Imaging of hepatic hypervascular tumors & clinical implications
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Citation for published version (APA):
The use of $^{18}$F-fluoromethylcholine PET/CT in differentiating focal nodular hyperplasia from hepatocellular adenoma: A prospective study of diagnostic accuracy

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Nuclear Medicine Communications
(2013) 34:146–154

Eur J Nucl Med Mol Imaging
(2011) 38:436–440
OBJECTIVE

Diagnosis of focal nodular hyperplasia (FNH) and hepatocellular adenoma (HCA) using conventional imaging techniques can be difficult; however, it is important to differentiate between them as these benign liver tumors require different therapeutic strategies. The aim of our study was to prospectively evaluate the use of PET/computed tomography (CT) with $^{18}$F-fluoromethylcholine ($^{18}$F-FCH) as a novel diagnostic approach in the differentiation between HCA and FNH.

SUBJECTS AND METHODS

Fifty-six consecutive patients with a suspicion of one or multiple HCAs or FNHs larger than 2 cm were prospectively included after written informed consent was obtained from them. All the patients underwent a PET/CT with $^{18}$F-FCH. Histopathology of the lesions was the standard of reference. The ratio of the standardized uptake value (SUV) of the lesions compared with normal liver uptake within the same patient was calculated. Statistical tests were evaluated at the 95% confidence interval.

RESULTS

Forty-nine patients with 60 lesions and histopathological diagnosis of FNH or HCA completed the study and were analyzed. The mean SUV ratio for FNH was 1.67±0.31 (mean±SD, n = 28), resulting in a positive likelihood ratio of 32.3 for PET-positive FNH. The mean SUV ratio for HCA was 0.82±0.17 (n= 32), with a likelihood ratio of 800 for PET-negative HCA. Receiver operating characteristic curve analysis revealed an optimal SUV ratio cutoff value of 1.13, which reached 100% sensitivity and 97% specificity in differentiating FNH from HCA.

CONCLUSION

This prospective study shows that PET/CT with $^{18}$F-FCH can accurately differentiate FNH from HCA and may become a valuable diagnostic tool when conventional imaging techniques fail to do so.

INTRODUCTION

Hepatocellular adenoma (HCA) and focal nodular hyperplasia (FNH) are benign focal hepatic lesions. It is generally accepted that FNH can be treated conservatively because of its benign nature and minimal risk of complications [1–3]. HCAs larger than 5 cm, unlike FNH, carries the risk for malignant transformation in up to 40% of cases [4,5]. In addition, spontaneous rupture and bleeding have been reported in about 30% of patients during long-term follow-up [6,10]. For these reasons, resection of HCAs larger than 5 cm is advised, emphasizing the importance of reliable differentiation between HCA and FNH. When using radiologic imaging modalities, MRI with hepatobiliary contrast is regarded to be the most sensitive in differentiating FNH from HCA [11]. When radiological evaluation remains inconclusive, an ultrasound-guided or computed tomography (CT)-guided liver biopsy may be required.

Therefore, there is a place for additional noninvasive diagnostic imaging techniques. With the use of PET, the uptake and metabolism of a specific compound labeled with a radioactive tracer can be assessed within an organ or tumor. $^{18}$F-Fluoromethylcholine ($^{18}$F-FCH) is one of those tracers. Through choline transporter(s) [12] or by facilitated diffusion, choline is transported into the cell. Three major metabolic pathways for choline are known (Fig. 1). The first is the cytidine diphosphocholine (CDP) or Kennedy pathway, in which choline is phosphorylated to phosphocholine, which is catalyzed by choline kinase. Phosphocholine is in part converted to CDPcholine and further altered to phosphatidylcholine, a major constituent of the cell membrane. A second pathway for choline is the oxidation to betaine, an organic osmolyte. Betaine can maintain intracellular volume homeostasis and can donate its methyl group for the formation of S-adenosylmethionine. Betaine also has a significant role in clearing homocysteine from the body [13]. Homocysteine can be incorporated into phosphatidylcholine through the methylation pathway. Third, choline can be converted to the neurotransmitter acetylcholine in neural cells. A study on pharmacokinetics and radiation dosimetry of fluoro-labeled choline by DeGrado et al. [14] resulted in the following conclusions and recommendations: 10 min after injection with $^{18}$F-FCH, a steady distribution of the tracer is found in the liver. Further, no substantial clearance of the tracer from the liver is seen besides the physical decay of $^{18}$F-FCH, which has a half-life of 110 min. Finally, the kidney is a dose-critical organ and a maximum $^{18}$F-FCH dose of 4.07 MBq/kg is advised for human research. Preliminary reports from France [15] and from our group suggested that $^{18}$F-FCH PET/CT might become a promising diagnostic tool in differentiating FNH from HCA with high sensitivity and specificity [16]. Herein, we present the final results of our completed prospective study.
Methods

