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Accuracy of ^{18}F-fluorocholine PET for the detection of parathyroid adenomas: prospective single center study

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Abstract

Purpose: The purpose of this prospective study was to determine the correct localization rate (CLR) of ^{18}F-fluorocholine (FCH) positron emission tomography (PET) for the detection of parathyroid adenomas in comparison to sestamibi imaging.

Materials and Methods: This was a single-arm prospective trial. Ninety-eight patients with biochemical evidence of primary hyperparathyroidism were imaged prior to parathyroidectomy using FCH PET/MRI. Sestamibi imaging performed separately from the study was evaluated for comparison. The primary endpoint of the study was the CLR on a patient level. Each imaging study was interpreted by 3 blinded readers on a per-region basis. Lesions were validated by histopathologic analysis of surgical specimens.

Results: Of the 98 patients who underwent FCH imaging, 77 subsequently underwent parathyroidectomy and 60 of those had sestamibi imaging. The CLR for FCH in patients who underwent parathyroidectomy based on the blinded reader consensus was 75% [0.63, 0.82]. In patients who underwent surgery and had an available sestamibi study, the CLR increased from 17% [0.10, 0.27] for sestamibi to 70% [0.59, 0.79] for FCH PET.

Conclusion: In this prospective study using blinded readers, the CLR for FCH was 75%. In patients with paired sestamibi, the use of FCH PET increased the CLR from 17% to 70%. FCH PET is a superior imaging modality for the localization of parathyroid adenomas.

Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder caused by a hyperfunctioning parathyroid adenoma in over 85% of cases. Surgery is the only curative therapy for PHPT, and is associated with decreased risk of fractures and nephrolithiasis as well as long-term improvement in quality of life (1-4). A minimally invasive unilateral surgical approach is preferred to lessen the morbidity associated with bilateral neck exploration, while providing similar cure rates and long-term benefits (5). This less invasive approach is only possible when pre-operative imaging studies can correctly localize the culprit parathyroid adenoma(s) (6). These studies include sestamibi scintigraphy and neck ultrasound, which are traditionally the most commonly used first-line imaging options for PHPT, as well as newer modalities such as four-dimensional CT.

Although most commonly reported for use in prostate cancer, ^{18}F-fluorocholine (FCH) has been studied extensively for the detection of parathyroid adenomas (7). It has been hypothesized that parathyroid adenomas have increased uptake of FCH due to upregulation of phospholipid/calcium^{2+}-dependent choline kinase (8). European centers have shown FCH PET to be highly accurate in the detection of parathyroid adenomas (9), particularly among patients with negative, discordant, or inconclusive results on conventional imaging as well as re-operative patients (10,11). Though most reports of FCH PET pair it with low-dose CT for anatomic mapping, our institution performs simultaneous MRI in order to avoid excess ionizing radiation. We have previously reported a 90% sensitivity and 100% positive predictive value for correct localization of parathyroid adenomas using FCH PET/MRI in a pilot study of 10 patients with PHPT and inconclusive results on US and sestamibi (12).

In this study, we aimed to prospectively evaluate the ability of FCH PET to correctly localize parathyroid adenomas and compare the correct localization rate of FCH PET to sestamibi imaging.

Materials and Methods

This study was approved by the local institutional review board, and informed consent was obtained from all subjects. Between September 2016 and July 2019, 98 patients were consecutively enrolled in this prospective study evaluating the use of FCH PET in patients with PHPT at the University of California, San Francisco (NCT03764007). This study was performed under a cost-recovery Investigational New Drug approval from the Food and Drug Administration (FDA). Inclusion criteria included biochemically proven PHPT, intention to treat with surgery, and age >13 years. Prior sestamibi imaging was not a requirement for enrollment. The Standards for Reporting of Diagnostic Accuracy (STARD) flow diagram is shown in **Figure 1**. The study was initiated, planned, conducted, analyzed, and published by the investigators. No financial support was received from commercial entities. The full protocol is available in the supplementary material.

18F-Fluorocholine synthesis

FCH was synthesized using the ORA Neptis Perform synthesizer (Optimized Radiochemical Applications, Philippeville, Belgium) as previously described using a nucleophilic substitution reaction (13). Dibromomethane (primary precursor) and N,N dimethylethanolamine (DMAE; secondary precursor) were obtained from Abx GmbH (Radeberg, Germany).

