Received: 16 August 2024 | Accepted: 4 October 2024

DOI: 10.1111/eci.14336

ORIGINAL ARTICLE

WILEY

Refining the role of presurgical PET/4D-CT in a large series of patients with primary hyperparathyroidism undergoing [^{18}F]Fluorocholine PET/CT

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Abstract

Background: 4D-CT has garnered attention as complementary imaging for patients with primary hyperparathyroidism (pHPT). Herein we evaluated a diagnostic strategy using [^{18}F]Fluorocholine Positron Emission Tomography/Computed Tomography (PET/CT), followed by 4D-CT integrated into PET/4D-CT after negative/inconclusive PET/CT results in a single-center retrospective cohort of 166 pHPT patients who underwent parathyroidectomy after [^{18}F]Fluorocholine PET/4D-CT.

Methods: PET/CT and 4D-CT images were interpreted by three nuclear medicine physicians and one expert radiologist. Pathological findings were documented, and concordance rates were assessed. PET/CT results were categorized as positive/negative, with positive cases rated on a 3-level certitude scale: low, moderate, high. Inconclusive cases included low/moderate positivity. The added

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value of PET/4D-CT was assessed for negative/inconclusive cases through joint reading.

Results: PET/CT lesion-based analysis showed almost perfect interobserver concordance (Cohen's kappa >.8). Across the cohort, PET/CT had a sensitivity of 83%, specificity of 97%, PPV of 90% and NPV of 94%. For 4D-CT, these values were sensitivity: 53%, specificity: 84%, PPV: 56% and NPV: 82%. PET/CT was significantly more accurate than 4D-CT. Among 44 patients with negative/inconclusive results, PET/CT had sensitivity: 60%, specificity: 91%, PPV: 71% and NPV: 86%. In the same patients, sensitivity and specificity of the sequential diagnostic algorithm increased to 80% and 97%, showing significantly better global accuracy (92% vs. 83%) than standard PET/CT.

Conclusions: We support a personalized imaging algorithm for pHPT, placing [^{18}F]Fluorocholine PET/CT at the forefront, followed by 4D-CT integrated into PET/4D-CT in the same imaging session for negative/inconclusive results. When PET/CT results are clearly positive, the additional sensitivity benefit of 4D-CT is minimal.

KEYWORDS

4D-CT, adenoma, fluorocholine, hyperparathyroidism, parathyroid, PET

1 | INTRODUCTION

Primary hyperparathyroidism (pHPT) involves dysregulated PTH secretion, leading to hypercalcemia. It is usually caused by a solitary adenoma (80%), with multiple-gland disease (15%–20%) or ectopic glands (16%) also possible. Minimally invasive parathyroidectomy (MIP) is preferred, requiring accurate preoperative imaging for success.[1–4]

Currently, neck ultrasound (US) and parathyroid scintigraphy using 99mTc-sestamibi are recommended as initial imaging modalities. However, the diagnostic accuracy of US can vary with the operator's expertise, and scintigraphy success greatly depends on the specific imaging protocol.[5–7] Significant advancements in imaging technologies have recently enhanced the presurgical approach to pHPT,[8] offering improved sensitivity and specificity in detecting abnormal parathyroid tissue. Among these, Positron Emission Tomography/Computed Tomography (PET/CT) utilizing [^{18}F]Fluorocholine has emerged as a valuable second-line imaging technique, with high resolution, minimal radiation exposure and shorter examination durations. This is particularly beneficial for patients with previously negative or inconclusive results from 99mTc-sestamibi scintigraphy and/or US.[9,10] Several studies indicate its efficacy, with sensitivity and detection rates up to 90% and 80%,[11] respectively, especially in patients with pHPT, including those with recurrent or persistent post-surgical HPT.[12] [^{18}F]Fluorocholine PET/CT appears more accurate and useful preoperatively than the 99mTc-sestamibi scan, even in pHPT patients with positive scintigraphic results.[13] Recent guidelines consider [^{18}F]Fluorocholine PET/CT as a potential first-line option whenever feasible.[14] Nevertheless, negative or inconclusive results are possible, prompting further investigations. Additionally, false-positive results involving inflammatory lymph nodes and/or thyroid nodules can be a limitation of [^{18}F]Fluorocholine PET/CT.[11]

4D-CT has garnered attention as a complementary imaging modality, offering high-resolution anatomical visualization and dynamic assessment of contrast enhancement patterns. Unlike conventional CT imaging, 4D-CT employs rapid sequential imaging acquisitions, enabling the characterization of parathyroid lesions based on their vascularity and contrast kinetics.[15,16] A recent meta-analysis involving five articles and 153 patients with pHPT demonstrated a pooled sensitivity of 77% for 4D-CT.[17] Similarly, another comprehensive study comprising 16 research articles revealed a pooled specificity of 85% for 4D-CT in localizing hyperfunctioning parathyroid glands preoperatively in pHPT patients.[18] The combined use of [^{18}F]Fluorocholine PET/CT and 4D-CT in an integrated manner has gained significant interest as a holistic approach to preoperative localization in pHPT.[19,20] This integrated imaging strategy aims to leverage the unique strengths of each modality, potentially improving localization accuracy and facilitating optimal surgical planning.[20] While its impact on sensitivity remains a topic of discussion,[17] the simultaneous use of [^{18}F]Fluorocholine

PET and 4D-CT in a single examination (PET/4D-CT) has the potential to aid in differential diagnosis, thereby reducing false positive PET/CT findings.[21] Thus, [^{18}F] Fluorocholine PET/4D-CT could represent a significant advancement in the management of pHPT, offering a streamlined approach to localization in difficult cases.

