



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

Lebriz Uslu-Beşli, MD^{1*}, Kerim Sonmezoglu, MD^{1*}, Serkan Teksoz, MD², Elife Akgun, MD¹, Emre Karayel, MSc³, Huseyin Pehlivanoglu, MSc³, Baresh Razavi Khosroshahi, MD¹, Meltem Ocak, PhD⁴, Levent Kabasakal, MD¹, Sait Sager, MD¹, Yusuf Bukey, MD²

Departments of ¹Nuclear Medicine, ²General Surgery, and ³Nuclear Medicine, Division of Radiopharmacy, Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Istanbul, Turkey; ⁴Department of Pharmaceutical Technology, Istanbul University, Pharmacy Faculty, Istanbul, Turkey

Objective: Our aim was to assess the diagnostic performance of F-18 fluorocholine (FCH) positron emission tomography/computed tomography (PET/CT) in detecting hyperfunctioning parathyroid tissue (HPT) in patients with elevated parathyroid hormone levels with negative or inconclusive conventional imaging results and to compare the findings with those obtained using technetium-99m sestamibi (MIBI) scintigraphy and neck ultrasonography (US).

Materials and Methods: Images of 105 patients with hyperparathyroidism who underwent FCH PET/CT, dual-phase MIBI parathyroid scintigraphy (median interval: 42 days), and neck US were retrospectively analyzed. The gold standard was histopathological findings for 81 patients who underwent parathyroidectomy and clinical follow-up findings in the remaining 24 patients. Sensitivities, positive predictive values (PPVs), and accuracies were calculated for all imaging modalities.

Results: Among the 81 patients who underwent parathyroidectomy, either parathyroid adenoma (n = 64), hyperplasia (n = 9), neoplasia (n = 4), or both parathyroid adenoma and hyperplasia (n = 1) were detected, except 3 patients who did not show HPT. Of the 24 (23%) patients who were followed-up without operation, 22 (92%) showed persistent hyperparathyroidism. FCH PET/CT showed significantly higher sensitivity than MIBI scintigraphy and US in detection of HPT (p < 0.01). Sensitivity, PPV, and accuracy of FCH PET/CT were 94.1% (95/101), 97.9% (95/97), and 92.4% (97/105), respectively. The corresponding values for MIBI scintigraphy and US were 45.1% (46/102), 97.9% (46/47), and 45.7% (48/105) and 44.1% (45/102), 93.8% (45/48), and 42.9% (45/105), respectively. Among the 35 patients showing negative MIBI scintigraphy and neck US findings, 30 (86%) showed positive results on FCH PET/CT. FCH PET/CT could demonstrate ectopic locations of HPT in 11 patients whereas MIBI and US showed positive findings in only 6 and 3 patients, respectively.

Conclusion: FCH PET/CT is an effective imaging modality for detection of HPT with the highest sensitivity among the available imaging techniques. Therefore, FCH PET/CT can be recommended especially for patients who show negative or inconclusive results on conventional imaging.

Keywords: Positron emission tomography; Computed tomography; Fluorocholine; Hyperparathyroidism; Tc-99m sestamibi; Parathyroid adenoma

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*These authors contributed equally to this work.

Corresponding author: Kerim Sonmezoglu, MD, Department of Nuclear Medicine, Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty Cerrahpaşa Fatih 34098, Istanbul, Turkey.

• Tel: (90) 212-414-3000 • Fax: (90) 212-414-3000

• E-mail: drkerim@istanbul.edu.tr

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INTRODUCTION

In patients with hyperparathyroidism, preoperative localization of hyperfunctioning parathyroid tissue (HPT) using noninvasive imaging techniques has become a mainstay in the management of disease because it facilitates targeted surgery such as minimally invasive parathyroidectomy (1). Although the combination of neck ultrasound (US) and technetium-99m (Tc-99m) methoxyisobutylisonitrile [sestamibi (MIBI)] dual-phase scintigraphy is the conventional imaging work-up to localize HPT, it may fail to identify abnormal hyperfunctioning glands in up to 30% of cases (2). Four-dimensional computed tomography (4D-CT) and dynamic magnetic resonance imaging (MRI) have emerged as second-line imaging modalities; however, there is currently no sufficient evidence to recommend their routine use in localizing HPT (3, 4). Furthermore, a high radiation burden is another concern associated with the use of 4D-CT (5).

Following the incidental discovery of fluorine-18 (F-18)-labeled fluorocholine (FCH) accumulation in parathyroid adenoma (6), several recent clinical studies showed that FCH positron emission tomography/computed tomography (PET/CT) is a promising modality for detection of HPT, even in patients with multi-glandular disease (7-12). However, the available data in the literature is still lacking. Therefore, we designed this study to assess the diagnostic performance of FCH PET/CT for detection of HPT in patients with elevated parathyroid hormone (PTH) levels who showed either

negative or inconclusive results on conventional imaging. In addition, we tried to assess whether dual-phase FCH PET/CT offers added benefits over MIBI and US in detecting HPT and to determine whether there is any relationship between FCH uptake intensity in HPT and the serum PTH level.

MATERIALS AND METHODS

This study was approved by Istanbul University Clinical Research Ethics Committee (08/01/2016-7689) and all subjects signed an informed consent form. The study was supported by Istanbul University Scientific Research Fund (project number: 24412) and conducted from June 2015 to May 2018.

Study Population

Data for a total of 105 patients with hyperparathyroidism (79 females, 26 males; age range, 16–95 years; mean age \pm standard deviation: 55 \pm 14.7 years) with negative or discordant results on MIBI and US were retrospectively analyzed (Fig. 1). Twelve (11%) patients had a previous parathyroidectomy operation and 11 patients had a prior thyroidectomy operation due to nodular goiter, of whom 7 were diagnosed as having papillary thyroid cancer. Twelve patients had nodular goiter and 3 patients had a history of radioiodine therapy due to hyperthyroidism.

