroidism: a proof of concept study. Clin Nucl Med 46:965-970, 2021
135. Thanseer NTK, Bhadada SK, Sood A, et al: Dual pathologies of parathyroid adenoma and papillary thyroid cancer on fluorocholine and fluorodeoxyglucose PET/CT. Nucl Med Mol Imaging 52:154-158, 2018
136. Foppiani L, Sola S, Pitto F, et al: A collision intrathyroidal tumor causing primary hyperparathyroidism: evidence from an 18F-choline PET/CT study. Clin Nucl Med 46:924-926, 2021
137. Broos WAM, Knol RJJ, Zant FMV, et al: Incidental findings on (18)F-fluorocholine PET/CT for parathyroid imaging. World J Nucl Med 21:192-199, 2022
138. Pislar N, Hocevar M: Intraoperative parathormone increase after focused parathyroidectomy in a patient with sarcoidosis - case report. Ann Med Surg (Lond) 68:102577, 2021
139. Burgers AMG, Wondergem M, van der Zant FM, et al: Incidental detection of a melanoma by 18F-fluorocholine PET/CT performed for evaluation of primary hyperparathyroidism. Clin Nucl Med 43:265-266, 2018
140. Paepegaey AC, Velayoudom FL, Housni S, et al: A hungry bone syndrome predicted by 18F-fluorocholine PET/CT. Clin Nucl Med 44:903-904, 2019
141. Carsote M, Nistor C: Forestalling hungry bone syndrome after parathyroidectomy in patients with primary and renal hyperparathyroidism. Diagnostics (Basel): 13, 2023
142. Balogova S, Huchet V, Egrot C, et al: Effect of erythropoietin on bone marrow uptake of 18F-fluorocholine in prostate cancer: comparison with 18F-fluoride uptake. Clinical nuclear medicine 38:200-202, 2013
143. d'Izarny-Gargas T, Isnard P, Boudhabhay I, et al: The spectrum of glomerular and vascular kidney pathology associated with myeloproliferative neoplasms. Kidney Int 104:1206-1218, 2023
144. Zhang-Yin J, Gaujoux S, Delbot T, et al: 18F-fluorocholine PET/CT imaging of brown tumors in a patient with severe primary hyperparathyroidism. Clin Nucl Med 44:971-974, 2019
145. Gonnelli S, Briot K, Cormier C, et al: Multiple brown tumors: a bone complication due to long-term untreated pseudohypoparathyroidism. Osteoporos Int 35:195-199, 2024

146. Ferrari C, Lavelli V, Santo G, et al: (18)F-fluorocholine PET/CT, Tc-99m-MIBI and TC-99m-MDP SPECT/CT in tertiary hyperparathyroidism with renal osteodystrophy. Diagnostics (Basel): 10, 2020
147. Jacquet-Francillon N, Prevot N: Brown tumors in nuclear medicine: a systematic review. Ann Nucl Med 37:255-270, 2023
148. Cassou-Mounat T, Balogova S, Nataf V, et al: 18F-fluorocholine versus 18F-fluorodeoxyglucose for PET/CT imaging in patients with suspected relapsing or progressive multiple myeloma: a pilot study. Eur J Nucl Med Mol Imaging 43:1995-2004, 2016
149. Bucerius J, Schmaljohann J, Böhm I, et al: Feasibility of 18F-fluoromethylcholine PET/CT for imaging of vessel wall alterations in humans—first results. Eur J Nucl Med Mol Imaging 35:815-820, 2008
150. Förster S, Rominger A, Saam T, et al: 18F-fluoroethylcholine uptake in arterial vessel walls and cardiovascular risk factors: correlation in a PET-CT study. Nuklearmedizin 49:148-153, 2010
151. Talbot JN, Périé S, Tassart M, et al: The presence of an arteria lusoria should be checked when reporting 18 F-FCH PET/CT performed to localize hyperfunctioning parathyroid glands. Clin Nucl Med 48:958-959, 2023
152. Whitman J, Allen IE, Bergsland EK, et al: Assessment and comparison of (18)F-Fluorocholine PET and (99m)Tc-Sestamibi scans in identifying parathyroid adenomas: a metaanalysis. J Nucl Med 62:1285-1291, 2021
153. Lee SW, Shim SR, Jeong SY, et al: Direct comparison of preoperative imaging modalities for localization of primary hyperparathyroidism: a systematic review and network meta-analysis. JAMA Otolaryngology - Head and Neck Surgery 147:692-706, 2021
154. Piccardo A, Bottoni G, Boccalatte LA, et al: Head-to-head comparison among 18F-choline PET/CT, 4D contrast-enhanced CT, and 18F-choline PET/4D contrast-enhanced CT in the detection of hyperfunctioning parathyroid glands: a systematic review and meta-analysis. Endocrine 74:404-412, 2021
155. Van den Bruel A, Bijnens J, Van Haecke H, et al: Preoperative imaging for hyperparathyroidism often takes upper parathyroid adenomas for lower adenomas. Sci Rep 13:7568, 2023
156. Boucher A, Delabie J, Lussey-Lepoutre C, et al: Performance of [(18)F] fluorocholine PET/CT in MEN1-related primary hyperparathyroidism before initial surgery or for persistent/recurrent disease. Eur J Nucl Med Mol Imaging 51:1349-1360, 2024
157. Baldazzi V, Tassi R, Lapini A, et al: Sunitinib-induced hyperparathyroidism. Cancer 118:3165-3172, 2012