In this study, a prospective, single-center study for the evaluation of the diagnostic accuracy of $^{18}$F-FCH PET/CT in the differentiation of HCA from FNH was conducted. The study included those from the pilot study conducted previously on 21 patients. The aim of the study was to assess the diagnostic accuracy of $^{18}$F-FCH PET/CT for the differentiation of HCA from FNH in a large prospective patient series.

This study is a prospective, single-center study for the evaluation of the diagnostic accuracy of $^{18}$F-FCH PET/CT in the differentiation of HCA from FNH. No financial support was granted for this study. The local medical ethics committee approved the study and written informed consent was obtained from all patients before inclusion in the study. Patients were referred to our center with suspicion of FNH or HCA larger than 2 cm based on ultrasound, CT, and/or MRI after they had presented elsewhere with symptoms, or they were incidentally identified. Patients aged 18 years or older, with no history of malignancy or chronic liver disease, and with normal serum a-fetoprotein levels were included. Patients with known allergy to fluoro-labeled tracers or with impaired renal function (serum creatinine > 140 mmol/l), as 50% of the $^{18}$F-FCH tracer is cleared by the kidneys, were excluded. A total of 56 patients were included in the study and they underwent $^{18}$F-FCH PET/CT between May 2008 and April 2011 (Fig. 2). Twenty-one patients who had been studied previously and whose results have been published as a chapter 3

**Figure 1**

Choline enters the cell by means of facilitated diffusion or through transporters. In the mitochondria of the hepatocyte the CDP pathway is adopted (top). Another pathway of choline metabolism is its oxidation to betaine, which can clear homocysteine from the cell or can act as an osmolyte to maintain cellular homeostasis. Further, not only the CDP pathway but also the methylation pathway in which S-adenosylmethionine and phosphatidylethanolamine are used can produce phosphatidylcholine, a compound of the cell membrane. The enzymes catalyzing the processes are in italics. CDP, cytidine (50) diphosphocholine; OCT, organic cation transporter; PE, phosphatidylethanolamine.

**Figure 2**

Flow chart of the study. A total of 56 patients presented with a suspicion of hepatocellular adenoma (HCA) and/or focal nodular hyperplasia (FNH). Of them, three were diagnosed with a different diagnosis on the basis of imaging before performing the PET and four more patients were excluded after the PET because of no standard of reference (n=3) or because of other diagnoses (n=1). Therefore, a total of 49 patients with 60 hepatic lesions were evaluated. CT, computed tomography.
preliminary report, were included in the present study [16]. The sample size was calculated on the basis of the initial published results of Bumsel and colleagues and first experience with the SUV ratio. Assuming an HCA SUV ratio of 1.0 (SD 0.3) and an FNH SUV ratio of 1.3 (SD 0.3), including 25 patients per group would yield sufficient power (90%, α=5%) to validate the hypothesis. Taken together, the results of 49 patients (mean age 41 years; range 20–69 years) with 60 lesions were included in the analysis.

18F-FCH PET/CT

18F-FCH synthesis 18F-FCH was synthesized as previously described by DeGrado et al. [17]. This resulted in 18F-FCH with a radiochemical purity of 98% or more. Decay-corrected radiochemical yield was 20–30%. 18F-FCH PET/CT was performed using a Philips Gemini TF-16 PET/CT scanner (Philips Medical Systems, Eindhoven, the Netherlands) with a spatial resolution of 4.8 mm near the center of the field of view in transverse and axial directions. A CT scan in the supine position was acquired from the midthorax to the midabdomen, encompassing the entire liver. The 16-channel helical CT scanning parameters were as follows: 120 kVp, 50 mA/slice, rotation time 0.75 s, and slice thickness/interval 5.0 mm. No intravenous contrast was used. Fifteen minutes after intravenous injection of 150 MBq of 18F-FCH, emission scans were acquired from the midthorax to the midabdomen, encompassing the entire liver over three to four bed positions at 3 min per position. Image reconstruction used a list-mode version of a maximum likelihood expectation maximization algorithm with a time-of-flight kernel applied in both the forward and back-projection operations. CT data were used for attenuation correction.

