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The efficacy of fluorine-18-choline PET/CT in comparison with ^{99m}Tc-MIBI SPECT/CT in the localization of a hyperfunctioning parathyroid gland in primary hyperparathyroidism

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Aim **The aim of this study was to determine the role of fluorine-18-choline (^{18}F-FCH) PET/CT in comparison with technetium-99m-methoxyisobutylisonitrile (^{99m}Tc-MIBI) single-photon emission computed tomography/computed tomography (SPECT/CT) in primary hyperparathyroidism and to investigate whether maximum standardized uptake value (SUV_{max}) may be indicative of disease severity.**

Patients and methods **Thirty-five primary hyperparathyroidism patients (24 females, 11 males, mean age: 55.31 ± 12.27, range: 25–72 years) who underwent ^{99m}Tc-MIBI SPECT/CT and ^{18}F-FCH PET/CT and had inconclusive neck ultrasonography (USG) were studied. The diagnostic power of both modalities and the relationship between SUV_{max} and biochemical [serum parathormone (PTH), calcium, phosphorus, vitamin D3 levels, urinary calcium excretion/24 h] and clinical (bone mineral densitometry and urinary USG results) parameters were analyzed.**

Results **In 29 of 35 patients, ^{99m}Tc-MIBI SPECT/CT and ^{18}F-FCH were concordant ($\kappa = 0.64$, $P = 0.001$). In five of 35 patients with a negative SPECT/CT, ^{18}F-FCH PET/CT accurately localized parathyroid adenomas. In one patient, ^{18}F-FCH was false negative and ^{99m}Tc-MIBI SPECT/CT showed the lesion. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of ^{99m}Tc-MIBI SPECT/CT and ^{18}F-FCH PET/CT were calculated to be 78, 100, 100, 70, 86%, and 96, 100, 100, 93, and 97%, respectively. SUV_{max} was correlated with lumbal *T* scores ($P = 0.026$). The mean serum PTH levels were significantly higher ($P = 0.026$) and lumbal and femur *T* scores were significantly lower ($P = 0.04$ and 0.008) in patients with SUV_{max} greater than 4.4 (i.e. the mean SUV_{max} calculated in positive cases).**

Conclusion **^{18}F-FCH PET/CT has a high diagnostic power in primary hyperparathyroidism and can be used for further evaluation of patients with inconclusive neck USG and ^{99m}Tc-MIBI SPECT/CT. SUV_{max} of the hyperfunctioning parathyroid gland seems to be predictive of disease severity in terms of serum PTH and bone mineral densitometry results. Studies with larger patient groups are needed to support these data.** *Nucl Med Commun* **00:000–000**
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Keywords: choline, PET, PET/CT, primary hyperparathyroidism

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Introduction

Hyperparathyroidism is a common endocrinological disorder that is caused by hypersecretion and release of parathormone (PTH). Serum calcium (Ca) levels are elevated and PTH levels are usually high or can sometimes be inappropriately normal. Primary hyperparathyroidism is the clinical state where one or more parathyroid glands are hyperfunctioning [1]. Single parathyroid adenoma is the most common cause of primary hyperparathyroidism (85%), followed by multiple adenomas, parathyroid hyperplasia, and parathyroid carcinoma [2,3].

Primary hyperparathyroidism is usually incidentally diagnosed at the asymptomatic stage by laboratory measurements or can be misdiagnosed because of nonspecific mild symptoms and patients may soon present with complications. Two critical organs affected at the late stage are the kidneys and bones. Hypercalciuria, nephrolithiasis, and a decrease in the glomerular filtration rate can be seen. Cortical bone resorption causes a high risk of fracture. Complications can be avoided or deteriorated functions can be restored partially by appropriate treatment on time [4].

The definitive treatment of primary hyperparathyroidism is surgical excision of the hyperfunctioning gland. Bilateral neck exploration is an old approach with a success rate of about 95% and is no longer a method of

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choice, except for a few complicated cases. Minimal invasive parathyroidectomy is a simpler operation, but localization of the hyperfunctioning parathyroid gland is needed, by preoperative and/or intraoperative radiological or functional imaging studies, before the operation [5].

