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Original Article

^{18}F-choline PET/CT in the study of primary hyperparathyroidism: Evaluation of the technique, visual and semi-quantitative analysis and correlation with other imaging techniques

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ABSTRACT

Objective: To assess the usefulness of performing a dual-time-point protocol in the acquisition of ^{18}F-choline (^{18}F-FCH) PET/CT in the pre-surgical localization of PHPT, and to demonstrate the impact of this imaging technique on the management and outcome-based surgical decision making, compared to other imaging techniques. To evaluate the diagnostic performance of the test to discriminate between pathological parathyroid gland and cervical lymph node, as well as to establish its correlation with other imaging techniques (scintigraphy, ultrasound, CT and MRI).
Patients and methods: We included 39 patients who underwent surgery for PHPT, in whom dual-time-point ^{18}F-FCH PET/CT was performed. Metabolic index of parathyroid (P-SUVmax; P-SUVpeak), lymph node (N-SUVpeak), thyroid (T-SUVpeak) and mediastinum (M-SUVpeak) uptake were analyzed visually and semiquantitatively in both images. PET/CT results were correlated with ^{99m}Tc-MIBI scintigraphy, ultrasound, MRI and CT.
Results: In 36 patients (92%), PET/CT was positive, localizing 38 pathological glands. The sensitivity (S) of PET/CT was 97% and positive predictive value (PPV) 94%. In the visual analysis, dual-time-point protocol was necessary in 61% of the cases. Correlation between PET/CT with MRI was 80%, with 4D-CT 50%, and with the other techniques <50%. P-SUVmax shows correlation with adenoma weight and size, and with presurgical PTH. The best cutoff point for SUVpeak to differentiate parathyroid vs. lymph node was 2.6 in early images (S = 70%; specificity = 75%; p = 0.007) and 0.86 for SUVpeak/T-SUVpeak index (S = 73%; specificity = 69%; p = 0.001).
Conclusion: ^{18}F-FCH PET/CT is an excellent preoperative localization technique in patients with HPTP with negative, doubtful or inconclusive imaging techniques, being of vital importance in guiding minimally invasive surgery. The dual-time-point protocol was necessary in more than half of the cases (61%). The SUVpeak cut-off points to discriminate between parathyroid gland and lymph nodes were statistically significant.

PET/TC con ^{18}F-colina en el estudio del hiperparatiroidismo primario: Valoración de la técnica, análisis visual y semicuantitativo y correlación con otras técnicas de imagen

RESUMEN

Objetivos: Valorar la utilidad del "dual-time-point" en la adquisición de la PET/TC con ^{18}F-colina (^{18}F-FCH) en la localización prequirúrgica del HPTP, y demostrar el impacto de esta técnica de imagen en el manejo y toma de decisiones quirúrgicas basadas en su resultado, en comparación con otras técnicas de imagen. Evaluar el rendimiento diagnóstico de la prueba para discriminar entre glándula paratiroides patológica y ganglio linfático, así como establecer su correlación con otras técnicas de imagen (gammagrafía, ecografía, TC y RM).
Material y métodos: Se incluyeron 39 pacientes intervenidos quirúrgicamente por HPTP, a los que se realizó una PET/TC con ^{18}F-FCH con el protocolo "dual-time-point". Se analizó visualmente y semicuantitativamente la captación y comportamiento de la paratiroides (P-SUVmax; P-SUVpico), ganglios linfaticos (N-SUVpico), tiroides (T-SUVpico) y mediastino (M-SUVpico) en ambas imágenes. Se correlacionaron los resultados de la PET/CT con los de la gammagrafía con ^{99m}Tc-MIBI, ecografía, RM y CT.

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Resultados: En 36 pacientes (92%), la PET/TC fue positiva, localizando 38 glándulas patológicas. La sensibilidad (S) de la PET/TC fue del 97% y el valor predictivo positivo (VPP) del 94%. En el análisis visual, el protocolo "dual-time-point" fue necesario en el 61% de los casos. La correlación entre PET/TC y RM fue del 80%, con 4D-TC del 50%, y con las demás técnicas <50%. P-SUVmax muestra correlación con el peso y tamaño del adenoma, y con la PTH prequirúrgica. El mejor punto de corte de SUVpico para diferenciar paratiroides vs ganglio linfático fue 2,6 en imágenes precoces (S = 70%; especificidad = 75%; p = 0,007) y 0,86 para el índice SUVpico/T-SUVpico (S = 73%; especificidad = 69%; p = 0,001).
Conclusión: La PET/TC con ^{18}F-FCH es una excelente técnica de localización prequirúrgica en pacientes con HPTP con técnicas de imagen negativas, dudosas o no concluyentes, siendo de vital importancia para guiar la cirugía mínimamente invasiva. El protocolo "dual-time-point", fue necesario en más de la mitad de los casos (61%). Los puntos de corte de SUVpico para discriminar entre glándula paratiroides y ganglios linfáticos fueron estadísticamente significativos.