18F-FCH PET/CT EVALUATION

PET images were analyzed by a nuclear radiologist and low-dose CT images by a radiologist experienced in abdominal radiology. Both readers were blinded to patient history and previous imaging results. 18F-FCH PET was performed and evaluated before histological analysis was carried out. Images were evaluated on a workstation (Hermes Medical Solutions, Stockholm, Sweden). As 18F-FCH uptake seems dependent on perfusion, variation in physiologic liver uptake was expected. Despite that, patients were asked to fast for 6 h before scanning. Compliance is a known bias, and therefore normalization of lesion uptake to normal liver uptake was performed. The maximum standardized uptake value (SUVmax) of the lesion(s) and the mean SUV of the surrounding nonaffected liver were determined. The SUV ratio was calculated by dividing the maximum SUV of the lesion (SUVmax lesion) by the mean SUV of the surrounding liver tissue (SUVmean liver): SUVratio = SUVmax lesion / SUVmean liver.

STANDARD OF REFERENCE

The final diagnosis of HCA or FNH was based on histopathological examination, and no treatment decisions were made on the basis of the results of 18F-FCH PET. The histological specimen was obtained by liver biopsy or by surgery and the evaluating pathologist was blinded to previous pathology reports, imaging reports, and patient history. Some patients were scheduled for surgery regardless of their histological diagnosis because of severe discomfort or because of the explicit wish of the patient. If this was not the case, patients underwent a biopsy on which diagnosis was based. Lesions larger than 5 cm for which biopsy revealed an HCA were subsequently resected. Therefore, some patients underwent both a biopsy and resection of the lesion. Standard liver stains for histomorphological diagnosis included hematoxylin and eosin, collagen, and cytokeratin-7. Morphological characteristics of HCA included proliferation of hepatocytes without cytonuclear atypia, with a well developed reticulin framework, and without the presence of stellate fibrous scarring. HCA was subclassified on the basis of morphological characteristics and additional immunohistochemical staining of C-reactive protein (CRP), serum amyloid A (SAA), glutamine synthetase (GS), and liver–fatty acid-binding protein (LFABP) [18]. Positive CRP and/or SAA immunostaining was regarded as diagnostic for inflammatory HCA. Negative LFABP staining compared with normal surrounding liver parenchyma was regarded as diagnostic for steatotic HCA due to an HNF-1α mutation. Diffuse GS staining was regarded as diagnostic for HCA due to a β-catenin mutation. Diagnosis of FNH was based on morphological characteristics, including the presence of stellate fibrous scarring, dystrophic arteries, a ductular reaction, and variable infiltrates, as well as the absence of cytological abnormalities. An immunohistochemical GS staining was performed for confirmation of histomorphological diagnosis [19] – FNH having a typical map-like staining pattern. The final diagnosis of HCA or FNH was based on histopathology, and no treatment decisions were made on the basis of 18F-FCH PET results (Figs 3–5).

On the basis of MR and/or CT imaging, a total of 36 patients presented with benign hepatic lesions, most likely HCA or FNH (Fig. 2). MRI and CT were performed and showed two hemangiomas and four benign but inconclusive lesions, besides HCA and FNH lesions. One of the lesions was proven by histopathology to be a cluster of hamartomas. Patients with hamartomas and hemangiomas were excluded from the study. The remaining 53 patients underwent the 18F-FCH PET/CT. No histopathological confirmation of diagnosis was obtained for three patients, and one patient had a hemangioma. These patients were excluded from further analysis. Forty-nine patients (two men and 47 women; mean age 42 years, range 20–69 years) were included in the study between May 2008 and April 2011. Suspicion of one or multiple FNHs and/or HCA was based on CT and/or MRI was raised in the case of 20 (44%) patients who presented with...
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Figure 3

A: The standardized uptake value (SUV) ratio was the most accurate and a cutoff value of 1.13 (dotted line) was determined as the most sensitive and specific in the receiver operating characteristic (ROC) analyses of the group with histologically confirmed lesions.