F-18 FCH Labeling Procedure

In-house FCH labeling via the nucleophilic method was

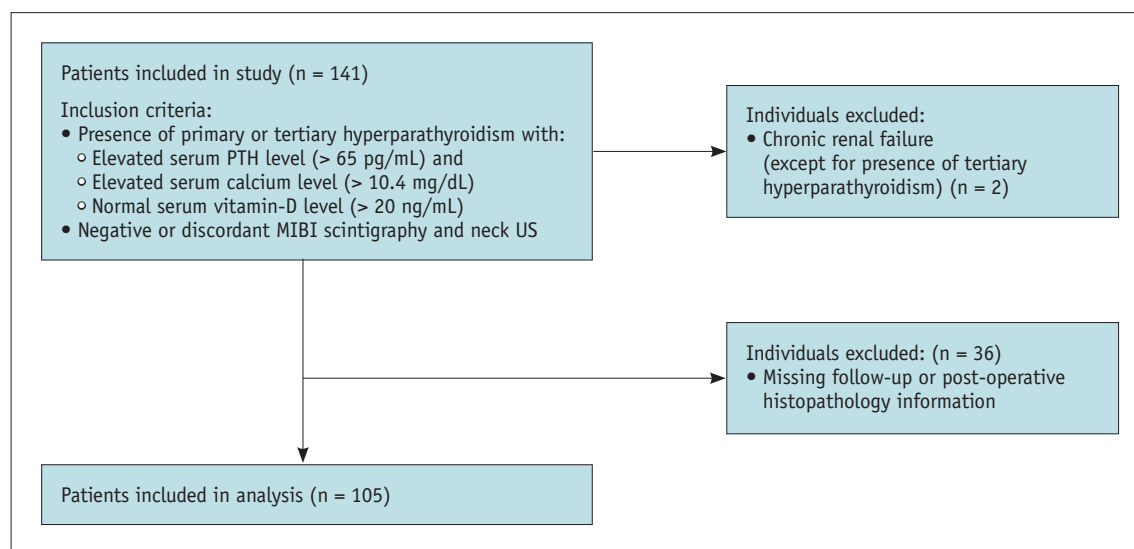


Fig. 1. Flow chart showing patient selection process. MIBI = technetium-99m sestamibi, n = number of patients, PTH = parathyroid hormone, US = ultrasonography

performed using a fully automated radiochemistry synthesis device (Trasis All-in-One; Ans, Belgium) according to the labeling procedure described by Kryza et al. (13). Quality control tests were performed following specifications described in European Pharmacopoeia. The total time for the entire synthesis procedure, including quality control tests, was 80–90 minutes.

Imaging Acquisition

PET/CT was performed after injecting a mean of 325.1 ± 86.7 MBq (8.8 ± 2.3 mCi) F-18 FCH intravenously. Dual-phase PET/CT images were acquired using PET/CT scanners (GE Discovery 710; Waukesha, WI, USA or Siemens Biograph 6, Knoxville, TN, USA) with an initial scan at 15 minutes post-injection (range: 12–17 minutes) covering the neck and upper chest and a late scan at 45 minutes post-injection (range: 36–60 minutes) covering the whole body (vertex-mid thigh) or the cervico-thoracic region. The CT topogram guide, low-dose (49–76 mAs) CT transmission scan for attenuation correction, and PET emission scan at 3 minutes per bed position were acquired.

Sixty-five patients (62%) underwent dual-phase MIBI scintigraphy at our institution. After injection of 740 ± 74 MBq (20 ± 2 mCi) Tc-99m MIBI, regional static images of the cervico-thoracic region were acquired at 15 and 90 minutes and single-photon emission computed tomography/computed tomography (SPECT/CT) scans of the head, neck, and thorax were acquired at 60 minutes using an integrated SPECT/CT camera (Siemens Symbia T16; Hoffman Estates, IL, USA). For the remaining 40 patients (38%), proper dual-phase MIBI scintigraphy with SPECT or SPECT/CT was performed at the referral centers. The median interval between FCH PET/CT and parathyroid MIBI scintigraphy was 42 days (range: 2–291 days). In all patients, at least one neck US examination was performed by a radiologist using a high-frequency linear probe (5–12 MHz) with a median interval of 30 days (range: 1–232 days).

Image Analysis

All PET/CT images were read separately by two experienced nuclear medicine physicians who were aware of the patients' clinical diagnosis and previous imaging and laboratory data. From the skull base to the lower part of mediastinum, any focal FCH uptake discernible from the background activity that was not related to thyroid tissue or a lymph node seen on CT slices was considered positive for HPT. All lesions involving an initial disagreement

between the readers were re-evaluated together by the readers to reach a final consensus. Additionally, maximum standardized uptake values (SUVmax) of all discernible suspicious lesions and mean SUV (SUVmean) from the thyroid gland were calculated for both initial and late FCH PET/CT images. All MIBI scans that were reported by different attending physicians were also re-evaluated by a nuclear medicine physician. Any focal MIBI uptake above the background activity that was not related to the thyroid tissue in the neck and upper mediastinum in the initial scan and/or any remaining focus inside the thyroid bed at the late scan other than the thyroid nodule was considered as positive for parathyroid adenoma. Any focus with initial MIBI uptake with wash-out pattern on late imaging was recorded as a suspicious lesion for parathyroid adenoma.