Imaging Protocol

All imaging was performed on a 3.0T time-of-flight PET/MRI (Signa, GE Healthcare, Waukesha, WI). Patients were injected with 6.0±0.7 mCi of 18F-fluorocholine, and imaging was performed 31±16 minutes after injection (the protocol window for uptake time was 20-60 minutes after injection). Two PET bed positions were acquired, the first centered over the thyroid, and the second more inferiorly, in order to catch any mediastinal adenomas. The first bed position over the neck was acquired for 20 minutes, and the chest bed position was acquired for 8 minutes. PET data sets were reconstructed by using a time-of-flight reconstruction with ordered subset expectation maximization by using two iterations and 28 subsets and a matrix size of 256x256. Axial sections were reconstructed at a thickness of 2.78 mm. In the neck, the MRI acquisition included axial T1 spin echo and axial T2 spin echo imaging with IDEAL fat saturation. In the chest, the MRI acquisition included a T2 spin echo sequence with two-point Dixon fat saturation, and T1 weighted spoiled gradient echo sequence with two-point Dixon fat saturation.

Image analysis

All FCH PET studies were reviewed by three nuclear medicine physicians not involved in the study and from different institutions (JC, EE, and GJ). The three readers had no prior experience interpreting FCH PET parathyroid studies, and each reviewed a 10 patient training dataset prior to performing the blinded reads for this study. The central readers were blinded to all aspects of the subject's history, and interpretation was performed using OsiriX (14).

Image interpretations were recorded in a centralized REDcap database for analysis. The location of the most likely parathyroid adenoma was recorded. For patients where multiple adenomas were visualized, all abnormal regions were recorded.

Two months separate from the FCH reads, the same three readers interpreted the sestamibi studies in the subset of patients in whom they were performed. The sestamibi studies were not performed as part of this protocol, and interpretation was made based on the images available in the Picture Archiving and Communication System (PACS). The sestamibi technique was not harmonized across all patients. Analysis also was performed using local reads, as bias may exist among the three blinded readers.

Surgical management

Patients who subsequently had surgical management underwent either focused unilateral parathyroidectomy or bilateral neck exploration at our institution per surgeon judgment, with the standard practice to offer focused parathyroidectomy with intraoperative PTH monitoring in cases with localizing preoperative imaging. Anatomic/embryologic designation of adenoma location was defined by the surgeon, and confirmed by histopathology as enlarged and/or hypercellular. For this study, surgical success was defined based on normalization of serum calcium and PTH levels 6 hours after parathyroidectomy, as well as serum calcium drawn at approximately 2 weeks after surgery.

Statistical analysis

The primary endpoint of this prospective study was the correct localization rate (CLR) of FCH PET compared to sestamibi imaging for the detection of parathyroid adenomas. Our analysis focused on CLR, which was chosen based on guidance to the investigators by the Food and Drug Administration during a pre-New Drug Application meeting. The use of CLR helps to minimize the benefit of overcalling lesions and to more accurately reflect the ability of the imaging study to guide a focused surgical approach. Correct localization was defined as positive on a patient level if at least one anatomic region (categorized into three groups - left neck, right neck and other) was correctly characterized as a true positive (TP) signal and no other regions were characterized as false positive (FP); the denominator for CLR are all patients available for analysis. A true negative (TN) patient was defined as a patient in whom all regions were called negative, and no parathyroid adenoma was found at the time of surgery. FP and false negative (FN) patients were defined respectively as a patient in whom one region was determined to be either FP or FN independent of whether or not a separate region was determined to be TP. For presentation purposes, the consensus read of the three blinded readers is used where the consensus was determined by the majority read from the initial assessment. Our predetermined statistical plan estimated that we needed 67 patients with pathology and sestamibi imaging to demonstrate a difference in sensitivity of 70% for sestamibi and 85% for FCH, with a power of 87, allowing for a drop-out of 10 patients. Inter-reader variability was calculated for the location of the parathyroid adenoma (left neck versus right neck versus other) using a Fleiss's κ and for all regions together for both FCH PET and sestamibi interpretations, and strength of agreement was determined according to the definition described by Landis and Koch (15). Statistical analysis was performed in R statistical software (version 3.3.3, R Foundation).

Safety of FCH PET imaging was assessed by the regular monitoring for adverse events (AEs) during and immediately after study acquisition, and measured as a secondary endpoint by the rate of reported AEs.