Once primary hyperparathyroidism is diagnosed, neck ultrasonography (USG) is the first step in preoperative localization of the hyperfunctioning parathyroid gland because it is a simple, cheap and highly sensitive method. Technetium-99m-methoxyisobutylisonitrile (MIBI) dual-phase single-photon emission computed tomography/computed tomography (SPECT/CT) is the preferred complementary nuclear imaging method in primary hyperparathyroidism. It is based on the rational that hyperfunctioning parathyroid glands show delayed activity retention compared with neighboring thyroid tissue and reported to have a high sensitivity, specificity, and accuracy [6]. SPECT/CT provides better delineation of parathyroid adenoma with a higher resolution and thus higher detection rates, confirmation of diagnosis, and more precise localization of the hyperfunctioning gland [7]. Although the combined use of USG and scintigraphy is usually reliable enough for preoperative localization, both can be equivocal or negative in some cases. Small or ectopic adenomas can be missed by the conventional approach and additional imaging may be needed. Among nuclear medicine imaging methods, some PET/CT agents have been trialed before for this purpose [8,9]. Fluorine-18-choline (^{18}F-FCH) has been proposed as a potential tool for parathyroid imaging, with better sensitivity and accuracy compared with ^{99m}Tc-MIBI [10]. ^{18}F-FCH is integrated into the structure of the cell membrane in proliferating cells [11]. Although the major data available on ^{18}F-FCH PET/CT are on its role in cancer, primarily prostate, parathyroid adenoma has now emerged as a benign condition in which it can be beneficial. A possible explanation for ^{18}F-FCH uptake in benign parathyroid adenomas has been suggested to be increased phospholipid-dependent choline kinase activity arising from hypersecretion of PTH [12].

The aim of this study was (i) to evaluate whether ^{18}F-FCH PET/CT may play a role in the detection of hyperfunctioning parathyroid glands in the preoperative period in comparison with ^{99m}Tc-MIBI SPECT/CT in patients with an inconclusive preoperative neck USG (ii) to investigate whether maximum standardized uptake value (SUV_{max}) may be predictive of disease severity by exploring a possible relationship between SUV_{max} levels of hyperfunctioning parathyroid gland and serum PTH, Ca, phosphorus (P) levels, and bone mineral densitometry (BMD) results.

Patients and methods

Patients

A total of 35 patients (age > 18 years) who were clinically and biochemically diagnosed with primary hyperparathyroidism, but had an inconclusive preoperative neck USG and were referred to Department of Nuclear Medicine, Medical Faculty, Ankara University for ^{99m}Tc-MIBI SPECT/CT and ^{18}F-FCH PET/CT between November 2017 and January 2018 were included in the study. Exclusion criteria were as follows: (i) secondary or tertiary hyperparathyroidism, (ii) existence of chronic renal disease, and (iii) evidence of any other malignancy including thyroid and parathyroid carcinoma. History of previous thyroid/parathyroid surgery, recent serum PTH, Ca, P levels, urinary Ca excretion/24 h, neck USG and ^{99m}Tc-MIBI parathyroid SPECT/CT findings, BMD of proximal femur and lumbal vertebrae and urinary USG for skeletal and renal involvement, clinical follow-up results as well as results of histopathological examination in cases who underwent parathyroidectomy were recorded.

^{99m}Tc-MIBI SPECT/CT protocol and image interpretation

Following an intravenous injection of 740 MBq ^{99m}Tc-MIBI, early (10 min) and late (120 min) static images of 10 min of the neck and thorax were obtained using a dual-head combined SPECT/BT camera (Optima NM/CT 640; General Electric Company, Tirat Hacarmel, Israel) with a low-energy high-resolution collimator in a 256 × 256 matrix. SPECT/CT was performed at the 120th minute immediately after static images for the neck and the thorax. SPECT data were acquired over 360°, yielding 60 projections at 15 s/projection in a 128 × 128 matrix with a 1.0 zoom. Computed tomography (CT) parameters were a tube current of 20 mAs, a voltage of 140 kVp, and 2.5 mm slice thickness.

