^{18}F-Fluorocholine-PET/CT for Localizing Hyperfunctioning Parathyroid Glands and Optimizing Surgical Treatment in Patients With Hyperparathyroidism

Jörn-Markus Gass
Luzerner Kantonsspital Zentrumsspital: Luzerner Kantonsspital
Corinna Wicke
Luzerner Kantonsspital Zentrumsspital: Luzerner Kantonsspital
Carolina Mona
Luzerner Kantonsspital Zentrumsspital: Luzerner Kantonsspital
Klaus Strobel
Luzerner Kantonsspital Zentrumsspital: Luzerner Kantonsspital
Werner Müller
Luzerner Kantonsspital Zentrumsspital: Luzerner Kantonsspital
Jürg Metzger
Luzerner Kantonsspital Zentrumsspital: Luzerner Kantonsspital
Isabelle Suter-Widmer
Luzerner Kantonsspital Zentrumsspital: Luzerner Kantonsspital
Christoph Henzen
Luzerner Kantonsspital Zentrumsspital: Luzerner Kantonsspital
Stefan Fischli (stefan.fischli@luks.ch)
Luzerner Kantonsspital https://orcid.org/0000-0003-1659-343X

Research Article

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Abstract

Purpose

Hyperparathyroidism (HPT) is a common disorder. Cure can only be achieved by removal of all diseased glands. Exact localization of hyperfunctioning glands is of importance to prevent extensive surgical exploration. The number of false negative/inconclusive results in standard imaging techniques is high. We aimed to evaluate the diagnostic accuracy of ^{18}F-Fluorocholine-PET/CT (FCH-PET/CT) and its sensitivity in patients with primary, secondary/tertiary and familial HPT with negative and/or discordant findings in ultrasound and/or ^{99m}Tc-sestamibi scintigraphy/SPECT/CT.

Methods

96 patients with HPT and negative/equivocal conventional imaging were referred for FCH-PET/CT. 69 patients who have undergone surgery and histopathologic workup were analyzed in this retrospective single institution study. 60 patients suffered from primary HPT, 4 from secondary or tertiary HPT and 5 from familial HPT. Sensitivities, positive predictive values, and accuracies were calculated.

Results

All patients showed normalized serum calcium levels in the postoperative period. The follow-up rate was 97%. 58 of 60 patients with primary HPT and 4 of 4 patients with secondary/tertiary HPT showed normal calcium- and PTH-levels after 6 months and were cured. 4 of 5 patients with familial HPT were cured. Sensitivity/positive predictive value (PPV) per lesion for primary HPT was 87.5/98.3%, for secondary/tertiary HPT 75/100% and for familial HPT 14.6/100%, respectively. Sensitivity/PPV per patient was 91.5/98.2% for primary HPT, 100/100% for secondary/tertiary HPT and 50/100% for familial HPT, respectively.

Conclusion

Diagnostic accuracy of ^{18}F-Fluorocholine-PET/CT for patients with pHPT is excellent. ^{18}F-Fluorocholine-PET/CT is a valuable tool for endocrine surgeons to optimize the surgical treatment of patients with hyperparathyroidism.

Introduction

Primary hyperparathyroidism (pHPT) is a common endocrine disorder with severe consequences for affected patients. The prevalence is estimated to be one to seven cases per 1000 adults. Females are predominantly affected with a ratio of 3–4 : 1 [1–4]. The underlying pathology in most cases is autonomous secretion of parathyroid hormone caused by a single adenoma [5]. In 10–20% a multiglandular disease or hyperplasia can be found [6]. This condition occurs very frequently in familial hyperparathyroidism, in secondary or tertiary disease and after lithium treatment. Classic symptoms are various, e.g., muscle weakness, constipation, polyuria, bone pain or mental disturbances.

Due to the embryological migration of the glands the localization is highly variable. Furthermore in 6–15% of all cases a fifth gland [7] can be found and is responsible for the biochemical markers and clinical signs and symptoms of the disease. Ectopic position of an additional gland is very frequent and complicates detection.

In all patients with symptomatic pHPT and in selected asymptomatic cases surgical removal of the hyperfunctioning tissue is the only definitive curative approach [8]. To prevent postoperative hypoparathyroidism the preservation of all healthy tissue intraoperatively is of paramount importance. In former times with inferior imaging techniques bilateral exploration was standard and the success of the procedure was primarily dependent on the expertise and experience of the surgeon. Nowadays, minimally invasive surgical techniques with a focused approach are gaining more and more popularity. Generally spoken the surgical trauma is reduced and in detail the risk for damaging the recurrent nerve on the contralateral side of the diseased gland is absent [9]. Furthermore, operative time is shorter and the risk of damaging healthy glands by devascularization during surgical exploration is minimized. Essential for a minimally invasive approach is precise preoperative localization of the responsible gland and detection of additional ectopic glands.