B: The diagnosis based on the standard of reference is shown in the ROC curve for ‘SUVmax of the lesion’ without correction for surrounding liver tissue (dashed) and as a ratio of SUVmax of the lesion (straight) and the SUVmean of the surrounding liver tissue.

Table 1 Results

<table>
<thead>
<tr>
<th>Histological diagnosis (mean SUV ratio±SD)</th>
<th>FHN</th>
<th>HCA</th>
</tr>
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<tbody>
<tr>
<td>18F-FCH PET/CT positive</td>
<td>28 (1.67±0.31)</td>
<td>1 (1.30)</td>
</tr>
<tr>
<td>SUV ratio &gt; 1.13</td>
<td>0</td>
<td>31 (0.82±0.17)</td>
</tr>
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CT, computed tomography; FHN, focal nodular hyperplasia; HCA, hepatocellular adenoma; 18F-FCH, 18F-fluoromethoxychlorine; LR, likelihood ratio; SUV, standardized uptake value.

The top three figures show transverse MR images of focal nodular hyperplasia from left to right: A: arterial enhancing lesion in segments 2–3 of the left liver (Gd-EOB-DTPA; T1w 5.77/2.54, flip angle 101, matrix 256×156). B: The lesion on the 18F-fluoromethoxychlorine (18F-FCH) PET image 15 min after injection of 18F-FCH shows clear hyperintensity compared with the surrounding tissues. C: The fusion of both images, which makes both assessment of 18F-FCH metabolism and anatomical localization possible. The lower three figures show transverse MR images of hepatocellular adenoma (from left to right) D: MR image in the arterial phase (Gd-EOB-DTPA; T1w 5.77/2.54, flip angle 101, matrix 256×156), in which a central hepatic lesion shows slight arterial enhancement with corresponding photopenia on (E) the 18F-FCH PET image and (F) the fusion 18F-FCH PET computed tomography image.

Abdominal discomfort or pain and in four (8%) patients who presented with elevated levels of liver enzymes in the serum. In 24 (49%) patients the lesions were incidentally found on imaging performed for other unrelated indications. In one patient the presenting symptoms were not recorded. Patients were followed up for a mean period of 21 months (range 6–36 months). Eighteen patients showed hepatic steatosis on imaging or histopathologic analysis (37%). Histological diagnosis of FNH or HCA was obtained from 60 lesions larger than 2 cm (28 FNHs and 32 HCAs). Results are summarized in Table 1. Diagnosis was made for resection specimens from 37 lesions and for biopsy specimens from 23 lesions. All cases of FNH showed a typical map-like staining pattern for GS, which was absent in HCA. Of
the two male patients, one presented with FNH and one with steatotic HCA. HCA was classified as inflammatory with overexpression of CRP and/or SAA in 56% (18/32); as steatotic with negative staining for LFABP in 16% (5/32); and as the β-cateninmutated subtype with diffuse GS staining in 0%; 28% (9/32) remained unclassified. In two of the unclassified cases the biopsy material was either of insufficient quality or of insufficient quantity to perform additional immunohistochemical assessment. In two resection specimens, extensive bleeding was found with a gradient of lower LFABP expression within the lesion when compared with the surrounding liver tissue, however, without pronounced steatosis. As the morphology and staining pattern were not typical for steatotic HCA and as additional molecular analysis could not be carried out, these HCAs were scored as unclassified. Four unclassified HCAs were found in the liver of one patient with extensive granulomatous hepatitis. Finally, in one resection specimen, CRP, SAA, and GS were not overexpressed and the LFABP was normally expressed. One patient presented with a lesion suspected to be HCA, but histopathologic evaluation after liver biopsy revealed hemangioma. Four patients with HCA and/or FNH also presented with typical hemangiomas on imaging, and one patient presented with concomitant bile duct hamartomas.