Introduction

Primary hyperparathyroidism (PHPT) is the third most common endocrine disease[1] and affects women 2–3 times more often than men.[2] It is caused by hyperfunction of one or more parathyroid glands, which produce parathyroid hormone (PTH) in excess. Hyperfunctioning glands are usually solitary adenomas (85%). Approximately 15–20% of cases are caused by multiglandular disease (MGD),[3] usually multiple adenomas or hyperplasia, whereas parathyroid carcinoma represents less than 1%. Most cases of PHPT (95%) occur sporadically, but approximately 5% are part of hereditary syndromes, such as multiple endocrine neoplasia types 1, 2 and 4 (MEN-1, MEN-2 and MEN- 4).[4] Its diagnosis is biochemical, and usually half of the patients are asymptomatic at the time of diagnosis, being hypercalcemia a casual finding in a routine laboratory study.

Parathyroid surgery is the only curative option, being the pre-surgical localization by performing an image study of vital importance to achieve surgical success, since the trend in recent years has been to perform minimally invasive surgery.[5] However, there are cases in which the image studies are not sufficient to find the pathologic gland or there is multiglandular disease not detected by conventional techniques (cervical ultrasound, ^{99m}Tc-methoxy-isobutyl-isonitrile (^{99m}Tc-MIBI) parathyroid scintigraphy). As for the minimum or absolute criteria for indicating parathyroidectomy in patients with asymptomatic PHPT are: patients less than 50 years, hypercalcemia >1 mg above the upper limit of normal (>11.2 mg/dl), hypercalciuria >400 mg/24 h, osteoporosis (T < 2.5 SD at any location), decreased creatinine clearance (30%) without other cause and impossibility of medical follow-up.[6]

Negativity and/or discordance in first-line studies (cervical ultrasound and parathyroid scintigraphy) requires more accurate imaging, reducing the likelihood of bilateral neck exploration or reoperation. ^{18}F-Choline (^{18}F-FCH) PET/CT is a second-line image study with an excellent detection rate of pathologic glands in this circumstance.[7]

The objectives of this study are to assess the usefulness of performing a dual-point-imaging protocol in the acquisition of ^{18}F-FCH PET/CT in the pre-surgical localization of PHPT, and to demonstrate the impact of this imaging technique on the management and outcome-based surgical decision making, compared to other imaging techniques. To evaluate the diagnostic performance of the test to discriminate between pathological parathyroid gland and cervical lymph node, as well as to establish its correlation with other imaging techniques (scintigraphy, ultrasound, CT and MRI).

Patients and methods

Patient selection and study design

This was a descriptive, observational and retrospective study. We included 39 patients (28 women, 11 men), with a mean age of 56.62 ± 15.31 years, with biochemical diagnosis of hyperparathyroidism in whom ^{18}F-FCH PET/CT was performed.

The inclusion criteria for this study were the following: (1) patients who underwent surgery beacuse of primary hyperparathyroidism, (2) who had undergone ^{18}F-FCH PET/CT with the dual-time-point" protocol; (3) the indication for PET/CT was presurgical localization in cases with other negative, doubtful or inconclusive imaging techniques.

Therefore, all patients had other previous first-line imaging techniques (cervical ultrasound, ^{99m}Tc-MIBI scintigraphy, CT or MRI), which did not localize the pathologic gland for surgery.

Patients who did not have follow-up longer than 6 months or who did not have postoperative PTH values recorded in the electronic medical record, were excluded. The criteria for the surgical decision was based on the clinical guidelines of the Spanish Society of Surgeons.[6]

Laboratory study

The following biochemical parameters were analyzed:

- Preoperative calcium and PTH.
- Intraoperative PTH at baseline and 15 min after glandular exeresis.
- Calcium and PTH at 3 and 6 months after surgery.

Hypocalcemia is defined as serum calcium values < 8.5 mg/dL and hypercalcemia as values >10.5 mg/dL. Elevated PTH is considered to be >77 pg/dL, and an adequate decrease is defined as an absolute serum value decrease of >50% from the baseline absolute value at any time (Miami criterion).[8]

Surgical intervention and histopathological analysis

Regarding the type of surgical intervention, 29 patients underwent selective approach, 5 unilateral, and 5 bilateral.