Traditionally ultrasound and ^{99Tc}sestamibi parathyroid scintigraphy or combination of both non-invasive methods delivers good sensitivity and positive predictive values. A well-known restriction for sonographic assessment is the operator dependency and the limitation for ectopic positions of the diseased gland and the impossibility to detect intrathoracic adenomas [10, 11]. The additional application of Sestamibi Single-Positron Emission Computed Tomography/Computed Tomography (MIBI-SPECT/CT) results in even better sensitivity rates but some lesions are still missed, especially in patients with low body mass index (BMI), concomitant multinodular thyroid disease, small size or lightweight parathyroid adenomas and multiglandular disease [12]. Although ^{99m}Tc-sestamibi scintigraphy is widely accepted as gold-standard diagnostic tool for preoperative localization in pHPT a number not to be underestimated shows negative or equivocal results before surgery [12–15].

With the recent introduction of ^{18}F-fluorocholine-PET/CT (FCH-PET/CT) for detecting adenomas some studies reported even superior results concerning sensitivity and positive predictive values compared to reference imaging techniques used so far, like ^{99m}Tc-sestamibi scintigraphy, ultrasound, and four-dimensional computed tomography [16–20]. In a former pilot study of our center the feasibility of this imaging technique in patients with pHPT was analyzed [21]. In addition to the above-mentioned results of the former study the aim of the present analysis is to evaluate the utility of FCH-PET/CT and its sensitivity in a large cohort of patients with primary as well as secondary/tertiary and familial hyperparathyroidism and discordant or negative results in traditional imaging.

Subjects And Methods

Patients

In our retrospective analysis we included patients with hyperparathyroidism older than 18 years who received ^{18}F-Fluorcholin-PET/CT between 2015–2020 at our institution. Patients qualified for focused parathyroidectomy as defined by current guidelines [22] and had preoperatively negative or equivocal localization imaging studies (neck ultrasound or ^{99m}Tc-sestamibi,scintigraphy/SPECT/CT). Of note ^{18}F-Fluorcholin-PET/CT is officially approved and reimbursed by insurance companies in Switzerland in patients with hyperparathyroidism and negative or discordant imaging with ultrasound / scintigraphy.

A total of 96 patients were referred for ^{18}F-Fluorcholin-PET/CT thereof we excluded 27 persons who finally were treated by conservative measures, refused surgical intervention, had incomplete documentation or – due to COVID-linked restrictions of surgical capacities – are still awaiting surgery (Fig. 1). We then included a total of 69 patients in our final analysis and stratified them into three different clinical groups: 1) patients with primary hyperparathyroidism (pHPT), 2) patients with secondary/tertiary hyperparathyroidism (sHPT/tHPT) and 3) patients with familial forms of hyperparathyroidism, i.e., multiple endocrine neoplasia 1, (fHPT).

Biochemical work-up

Albumin-corrected Calcium, Phosphate, PTH- and 25-OH-vitamin D-levels were measured preoperatively and on the first postoperative day. A normal albumin-corrected serum calcium level 6 months after parathyroidectomy defined biochemical cure of hyperparathyroidism in patients with primary, familial and tertiary hyperparathyroidism. Due to a lacking universal definition of “cure” after parathyroidectomy for patients with sHPT, we chose a PTH-cut of ≤ 200 pg/mL after 6 months [23].

^{18}F-Fluorocholine-PET/CT

^{18}F-fluorocholine PET/CT was performed 45 min after intravenous injection (median applied activity, 194 MBq; range 125–234) on a dedicated PET/CT scanner (Discovery 600; GE Healthcare, USA). A diagnostic contrast-enhanced CT was acquired from the base of the skull to the diaphragm and also used for attenuation correction. PET images were obtained with 3-min acquisition time per bed position and all images were analyzed by a physician, doubly board certified in radiology and nuclear medicine. Significant focal tracer uptake on PET images corresponding with nodular lesions in CT in typical locations for orthotopic or heterotopic parathyroid tissues were rated as positive for parathyroid adenoma.

Surgical Methods

The surgical procedure was an open minimally invasive parathyroidectomy with recurrent nerve monitoring in 66 patients. In three patients, ectopic/mediastinal adenoma resection was performed by a thoracoscopic approach. Depending on the diagnostic result of the preoperative FCH-PET/CT, focused, unilateral or bilateral neck exploration was performed.

The total intraoperative number of lesions found, and their location were recorded. Intraoperative neuromonitoring, intraoperative frozen section and intraoperative PTH-monitoring using a standardized protocol were used to confirm surgical success. Surgical outcome and eventual complications are documented in all cases and are recorded in the endocrine surgical quality registry EUROCRINE since January 2019 [24].

Performance Analysis

FCH-PET/CT imaging results were compared with the intraoperative situs and the definitive histopathological examination as the gold standard for the diagnosis of hyperfunctioning parathyroid tissue. The results of the FCH-PET/CT were classified as (a) *true-positive (TP)*: the regional tracer uptake correlated with the histological results of hyperfunctioning parathyroid tissue, (b) *false positive (FP)*: a regional tracer uptake with histology other than hyperfunctioning parathyroid tissue, (c) *false negative (FN)*: an absent regional tracer uptake with a histology of hyperfunctioning parathyroid tissue, and (d) *true negative (TN)*: an absent regional tracer uptake and histological findings of normal parathyroid tissue.