18F-FCH PET/CT

Histological diagnosis showed a mean SUV ratio of 1.67±0.31 (n=28) for FNH and 0.81±0.19 (n=32, P=0.001) for HCA. The SUVmax of HCA had a mean of 7.72±2.15 (4.31–10.04) compared with 15.99±4.09 (10.19–27.43) for FNH. The SUVmean of the liver was 9.54±2.09 (5.84–16.49). Results are summarized in Table 1 and Supplementary Table 2. As predicted, the SUV ratio was more sensitive than the SUVmax of the lesion, and receiver operating characteristic curve analysis suggested that an SUV ratio cutoff value of 1.13 predicted patients with FNH as against those with HCA with 100% sensitivity (95% CI 88–100%) and 97% specificity (95% CI 84–99%). The LR of FNH was 32.3 when 18F-FCH PET/CT was evaluated as positive, with a 98% post-test probability for FNH. The LR of HCA was greater than 100 when 18F-FCH PET/CT was evaluated as negative, with a 99.9% posttest probability for HCA. Patients with liver steatosis based on MRI or histopathological diagnosis (n=18) revealed an SUVmean of the liver of 10.16±1.69 (7.65–13.95) and those without liver steatosis (n=31) revealed an SUVmean of the liver of 9.18±2.24 (5.84–16.49). There was no significant difference in the SUVmean of the liver between patients with and those without liver steatosis (P=0.644). The inflammatory subtype showed a mean SUV ratio of 0.83±0.21 (n=18), the steatotic subtype showed a mean SUV ratio of 0.95±0.11 (n=5), and the unclassified group of HCA showed a mean SUV ratio of 0.77±0.16 (n=9). In one patient with a histological diagnosis of unclassified HCA, the lesion showed uptake of 18F-FCH with an SUV ratio of 1.0. Finally, evaluation of additional lesions showed the following results. Five patients presented with hemangiomas; 1/6 hemangiomas were larger than 1 cm and were evaluated [mean SUVmax 5.57 (2.9–5.6–8.2); mean SUV ratio 0.49 (0.33–0.50–0.65)]. One patient presented with an FNH and multiple small hamartomas, which were histopathologically confirmed. The largest lesion showed an SUVmax of 5.8, SUVmean of the liver of 9.9, and an SUV ratio of 0.59. None of the patients experienced acute adverse events from 18F-FCH PET/CT due to the administrated 18F-FCH tracer.

Three hepatic lesions in a 58-year-old patient. A: Transverse images of computed tomography (CT; portal phase). White arrows indicate the lesions. B: PET images show the corresponding 18F-FCH hyperintense lesions (white arrows). C: Fusion of the 18F-FCH PET images with the CT images. In the fusion images, there is relative organ position mismatch between CT and PET because of different breath-hold techniques on acquisition, and hence the PET is focused on the target lesion. The hyperintensity of the lesions suggests focal nodular hyperplasia, but histopathology and MRI of the lesions showed a hepatocellular adenoma (unclassified subtype).
Our study shows that $^{18}$F-FCH PET/CT accurately differentiates FNH from HCA. On using an SUV ratio cutoff value greater than 1.13, high sensitivity and specificity were observed. Therefore, $^{18}$F-FCH PET/CT could be used as a valuable diagnostic imaging tool.

This could very well be preferred over an invasive liver biopsy, which is associated with complications (bleeding) and is subject to sampling errors. The outcome of our study confirms our preliminary results reported previously [16], as well as preliminary results reported by others [15]. The study by Talbot et al. [23] focuses on the comparison between the PET tracers $^{18}$F-FCH and $^{18}$FDG in detecting liver lesions, particularly hepatocellular carcinomas (HCCs). The authors report 115 hepatic lesions, including eight FNHs (7/8 positive on $^{18}$F-FCH PET/CT) and eight HCAs (1/8 positive on $^{18}$F-FCH PET/CT), and, although this is a small sample size, it shows a trend similar to that seen in our study.

