Dual-time-point $^{18}$F-fluorocholine PET/CT in Parathyroid Imaging

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ABSTRACT

¹⁸F-fluorocholine (FCH) PET/CT is a promising and increasingly used scan technique in preoperative imaging of parathyroid adenoma. Several acquisition methods have been evaluated in literature but the optimal image acquisition time point after administration of the tracer is still under debate. **Methods:** Patients with hyperparathyroidism, who received a dual-time-point FCH PET/CT (image acquisition 5 min and 60 min post injection) with histologically proven pathological parathyroid glands were retrospectively included in the study. The early versus late images were compared both visually and quantitatively. **Results:** Forty-six patients were included and a total of 71 parathyroid glands were surgically removed. Visually, there were no differences between early and late images of hyperfunctioning parathyroid glands in 44 patients (69%), in 13 patients (20%) visualization on early images was better, in 6 patients (9%) visualization of hyperfunctioning glands was best on late images whereas in 1 patient (2%), the lesion was exclusively visualized on late images. For the total cohort, there was a significant decrease in FCH uptake in the glands on late versus early time points (p=0.001), but a significant increase of parathyroid-to-thyroid ratio (p=0.037). The group of patients with better visualization on early images showed a decrease over time in both parathyroid uptake and parathyroid-to-thyroid ratio, significant in comparison to both the group with better visualization at the later time point and the group in which visualization was similar at both time points (p-values ranging 0.000-0.018). There were no significant differences in FCH uptake and parathyroid-to-thyroid ratio between the latter two groups (p-values ranging 0.200-0.709). **Conclusion:** In the majority of patients (89%), hyperfunctioning parathyroid glands are adequately visualized on early imaging, however in a subset of patients (11%) such glands are best visualized at a later time point. Therefore, it is recommended to acquire dual-time-point images in parathyroid imaging with FCH PET/CT, or to create an opportunity to acquire additional late images after reviewing early images when findings are inconclusive.

**Key words:** ¹⁸F-fluorocholine; PET/CT; dual-time-point; hyperparathyroidism; parathyroid adenoma
INTRODUCTION

Hyperparathyroidism covers a spectrum of parathyroid diseases, with primary hyperparathyroidism being the most common. This disease develops as a result of autonomous production and secretion of parathyroid hormone (PTH) from parathyroid glands, with a 3/1000 prevalence in the general population and up to 21/1000 in postmenopausal females (1,2). Secondary hyperparathyroidism typically occurs in patients with chronic renal disease due to derangements in calcium and phosphorus levels resulting in increased PTH. Tertiary hyperparathyroidism is the condition that may follow after secondary hyperparathyroidism when PTH secretion transforms from compensatory to autonomous.

Symptomatic primary hyperparathyroidism is routinely treated with parathyroidectomy, in which accurate localization of hyperfunctioning parathyroid glands can be beneficial in preoperative planning and is a prerequisite in case of minimal invasive surgery. In secondary and tertiary hyperparathyroidism, which also may be treated with parathyroidectomy, imaging is mainly performed to detect ectopic or supernumerary glands (3). To visualize parathyroid lesions, various morphology-based imaging techniques can be used such as ultrasonography, computed tomography and magnetic resonance imaging; however, the current reference method is functional imaging with $^{99m}$Tc-sestamibi. Recently, $^{18}$F-fluorocholine (FCH) PET/CT was proposed and investigated as a tool for detection of hyperfunctioning parathyroid tissue, with promising results (4,5).

Although various acquisition protocols have been described, the optimal time point for image acquisition after injection of FCH is still under debate. In previous studies, time points ranging from 0 to 120 min post injection (p.i.) have been used, with conflicting results. Both scanning at early as well as at late time points have been suggested, and authors have reported lesions that were visualized on early images only (6-8). The objective of the present study was to evaluate different uptake patterns and differences between visualization of parathyroid glands on early versus late images using dual-time-point FCH PET/CTs in patients with hyperparathyroidism.
METHODS

Patient Selection

Patients who received a dual-time-point FCH PET/CT for evaluation of hyperparathyroidism were included in this study, when PET/CT was both positive and followed by surgery, and when parathyroid adenoma or hyperplasia was histopathologically proven. All patient data, including baseline characteristics, scan results and quantitative measurements, were prospectively entered into a database. Additional follow-up data were retrieved from the electronic patient records. Patients were classified based on clinical indication: primary, secondary or tertiary hyperparathyroidism. Primary hyperparathyroidism was defined as persistent elevation of serum calcium levels with corresponding elevated or nonsuppressed PTH levels, or high PTH levels and normal serum calcium levels (i.e. normocalcemic hyperparathyroidism)(9). Secondary hyperparathyroidism was defined as low serum calcium levels and high PTH levels associated with chronic renal failure, and tertiary hyperparathyroidism as persistent elevated PTH levels after treatment of secondary hyperparathyroidism due to autonomous PTH production.