Statistical Analysis

Based on the performance analysis (cf. above), sensitivities were calculated on a per-patient and a per-lesion basis using the quotient of true positive/true positive + false negative. 95% confidence intervals (CI) for sensitivities were calculated by the Clopper–Pearson method. If not stated otherwise, values were expressed as median and range.

Results

The baseline, biochemical and histopathological characteristics of the patients are displayed in Table 1. A total of 60 patients with pHPT, 4 patients with sHPT/tHPT and 5 patients with fHPT were operated. PET displayed 57, 6 and 1 foci and overall, 76, 8 and 11 lesions were resected respectively. 17 patients had goiters and in 8 patients (4 pHPT, 3 sHPT/tHPT and 1 fHPT) the intervention was a redo-surgery.

Table 1
Baseline characteristics

	Primary HPT (n = 60)	Secondary/tertiary HPT (n = 4)	Familial HPT (n = 5)
Age [years]	71 (44–89)	59.5 (25–75)	37 (16–76)
Sex m/f	18/42	2/2	2/3
Serum Calcium preop. [mmol/L][1]	2.65 (2.1–3.73)	2.41 (2.32–2.6)	2.77 (2.45–3.07)
PTH preop. [pg/mL]	120 (48.7–473)	777.5 (115–1614)	100 (68.8–164)
Phosphate preop. [mmol/L]	0.8 (0.46–1.26)	1.64 (0.97–2.19)	0.77 (0.44–1.12)
25-OH-vitamin D preop. [nmol/L]	55.1 (13–134)	77.5 (45-92.1)	46 (41–70)
Serum Calcium 1st day postop. [mmol/L]	2.24 (1.94-3)	2.22 (2.06–2.38)	2.15 (1.95–2.68)
PTH 1st day postop. [pg/mL)	20.3 (5-76.4)	121.5 (28.8–366)	36 (20–61)
Intraop. PTH-decrease [%]	78 (45–90)	80 (50–93)	60 (40–87)
Total resected lesions [n]	76	8	12
Weight of adenoma/ hyperplastic gland [g]	0.5 (0.004-15)	0.14 (0.08–1.6)	0.22 (0.004–0.877)

In 54/60 patients with pHPT, 4/4 with sHPT/tHPT and 2/5 with fHPT PET localized hyperfunctioning parathyroid lesions correctly which translates into a *per-person* sensitivity of 91.5%, 100% and 50% respectively (table 2).

Table 2

Diagnostic performance of ^{18}F-Cholin PET/CT

	Primary HPT	Secondary/tertiary HPT	Familial HPT
Per-lesion basis			
Sensitivity [%] (95% CI)	87.5 (76.9-94.5)	75 (34.9-96.8)	14.6 (0.36-57.87)
PPV [%] (95% CI)	98.3 (89.6-99.8)	100	100
Accuracy [%] (95% CI)	88.2 (78.7-94.4)	N.A.	45.5 (16.8-76.6)
Per-patient basis			
Sensitivity [%] (95% CI)	91.5 (81.3-97.2)	100 (39.8-100)	50 (6.8-93.2)
PPV [%] (95% CI)	98.2 (98.0-98.3)	100	100
Accuracy [%] (95% CI)	90.0 (79.5-96.2)	N.A.	N.A.

On a *per-lesion* basis there were 56 TP, 1 FP, 8 FN, and 11 TN lesions in patients with pHPT, 6 TP and 2 FN in patients with sHPT/tHPT and 1 TP, 6 TN and 4 TN in patients with fHPT, which accounts for a *per-lesion* sensitivity of 87.5%, 75% and 14.6% respectively (table 2). Compared to pHPT (11%) and sHPT/tHPT (25%) rate of false negative lesions was highest in the fHPT group (55%). In the pHPT there were in total 4 PET-negative patients. However, the reasons for this remain unclear.

Figure 2 shows an example of a 78-year-old female patient with primary hyperparathyroidism, a serum calcium of 2.84 mmol/L and osteoporosis. Preoperative ultrasound and ^{99m}Tc-sestamibi scintigraphy/SPECT/CT were negative. ^{18}F-Cholin PET/CT detected a small nodule measuring 6x10x7mm with intense choline-uptake the lower pole of the left thyroid lobe which could be identified on histological work-up as a hyperplastic parathyroid gland. The patient was cured after parathyroidectomy.

Figure 3 depicts the case of a 22-year-old female patient suffering from nephrolithiasis and primary hyperparathyroidism. Ultrasound and ^{99m}Tc-sestamibi scintigraphy/SPECT/CT were both negative. ^{18}F-Cholin PET/CT found a right-sided intrathymic lesion. Mediastinoscopy with thymectomy was performed, histology proved the lesion to be an ectopic parathyroid adenoma. The patient was cured after surgery.