When using imaging modalities, MRI with hepatobiliary contrast has proven to be the most sensitive in differentiating FNH from HCA [24]. The sensitivity of MRI in differentiating HCA from FNH is 94%. In the remaining cases, in which diagnosis is inconclusive but clinically relevant for treatment decisions, $^{18}$F-FCH PET/CT provides a noninvasive alternative modality with high sensitivity. Subclassification of HCA is important because the b-catenin subgroup is thought to have a higher potential for malignant transformation compared with the other subtypes [25]. Diagnosis in this subgroup by means of noninvasive $^{18}$F-FCH PET/CT would provide a clear clinical benefit for these patients. This issue becomes even more relevant when $^{18}$F-FCH PET/CT is able to depict malignant transformation of HCA during followup. Well-differentiated HCCs show uptake of $^{18}$F-FCH and might therefore be differentiated from HCA [26]. However, no b-catenin-mutated HCAs were found in our patient series. It is noteworthy that in our study the HCA subtypes showed a trend in the uptake of $^{18}$F-FCH, although it was not significant. The steatotic subtype showed the highest mean SUV ratio of 0.95 compared with 0.83 in inflammatory HCA and 0.77 in unclassified HCA. Therefore, we call for a prospective study including all HCA subtypes to determine the usefulness of $^{18}$F-FCH PET/CT in subtyping HCA and its possible usefulness in the follow-up of high-risk HCAs.

In the HCA series presented in this study, a relatively high percentage of unclassified HCAs was found (55%), which is in line with the results of a previous Dutch study, which had 51% unclassified HCAs [27]. In two cases this was because of insufficient biopsy material hindering complete classification. In two resection specimens, extensive bleeding was found, interfering with immunohistochemical analyses. In the other unclassified HCA lesions, CRP, SAA, GS, and LFABP staining results were inconclusive.

The mechanism of enhanced $^{18}$F-FCH uptake in FNH is unclear. Hypothetically, this could be caused by an increased expression of choline transporters [12]. Further, the gradient of choline over the cell membrane could be altered, facilitating choline transport through the organic cation transporter OCT1. As mentioned above, three major pathways are known for choline metabolism (Fig. 1). First, the CDP pathway, in which phosphorylation of choline can be upregulated. Malignant tumor cells are known to have enhanced mitotic activity and cell duplication rates and therefore have an increased need for choline as a substrate for cell membranes [28]. This has been described in well-differentiated HCCs, and these lesions are known to show enhanced uptake of $^{18}$F-FCH [26, 29]. FNH is a benign liver lesion potentially caused by a vasculopathy and proliferates slowly, if at all. Thus, enhanced uptake of $^{18}$F-FCH in FNH can barely be explained by mechanisms involved in tracer accumulation in HCCs. Within this CDP pathway, a possible explanation is the metabolism of very-low-density-lipoproteins (VLDLs). Phosphatidylcholine is an important component of VLDL particles. Within the liver, fat and cholesterol are wrapped in these VLDL particles to make their transport through blood possible. These hypotheses will need further research to determine their possible role in the enhancement of $^{18}$F-FCH uptake in hepatic tumors.

In one patient with HCA we saw uptake of $^{18}$F-FCH. Histological diagnosis was made on the basis of a biopsy specimen in which no signs of malignancy were found. This HCA remained unclassified, as all immunohistochemical stainings were without abnormal staining patterns. A possible explanation for the uptake of $^{18}$F-FCH could be possible focal malignant transformation within the HCA lesion. As mentioned above, well-differentiated HCCs are $^{18}$F-FCH PET/CT positive. Focal sites of malignant transformation could easily be missed by liver biopsy because of sampling of a different area of the lesion but might still cause the $^{18}$F-FCH PET/CT-positive results. However, the patient was in good clinical condition after 12 months of follow-up without any signs of malignancy.

The results of this study can be interpreted only in the light of its strict inclusion and exclusion criteria. Only if a malignancy is unlikely and the differential diagnosis is mainly FNH or HCA are the results of this study applicable to the patient. As discussed above, HCC could also show uptake of $^{18}$F-FCH. Therefore, the results of this study cannot be extrapolated to a general patient with a focal liver lesion. Further, although all consecutive patients were included, some degree of selection bias did occur. Of the patients included, 52% had FNH and 48% had HCA, whereas in the general population the estimated prevalence of FNH is 10 times higher than that of HCA [26]. Referral of patients with HCA may have been more likely for the following reasons: because patients presented with symptoms, for example, after bleeding when intervention was needed, or because patients presented with larger lesions for which resection was indicated. Patients with typical FNH may have been less likely referred, because there are no surgical consequences to this diagnosis. The current bias is therefore toward cases with a more problematic diagnosis.
CONCLUSIONS

This prospective study shows that 18F-FCH PET/CT can accurately differentiate FNH from HCA. It is an additional diagnostic tool to confirm uncertain diagnosis based on conventional imaging studies.

REFERENCES