Parathyroidectomy and Histopathology

Eighty-one out of 105 (77%) patients underwent parathyroidectomy, of which 49 (60%) underwent minimal invasive parathyroidectomy. Of these 81 patients, 53 (65%) were operated on at our institute by an experienced endocrine surgeon, while the remaining 38 (35%) were operated on at different centers. Pathological results were obtained and recorded. Patients who were not operated on due to negative imaging results or because of unwillingness to undergo the surgery or a contraindication for surgery were followed-up and their serum calcium and PTH levels were determined at 3–6-month intervals for at least 12 months.

Statistical Analysis

Statistical analysis was performed using SPSS software version 21.0 (IBM Corp., Armonk, NY, USA), and the level of significance was set at a p value < 0.05 . Sensitivity, positive predictive value (PPV), and accuracy were calculated for all three imaging modalities while counting suspicious imaging results as all positive. Specificity and negative predictive value were not calculated due to the bias in selecting patients with discordant or equivocal results in conventional imaging. Postoperative histopathological results or persistently elevated serum PTH and calcium levels in non-operated patients were considered as the reference standards. McNemar's test was used to compare the sensitivity of the imaging modalities. Wilcoxon signed-rank test was used for comparison of early and delayed SUVs. Pearson's correlation coefficient was used for assessment of the correlation between early and delayed SUVs and between the SUVs and serum PTH levels.

RESULTS

Mean serum PTH and calcium levels were 199.3 ± 206.1 pg/mL (reference value: 15–65 pg/mL) and 11.0 ± 0.84 mg/dL (reference value: 8.4–10.2 mg/dL), respectively. There was only weak correlation between SUVs and PTH levels (early SUVmax: $r = 0.236$, $p = 0.026$; delayed SUVmax: $r = 0.259$, $p = 0.014$).

Of the 81 patients who underwent parathyroidectomy, parathyroid adenoma was diagnosed in 64 (79%), parathyroid hyperplasia in 9 (11%), parathyroid neoplasia in 4 (5%), and both adenoma and hyperplasia in 1 (1%) patient. In the remaining 3 (4%) patients, no parathyroid tissue could be found in histopathological analysis. Among these, 1

patient showed a negative preoperative FCH PET/CT scan, and the follow-up PTH levels decreased to the normal range, while in the remaining 2 patients with positive preoperative FCH PET/CT scans, the raised PTH levels persisted during follow-up. Of the 24 (23%) patients who did not undergo an operation, 22 (92%) had persistently elevated PTH levels during follow-up and were also considered to have proven HPT.

Sensitivity, PPV, and accuracy of FCH PET/CT in the detection of HPT were 94.1%, 97.9%, and 92.4%, respectively. The corresponding values for MIBI and US were 45.1%, 97.9%, and 45.7% and 44.1%, 93.8%, and 42.9%, respectively. The difference between FCH PET/CT and other imaging modalities was statistically significant ($p < 0.001$) (Table 1).

Table 1. Sensitivity, PPV, and Accuracy of Each Imaging Modality

	Sensitivity (%)	PPV (%)	Accuracy (%)
All patients (n = 105)			
FCH PET/CT	94.1 (95/101)	97.9 (95/97)	92.4 (97/105)
MIBI scintigraphy	45.1 (46/102)	97.9 (46/47)	45.7 (48/105)
US	44.1 (45/102)	93.8 (45/48)	42.9 (45/105)
Only histopathology-proven patients (n = 81)			
FCH PET/CT	96.2 (76/79)	98.7 (76/77)	95.1 (77/81)
MIBI scintigraphy	48.8 (39/80)	97.5 (39/40)	48.1 (39/81)
US	45.0 (36/80)	97.3 (36/37)	44.4 (36/81)
MIBI scintigraphy and US negative patients (n = 35)			
FCH PET/CT	85.7 (30/35)	100 (30/30)	

FCH = fluorine-18 fluorocholine, MIBI = technetium-99m sestamibi, n = number of patients, PET/CT = positron emission tomography/computed tomography, PPV = positive predictive value, US = ultrasonography