58 of 60 patients with pHPT and 4/5 with fHPT showed a normal corrected calcium level at 6-months follow-up and were cured from their hyperparathyroidism. In two patients with pHPT follow-up levels of serum calcium at 6 months were not available (1 patients deceased and 1 patient lost in follow-up). 4/4 of patients with sHPT/tHPT had normal calcium levels and a PTH $\leq$ 200pg/ml at follow-up.

All patients after cervical exploration had normal vocal cord function; one patient after right thoracoscopic exploration had permanent recurrent nerve palsy. There were no cases of permanent

postoperative hypoparathyroidism.

Discussion

Our study in patients with different types of HPT, negative/discordant conventional imaging and a high rate of concomitant thyroid pathologies and redo-surgeries respectively found a) an excellent per-patient and per-lesion sensitivity in patients with pHPT for preoperative detection of hyperfunctioning parathyroid tissue leading b) to a cure rate of almost 100% in all patient groups. The perioperative complication rate was very low.

Parathyroidectomy is the only definite treatment of HPT [25]. However, parathyroid surgery remains a challenge for every endocrine surgeon. The range of clinical scenarios varies from exact identification of a single diseased gland with cervical ultrasonography leading to focused exploration to unidentified multiglandular disease with negative preoperative imaging leading to bilateral exploration. The surgical outcome depends on the patient's individual pathology and surgical expertise. High-resolution imaging combined with intraoperative parathyroid hormone measurement are important pillars for high cure rates. Identifying the patient at risk for a potentially unsuccessful surgical exploration is the common goal of the treating interdisciplinary team. Successful preoperative localization of enlarged and hyperfunctioning parathyroids increases cure rates. If preoperative imaging results remain negative, surgical success rates are reduced [26]. Also cases of postoperatively persistent or recurrent disease remain a challenging entity [27]. At the same time imaging results should not be used to select patients for surgical referral. Patients with negative imaging results still remain surgical candidates.

During the past 20 years new preoperative localization techniques, such as sestamibi-SPECT, 4D-CT or PET/CT with various tracers were introduced. All modalities depend on the investigator's experience, technical factors and the anatomical localization of the pathology.

In Switzerland, the use of ^{18}F-Fluorocholine-PET/CT is well established and nowadays reimbursed by the insurance in patients with negative/equivocal conventional imaging. The use of alternative tracers (methionine-PET/CT) has been described in the literature [28]. Currently both, ^{11}C-methionine and ^{18}F-fluorocholine tracers provide excellent results with detection rates of approximately 90% for single-gland adenoma, detect parathyroid adenoma in atypical localization (i.e. mediastinum) and are therefore recommended for further localization studies [29]. Compared to scintigraphy PET offers several advantages: a higher spatial resolution and a lower radiation dose [30]. The disadvantage in both methods is lower localization rates for multiglandular disease, relatively high costs, the potential for a false-positive in thyroid-nodules and lymph nodes and a potentially restricted availability of the tracers.

This single-center retrospective study shows that strategically well-planned parathyroid exploration and high cure-rates for hyperparathyroidism (HPT) can be successfully achieved using ^{18}F-Fluorocholine-PET/CT in the preoperative work-up of patients with negative or equivocal imaging. We included morphological and functional imaging of the parathyroid in our clinical protocol and based our

preoperative clinical algorithm on our previously published study [21]. In this study the *per-patient* and *per-lesion* sensitivity of ^{18}F-Fluorocholine-PET/CT in patients with pHPT was high and compares to other existing studies [17, 18, 31–33].

However, sensitivity showed marked differences between the patient groups. It was highest in the pHPT group but lowest in the familial HPT group with a per-lesion sensitivity of only 14.6%. All of these patients were cured and showed normal serum calcium levels postoperatively underlining the importance of the above mentioned sophisticated surgical approach. Keeping in mind that the number of patients with familial HPT was low it can be speculated that compared to a single adenoma in pHPT detection multiglandular hyperplasia of all 4 glands in MEN-1-patients remains much more difficult even when PET-techniques are applied. Nevertheless, we emphasize the use of ^{18}F-fluorocholine-PET/CT in patients with fHPT as an important preoperative procedure allowing the detection of the leading pathologies and the exclusion of ectopic localization of parathyroid glands.

Our study has limitations. Apart from the retrospective nature a quite high percentage of patients underwent scanning with ^{18}F-fluorocholin-PET/CT but then were not operated and included in the final analysis. The reasons were manifold, and we are aware that this could have led to a selection bias. Of these 10 had negative PET/CT. According to guidelines we defined cure of the HPT (in primary and familial forms) as a normal serum calcium 6 months postoperatively. The duration of the long-term follow-up after apparently curative parathyroidectomy is still controversially discussed [34, 35]. However, this study has also several strengths: We included quite a high number of patients with complex pathologies, we studied the entire broad clinical spectrum of hyperparathyroidism and our follow-up rate nearly was 100%.