To contribute to the ongoing discussion on the optimal imaging strategy for preoperative parathyroid localization in pHPT, we have retrospectively evaluated the diagnostic impact of a protocol involving PET/CT followed by sequential 4D-CT in the same imaging session for cases with negative or inconclusive PET/CT results. This approach aims to develop a personalized diagnostic strategy by incorporating the sequential use of 4D-CT after conventional PET/CT with non-contributory findings.

2 | MATERIALS AND METHODS

2.1 | Patient population

This is a monocentric, retrospective, noninterventional study including patients with HPT addressed to our institution for [^{18}F]Fluorocholine PET/CT between May 2018 and November 2021. Only patients satisfying the following criteria were retrospectively included: (1) patients with pHPT, (2) patients underwent integrated [^{18}F] Fluorocholine PET/4D-CT and (3) patients with parathyroid surgery achieved after PET/CT. The following clinical, imaging and biological data were retrieved from hospital databases, clinician reports and biomedical laboratories: sex, age, previous parathyroid surgery, the results of diagnostic parathyroid imaging performed before [^{18}F] Fluorocholine PET/CT (i.e., neck US, parathyroid CT, or MRI), patient genetic status, calcimimetic treatment, hypercalcemia-related symptoms, PTH and calcium serum concentrations. Surgical procedures, perioperative and post-surgical follow-up PTH measurements and pathological reports concerning the parathyroid surgery after [^{18}F]Fluorocholine PET/CT were collected.

In accordance with local institutional guidelines, all patients included provided free and written informed consent for the use of anonymous personal medical data extracted from their files for scientific or epidemiological purposes. The local Institutional Review Board approved this retrospective study (IRB-2024-14).

2.2 | [^{18}F]Fluorocholine PET/4D-CT technical procedures

Integrated [^{18}F]Fluorocholine PET/4D-CT were performed using a combined PET/CT device equipped with time-of-flight measurement capacity (Biograph128 mCT, 2018–2019; Biograph Vision, 2020–2021; Siemens Healthcare, Erlanger, Germany). PET/4D-CT imaging protocol included:

1. A dynamic four-phase CT scan including non-enhanced CT (140 kV, 115 mA, 1 s per rotation and pitch .8, slice thickness of 1 mm) followed by arterial phase (10–15 s after injection, aortic arch threshold >80 HU), venous phase (45 s after injection) and late-venous phase (70 s after injection). 75 mL of iodine contrast agent (Iomeron 400 mg/mL) was intravenously injected with a 2.5–3 mL/s flow rate followed by a saline chaser. CT parameters of arterial and venous phases were: 120 kV, 1 and 15 mAs, 1 s rotation time, pitch .8, slice thickness of 1 mm. CT CARE Dose 4D combined with sinogram-armed iterative reconstruction (SAFIRE) was used. Diabetic patients withdrew metformin treatment for 2 days after the study, and abundant hydration was recommended.
2. A standard 10-min PET acquisition from the mandible to the carina performed in the supine position with arms along the body and a headrest at approximately 60 min after intravenous injection of 3–3.5 MBq/kg of [^{18}F]Fluorocholine. PET datasets were reconstructed iteratively using no contrast-enhanced CT for attenuation correction. PET data were also corrected for scattering, random coincidences and radioactive decay.

2.3 | Parathyroid imaging interpretation

[^{18}F]Fluorocholine PET/CT and 4D-CT were independently interpreted on a dedicated workstation. [^{18}F]Fluorocholine PET/CT were evaluated separately by three nuclear medicine physicians: one resident, one expert reader highly experienced in PET/CT imaging and parathyroid imaging, and one non-expert reader skilled in PET/CT imaging (primarily oncology) and some experience with parathyroid imaging. 4D-CT scans were evaluated by a radiologist who was competent in CT imaging and had some experience with parathyroid imaging. Referring physicians were aware of the patient history, clinical features and biological data but were blinded to the results of either PET or 4D-CT. Focal nonphysiological uptake corresponding to any cervical or thoracic nodule discriminable from thyroid tissue, positioned in typical parathyroid sites or in ectopic areas, was considered pathologic on [^{18}F]Fluorocholine PET imaging. For each positive gland, the maximum standardized uptake value (SUVmax) was assessed. Cervical or thoracic tissular nodules with contrast-media enhancement and washout of more than 20 HU at late-venous phase, positioned in typical parathyroid sites or in suggestive ectopic areas,

were considered positive on 4D-CT imaging.[15] The number and location of pathological findings on [^{18}F]Fluorocholine PET/CT and 4D-CT were recorded.