All parathyroid SPECT/CT studies were re-evaluated by two nuclear medicine specialists retrospectively, who were blinded to all clinical, radiological, and laboratory data. For equivocal cases, a consensus was achieved. The ^{99m}Tc-MIBI SPECT/CT study was considered positive if focal activity retention was detectable on both early and late static images. Focal increased uptake areas identified only by SPECT, but not on planar images and with a corresponding asymmetrical nodular lesion on CT, were also interpreted as a positive scan.

^{18}F-FCH PET/CT protocol and image interpretation

PET/CT images of the neck and thorax were acquired using a combined PET/CT scanner (Discovery 710; General Electric Company, Milwaukee, Wisconsin, USA) 45–60 min after an intravenous injection of ~100 MBq ^{18}F-FCH in the supine position. PET images were acquired for 2 min/bed position. PET images were reconstructed with noncontrast low-dose CT images. CT images were obtained with a standardized protocol of 140 kV, 70 mA, tube rotation time of 0.5 s/rotation, a pitch of 6, and a slice thickness of 5 mm. Patients were allowed to breathe normally during the procedure. Attenuation-corrected PET/CT fusion images were reviewed in three planes (transaxial, coronal, and sagittal) on Advance

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Workstation Volumeshare 5 (GE Medical Systems, Buc, France).

All PET/CT images were evaluated by two nuclear medicine specialists. A focal uptake higher than the adjacent background activity located in the neck or mediastinum and with a corresponding nodular lesion on CT was considered positive.

Statistical analysis

The descriptive statistics of the variables were performed first (mean, median, and 25–75% range). Results of neck USG, ^{99m}Tc-MIBI SPECT/CT, and ^{18}F-FCH PET/CT results were compared by considering clinical and/or histopathological examination results as the gold standard.

For comparison of agreement between ^{18}F-FCH and ^{99m}Tc-MIBI results, the κ-test was used. Normality was checked using the Kolmogorov–Smirnov test. For normally distributed variables ($P > 0.05$), Pearson's correlation analysis was used and a correlation constant was calculated (P). Student's t-test was carried out to compare the means of two groups. The compatibility of two functional imaging modalities was analyzed statistically using Pearson's χ^2-test. For each patient, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for ^{18}F-FCH PET/CT.

Values of P less than 0.05 were considered significant. Statistical analysis was carried out using the Statistical Package for Social Sciences, 17.0 (SPSS Inc., Chicago, Illinois, USA).

Results

A total of 35 patients (24 females, 11 males, mean age: 55.31 ± 12.27, range: 25–72 years) who fulfilled the inclusion criteria were enrolled in the study. Descriptive statistics of the variables are shown in Table 1. BMD results could be obtained for 21 (60%) patients. Urinary USG was performed to 23 (65%) patients. Two patients had undergone unilateral parathyroidectomy before. Three patients had a history of total thyroidectomy and two patients had undergone a lobectomy.

Table 1 Descriptive characteristics of the patients enrolled in the study

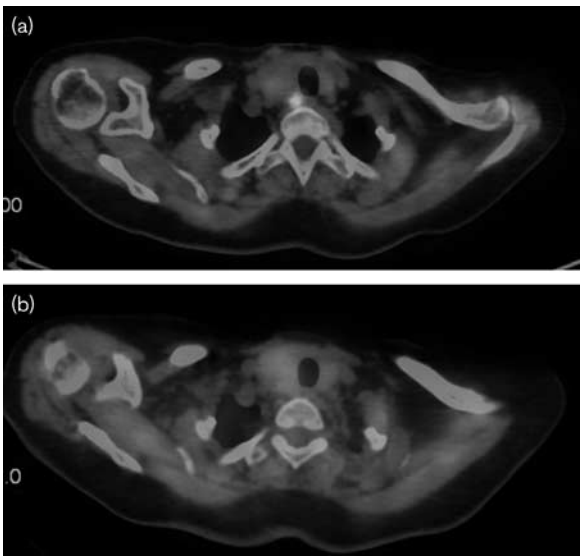
Characteristics	Minimum	Maximum	Mean	SD
Age	25	72	55.31	12.27
Serum PTH	47.80	186.20	123.06	34.82
Serum Ca	9.60	11.96	10.91	0.55
Serum P	1.68	6.00	2.90	0.83
Serum vitamin D3	7.80	35.58	23.30	10.14
Urinary Ca/24 h	5.10	935	352.13	251.01
SUV_{max}	2.20	7.30	4.42	1.63
Lumbal T-score	−3.00	1.00	1.98	1.22
Femur T-score	−3.20	0.10	1.21	0.87

Ca, calcium; P, phosphorus; PTH, parathormone; SUV_{max}, maximum standardized uptake value.