Curative parathyroidectomy is of paramount importance for the patient and justifies extensive preoperative work-up. The study shows that positive imaging with ^{18}F-Fluorocholine-PET/CT successfully guides surgical strategy but also that patients with negative imaging with ^{18}F-Fluorocholine-PET/CT can still have a high cure rate in the hands of experienced endocrine surgeons. Both focused, image-guided surgery (targeted parathyroidectomy) and bilateral exploration are appropriate operations that achieve high cure rates. Based on the growing experience with ^{18}F-Fluorocholine-PET/CT this method might replace other methods of preoperative imaging in the long-run [36]. From a clinical point of view the cure of patients with hyperparathyroidism always rests on the combination of a reliable and sensitive preoperative imaging technique together with an experienced surgical approach.

Declarations

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This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Conflicts of interest

The authors declare no competing interests.

Availability of data

All datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Ethical approval

Written informed consent was obtained from all patients and the study was approved by the local ethics committee (Ethikkomission Nordwest- und Zentralschweiz, EKNZ, Nr. 2020-02142).

References

1. M. W. Yeh, P. H. G. Ituarte, H. C. Zhou, S. Nishimoto, I.-L. A. Liu, A. Harari, P. I. Haigh, and A. L. Adams, J. Clin. Endocrinol. Metab. 98, 1122 (2013).
2. R. A. Wermers, S. Khosla, E. J. Atkinson, S. J. Achenbach, A. L. Oberg, C. S. Grant, and L. J. Melton, J Bone Miner Res 21, 171 (2006).
3. D. M. Press, A. E. Siperstein, E. Berber, J. J. Shin, R. Metzger, R. Monteiro, J. Mino, W. Swagel, and J. C. Mitchell, Surgery 154, 1232 (2013).
4. M. D. Walker and S. J. Silverberg, Nat Rev Endocrinol 14, 115 (2018).
5. A. A. Khan, D. A. Hanley, R. Rizzoli, J. Bollerslev, J. E. M. Young, L. Rejnmark, R. Thakker, P. D'Amour, T. Paul, S. Van Uum, M. Z. Shrayyef, D. Goltzman, S. Kaiser, N. E. Cusano, R. Bouillon, L. Mosekilde, A. W. Kung, S. D. Rao, S. K. Bhadada, B. L. Clarke, J. Liu, Q. Duh, E. M. Lewiecki, F. Bandeira, R. Eastell, C. Marcocci, S. J. Silverberg, R. Udelsman, K. S. Davison, J. T. Potts, M. L. Brandi, and J. P. Bilezikian, Osteoporos Int 28, 1 (2017).
6. J. P. Bilezikian, L. Bandeira, A. Khan, and N. E. Cusano, Lancet 391, 168 (2018).
7. G. Akerström, J. Malmaeus, and R. Bergström, Surgery 95, 14 (1984).
8. A. Imperiale, D. Taïeb, and E. Hindié, Eur J Nucl Med Mol Imaging 45, 654 (2018).
9. R. Udelsman, Z. Lin, and P. Donovan, Ann. Surg. 253, 585 (2011).
10. J. M. Ruda, C. S. Hollenbeak, and B. C. Stack, Otolaryngol Head Neck Surg 132, 359 (2005).
11. M. Kobylecka, M. T. Płazińska, W. Chudziński, K. Fronczewska-Wieniawska, J. Mączewska, A. Bajera, M. Karlińska, and L. Królicki, J Ultrason 17, 17 (2017).
12. M. Beheshti, L. Hehenwarter, Z. Paymani, G. Rendl, L. Imamovic, R. Rettenbacher, O. Tsybrovskyy, W. Langsteger, and C. Pirich, Eur J Nucl Med Mol Imaging 45, 1762 (2018).
13. R. Yeh, Y.-K. D. Tay, G. Tabacco, L. Dercle, J. H. Kuo, L. Bandeira, C. McManus, D. K. Leung, J. A. Lee, and J. P. Bilezikian, Radiology 291, 469 (2019).
14. D. R. Neumann, N. A. Obuchowski, and F. P. Difilippo, J Nucl Med 49, 2012 (2008).