The concordance rate for [^{18}F]Fluorocholine PET/CT interpretation was evaluated according to reviewer experience: resident vs. expert and expert vs. non-expert. In line with the findings reported by the expert reader, results of [^{18}F]Fluorocholine PET/CT scans were categorized as either positive or negative. In cases classified as positive, the referring physician's level of certainty regarding the interpretation of [^{18}F]Fluorocholine PET/CT findings (indicative of the presence of pathologic parathyroid) was rated on a three-level scale: low, moderate and high certitude. [^{18}F]Fluorocholine PET/CT with 'low' and 'moderate' positivity were considered as inconclusive studies. In these cases, along with the negative cases, the added value of 4D-CT was assessed by a joint consensual re-reading of hybrid [^{18}F]Fluorocholine PET/4D-CT by an expert nuclear medicine physician and radiologist, both blinded to the first interpretation of both PET and 4D-CT studies. Hyperfunctioning parathyroids were diagnosed in case of any focal non-physiological [^{18}F]Fluorocholine uptake on PET images, corresponding to any cervical or thoracic lesion with typical contrast-enhancement pattern on the 4D-CT. If distinct appearance in 4D-CT strongly supported the conclusion of hyperfunctioning parathyroid, the lesion was considered as positive and diagnosed according to the 4D-CT, even in cases of lack of significant [^{18}F]Fluorocholine uptake.

2.4 | Gold standard

Post-parathyroidectomy histopathology, accompanied by a reduction exceeding 50% in perioperative PTH blood levels (*per* the Miami criterion) and/or a 6-month biological monitoring period, were employed to ensure surgical success, validating the complete removal of all hyperfunctioning parathyroid tissue (true positive outcomes).[22] Additionally, intraoperative PTH monitoring served to safeguard the functionality of unaffected parathyroid glands during excision, thereby preserving their normal function. Identification of normal glands (true negative outcomes) was based on a comprehensive assessment including surgical exploration findings, ongoing biological monitoring (such as PTH and serum calcium levels) and adherence to the Miami criterion indicating a 'more than 50% intraoperative PTH drop'.

2.5 | Statistical analysis

Categorical variables were presented as numbers and percentages. Results for continuous data were expressed as median and range. Sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) were assessed for [^{18}F]Fluorocholine PET/CT, 4D-CT and [^{18}F]Fluorocholine PET/4D-CT in detecting hyperfunctioning parathyroids. Cohen's kappa coefficients were used to assess interobserver reproducibility. Kappa coefficients were interpreted using the benchmarks of Landis and Koch (.81–1, almost perfect agreement; .61–.8, substantial agreement; .41–.6, moderate agreement; .21–.4, fair agreement; .01–.2, slight agreement). Differences between groups were assessed by Mann–Whitney *U* test for continuous variables. Two-sided *p* values less than .05 were considered statistically significant. Statistical analysis has been provided using the open access software biostatgv (biostatgv.sentiweb.fr, Institut Pierre Louis d'Epidémiologie et de Santé Publique, UMR S1136, INSERM – Sorbonne University, Paris, France).

3 | RESULTS

3.1 | Patient population

Among the 655 patients with hyperparathyroidism underwent [^{18}F]Fluorocholine PET/CT between May 2018 and November 2021, 166 patients with pHPT were evaluated by hybrid [^{18}F]Fluorocholine PET/4D-CT before surgery and finally enrolled in the study (Table 1). Population median age was 61.7 years (range 15.6–85.4), with a female to male ratio of 3.5 (129:37). The preoperative median PTH and serum calcium levels were 122.0 ng/L (range: 40.4–575.0) and 2.70 mmol/L (range: 1.50–3.50), respectively. 62/166 (37.3%) patients presented clinical symptomatology at time of PET (symptomatic renal or biliary lithiasis, osteoporosis, articular pain, bone fracture). 45/166 (27.1%) patients presented with concurrent thyroid pathology (multinodular goitre isolated nodule, Basedow disease). 17/166 patients (10.2%) presented with recurrent/persistent pHPT, and the remaining 149 cases (89.8%) had no previous parathyroid surgery. Thus, a total of 645 glands were considered for further analysis. After [^{18}F]Fluorocholine PET/CT, 80 patients underwent MIP (48.2%), 59 exploratory cervicotomy (35.5%) and 5 thoracoscopy (3.0%). In 22 patients (13.3%) the surgical procedure was not available. Finally, a total of 193 parathyroid glands were excised: 140 adenomas, 26 hyperplasia, 14 hypercellular glands and 13 normal glands. Size and weight of the pathologic parathyroid specimen were available only for 145 and 131 glands, respectively, and the median values were 1.4 mm (range: .4–5.5) and .30 g (range: .08–3.00), respectively. Twenty out of 166 patients (12.0%) had MGD.

TABLE 1 Overview of the clinical and biological characteristics of the included patients.

Criteria	
Patients (F/M)	166 (129/37)
Age (median, range)	61.7 years (15.6–85.4 years)
Biological features (median, range)	
PTH	122 ng/L (40–575 ng/L)
Calcemia (mmol/L)	2.70 mmol/L (1.50–3.50 mmol/L)
Patient clinical symptomatology (%)	62 patients (37.3%): symptomatic renal or biliary lithiasis, osteoporosis, articular pain, bone fracture
Concurrent thyroid pathology (%)	45 (27.1%) patients: goitre, isolated nodule, Basedow disease
Recurrent/Persistent pHPT	17 (10.2%) patients
Surgical procedure after imaging	
MIP	80 (48.2%) patients
Exploratory cervicotomy	59 (35.5%) patients
Thoracoscopy	5 (3.0%) patients
Not available	22 (13.3%) patients
Pathology after surgery	
Adenomas	140
Hyperplasia	26
Hypercellular gland (Ad/Hpl)	14
Normal glands	13
UGD/MGD	146 (88%)/20 (12.0%)

Abbreviations: Ad/Hpl, Adenomas/Hyperplasia; F/M, Female/Male; MGD, multiglandular parathyroid disease; MIP, mini-invasive parathyroidectomy; UGD, uniglandular parathyroid disease.