Results

In total, of the 99 patients who enrolled in the study, 98 patients were ultimately imaged using FCH PET/MRI, 72 of whom were female (**Table 1**). Forty-one patients (42%) had prior parathyroidectomy, a disproportionate number reflecting the higher frequency of more complex clinical cases evaluated at a tertiary-care referral center.

18F-fluorocholine accuracy compared to pathology

Seventy-seven of the 98 patients (79%) subsequently underwent parathyroidectomy an average of 85±66 days after FCH PET imaging. At surgery, 75 patients had an adenoma removed, and 65 patients (87%) had biochemical cure after surgery. During surgery, 56 patients underwent targeted unliteral minimally invasive surgery based on the findings from FCH PET. Of the 21 patients that underwent bilateral neck exploration, 14 were due to bilateral lesions seen on FCH PET, 3 were unplanned and due to an insufficient drop in PTH when the adenoma visualized on the FCH PET was removed, 2 were planned due to negative FCH PETs, and two were for removal of goiter.

Of the 12 patients who did not have evidence of biochemical cure, 5 patients had persistently elevated laboratory values after surgery, 4 patients had no laboratory follow-up, and 3 patients were found to have parathyromatosis. In the first patient who had no cure, two hypercellular adenomas were removed at time of surgery, but a known mediastinal adenoma was knowingly left in place. In the second patient without cure, a hypercellular adenoma seen on FCH PET was removed, but the hypercalcemia persistent and a repeat surgery removed a second adenoma also seen on the original FCH PET. In the third patient without cure, the adenoma on FCH PET came back hypercellular, but the hypercalcemia persisted. In the fourth patient without cure, the adenoma seen on FCH PET came back normal and a hypercellular adenoma on the opposite side was removed at surgery, but again the hypercalcemia persisted. In the fifth patient without cure, no adenoma was removed at surgery, and the adenoma seen on FCH PET was believed to have been missed and was subsequently successfully removed at repeat surgery. Separately, one additional patient had no adenoma found on pathology although a lesion was seen on FCH PET, and on follow-up laboratory values normalized.

Ninety-seven percent (75/77) of the imaging studies were read as positive by consensus blinded reads. Based on local reads, 52 patients were correctly localized, with 20 FP and 5 FN patients, resulting in a CLR of 68% [95% confidence interval (CI) 0.57, 0.77]. Based on the consensus of the three blinded readers, 56 patients were correctly localized with 16 FP and 4 FN patients, resulting in a CLR of 74% [0.63, 0.82]. The CLRs of the three readers were 74% [0.63, 0.82], 64% [0.53, 0.74] and 64% [0.53, 0.74]. Of 20 FP based on local reads, five were TP in one region and FP in a separate region.

18F-fluorocholine compared to sestamibi

Seventy-three patients also underwent sestamibi scan; of these, 60 patients underwent both sestamibi and FCH PET within 12 months of one another, and subsequently underwent parathyroidectomy. FCH PET outperformed sestamibi imaging for the detection of parathyroid adenomas (**Table 2** and **Figure 2**). Based on local reads, the CLR increased from 25% [0.17, 0.36] with sestamibi to 75% [0.64, 0.83] with FCH PET. Based on the three blinded readers, the CLR increased from 17% [0.10, 0.27] with sestamibi to 70% [0.59, 0.79] with FCH PET (Table 2).

Reader Agreement

For FCH PET, the inter-reader agreement was substantial for the left neck (κ = 0.75; 95% CI, 0.66-0.83) and right neck (κ = 0.64; 95% CI, 0.54-0.73), and was moderate for other (κ = 0.50; 95% CI, 0.40-0.60). Across all three regions, the inter-reader agreement for FCH PET was substantial, with a κ of 0.71 (95% CI, 0.66-0.76). For sestamibi imaging, the inter-reader agreement was moderate for the left neck (κ = 0.47; 95% CI, 0.37-0.58) and right neck (κ = 0.47; 95% CI, 0.36-0.57), and was fair for other (κ = 0.32; 95% CI, 0.22-0.42). Across all three regions, the inter-reader agreement for sestamibi was moderate, with a κ of 0.47 (95% CI, 0.41-0.53).

Safety

All patients were evaluated for potential AEs. There were no reported AEs from any patient.