^{99m}Tc-MIBI SPECT/CT and ^{18}F-FCH PET/CT results were compatible in 29 (83%) patients, with a calculated κ of 0.64 and P of 0.001. In five (14%) of 35 patients who had a negative ^{99m}Tc-MIBI SPECT/CT, ^{18}F-FCH PET/CT could accurately localize hyperfunctioning parathyroid gland. This was confirmed by histopathology in four (12%) patients and by PTH washout in one (2%) patient (Fig. 1a and b). In one (2%) patient, ^{99m}Tc-MIBI SPECT/CT was positive, but ^{18}F-FCH PET/CT was false negative. This negative case was a 53-year-old female patient with serum levels as follows: PTH = 134.6 ng/l, Ca = 11.8 mg/dl, P = 2.9 mg/dl, 25-hydroxy vitamin D3 = 34.81 μg/l, and urinary Ca excretion: 591 mg/24 h. On neck USG, the right lobe of the thyroid consisted of a $36 \times 27 \times 36$ mm nodule with a complex echo pattern. No sonographic finding of a parathyroid adenoma was found. Fine-needle aspiration biopsy of this nodule was reported as 'Follicular lesion of undetermined significance.' Total thyroidectomy indicated an atypical parathyroid adenoma located in the right lobe of the thyroid.

The sensitivity, specificity, PPV, NPV, and accuracy were calculated to be 78, 100, 100, 70, and 86% for ^{99m}Tc-MIBI SPECT and 96, 100, 100, 93, and 97%, for ^{18}F-FCH PET/CT, respectively.

Fig. 1



(a) Demonstration of parathyroid adenoma on the axial section of ^{18}F-FCH PET/CT fused images. The patient was a 64-year-old woman with serum PTH: 186.2 ng/l, serum Ca: 10.7 mg/dl, and serum P: 3.2 mg/dl. She had a history of nephrolithiasis. (b) ^{99m}Tc-MIBI SPECT/CT axial fused image of the same section, no activity retention linked to a parathyroid adenoma was detected. Ca, calcium; CT, computed tomography; ^{18}F-FCH, fluorine-18-chloine; P, phosphorus; PTH, parathormone; SPECT/CT, single-photon emission computed tomography/computed tomography; ^{99m}Tc-MIBI, technetium-99m-methoxyisobutylisonitrile.

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The variables were distributed normally ($P > 0.05$). The mean SUV_{max} level was 4.4 ± 1.63. SUV_{max} was not directly found to be predictive of disease severity or the biochemical state of the disease, except for a correlation between lumbal *T* values ($P = 0.026$). However, serum PTH levels were significantly higher ($P = 0.026$) and femoral and lumbal *T* values were lower ($P = 0.04$ and 0.008) in patients with SUV_{max} greater than 4.4 (Table 2).

Discussion

In contrast to many other previous reports, secondary and tertiary hyperparathyroidism cases were excluded in this study to retain homogeneity and to target the largest group of hyperparathyroidism, that is, cases of primary hyperparathyroidism.