3.2 | [^{18}F]Fluorocholine PET/CT reading concordance

The study utilized interpretations of [^{18}F]Fluorocholine PET/CT scans by resident, expert and non-expert readers to evaluate the concordance rate. In the comparison between resident and expert reading, the concordance rate stood at 78.3% for patient-based analysis and 92.6% for lesion-based analysis. Meanwhile, for expert versus non-expert reading, the concordance rate reached 80.7% and 94.6% for patient- and lesion-based analysis, respectively. The Cohen's kappa coefficient was .89 (95% CI .86–.93) between resident ad expert reading, and .84 (95% CI .79–.88) between expert and non-expert reading. In both cases, the interobserver agreement was almost perfect.

As previously defined, for positive cases, the level of certainty in interpreting [^{18}F]Fluorocholine PET/CT findings (presence of pathologic parathyroid) was evaluated using a three-level rating scale: low, moderate, and high diagnostic certainty. Resident interpreted 119/645 glands as pathological with high certainty (18.5%), 66 positive with low/moderate certainty (inconclusive studies) (10.2%), and 460 as normal. Accordingly, non-expert and expert readers showed 134 (20.8%) and 133 (20.6%) pathological glands with high certainty, 59 (9.1%) and 38 (5.9%) inconclusive studies, and 452 and 474 as normal, respectively.

3.3 | Diagnostic performances in the whole population

3.3.1 | [^{18}F]Fluorocholine PET/CT

[^{18}F]Fluorocholine PET/CT diagnostic performances were assessed based on evaluation provided by an expert referring physician (Table 2). According to a lesion-based analysis after validation against gold standard data, [^{18}F]Fluorocholine PET/CT was true-positive (TP) in 152 cases, true-negative (TN) in 446 cases, false-positive (FP) in 16 cases and false-negative (FN) in 31 cases. Consequently, the diagnostic performance of [^{18}F]Fluorocholine PET/CT for hyperfunctioning parathyroid detection was delineated as follows: Se: 83%, Sp: 97%, PPV: 91% and NPV: 94%. The median SUVmax of hyperfunctioning parathyroids was 5.8 (range: 2.4–17.6). Patients exhibited a median PTH level of 122 ng/L (range: 40–575 ng/L) and a median serum calcium level of 2.7 mmol/L (range: 1.5–3.5 mmol/L).

Considering only 122 patients (477 glands) with high certainty positive results, the Se, Sp, PPV and NPV of [^{18}F]Fluorocholine PET/CT in a *per-lesion* analysis were 91%, 99%, 96% and 96%, respectively (5 FP, 13 FN). Regarding the biological profile in this cohort, patients exhibited a median PTH level of 122 ng/L (range: 50–575 ng/L) and a median serum calcium level of 2.69 mmol/L (range: 1.49–3.50 mmol/L).

On the other hand, a *per lesion* analysis of [^{18}F]Fluorocholine PET/CT data from 9 patients with negative results revealed Sp and NPV of 100% and 82%, respectively (28 TN and 6 FN). As previously defined, all [^{18}F]Fluorocholine PET/CT interpreted as positive with low and moderate certitude have been classified as inconclusive. When considered 36 patients with inconclusive results, Se, Sp, PPV, and NPV of [^{18}F]Fluorocholine PET/CT were 69%, 89%, 71%, and 88%, respectively (32 TP, 96 TN, 3 FP and 7 FN). Pooling data from 44 patients with negative and inconclusive results, Se, Sp, PPV and NPV were 60%, 91%, 71% and 86%, respectively (27 TP, 112 TN, 11 FP and 18 FN). As for the biological profile within this cohort, patients exhibited a median PTH level of 124 ng/L (range: 40–440 ng/L) and a median serum calcium level of 2.65 mmol/L (range: 1.7–3 mmol/L). Those values were not significantly different compared to those obtained

TABLE 2 Head-to-head comparison (per lesion analysis) of diagnostic performances of parathyroid 4D-CT, [^{18}F]Fluorocholine PET/CT and sequential diagnostic algorithm including 4D-CT integrated in a PET/4D-CT after negative or inconclusive standard PET/CT examination.