Informed Consent

The institutional research department approved this retrospective study and all subjects signed a written informed consent for use of their anonymized data for scientific purposes. Besides the standard imaging protocol and clinical management no additional measurements or actions affecting the patient were performed. The study was performed in accordance with the Declaration of Helsinki. Approval of the local ethical committee for the present study was not necessary since the study does not fall within the scope of the Dutch Medical Research Involving Human Subjects Act (section 1.b WMO, 26th February 1998).
Scan Acquisition

PET/CT images were acquired on a Siemens Biograph-16 TruePoint PET/CT camera (Siemens Healthcare, Knoxville, TN, USA). Early images of the thyroid region were acquired 5 min after intravenous injection of approximately 150 MBq FCH. The following acquisition parameters were used: one bed position of 480 s with matrix size 256×256 and low dose CT for attenuation correction using a tube current of 40 mAs at 100 kV with CARE Dose 4D dose modulation, collimation of 24x1.2 mm and a pitch of 0.95. Late images were acquired 60 min p.i. ranging from the temporomandibular joint to the diaphragm. Corresponding with early images, late images were acquired at 480 s per bed position and a matrix size of 256×256. Late CT images for attenuation correction and anatomical mapping were acquired using a tube current of 80 mAs at 120 kV, collimation 16x1.2 mm and a pitch of 0.95. Both early and late PET images were reconstructed with an iterative 3D method using 5 iterations, 8 subsets and a Gaussian filter. Interpretation of the images and quantitative measurements were done with dedicated software (Syngo.via, Siemens Medical Solutions, Malvern, PA, USA). Patient preparation consisted of hydration with 1L water and, if applicable, discontinuation of colchicine 48 hours prior to FCH administration. Discontinuation of calcimimetic drugs or other medications was not required.

Image Interpretation

Imaging results were prospectively recorded in a database after scan reading. Each FCH PET/CT was scored as negative, equivocal or positive for hyperfunctioning parathyroid glands. In presence of well-defined focal FCH uptake at typical locations, the scan was considered positive for hyperfunctioning parathyroid tissue. If tracer uptake was of very low intensity or could not be distinguished from uptake in the thyroid gland, the scan was considered equivocal. A physiological distribution of FCH or abnormal distribution with an alternative explanation rather than hyperfunctioning parathyroid tissue defined the scan as negative.

Other image data that was entered into the database included location of abnormal foci (left or right, cranial or caudal in respect to the thyroid gland, intrathyroidal or ectopic) and number of abnormal
foci (solitary adenoma, multiple adenomas or four-gland hyperplasia). The early and late images were compared both quantitatively and visually. Visually, the scans were compared independently by two nuclear medicine physicians (WB and MW). Each scan was categorized into one of five subcategories: visualization on early images only, best visualization on early images, no essential difference, best visualization on late images and visualization on late images only. In case of discrepancy between the two readings, the appropriate category was assigned in consensus. Acquired quantitative measurements of abnormal foci were maximum and peak standardized uptake value (SUV$_{\text{max}}$ and SUV$_{\text{peak}}$). Additionally, the SUVs of the thyroid gland were measured as reference, and parathyroid-to-thyroid (P/T) ratios were calculated.

**Statistical Analysis**

Normally distributed continuous data was expressed as mean ± standard deviation and range, non-normal continuous data as median with interquartile range. Non-continuous data was expressed as numbers with percentages. A paired samples t-test or a Mann-Whitney U test was used where appropriate to compare differences between early and late time points and between subgroups. A p-value < 0.05 was considered significant. Statistical analysis was carried out using the Statistical Package for Social Sciences 20 (IBM SPSS Statistics, Chicago, IL, USA).