The histopathological analysis of the surgical specimen was performed by an experienced operator, determining the histological result with hematoxylin-eosin staining on the samples.

The results of intraoperative localization, histology of the removed specimen, size and weight of the adenoma were collected.

F-FCH PET/CT procedure: image acquisition and processing

Images were acquired in two PET/CT devices, centered on the cervico-mediastinal region at early (5 min after injection) and delayed (after 60 min) times (dual-point-imaging), after the intravenous (IV) administration of ^{18}5 MBq of ^{18}F-FCH.

The equipment used for image acquisition and the protocol applied were: (A) Biograph mCT 20®, flowmotion technology (Siemens). Iterative 3D reconstruction with TOF (time of flight) was used with 2 iterations and 21 FWHM subsets of 5 mm in both early and delayed phase acquisitions (image 200 × 200) at a speed of 0.8 mm/sec. (B) Biographp 128_Vision 600 Edge, flowmotion technology (Siemens), 3D iterative reconstruction with TOF (time of flight) with 5 iterations and 4 FWHM subsets of 5 mm in both early and delayed phases (image 440 × 440) at a speed of 1.2 mm/sec.

The reconstructions of both devices are comparable due to their EARL Standard 2 accreditation.

Image analysis

The study was analyzed by two independent observers, considering as positive a focal uptake of the radiopharmaceutical in both early and delayed images in the cervical or mediastinal region, with anatomical correlation in CT. On the other hand, the study was considered negative if there was no focal uptake of fluorocholine observed in the cervico-mediastinal region or there were other foci due to other structures not suggestive of pathologic parathyroid glands.

The visual analysis to evaluate the dual-point-imaging protocol was performed independently by two nuclear physicians. The aim was to establish the superiority of one of the two imaging times. It was visually assessed if the focal uptake of fluorocholine corresponding to the pathological parathyroid, had a better identification in one of the two images, either because of its higher uptake intensity, its location or its better differentiation with the nearby structures.

In the semiquantitative analysis, pathologic parathyroid SUVmax and SUVpeak (P-SUVmax and P-SUVpeak), thyroid gland SUVpeak (T-SUVpeak), mediastinal SUVpeak (M-SUVpeak) and cervical lymph node SUVpeak (N-SUVpeak) were obtained in both early and delayed images. Two index were calculated in both images: P-SUVmax/T-SUVpeak and P-SUVmax/M-SUVpeak; and four index only in delayed images: P-SUVpeak/T-SUVpeak, N-SUVpeak/T-SUVpeak, P-SUVpeak/M-SUVpeak and N-SUVpeak/M-SUVpeak.

Other imaging techniques

The results of ^{18}F-FCH PET/CT were compared with other imaging techniques that were performed before the PET study for pre-surgical localization: dual-phase ^{99m}Tc-MIBI scintigraphy (36), cervical ultrasound (26), cervical CT (16), cervical MRI (5) and cervical 4D-CT (8).

About the ^{99m}Tc-MIBI parathyroid scintigraphy, a dual-phase acquisition protocol was performed, with two planar images 15 min and 2 h after the IV administration of 740 MBq of the radiopharmaceutical, and early SPECT/CT (after the acquisition of the 5 min planar image).

For contrast-enhanced CT, the protocol of our center includes the IV administration of 100 cc of contrast at 2 cc/sec with a delay of 55 seconds after contrast administration.

In relation to 4D-CT, a CT scan without contrast is first acquired, followed by a CT scan in the arterial phase 20 seconds after contrast administration and another in the venous phase at 80 seconds, with the addition of the fourth dimension being the enhancement over time in the different phases. Nodular images showing enhancement in the arterial phase with washout in the venous phase were considered pathological parathyroid glands.

Statistical analysis

Statistical analysis was performed using SPSS version 29.0.

Pearson's correlation test was used to calculate the correlation between P-SUVmax with calcium, PTH levels, and adenoma size and weight.

The Mann-Whitney U test was used to assess the differences between: P-SUVmax early vs delayed, the early vs delayed P-SUVmax/T-SUVpeak index and the early vs delayed P-SUVmax/M-SUVpeak index.

In addition, to evaluate the diagnostic performance of the test to discriminate between pathological parathyroid gland and lymph node, it was evaluated by receiver operating characteristic (ROC) curve analysis, comparing P-SUVpeak vs N-SUVpeak, in early and delayed images and the following index in delayed images: P-SUVpeak/T-SUVpeak vs N-SUVpeak/T-SUVpeak and P-SUVpeak/M-SUVpeak vs N-SUVpeak/M-SUVpeak.