	Pts	Gls	TP	FP	TN	FN	Se (%)	Sp (%)	PPV (%)	NPV (%)	Accuracy (%)
4D-CT whole population	166	645	96	76	388	85	53 (45–60)	84 (80–87)	56 (50–62)	82 (80–84)	75 (72–78)
PET/CT whole population	166	645	152	16	446	31	83 (77–88)	97 (94–98)	91 (86–95)	94 (91–96)	93 (91–95)
PET/CT certainly positive	122	477	125	5	334	13	91 (85–95)	99 (97–99)	96 (93–99)	96 (94–98)	96 (95–98)
PET/CT negative/ inconclusive	44	168	27	11	112	18	60 (45–73)	91 (85–95)	71 (57–86)	86 (80–92)	83 (77–88)
Sequential algorithm whole population	166	645	161	9	453	22	88 (82–92)	98 (96–99)	95 (91–98)	95 (94–97)	95 (94–97)
Sequential algorithm negative/inconclusive	44	168	36	4	119	9	80 (66–89)	97 (92–99)	90 (81–99)	93 (89–97)	92 (88–96)

Note: In parentheses are reported the 95% CI values.

Abbreviations: FN, false-negative; FP, false-positive; Gls, glandes; NPV, negative predictive value; PPV, positive predictive value; Pts, patients; Se, Sensitivity; Sp, specificity; TN, true-negative; TP, true-positive.

from patients with high certitude positive PET ($p = .66$ for PTH, $p = .22$ for serum calcium).

3.3.2 | 4D-CT

Concerning the 4D-CT, the TP rate was determined to be 96 out of 645 (14.9%), while the TN rate stood at 388 out of 645 (60.2%). The FP rate was calculated as 76 out of 645 (11.8%), and the FN rate as 85 out of 645 (13.2%). Subsequently, the diagnostic performance of 4D-CT for lesion detection was assessed as follows: Se: 53%, Sp: 84%, PPV: 56% and NPV: 82%. 4D-CT demonstrated significantly lower Se, Sp, NPV and PPV than [^{18}F]Fluorocholine (Table 2).

3.4 | Impact of sequential 4D-CT integrated in [^{18}F]Fluorocholine PET/4D-CT

3.4.1 | Patients with negative/inconclusive PET/CT results

In 8 patients with negative PET/CT results, the use of 4D-CT integrated in a [^{18}F]Fluorocholine PET/4D-CT allowed in a per lesion analysis Se, Sp, PPV and NPV of 67%, 96%, 80% and 92%, respectively (4 TP, 23 TN, 1 FP and 2 FN). When considered 36 patients with inconclusive PET/CT results, Se, Sp, PPV and NPV of [^{18}F]Fluorocholine PET/4D-CT were 82%, 97%, 91% and 93%, respectively (32 TP, 96 TN, 3 FP and 7 FN).

Pooling data from 44 patients with negative and inconclusive results in a per lesion analysis Se, Sp, PPV and NPV of sequential diagnostic approach including 4D-CT integrated in [^{18}F]Fluorocholine PET/4D-CT were 80%, 97%, 90% and 93%, respectively (36 TP, 119 TN, 4 FP and 9 FN) (Table 2). Sequential imaging algorithm was superior to standard [^{18}F]Fluorocholine PET/CT by 20% for Se, 6% for Sp, 19% for PPV and 6% for NPV, showing significantly better global accuracy (92%, 95% CI: 88%–96% vs. 83%, 95% CI: 77%–88%). In patients with negative and inconclusive PET/CT results, the combined utilization of [^{18}F]Fluorocholine PET/4D-CT enabled the detection of 9 pathologic parathyroid glands missed by [^{18}F]Fluorocholine PET/CT in 8 patients (Figures 1 and 2), as well as the reevaluation of 7 FP interpretations in 7 patients (Figure 3).

3.4.2 | Whole patient population

Assuming to use the sequential diagnostic algorithm involving 4D-CT integrated in a PET/4D-CT after negative or inconclusive standard PET/CT (44 patients), the *per lesion*-based Se, Sp, PPV and NPV evaluated in all 166 included patients were 88%, 98%, 95% and 95%. Accordingly, the TP rate of [^{18}F]Fluorocholine PET/CT emerged as 25% (161 TP), the TN rate as 70.2% (453 TN), the FP rate as 1.4% (9 FP) and the FN rate as 3.4% (22 FN). In the whole population, the evaluation of the difference in Se and Sp among the two imaging procedures found only a slight and not significant superiority of sequential PET/4D-CT when compared with standard PET/CT (Table 2).

4 | DISCUSSION

The preoperative assessment of primary hyperparathyroidism (pHPT) is challenging due to the variable location and size of hyperfunctioning parathyroid glands. Optimal