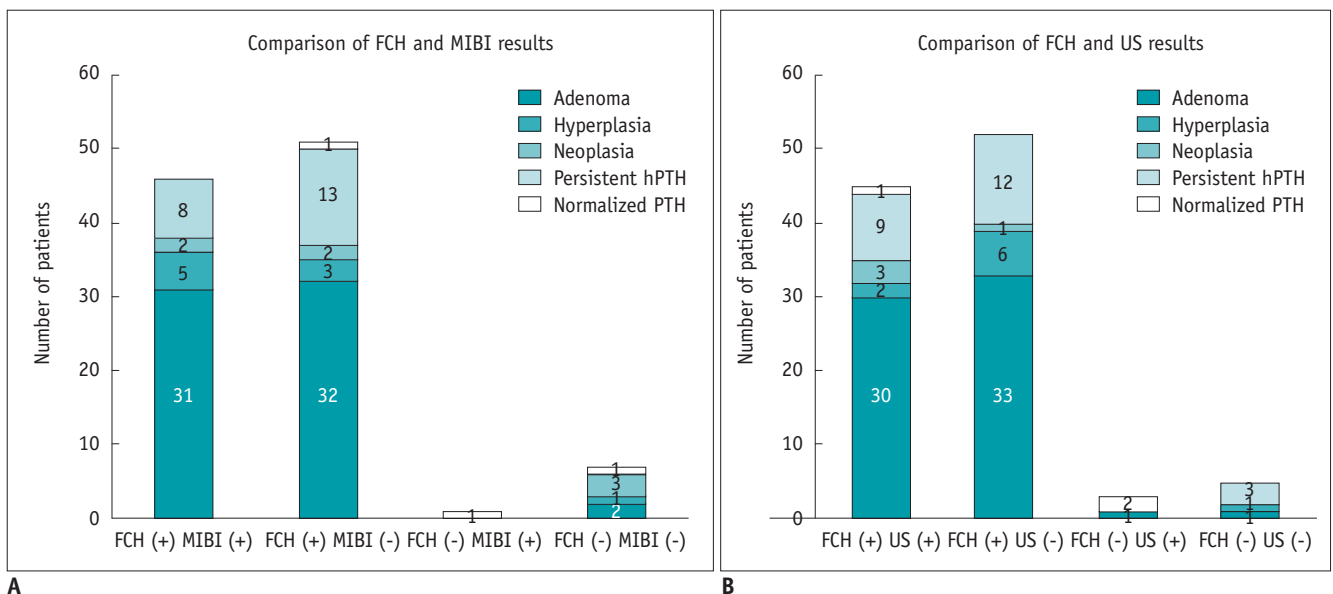


Fig. 2. Distribution of concordant and discordant cases between FCH PET/CT and MIBI scintigraphy (A) and neck ultrasonography (B) according to patients' final status based on findings from postoperative histopathological assessments or clinical follow-up examinations. FCH = fluorine-18 fluorocholine, hPTH = persistent raised PTH, PET/CT = positron emission tomography/computed tomography

Comparison of FCH PET/CT with Tc-99m MIBI Scintigraphy

FCH PET/CT and MIBI scintigraphy showed concordant results in 53 patients (50%) (46 positive; 7 negative) and discordant results in 52 (50%) patients (51 with positive FCH versus negative MIBI results; 1 with negative FCH versus positive MIBI results) (Fig. 2A, Table 2). In all 46 patients with concordantly positive results, HPT was proven by either histopathological examination (38 patients) or clinical follow-up (8 patients). Among the 7 patients with concordantly negative results, follow-up PTH levels decreased to the normal range in only 1 patient. However, 3 patients showed proven HPT in parathyroidectomy specimens and the remaining 3 showed persistently elevated PTH levels during follow-up.

Among the 51 patients with FCH-PET/CT-positive and

MIBI-negative results, 38 received parathyroidectomy, revealing adenoma in 32, parathyroid hyperplasia in 3, and parathyroid neoplasia in 2 patients. One patient was operated on but showed no parathyroid tissue in the postoperative histopathological assessment, and the elevated PTH levels persisted during follow-up. In the remaining 13 patients who did not undergo surgery, 12 had persistently elevated PTH levels (median PTH: 133.5 pg/mL) and one had normalized PTH levels during follow-up (47 pg/mL).

One patient with negative FCH PET/CT and positive MIBI scans underwent parathyroid surgery, but postoperative histopathological assessment revealed no parathyroid tissue and showed benign thyroid nodules instead.

Table 2. Comparison of FCH PET/CT and MIBI Scintigraphy Findings in 105 Patients

	n
FCH and MIBI positive	46
Parathyroidectomy operation	
Adenoma	31
Hyperplasia	5
Neoplasia	2
Parathyroid tissue could not be found at surgery (elevated PTH value during follow-up)	1
Follow-up without surgery	
Persistently elevated PTH values	7
FCH and MIBI negative	7
Parathyroidectomy operation	
Adenoma	1
Adenoma and hyperplasia	1
Hyperplasia	1
Follow-up without surgery	
Persistently elevated PTH values	3
Normal PTH values	1
FCH positive and MIBI negative	51
Parathyroidectomy operation	
Adenoma	32
Hyperplasia	3
Neoplasia	2
Parathyroid tissue could not be found at surgery (elevated PTH value during follow-up)	1
Follow-up without surgery	
Persistently elevated PTH values	12
Normal PTH values	1
FCH negative and MIBI positive	1
Parathyroidectomy operation	
No parathyroid tissue detected	1

PTH = parathyroid hormone

Table 3. Comparison of FCH PET/CT and Neck US Findings in 105 Patients

	n
FCH and US positive	45
Parathyroidectomy operation	
Adenoma	30
Hyperplasia	2
Neoplasia	3
Follow-up	
Persistently elevated PTH values	9
Normal PTH values	1
FCH and US negative	5
Parathyroidectomy operation	
Adenoma and hyperplasia	1
Hyperplasia	1
Follow-up	
Persistently elevated PTH values	3
FCH positive and US negative	52
Parathyroidectomy operation	
Adenoma	33
Hyperplasia	6
Neoplasia	1
Parathyroid tissue could not be found at surgery (elevated PTH value during follow-up)	2
Follow-up	
Persistently elevated PTH values	10
FCH negative and US positive	3
Parathyroidectomy operation	
Adenoma	1
Parathyroid tissue could not be found at surgery (decreased PTH value during follow-up)	1
Follow-up	
Normal PTH values	1

Comparison of FCH PET/CT with Neck US Examination

When FCH PET/CT was compared with neck US, 50 patients showed concordant results (45 positive; 5 negative) and 55 showed discordant results (52 with positive FCH and negative US findings; 3 with negative FCH and positive US findings) (Fig. 2B, Table 3). Among the 45 patients with concordantly positive results, HPT was proven in all except one by either pathological evaluation (35 patients) or clinical follow-up (9 patients). On the other hand, 5 patients with concordantly negative results had proven HPT.