15. N. Thanseer, S. K. Bhadada, A. Sood, B. R. Mittal, A. Behera, A. K. R. Gorla, R. R. Kalathoorakathu, P. Singh, D. Dahiya, U. N. Saikia, and S. D. Rao, Clin Nucl Med 42, e491 (2017).
16. S.-J. Kim, S.-W. Lee, S. Y. Jeong, K. Pak, and K. Kim, Horm Cancer 9, 440 (2018).
17. G. Treglia, A. Piccardo, A. Imperiale, K. Strobel, P. A. Kaufmann, J. O. Prior, and L. Giovanella, Eur J Nucl Med Mol Imaging 46, 751 (2019).
18. M. Hocevar, L. Lezaic, S. Rep, K. Zaletel, T. Kocjan, M. J. Sever, J. Zgajnar, and B. Peric, Eur J Surg Oncol 43, 133 (2017).
19. E. Quak, D. Blanchard, B. Houdu, Y. Le Roux, R. Ciappuccini, B. Lireux, D. de Raucourt, J.-M. Grellard, I. Licaj, S. Bardet, Y. Reznik, B. Clarisse, and N. Aide, Eur J Nucl Med Mol Imaging 45, 658 (2018).
20. W. A. M. Broos, M. Wondergem, R. J. J. Knol, and F. M. van der Zant, EJNMMI Res 9, 72 (2019).
21. S. Fischli, I. Suter-Widmer, B. T. Nguyen, W. Müller, J. Metzger, K. Strobel, H. Grünig, and C. Henzen, Front Endocrinol (Lausanne) 8, 380 (2017).
22. J. P. Bilezikian, M. L. Brandi, R. Eastell, S. J. Silverberg, R. Udelsman, C. Marcocci, and J. T. Potts, J. Clin. Endocrinol. Metab. 99, 3561 (2014).
23. F.-F. Chou, C.-H. Lee, H.-Y. Chen, J.-B. Chen, K.-T. Hsu, and S.-M. Sheen-Chen, Ann Surg 235, 99 (2002).
24. https://eurocrine.eu/, last accessed 05th may 2021.
25. S. M. Wilhelm, T. S. Wang, D. T. Ruan, J. A. Lee, S. L. Asa, Q.-Y. Duh, G. M. Doherty, M. F. Herrera, J. L. Pasieka, N. D. Perrier, S. J. Silverberg, C. C. Solórzano, C. Sturgeon, M. E. Tublin, R. Udelsman, and S. E. Carty, JAMA Surg 151, 959 (2016).
26. B. M. Dy, M. L. Richards, B. J. Vazquez, G. B. Thompson, D. R. Farley, and C. S. Grant, Ann Surg Oncol 19, 2272 (2012).
27. E. Karakas, H.-H. Müller, T. Schlosshauer, M. Rothmund, and D. K. Bartsch, Langenbecks Arch Surg 398, 99 (2013).
28. T. Weber, M. Gottstein, S. Schwenzer, A. Beer, and M. Luster, World J Surg 41, 980 (2017).
29. P. Petranović Ovčariček, L. Giovanella, I. Carrió Gasset, E. Hindié, M. W. Huellner, M. Luster, A. Piccardo, T. Weber, J.-N. Talbot, and F. A. Verburg, Eur J Nucl Med Mol Imaging (2021).
30. S. Rep, M. Hocevar, J. Vaupotic, U. Zdesar, K. Zaletel, and L. Lezaic, J Radiol Prot 38, 343 (2018).
31. L. Michaud, S. Balogova, A. Burgess, J. Ohnona, V. Huchet, K. Kerrou, M. Lefèvre, M. Tassart, F. Montravers, S. Périé, and J.-N. Talbot, Medicine (Baltimore) 94, e1701 (2015).
32. A. Cuderman, K. Senica, S. Rep, M. Hocevar, T. Kocjan, M. J. Sever, K. Zaletel, and L. Lezaic, J Nucl Med 61, 577 (2020).
33. D. A. López-Mora, M. Sizova, M. Estorch, A. Flotats, V. Camacho, A. Fernández, S. Abouzian, F. Fuentes-Ocampo, J. I. P. Garcia, A. I. C. Ballesteros, J. Duch, A. Domènech, A. M. Duarte, and I. Carrió, Eur J Nucl Med Mol Imaging 47, 572 (2020).
34. I. Lou, C. Balentine, S. Clarkson, D. F. Schneider, R. S. Sippel, and H. Chen, Surgery 161, 54 (2017).
35. R. Mallick, K. J. Nicholson, L. Yip, S. E. Carty, and K. L. McCoy, Surgery 167, 160 (2020).