**RESULTS**

Sixty-four patients were included in the study and FCH scans were performed from April 28$^{\text{th}}$ 2016 to March 14$^{\text{th}}$ 2018 (Table 1). Clinical indications for FCH PET/CT were primary hyperparathyroidism (including MEN2a associated and lithium induced disease) in 61 patients, secondary hyperparathyroidism in two patients and tertiary hyperparathyroidism in one patient. A total of 71 glands were surgically removed. Nine (13%) of the removed glands were located left superior, 25 (35%) left inferior, 6 (9%) right superior, 27 (38%) right inferior, one gland (1%) was located within the thyroid gland and 3 (4%) glands were ectopically located. Histopathological examination yielded 59 single
adenomas and 2 double adenomas, concordant with the scan results. One patient with secondary hyperparathyroidism showed a four-gland hyperplasia on the scan, of which three excised glands were histologically confirmed to be hyperplastic, the fourth gland was not found and was left in situ. The scan of the other patient with clinically suspected secondary hyperparathyroidism showed single gland disease (recurrent hyperparathyroidism after earlier excision of a contralateral parathyroid adenoma). The patient with tertiary hyperparathyroidism also showed a four-gland hyperplasia on the scan, which were all removed and histopathologically confirmed to be hyperplastic. All patients showed a clinically significant decrease of PTH after surgery (at least 50% reduction).

In patients with multiple pathologic parathyroid glands on FCH PET/CT, one gland was randomly selected for further analysis to avoid potential bias due to non-independent observations resulting in a total of 64 analyzed lesions. Visual comparison yielded no essential difference in visibility of the pathological parathyroid gland between the early and late images in 44 scans (69%). Thirteen scans (20%) showed better visualization on early images and 6 scans (9%) on late images. One scan (2%) was negative on the early images but showed a single parathyroid adenoma on late images, whereas no scans were exclusively positive on early images. Scan examples of best visualization on early and late images are showed in Figures 1 and 2, respectively. Two scans were considered equivocal on both early and late images, of which one displayed an intrathyroidal hotspot with differential diagnosis thyroid adenoma, whereas the other showed an isointense lesion close to the thyroid. At histopathology, both lesions proved to be parathyroid adenomas.

The scan in which the parathyroid gland was only visualized on late images was excluded for further quantitative analysis. For the cohort in total, early SUV\textsubscript{max} was significantly higher, whereas early SUV\textsubscript{max} P/T ratio was significantly lower as compared to those values for late images (absolute difference p=0.001 and ratio difference p=0.037, paired samples t-test). More or less the same results were found for measured SUV\textsubscript{peak} (absolute difference p <0.000 and ratio difference p=0.021, paired samples t-test) (Fig. 3). As can be appreciated from Figure 4, there are several differences in quantitative results between the subgroups based on visual interpretation. There is a decrease in FCH uptake on late images for the ‘better
visualization on early images’ subgroup, which is more apparent for the *absolute difference* than for the *ratio difference*, and there is a slight trend towards a higher absolute FCH uptake in the parathyroid lesions and higher relative uptake compared to the thyroid gland for the ‘better visualization on late images’ subgroup. Statistically, a significant difference was found between the subgroup ‘better visualization on early images’ versus ‘better visualization on late images’ (*absolute difference* p=0.001 and *ratio difference* p=0.001, Mann-Whitney U test) as well as versus the subgroup ‘equivocal visualization’ (*absolute difference* p<0.001 and *ratio difference* p<0.001, Mann-Whitney U test). No significant difference was found between the subgroups ‘better visualization on late images’ and ‘equivocal visualization’ (*absolute difference* p=0.221 and *ratio difference* p=0.200, Mann-Whitney U test). Analysis of the SUV\textsubscript{peak} measurements did not lead to different conclusions (Fig 5).

**DISCUSSION**

In this study, differences between parathyroid imaging with FCH PET/CT at 5 min p.i. and 60 min p.i. were analyzed. Overall, the parathyroid lesions showed a higher FCH uptake on early images and a higher P/T ratio on late images. However, different patterns were recognized, and scans with better visualization on early images as well as better visualization on late images were observed.