Discussion

In this prospective study of the largest cohort in the United States to undergo FCH PET imaging for preoperative localization in patients with PHPT, FCH PET demonstrated a higher CLR for the detection of parathyroid adenomas in patients compared to sestamibi imaging. These results support the use of FCH PET for the localization of parathyroid adenomas in patients with PHPT.

Published studies on FCH PET report sensitivities ranging from 81-100%, and specificities of 95-100% (16). Our analysis focused on the CLR, which was suggested to the investigators by the FDA during a pre-New Drug Application meeting. CLR is more stringent than patient level sensitivity, where identification of any TP region would convert a patient to a TP study. Using conventional sensitivity analysis, FCH PET in this study would have had a sensitivity of 98%, 98% and 95% for each of the three readers for the 60 patients that underwent sestamibi and FCH PET. The CLR approach minimizes the benefit of overcalling lesions during interpretation, which provides a better representation of the ability of the study to direct minimally invasive surgery.

Better pre-operative localization is likely to increase the number of PHPT patients definitively treated with surgery. Patients with negative imaging are less likely to be referred to a surgeon and, even when referred, remain less likely to undergo parathyroidectomy (17). The benefits of parathyroidectomy are well-established, including decreased risk of bone fracture and kidney stones (2,3) and better quality of life (18). Parathyroidectomy is more cost-effective than medical management (19), even in mild or asymptomatic PHPT.

This study was performed using PET/MRI for imaging rather than PET/CT. MRI has a role in diagnosing parathyroid adenomas and in particular dynamic post-contrast images of the neck can be helpful to characterize parathyroid adenomas due to the early brisk enhancement (20). The use of MRI for this study was used only for anatomic localization, and dynamic post-contrast images were not acquired. In our first work using PET/MRI in this setting, we utilized contrast and did not find that it added significantly to FCH PET (21), therefore limited our MRI protocol to non-contrast T1 and T2 weighted imaging.

One of the strengths of our study is the interpretation of the imaging studies using both local and three blinded reads, which limits bias present in many retrospective imaging studies that use single readers at the same institution where the studies were performed. It should be noted that although none of the three blinded readers have experience interpretating FCH PET at their individual institutions, that the interreader agreement was substantial for FCH interpretation. Nonetheless there is a small learning curve required, particularly in regards to the low level of uptake seen in cervical lymph nodes. Additionally, our study was a prospective study that included sequential patients. This is the first study to examine FCH PET for PHPT on a large scale in North America.

Our study has several limitations. First, the sestamibi studies included in our trial were not all performed on site and had heterogeneous techniques. Of the 77 sestamibi studies evaluated, 63 of them were performed with SPECT/CT, 8 with SPECT, and 6 with planar imaging. Second, our study did not compare the performance of FCH PET to all other parathyroid imaging modalities such as ultrasound and four-dimensional CT; instead, we chose sestamibi as the most appropriate comparator because of its widespread use as well as its commonality with FCH PET as a nuclear medicine-based imaging tool. We anticipate that future studies will examine in greater detail the relative accuracy and role of FCH PET in the current armamentarium of parathyroid imaging options.

Third, 21 patients in our cohort did not undergo surgical parathyroidectomy after imaging with FCH PET. There are many reasons for this including patient preference for surgical management, but there is concern that a reason for forgoing surgery was a negative FCH PET. The rate of positive FCH PETs was lower in the non-surgery group (81% versus 97%), although that only represents four patients with negative FCH PETs who did not undergo surgery.

Fourth, long-term biochemical cure of PHPT is traditionally assessed by measuring serum calcium and PTH levels at 6 months after surgery, which was beyond the time scope of our current study (we are currently accruing this long-term data for a future report). However, we believe the postoperative biochemical data we obtained, when interpreted together with the pathology results, provide robust evidence of the efficacy of FCH PET in the localization of parathyroid tumors that can be targeted for subsequent surgical removal.

Fifth, our study evaluated a large number of patients without localization on ultrasound or sestamibi, which does not reflect the overall population of patients with PHPT. There were several sources of this bias. First, our institution serves as a referral center for parathyroidectomies, and our population reflects a cohort in which localization is more difficult. Second, patients without localization on sestamibi or ultrasound were preferentially sent for advanced imaging using FCH PET. Third, 42% of our study population had undergone a previous parathyroidectomy, and both ultrasound and sestamibi are less accurate in the re-operative setting than in primary disease (22). Our complex cohort likely resulted in the unusually low CLR for sestamibi (25% base on local reads), which is significantly lower than in previous studies. Considering that our study population in whom FCH PET demonstrated excellent accuracy was highly enriched for those with more complex clinical scenarios, we hypothesize that FCH PET performed in the broader population of PHPT patients would localize at an even higher rate.