36. L. Giovanella, L. Bacigalupo, G. Treglia, and A. Piccardo, Endocrine 71, 285 (2021).

Figures

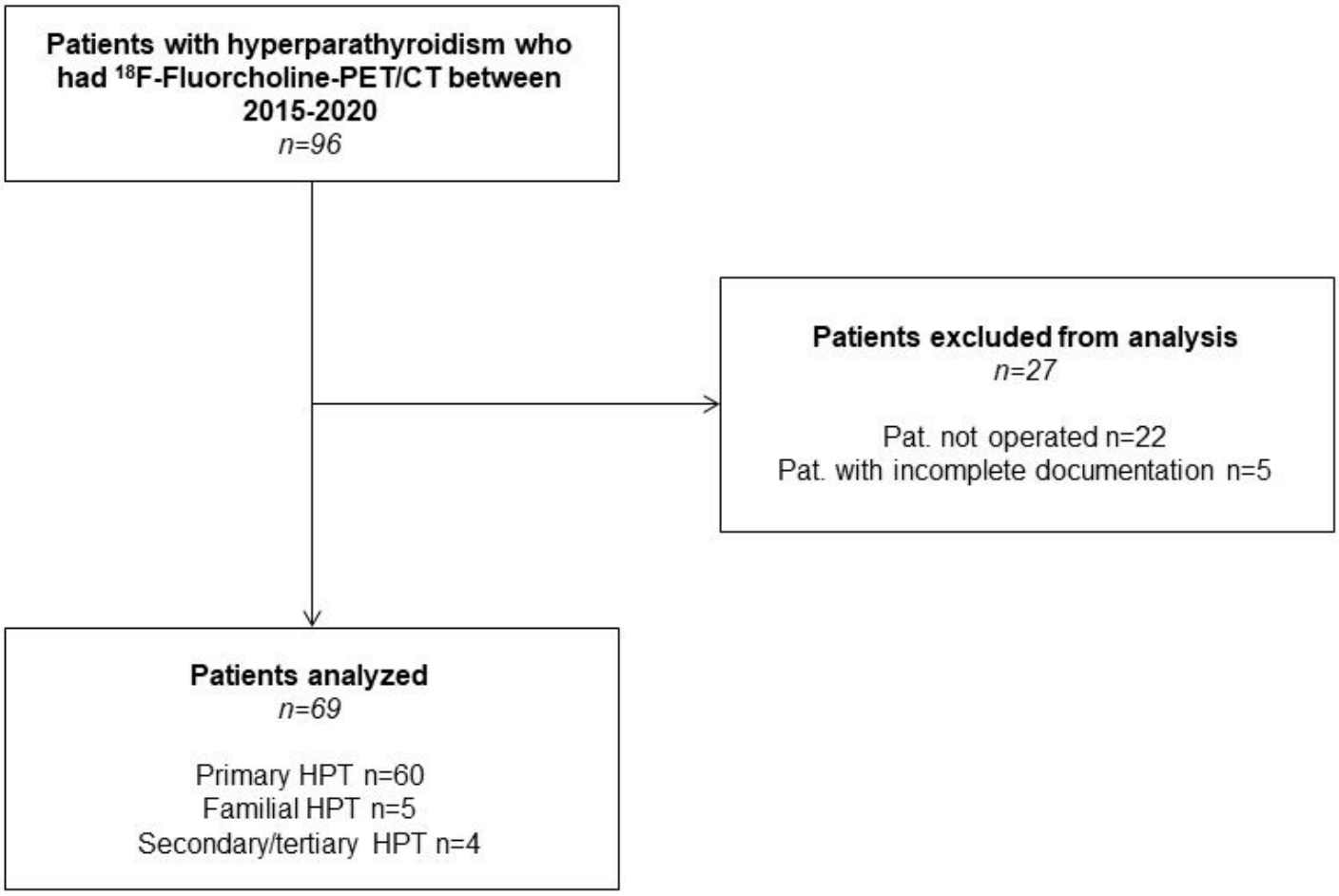

Figure 1

Selection of patients

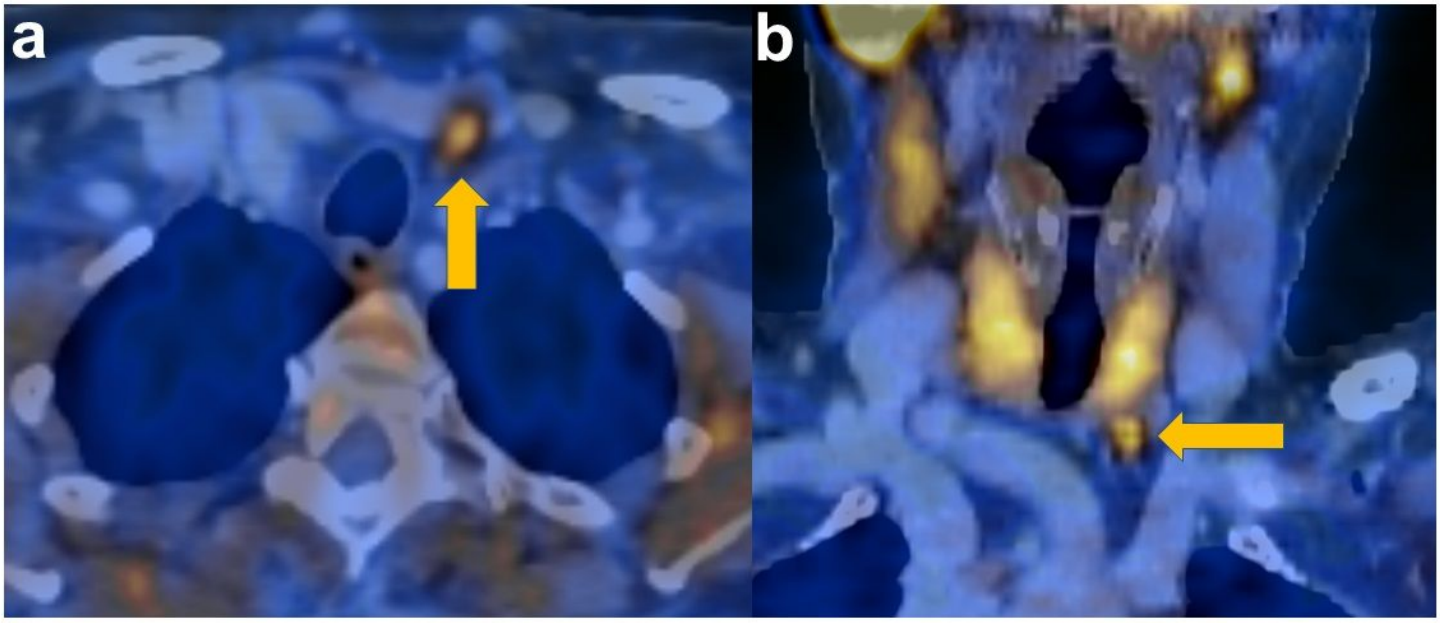

Figure 2

Patients vignette 18F-choline PET/CT (a) axial b) coronal section) of