Fifty-two patients showed positive FCH PET/CT findings despite showing negative US results. Of these, 42 were operated on and HPT was found in 40 (adenoma in 33, hyperplasia in 6, and neoplasia in one) while no parathyroid tissue was found in 2 patients despite showing persistently elevated PTH levels during follow-up, with one of these patients showing a positive focus in the mediastinum on FCH PET/CT. Among the 10 patients with positive FCH-PET/CT and negative US findings who did not undergo surgery, all had persistently elevated PTH levels during follow-up. Of the 3 patients with negative FCH-PET/CT and positive US findings, 2 patients underwent surgery, which revealed parathyroid adenoma in one. However, no parathyroid tissue was detected in the other patient on histopathological examination. Among the remaining 5 patients with concordantly negative results, 2 were operated on and showed HPT, whereas the remaining 3 did not undergo surgery and showed persistently elevated PTH levels during follow-up.

Among the 35 (33%) patients with both negative MIBI and US findings, 30 (86%) showed positive FCH PET/CT findings resulting in a proven HPT (22 by histopathology and 8 by clinical follow-up) (Fig. 3). In addition, FCH PET/CT demonstrated an ectopic location of HPT (1 submandibular, 4 para/retroesophageal, 6 mediastinal) in 11 patients (Fig. 4). MIBI and US showed positive results in only 6 and 3 of these cases, respectively.

Of the 12 patients showing clinical findings of recurrent hyperparathyroidism, 11 showed positive FCH PET/CT findings, and HPT was confirmed by histopathological examination in 10 of these patients. Among these 10 patients, 5 showed positive findings with FCH PET/CT despite showing negative MIBI and US findings. MIBI yielded true-positive findings in 5 patients while US showed true-positive findings in 4 patients in this subgroup.

There were 4 cases with parathyroid neoplasia in our series. In all of them, FCH PET/CT yielded positive results

with higher early SUVmax (10.8 ± 5.0 vs. 7.1 ± 3.5) and late SUVmax (11.8 ± 5.8 vs. 7.3 ± 3.6) compared to the mean values for whole patients. There was no finding suggestive of local or distant metastasis in whole-body FCH PET/CT in this particular subgroup. MIBI showed 2 true-positive cases and US showed 3 true-positive cases in the neoplasia group.

Two patients with chronic renal failure were included as possible cases of tertiary hyperparathyroidism, since both FCH PET/CT and US demonstrated a single parathyroid adenoma. One of these cases also showed brown tumors that were identified by both FCH PET/CT and MIBI (Fig. 5).

Comparison of Early and Delayed FCH PET/CT Imaging

A total of 97 patients showed positive findings with FCH PET/CT. There was no statistically significant difference between the SUVmax of parathyroid lesions in early (mean SUVmax: 7.1 ± 3.5 , median SUVmax: 6.1, range: 1.9–19.4) and late imaging (mean SUVmax: 7.3 ± 3.6 , median SUVmax: 6.4, range: 2.0–22.4) ($p = 0.190$). However, significant differences were found in the parathyroid SUVmax/thyroid SUVmean ratio between early (mean ratio: 2.5 ± 1.5 , range: 0.8–7.8) and delayed imaging (mean ratio: 2.9 ± 1.5 , range: 1.0–10.0) ($p < 0.001$) among patients without any previous thyroidectomy operation. Strong positive correlations were observed between early and delayed SUVmax of parathyroid lesions ($r = 0.898$), as well as for parathyroid/thyroid SUV ratios ($r = 0.896$). On visual analysis, 12 lesions were more prominent on early imaging, whereas 10 were more prominent on delayed imaging. For the remaining lesions, the results were equivocal for both early and delayed imaging.

DISCUSSION

Following incidental detection of FCH uptake in parathyroid adenoma, several clinical studies have been published on the role of FCH PET/CT in hyperparathyroidism, and they have shown better diagnostic performance of FCH PET/CT in comparison with other conventional imaging methods, with higher sensitivity and equally high specificity (7-12, 14-17). A recent meta-analysis evaluating the diagnostic performance of FCH PET/CT in hyperparathyroidism revealed that the sensitivity and specificity of FCH PET/CT were 90% and 94%, respectively (18), and another study also reported excellent sensitivity, PPV, and detection rate of 95%, 97%, and 91%, respectively (19). Furthermore, PET/MRI was reported to have better diagnostic performance