Accurate localization of the adenoma is crucial in the preoperative period for a successful minimal invasive surgery. Well-established first-step imaging in primary hyperparathyroidism includes neck USG and parathyroid scintigraphy. In a meta-analysis investigating the diagnostic power of ^{99m}Tc-MIBI dual-phase scintigraphy in parathyroid adenoma location, pooled analysis showed that planar scintigraphy had a sensitivity of 70%. Better sensitivity values were calculated for SPECT (74%) and SPECT/CT (86%). Ectopic adenomas could also be identified more accurately by SPECT and preferably SPECT/CT. Additional anatomical correlation to functional planar imaging provides a more accurate lesion detection with better resolution [13]. A recent study by McCoy and colleagues carried out on a considerably large patient population compared the success rates of SPECT/CT and SPECT only. SPECT showed a higher PPV and accuracy for single-gland disease (90 vs. 85% and 83 vs. 77%) [14]. In this study, we calculated relatively lower sensitivity (78%) and accuracy (86%) for ^{99m}Tc-MIBI SPECT/CT. ^{99m}Tc-MIBI scintigraphy may still be insufficient in some cases even if SPECT/CT is added. The principle in dual-phase ^{99m}Tc-MIBI scintigraphy is the identification of parathyroid adenomas as focal activity retention sites in delayed images where adjacent thyroid tissue shows washout. In parathyroid adenomas with a relatively faster washout pattern, even SPECT/CT may be inadequate to detect the pathology [7]. Relatively higher rates of false negativity in small, intrathyroidal, ectopic lesions, or adenomas with an early ^{99m}Tc-MIBI washout and false positivity (lymph nodes, thyroid nodules, etc.) have lead a seek for other tracers, particularly PET tracers, which may provide better spatial resolution than SPECT. ^{18}F-FCH is a nonspecific tumor agent and parathyroidal uptake was previously reported as an incidental finding [15]. Since then, some other clinical studies have investigated whether it could also be beneficial for the detection of a benign pathology, parathyroid adenoma. Lezaic *et al*. [10] have reported that the sensitivity and specificity of ^{18}F-FCH PET/CT (92 and 100%, respectively) were higher than those of conventional imaging methods, especially in patients with multigland disease. Failure to detect multiple adenoma or parathyroid hyperplasia by parathyroid scintigraphy has been attributed to the small size of these lesions [16]. The authors have concluded that the high spatial resolution achieved by PET/CT enabled the detection of multiple hyperfunctioning glands [10].

Michaud and colleagues reported on a series of 17 patients including both primary and secondary hyperparathyrodism patients. ^{18}F-FCH PET/CT findings were compared with ^{123}I/^{99m}Tc-MIBI subtraction scintigraphy. ^{18}F-FCH PET/CT was superior to scintigraphy with a sensitivity of 94% [17]. Hocevar and colleagues investigated whether ^{18}F-FCH was reliable enough for minimal invasive parathyroidectomy without intraoperative PTH sampling. ^{18}F-FCH PET/CT failed to show a parathyroid lesion in only two of 151 patients, given a PPV of 95.2% [18]. In a recent study, 26 patients with hyperparathyroidism with conflicting USG and scintigraphic results underwent ^{18}F-FCH PET/CT or PET/MRI before surgery. ^{18}F-FCH was successful in almost all cases (sensitivity: 96% and PPV: 100%), as confirmed by histopathology [19]. A recent study by Thanseer and colleagues showed 100% sensitivity and 96.3% PPV for ^{18}F-FCH PET/CT in parathyroid adenoma localization. In this series, there were no false negative or true negatives both in the lesion-based and the patient-based analysis for ^{18}F-FCH PET/CT, which is mentioned as a limitation in the text [20]. In contrast, we observed one false-negative case and 11 true-negative cases. Thus, we obtained a slightly lower value of sensitivity (96%), but this percentage was compatible with other previous studies. PPV of 100% was also similar to other published results. The false-negative case in this series was proven to be an intrathyroidal atypical parathyroid adenoma. Atypical parathyroid adenoma is a rare entity with borderline pathological characteristics between adenoma and carcinoma [21]. An intrathyroidal parathyroid adenoma missed by ^{18}F-FCH PET/CT was reported in a series, but to the best of our knowledge, ^{18}F-FCH negativity in an intrathyroidal atypical parathyroid adenoma has not been reported before [17]. This novel case contributes

Table 2 Comparison results of the mean values of variables below and above a cutoff value of $SUV_{max} = 4.4$

	SUV	Mean	SD	*P*
Serum PTH	≥4.40	147.92	31.92	0.026
	<4.40	108.70	38.68	
Serum P	≥4.40	2.86	0.58	0.526
	<4.40	3.16	1.25	
Serum Ca	≥4.40	10.64	0.61	0.415
	<4.40	10.84	0.41	
Lumbal *T* score	≥4.40	2.78	0.61	0.008
	<4.40	1.46	0.81	
Femur *T* score	≥4.40	1.58	0.54	0.044
	<4.40	0.86	0.58	

Ca, calcium; P, phosphorus; PTH, parathormone; SUV, standardized uptake value; SUV_{max}, maximum standardized uptake value.