Ethical considerations

The protocol of the present study was previously approved by the Ethics Committee for Investigation with medicinal products of the Salamanca Health Area (CEIm Code: PI 2023 07 1355), authorising the collection and analysis of the corresponding data. The study was conducted in accordance with the provisions of the Declaration of Helsinki[20] and in compliance with international ethical standards for research on human subjects, guaranteeing the protection, privacy and confidentiality of the participants' data.

Results

Glandular localization and surgical success

In the 39 patients studied, ^{18}F-FCH PET/CT was positive in 36 of them, locating 38 pathologic glands. In relation with their location, 16 of them were located in the posterior aspect of the inferior pole of the left thyroid lobe (including 3 ectopic, 1 paratracheal and 2 paraesophageal), 2 posterior to the superior pole of that lobe, 15 posterior to the inferior pole of the right thyroid lobe (1 ectopic paratracheal), and another 5 ectopic: 4 right intrathyroidal and one located at the left paralaryngeal level.

During surgery the pathological gland was located in 34 patients (87.2%), 32 of them had solitary adenomas and 2 double adenomas. All patients had normalization of PTH levels.

In the remaining 5 cases there was no normalization of PTH:

- Two of the glands located at the right intrathyroid level were false positive for ^{18}F-FCH PET/CT. During surgery the right thyroid lobe was removed, and histopathological analysis determined a papillary thyroid carcinoma and a thyroid oncocytic adenoma.
- Another case was a false negative ^{18}F-FCH PET/CT, in a patient with multiglandular disease not localized on any other image test.
- In the remaining two cases the PET/CT was negative, and even so a bilateral neck exploration was performed. The hyperfunctioning gland was not found during surgery.

Correlation with other imaging techniques

The concordance between PET/CT and the other techniques was 12/36 with dual-phase ^{99m}Tc-MIBI scintigraphy, 11/26 with cervi-

Table 1
Concordance between PET images and other imaging techniques. Histological confirmation of the localization by imaging test.

Imaging technique	Concordance with PET/CT	False positives	False negatives	Sensitivity
Scintigraphy	33%	3	15	22%
Cervical ultrasound	42%	0	15	42%
Cervical CT	37%	0	10	38%
Cervical MRI	80%	1	1	60%
4D CT	50%	1	5	25%