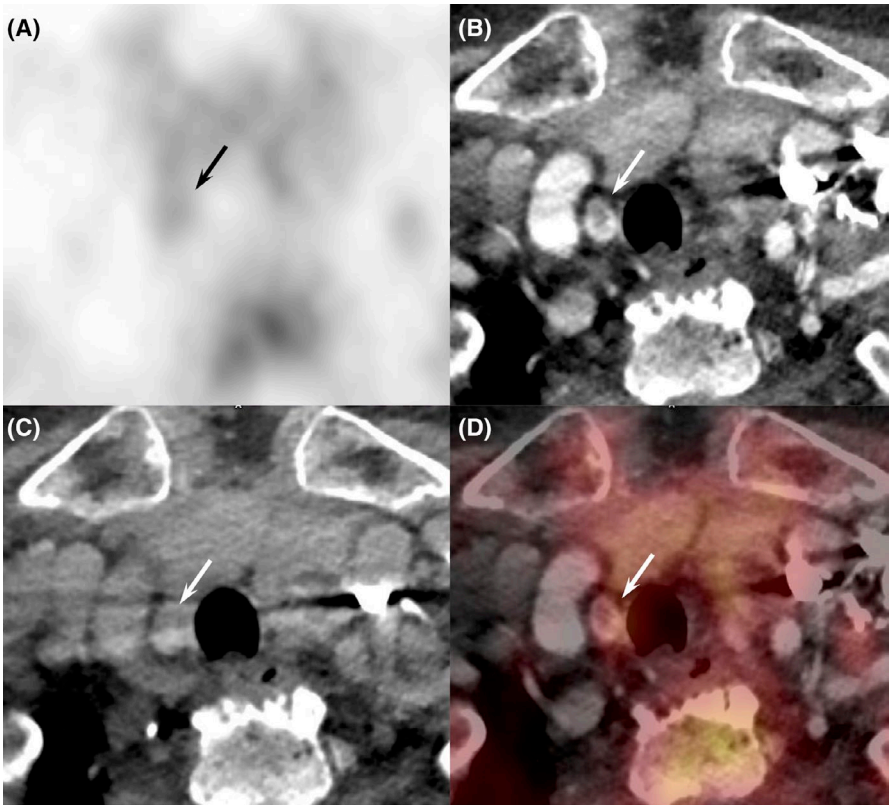

FIGURE 1 Results of sequential imaging approach in a 76-y-old woman with pHPT (PTH: 229 ng/L, calcemia: 2.7 mmol/L) and negative [^{18}F] Fluorocholine PET/CT (A). 4D-CT (axial slice, B: Arterial phase, C: Portal venous phase) integrated in a [^{18}F]Fluorocholine PET/4D-CT (D) allowed the identification of a pathological right inferior parathyroid (arrows) with intense peripheral contrast-enhancement and rapid wash-out. Cystic appearance contributes to explain PET false negative result. Parathyroid adenoma was confirmed by pathology after parathyroidectomy.

imaging strategies depend on patient characteristics, available resources, and medical team expertise. Advances in imaging technology and ongoing research further influence these strategies. Recent guidelines suggest [^{18}F] Fluorocholine PET/CT as a potential first-line imaging option for pHPT.[14] Combining [^{18}F]Fluorocholine PET/CT with 4D-CT, as a second-line imaging procedure, has gained attention for comprehensive preoperative localization.[19,20]

Our study supports the critical role of [^{18}F] Fluorocholine PET/CT in identifying hyperfunctioning parathyroid glands, showing sensitivity consistent with published data[11,17] and exceeding that of 4D-CT. The sensitivity of 4D-CT in our study was lower than previously reported but higher than recent findings by Noltes et al.,[23] who compared the effectiveness of 4D-CT, [^{11}C] methionine PET/CT, and [^{11}C]choline PET/CT in patients with negative or discordant first-line imaging. Differences in CT scanners, imaging protocols, CT beam hardening, streak artefacts, and radiological reviewer's experience in parathyroid pathology may explain these discrepancies.[17]

Our study introduces significant elements for discussion, specifically assessing the diagnostic utility of sequential 4D-CT after a negative or inconclusive [^{18}F] Fluorocholine PET/CT.[8] This approach benefits patients by providing 4D-CT in the same imaging session without additional discomfort. Although [^{18}F]Fluorocholine PET/4D-CT shows higher sensitivity than [^{18}F] Fluorocholine PET/CT alone, the marginal improvement may not justify routine use. Patient selection is crucial to maximize diagnostic synergy between PET and 4D-CT. The advantage of [^{18}F]Fluorocholine PET/4D-CT is more pronounced in challenging cases, where it can accurately diagnose cases misclassified by PET/CT alone.

In our series, the sequential algorithm showed higher diagnostic accuracy than the standard PET/CT approach (92%, 95% CI: 88%–96% vs. 83%, 95% CI: 77%–88%). This approach increased true positive results (27 to 36) and reduced false positives (11 to 4) and false negatives (18 to 9). Therefore, diagnostic 4D-CT should be considered individually, within a hybrid imaging session, to differentiate faint physiological radiopharmaceutical uptake from small hyperplastic parathyroid glands.[19]

Interobserver concordance of [^{18}F]Fluorocholine PET/CT is critical for its clinical utility and may relate to the interpreting physician's experience. High concordance ensures consistent interpretation for accurate diagnosis and effective treatment planning. Christensen et al.[24] found 'good' to 'near perfect' intra-observer agreement in [^{11}C]-Choline PET/CT among expert and non-expert readers, with high sensitivity (above 75%) and specificity (above 94%). Our findings align, showing an 80.7% concordance rate for patient-based analysis and 94.3% for lesion-based analysis between expert and non-expert readings. Concordance was also high between resident