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toward the literature as a possible reason for missed cases in ^{18}F-FCH PET/CT. There exists no published possible molecular mechanism for this situation.

One possible reason for the discordant findings between ^{99m}Tc-MIBI and ^{18}F-FCH uptake in parathyroid adenomas could be the difference between the uptake mechanisms of the two radiopharmaceuticals. ^{99m}Tc-MIBI uptake in parathyroid adenomas mainly depends on the mitochondria-rich oxyphilic cell content of the adenoma [22]. However, ^{18}F-FCH uptake in the parathyroid gland has been attributed to phospholipid-dependent choline kinase activity, which is known to take place in PTH secretion [12]. Because PTH secretion takes place in the main cells of the parathyroid, ^{18}F-FCH uptake was not related to the oxyphilic cell content. Therefore, because the two radiopharmaceuticals use different pathways to label parathyroid adenomas, they seem to be complementary in detecting parathyroid adenomas.

Together with the diagnostic power, the predictive value of functional imaging studies has also been studied in many clinical conditions. Quantitative indices derived from ^{99m}Tc-MIBI SPECT/CT studies have been reported to have a correlation with intact PTH levels [23]. Because of limited data on ^{18}F-FCH PET/CT in primary hyperparathyroidism, there was no evidence of a relationship between SUV_{max} of ^{18}F-FCH PET/CT and biochemical and clinical indices [17]. For a calculated mean SUV_{max} of 4.4, the mean serum PTH levels were significantly higher in patients with higher SUV_{max} values. The activity of phospholipid/Ca^{2+} dependent choline kinase, an enzyme which is responsible for ^{18}F-FCH uptake, has been reported to be higher in hypersecreting parathyroid adenomas compared with atrophic parathyroid glands [12]. Although no direct correlation could be found between SUV_{max} and serum PTH levels and no cutoff value indicative of a positive ^{18}F-FCH PET/CT could be calculated, it is still reasonable to observe higher ^{18}F-FCH uptake in adenomas with a higher PTH secretion rate. However, the same was not true for serum Ca levels. Because Ca levels vary in a very small range and are affected by serum vitamin D3 levels, a statistical correlation may not have been found. A very recent study by Beheshti and colleagues has shown that in logistic regression analysis, SUV_{max} was the most significant predictive factor for the final histopathology. Serum PTH levels did not have any significant correlation with pathology. However, the authors did not investigate a possible correlation between SUV_{max} and biochemical and clinical parameters [24].

Persistent elevation in serum PTH causes bone resorption and thus reduction in BMD results.

In a previous study, serum BMD levels were found to be significantly lower in primary hyperparathyroidism patients with a positive ^{99m}Tc-MIBI scan compared with the patients with a negative scintigraphy [25]. It has also been reported that cortical trabecular bone loss is correlated with serum PTH levels [26].

Here, we found a direct correlation with SUV_{max} and femoral *T* scores and both femoral and lumbal *T* scores were lower in patients with a SUV_{max} greater than 4.4. No significant difference was detected in the comparison of mean SUV_{max} between patients with nephrolithiasis and normal urinary USG. The relationship between densitometric results and SUV_{max} seems to be meaningful, although BMD results were obtained only in a small number of patients, which is the major drawback of the study. More patients are obviously needed for a more precise statistical analysis. A possible direct correlation between SUV_{max} and PTH levels (a known biochemical predictor for disease severity) could be shown and a cutoff for serum PTH or Ca levels to be indicative of a positive ^{18}F-FCH PET/CT or a cutoff for SUV_{max} above which osteopenic values could be expected could have been calculated reliably in a larger patient group.

Conclusion

Compared with ^{99m}Tc-MIBI SPECT/CT, ^{18}F-FCH PET/CT has a higher sensitivity and accuracy in the evaluation of a hyperfunctioning parathyroid gland, although they still seem to complement each other in the preoperative assessment in primary hyperparathyroidism when sonographic findings are inconclusive. SUV_{max} of the parathyroid is indicative of disease severity in terms of serum PTH levels and BMD scores. Further large-scale prospective studies would be useful to support these data.

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Conflicts of interest

There are no conflicts of interest.

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