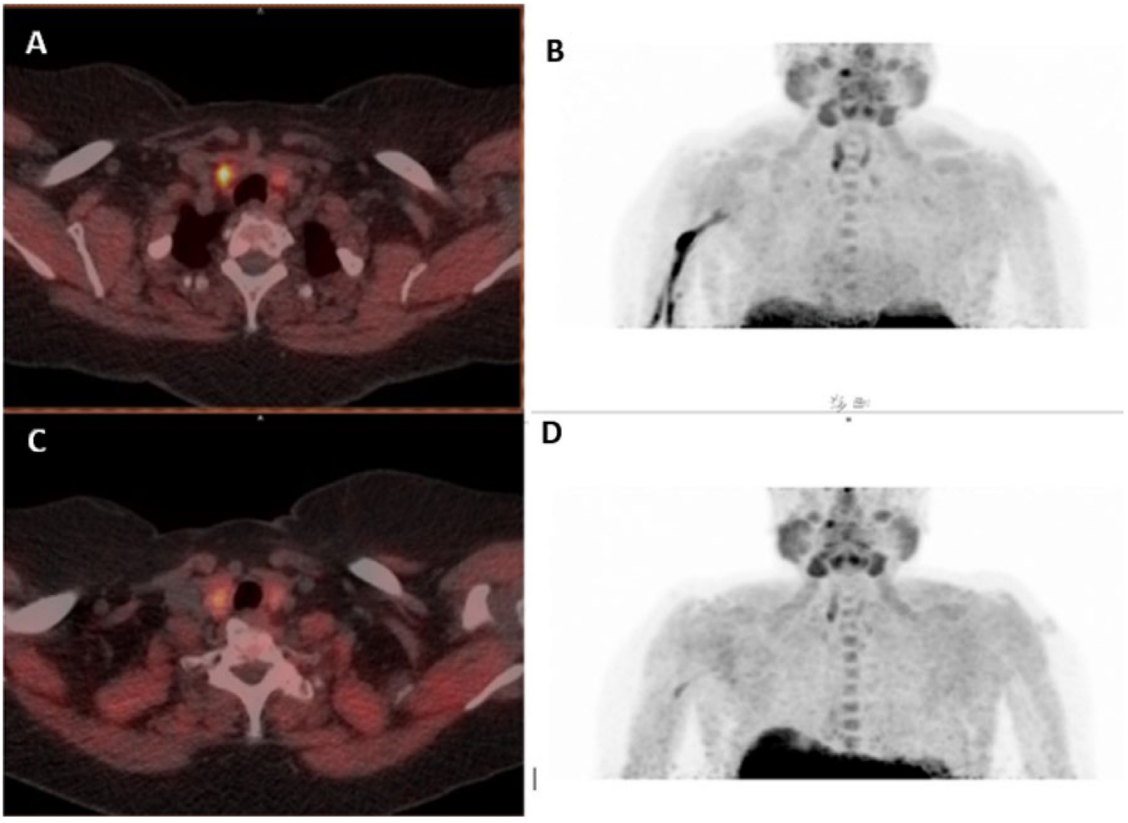

Figure 1. Right inferior pathologic parathyroid gland. A, B: early images. C, D: delayed images. A, C: axial PET/CT fusion images. B, D: maximum intensity projection (MIP) images. Focal uptake of ^{18}F-FCH located inferior to the right thyroid lobe with greater uptake in the early images (A, B).

cal ultrasound, 6/16 with cervical CT, 4/8 with 4D-CT and 4/5 with cervical MRI.

Scintigraphy localized 11 glands, 8 of which were confirmed during surgery. Regarding the rest of the techniques, these were the results: cervical ultrasound 11/26, cervical CT 6/16, 4D-CT 2/8 and MRI 3/5. It is important to emphasize that in 11/39 cases, the only positive test was PET/CT. The sensitivity of PET/CT is 97% and the PPV is 94% (Table 1).

Correlation with analytical and histological parameters

Regarding analytical and histological values, correlation between P-SUVmax with weight (early: R = 0.86; delayed: R = 0.62) and size (early: R = 0.69; delayed: R = 0.62) of the adenoma, as well as with pre-surgical PTH (early: R = 0.66; delayed: R = 0.68) was observed. All of them with p = 0.000. No correlation was obtained with pre-surgical calcium.

Analysis of the dual-time-point technique

In the visual analysis of the 36 ^{18}F-FCH PET/CT positive studies: in 14 cases the delayed image provides relevant information, in 8 the early image; in the other 14, both provide the same information (Fig. 1).

No early washout of pathological glands was observed, 12 patients showed stable uptake in both images, and 24 patients showed a decrease in radiopharmaceutical avidity in the delayed image.

In the semiquantitative analysis, the early P-SUVmax value (4.79 ± 2.73) decreased in the delayed images (4.29 ± 2.39) in 66.7% of the patients. These differences were not statistically significant (n.s). On the other hand, the same behavior was observed in the T-SUVpeak, with a decrease in its value in the delayed images in 88.9% (early SUVpeak: 2.97 ± 1.22; delayed SUVpeak 2.52 ± 0.99) (Table 2).

The P-SUVmax/T-SUVpeak index does not show significant differences between early and delayed imaging 1.74 ± 1.21 vs 1.79 ± 0.72; but the early vs delayed P-SUVmax/M-SUVpeak index (p = 0.000), 3.36 ± 2.34 vs 5.82 ± 3.75, respectively (Table 3).

ROC curves showed a cutoff point of 2.6 for P-SUVpeak vs N-SUVpeak in early images (S = 70%, E = 75%, p = 0.007) and 2 in delayed images (S = 67%, E = 70%, p = 0.005). The cutoff point for P-SUVpeak/T-SUVpeak vs N-SUVpeak/T-SUVpeak index was 0.86 (S = 73%, E = 69%, p = 0.001) and 3 for P-SUVpeak/M-SUVpeak vs N-SUVpeak/M-SUVpeak index (S = 66%, E = 68%, p = 0.007) (Table 4).

Table 2
Percentage change in SUV values in early vs delayed imaging.

Semiquantitative value	Early (mean ± SD)	Delayed (mean ± SD)	Percentage change
P-SUVmax	4.79 ± 2.73	4.29 ± 2.39	66.7%
T-SUVpeak	2.97 ± 1.22	2.52 ± 0.99	88.9%
M-SUVpeak	1.71 ± 1.07	1.01 ± 1.03	94.7%
N-SUVpeak	2.45 ± 1.05	1.95 ± 0.94	94.7%

Table 3
Semiquantitative analysis of P-SUVmax in early and delayed images.

Semiquantitative analysis	Early (mean ± SD)	Delayed (mean ± SD)	p-value
P-SUVmax	4.79 ± 2.73	4.29 ± 2.39	n.s.
P-SUVmax/T-SUVpeak	1.74 ± 1.21	1.79 ± 0.72	n.s.
P-SUVmax/M-SUVpeak	3.36 ± 2.34	5.82 ± 3.75	0.000

Table 4
ROC curve cutoff points.