the patients vignette 1 described in the text showing a small cholin-positive lesion (arrow).

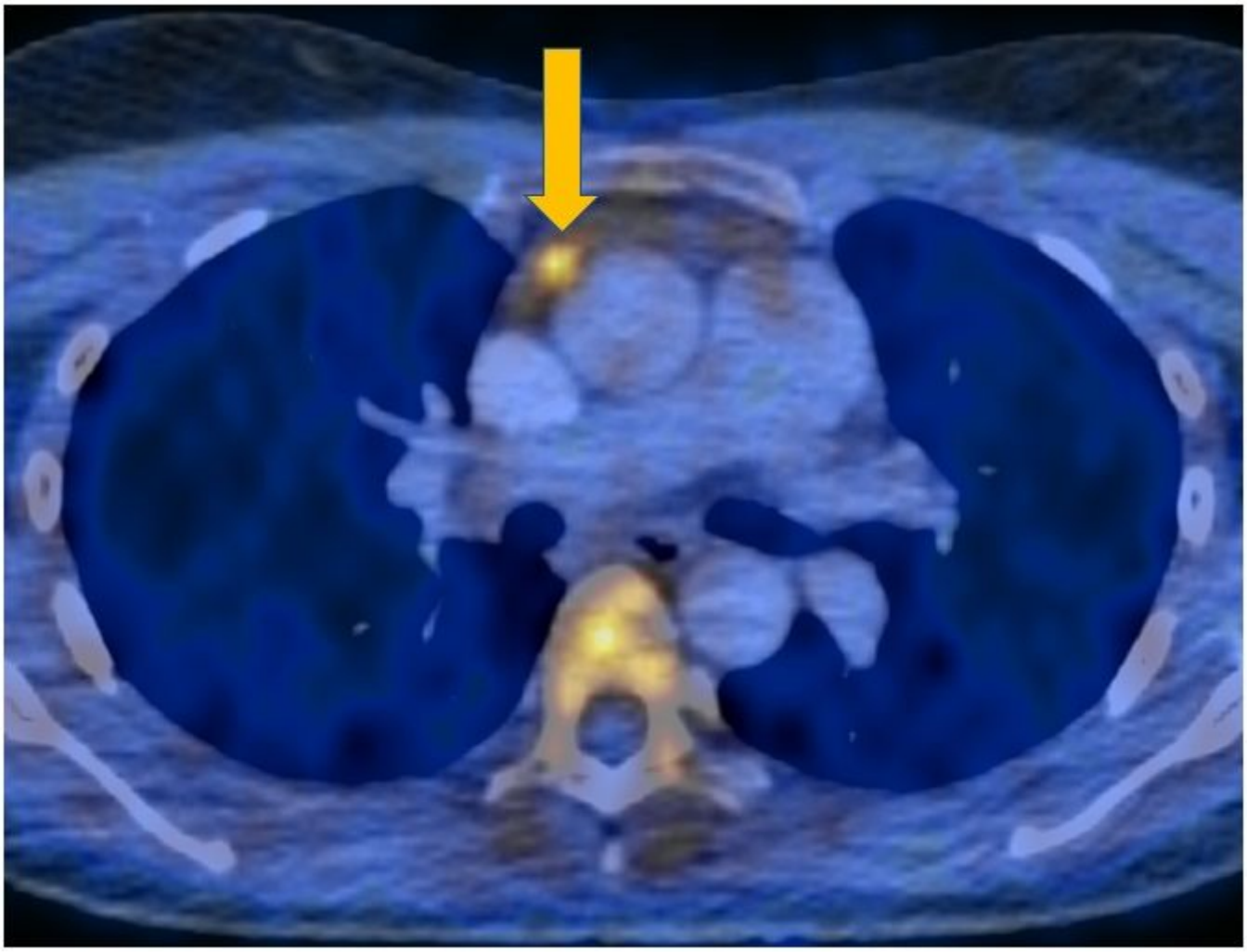

Figure 3

Patients vignette 18F-choline PET/CT (axial section) of the patients vignette 2 described in the text showing a cholin-positive lesion (arrow).