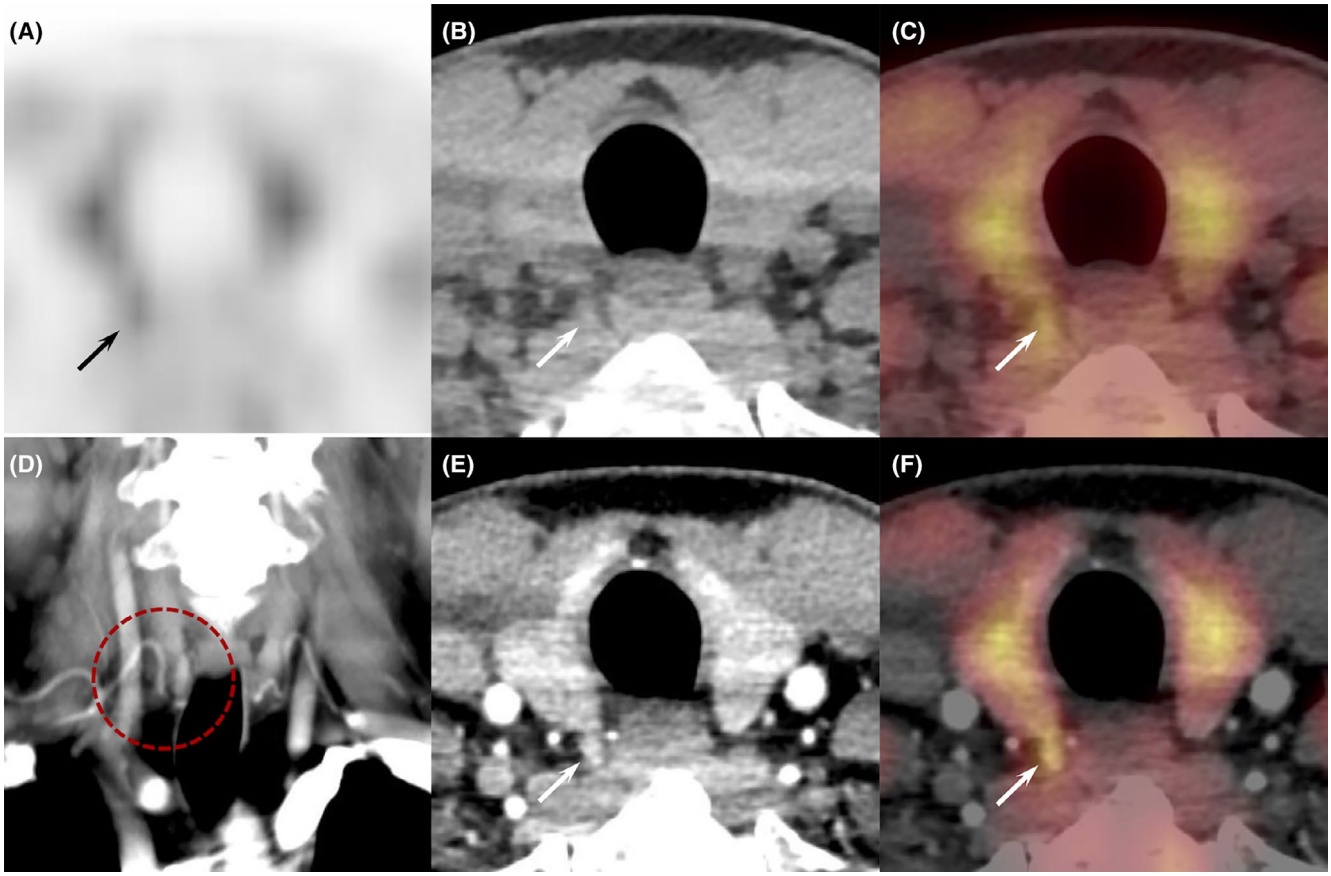

FIGURE 2 Inconclusive [^{18}F]Fluorocholine PET/CT results in a 51-y-old man with pHPT (PTH: 60 ng/L, calcemia: 2.7 mmol/L), showing faint focal right latero-oesophageal uptake without evident morphologic abnormalities on no-contrast enhanced CT (arrows, axial slice, A: PET, B: CT, C: PET/CT). 4D-CT (arterial phase, (D) 10-mm thick coronal slice, (E) Axial slice) integrated in a [^{18}F]Fluorocholine PET/4D-CT (F) allowed the identification of a pathological right inferior parathyroid with moderate [^{18}F]Fluorocholine uptake and typical 4D-CT features. The presence of parathyroid adenoma was pathologically confirmed after neck surgery.

and expert readings (77.8% and 92.4% for patient- and lesion-based analysis, respectively). Experienced readers reduced doubtful cases (10.2%–5.9%) but had less impact on positive responses with high certainty (18.5% vs. 20.6%). Standardized imaging protocols and well-defined interpretation criteria contribute to high concordance rates. The robust interobserver concordance of [^{18}F]Fluorocholine PET supports its reliability, providing consistent and reproducible results essential for optimal patient care. Ongoing education and collaboration among nuclear medicine professionals are vital for maintaining high diagnostic performance in pHPT management.

A multimodal imaging approach can improve diagnostic precision and surgical planning for pHPT. Effective collaboration between nuclear medicine physicians, radiologists, and technicians is key to enhancing PET/CT report quality, minimizing patient discomfort, and reducing time and costs. Van Mossel et al.[25] highlighted the cost-effectiveness of first-line [^{18}F]Fluorocholine PET/CT in Europe, integrating it into routine practice with minimal additional costs. This approach is reducing the use of [^{99m}Tc]MIBI scintigraphy in pHPT management due to its inferior diagnostic performance.