Conclusion

This study demonstrates that in a cohort of PHPT patients, FCH PET outperforms sestamibi imaging. Based on consensus interpretation of centrally blinded readers, the use of FCH PET increased the CLR from 17% to 70% compared to sestamibi. These results support the use of FCH PET for the localization of parathyroid adenomas in patients with PHPT.

Disclosures

No potential conflicts of interest relevant to this article exist. TAH receives institutional research funding from Advanced Accelerator Applications and Philips, and is a consultant for Curium. JAS is a member of the Data Monitoring Committee of the Medullary Thyroid Cancer Consortium Registry supported by GlaxoSmithKline, Novo Nordisk, Astra Zeneca, and Eli Lilly. She receives institutional research funding from Exelixis and Eli Lilly. IS is a consultant for Prescient Surgical, Medtronic, and Gerson Lehman Group.

KEY POINTS

QUESTION: Is 18F-fluorocholine superior than sestamibi for the localization of parathyroid adenomas?

PERTINENT FINDINGS: In this prospective study using three blinded readers, 18F-fluorocholine had a 70% correct localization rate compared to 17% for sestamibi imaging.

IMPLICATIONS FOR PATIENT CARE: 18F-fluorocholine is superior to sestamibi imaging for the localization of parathyroid adenomas.

Tables

Table 1: Characteristics of the Patients at Baseline. Number and (percent) unless otherwise listed. n/a = not applicable.

		Efficacy cohort	
	All patients (N=98)	Surgery cohort (N=77)	Sestamibi cohort (N=60)
Age, median (range), y	64 (17-90)	66 (17-86)	65 (17-85)
Sex			
Male	26 (27)	18 (23)	13 (22)
Female	72 (73)	59 (77)	47 (78)
Prior parathyroidectomy	41 (42)	26 (34)	24 (40)
Prior imaging			
Sestamibi, total	92 (94)	73 (95)	n/a
Sestamibi, within 12 months	77 (79)	62 (81)	n/a
Number positive	44 (57)	43 (59)	n/a
Ultrasound	94 (96)	76 (99)	59 (98)
Number positive	45 (48)	41 (54)	33 (56)
Baseline laboratory values (mean±SD)			
Calcium	10.6±0.6	10.7±0.6	10.7±0.5
Parathyroid hormone	116±119	122±132	125±143
18F-fluorocholine results			
Positive for adenoma**	94 (96)	75 (97)	58 (97)
Surgical results			
Adenoma found at surgery	n/a	75 (97)	58 (97)
Biochemical cure after surgery	n/a	63 (85)*	48 (84)*

* three patients had no follow-up laboratory values available for review
** positive determined by consensus of blinded readers

Table 2: Comparison of Sestamibi and 18F-fluorocholine (FCH) PET results in patients who underwent both sestamibi and FCH PET, and underwent surgery. Based on local reads the correct localization rate (CLR) increased from 25% to 75%, and based on the three blinded readers, the CLR increased from 17% to 70%. Cons = consensus interpretation, R1 = reader 1, R2 = reader 2 and R3 = reader 3.

	Sestamibi					FCH				
	Local	R1	R2	R3	Cons	Local	R1	R2	R3	Cons
Correct Localization	15	8	10	15	10	52	44	37	40	42
False positive	8	1	3	6	3	13	13	19	15	15
False negative	36	49	46	38	46	4	3	4	5	3
True negative	1	2	1	1	1	0	0	0	0	0
Correct localization rate	25%	14%	17%	25%	17%	75%	73%	62%	67%	70%