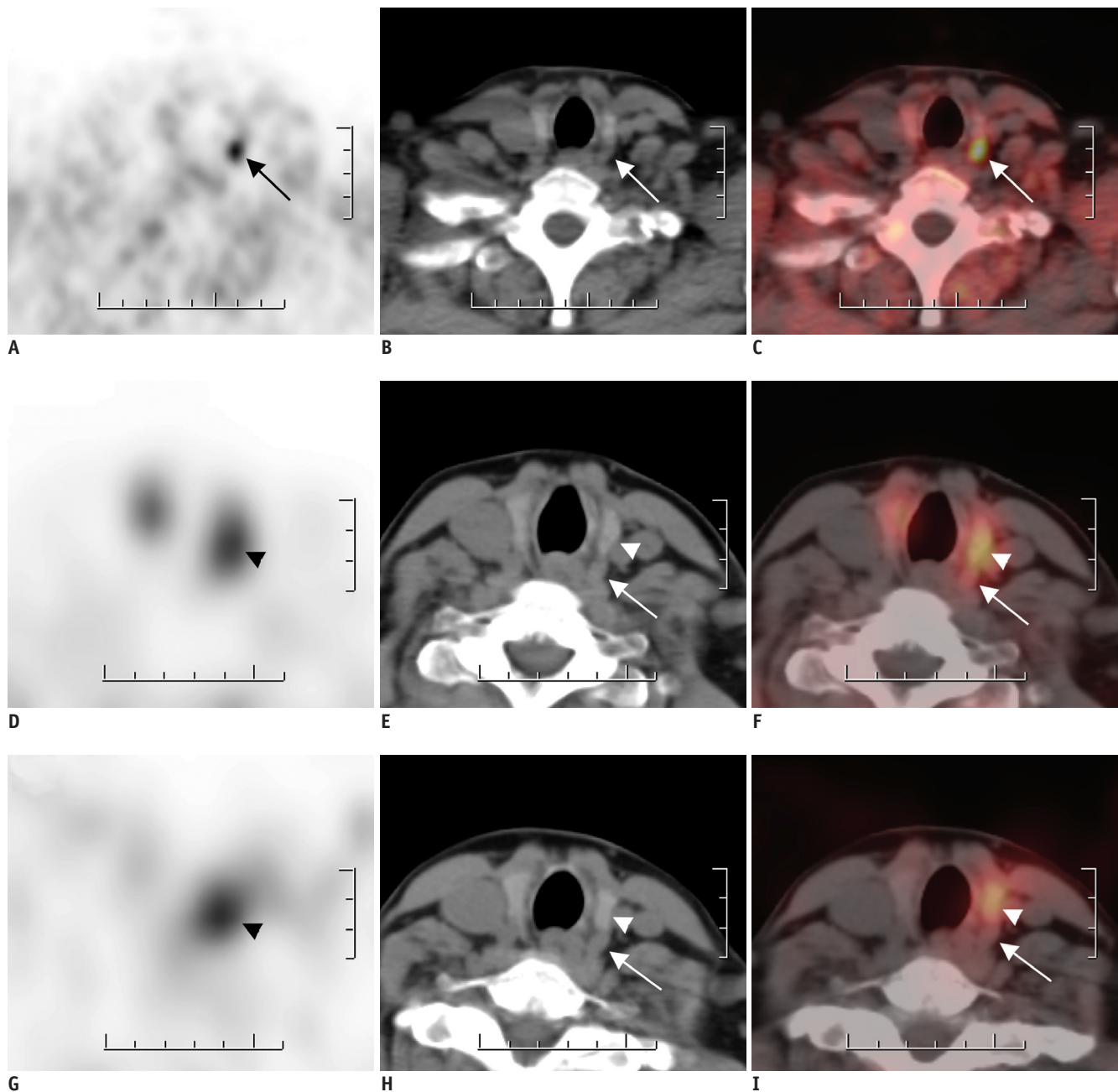


Fig. 3. FCH PET/CT (A-C) and MIBI SPECT/CT (D-I) findings for 48-year-old female with hyperparathyroidism (PTH level: 191 pg/mL). FCH PET (A), CT (B), and fused PET/CT (C) images in FCH PET/CT reveal nodular lesion with intense FCH uptake (arrows) posterior to left thyroid lobe, which was confirmed to be parathyroid adenoma. Patient also showed papillary thyroid microcarcinoma in left thyroid lobe with no FCH uptake. In early MIBI SPECT (D), CT (E), and fused SPECT/CT (F) images, MIBI uptake was noted on left thyroid lobe. Moreover, MIBI uptake persisted in late SPECT (G), CT (H), and fused SPECT/CT (I) images (arrowheads). However, parathyroid lesion posterior to left thyroid lobe did not exhibit any MIBI uptake in early and late SPECT/CT scans (arrows). SPECT = single-photon emission computed tomography

than MRI alone in 10 patients with primary HPT (20).

Our study also demonstrated the encouraging performance of FCH PET/CT in the detection of HPT. Because our study population included a difficult series of selected patients with negative or discrepant US and MIBI results, the

sensitivities of both US and MIBI were lower than those reported in the literature (2, 21-23). Even in this difficult population, FCH PET/CT presented impressive results with high sensitivity, PPV, and accuracy of 94.1%, 97.9%, and 92.4%, respectively, whereas the corresponding values for

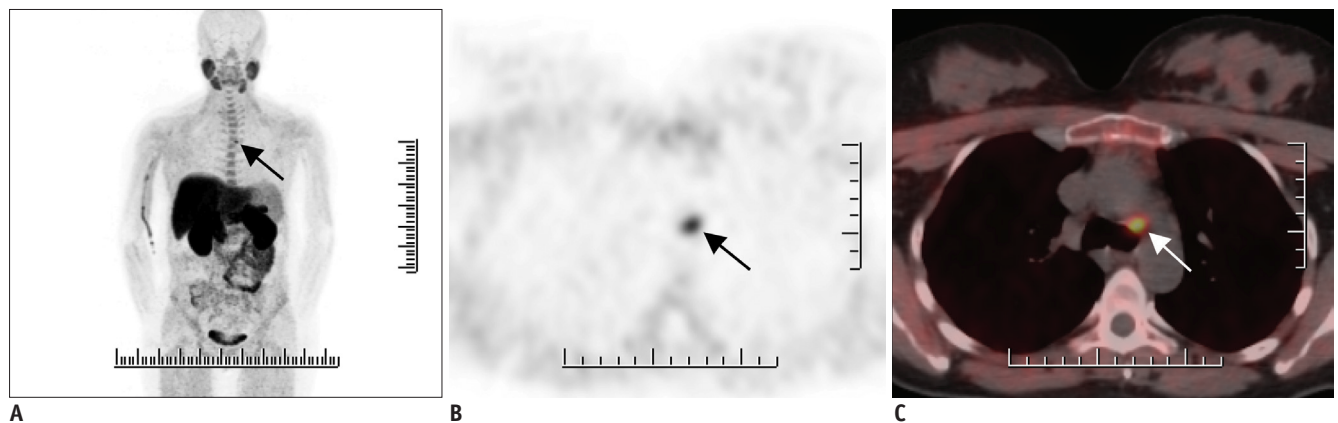


Fig. 4. 39-year-old female patient with hyperparathyroidism (PTH level: 203.0 pg/mL) showing negative MIBI and ultrasonography results (not shown). FCH PET/CT MIP image (A) shows focus of FCH uptake on upper mediastinum (arrow). Axial PET (B) and fused PET/CT (C) images reveal 1-cm nodular lesion with intense FCH uptake in aortopulmonary window (arrows). Postoperative histopathology revealed presence of ectopic mediastinal parathyroid adenoma. MIP = maximum intensity projection

MIBI and US were 45.1%, 97.9%, and 45.7% and 44.1%, 93.5%, and 42.9%, respectively.