Using 4D-CT increases patient radiation exposure, necessitating optimization of the CT protocol by reducing acquired phases[26] and using dual-energy technology.[27] Indeed, the combination of both non-enhanced CT and arterial phase could be enough to lower false-positive results reducing radiation exposure.[28,29] 4D-MRI, providing good soft tissue contrast without radiation exposure, could differentiate parathyroid from other tissues better than CT. Thus, [^{18}F]Fluorocholine PET/MR may be the next step in pHPT assessment,[30] though its benefit over [^{18}F]Fluorocholine PET/CT is not yet defined, particularly in nonlocalized disease with negative or inconclusive standard examination results.[31]

The retrospective and monocentric nature of our study are limitations, but the large, homogenous population and consistent use of the same imaging protocols enhance reliability.

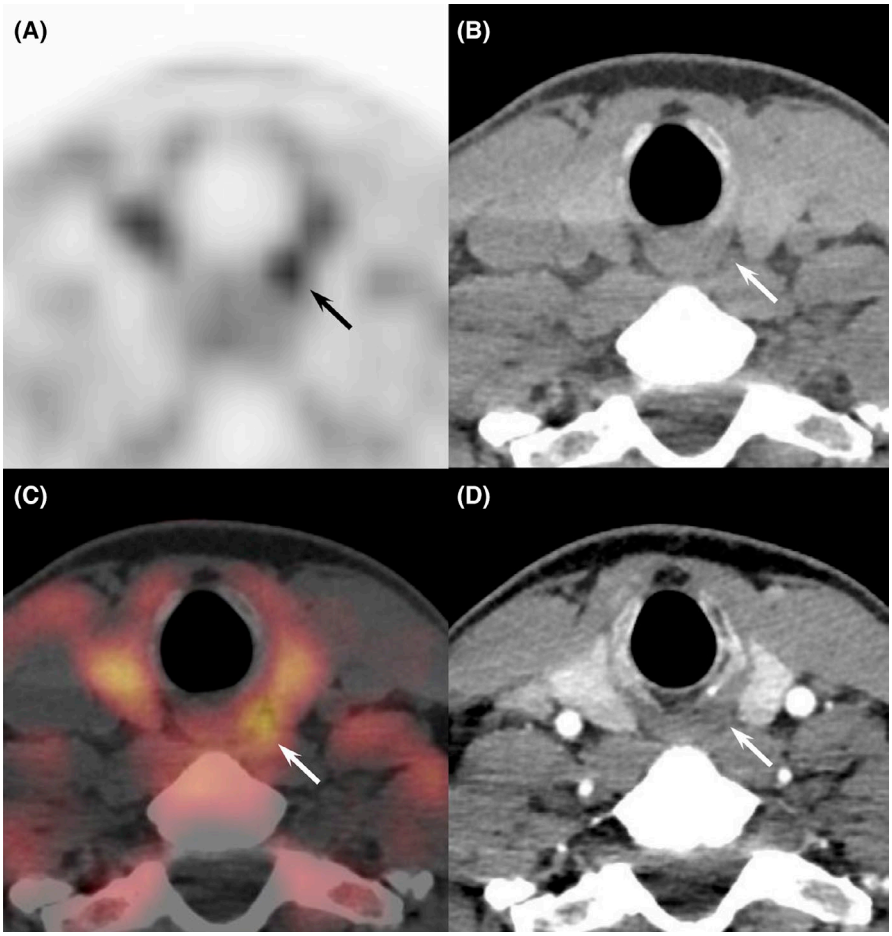

FIGURE 3 False positive result of [^{18}F]Fluorocholine PET/CT (axial slice, A: PET, B: No-contrast CT, C: PET/CT) corresponding to a moderate focal uptake next to left cervical oesophagus (arrows), suggesting the presence of hyperfunctioning superior left parathyroid. No morphological abnormalities were detected on the 4D-CT (D, arterial phase) integrated in the PET/4D-CT.

In conclusion, we recommend evolving the preoperative diagnostic strategy for pHPT, prioritizing [^{18}F] Fluorocholine PET/CT,[32] followed by sequential 4D-CT in the same session for negative or inconclusive PET/CT results. This personalized algorithm could enhance hyperfunctioning parathyroid gland detection in challenging cases. When PET/CT results are clearly positive, the added value of 4D-CT is marginal. Applying 4D-CT only to the negative/inconclusive group maintains diagnostic accuracy while reducing radiation exposure and costs. Further prospective studies with more cases of negative/inconclusive results are needed to determine the clinical benefits of this approach compared to standard algorithms.

AUTHOR CONTRIBUTIONS

AK, HB, AL and AI contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by AK, HB, AL and AI. The first draft of the manuscript was written by AK, HB, AL and AI. All authors commented on previous versions of the manuscript.

FUNDING INFORMATION

The authors declare that no funds, grants or other support were received during the preparation of this manuscript.

CONFLICT OF INTEREST STATEMENT

The authors have no relevant financial or non-financial interests to disclose.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

CONSENT TO PARTICIPATE

Informed consent was obtained from all individual participants included in the study.

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How to cite this article: Kaseb A, Benider H, Treglia G, et al. Refining the role of presurgical PET/4D-CT in a large series of patients with primary hyperparathyroidism undergoing [^{18}F] Fluorocholine PET/CT. *Eur J Clin Invest*. 2025;55:e14336. doi:10.1111/eci.14336