ROC Index	Cutoff point	Sensitivity (%)	Specificity (%)	p-value	Confidence interval (95%)
P-SUVpeak vs N-SUVpeak (early image)	2.6	70	75	0.007	(0.583, 0.864)
P-SUVpeak vs N-SUVpeak (delayed image)	2.0	67	70	0.005	(0.586, 0.881)
P-SUVpeak/T-SUVpeak vs N-SUVpeak/T-SUVpeak	0.86	73	69	0.001	(0.603, 0.885)
P-SUVpeak/M-SUVpeak vs N-SUVpeak/M-SUVpeak	3.0	66	68	0.007	(0.732, 0.968)

Disscusion

In the past few years, interest in ^{18}F-FCH PET/CT has grown due to the increase in PET/CT equipment and the superiority of PET/CT technology over scintigraphy, as well as the complementary role it provides in the pre-surgical localization of PHPT to conventional image studies.

Dual-phase ^{99m}Tc-MIBI scintigraphy is the most commonly used technique and is it based on the differential washout of the tracer from thyroid tissue compared to hyperfunctioning parathyroid tissue. Combined with SPECT/CT allows a better localization of the parathyroid adenoma.[9] However, some of its disadvantages include lower sensitivity in small lesions, difficult to detect due to the limited spatial resolution of the test, or patients with multiglandular disease, as well as lower specificity in patients with thyroid nodules.[10] In relation to our sample, 66.7% of the patients had a negative scintigraphy.

Choline is a precursor molecule of phospholipids, necessary for membrane synthesis and cell proliferation, and labeled with F-18, it allows localization of pathological parathyroid glands. In a 2019 systematic review, a sensitivity of 80%–100% and a specificity of 95%–100% were obtained.[11] Treglia et al.[12] performed a meta-analysis on ^{18}F-FCH PET/CT as a preoperative localization technique in PHPT. Fourteen studies were selected, resulting, by patient: sensitivity of 95%, PPV of 97% and detection rate of 91%. In the analysis by lesion: sensitivity and PPV of 92%, in both cases. Likewise, Kluijfhout et al.[13] reported the results of a Dutch multicenter study, with 44 patients, on the use of ^{18}F-FCH PET/CT as a second-line imaging, demonstrating its usefulness in patients with PHPT and inconclusive conventional imaging (cervical ultrasound + ^{99m}Tc-MIBI scintigraphy). PET/CT was positive in 34/44 patients. Out of the 34 pathologic glands resected, PET/CT was able to successfully localize 33, with only one false positive (PPV 97.1%). The comparaison of the 10 patients with negative PET/CT and the 34 patients with positive PET/CT showed no significant differences in age, sex, preoperative calcium, history of previous cervical surgery or concomitant multinodular thyroid disease. In our sample, the sensitivity of PET/CT is 97% and the PPV is 94%.

There are several studies that propose ^{18}F-FCH PET/CT as a first-line imaging modality due to its hight detection rate. Broos WAM et al.[22] performed a study with a large cohort of 271 patients, in wich 139 underwent parathyroidectomy with a rate of correct detection of 96% and 90%, on a per patient-based and per lesion-based analysis, respectively. Likewise, in complex cases such as in patients presenting MEN 1 syndrome, the sensitivity of ^{18}F-FCH PET/CT in detecting hyperfunctioning parathyroid glands ranged from 98.5 to 100%,[23] and it should be considered as a clinical indication for ^{18}F-FCH PET/CT.[24]

^{18}F-FCH PET/CT has several advantages over scintigraphy, apart from its improved sensitivity. Firstly, it requires less acquisition time, which results in more comfort for the patient, since scintigraphy requires 20 min for planar images (10 min for each acquisition), carried out 10 and 120 min after the inyection, and 13 min for SPECT/CT in early phase. Currently, we perform PET/CT on a digital equipment, which consumes 8 min, 4 min for each acquisition (at 5 and 60 min post-injection).

Regarding other imaging techniques, only 5 patients out of the 39 in the sample studied have cervical MRI, so studies with a larger sample of patients who have undergone MRI may be required to analyse the correlation. Of the two patients where the MRI did not correctly diagnose the pathological gland, one was a false negative where the MRI was reported as negative for pathological parathyroid glands, and the other was a false positive where the gland was mislocalised. About CT-4D, only 8 patients underwent this imaging technique, and there were 5 false negatives. 4D-CT has a better spatial resolution than PET/CT and it would have been expected that both techniques, despite the small number of patients with 4D-CT, would be comparable. On the other hand, PET/CT shows a higher sensitivity and detection rate,[21] and identifies more accurately ectopic glands and multiglandular disease, as argued in the literature.