In literature, multiple acquisition protocols have been used in parathyroid imaging with FCH PET/CT and several studies used a dual-time-point or triple-time-point protocol\cite{5,6,10-15}. Lezaic et al. observed a better lesion-to-background and a lesion-to-thyroid contrast on late images, but all lesions were visible at both time points\cite{10}. Also, in two studies by Michaud et al., the late images did not yield additional findings\cite{11,12}. Two studies noticed an increase of SUV\textsubscript{max} on late images, in contrast to the observations of the present study, and one of those studies also suggested that a single late acquisition may suffice in patients with high PTH\cite{4,14}. Some reports mentioned a dual-time-point scanning protocol without further explication of different scan results\cite{5,13,15}. In a study by Rep et al., the only study with a triple-time-point protocol, it was concluded that the optimal scan time is 60 min after injection of the tracer, with a higher accuracy compared to early images and identical accuracy compared to images
obtained at 120 min (accuracy of 94.1%, 96.5% and 96.5% at 5, 60 and 120 minutes p.i. respectively)(6).

This was due to non-visualization of three parathyroid lesions on early images. Over time, a decrease of absolute uptake was observed, as well as an increase in contrast to the thyroid gland, due to lower FCH retention in the thyroid tissue, which is in agreement with the findings of the present study.

In the present study, none of the parathyroid lesions were exclusively visualized on early images, but failure to detect parathyroid lesions on delayed imaging has been reported in the literature. In one case this comprised a cystic parathyroid adenoma with a possible fast tracer washout due to rich blood supply(7). Because of the highest activity in the first minutes on dynamic scans it was also hypothesized by another author that a major portion of the SUV in the early phase represents blood flow in the adenoma(16). However, no correlation between parathyroid vascularization and choline metabolism was found in a study comparing FCH PET/CT at 10 min p.i. with dual phase contrast enhanced CT (arterial phase images acquired 10-15 s after enhancement of the thoracic arch) (17).

In one case from the aforementioned cohort by Rep et al., one adenoma could not be visualized on late images due to intense FCH accumulation in bone marrow in a patient with polycythaemia vera(6). Fast choline washout was also observed in a small series of 7 patients who underwent a 30 min dynamic scan in combination with a static 60 min p.i. acquisition(18). Three different uptake patterns were recognized (early washout, stable uptake and late increase), indicating the importance of early acquisition in order to avoid non-detection of parathyroid lesions with fast washout. Prabhu et al. prospectively compared early dynamic imaging during the first 15 min p.i. with delayed imaging after 45 min(8). Higher $SUV_{\text{max}}$ was observed on dynamic images, whereas difference in P/T ratio between early dynamic and late images was not significant and it was suggested that only early imaging could suffice.

For the analysis of the FCH uptake in the present study, both commonly used parameters $SUV_{\text{max}}$ and $SUV_{\text{peak}}$ were measured, known to have a low interobserver variability(19). It was decided not to use $SUV_{\text{mean}}$, since this value is strongly dependent on the way of drawing the volume of interest and therefore has higher interobserver variability, especially with small parathyroid lesions. In this study, the
use of SUV_{peak} did not lead to different results compared to SUV_{max}, and it seems that both methods are suitable for SUV measurements on parathyroid lesions.

Since the aim of the study was to analyze the FCH uptake patterns in hyperfunctioning parathyroid glands, it was decided to only include histologically proven pathologic lesions. As a consequence, no difference in accuracy of early versus late imaging could be calculated. Histopathological examination was used as reference standard in the present study. The histopathological examination of parathyroid tissue can be difficult in certain cases, and especially the distinction between adenoma and hyperplasia is not always clear\(^{(20)}\). Because of the low number of hyperplastic parathyroid glands versus parathyroid adenomas, no subgroup analysis was performed in this study. Additionally, evaluation of correlation between uptake patterns, laboratory values and size or weight of the parathyroid glands may be of interest for future research. A known pitfall in FCH PET/CT is tracer uptake in lymph nodes, which can cause false positive results in parathyroid scanning, especially for foci in ectopic locations. Multiple time point scanning can help to identify benign lymph nodes\(^{(21)}\). Moreover, Prabhu et al. reported that early dynamic imaging was also able to differentiate between adenomas and cervical lymph nodes\(^{(8)}\). Prior to the PET/CT, patients in our study did not have to discontinue calcimimetic drugs or other medications, except for colchicine\(^{(22)}\). In previous studies on parathyroid imaging with FCH PET/CT, discontinuation of parathyroid drugs was not applied as well, but no specific research has been done on this matter. Moreover, with conventional \(^{99m}\)Tc-sestamibi parathyroid imaging, the discontinuation of medications is also disputable\(^{(23,24)}\).