Even though our study included 10 histopathologically proven recurrent HPT cases, FCH PET/CT was able to localize all lesions, providing excellent sensitivity (100%) in comparison with MIBI (5 true-positive results) and US (4 true-positive results). FCH PET/CT could also identify all 4 cases with parathyroid neoplasia, whereas both MIBI and US showed positive findings in only 2 cases. Furthermore, FCH PET/CT was superior in demonstrating ectopic localization of HPT in comparison with US and MIBI. Similar to MIBI scintigraphy, FCH PET/CT could identify brown tumors, which are bone lesions that arise as a result of increased osteoclastic activity in hyperparathyroidism and mimic bone metastasis (24-26), which was also documented by Taywade et al. (27) previously.

We believe that the superior spatial resolution of PET technology over SPECT is one of the important factors influencing the better diagnostic performance of FCH PET/CT. Indeed, in this study, MIBI could reveal only 5 (55.6%) of 9 cases of parathyroid hyperplasia while FCH PET/CT demonstrated the lesions in 7 (78%) cases. In addition, the differences in the molecular properties and uptake mechanisms of FCH and MIBI may be responsible for the superiority of FCH PET/CT. Therefore, the additional molecular potential of FCH in terms of its uptake mechanism in HPT should be elucidated. MIBI is a lipophilic cationic isonitrile derivative that is accumulated in mitochondria-rich oxyphilic cells (28). P-glycoprotein may also be responsible for MIBI uptake (29). In contrast, increased FCH uptake in HPT may be related to accelerated phosphatidylcholine

turnover or upregulation of phospholipid-dependent choline kinase activity (30-32). FCH uptake in benign secreting tumors such as parathyroid adenomas was proposed to be related to cholinergic autocrine loop upregulation and increased expression of choline transporters rather than the membrane proliferation rate (33). In contrast to studies showing that MIBI is preferentially accumulated by oxyphilic cells, there is no study yet demonstrating the type of parathyroid cells that preferentially accumulate FCH. As a proposal, if FCH was capable of accumulating in chief cells rather than oxyphilic cells, then it might have a molecular advantage over MIBI in detecting HPT. Further research is needed to elucidate the exact biological processes underlying the FCH uptake in HPT.

Another advantage of FCH PET/CT would be the shorter imaging time. Early imaging within the first 15 minutes appeared to be good enough to reveal the majority of the lesions in this study. However, among the proven HPT cases (n = 102), we found an SUVmax increase of more than 5% (up to 37%) in 46 (45%) parathyroid lesions and an SUVmax decrease of more than 5% (up to 54%) in 33 (32%) parathyroid lesions in late scans. These findings suggest that single time-point imaging either in early (15 minutes) or late (45-60 minutes) imaging may be associated with a potential risk of missing lesions. Nevertheless, we have not seen any lesion that was identified in early imaging and completely disappeared in late scans or vice versa. Lezaic et al. (7) reported better lesion contrast at 60-minute imaging compared to the 5-minute scan. We also demonstrated a significantly higher parathyroid-SUVmax/thyroid-SUVmean ratio at 45 minutes compared to that obtained with

15-minute imaging, even though 32% of the cases showed reduced SUVmax in late imaging. Accordingly, we suggest early imaging at 15 minutes with late imaging at 45–60

minutes for selected patients with inconclusive or negative early imaging findings.