Figures

Figure 1: STARD Flow Diagram for the Efficacy Cohort

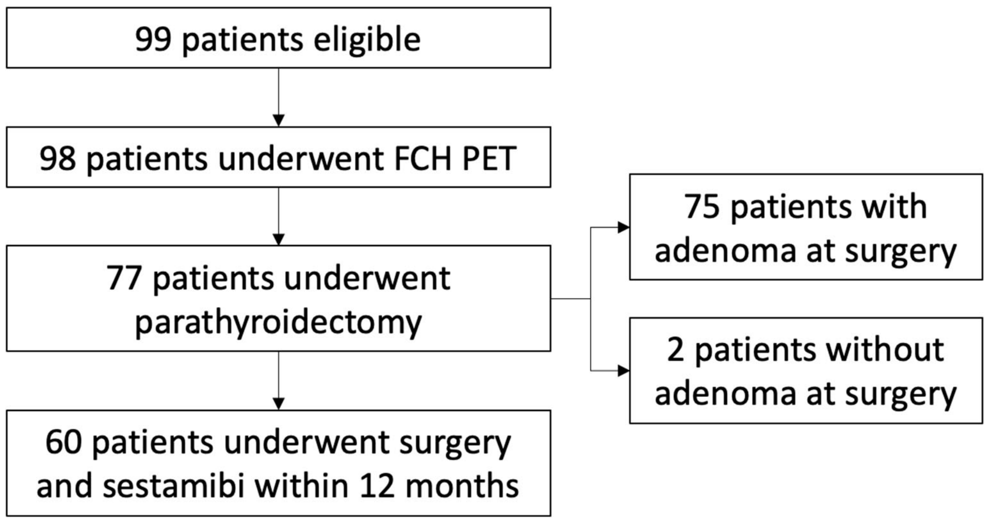
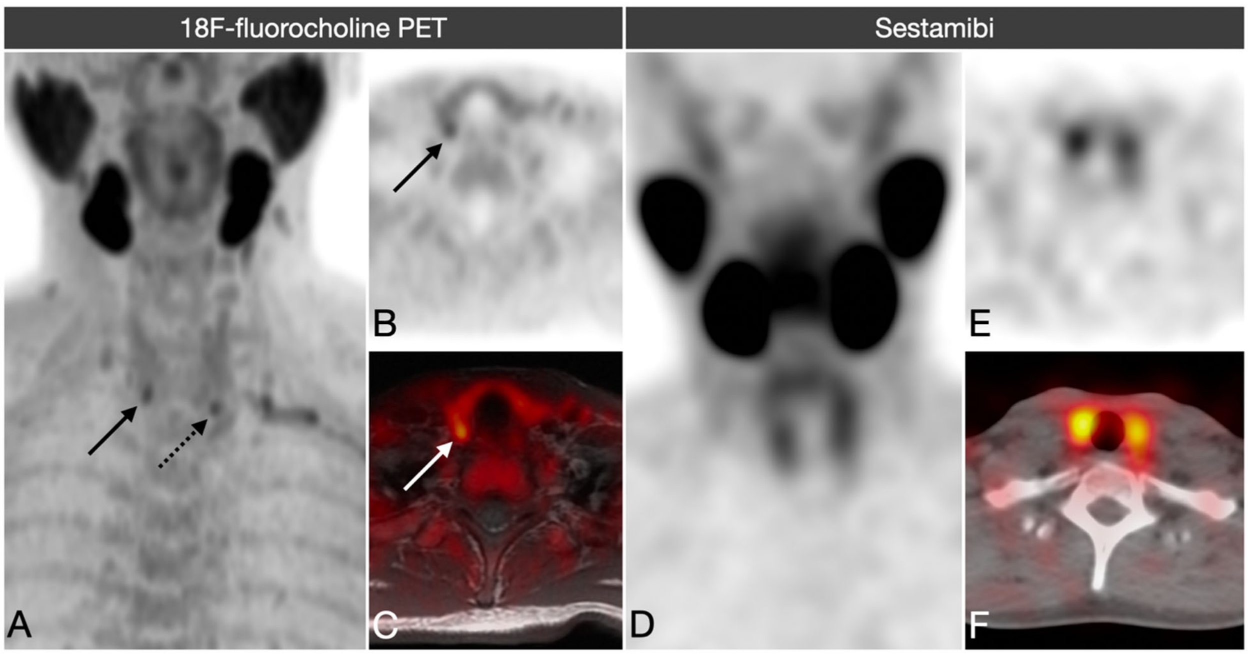


Figure 2: Example patient who underwent both 18F-fluorocholine PET and sestamibi imaging. The FCH PET (A-C) was correctly localized by all three readers as positive on both the right (solid black arrow) and left (dotted arrow). The sestamibi imaging study (which include an immediate and two-hour SPECT, although only the two-hour is shown D-F) was called as negative by all three readers. At parathyroidectomy, both lesions seen on FCH PET were confirmed to be parathyroid adenomas.



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Graphical Abstract