**CONCLUSION**

In conclusion, variable FCH uptake patterns were observed on dual-time-point FCH PET/CT parathyroid imaging. Although most hyperfunctioning parathyroid glands were visualized on both early and late images, some lesions may be missed if only one time point is used. Therefore, it is recommended to acquire dual-time-point images in parathyroid imaging with FCH PET/CT, or to create an opportunity to acquire additional late images after reviewing early images when findings are inconclusive.
DISCLOSURE

The authors declare that they have no conflicts of interest.

KEY POINTS

Question: What is the value of performing $^{18}$F-fluorocholine PET/CT at two time points in parathyroid imaging?

Pertinent Findings: This retrospective cohort study showed variable uptake patterns with significant differences in parathyroid lesion uptake between early and late images. In some cases, scanning at one time point did not suffice, therefore it is recommended to acquire dual-time-point images.

Implications for Patient Care: In this upcoming imaging technique, these findings are of importance in improving scanning protocols to optimize the accuracy of parathyroid lesion detection.
REFERENCES


FIGURE 1. Example of a dual-time-point FCH PET/CT with best visualization of a parathyroid adenoma on early images. Early images (A: AC PET, PET/CT fusion and MIP images acquired at 5 min p.i.) show an intense tracer uptake in a right inferior parathyroid adenoma. Late images (B: AC PET, PET/CT fusion and MIP images at 60 min p.i.) show near complete washout of the tracer.

FCH: $^{18}$F-fluorocholine, AC: attenuation corrected, MIP: maximum intensity projection, p.i.: post injection.
FIGURE 2. Example of a dual-time-point FCH PET/CT with best visualization of a parathyroid adenoma on late images. A left superior parathyroid adenoma is visualized on the early images with approximately isointense tracer uptake compared to the thyroid gland (A: AC PET, PET/CT fusion and MIP images acquired at 5 min p.i.). On the late images, the adenoma is more apparent due to faster washout of the tracer from the thyroid gland (B: AC PET, PET/CT fusion and MIP images at 60 min p.i.).

FCH: $^{18}$F-fluorocholine, AC: attenuation corrected, MIP: maximum intensity projection, p.i.: post injection.
FIGURE 3. Comparison of early versus late SUV-measurements and parathyroid-to-thyroid (P/T) ratios.
FIGURE 4. Bland-Altman plots. Difference between FCH uptake (SUV\textsubscript{max}) in parathyroid lesions is plotted against the mean uptake in each lesion (upper left panel) and the difference between the parathyroid-to-thyroid uptake ratio (SUV\textsubscript{max}) is plotted against the mean ratio for each lesion (lower left panel). For SUV\textsubscript{peak}, this data is plotted similarly in the upper right and lower right panel, respectively. The dotted lines are the mean values and 95% intervals for the total cohort.
FIGURE 5. Differences between the three subgroups based on visual interpretation; better visualization on early images (‘early better’), equivocal visualization (‘equivocal’) and better visualization on late images (‘late better’). This is shown for SUV\textsubscript{max} absolute differences (upper left panel), SUV\textsubscript{max} ratio differences (lower left panel), SUV\textsubscript{peak} absolute differences (upper right panel) and SUV\textsubscript{peak} ratio differences (lower right panel).
**TABLE 1.** Patient characteristics

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<tr>
<td>Age [mean ± SD (range)] (years)</td>
<td>60 ± 12 (28-81)</td>
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<td>Sex [n (%)]</td>
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</tr>
<tr>
<td>Male</td>
<td>17 (27)</td>
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<tr>
<td>Female</td>
<td>47 (73)</td>
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<td>PTH [mean ± SD (range)] (pmol/L)</td>
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<td>(normal range: 1.3–6.8 pmol/L)</td>
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<td>Serum calcium [mean ± SD (range)] (mmol/L)</td>
<td>2.67 ± 0.19 (2.11-3.30)</td>
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<td>(normal range: 2.10–2.50 mmol/L)</td>
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PTH: parathyroid hormone