Because the biggest disadvantage of FCH PET/CT is its high

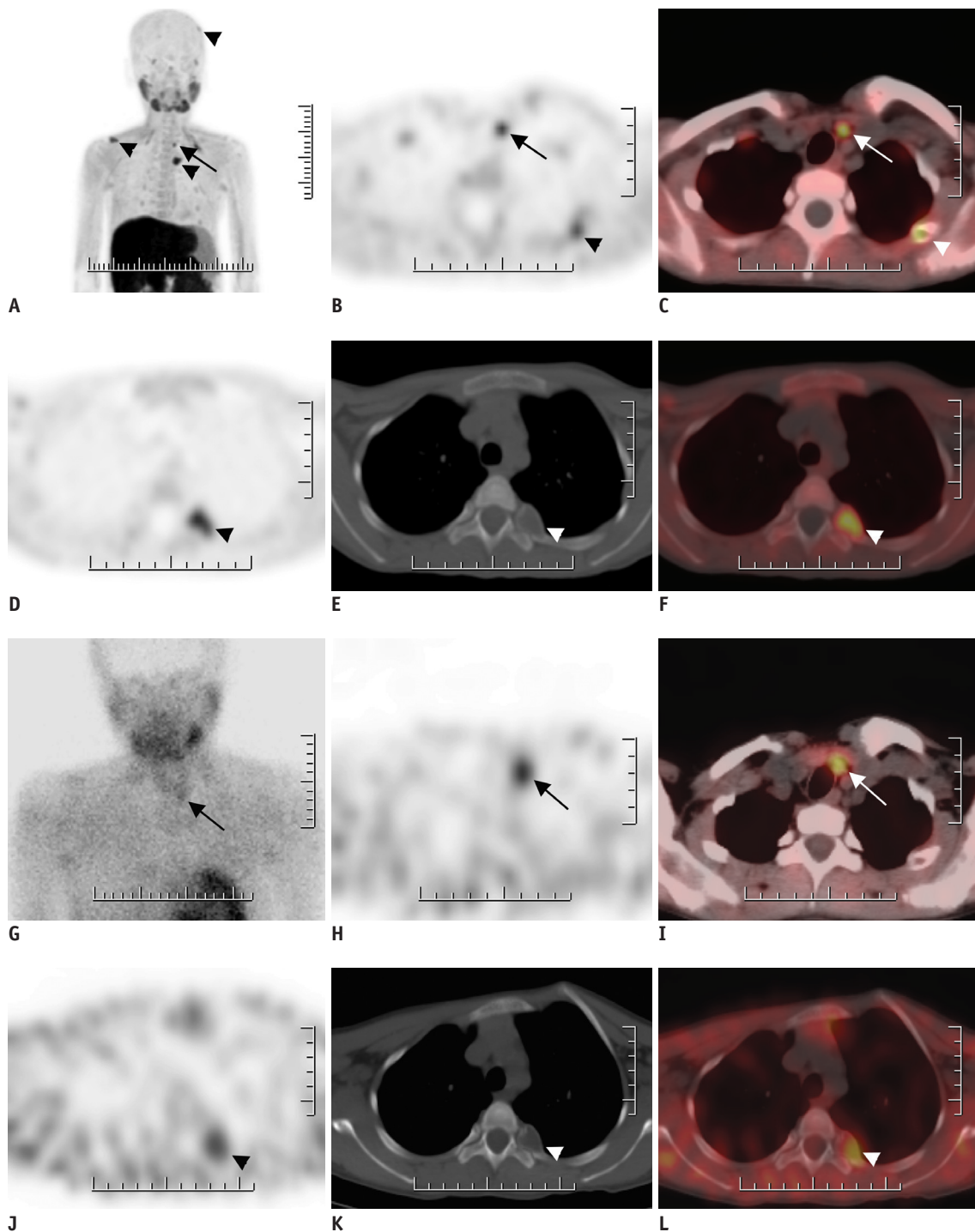


Fig. 5. 16-year-old female patient with chronic renal failure.

A-F. FCH PET/CT MIP image (A) reveals multiple foci of increased FCH uptake. Axial PET (B) and fused PET/CT (C) images on lower neck region reveal intense FCH uptake on left side that was found to be in accordance with parathyroid adenoma in surgical specimen (arrows). Brown tumors also demonstrate increased FCH uptake (arrowheads). **G-L.** MIBI SPECT/CT images of same patient. MIBI uptake at late planar (G), SPECT (H), and fused SPECT/CT (I) images reveal MIBI uptake on parathyroid adenoma (arrows). Brown tumors also demonstrate increased MIBI uptake (arrow heads).

cost in comparison with MIBI, the use of FCH PET/CT as a second-line imaging tool for difficult cases with negative or discordant conventional imaging findings seems to be more feasible. Another potential drawback of FCH PET/CT is that FCH is not a specific tracer for parathyroid tissue. Therefore, physiological uptake of FCH in thyroid parenchyma and preferential accumulation in well-differentiated thyroid cancers and metastatic or inflammatory lymph nodes may occur. In our study, there were 2 cases with papillary thyroid cancer with increased FCH uptake in which the parathyroid lesions could be differentiated accurately by considering their location. In another case, we considered an FCH-positive lesion in the neck as an enlarged parathyroid tissue, but histopathological examination did not confirm any parathyroid tissue and indicated an inflammatory lymph node instead. Although we do not recommend routine intravenous contrast medium administration for FCH PET/CT imaging, its usage may further improve results in selected cases with inconclusive results.

There are several limitations in this study. First, there was a bias in selecting the patient population, which mainly included patients with negative or discrepant conventional imaging findings, leading to reduced sensitivity values for both US and MIBI in comparison with those reported in previous studies. Second, more than half of the US examinations and 38% (40/105) of MIBI examinations were performed at different referral centers and reported by various physicians, which may also have created severe imaging variability and bias. Finally, 24 out of 105 patients (23%) were not operated on after imaging. Instead, follow-up serum PTH and serum calcium level measurements were used as reference standards, which might have the potential to create a bias. However, the sensitivity, PPV, and accuracy of the histopathology-proven group were similar to those of the entire study population.

In conclusion, FCH PET/CT is an effective imaging modality for localization of HPT with the highest sensitivity among the available imaging techniques. Therefore, FCH PET/CT may play a key role as a problem-solving imaging modality in difficult cases such as those showing recurrent hyperparathyroidism and ectopic localizations of HPT.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

ORCID iDs

Kerim Sonmezoglu
<https://orcid.org/0000-0003-1215-5184>
 Lebriz Uslu-Bešli
<https://orcid.org/0000-0003-1868-3957>
 Serkan Teksoz
<https://orcid.org/0000-0002-6733-5644>
 Elife Akgun
<https://orcid.org/0000-0001-5625-9749>
 Emre Karayel
<https://orcid.org/0000-0001-8114-2315>
 Huseyin Pehlivanoglu
<https://orcid.org/0000-0003-4833-0976>
 Baresh Razavi Khosroshahi
<https://orcid.org/0000-0002-6272-4384>
 Meltem Ocak
<https://orcid.org/0000-0001-9214-3938>
 Levent Kabasakal
<https://orcid.org/0000-0002-4050-1972>
 Sait Sager
<https://orcid.org/0000-0003-2013-5845>
 Yusuf Bukey
<https://orcid.org/0000-0003-4122-6594>

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