Another important aspect is the radiation exposure of the patient undergoing these two scans. The ^{18}F-FCH PET/CT studies have an advantage in dosimetry compared to the conventional study with ^{99m}Tc-MIBI. In our center it is usual to administer an activity of ^{18}5 MBq of ^{18}F-FCH, in contrast to the usual 740 MBq in ^{99m}Tc-MIBI. Following the patient dose estimation procedure recommended by the ICRP in its publication No. 128,[14] this implies an absorbed dose of 3.7 mSv in the use of ^{18}F-FCH PET/CT versus 6.7 mSv in ^{99m}Tc-MIBI. Therefore, we find that this study in PET/CT provides approximately half of the dose. The values obtained in our center agree with the results found after a bibliographic review of

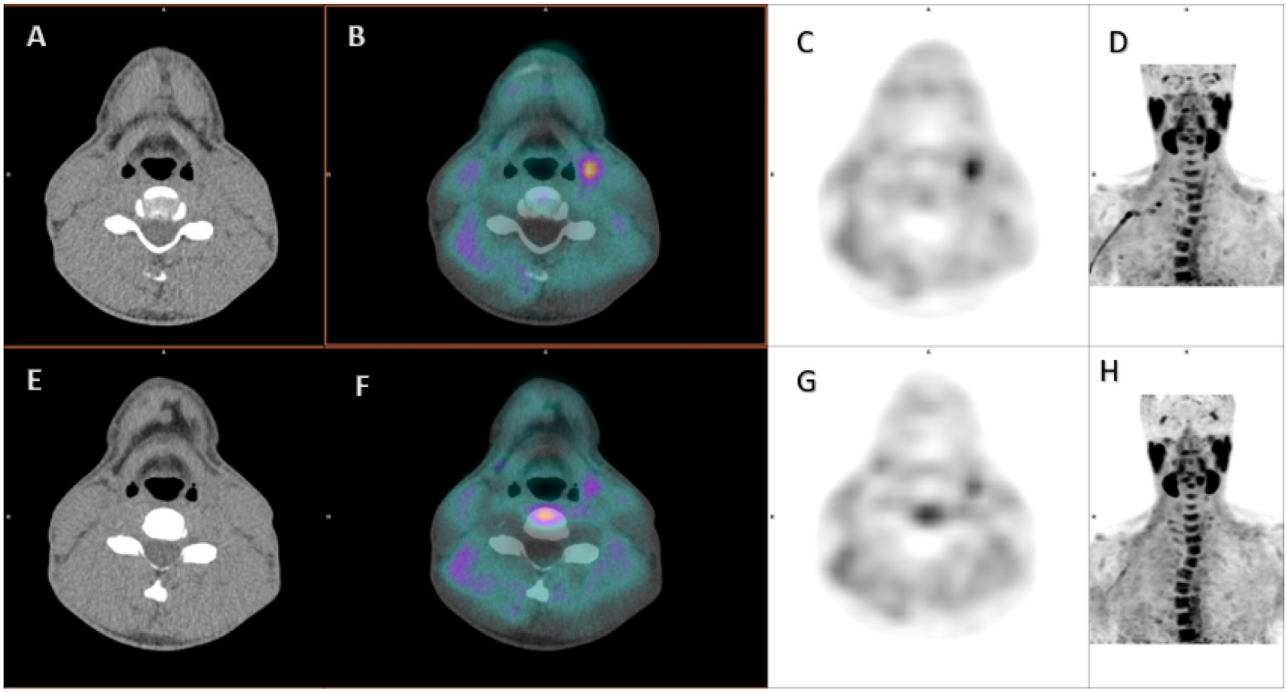

Figure 2. Focal uptake located at left paralaryngeal level that corresponds with pathological ectopic parathyroid gland with better visualization in early images. A, B, C, D: early images. E, F, G, H: delayed images. A, E: axial CT images. B, F: axial PET/CT fusion images. C, G: axial PET images. D, H: MIP images.

the experience of other professionals. In the worst-case scenario, similar dose is estimated for both studies,[15] thus maintaining the overall advantage of the ^{18}F-FCH PET/CT study over ^{99m}Tc-MIBI scintigraphy.

Regarding the protocol of this technique, it changes according to the possibilities of each center and the gained experience. European guidelines recommend the acquisition of an image 60 min after the injection of 100–300 MBq or 1.5–3.2 MBq/kg and, if possible, the acquisition of an early image at 5 min (starting with a dynamic acquisition followed by a static one). Another proposed option is to perform an acquisition 20 min after injection, and then perform delayed imaging in case the study is negative.[16] Due to the pressure of hospital care, we wanted to evaluate the usefulness of the dual-time-point protocol in our population in order to manage without one of the two images and reduce the PET/CT occupancy time; however, in our study we have demonstrated the usefulness of combining these images in two times.

Based on the recommendations of the European Association of Nuclear Medicine, in our center we acquired an early image at 5 min and a delayed image at 60 min.[16] Early imaging, typically acquired within the first 5–10 min after radiopharmaceutical injection, is useful for rapid and early identification of the focal uptake of fluorocholine in hyperfunctioning parathyroid glands, which is useful in centers where time is a critical factor due to the workload. As a disadvantadge, the rapid distribution of the radionuclide results in increased background activity in other structures such as the thyroid gland, lymph nodes or mediastinum, which can complicate the interpretation in some cases and make it difficult to identify the pathologic gland, decreasing the contrast between the parathyroid glands and the surrounding tissue. This circumstance could be related to potential false positives because the initial uptake in other anatomical structures or inflammatory processes can lead to erroneous interpretations, due to the fact that choline is a marker of cell proliferation that is not specific to this pathology. In the study caried out by Prabhu et al.,[17] they perform a dynamic study for the identification of the pathologic gland, obtaining higher SUV values in the first 1–2 min after asquisition with a progressive decrease in the images during the study. On the other hand, Broos WAM et al.[18] analyze the behavior and washout during the acquisition of a dynamic study, observing a lower uptake in lymph nodes with respect to parathyroid adenomas, and describe the first 5 min as the most accurate time to discriminate parathyroid adenomas vs lymph nodes. In our sample, the thyroid gland, mediastinum and lymph nodes, decrease uptake intensity and SUV values in the delayed images, being the percentage of change higher in these structures than the visualized in the parathyroid glands (Table 3). This allows a more differentiated and detailed evaluation of the radiopharmaceutical accumulation allowing a better lesion/background ratio with better contrast between the hyperfunctioning parathyroid glands and the surrounding tissue, facilitating its localization. As an inconvenience, it requires longer waiting time for the patient making them staying more time in the center, and longer time of occupation of the equipment. On the other hand, in our opinion, performing only the delayed images carries the risk of potential false negatives in cases in which the pathologic glands show scarce activity in the delayed imaging, especially in small adenomas with low metabolic activity.

In the visual analysis of ^{18}F-FCH PET/CT of our sample, in 14/36 cases both images provided the same information, however in the other 22 (8 cases in the early images and 14 in the delayed), one of the two imaging times provided a better localization of the gland (Fig. 2).

Referring to the semiquantitative analysis, parathyroid SUVmax decreased in delayed images in 66.7% of patients, in agreement with the reviewed literature. In a preliminary study of 14 patients by Prabhu et al.,[17] all patients had higher parathyroid SUVmax on early dynamic study compared to delayed imaging. This could be related to a higher vascularization seen after injection of the radiopharmaceutical in the early images.[15]

On the other hand, we calculated index that could provide a more reproducible value between patients, with different conditions and PET/CT equipment. In our study, we obtained a cutoff point of 0.86 for the SUVpeak/T-SUVpeak index to discriminate between a pathological parathyroid and a lymph node, with

sensitivity and specificity values of 73% and 69%, respectively (Table 4).

In relation to the analytical and histological values, correlation of P-SUVmax was observed with the weight and size of the adenoma, as well as with preoperative PTH. No correlation was observed with presurgical calcium. In the study performed by LA. Boccalatte et al.,[19] they obtained a statistically significant correlation between preoperative PTH vs adenoma size (Spearman's coefficient = 0.66; p = 0.0014), with no correlation with calcium.

Conclusion

^{18}F-FCH PET/CT is an excellent preoperative localization technique recommended in patients with PHPT with other negative, equivocal or inconclusive imaging techniques, showing good correlation with intraoperative findings with a sensitivity of 97% and a PPV of 94%. This technique has an important role in guiding minimally invasive surgery.

Pathologic parathyroid uptake shows a good correlation with adenoma characteristics (adenoma weight and size) and biochemical parameters (pre-surgical PTH).

The dual-time-point protocol was necessary for the localization of the pathological parathyroid gland in more than half of the cases (61%), so we can conclude that both images are needed to perform a correct pre-surgical localization.

The best SUVpeak cutoff point to discriminate between parathyroid gland and lymph nodes was 2.6 with a sensitivity of 70% and specificity of 75% in early imaging and 0.86 for the SUVpeak/T-SUVpeak index, with sensitivity and specificity values of 73% and 69%, respectively.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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